Right ventricular function and iron deficiency in acute heart failure

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Aims
Iron deficiency (ID) is a frequent finding in patients with chronic and acute heart failure (AHF) along the full spectrum of left ventricular ejection fraction (LVEF). Iron deficiency has been related to ventricular systolic dysfunction, but its role in right ventricular function has not been evaluated. We sought to evaluate whether ID identifies patients with greater right ventricular dysfunction in the setting of AHF.

Methods and results
We prospectively included 903 patients admitted with AHF. Right systolic function was evaluated by tricuspid annular plane systolic excursion (TAPSE) and the ratio TAPSE/pulmonary artery systolic pressure (TAPSE/PASP). Iron deficiency was defined, according to European Society of Cardiology criteria, as serum ferritin <100 mg/dL (absolute ID) or ferritin 100–299 mg/dL and transferrin saturation (TSAT) <20% (functional ID). The relationships among the exposures with right ventricular systolic function were evaluated by multivariate linear regression analyses. The mean age of the sample was 74.3 ± 10.6 years, 441 (48.8%) were female, 471 (52.2%) exhibited heart failure with preserved ejection fraction, and 677 (75.0%) showed ID. The mean LVEF, TAPSE, and TAPSE/PASP were 49 ± 15%, 18.6 ± 3.9 mm, and 0.45 ± 0.18, respectively. The median (interquartile range) amino-terminal pro-brain natriuretic peptide was 4015 (1807–8775) pg/mL. In a multivariable setting, lower TSAT and ferritin were independently associated with lower TAPSE (P < 0.05 for both comparisons). Transferrin saturation (P = 0.017), and not ferritin (P = 0.633), was independently associated with TAPSE/PASP.

Conclusion
In AHF, proxies of ID were associated with right ventricular dysfunction. Further studies should confirm these findings and evaluate the pathophysiological facts behind this association.

Keywords
Iron deficiency • Left ventricle ejection fraction • Right ventricle ejection fraction • Tricuspid annular plane systolic excursion

Introduction
Iron deficiency (ID), a common condition in patients with heart failure (HF),1 is associated with reduced functional capacity, quality of life, and a worse prognosis.1–3 There is compelling evidence showing that ID results in impairment in mitochondrial function and cardiomyocyte contractility.4–6 In patients with HF, the evidence endorsing the role of ID in the pathophysiology and clinical status is mostly limited to stable patients with reduced ejection fraction.1 However, recent reports suggest ID is even more prevalent in acute heart failure...
(AHF) syndromes with rates up to 80%. However, the pathophysiology and clinical implications of ID in AHF are poorly understood. Indeed, the European Society of Cardiology (ESC) definition of ID is somewhat arbitrary, and the adequacy of this definition is even more uncertain in patients with AHF, in which inflammation and congestion play a crucial role. Recent studies further suggest that ID identifies patients at higher risk of short-term adverse outcomes.1,4

In this work, we aimed to evaluate whether traditional parameters of ID [ferritin and transferrin saturation (TSAT)] and the current ESC definition of ID are associated with greater right systolic dysfunction and left ventricle ejection fraction.

Methods

Study population
In this ongoing registry, we retrospectively studied a cohort of 981 consecutive patients admitted due to AHF to the Cardiology Department of a third-level teaching centre between March 2011 and May 2018. Acute heart failure was diagnosed according to the definition proposed by guidelines (rapid onset or worsening of symptoms and/or signs of HF requiring urgent evaluation and treatment, typically leading to urgent hospital admission). Eligible patients included those with new-onset AHF and those with decompensated chronic HF. By design, our analysis excluded patients with in-hospital death (n = 28), primary tricuspid disease (n = 2), severe mitral rheumatic stenosis (n = 12), and final diagnosis of an acute coronary syndrome (n = 21) or pneumonia (n = 15). The final study sample included 903 patients.

During hospitalization, pre-established electronic questionnaires were used to routinely record information related to demographics, medical history, vital signs, 12-lead electrocardiogram, and standard and pharmacologic therapies. Tumour marker carbohydrate antigen 125 (CA125), vital signs, and left ventricle ejection fraction were evaluated by multivariate linear regression analysis. The contribution of continuous variables and the variables were transformed with fractional polynomials, when appropriate. Next, we derived a reduced and parsimonious model by using backward step-down selection.

Iron deficiency parameters assessment and definitions
Routine blood tests were obtained during the index admission, after clinical stabilization (mean of 120 ± 24 h after admission). Clinical stabilization was defined as the cessation of intravenous therapy, reinstitution of oral diuretics, and haemodynamic stability without requiring mechanical ventilation or ventilator support. Iron deficiency was defined, according to ESC criteria, as serum ferritin <100 mg/dL (absolute ID) or ferritin 100–299 mg/dL and TSAT <20% (functional ID). The cut-point of TSAT proposed by Grote Beverborg et al.11 (<19.8%) was also evaluated. Anaemia was defined according to the World Health Organization (WHO) criteria, as haemoglobin levels <12 g/dL in women and <13 g/dL in men. Amino-terminal pro-brain natriuretic peptide (NT-proBNP) was measured on admission and during mid-hospitalization (72 ± 24 h).

Serum ferritin concentration was measured by an immunoturbidimetric assay on the Olympus AU 5400 system (Beckman Coulter). Colorimetric methods were used to measure serum iron concentration and unsaturated iron-binding capacity (UIBC) using the Olympus AU 5400 analyser (Beckman Coulter). Total iron-binding capacity (TIBC) was determined indirectly using the sum of serum iron concentration and UIBC. Transferrin saturation was calculated by dividing the serum iron concentration by TIBC, multiplied by 100.

Echocardiographic evaluation
After clinical stabilization (108 ± 24 h after admission), a comprehensive transthoracic echocardiographic examination was performed using commercially available systems (IE33 and EPIQ Philips, MA, USA). Clinical stabilization was defined as the cessation of intravenous therapy, reinstitution of oral diuretics, and haemodynamic stability without requiring mechanical ventilation or ventilator support. We acquired two-dimensional and Doppler measurements according to international recommendations, using standard views and techniques. Left ventricular ejection fraction (LVEF) was calculated by the biplane Simpson method.

Right ventricular systolic dysfunction was evaluated based on the tricuspid annular plane systolic excursion (TAPSE) that was tracked in the four-chamber view per M-mode, as recommended. Pulmonary artery systolic pressure (PASP) was estimated by measuring the maximum continuous Doppler-derived velocity of the tricuspid regurgitation jet. Right atrial pressure was estimated in the subcostal view according to inferior vena cava (IVC) size and its breathing-related collapsibility, following a normal sniff as follows: 3 mmHg if IVC <21 mm that collapses >50%, 15 mmHg if IVC >21 mm that collapses <50%, and an intermediate value of 8 mmHg in the situations in which IVC diameter and collapse did not fit this paradigm. Pulmonary artery systolic pressure could be measured in 638 patients (70.6% of the study sample). The ratio TAPSE/PASP was evaluated as a measure of right ventricular–pulmonary arterial coupling in 638 patients.

Endpoints
The co-primary endpoints were to evaluate whether ID parameters (ferritin, TSAT, and ESC ID definition) were associated with systolic right ventricular function assessed by TAPSE and the ratio TAPSE/PASP. The secondary endpoints included the association between ID parameters with surrogates of the left ventricular function evaluated by LVEF and NT-proBNP.

Statistical analysis
Continuous variables are presented as mean (± standard deviation) or median [interquartile range (IQR)], as appropriate. Categorical variables are expressed as percentages. Baseline continuous variables were compared according to ID status using the Student’s t-test or Wilcoxon rank-sum test, as appropriate. Discrete variables were compared using the χ² test.

The variables associated with TAPSE, TAPSE/PASP, and LVEF were evaluated by multivariate linear regression analysis. The contribution of the exposures to the proportion of the dependent variable variation was evaluated by R².

In the multivariable models, all variables listed in Table 1 were tested based on previous knowledge/biological plausibility, independent of the P-value. We simultaneously tested the linearity assumption for all continuous variables, and the variables were transformed with fractional polynomials, when appropriate. Next, we derived a reduced and parsimonious model by using backward step-down selection.

For TAPSE and TAPSE/PASP, the covariates included in the final model were age, gender, prior New York Heart Association (NYHA) class before admission, ischaemic heart disease, systolic blood pressure, bundle branch block (BBB), atrial fibrillation, haemoglobin, gamma-glutamyl transferase (GGT), low-density lipoprotein, and CA125.

The covariates included in the multivariate model for LVEF were age, gender, ischaemic heart disease, diabetes, smoker, prior use of diuretics, systolic blood pressure, BBB, heart rate, atrial fibrillation, serum sodium,
| Variables                                      | All (n = 903) | No ID* (n = 266) | ID* (n = 677) | P-value |
|------------------------------------------------|---------------|-----------------|---------------|---------|
| Demographics and medical history               |               |                 |               |         |
| Age (years)                                    | 74 ± 11       | 73 ± 11         | 75 ± 10       | 0.107   |
| Gender (male), n (%)                           | 441 (48.8)     | 141 (62.4)      | 321 (47.4)    | <0.001  |
| Hypertension, n (%)                            | 720 (79.7)     | 169 (78.8)      | 551 (81.4)    | 0.032   |
| Diabetes mellitus, n (%)                       | 428 (47.4)     | 87 (38.5)       | 341 (50.4)    | 0.002   |
| Dyslipidaemia, n (%)                           | 561 (62.1)     | 125 (55.3)      | 436 (64.4)    | 0.015   |
| IHD, n (%)                                     | 291 (32.2)     | 71 (31.4)       | 220 (32.5)    | 0.763   |
| Smoker, n (%)                                  | 114 (12.6)     | 38 (16.8)       | 76 (11.2)     | 0.029   |
| Valve heart disease, n (%)                     | 306 (38.9)     | 67 (29.6)       | 239 (35.3)    | 0.120   |
| Prior admission for AHF, n (%)                 | 324 (39.5)     | 73 (32.3)       | 251 (37.1)    | 0.195   |
| Charlson index, points                         | 2 (1–4)        | 2 (1–4)         | 2 (1–4)       | 0.823   |
| Pleural effusion, n (%)                        | 466 (51.6)     | 105 (46.5)      | 361 (53.3)    | <0.001  |
| Peripheral oedema, n (%)                       | 624 (69.1)     | 131 (58.0)      | 493 (72.8)    | <0.001  |
| NYHA III–IV prior to admission (%)             | 136 (15.1)     | 31 (13.7)       | 105 (15.5)    | 0.514   |
| Diuretic treatment prior to admission, n (%)   | 562 (62.2)     | 135 (59.7)      | 427 (63.1)    | 0.370   |
| Vital signs                                    |               |                 |               |         |
| Heart rate (b.p.m.)                            | 100 ± 27       | 98 ± 28         | 96 ± 27       | 0.278   |
| SBP (mmHg)                                     | 143 ± 31       | 144 ± 33        | 142 ± 30      | 0.486   |
| DBP (mmHg)                                     | 79 ± 20        | 80 ± 21         | 79 ± 19       | 0.642   |
| Electrocardiogram                              |               |                 |               |         |
| Atrial fibrillation, n (%)                     | 412 (45.6)     | 93 (41.1)       | 319 (47.1)    | 0.119   |
| BBB, n (%)                                     | 287 (31.8)     | 77 (34.1)       | 210 (31.0)    | 0.394   |
| Echocardiography                               |               |                 |               |         |
| LVEF (%)                                       | 48.6 ± 15.3    | 48.6 ± 15.7     | 48.6 ± 15.2   | 0.978   |
| LAD (mm)                                       | 44.1 ± 7.9     | 43.6 ± 7.4      | 44.3 ± 8.1    | 0.239   |
| TAPSE (mm)                                     | 18.6 ± 3.9     | 19.3 ± 3.9      | 18.3 ± 3.8    | 0.002   |
| PASP (mmHg)b,c                                 | 41 (34–50)     | 38 (32–52)      | 42 (34–50)    | 0.193   |
| TAPSE/PASPc                                     | 0.45 ± 0.18    | 0.48 ± 0.18     | 0.44 ± 0.17   | 0.024   |
| Laboratory data                                |               |                 |               |         |
| Haemoglobin (g/dL)                             | 12.2 ± 2.0     | 12.6 ± 2.3      | 12.0 ± 1.9    | <0.001  |
| Haematoctrit (%)                               | 37.8 ± 5.5     | 38.5 ± 6.3      | 37.6 ± 5.2    | 0.034   |
| Anaemia (WHO criteria), n (%)                  | 489 (54.1)     | 106 (46.9)      | 383 (56.6)    | 0.012   |
| Ferritin (mg/dL)b                              | 101 (55–201)   | 330 (173–448)   | 78 (45–129)   | <0.001  |
| TSAT (%)b                                      | 13.5 (8.6–20.1) | 23.65 (16.9–30.5) | 11.6 (7.87–16.5) | <0.001  |
| White blood cell count (< 10³ cells/mL)        | 9373 ± 3599    | 9762 ± 4212     | 9243 ± 3363   | 0.644   |
| Lymphocyte count (< 10³ cells/mL)              | 1588 ± 1220    | 1694 ± 1289     | 1552 ± 1195   | 0.130   |
| Creatinine (mg/dL)                             | 1.3 ± 0.6      | 1.4 ± 0.6       | 1.2 ± 0.6     | <0.001  |
| eGFR (MDRD formula) (mL/min/1.73 m²)           | 63 ± 31        | 61 ± 29         | 64 ± 31       | 0.123   |
| Serum sodium (mEq/L)                           | 138 ± 8.5      | 137 ± 5         | 138 ± 4       | 0.153   |
| Serum potassium (mEq/L)                        | 4.3 ± 0.7      | 4.3 ± 0.6       | 4.3 ± 0.7     | 0.607   |
| Total cholesterol (mg/dL)                      | 156 ± 43       | 161 ± 49        | 154 ± 41      | 0.034   |
| LDL-cholesterol (mg/dL)                        | 100 ± 32       | 104 ± 36        | 99 ± 30       | 0.035   |
| HDL-cholesterol (mg/dL)                        | 44 ± 13        | 43 ± 13         | 44 ± 13       | 0.553   |
| C-reactive protein (mg/L)b                     | 10.4 (6.6–17.0) | 23.9 (13.5–41.1) | 15.6 (10–27.3) | <0.001  |
| Fibrinogen (mg/mL)b                            | 5.6 ± 2.9      | 5.7 ± 1.1       | 5.6 ± 3.3     | 0.900   |
| NT-proBNP (pg/mL)b                             | 4015 (1807–8775) | 4006 (1679–9021) | 4030 (1862–8680) | 0.795   |
| CA125 (U/mL)b                                  | 61 (27–128)    | 55 (23–118)     | 65 (29–134)   | 0.144   |

Continued
haemoglobin, estimated glomerular filtration rate (eGFR), NT-proBNP, C-reactive protein, GGT, CA125, aspartate aminotransferase, and TAPSE. The covariates included in the model for NT-proBNP were age, diabetes, prior use of diuretics, LVEF, systolic blood pressure, haemoglobin, eGFR, C-reactive protein, GGT, CA125, fibrinogen, and high-sensitivity troponin T.

The association of the ESC ID definition and other recent proposed definitions (TSAT <19.8%)11 with TAPSE and LVEF were also evaluated under the same multivariate setting.

A two-tailed P-value of <0.05 was statistically significant in all analyses. All survival analyses were performed using STATA 15.1 (StataCorp, 2017, Stata Statistical Software: Release 15; StataCorp, LLC, College Station, TX, USA).

Results
The mean age of the sample was 74.3 ± 10.6 years, 441 (48.8%) were female, and 324 (35.9%) had a prior admission for AHF. Regarding LVEF status, 471 (52.2%) patients exhibited HF with preserved ejection fraction, 132 (14.6%) mid-range ejection fraction, and 300 (33.2%) reduced ejection fraction. The mean LVEF, TAPSE, and TAPSE/PASP were 49 ± 15%, 18.6 ± 3.9 mm, and 4.05 ± 0.18, respectively. The median (IQR) for TSAT, ferritin, and NT-proBNP were 13.5% (8.6–20.1%), 101 (55–201) mg/mL, and 4015 (1807–8775) pg/mL, respectively. We found ID and anaemia in 677 (75.0%) and 409 (46.2%) patients, respectively.

Baseline characteristics according to iron deficiency parameters
Iron deficiency was present in 677 patients [446 (49.4%) with absolute ID] and 231 (25.6%) with functional ID. Table 1 presents the patients’ baseline characteristics according to the presence of ID. Overall, patients with ID were more frequently women and displayed more often a history of hypertension, diabetes, and dyslipidaemia. Iron deficiency patients also showed higher rates of peripheral oedema, lower values of haemoglobin, cholesterol lipoproteins, C-reactive protein, aspartate aminotransferase, and GGT. We did not find differences in the median values of NT-proBNP (Table 1). Regarding echocardiographic parameters, patients with ID displayed lower values of TAPSE and TAPSE/PASP, without differences in LVEF or PASP (Table 1). Supplementary material online, File S1 shows the patients’ baseline characteristics according to ferritin (<100 vs. ≥100 pg/mL) and TSAT (<20% vs. ≥20%) categories.

Iron deficiency parameters and right systolic function
Transferrin saturation and ferritin were positively correlated with TAPSE (r = 0.152, P < 0.001 and r = 0.136, P < 0.001, respectively). Transferrin saturation was correlated with TAPSE/PASP (r = 0.146, P < 0.001) but not ferritin (r = 0.013, P = 0.748).

In the multivariate linear regression analysis, the most important factors related to TAPSE together with the direction and contribution of each covariate on its proportion of variation (R²) were LVEF (positive, R²: 28.2%), atrial fibrillation (negative, R²: 24.7%), CA125 (negative, R²:15.6%), ID parameters (R²: 9.7%, R²: 5.3% for TSAT, and R²: 4.4% for ferritin), age (negative, R²: 4.1%), and GGT (negative, R²: 3.9%) (Supplementary material online, File S2). The gradients of risk for all these covariates are shown in Supplementary material online, File S3.

For ID parameters, TSAT remained independent, positive, and linearly associated with TAPSE (P = 0.003), as is shown in Figure 1A. Likewise, ferritin was positive and significantly related to TAPSE (P = 0.001). In this case, the association was non-linear with a steadily increased risk of right systolic dysfunction among those patients with ferritin <100 pg/mL (Figure 1B).

In a sensitivity analysis, adjusting for PASP when available (N = 638 patients), lower TSAT and ferritin remained associated with lower TAPSE (Supplementary material online, File S4). Predictors of TAPSE/PASP are displayed in Supplementary material online, File S5. Transferrin saturation (P = 0.045), and not ferritin (P = 0.814), was independently associated with TAPSE/PASP (Figure 2A and B).

European Society of Cardiology iron deficiency definition and right systolic function
Under the same prior multivariate setting, the current definition of ID was also associated with lower TAPSE (P = 0.002). European

Table 1

| Variables | All (n = 903) | No ID (n = 266) | ID (n = 677) | P-value |
|-----------|--------------|----------------|-------------|--------|
| hsTnT (pg/mL) | 39.4 (26.0–67.3) | 40.6 (26.5–75.0) | 39.2 (25.9–66.3) | 0.356 |
| AST (U/L) | 25.7 (20.4–32.4) | 28.0 (21.4–35.2) | 25.0 (20.0–31.9) | <0.001 |
| GGT (U/L) | 48 (29–87) | 55.5 (32–109) | 46 (28–82) | 0.002 |

Values for continuous variables are expressed as mean ± standard deviation.

AHF, acute heart failure; AST, aspartate aminotransferase; BBB, bundle branch block; CA125, carbohydrate antigen 125; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; hsTnT, high-sensitivity troponin T; ID, iron deficiency; IHD, ischaemic heart disease; LAD, left atrial diameter; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MRD, Modification of Diet in Renal Disease; NT-proBNP, amino-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion; TSAT, transferrin saturation; WHO, World Health Organization.

aID defined as serum ferritin <100 mg/dL (absolute ID) or ferritin 100–299 mg/dL and TSAT <20% (functional ID).

bValues expressed as mean (interquartile range).

data available in 638 patients.

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Under the same multivariate setting, the current definition of ID was also associated with lower TAPSE (P = 0.002).
Society of Cardiology definitions of absolute and functional ID were both independently associated with lower TAPSE ($b$-coefficient = -1.070; 95% confidence interval (CI) -1.583 to 0.450; $P < 0.001$ and -0.611; 95% CI -1.24 to 0.021; $P = 0.045$). Transferrin saturation $<_{19.8\%}$ was also significantly associated with lower TAPSE ($b$-coefficient = -0.786; 95% CI -1.327 to 0.244; $P = 0.005$).

Iron deficiency definition was borderline associated to lower TAPSE/ PASP ($b$-coefficient = -0.026; 95% CI -0.055 to 0.003; $P = 0.075$).

Iron deficiency parameters and parameters of left ventricular dysfunction
Transferrin saturation and ferritin were not correlated with LVEF ($r = 0.01$, $P = 0.737$ and $r = 0.01$, $P = 0.781$, respectively). The multivariate analysis revealed that the most important independent variables associated with LVEF were age ($R^2$: 22.0%), NT-proBNP...
iron parameters. Recently, a small randomized clinical trial showed that treatment with ferric carboxymaltose resulted in significant short-term improvement in cardiac magnetic resonance (CMR) sequences indicative of myocardial iron repletion in patients with HF and ID. In this study, myocardial iron depletion was significantly associated with short-term improvement in LVEF.18 Interestingly, in this study, performed in a representative cohort of patients with AHF, parameters of ID were not importantly related to the degree of left systolic ventricular function. These findings highlight the heterogeneous pathophysiology of systolic left ventricular impairment and the fact that the severity of AHF syndromes is determined by multiple factors beyond the degree of left systolic dysfunction.

Regarding the relationship of the ID parameters with the NT-proBNP values, van der Wal et al.19 reported that the ID, defined by TSAT <20%, was associated with higher NT-proBNP values in patients with worsening HF. Our results confirm these findings, as a significant association between lower TSAT and higher NT-proBNP was found, while the relationship between ferritin and NT-proBNP was also significant but positive, suggesting that TSAT could have a more accurate role in identifying patients with ID in this setting.

Iron deficiency and right ventricular dysfunction

Theoretically, the relationship between ID and right-sided ventricular dysfunction might be multifactorial, and probably, bidirectional. First, the severity of venous congestion is greater in patients with right ventricular systolic dysfunction,20 and right-sided congestion features are also independent predictors of ID in worsening HF, as it has been shown in the BIОСSTAT-CHF and DEFINE-HF cohorts.19,21 Congestion can indeed worsen iron status in HF through different mechanisms that are incompletely understood. In this line, accumulated data have shown that congestion is causally linked to liver dysfunction during episodes of decompression.22 Thus, and given that the liver is the primary place for ferritin and transferrin synthesis, it is easy to understand the relationship between congestion liver dysfunction ID. Also, some authors have suggested that inappropriately increased hepcidin levels in patients with HF and liver congestion could play a role in the development of ID in these patients.23–25 As hepcidin excess causes ID by inhibiting iron absorption from the intestine and iron release from macrophage stores.23–25 However, the role of hepcidin in this scenario remains controversial given that other authors17 described low hepcidin values in patients with ID and even an inverse relationship with NYHA class.13 Although no prior data has accurately analysed the trajectory of iron biomarkers (TSAT and ferritin) across HF clinical status, previous findings suggest higher data has accurately analysed the trajectory of iron biomarkers (TSAT and ferritin) across HF clinical status, previous findings suggest higher

Iron deficiency in acute heart failure syndromes

Iron deficiency is a common comorbidity in patients with HF, with a prevalence ranging from 30% to 50% in chronic HF13 and from 70% to 80% in those with AHF,17 and is associated with a worse prognosis, quality of life, and functional capacity.1–3 Different mechanisms, such as nutritional deficits, cardiorenal interactions, liver congestion, or chronic inflammation, have been proposed to explain the high prevalence of ID in AHF. Still, the pathophysiological aspects behind this association are not fully understood.14,15

Iron deficiency and ventricular systolic dysfunction

Iron, as an essential micronutrient in the mitochondrial function and energy production, has been suggested to play a causal role in the pathogenesis of systolic and diastolic myocardial dysfunction.4,5,7,10,16 In vitro studies have shown deleterious effects of iron depletion on cardiomyocytes contractile function, as well as its reversal after iron repletion.4,7,10,16 In humans, a decrease in myocardial iron content6 has also been reported in patients with advanced HF.5,10

From a clinical perspective, Toblli et al.17 showed that treatment with iron sucrose resulted in a significant 6-month improvement in LVEF estimated by echocardiography in 60 patients with HF, chronic kidney disease, and ID anaemia. Recently, a small randomized clinical trial showed that treatment with ferric carboxymaltose resulted in significant short-term improvement in cardiac magnetic resonance (CMR) sequences indicative of myocardial iron repletion in patients with HF and ID. In this study, myocardial iron depletion was significantly associated with short-term improvement in LVEF.18

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Intriguingly, this association could also, at least in part, be in the opposite direction. There is growing data on the structural and functional consequences of ID on the left ventricle, from in vivo and animal models to clinical studies.5,4 However, there is scarce evidence supporting the relationship between ID and structural changes in the right heart. Interestingly, the myocardial iron load is also reduced in the right ventricle in advanced HF.27 Likewise, Alioglu et al.28 showed...
that ID anaemia was negatively associated with myocardial function in a small study performed in children. There is evidence from animal models that ID can direct and rapidly promote pulmonary vascular remodelling, pulmonary hypertension, and right ventricular hypertrophy, besides the haemodynamic and pulmonary vascular remodelling induced by ID in rats may be reversed by iron replacement. The potential benefit of iron replacement therapy in the right ventricle and pulmonary circulation is an area of utmost interest. However, data in HF are scarce. Anker et al. reported, in a meta-analysis including 839 ambulatory HF patients, that treatment with

Figure 3 Left ventricular ejection fraction values along the continuum of transferrin saturation and ferritin. Sensitivity analysis. (A) Heart failure with reduced ejection fraction. (B) Heart failure with mid-range ejection fraction. (C) Heart failure with preserved ejection fraction. LVEF, left ventricle ejection fraction; TSAT, transferrin saturation.
ferric carboxymaltose was associated with a significant reduction in clinical events. However, a substantially lower effect was observed in those with TSAT \(\geq\) 20.1%. Unlike pulmonary arterial hypertension, the potential benefit of iron replacement therapies on the right heart has not been described yet. Treatment with intravenous iron has pre-
liminarily shown to be able to improve decongestion.\(^{31}\) Thus, we speculate ID might promote pulmonary artery hypertension and right systolic dysfunction,\(^{4,7,10,16,32–34}\) developing an establishment of posi-
tive feedback, as is suggested in the graphical abstract. The potential association of iron status and right HF should be confirmed and explored in upcoming studies.

**Limitations**

This study has the inherent limitations of being a cross-sectional single-centre observational study. As such, our conclusions do not apply to patients with stable chronic HF. Other parameters of the right ventricle function, such as fractional area change, and tissue Doppler lateral tricuspid annular systolic velocity were not available. Likewise, other proxies of left ventricular function such as left ventricular volumes, global longitudinal strain, and tissue Doppler were not evaluated.

Other biomarkers of iron metabolism, such as hepcidin or soluble transferrin receptor, were also not determined. As data regarding ID status during follow-up was not available, the relation-
ship between evolutive changes in ID parameters and the right and left ventricle function could not be evaluated. As echocardiog-
raphy studies were performed at rest, the LV function during ex-
cise was not evaluated. Finally, TSAT and ferritin were not measured at discharge and therefore steady-state may not have been reached.

**Conclusions**

In this cross-sectional study in patients with AHF, we found that lower TSAT and ferritin were associated with right ventricular dys-
function assessed by TAPSE. Likewise, lower TSAT, but not ferritin, was related to right ventricular–pulmonary arterial uncoupling. Regarding left ventricular parameters, systemic iron status was mar-
ginally or not related to LVEF. However, TSAT was inversely associ-
ated with higher natriuretic peptides. Further studies should confirm these findings and evaluate the pathophysiological facts behind this asso-
ciation, as well as to assess the effect of iron repletion on the right systolic function.

**Supplementary material**

Supplementary material is available at European Heart Journal – Acute Cardiovascular Care online.

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