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Editorial

What Should We Target in Heart Failure: Hemoglobin or Iron?

¿Cuál debe ser el objetivo en la insuficiencia cardiaca: la hemoglobina o el hierro?

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Our understanding of the mechanisms of heart failure (HF) has evolved over the past decades. Initially thought to be an isolated condition of the heart resulting in "dropsy", the pathophysiologic basis was extended to include overactivation of neurohormonal pathways and the sympathetic nervous system. There has been interest in inflammatory and metabolic mediators of HF,[1,2] with anemia recently drawing much attention. Anemia is a prevalent condition in HF.[3] The common causes of anemia in this setting are iron deficiency, as well as anemia of chronic or renal disease. Although iron deficiency is conventionally defined by a serum ferritin level of < 30 μg/L, ferritin is elevated in HF due to the inflammatory state. In their 2012 guidelines, the European Society of Cardiology introduced the definition of iron deficiency in HF as either serum ferritin < 100 μg/L or 100-299 μg/L and transferrin saturation $< 20\%$.[4]

In a large cohort of ambulatory HF patients with longitudinal assessment of hemoglobin, we previously reported that those with no or resolved anemia had better long-term outcomes than those with persistent or new-onset anemia.[5] The article published in *Revista Española de Cardiología* by Díez-López *et al*[6] revisited the change in anemia status over a 6-month period and its influence on long-term outcomes in a large HF population with predominantly reduced ejection fraction. Anemia was present at baseline in almost half the cohort, while one quarter of baseline anemic patients had transient anemia (resolution of anemia by 6 months). Normal hemoglobin values conferred a survival advantage over those with persistent anemia, new anemia, and even transient anemia. However, on multivariable analysis, those with persistent anemia had statistically significant poorer prognosis compared with other groups. The subgroup of persistent anemia were older, had poorer renal function, worse symptoms, and more use of loop diuretics, likely indicating a poor overall substrate and more advanced disease. These results are confirmatory to our previous report,[5] albeit in a patient population with more advanced disease with relatively higher mortality and anemia rates. Hence, whether anemia is truly a therapeutic target, or merely a marker of poor outcomes due to its association with unaccounted metabolic and inflammatory markers, is still debatable.

Despite promising results such as those reported by Díez-López *et al* showing lower event rates in patients with transient anemia, there is currently no rationale to target hemoglobin in the management of HF. In fact, prospective randomized controlled trials have failed to demonstrate potential benefits of novel erythropoietin-stimulating proteins in patients with HF.[7] Instead, the therapeutic focus has shifted towards iron therapy, specifically intravenous iron. The largest of the 5 randomized trials, the FAIR-HF trial, established the symptomatic and functional benefit of intravenous iron through improvements in patient-derived health status measures, New York Heart Association class, and 6-minute walk time, with no signal for harm.[8] Importantly, a benefit was seen regardless of hemoglobin levels, further emphasizing discordance between the roles of anemia and iron deficiency in HF. These findings were confirmed in the recent CONFIRM-HF trial, which additionally showed a significant reduction in HF hospitalization.[9] Moreover, in the Spanish health care setting, this approach has shown cost-effectiveness.[10] Intravenous iron provides a practical strategy to replenish iron stores even in the outpatient setting, in which most patients required a maximum of only 2 injections of ferric carboxymaltose to restore an iron deficit of about 1 gram. Due to its low bioavailability, months of oral iron therapy would be required to achieve similar levels. The prevalence of iron deficiency is widespread even in the absence of anemia,[11] justifying the need to consider a universal evaluation of red blood cell indices and iron studies in all HF patients, including nonanemic patients. Several studies are ongoing to further examine whether iron supplementation, either by oral or intravenous administration, can improve functional capacity and long-term outcomes. We look forward to these results.

CONFLICTS OF INTEREST

None declared.

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