EDITORIAL COMMENT
Anemia in Heart Failure
Time to Rethink Its Etiology and Treatment?*
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The occurrence of anemia (hemoglobin concentration <13.0 g/dl in men and <12.0 g/dl in women) in patients with chronic heart failure has recently received increased attention. Its prevalence ranges from <10% among patients with mild heart failure to more than 50% for those with advanced disease (1). A clinical profile of the anemic heart failure patient has gradually emerged. This individual tends to be older; female; have more advanced symptoms and signs of heart failure, has greater functional impairment and hypertension (2). Anemic patients also have lower peak oxygen consumption on exercise testing compared with nonanemic patients (2).

Anemia has convincingly been shown to be a powerful predictor of rehospitalization rates (3) and survival in chronic heart failure (2–6). Most studies have shown a linear relationship between hematocrit or hemoglobin and survival with the SOLVD (Studies of Left Ventricular Dysfunction) trial reporting a 2.7% increase in the adjusted risk of death per 1% reduction in hematocrit and the PRAISE (Prospective Randomized Amlodipine Survival Evaluation) trial describing a 3% increase in risk for each 1% decline in hematocrit (4,5).

The significance of anemia among patients hospitalized with acute decompensated heart failure also has been examined (7). Felker et al. (7) retrospectively analyzed the OPTIME-CHF (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure) results and found that hemoglobin level independently predicted adverse events, even after adjustment for other covariates. For every 1 g/dl decrease in admission hemoglobin value, a 12% increase in the probability of death or rehospitalization within 60 days of treatment was observed. Recently, the same investigators studied anemia in patients with heart failure and preserved systolic function (8). Anemia was once again found to be independently associated with adverse outcomes (adjusted hazard ratio: 1.6 to 1).

Why should anemia increase the risk of mortality in patients with heart failure? Although most published reports have not examined specific pathophysiologic mechanisms, a variety of plausible explanations exist. Anemia may simply be a marker for other conventional factors that increase mortality among patients with heart failure. For example, anemia often is associated with impaired renal function. This explanation seems unlikely because most studies have controlled for such comorbidities, including renal dysfunction (2,3,6). Anemia also may be a marker for higher circulating cytokines and chemokines, which are known to predict higher mortality in this population (6). Hemodynamic changes accompanying severe anemia include increased preload, reduced peripheral vascular resistance, and increased cardiac output. These adaptive responses may ultimately lead to a detrimental increase in left ventricular mass. Anand et al. (9) have reported that a 1 g/dl increase in hemoglobin concentration is associated with a 4.1 g/m² decrease in left ventricular mass index during a 24-week period (9). Increased left ventricular mass consistently has been demonstrated to be a significant factor for poor prognosis (5,9). Myocardial ischemia also may be precipitated from reduced oxygen-carrying capacity combined with increased left ventricular mass and increased wall stress. In addition, anemia has been shown to be associated with reversible elevations in plasma catecholamines and alphax₂-receptor densities among patients with renal failure. Finally, chronically increased myocardial work and adrenergic stimulation caused by decreased oxygen-carrying capacity may ultimately lead to progression of heart failure and may accelerate adverse ventricular remodeling (4).

A variety of potential mechanisms may contribute to anemia in heart failure (Table 1). It is highly likely that a complex interaction between impaired cardiac performance, neurohormonal and inflammatory activation, renal dysfunction, and bone marrow hypo responsiveness contribute to its development.

Expansion of plasma volume is common in heart failure; hence, anemia may be dilutional rather than due to a true decrease in red cell mass. Androne et al. (10) reported that hemodilution accounted 46% of anemic heart failure patients. Circulating levels of erythropoietin are either normal or mild/moderately elevated in chronic heart failure (8). Increased renal production of erythropoietin may be stimulated by renal hypoperfusion and hypoxia. Alternatively, heart failure patients may have relative resistance to erythropoietin due to the influence of pro-inflammatory cytokines or malnutrition (6).

Circulating proinflammatory cytokines increase with disease severity and predict worse clinical outcomes. Tumor necrosis factor-alpha (TNF-α), interleukin-1, and interleukin-6 have direct effects on bone marrow function and have been implicated in the production of anemia of chronic disease.
Journal provides a new insight into the pathogenesis of heart failure. Patients without a diagnosis by these methods underwent red cell mass measurements by chromium-51 assay. Unlike earlier reports, iron deficiency anemia was confirmed by bone marrow aspiration in 27 patients (73%), 19% had anemia of chronic disease, and only 5% had predominantly dilutional anemia. Although mean corpuscular hemoglobin concentration was lower among iron-deficient patients, neither serum iron nor ferritin levels proved to be reliable markers of iron deficiency. Thus, the authors emphasized the need for bone marrow aspiration to exclude iron deficiency among anemic heart failure patients. Although provocative, several methodologic limitations must be acknowledged. The number of patients evaluated was quite small, and all had advanced decompensated symptoms. Unlike earlier published series, the mean age of the population (58 years) was substantially younger than typical heart failure populations; more than 90% were men. Further, only patients with previously undiagnosed anemia were included in this series. Finally, the true incidence of hemodilutional anemia cannot be estimated since only a minority of patients underwent quantitative measurement of red cell mass.

Like all good studies, this report raises a number of important questions. First, is a high prevalence of iron deficiency simply characteristic of hospitalized patients with decompensated heart failure or may it also be a more common underlying pathophysiologic mechanism among ambulatory patients with New York Heart Association (NYHA) functional class II or III symptoms? Second, why did this patient population not demonstrate the expected low serum ferritin concentration? It is possible that the relative increase in ferritin may have been due to inflammatory mediators that accompany the heart failure syndrome. Similarly, the relatively low erythropoietin levels could reflect cytokine inhibition of erythropoietin production. Third, given the inaccuracy of serum hematologic measures, which anemic patients should be considered for bone marrow aspiration in order to detect true iron deficiency? Finally, should our therapeutic approach to anemia among heart failure patients also undergo re-evaluation? Recombinant human erythropoietin has been studied in several small heart failure cohorts (13,14). In an uncontrolled study by Silverberg et al. (13), an improvement in ejection fraction, NYHA functional class, and hospitalization rates after treatment with erythropoietin and intravenous iron replacement was noted for patients with NYHA class III or IV heart failure symptoms. Mancini et al. (14) have reported erythropoietin-treated patients experienced significant improvement in peak oxygen uptake in a randomized, single-blind, placebo-controlled, 3-month trial of erythropoietin therapy in anemic patients with advanced symptoms. Newer erythropoietin analogs have been developed (such as darbepoetin-α) that have a longer half-life and require less frequent administration. An ongoing phase 2 clinical trial of darbepoetin-α in patients with heart failure should provide...
important information on the potential efficacy of this new agent. Despite its promise, erythropoietin is extremely expensive and it is often administered for only short periods of time. If a sizable percentage of anemic patients are iron deficient, the possibility of long-term oral or intermittent intravenous iron repletion may offer a more effective and lower cost treatment alternative in this population. Prospective, randomized control trials of new therapeutic approaches to anemia in patients with heart failure are needed and may address the unanswered-but-crucial question of whether correction of anemia will ultimately result in improved outcomes in this high-risk population.

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