**EDITORIAL COMMENT**

**Anemia in Heart Failure**

**Marker or Mediator of Adverse Prognosis?***

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*A dropsy first shows itself, by the swelling of the legs about the ankles, in such a manner as to retain the impression of your finger. The swelling appear most at night, and is usually attended with a shortness and difficulty of breath, ever most troublesome when the patient lies down.

He must therefore resolve upon proper remedies, before the waters rise high enough to drown; and, if he have but the gift of self denial, he may, by God's Help, get the better of this mortal enemy; provided there be no universal decay, no deprivation of the liver, or other organs, necessary for blood-making.

John Tennent, *The Poor Planter’s Physician*, 1736 (1)

It has long been known that anemia portends a poor prognosis in the general population (2) and in patients with hypertension (3), chronic kidney disease (4), cancer, acute myocardial infarction (5), coronary artery bypass grafting (6), percutaneous coronary intervention (7), and heart failure (HF) (8,9), as described by John Tennent almost 3 centuries ago. What is uncertain is whether anemia is another marker of inflammation, and thus a risk marker like C-reactive protein, phospholipase A2, and high white blood cell count, or whether anemia is a mediator of the adverse prognosis in these diverse settings. If anemia is a marker, treatment may not obviate the increased risk associated with anemia. If it is a mediator, treatment may be a novel tool to reduce morbidity and mortality in HF.

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In HF patients, the prevalence of anemia is higher with advanced New York Heart Association functional class, older age, worse renal function, and more comorbidities. In the paper by Tang et al. (10) in this issue of the *Journal*, anemia was associated with older age; diabetes mellitus; male gender; lower glomerular filtration rate; higher ejection fraction; diuretic use; and neurohormonal activation, exemplified by low serum sodium, low total cholesterol, and high B-type natriuretic peptide (10). Although angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may lower hemoglobin levels by −0.3 g/dl (3), the use of angiotensin-converting enzyme inhibitors and beta-blockers was less common in the anemic patients.

The paper by Tang et al. (10) demonstrates that persistent or new-onset anemia confers a marked increase in risk for HF patients, whereas anemia that resolved, which occurred in 43% of anemic patients, did not confer increased risk. For each 1 g/dl decrease in hemoglobin, there was a 20% increase in the multivariate adjusted risk of death. This is similar to or higher than previous analyses of the risk associated with anemia. We do not know whether specific treatment for the anemia, such as intravenous iron or erythropoiesis-stimulating proteins (ESP), would also obviate the risk associated with anemia.

Cardiologists have only lately started to recognize, evaluate, and treat anemia. The 2001 American College of Cardiology/American Heart Association HF guidelines make no mention of anemia as a risk factor or target for treatment (11). Tang et al. (10) found that <20% of all anemic HF patients had a laboratory evaluation for the anemia, and only ~30% had a repeat hemoglobin within 6 months. Tang et al. (10) state that “hemoglobin levels have not been commonly recognized as relevant measurement in the management of heart failure until recently.”

Anemia should be evaluated with standard laboratory tests, including iron saturation, ferritin, folate, vitamin B12, reticulocyte count, stool guaiac, and possibly erythropoietin levels and soluble transferrin receptors. In diseases where inflammation is present, such as HF, ferritin may be falsely elevated like other acute–phase response proteins. A very simple method to determine whether a low iron saturation is due to anemia of chronic disease or iron deficiency is to perform an oral iron absorption test (12,13). This test can be performed in the outpatient or inpatient setting by administering 10 ml of ferrous sulfate solution (650 mg) orally and measuring the serum iron level at baseline and 2 h later. A normal response, suggesting that the oral iron is being absorbed and transported to the bone marrow, is an increase of ~150 μg/dl in the iron level (i.e., 25 to 175 μg/dl). This suggests that the low iron level can be treated with oral iron. An increase of ≤50 μg/dl suggests that there is a failure of the oral iron to reach the systemic circulation. I suspect that this may be due to interruption of the intestinal mucosa by gut edema in HF patients and to elevated levels of hepcidin. If patients have a low iron saturation and absorb oral iron appropriately, then they likely have iron-deficiency anemia, and the hemoglobin will respond to iron repletion (13). If patients do not absorb oral iron, they may have anemia of chronic disease and will likely require intravenous iron therapy. Newer intravenous iron preparations such as iron sucrose and ferric gluconate have a much lower incidence of
adverse side effects than older agents such as iron dextran and can be used in patients who do not adequately absorb oral iron. Intravenous iron therapy alone may improve anemia in many HF patients (14) and is being studied in a large randomized trial, IRON–HF (15).

What is unknown is whether treatment of anemia with ESPs is beneficial in cardiac patients. Erythropoietin receptors are present in the myocardium (16) and throughout many organs. In the normal subject, as the hemoglobin decreases, the erythropoietin levels increase, with a level of ∼25 mU/ml at a hemoglobin of 12 g/dl and ∼100 mU/ml at a hemoglobin of 10 g/dl (17). Erythropoietin levels below these values suggest relative levels of deficiency. The ESPs work by inhibiting apoptosis of the erythroblasts in the bone marrow (18). This anti-apoptotic effect may be detrimental in cancer patients (19), but it might be beneficial in cardiac patients. In animal models, treatment with ESPs prevented cardiomyocyte apoptosis induced by ischemia (20) and norepinephrine (21).

Phase 2 clinical trials of ESPs in HF patients (n = 475 patients) have shown that ESPs can increase hemoglobin, improve HF symptoms, and improve exercise capacity and may reduce morbidity/mortality (hazard ratio 0.67, 95% confidence interval 0.44 to 1.03, p = 0.07) (22). This hypothesis is being tested in an ongoing trial, the RED-HF (Reduction in Events with darbepoeitin alpha in Heart Failure) trial, a double-blind randomized trial in 3,400 anemic New York Heart Association functional class II to IV systolic HF patients.

Recent trials in chronic kidney disease patients (23) found that attempting to normalize the hemoglobin with higher doses of ESPs (rather than using ESPs to keep the hemoglobin in the 11 to 12 g/dl range) was associated with harm. We do not know why this harm might have occurred, but it has led to labeling changes for ESP agents to target the hemoglobin to the 11 to 12 g/dl range.

In conclusion, anemia is prevalent in medical practice and confers an adverse risk in most diseases. Anemia may be transient and resolve without specific intervention, for example, in gastrointestinal blood loss, recent hospitalization, acute myocardial infarction, or surgery. If anemia persists, evaluation and treatment of the underlying cause is appropriate. We do not know whether resolution of the anemia with treatment will obviate the risk, as was observed with spontaneous resolution of anemia by Tang et al. (10). Randomized trials of intravenous iron or ESPs to treat anemia in HF are ongoing. Only then will we know whether anemia is a marker or a mediator of the adverse risk in HF.

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REFERENCES


