International Journal of Cardiology 243 (2017) 360–366

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Clinical correlates and prognostic impact of impaired iron storage versus impaired iron transport in an international cohort of 1821 patients with chronic heart failure

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ARTICLE INFO

Article history:
Received 9 November 2016
Received in revised form 6 April 2017
Accepted 17 April 2017
Available online 3 May 2017

Keywords:
Iron deficiency
Heart failure
Outcomes
Anaemia

ABSTRACT

Aims: To define iron deficiency in chronic heart failure (CHF), both, ferritin < 100 μg/L (indicating reduced iron storage) and transferrin saturation (TSAT) < 20% (indicating reduced iron transport) are used. The aim of the study was to evaluate clinical outcomes and prognosis of either low ferritin or low TSAT in patients with CHF.
Methods and results: We evaluated the clinical impact of impaired iron storage (IIS) and impaired iron transport (IIT) either alone or in combination compared to patients with normal iron status (NIS), in an international cohort of 1821 patients with CHF with a mean age of 66 ± 13 years and mean left ventricular ejection fraction of 35% ± 15. Isolated IIS was observed in 219 patients (12%), isolated IIT in 454 (25%) and coexistence of both conditions (IIS + IIT) were seen in 389 (21%).
In adjusted models we found that patients with IIS + IIT and patients with isolated IIT had higher NT-proBNP levels (OR 2.2 [1.6–3.1] and OR 2.1 [1.5–2.9] respectively) and worse quality of life (OR 1.8 [1.2–2.7] and OR 1.7 [1.2–2.5] respectively) compared with isolated IIS. Multivariate Cox analyses showed that IIS + IIT and isolated IIT were independently associated with all-cause mortality (OR 1.41 [1.06–1.86] and OR 1.47 [1.13–1.92] respectively). Patients with isolated IIS did not differ from NIS patients in terms of severity or outcomes.
Conclusions: Impaired iron transport alone or in combination with impaired iron storage is associated with worse clinical profile and increased risk of mortality in patients with CHF. Patients with isolated impaired iron storage may have a milder form of iron deficiency.

1. Introduction

Iron deficiency (ID) is associated with a worse clinical profile and prognosis in patients with chronic heart failure (CHF) [1–5]. The FAIR-HF and the CONFIRM-HF studies have demonstrated that treatment with intravenous iron supplementation in patients with ID and CHF improves their symptoms, New York Heart Association (NYHA) functional class, exercise capacity and health-related quality of life (HRQoL) and reduces the risk of heart failure readmission with a good safety profile [5–9].

In these randomized controlled trials and other observational studies [1,3–9,11,12], a serum ferritin < 100 μg/mL or ferritin 100–300 μg/mL in combination with a transferrin saturation (TSAT) < 20% defined the diagnosis of ID. This definition combines the information obtained from two distinct biochemical parameters [6]. Ferritin provides

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http://dx.doi.org/10.1016/j.ijcard.2017.04.110
0167-5273/

information about body iron storage and is a measure of iron availability. On the other hand, TSAT informs about the amount of iron that is transported in the blood and serves as a measure of iron supply [10].

Based on this information patients fulfilling criteria of ID according the FAIR-HF definition constitute a heterogeneous group, composed by patients with different profiles of disordered iron status regarding the predominant abnormality (impaired iron storage, impaired iron transport or both).

Thus, based on values of ferritin and TSAT, individual patients can be classified into 4 iron-states categories ranging from combination of impaired storage and transport to normal iron status [13].

It is unknown if these distinct iron-deficient states correlate with different clinical profiles and have implications in terms of outcomes in CHF patients. Therefore, the aim of our study was to describe the iron status of a large international cohort of patients with CHF according the different iron-deficient states, and evaluate their impact on clinical measures of CHF severity and patients' outcomes.

2. Methods

This methodology has been published previously by our group [1]. The European Iron Consortium (EIC) cohort comprised 1821 patients with CHF and reduced or preserved left ventricular ejection fraction (LVEF) from 5 different cohorts recruited in Poland, Spain and the Netherlands. Heart failure with preserved ejection fraction (HFpEF) was defined as the presence of signs and symptoms of heart failure in patients with LVEF > 45% [14]. The inclusion and exclusion criteria per participating study cohort have been published previously by our group [1,3,15–18]. All study protocols were approved by local ethics committees and all patients gave written informed consent for the present study. The study was conducted in accordance with the Declaration of Helsinki.

The pooled data in the present study were all assessed at a patient level. All 5 cohorts were chosen for the present analysis because they had comparable clinical information available. None of the patients received blood transfusions, erythropoietin therapy or intravenous iron therapy at the time of inclusion. Vital status was determined via direct contact with patients or relatives or review of chronic HF clinical databases or hospital records [1,4,11,12].

2.1. Iron status and other laboratory measurements

The following blood biomarkers reflecting iron status were measured: ferritin (μg/L), serum iron (μg/L), total iron binding capacity (μg/L) and transferrin (mg/dL). Transferrin saturation was reported as a ratio of 0.7217 × serum iron and transferrin, multiplied by 100 [18]. When transferrin was not available, transferrin saturation (TSAT) was reported as a ratio of serum iron (μg/L) and total iron binding capacity (TIBC, μg/L) multiplied by 100. Concentrations of N-terminal pro-brain-type natriuretic peptide (NTproBNP, pg/mL) were measured using an immunoassay based on electrochemiluminescence on the Elecsys System (Roche Diagnostics). Renal function was assessed by using the abbreviated Modification of Diet in Renal Disease (MDRD) equation to estimate the glomerular filtration rate (eGFR, mL/min/1.73 m2). Serum concentrations of high-sensitive C-reactive protein (hs-CRP, mg/L) were assessed at each institution using standard methods. Increased inflammatory status was defined as hs-CRP above median values (0.7 mg/dL for the Spanish cohort and 2.87 mg/L for the Polish or Dutch cohorts).

sTfR was measured with the Beckman Coulter Assay in Spanish patients and using the Siemens Nephelometry assay for the Dutch and Polish cohorts. Raised sTfR, indicating impaired iron status, was defined as soluble transferrin receptor levels over upper limit of normality according to the manufacturers of the assays (2.01 mg/dL for the assay used in the Spanish cohort and 1.36 mg/dL for the assays used in the Polish and Dutch cohorts).

2.2. Definitions and study endpoints

In the basis of iron status biomarkers indicating reduced availability and/or reduced supply of iron, we classified iron status in 4 different states. The first state represents normal iron status (NIS) and is defined by a serum ferritin ≥ 100 μg/mL and a TSAT ≥ 20% suggesting a preserved iron storage and transport. The second ID state represents isolated impairment at the iron storage compartment (isolated impaired iron storage, iIIS). This would define a subset of patients with a predominant impairment in iron availability with otherwise still preserved iron transport (ferritin < 100 μg/mL and TSAT ≥ 20%). The third ID state represents isolated impairment of iron transport (iIIT) and would define a subset of patients with reduced iron supply with otherwise a still apparently preserved iron storage (TSAT < 20% and ferritin ≥ 100 μg/mL). Finally we describe a fourth state that represents the coexistence of disordered iron storage and iron transport (IIS and IIT). This stage would define a subset of patients suffering simultaneously from both, reduced supply and availability of iron (ferritin < 100 μg/mL and TSAT < 20%).

We aimed to explore each of these ID states in a large international cohort of CHF patients and evaluate the potential differences in terms of clinical characteristics and outcomes between the different categories. Main study endpoints for this particular analysis were: all-cause death, HRQoL, NYHA functional class, NT-proBNP levels and the presence of anaemia (haemoglobin level < 12 g/dL in women and <13 g/dL in men) [20].

Data regarding demographics and clinical signs (age at diagnosis, sex, HF aetiology, renal function, EF, blood pressure and comorbidities), haematinics and therapeutics were available for the entire cohort (1821 patients). Raised NTproBNP was defined as NTproBNP over the median (1440 pg/mL). HRQoL was measured using the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and was available in 1277 patients [4]. Impaired HRQoL was defined as MLHFQ scores > 55 points (median value). Vital status was determined via direct contact with patients or relatives or review of hospital records. All-cause mortality was available in 1519 patients [1].

2.3. Statistical methods

Data are expressed as means ± SD (standard deviation) when normally distributed or as medians with interquartile range when non-normally distributed. Inter-group differences were tested using one-way analysis of variance test (ANOVA) or Kruskal–Wallis test, when appropriate.

To evaluate clinical predictors of IIS or IIT we used univariate and multivariate logistic regression analyses adjusted for covariates, following stepwise backwards conditional methods.

To evaluate the effect of each iron-deficient state on study endpoints we developed several multivariable models, adjusted for covariates associated with disease severity following stepwise forward conditional methods taking as reference category normal iron status (NIS). These multivariate models included the following variables as covariates: center, sex, age, systolic blood pressure, diabetes, HF aetiology, LVEF, LVEDD, eGFR, serum NTproBNP, haemoglobin, CRP, body mass index (BMI), NYHA functional class, and treatment with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, statins, and diuretics.

All models were internally validated using resampling methods: bootstrap resampling (1000 cycles) of the multivariable model were performed to validate the estimated models. Variables selected >700 times were assumed to be accurate. Following these multivariable models we explored the impact of iron states on functional and other clinical variables using binary logistic regression analyses.

The impact on mortality was assessed using Cox proportional hazard models adjusted for covariates as stated previously. SPSS version 22.0 (IBM, Armonk, NY, USA) was used for statistical analyses.

3. Results

In this study, 1821 patients were included. Baseline characteristics and demographics according to each ID state are shown in Table 1. Isolated IIS (iIIS: low ferritin, normal TSAT) was observed in 219 patients (12%), isolated IIT (iIIT: normal ferritin, low TSAT) in 454 (25%) and combination of both conditions (IIS + IIT: low ferritin, low TSAT) was seen in 389 (21%). Any abnormal iron status was observed in 58% of patients and consequently NIS in the remaining 759 patients (42%). All patients in iIIS group, and all patients in the group of combined IIS and IIT, met the criteria of ID according to FAIR-HF definition [6]. Although most patients in iIIT group could be classified as iron-deficient according to the FAIR-HF definition, 117 of this group with a serum ferritin > 300 μg/L could not, which would represent the 12% of all ID patients.

In these unadjusted analyses, patients with iIIS seemed to have a better clinical profile than patients with iIIT or the combination of IIT and IIS, but worse clinical profile compared to patients with normal iron status. Stratification by NYHA functional class revealed that iIIS was less prevalent in higher NYHA classes whereas iIIT and the combination of IIT and IIS were more prevalent in NYHA functional class III and IV (Suppl. Fig. 1). Biomarkers of iron status and haematinics according to ID states, including important parameters as RDW or haemoglobin are described in Supplementary Table 1.

To explore the iron demand in each group we studied sTfR concentrations and ferritin index [19]. The proportion of patients with increased iron demand (measured as sTfR above the upper normal reference limit) progressively decreased from combined IIS + IIT group to iIIS group, and these proportions were significantly higher than the proportion observed in patients with NIS (p-value < 0.001 for trend), suggesting and increased tissue iron demand, even in patients with isolated impaired iron stores (Suppl. Fig. 2A). In line with this, the distribution of the ferritin index ratio (sTfR/$\log_{10}$[ferritin]) across ID stages showed a similar pattern (Suppl. Fig 2B).

In the multivariable logistic adjusted regression models (Fig. 1) we found that compared to the NIS group, the combination of IIS + IIT,