Too Much, Too Little, or Just Right?: Untangling Endogenous Erythropoietin in Heart Failure

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“Why then, can one desire too much of a good thing?”
—William Shakespeare, As You Like It, Act IV

Anemia is common in patients with heart failure and is associated with adverse outcomes. This observation has now been replicated in chronic systolic heart failure,1 heart failure with preserved ejection fraction,2 and acute decompensated heart failure.3 These data have led to the hypotheses that treating anemia in patients with heart failure may improve outcomes, and therapeutic trials of both the erythropoietin-stimulating agent darbepoetin4 and intravenous iron5 in heart failure are currently ongoing. Despite the accumulation of data on the potential importance of anemia in heart failure, much about the pathophysiology of this association remains poorly understood.

What explains the high prevalence of anemia in heart failure? In addressing this issue, it is important to recognize that anemia in heart failure is not a single clinical entity, and there are numerous potential contributors to anemia in this population. First, previous data in patients with advanced heart failure indicate that approximately half of patients with low hemoglobin have hemodilution rather than a true decrease in red blood cell mass.6 Iron deficiency may contribute to anemia in heart failure patients, although the true prevalence of iron deficiency in heart failure remains uncertain, and published estimates have varied widely.7,8 Regardless of whether frank iron deficiency exists, there seems to be a functional iron deficiency in many patients with heart failure and anemia associated with impaired ability to utilize available iron stores.8 The combination of systemic inflammation, blunted bone marrow responsiveness to erythropoietin, and impaired iron mobilization is consistent with anemia of chronic disease.9 Angiotensin-converting enzyme inhibitors have also been demonstrated to contribute to anemia,10 potentially through the actions of the hematopoiesis inhibitor N-acetyl-serly-aspartyl-lysyl-proline.11 Finally, chronic kidney disease is common in heart failure and is associated with decreased erythropoietin production and anemia.

Given this variety of contributing factors, the interpretation of erythropoietin levels in heart failure represents a considerable challenge. Erythropoietin is the primary regulatory hormone of erythropoiesis and is produced by the peritubular fibroblasts in the kidney in response to low oxygen tension. Although heart failure patients in general have higher erythropoietin levels than do normal control individuals, previous data have shown that erythropoietin levels are poorly correlated with hemoglobin in patients with heart failure.12 One explanation for this variability rests in the heterogeneous causes of anemia outlined above. Anemia in heart failure patients may be associated with erythropoietin levels that are low (eg, chronic kidney disease), normal (eg, plasma volume expansion or “pseudoanemia”) or high (eg, bone marrow resistance to the effects of erythropoietin as in anemia of chronic disease).

In this issue of Circulation, Belonje et al13 provide important incremental data for understanding the links between erythropoietin and anemia in heart failure. These investigators analyzed erythropoietin levels at baseline and at 6 months in a subset of 605 patients enrolled in the Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH) study, a multicenter randomized study of disease management strategies in heart failure.14 They found that elevated levels of endogenous erythropoietin were independent predictors of adverse outcomes, even after adjustment for hemoglobin, glomerular filtration rate, age, and NTproBNP levels. Patients with persistently high erythropoietin levels at 6 months had a substantially higher risk of poor outcomes than did those whose erythropoietin levels decreased to below the median during follow-up, whereas a change in hemoglobin over the same time period did not predict risk. In an analysis confined to anemic patients, observed levels of erythropoietin were compared with those predicted on the basis of hemoglobin levels (the O/P ratio). Most anemic patients (79%) had O/P ratios lower than predicted. Higher than expected erythropoietin level (ie, a high O/P ratio) was uncommon (9% of anemic patients) but was a predictor of poor outcomes.

In general, these findings confirm and extend previous work on the role of erythropoietin in heart failure. Elevated erythropoietin levels have previously been shown to be associated with adverse outcomes in heart failure,12,15 but the current study is the first to investigate the prognostic importance of serial erythropoietin measurements. Lower than expected erythropoietin levels for a given level of hemoglobin in the majority of patients with heart failure have also been shown previously.6 Prior data have also suggested an association between higher than expected erythropoietin levels and poor prognosis.16 Although the current analysis is the largest yet focused on this topic, the authors appropriately point out several important limitations. The overall sample
size is still modest, particularly with regard to the analysis of anemic patients (n = 135). This limited number of events limits the ability to adjust for other potentially important covariates of interest. The formula for estimating a “predicted” level of erythropoietin production for a given patient was derived from a very limited dataset of 20 patients. Additionally, inasmuch as the primary driver of erythropoietin production in the kidney is hypoxia rather than hemoglobin, the concept of a “predicted level” of erythropoietin based solely on a hemoglobin value is of uncertain validity. Particularly in the setting of heart failure, many other hemodynamic and metabolic factors besides hemoglobin may contribute to regulation of erythropoietin levels.

Despite these limitations, it is clear from this study and prior data that elevated erythropoietin levels in heart failure are a biomarker of adverse outcomes. Why do some heart failure patients have “too much” endogenous erythropoietin, and what explains its association with increased risk? There are certainly analogous conditions wherein elevated levels of endogenous regulatory hormones are markers of increased risk, both in the field of heart failure (natriuretic peptide levels) and in other disease states (insulin levels). With regard to the causes of elevated erythropoietin levels in some heart failure patients, the authors posit several potential explanations, including impaired renal perfusion, shifting of the oxygen-hemoglobin dissociation curve as a result of metabolic alterations, the effects of angiotensin II, or inflammatory stress. Although any or all of these mechanisms may contribute, the role of inflammatory mediators seems to represent a compelling mechanistic link between elevated erythropoietin and adverse outcomes in heart failure. Chronic inflammation is a well-described phenomenon in heart failure and is associated with disease progression and mortality. Proinflammatory mediators such as tumor necrosis factor-α and interleukin-6 inhibit the actions of erythropoietin on the bone marrow and can impair effective utilization of iron stores through upregulation of the iron regulatory hormone hepcidin. In support of this concept, previous data have shown a strong correlation between erythropoietin levels and interleukin-6 in anemic heart failure patients. Of potential relevance to this issue are recent data from our group and others that have shown a strong relationship between elevations of red blood cell distribution width (RDW) and adverse outcomes in patients with cardiovascular disease. Elevations in RDW, which is a measure of variability in erythrocyte size, are a marker of impaired erythropoiesis. As with data on RDW are not reported in the current study, one might speculate that the group with elevated O/P ratios would also be most likely to have elevations of RDW. If so, RDW could represent a readily available marker of a state of erythropoietin resistance that might have implications for prognosis. Taken together, the prior data on RDW and this report by Belonje et al suggest a mechanistic framework for linking inflammation, bone marrow responsiveness, anemia, and cardiac function. Future studies that include careful evaluation of red blood cell indices, iron stores, inflammatory markers, and erythropoietin levels in larger heart failure cohorts will help further the understanding of these relationships and provide greater insight into underlying mechanisms. For now, it seems clear that elevations in endogenous erythropoietin levels are a biomarker of increased risk, and erythropoietin can be added to the alphabet soup of prognostic markers in heart failure. As with natriuretic peptide levels, elevations of endogenous erythropoietin in heart failure seem to represent “too much of a good thing.”

Disclosures

Dr. Felker has served as a consultant and received research grants from Amgen, and is a member of the Steering Committee for the ongoing Reduction of Events with Darbepoetin in Heart Failure (RED-HF) Study.

References


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