

Original article

Iron Status in Chronic Heart Failure: Impact on Symptoms, Functional Class and Submaximal Exercise Capacity

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ABSTRACT

Introduction and objectives: To evaluate the effect of iron deficiency and anemia on submaximal exercise capacity in patients with chronic heart failure.**Methods:** We undertook a single-center cross-sectional study in a group of stable patients with chronic heart failure. At recruitment, patients provided baseline information and completed a 6-minute walk test to evaluate submaximal exercise capacity and exercise-induced symptoms. At the same time, blood samples were taken for serological evaluation. Iron deficiency was defined as ferritin < 100 ng/mL or transferrin saturation < 20% when ferritin is < 800 ng/mL. Additional markers of iron status were also measured.**Results:** A total of 538 heart failure patients were eligible for inclusion, with an average age of 71 years and 33% were in New York Heart Association class III/IV. The mean distance walked in the test was 285 ± 101 meters among those with impaired iron status, vs 322 ± 113 meters ($P = .002$). Symptoms during the test were more frequent in iron deficiency patients (35% vs 27%; $P = .028$) and the most common symptom reported was fatigue. Multivariate logistic regression analyses showed that increased levels of soluble transferrin receptor indicating abnormal iron status were independently associated with advanced New York Heart Association class ($P < .05$). Multivariable analysis using generalized additive models, soluble transferrin receptor and ferritin index, both biomarkers measuring iron status, showed a significant, independent and linear association with submaximal exercise capacity ($P = .03$ for both). In contrast, hemoglobin levels were not significantly associated with 6-minute walk test distance in the multivariable analysis.**Conclusions:** In patients with chronic heart failure, iron deficiency but not anemia was associated with impaired submaximal exercise capacity and symptomatic functional limitation.

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Estado del hierro en la insuficiencia cardíaca crónica: impacto en síntomas, clase funcional y capacidad de ejercicio submáxima

RESUMEN

Introducción y objetivos: Evaluar el efecto del déficit de hierro y la anemia en la capacidad de esfuerzo submáxima de pacientes con insuficiencia cardíaca crónica.**Métodos:** Se llevó a cabo un estudio transversal unicéntrico en un grupo de pacientes estables con insuficiencia cardíaca crónica. En el momento de incluirlos en el estudio, los pacientes aportaron información basal y realizaron una prueba de marcha de 6 minutos para evaluar la capacidad de ejercicio submáxima y los síntomas desencadenados por el esfuerzo. Al mismo tiempo, se obtuvieron muestras de sangre para la evaluación serológica. El déficit de hierro se definió como un valor de ferritina < 100 ng/ml o una saturación de transferrina < 20% cuando la ferritina era < 800 ng/ml. Se efectuaron también determinaciones de otros marcadores del estado del hierro.**Resultados:** Se consideró aptos para la inclusión en el estudio a 538 pacientes con insuficiencia cardíaca. La media de edad era 71 años y el 33% se encontraba en las clases III/IV de la *New York Heart Association*. La distancia media recorrida en la prueba de marcha de 6 minutos por los pacientes con alteración del estado del hierro fue 285 ± 101 m, en comparación con los 322 ± 113 m del otro grupo ($p = 0,002$). Los

Palabras clave:

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síntomas durante la prueba fueron más frecuentes en los pacientes con déficit de hierro (el 35 frente al 27%; $p = 0,028$) y el síntoma registrado con más frecuencia fue la fatiga. Los análisis de regresión logística multivariantes mostraron que el aumento de la concentración de receptor de transferrina soluble, que indica un estado anormal del hierro, se asociaba de manera independiente con una clase avanzada de la *New York Heart Association* ($p < 0,05$). En el análisis multivariante realizado empleando modelos aditivos generalizados, el receptor de transferrina soluble y el índice de ferritina, biomarcadores que miden el estado del hierro, mostraron una asociación lineal, significativa e independiente con la capacidad de ejercicio submáxima ($p = 0,03$ en ambos casos). En cambio, en el análisis multivariante los valores de hemoglobina no mostraron una asociación significativa con la distancia recorrida en la prueba de marcha de 6 minutos.

Conclusiones: En los pacientes con insuficiencia cardíaca crónica, el déficit de hierro, pero no así la anemia, se asoció con deterioro de la capacidad de ejercicio submáxima y limitación funcional sintomática.

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Abbreviations

6MWT: 6-minute walk test
 CHF: chronic heart failure
 HRQoL: health-related quality of life
 ID: iron deficiency
 NYHA: New York Heart Association
 sTfR: serum soluble transferrin receptor

INTRODUCTION

Despite the introduction of new therapies and recent developments in the management of chronic heart failure (CHF), functional limitation and the presence of limiting symptoms are common in optimally treated patients. Dyspnea and fatigue are the main symptoms, leading to impaired exercise capacity.¹ These factors promote the inability to perform daily activities and impact patients' self-perceived health status. Thus, impaired health-related quality of life (HRQoL) and the occurrence of symptoms such as dyspnea or fatigue leading to advanced New York Heart Association (NYHA) functional class have become important patient-centered outcomes that need to be addressed.²

The objective assessment of functional status has been commonly undertaken by measuring peak exercise capacity using the cardiopulmonary gas exchange exercise test.³ However, functional limitations in performing daily activities imposed by CHF may also be estimated when submaximal exercise capacity is studied. As an alternative to the cardiopulmonary gas exchange exercise test, the 6-minute walk test (6MWT) or corridor test is an easy method to objectively measure patients' submaximal functional capacity and thus gain a more realistic insight into patients' ability to perform daily activities.^{4,5}

The underlying mechanisms of impaired exercise capacity in CHF are numerous and not fully understood. This may explain why therapeutic options with good impact on prognosis, such as beta-blockers, have failed to show benefits in terms of functional capacity.⁶ Recent evidence suggests that iron deficiency (ID) is a common comorbidity⁷ and may be associated with impaired peak exercise capacity,⁸ worse HRQoL,^{9,10} and poorer outcomes¹¹ in CHF patients, regardless of the presence of anemia. Furthermore, several trials have shown that intravenous iron administration can improve functional capacity and symptoms of patients with CHF and ID.^{12,13} Data from these studies suggest that iron status may play a role in submaximal exercise capacity. However, these studies focused only on selected patients with ID and thus had a limited power to assess the influence of iron status and/or the presence of anemia on submaximal exercise capacity and the occurrence of symptoms in a broader spectrum of patients. Therefore, we aimed to investigate the impact of iron status on

submaximal exercise capacity estimated with the distance walked in the 6MWT. We also wanted to explore the influence of iron status on NYHA functional class and the occurrence of symptoms in a cohort of CHF patients seen in daily clinical practice.¹⁴

METHODS

Study Population and Recruitment

For the purpose of this study, we analyzed the association of submaximal exercise capacity and iron/anemia status in a cohort of stable euvolemic patients with CHF. The methodology of this study has been previously reported.⁹ The study was conducted in accordance with the Declaration of Helsinki, the study protocol was approved by the local clinical research ethics committee, and all patients gave written informed consent after recruitment. For inclusion in the study, patients had to be in a stable condition and diagnosed with CHF with either reduced or preserved ($\geq 45\%$) LVEF (left ventricular ejection fraction), according to the European Society of Cardiology diagnostic criteria.¹⁵ Exclusion criteria for the study were: inability to perform the 6MWT, significant primary valvular disease, hemoglobin levels < 8.5 g/dL, clinical signs of fluid overload, pericardial disease, restrictive cardiomyopathy, hypertrophic cardiomyopathy, active malignancy, and chronic liver disease. Patients without iron status evaluation or 6MWT available at screening were also excluded. According to these criteria, the final cohort consisted of 538 patients. At recruitment, all patients provided peripheral blood samples and relevant clinical and demographic information, including NYHA functional class, current medical therapy, and the most recent LVEF evaluation.

Medical and nursing personnel involved in recruitment and data collection were blinded to patients' ID and anemia status.

Iron Status and Other Laboratory Measurements

Iron deficiency was defined using the Kidney Disease Outcomes Quality Initiative guidelines criteria: ferritin < 100 ng/mL or transferrin saturation (TSAT) $< 20\%$ when ferritin is < 800 ng/mL.¹⁶ Serum iron was measured using spectrophotometry; serum ferritin and transferrin were measured using immunoturbidimetry. The TSAT was estimated using the formula: $\text{TSAT} = \frac{\text{serum iron } (\mu\text{g/dL})}{[\text{serum transferrin } (\text{mg/dL}) \times 1.25]}$.¹⁷ Additional measures of iron status were: red cell distribution width,¹⁸ where values $> 15\%$ are indicative of ID anisocytosis, serum soluble transferrin receptor (sTfR) (measured using an enzyme immunoassay),¹⁹ and ferritin index. Ferritin index has been proposed as a useful tool in the diagnosis of ID states, where ratios > 2 suggest ID. The ferritin index is calculated by dividing sTfR (expressed in nmol/L or mg/L) by \log_{10} ferritin (measured in ng/mL) and is thus

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