Pathogenesis of Anemia in Heart Failure

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Anemia is a common comorbidity in patients with heart failure and is associated with worse long-term outcomes. Although the mechanisms involved in the development of anemia in patients with heart failure are unclear, data suggest that renal dysfunction, neurohormonal, and proinflammatory cytokine activation in heart failure lead to anemia of chronic disease with defective iron utilization, inappropriate erythropoietin responsiveness, and depressed bone marrow function. Likewise, the mechanisms by which anemia worsens heart failure outcomes are also uncertain and may be related to increased myocardial workload to compensate for reduced tissue oxygen delivery leading to unfavorable cardiac remodeling, to the effects of factors that cause anemia in patients with heart failure or because of aggravation of other comorbidities seen in these patients. Patients with heart failure and anemia are more likely to be older, have diabetes mellitus, chronic kidney disease, more severe heart failure, lower blood pressure, and greater neurohormonal and proinflammatory cytokine activation. Most multivariable analyses, apart from a few exceptions, have reported that anemia is an independent predictor of mortality and morbidity in a variety of patients with heart failure including men and women, patients with acute decompensated and chronic heart failure, and those with impaired or preserved ejection fraction. Thus, correcting anemia may be an important therapeutic target to improve long-term outcomes in such patients. Although the results of several small studies in patients with anemia and heart failure with reduced ejection fraction have shown that erythropoiesis-stimulating agents increase hemoglobin and have some beneficial effects on clinical outcomes, the neutral results of treating anemic patients with darbepoetin in the large, more definitive the Reduction of Events by Darbepoetin Alfa in Heart Failure (RED-HF) trial indicate that we need to better understand the pathogenesis of anemia and whether it is just a marker of the severity of heart failure.

In this issue of Circulation: Heart Failure, O’Meara et al report their findings of a prospective study of 151 patients with heart failure with reduced ejection fraction and anemia (group 1), heart failure with reduced ejection fraction without anemia (group 2), and patients with chronic kidney disease with preserved ejection fraction without heart failure (group 3). They sought to improve our understanding of the likely complex mechanisms involved in the relationship between the severity of heart failure and the development of anemia by comparing these groups on several biomarkers believed to be involved in the pathogenesis of anemia, including markers of collagen metabolism, myocardial stretch, myocyte death, inflammatory cytokines, and echocardiographic parameters. They were particularly interested in the roles of renal dysfunction and inflammation that previously have been related to anemia in patients with heart failure and logically must be linked to cardiac remodeling. Their findings confirm previous studies that anemic patients with heart failure with reduced ejection fraction have features of more severe heart failure with more extensive left ventricular remodeling and higher levels of biomarkers of advanced heart failure, higher inflammatory and collagen markers, worse renal function, and erythropoietin resistance.

Ideally, studies of the pathogenesis of anemia would begin with a conceptual model that would guide the study design and analyses to test the hypothesized relationships summarized as estimated correlation coefficients rather than differences in group means and proportions. The conceptual model of anemia in patients with heart failure diagrammed by O’Meara et al begins with several measures of ventricular structure and function (remodeling) that conceptually can be considered to be measures of the severity of heart failure that logically must precede the development of anemia if anemia is caused by the heart failure. Their cross-sectional study cannot establish the extent of cardiac remodeling that preceded the development of anemia. Their conceptual model appropriately incorporates the possibility of a bidirectional relationship whereby anemia could worsen the severity of heart failure as measured by ventricular structure and function. However, the cross-sectional group comparisons cannot determine how much of the observed relationships between the measures of cardiac structure and function reflect the development of anemia or vice versa. Thus, the magnitude of the observed relationships between measures of cardiac structure and function may not entirely represent pathogenic pathways to anemia.

 Appropriately their conceptual model does not hypothesize a direct (unmediated) relationship between the measures of ventricular structure and function and anemia. There is no evidence or reason to hypothesize that these measures of the severity of heart failure can directly cause anemia. Changes in cardiac structure and function must merely initiate intermediary causal pathways. The question is how much of the relationships between measures of heart failure and anemia are mediated by the pathway to renal dysfunction and erythropoietin abnormalities (resistance) that have previously been

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documented by several studies of patients with heart failure? Unfortunately, the analyses done by O’Meara et al. are not sufficient to address this question. They did confirm that measures of renal dysfunction and erythropoietin were related to the presence of anemia in patients with heart failure, which is a necessary component of establishing mediation. However, to complete the test for mediation, the analysis would have to show that controlling for measures of renal dysfunction and erythropoietin substantially reduces or eliminates the relationship between measures of heart failure and anemia. Their conceptual model also posits that inflammation, iron metabolism, and inhibitors of the renin–angiotensin system can intensify the abnormalities of renal dysfunction and erythropoietin and thereby modify their mediator effects. However, the reported analyses did not test either of these hypotheses or the hypotheses implied by their conceptual model that inflammation and iron abnormalities also partially mediate the relationship between heart failure and anemia. The investigators controlled for some known correlates of morbidity and mortality in patients with heart failure, such as age, coronary artery disease, diabetes mellitus, hypertension, atrial fibrillation, and jugular venous distension in their multivariable analyses of the predictors of anemia. However, the hypothetical role that these variables play in the pathogenesis of anemia in patients with heart failure is not clear. These variables need to be added to their conceptual model to determine whether their effects should be controlled, analyzed as pathway modifiers, or even excluded from the analyses as irrelevant. Without this information, the interpretation of the independent effects in their multivariable regression analysis of hemoglobin levels (not necessarily anemia) is not obvious. Their multivariable regression analyses do not include any of the variables representing the main causal pathways in their conceptual model of anemia. If such adjustments would have been made, then the multivariable analyses may have helped determine whether these factors had an independent relationship to anemia. Otherwise, the rationale for including these measures is questionable especially because the cross-sectional study did not ascertain any patient outcomes.

Our understanding of the pathogenesis of anemia that is commonly seen in patients with heart failure who usually do exhibit several potential contributing factors and comorbidities requires further study, as does the assertion that anemia in heart failure is a viable therapeutic target.

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References


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