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GUIDELINES

Diagnosis and treatment of iron deficiency in patients with heart failure: Expert position paper from French cardiologists

Diagnostic et traitement de la carence martiale chez les patients insuffisants cardiaques : le point de vue d'experts cardiologues français

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Summary The prevalence of iron deficiency is high — even in the absence of anaemia — in patients with chronic heart failure (HF). Although iron deficiency is easily diagnosed with two biomarkers (serum ferritin and transferrin saturation), it is underdiagnosed in patients with HF. Iron is not only necessary for red blood cells, but also for cells in tissues with high-energy

Abbreviations: ESC, European Society of Cardiology; HF, Heart Failure; LVEF, Left Ventricular Ejection Fraction; NT-proBNP, N-Terminal Fragment of pro-B-type Natriuretic Peptide; NYHA, New York Heart Association; pVO_2, Peak Oxygen Uptake; TIBC, Total Iron Binding Capacity; TSA, Ttransferrin Saturation.

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Serum ferritin;
Transferrin saturation

demands (heart, muscle, brain). Even before the onset of anaemia, HF patients with iron deficiency have decreased physical and cognitive performances and a poorer quality of life. Moreover, iron deficiency is a risk factor, independent of anaemia, of unfavourable outcome (death or heart transplantation) in patients with chronic HF. Several randomized controlled studies have shown improvement in exercise capacity, New York Heart Association functional class and quality of life after correction of iron deficiency. The results of these clinical trials, which are supported by European guidelines, suggest considering iron deficiency in HF as a possible therapeutic target.

MOTS CLÉS
Insuffisance cardiaque ;
Carence martiale ;
Fer injectable ;
Ferritine sérique ;
Coefficient de saturation de la transferrine

Résumé La prévalence de la carence martiale— même en l'absence d'anémie —est élevée chez les patients présentant une insuffisance cardiaque chronique. Bien que la carence martiale soit facilement diagnostiquée avec deux paramètres biologiques (ferritine sérique et coefficient de saturation de la transferrine), elle reste toutefois sous-diagnostiquée chez ces patients. Le fer est nécessaire, non seulement aux cellules de la lignée érythrocytaire, mais également aux tissus ayant une consommation énergétique importante (cœur, muscles, cerveau). Bien avant que l'anémie ferriprive soit constituée, les patients avec une carence martiale ont des performances physiques et cognitives diminuées et une qualité de vie dégradée. Chez les patients insuffisants cardiaques, la carence martiale est un facteur de risque (décès, transplantation cardiaque), indépendant de l'anémie. Plusieurs essais randomisés contrôlés ont montré l'amélioration des performances physiques, de la classe fonctionnelle NYHA, et de la qualité de vie après correction de la carence martiale. Les résultats de ces essais cliniques, soutenus par des recommandations européennes, suggèrent de considérer la carence martiale des patients insuffisants cardiaques comme une cible thérapeutique potentielle.

Background

This position paper reports data on iron deficiency in patients with heart failure (HF), which are based on: a review and analysis of recent articles on iron metabolism and HF; national and international guidelines for the management of HF, and iron deficiency diagnosis and treatment; and the experience of the authors with iron deficiency in HF patients.

In recent years, iron deficiency has emerged as a newly recognized co-morbidity of chronic HF. Independently of anaemia, iron deficiency occurs frequently in HF patients, contributing to cardiac and peripheral muscle dysfunction, and is a strong predictor of poor clinical outcome [1—3]. Recent controlled randomized studies have shown that iron treatment in chronic HF has favourable effects on exercise capacity, New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF) and quality of life [4—8]. Despite this, the diagnosis and management of HF patients with iron deficiency remains largely unrecognized in the cardiologist community. However, diagnostic tools and treatments already exist are relatively inexpensive and may lead to important health benefits for HF patients.

This document is intended for use by cardiologists, and the recommendations herein propose preferred approaches for the diagnosis and treatment of iron deficiency in HF. Recommendations from position papers are not considered to have the prominence of practice guidelines. Nevertheless, based on the latest literature, this position paper should facilitate and improve patient care by presenting the best practices in this emerging area.

Recent perspectives on iron deficiency physiopathology

Iron is necessary not only in the haem of haemoglobin for oxygen transport, but also as a cofactor for several enzymes. For example, iron ions play central roles in the mitochondrial respiratory chain and in tissue oxygen storage in myoglobin [9]. Therefore, iron is necessary in cells that require sustained adenosine triphosphate synthesis, such as skeletal myocytes and cardiomyocytes, in addition to cells of the erythropoietic lineage [10,11].

In healthy individuals, approximately two-thirds of body iron is contained in the haemoglobin of mature erythrocytes (1800 mg) and precursors of the erythropoietic lineage (300 mg) [12]. Iron is also stored in liver parenchymal cells (1000 mg), with 10—15% found in myoglobin and different enzymes. About 10 mg of iron are ingested daily, although only 1—2 mg are absorbed by duodenal cells. Approximately 3 mg of iron (< 0.2% of total iron) are bound to serum transferrin. Iron is also recycled from senescent red blood cells (600 mg) in macrophages of the reticuloendothelial system (liver, spleen, bone marrow). Thus, iron is continuously exchanged between senescent red blood cells and bone marrow (daily recycling of 20—25 mg of iron).

Iron metabolism and regulation have been revisited recently, and classical clinical findings, such as iron sequestration during chronic inflammation, are now elucidated at the molecular level [13,14]. The proteins ferritin and transferrin play key roles in the storage and transport of iron. Ferritin stores iron in tissues and, in practice, serum ferritin