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ORIGINAL PAPER

Iron deficiency in patients with heart failure with preserved ejection fraction and its association with reduced exercise capacity, muscle strength and quality of life

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Abstract

Background The prevalence of iron deficiency (ID) in outpatients with heart failure with preserved ejection fraction (HFpEF) and its relation to exercise capacity and quality of life (QoL) is unknown.

Methods 190 symptomatic outpatients with HFpEF (LVEF 58 ± 7%; age 71 ± 9 years; NYHA 2.4 ± 0.5; BMI 31 ± 6 kg/m^2) were enrolled as part of SICA-HF in Germany, England and Slovenia. ID was defined as ferritin < 100 or 100–299 µg/L with transferrin saturation (TSAT) < 20%. Anemia was defined as Hb < 13 g/dL in men, < 12 g/dL in women. Low ferritin-ID was defined as ferritin < 100 µg/L. Patients were divided into 3 groups according to *E/e′* at echocardiography: *E/e′* ≤ 8; *E/e′* 9–14; *E/e′* ≥ 15. All patients underwent echocardiography, cardiopulmonary exercise test (CPX), 6-min walk test (6-MWT), and QoL assessment using the EQ5D questionnaire.

Results Overall, 111 patients (58.4%) showed ID with 89 having low ferritin-ID (46.84%). 78 (41.1%) patients had isolated ID without anemia and 54 patients showed anemia (28.4%). ID was more prevalent in patients with more severe diastolic dysfunction: *E/e′* ≤ 8: 44.8% vs. *E/e′*: 9–14: 53.2% vs. *E/e′* ≥ 15: 86.5% ($p = 0.0004$). Patients with ID performed worse during the 6MWT (420 ± 137 vs. 344 ± 124 m; $p = 0.008$) and had worse exercise time in CPX (645 ± 168 vs. 538 ± 178 s, $p = 0.03$). Patients with low ferritin-ID had lower QoL compared to those without ID ($p = 0.03$).

Conclusion ID is a frequent co-morbidity in HFpEF and is associated with reduced exercise capacity and QoL. Its prevalence increases with increasing severity of diastolic dysfunction.

Keywords Heart failure with preserved ejection fraction · Iron deficiency · Exercise capacity · Quality of life

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Abbreviations

ANOVA	Analysis of variance
ATP	Adenosine triphosphate
BMI	Body mass index
CPX	Cardiopulmonary exercise test
DEXA	Dual energy X-ray absorptiometry
HB	Hemoglobin
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
ID	Iron deficiency
LAVI	Left atrial volume index
LV	Left ventricular
6-MWT	6-min walk test
NYHA	New York Heart Association
QoL	Quality of life
SD	Standard deviation
SICA-HF	Studies investigating co-morbidities aggravating heart failure
TSAT	Transferrin saturation

Introduction

About 50% of patients with heart failure (HF) have heart failure with preserved left ventricular ejection fraction (HFpEF) on imaging tests [1]. The main clinical symptom of these patients is exercise intolerance [2–6]. The underlying causes are heterogeneous and not well-understood, as different mechanisms including reduced left ventricular (LV) longitudinal strain function [7], higher LV filling pressures [8] and other factors might play a role in its pathophysiology. Moreover, different mechanisms, potentially unrelated to hemodynamic dysfunction, may attribute to the development of exercise intolerance. As an example, anemia is a known co-morbidity across the spectrum of HF with either preserved or reduced ejection fraction, but also across different regional backgrounds [9]. Anemia is associated with worse prognosis and reduced functional capacity in this group of patients [9]. Insufficient oxygen supply and impaired oxygen use by skeletal muscle during exercise are other examples [10–12].

Iron plays a key role in oxygen uptake, transport, and storage, as well as oxidative metabolism in the skeletal muscle; it is also involved in erythropoiesis [13, 14]. However, erythropoiesis remains undisturbed until late in the course of iron depletion [15, 16]. Indeed, it has been reported that iron deficiency (ID) with or without anemia impairs the aerobic performance and leads to fatigue and exercise intolerance [17–19]. It is also known that the intravenous repletion—as opposed to oral administration [20]—of iron in patients with HFrEF improves functional capacity, symptoms and QoL and may be associated with reduced hospitalization rates for worsening in HF [10, 21].

ID is an extremely common nutritional disorder that affects up to 2 billion people worldwide [15], and it has recently been reported as a frequent co-morbidity in stable HF patients [22–24]. Furthermore, ID—but not anemia—was found to be an independent predictor of worse outcome in HFrEF patients [25]. However, our knowledge regarding ID in HFpEF patients is limited. In this multicenter, prospective, cross-sectional study, we describe the prevalence of ID in HFpEF patients and its relation to exercise capacity, muscle strength, pulmonary arterial systolic pressure and QoL.

Methods

Study population

Between March 2010 and September 2013, patients with HF were enrolled into the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF), a European multicenter observational study into the prevalence, incidence and impact of key co-morbidities in outpatients with a clinical diagnosis of chronic stable HF with either reduced or preserved left ventricular ejection fraction. For the current sub-study, subjects were included from the Departments of Cardiology at Charité Medical School, Campus Virchow-Klinikum, Berlin, Germany; Hull University Hospital, Hull, England; and Golnik University, Golnik, Slovenia. All subjects provided written informed consent at enrolment, and the protocol was approved by the local ethic committee [26]. The study was funded by the European Commission's 7th Framework program (FP7/2007-2013) under grant agreement number 241558 (clinical.trial.gov) and fulfilled all principles of the Declaration of Helsinki. The protocol is registered at clinicaltrial.gov under the unique identifier NCT01872299.

HFpEF was defined as presence of signs and symptoms of HF, left ventricular ejection fraction ≥ 50% on echocardiography and at least one of the following criteria: dilated left atrium (left atrial volume index ≥ 34 ml/m^2) or evidence of diastolic dysfunction at tissue doppler (septal $e' < 8$, and/or lateral $e' < 10$) [27, 28]. Patients with severe valve stenosis or regurgitation were excluded. Overall, 190 suitable patients (60 patients from Charité Berlin, Germany, 109 patients from Hull, England and 21 from Golnik, Slovenia) were identified. We used for calculating *E/e′* the average of septal and lateral e′. Patients were sub-grouped according to *E/e′* into three groups (group A: average $E/e' \leq 8$ [$n = 29$], group B: average *E/e′* 9–14 [$n = 124$], group C: average $E/e' \geq 15$ [$n = 37$]) [27, 28].

Clinical assessments

Iron deficiency (ID) was defined as ferritin < 100 or 100–299 µg/L with transferrin saturation (TSAT) < 20% [10]. Anemia was defined as Hb < 13 g/dL in men, < 12 g/dL in women. Dual-energy X-ray absorptiometry (DEXA) was used to assess the appendicular lean mass, i.e., muscle mass in both arms and legs. The knee extension strength (quadriceps strength) was measured in both legs in a sitting position with the patient's legs hanging freely, the ankle fixed by a pressure transducer (kilograms). The best of three measurements was used in each of knee extension strength tests as defined in the protocol [26]. The maximum uptake of oxygen (peak VO_2-ml/kg/min) was measured using cardiopulmonary exercise testing in 50 patients using a treadmill and the modified Bruce protocol [29]. In selected patients, a modified Naughton protocol was used [30]. In addition, a 6-min walk test (6-MWT) was performed in 88 patients. QoL was assessed using the EQ5D questionnaire.

Statistical analysis

Data are presented as mean ± standard deviation (SD) or median with percentiles. StatView 5.0 (SAS Institute, inc., Cary, USA) and the Statistical Package for the Social Sciences (SPSS version 21) were used for statistical analyses. Analysis of variance (ANOVA), Student's unpaired *t* test, Fisher's exact test, Pearson's simple regression and logistic regression were used as appropriate. A two-tailed *p* value ≤ 0.05 indicates statistical significance.

Results

Overall, 111 of 190 patients had ID (58.4%), 54 patients had anemia (28.5%). Among all patients, 78 (41.1%) patients had isolated ID, i.e., ID without anemia. A low ferritin < 100 µg/L was noted in 89 patients (46.8%), (Fig. 1a, b). ID was more common in patients with more severe diastolic dysfunction: (prevalence according to group $E/e' \leq 8$: 44.8% vs. E/e': 9–14: 53.2% vs. $E/e' \geq 15$: 86.5%, $p = 0.0004$), (Fig. 2,; Tables 1, 2).

In total, patients with ID (with or without anemia) performed worse in the 6-MWT (420 ± 137 vs. 344 ± 124 m, $p = 0.008$), had lower exercise time in CPX (645 ± 168 vs. 538 ± 178 s, $p = 0.03$) and had less muscle strength/muscle mass in both legs (left leg: 4.5 ± 1.1 vs. 3.4 ± 0.9, $p = 0.0004$, right leg: 4.2 ± 1.4 vs. 3.5 ± 1.0, $p = 0.03$), (Fig. 3). These patients showed a trend towards lower QoL using EQ5D assessment (16,369 ± 5280 vs. 18,171 ± 4967, $p = 0.06$).

Patients with isolated ID compared to those without either ID or anemia showed similarly reduced exercise capacity: 6MWT (437 ± 130 vs. 343 ± 136 meters, $p = 0.007$), (Fig. 4). Patients with low ferritin-ID compared to those without ID had worse diastolic function measured by E/e' (11 ± 4 vs.

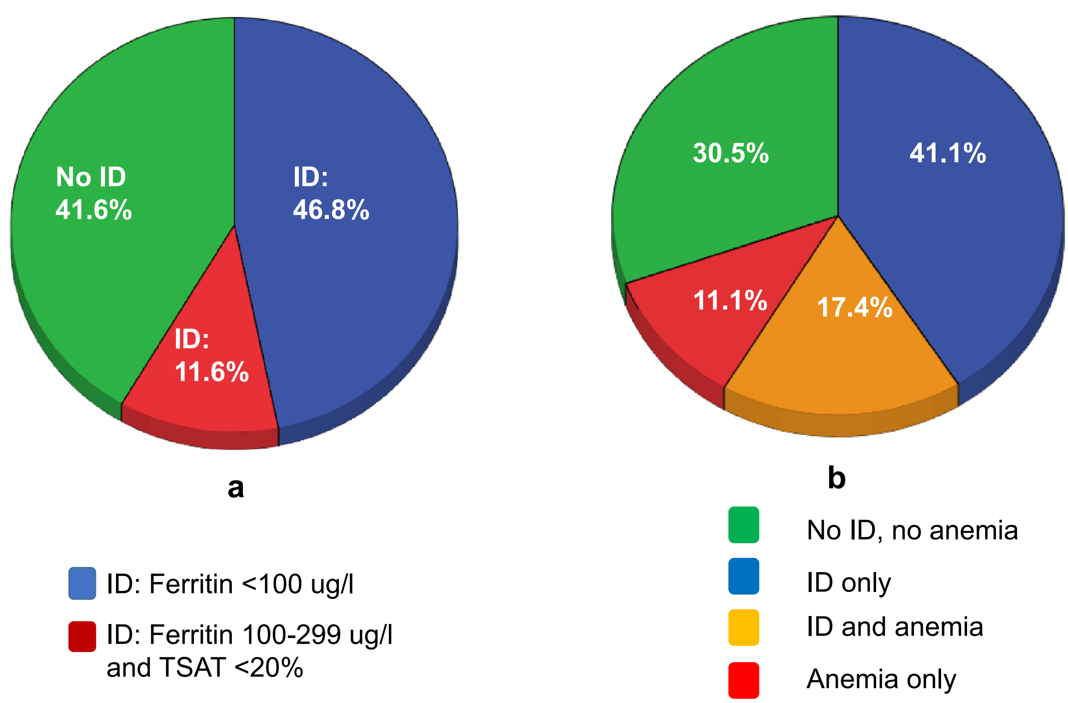

Fig. 1 **a** Prevalence of iron deficiency both with ferritin < 100ug/ml and ferritin between 100 and 299 ug/ml with TSAT < 20% in patients with HFpEF. **b** Prevalence of both ID and anemia in patients with HFpEF

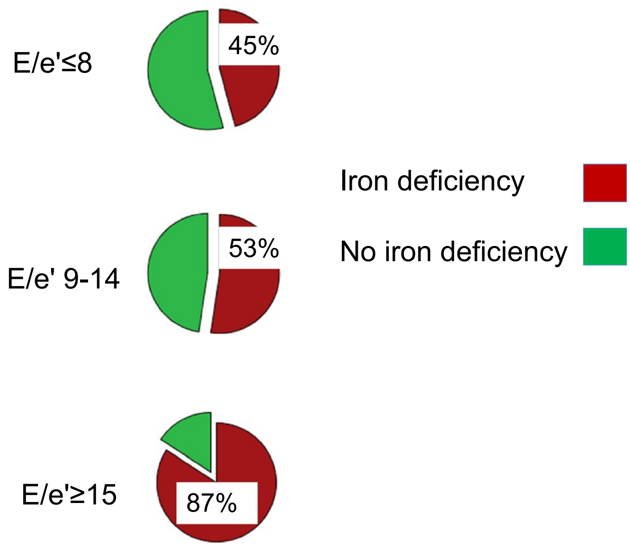

Fig. 2 Prevalence of ID in groups with different severities of HFpEF

14 ± 6, $p = 0.0004$) and worse QoL estimated with EQ5D (16,396 ± 5280 vs. 18,525 ± 4816, $p = 0.03$), (Fig. 5).

Lower values of ferritin were associated with worse exercise time ($r = 0.38$, $p = 0.004$), peak VO_2 on CPX ($r = 0.41$, $p = 0.003$) and worse *E/e′* values ($r = -0.18$, $p = 0.01$). TSAT was inversely correlated with *E/e′* ($r = -0.24$, $p = 0.001$), QoL estimated with EQ5D ($r = -0.28$, $p = 0.001$) and estimated pulmonary arterial systolic pressure in echocardiography ($r = -0.26$, $p = 0.01$), (Fig. 6).

Designing a multinomial logistic regression model including ID (yes/no), Hb, NT-proBNP, hsCRP, *E/e′*, we found that ID (yes) and NT-pro-BNP are independent predictor factors for reduced exercise capacity measured by walking distance less than 378 m (this is the mean of the whole cohort) in 6MWT: [(ID (yes): odds ratio = 3,7, $p = 0.04$); (NT-pro-BNP: odds ratio = 1,003, $p = 0.003$)].

Analyzing the cohort according to TSAT < or > 20%, we found that patients with reduced TSAT (< 20%) showed reduced exercise capacity measured by chair stand (2.5 vs.

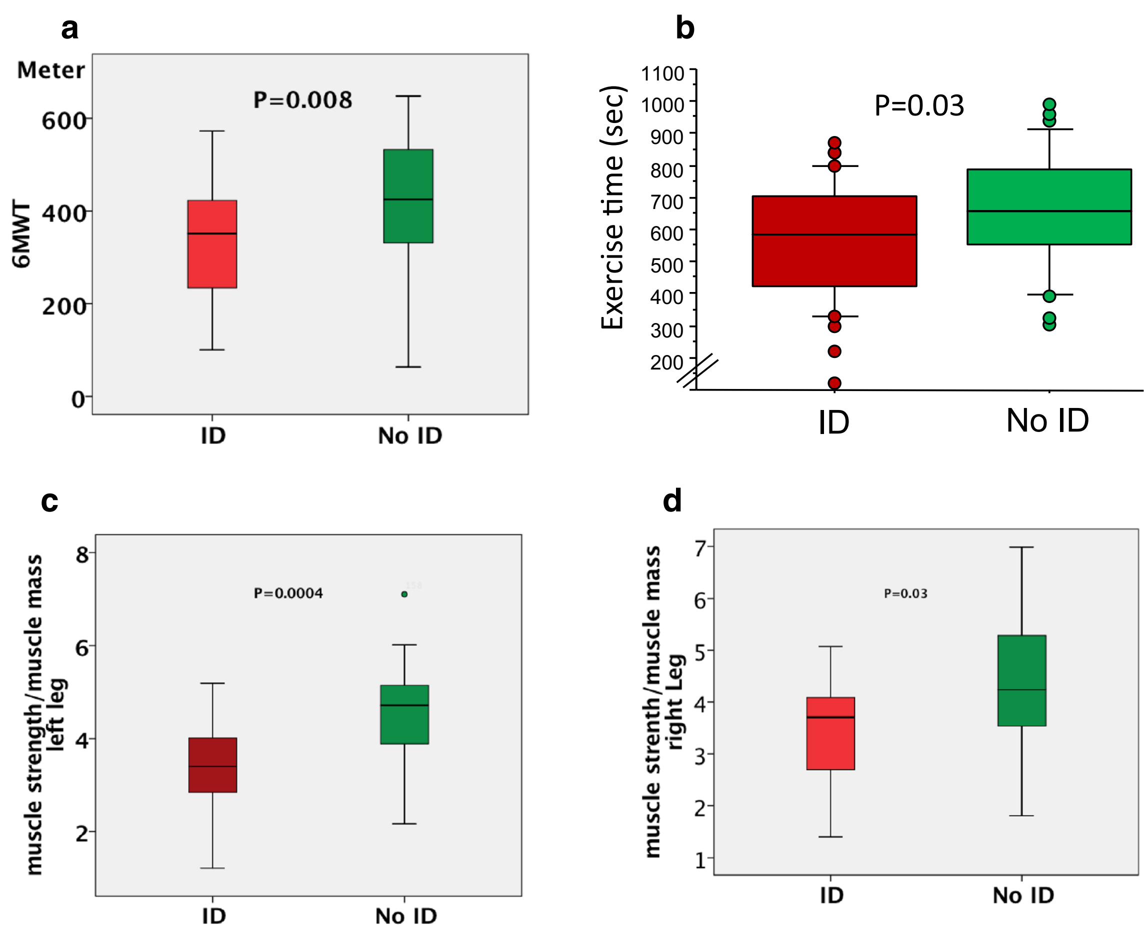

Fig. 3 **a** Exercise capacity assessed by the distance walked in 6-min walk test (mean values) in patients with and without iron deficiency. **b** Exercise time assessed by a treadmill in the cardiopulmonary exercise test (mean values) in patients with and without iron deficiency. **c, d** Muscle strength/muscle mass in both legs (mean values) in patients with and without iron deficiency

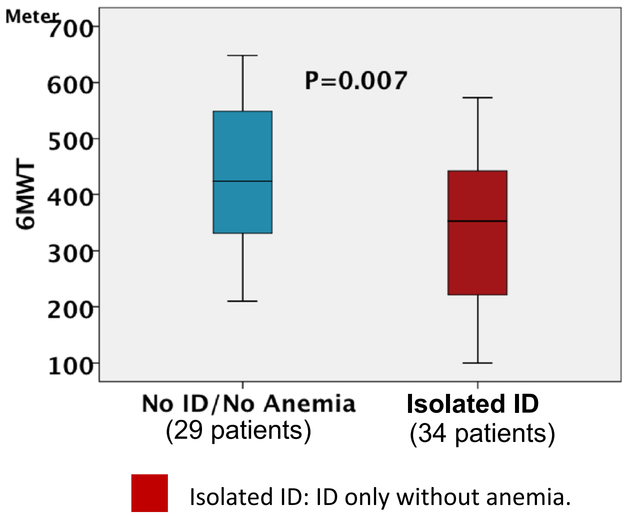

Fig. 4 Exercise capacity assessed by the distance walked in 6-min walk test (mean values) in patients with iron deficiency without anemia

3.3, $p = 0.007$) and reduced QoL measured by EQ5D (18,903 vs. 16,489, $p = 0.01$).

Discussion

The main symptom in patients with HFpEF is exercise intolerance whose etiology has been deemed multifactorial. Different mechanisms, which could be unrelated to hemodynamic dysfunction of HF, such ID may attribute to the explanation of exercise intolerance in patients with HF. This has also been shown in HFrEF [10, 21]. However, no sufficient data exist derived from HFpEF patients.

The current study is the first multicenter European study that describes the prevalence of ID in patients with HFpEF and its relation to exercise capacity, muscle strength, pulmonary arterial systolic pressure and quality of life. Overall, 111 patients (58.4%) of symptomatic stable HFpEF outpatients in our cohort presented with ID. 78 patients (41.1%) presented with isolated ID, i.e., without anemia. These patients (both with isolated ID or those with ID and anemia) showed reduced exercise capacity, measured by CPX testing as well as in the 6-MWT. Furthermore, patients with low ferritin values (i.e., < 100 µg/L) compared to those without ID had worse QoL estimated with EQ5D. The prevalence of ID was higher in patients with more severe diastolic dysfunction. In addition, there was a steady increase in absolute peak VO_2 and exercise time in parallel to increasing values of ferritin. TSAT was inversely correlated with estimated pulmonary arterial systolic pressure on echocardiography. This may indicate a relationship between ID and elevated pulmonary pressure.

Exercise intolerance in HFpEF patients might be related to anemia, insufficient oxygen supply or impaired oxygen use by the skeletal muscle during exercise [11, 12]. Iron plays a key role in oxygen uptake, transport, and storage, as well as oxidative metabolism in the skeletal muscle; furthermore, it is also involved in erythropoiesis [13, 14]. It is known that absorption of iron in cases of inflammatory disorders is reduced due to intestinal edema and other factors [31–34]. Moreover, iron can accumulate inside reticuloendothelial stores, which reduces the availability of iron for target tissues and stores despite adequate iron stores in the

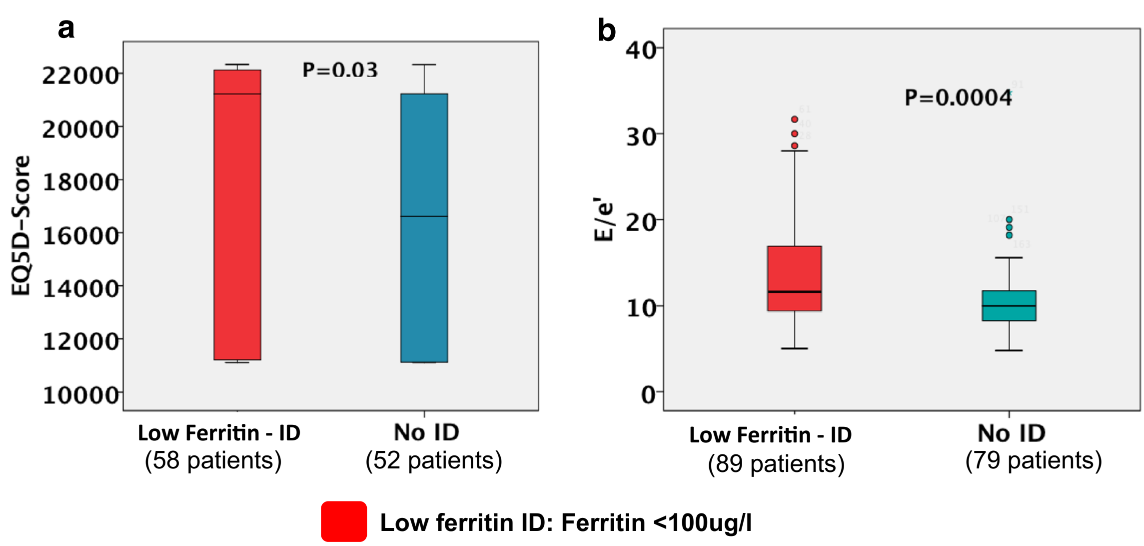

Fig. 5 **a** Quality of life using EQ-5D (mean values) in patients with and without low ferritin-iron deficiency. **b** The severity of diastolic dysfunction (*E*/*e*′) in patients with and without low ferritin-iron deficiency

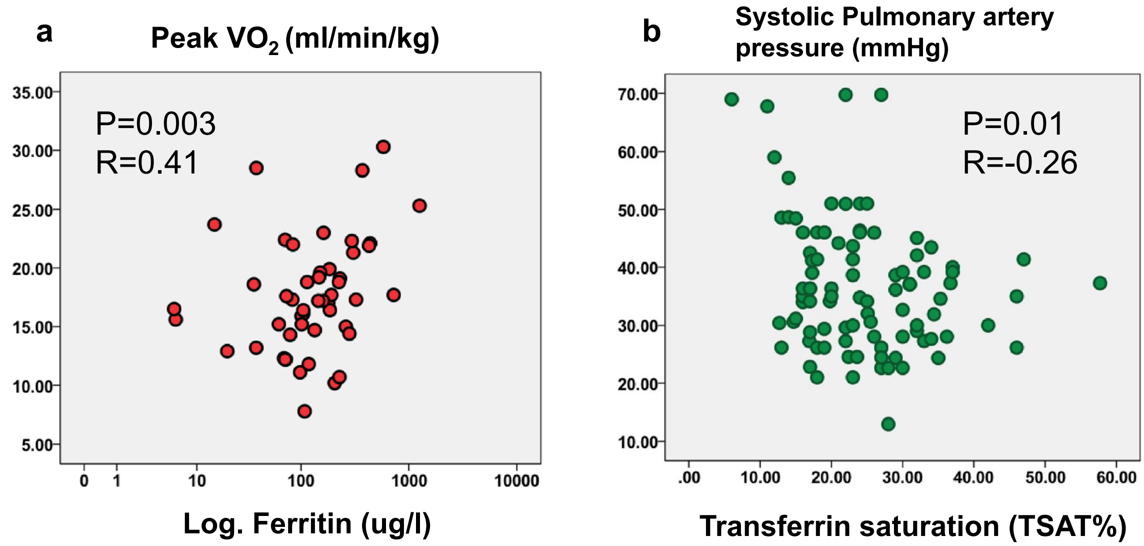

Fig. 6 **a** Simple regression analysis of ferritin and peak VO_2. **b** Simple regression analysis of transferrin saturation % and pulmonary artery pressure

Table 1 Baseline characteristics of patients with ID vs. without ID:

Variable	All patients ($n = 190$)	Patients without ID ($n = 79$)	Patients with ID ($n = 111$)	p value
Sex (m/f %)	67.5/32.5	62.8/37.2	87/13.0	0.6
Age (years)	71.9 ± 9.0	70.5 ± 9.3	72.9 ± 8.7	0.07
BMI (kg/m^2)	31.2 ± 6.2	31.1 ± 5.9	31.3 ± 6.4	0.86
NYHA	2.4 ± 0.5	2.3 ± 0.5	2.5 ± 0.5	0.11
NT-proBNP (60 patients) (pg/ml)	844.7 ± 631.3	1013 ± 754.6	746.5 ± 529.3	0.047
Hemoglobin (g/dL)	13.2 ± 1.5	13.3 ± 1.6	13.1 ± 1.5	0.37
Creatinin (mg/dL)	1.3 ± 0.7	1.3 ± 0.9	1.3 ± 0.5	0.66
LDL-Cholesterol (mg/dL)	89.9 ± 37.9	91.3 ± 39.6	88.9 ± 36.7	0.69
Ferritin (ng/ml)	163.8 ± 168.3	208.2 ± 198.1	81.1 ± 64.7	< 0.0001
LVEF %	58.2 ± 6.65	56.7 ± 5.4	59.3 ± 7.2	0.008
Left ventricular mass index (gm/m^2)	127.8 ± 35.5	128.7 ± 35.2	127.1 ± 36.0	0.83
LAVI (ml/m^2)§	39.4 ± 15.3	40.2 ± 17.3	38.7 ± 13.7	0.53
PAP (mmm/Hg)	36.5 ± 11.2	35.5 ± 10.7	37.3 ± 11.5	0.43
E/e'	12.1 ± 5.1	10.6 ± 4.0	13.1 ± 5.6	0.001
6MWT (88 patients) (m)	377.5 ± 134.5	420.7 ± 123.8	344.0 ± 123.8	0.008
Exercise time (50 patients) (s)	588.2 ± 179.6	644.7 ± 167.5	537.6 ± 177.6	0.03
EQ5D	17449.9 ± 5150.7	16395.7 ± 5279.6	18171.2 ± 49667.0	0.06

BMI body mass index, *LVEF* left ventricular ejection fraction, *LAVI* left atrium volume index, *PAP* pulmonary artery pressure

body, a phenomenon known as functional iron deficiency [35]. Furthermore, diastolic dysfunction has been shown to be associated with reduced cardiac energetic reserve [24, 36]. Here, iron plays also an essential role in oxygen metabolism and cellular energetics. This is of special importance in the diastolic phase of the cardiac cycle including LV relaxation and filling due to the crucial role of sufficient cellular energetic supply through adenosine triphosphate (ATP) in the physiology of this phase. Therefore, ID may lead to an impairment of LV diastolic function and cardiac performance as well as reduced exercise capacity through impaired energetic balance and abnormal oxidative mitochondrial function [10, 17]. In our current analysis, lower values of ferritin were associated with impaired *E/e'* values. ID was more common in patients with more severe diastolic dysfunction. As a result, the maintenance of normal iron metabolism and iron storage appears important for the maintenance of cardiac function and physiology [37, 38].

Table 2 Baseline characteristics of HFpEF patients

Variable	Group A $E/e' \leq 8$ $n = 29$	Group B E/e' 9–14 $n = 124$	Group C $E/e' \geq 15$ $n = 37$	p value ANOVA
Age (years)	68.9 ± 10.1	71.9 ± 8.6	74.1 ± 8.8	0.06
Sex (m/f %)	82.8/17.2	68.5/31.5	32.4/67.6	< 0.0001
BMI (kg/m^2)	30.1 ± 4.4	31. 2 ± 6.4	31.9 ± 6.3	0.50
NYHA	2.3 ± 0.5	2.5 ± 0.5	2.3 ± 0.5	0.37
Left ventricular mass index (gm/m^2)	113.2 ± 32.6	126.6 ± 33.3	145.6 ± 41.2	0.04
LAVI (ml/m^2)	33.5 ± 13.2	38.6 ± 11.6	46.2 ± 22.8	0.004
PAP (mmHG)	34.5 ± 9.7	35.2 ± 10.3	42.5 ± 13.5	0.03
LVEDVI (ml/m^2)	51.3 ± 17.3	52.2 ± 17.6	49.2 ± 15.1	0.67
LVESVI (ml/m^2)	22.3 ± 9.5	22.9 ± 9.0	20.1 ± 7.8	0.28
LVEF (%)	57.7 ± 7.1	58.0 ± 6.5	59.4 ± 6.9	0.47
Hb (mg/dL)	13.4 ± 1.5	13.4 ± 1.6	12.7 ± 1.4	< 0.05
Creatinine (mg/dL)	1.3 ± 0.6	1.2 ± 0.8	1.3 ± 0.6	0.72
Muscle strength of the right hand (kg)	43.3 ± 10.7	34.0 ± 11.3	23.5 ± 5.3	0.0009
Quadriceps strength of the right leg (kg)	45.5 ± 13.7	32.3 ± 10.4	28.7 ± 16.3	0.008

LAVI left atrium volume index, *PAP* pulmonary artery pressure, *LVEDVI* left ventricular end diastolic volume index, *LVESVI* left ventricular end systolic volume index, *LVEF* left ventricular ejection fraction

In one single study in HFpEF patients, Kasner et al. have shown that there is no relationship between functional ID and exercise capacity [24]. We believe that this was related to the very small sample volume (26 patients), already recognized as a study limitation by the authors. Interestingly, even in this small group of patients, the prevalence of isolated ID was as high as 58%.

The treatment of ID in patients with HF and an LVEF < 45% and ID in the FAIR-HF trial showed an improvement in 6-MWT distance and QoL after 24 weeks [10]. In the CONFIRM-HF study, this therapy reduced the hospitalization rate after 52 weeks, a result confirmed in a recent meta-analysis [21]. The FAIR-HFpEF trial will enroll patients with HFpEF and ID for the substitution of intravenous iron [15]. Just like in the FAIR-HF and the CONFIRM-HF trials, the primary outcome of this study is exercise capacity after intravenous iron administration in patients with HFpEF.

In conclusion, ID is a frequent co-morbidity in patients with HFpEF and is associated with reduced exercise capacity, muscle strength and QoL. Its prevalence increases with increased severity of diastolic dysfunction. One of the major limitations in our study was getting rather weak correlations in the simple regression analysis as well as not doing NT-pro-BNP-measurement in all patients. These findings might have important therapeutic implications and support the need for further prospective studies analyzing the impact of iron supplementation in patients with HFpEF.

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Compliance with ethical standards

Conflict of interest SvH is consulting and has received honoraria for speaking from Solartium Dietetics, Professional Dietetics, Vifor, Novartis, Respicardia, Sorin, and Pfizer. SDA is consulting, has received honoraria for speaking and/or attended advisory boards for Amgen Inc, Professional Dietetics, Psioxus Therapeutics, GTx, Helsinn, GSK, Sanofi, Regeneron, Novartis, Takeda, Servier, Chugai and Vifor. All other authors report no conflict of interest.

References

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM (2006) Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 355:251–259
2. Haykowsky MJ, Brubaker PH, John JM, Stewart KP, Morgan TM, Kitzman DW (2011) Determinants of exercise intolerance in elderly heart failure patients with preserved ejection fraction. J Am Coll Cardiol 58:265–274
3. Borlaug BA, Melenovsky V, Russell SD, Kessler K, Pacak K, Becker LC, Kass DA (2006) Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. Circulation 114:2138–2147
4. Borlaug BA, Olson TP, Lam CS, Flood KS, Lerman A, Johnson BD, Redfield MM (2010) Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. J Am Coll Cardiol 56:845–854
5. Bhella PS, Prasad A, Heinicke K, Hastings JL, Arbab-Zadeh A, Adams-Huet B, Pacini EL, Shibata S, Palmer MD, Newcomer BR, Levine BD (2011) Abnormal haemodynamic response to exercise in heart failure with preserved ejection fraction. Eur J Heart Fail 13:1296–1304
6. Maeder MT, Thompson BR, Brunner-La Rocca HP, Kaye DM (2010) Hemodynamic basis of exercise limitation in patients with heart failure and normal ejection fraction. J Am Coll Cardiol 56:855–863

7. Pellicori P, Kallvikbacka-Bennett A, Khaleva O, Carubelli V, Costanzo P, Castiello T, Wong K, Zhang J, Cleland JG, Clark AL (2014) Global longitudinal strain in patients with suspected heart failure and a normal ejection fraction: does it improve diagnosis and risk stratification? Int J Cardiovasc Imaging 30:69–79
8. Kitzman DW, Higginbotham MB, Cobb FR, Sheikh KH, Sullivan MJ (1991) Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. J Am Coll Cardiol 17:1065–1072
9. von Haehling S, van Veldhuisen DJ, Roughton M, Babalis D, de Boer RA, Coats AJS, Manzano L, Flather M, Anker S (2011) D. Anaemia among patients with heart failure and preserved or reduced ejection fraction: results from the SENIORS study. Eur J Heart Fail 13:656–663
10. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, Lüscher TF, Bart B, Banasiak W, Niegowska J, Kirwan BA, Mori C, von Eisenhart Rothe B, Pocock SJ, Poole-Wilson PA, Ponikowski P (2009) FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med 361:2436–2448
11. Clark AL, Poole-Wilson PA, Coats AJ (1996) Exercise limitation in chronic heart failure: central role of the periphery. J Am Coll Cardiol 28:1092–1102
12. Massie BM, Conway M, Rajagopalan B, Yonge R, Frostick S, Ledingham J, Sleight P, Radda G (1988) Skeletal muscle metabolism during exercise under ischemic conditions in congestive heart failure: evidence for abnormalities unrelated to blood flow. Circulation 78:320–326
13. Dunn LL, Rahmanto YS, Richardson DR (2007) Iron uptake and metabolism in the new millennium. Trends Cell Biol 17:93–100
14. Fairbanks V, Beutler E (2001) Iron deficiency. In: Beutler E (ed) Williams hematology, 6th edn. McGraw-Hill, New York, pp 295–304 (**447–70**).
15. von Haehling S, Jankowska EA, van Veldhuisen DJ, Ponikowski P, Anker SD (2015) Iron deficiency and cardiovascular disease. Nat Rev Cardiol. https://doi.org/10.1038/nrcardio.2015.109
16. Andrews NC, Schmidt P (2007) J.Iron homeostasis. Annu Rev Physiol 69:69–85
17. Haas JD, Brownlie TIV (2001) Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. J Nutr 131(Suppl 2):676–688
18. Konishi M, Ishida J, Springer J, von Haehling S, Akashi YJ, Shimokawa H, Anker SD (2016) Heart failure epidemiology and novel treatments in Japan: facts and numbers. ESC Heart Fail 3(3):145–151
19. Yeo TJ, Yeo PS, Hadi FA, Cushway T, Lee KY, Tai BC, Lam CS (2016) Rationale and design of a pilot randomized controlled trial to assess the role of intravenous ferric carboxymaltose in Asian patients with heart failure (PRACTICE-ASIA-HF). ESC Heart Fail 3(2):71–76
20. Lewis GD, Malhotra R, Hernandez AF, McNulty SE, Smith A, Felker GM, Tang WHW, LaRue SJ, Redfield MM, Semigran MJ, Givertz MM, Van Buren P, Whellan D, Anstrom KJ, Shah MR, Desvigne-Nickens P, Butler J, Braunwald E (2017) Effect of Oral Iron Repletion on Exercise Capacity in Patients With Heart Failure With Reduced Ejection Fraction and Iron Deficiency: the IRONOUT HF randomized clinical trial. JAMA 19:1958–1966
21. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, McDonagh Th, Parkhomenko A, Tavazzi L, Levesque V, Mori C, Roubert B, Filippatos G, Ruschitzka F, Anker SD (2015). on behalf of for the CONFIRM-HF Investigators. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. Eur Heart J 36:657–668
22. Klip IT, Comin-Colet J, Voors AA, Ponikowski P, Enjuanes C, Banasiak W, Lok DJ, Rosentryt P, Torrens A, Polonski L, van Veldhuisen DJ, van der Meer P, Jankowska EA (2013) Iron deficiency in chronic heart failure: an international pooled analysis. Am Heart J 165:575–582
23. Okonko DO, Mandal AKJ, Missouris CG, Poole-Wilson PA (2011) Disordered iron homeostasis in chronic heart failure: prevalence, predictors, and relations to anemia, exercise capacity, and survival. J Am Coll Cardiol 58:1241–1251
24. Kasner M, Aleksandrov AS, Westermann D, Lassner D, Gross M, von Haehling S, Anker SD, Schultheiss HP, Tschöpe C (2013) Functional iron deficiency and diastolic function in heart failure with preserved ejection fraction. Int J Cardiol 168:4652–4657
25. Jankowska EA, Rozentryt P, Witkowska A, Nowak J, Hartmann O, Ponikowska B, Borodulin-Nadzieja L, Banasiak W, Polonski L, Filippatos G, McMurray JJ, Anker SD, Ponikowski P (2010) Iron deficiency: an ominous sign in patients with systolic chronic heart failure. Eur Heart J 31:1872–1880
26. von Haehling S, Lainscak M, Doehner W, Ponikowski P, Rosano G, Jordan J, Rozentryt P, Rauchhaus M, Karpov R, Tkachuk V, Parfyonova Y, Zaritskey AY, Shlyakhto EV, Cleland JG, Anker SD (2010) Diabetes mellitus, cachexia and obesity in heart failure: rationale and design of the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF). J Cachexia Sarcopenia Muscle 1:187–194
27. Paulus WJ, Tschöpe C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbély A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL (2007) How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 28:2539–2550
28. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelisa A (2009) Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr 10:165–193
29. Bruce RA, Blackmon JR, Jones JW, Strait G (1963) Exercise testing in adult normal subjects and cardiac patients. Pediatrics 32:742–756
30. Naughton J, Sevellus G, Balke B (1963) Physiologic responses of normal and pathologic subjects to a modified work capacity test. J Sports Med 31:201
31. Krack A, Sharma R, Figulla HR, Anker SD (2005) The importance of the gastrointestinal system in the pathogenesis of heart failure. Eur Heart J 26:2368–2374
32. Silverberg DS (2011) The role of erythropoiesis stimulating agents and intravenous (IV) iron in the cardio renal anemia syndrome. Heart Fail Rev 16:609–614
33. Weiss G, Goodnough LT (2005) Anemia of chronic disease. N Engl J Med 352:1011–1023
34. Sandek A, Bauditz J, Swidsinski A, Buhner S, Weber-Eibel J, von Haehling S, Schroedl W, Karhausen T, Doehner W, Rauchhaus M, Poole-Wilson P, Volk HD, Lochs H, Anker SD (2007) Altered intestinal function in patients with chronic heart failure. J Am Coll Cardiol 50:1561–1569
35. Weiss G, Goodnough LT (2005) Anemia of chronic disease. N Engl J Med 352(10):1011–1023
36. Phan TT, Abozguia K, Nallur Shivu G, Mahadevan G, Ahmed I, Williams L, Dwivedi G, Patel K, Steendijk P, Ashrafian H, Henning A, Frenneaux M (2009) Heart failure with preserved ejection fraction is characterized by dynamic impairment of active relaxation and contraction of the left ventricle on exercise

and associated with myocardial energy deficiency. J Am Coll Cardiol 54:402–409
37. Anker SD, Colet JC, Filippatos G et al (2009) Rationale and design of Ferinject assessment in patients with IRon deficiency and chronic Heart Failure (FAIR-HF) study: a randomized, placebo-controlled study of intravenous iron supplementation in patients with and without anaemia. Eur J Heart Fail 11:1084–1091
38. van Veldhuisen DJ, Anker SD, Ponikowski P, Macdougall IC (2011) Anemia and iron deficiency in heart failure: mechanisms and therapeutic approaches. Nat Rev Cardiol 8:485–493