Anemia in Chronic Heart Failure
Should We Treat It and How?*
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In recent years, the occurrence of anemia in patients with chronic heart failure (CHF) has received increasing attention. The prevalence of anemia reported in cohorts of patients or controlled randomized trials varies considerably (1,2). This variation is due not only to different recruitment profiles but also to the fact that there is no consensus on the definition of anemia in cardiology and, consequently, that different threshold hemoglobin or hematocrit levels have been used. However, general agreement exists that anemia is a frequent comorbidity and that it is associated with increased mortality or rates of hospital admissions and decreased quality of life or exercise tolerance, particularly when severe (3,4). There is also evidence suggesting that anemia is an evolving process and that new-onset anemia is common in CHF (5,6). The mechanism of anemia in CHF is a matter of debate and appears multifactorial. Impaired erythropoietin (EPO) production or resistance, iron and other hematin deficiencies, inflammation through cytokine activation, and hemodilution can play a role in the development of anemia in patients with CHF (7). Interestingly, some CHF medications, namely angiotensin-converting enzyme inhibitors or some beta-blockers, also may be associated with the occurrence of anemia (5,8). In this context, different medical interventions have been proposed to correct anemia. Two distinct strategies can be discussed: iron supplementation and/or subcutaneous EPO administration. The article by Ponikowski et al. (9) in this issue of the Journal is an elegant randomized, double-blind, and placebo-controlled study using darbepoietin alpha, a long-acting erythropoiesis-stimulating protein or placebo in patients with symptomatic CHF, low ejection fraction, and anemia defined by a hemoglobin concentration from 9 to 12 g/dl. The primary end point was the change from baseline in exercise tolerance measured by peak oxygen consumption ($\text{VO}_2$) adjusted for body weight. Other end points included exercise duration, hemoglobin, New York Heart Association (NYHA) functional classification, quality of life, brain natriuretic peptide, and hospitalizations. After 26 weeks of observation, a significant increase in hemoglobin concentration was observed in patients receiving darbepoietin alpha compared with those receiving placebo. The mean change between the 2 groups was 1.5 g/dl. However, there was no difference in peak $\text{VO}_2$, absolute peak $\text{VO}_2$, and exercise duration, although the observed changes went into the right direction. The only favorable difference observed with darbepoietin alpha was an improvement in self-reported patient global assessment, whereas no difference was observed when using 2 other disease-specific instruments, the Kansas City Cardiomyopathy questionnaire and the Minnesota Living with Heart Failure Questionnaire, or in NYHA functional class. Finally, there was no significant difference in the change in plasma brain natriuretic peptide or hospitalization rate. No major safety issue was reported by the investigators.

These results are in contradiction with previous small studies suggesting that EPO improves functional capacity, quality of life, and exercise tolerance (10,11). However, most of the preliminary reports had limitations, including lack of double-blind or placebo-controlled design, whereas the article by Ponikowski et al. (9) used a rigorous double-blind, placebo-controlled design. One potential explanation for the lack of impact of the observed increase in hemoglobin concentration on most of the efficacy end points is the relatively small sample size, and, indeed, there was a trend toward an improvement of all the efficacy parameters.

Another potential factor is the inclusion of mildly symptomatic heart failure patients, as more than 50% of those receiving darbepoietin alpha were in NYHA functional class II. We do not know at present whether only severely symptomatic patients or patients with severe anemia might benefit of EPO or whether a broader spectrum of patients could improve under this therapy.

As they stand, however, the results of this study suggest that correction of low hemoglobin levels in patients with CHF is safe and improves their quality of life. They support the idea of conducting larger placebo-controlled randomized trials with EPO in anemic patients with CHF to assess the safety and the potential benefit of this intervention on hospitalizations, functional capacity, quality of life, and exercise tolerance. We need to learn more on EPO dose regimens; definition of patients likely to benefit from EPO, including functional severity, hemoglobin threshold for intervention, and target values; and on the long-term safety. Until this information is available, we cannot make any recommendation on the potential benefit of EPO in the management of CHF.

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