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Editorial

Iron and Exercise in Heart Failure: How to Assess Relevant Changes?

Hierro y ejercicio en la insuficiencia cardiaca: ¿cómo evaluar los cambios relevantes?

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Both the clinical picture and the prognosis of patients with chronic heart failure (HF) are characterized by impaired exercise tolerance and dyspnea; the impact of respiratory muscle dysfunction[1] on these symptoms has been evaluated since the early 1990s.[2] Recent studies have shown that iron deficiency (ID) is very common in patients with HF[3] and its prevalence increases with increasing New York Heart Association class or accompanying anemia. Overall, it appears that at least one third of all patients with HF is affected; other authors estimate that up to half of all patients have ID. Patients with chronic HF develop iron deficiency through deranged iron absorption or by diminished availability of iron in the reticulo-endothelial system. Iron deficiency seems more prevalent in patients with HF than anemia and both cause reduced exercise capacity. The presence of ID may have multifaceted clinical consequences, not only directly related to impaired erythropoiesis, but also to marked impairment of oxidative metabolism, cellular energetics, and cellular immune mechanisms.[4] Iron deficiency with and without anemia is accompanied by reduced aerobic[5] performance and subjective complaints of poor physical condition. Its correction improves cognitive, symptomatic, and exercise performance.[4] Interestingly, intravenous iron supplementation with ferric carboxymaltose has been shown to improve exercise capacity in patients with and without additional anemia as well as patients' overall wellbeing.[6] In general, the aim of treatment is to supply enough iron to normalize hemoglobin concentrations and to replenish iron stores, and thus improve quality of life. Two distinct approaches exist: first, prevention strategies targeted at populations at risk and, second, active iron supplementation approaches in patients with either confirmed ID or those who have already developed ID anemia.[7] Clinically, it would be helpful to detect the earliest changes in red cell indices that reflect iron-restricted erythropoiesis. One approach would be to identify newly formed iron-deficient cells as they are released from the bone marrow as reticulocytes.[8] It would be also helpful to analyze the complex interplay between ID and exercise response in patients with chronic HF.

The study by Enjuanes et al[9] published in *Revista Española de Cardiología* therefore comes as a welcome addition to the ID in HF portfolio. The authors present data from patients with chronic HF and analyze the association of exercise capacity and iron status in these patients. Exercise capacity was measured with the 6-minute walk test. The authors advocate the 6-minute walk test to be used as an alternative method and as more objective assessment of functional status than the cardiopulmonary gas exchange exercise test. Although we agree that the 6-minute walk test is a useful addition to understanding patients' exercise capacity, we still believe that the measurement of maximum oxygen consumption peak VO_2 using spiroergometry is the most accurate technique to assess exercise capacity as it is less prone to observer-influence.[10] Of course, this is true only when the target respiratory exchange ratio value is reached. Most authors have used a cut-off for validity set at ≥ 1.10, even though others have argued that a threshold of > 1.05 can still be valid or that a cutoff > 1.00 or > 0.95 may still be acceptable if this represents a change of at least 0.15 over baseline.[11]

To properly interpret the study by Enjuanes et al[9] it should be noted that the definition used to identify ID has not been used in large-scale studies and may overestimate the true prevalence of ID. Most large studies in HF have used 2 parallel definitions to identify ID, either serum ferritin < 100 ng/mL or serum ferritin < 300 ng/mL together with a transferrin saturation $< 20\%$.[5,12] Overestimation may occur because their definition embraces serum ferritin values up to 800 ng/mL. Importantly, neither serum iron nor serum transferrin alone should be used as biomarkers of iron status. Instead, transferrin saturation, the percentage of transferrin that has iron bound to it, is recommended. Enjuanes et al additionally measured different parameters of iron status. One of these parameters was red cell distribution width, where values $> 15\%$ are indicative of iron deficient anisocytosis, and the other ones were serum soluble transferrin receptor (sTfR) and the ferritin index. The ferritin index has been proposed to be a useful tool in the diagnosis of ID states, where ratios > 2 suggest iron depletion. The ferritin index is calculated by dividing sTfR by log10 ferritin and is increased whenever sTfR is raised and or ferritin is reduced. Enjuanes et al included a total of 538 patients. The surprising results of this study showed that patients with preserved left ventricular ejection fraction showed significantly lower exercise capacity measured as the 6-minute walk distance than patients with reduced left ventricular ejection fraction. The mean distance walked in patients with preserved left ventricular ejection fraction was 288±103 m compared with patients with reduced left ventricular ejection fraction (319 ± 112 m, $P = .001$). Patients with reduced left ventricular ejection fraction tended to show lower exercise capacity than patients with preserved left ventricular

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ejection fraction. The study presented elegantly shows that different markers of ID (sTfR and ferritin index) may be useful to identify those with impaired exercise capacity. They question the use of commonly used laboratory tests such as serum iron, total iron-binding capacity, mean corpuscular volume, transferrin saturation, and ferritin with regards to their diagnostic value.[8] We still believe that transferrin saturation is the most useful tool in daily clinical practice, because it is not as prone as serum ferritin to acute phase reactions and because its assessment is much cheaper than that of sTfR. Indeed, we feel that recommending the measurement of sTfR in daily clinical practice may hamper its routine assessment because of its comparatively high price. On the other hand, increased sTfR has been reported to be a valid indicator of ID,[8,13] because sTfR is released by erythropoietic precursors in proportion to their expansion and is not increased by inflammation. One may simply remember its role as an indicator of cells' personal ID. sTfR derive from proteolysis of the membrane transferrin receptor and are on the surface of erythroblasts in the bone marrow, which internalizes the iron-transferrin complex to provide iron to the cell.[14] The sTfR reflects the level of receptor on the erythroblast surface, and is increased when bone marrow cells are not provided with sufficient iron for normal erythropoiesis.[14] This process shows tissue ID and inversely the amount of iron available for erythropoiesis.[7] However, the assays used in previous studies[15,16] have shown a specificity of 84% and a positive predictive value of only 58% in a population of patients likely to be typical of the most difficult diagnostic environments for assessing iron status.[8] Interpretation of increased sTfR may therefore be challenging, even in the absence of known causes of increased erythropoiesis other than ID. Similarly, attempts to combine ferritin and sTfR results (sTfR/log ferritin) still fall short when analyzed for diagnostic sensitivity and specificity and must be corrected for acute phase reactant changes in the setting of inflammation. Nevertheless, the study by Enjuanes et al shows that sTfR and the ferritin index reflect exercise intolerance in patients with chronic HF and could help in treatment decisions.

CONFLICTS OF INTEREST

S. von Haehling has been a paid consultant to Respicardia and Vifor Pharma. He has received speaker's fees from Amgen.

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