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/m²) were enrolled as part of SICA-HF in Germany, England and Slovenia. ID was defined as ferritin<100 µg/L 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-minute 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 sec, 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

Abbreviations list:

ANOVA: Analysis of variance.

ATP: Adenosine triphosphate.

BMI: Body mass index.

CPX: Cardiopulmonary exercise test.

DEXA: Dual Energy X-ray Absorptiometry.

HB: Haemoglobin.

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-minute 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 multi-center observational study into the prevalence, incidence and impact of key co-morbidities in out-patients 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 comittes.[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'≤ 8 [n=29], group B: average E/e'9-14 [n=124], group C: average E/e'≥15 [n=37]). 27,28

Clinical assessments

Iron deficiency (ID) was defined as ferritin <100 µg /L 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-minute 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%). Figures 1a and 1b. ID was more common in patients with more severe diastolic dysfunction: (prevalence according to group E/e'≤8: 44.8% *vs.* E/e': 9-14: 53.2% vs. E/e'≥15: 86.5%, p=0.0004) figure 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 sec, 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). Figure 3. These patients showed a trend towards lower QoL using EQ5D assessment (16369±5280 vs. 18171±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). Figure 4. Patients with low ferritin - ID compared to those without ID had worse diastolic function measured by E/e' (11±4 vs. 14±6, p=0.0004) and worse QoL estimated with EQ5D (16396±5280 vs. 18525±4816, p=0.03). Figure 6.

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). Figure 5. 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)].

Analysing 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. 3.3, p=0.007) and reduced QoL measured by EQ5D (18903 vs. 16489, 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 or insufficient oxygen supply and impaired oxygen use by 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; further, 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 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.

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.

Competing interests

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.

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Figures:

Figure 1: a: Prevalence of Iron deficiency both with Ferritin <100ug/l and ferritin between 100-299 ug/l with TSAT <20% in patients with HFpEF. b: Prevalence of both ID and anemia in patients with HFpEF.

Figure 2: Prevalence of ID in groups with different severities of HFpEF.

Figure 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 and d:** Muscle strength/muscle mass in both legs (mean values) in patients with and without Iron Deficiency.

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

Figure 5: a: Simple regression analysis of ferritin and peak VO_2. **b:** Simple regression analysis of transferrin saturation % and pulmonary artery pressure.

Figure 6: 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.

Tables: 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/m²)*	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) (meter)	377.5±134.5	420.7±123.8	344.0±123.8	0.008
Exercise time (50 patients) (sec)	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.

Table 2: Baseline characteristics of HFpEF patients

Variable	Group A E/e' ≤8 n=29	Group B E/e' 9-14 n=124	Group C E/e' ≥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 right hand (kg)	43.3±10.7	34.0±11.3	23.5±5.3	0.0009
Quadriceps strength 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.

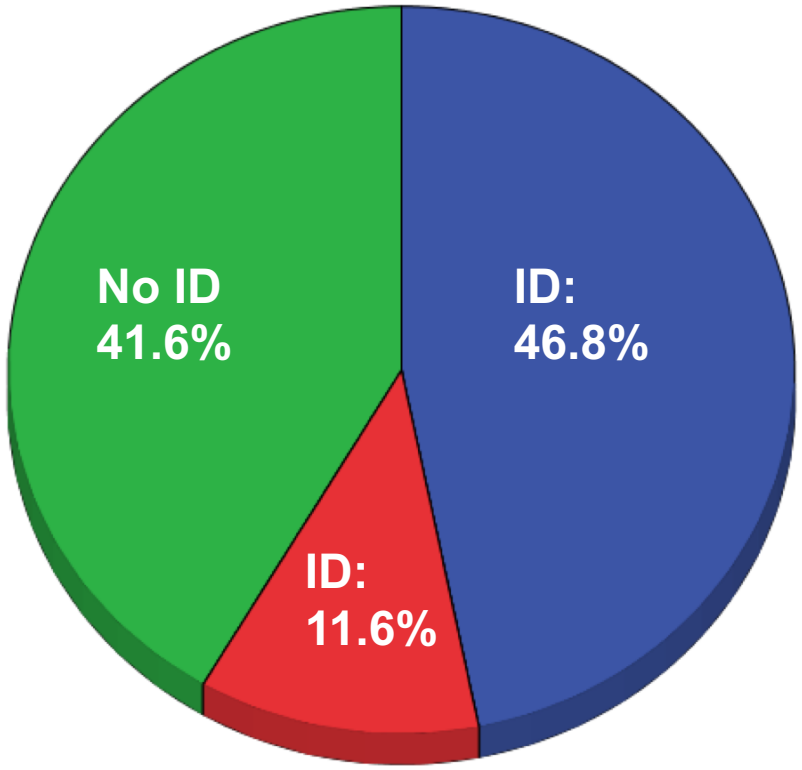

Figure 1a

ID: Ferritin <100 ug/l

ID: Ferritin 100-299 ug/l
and TSAT <20%

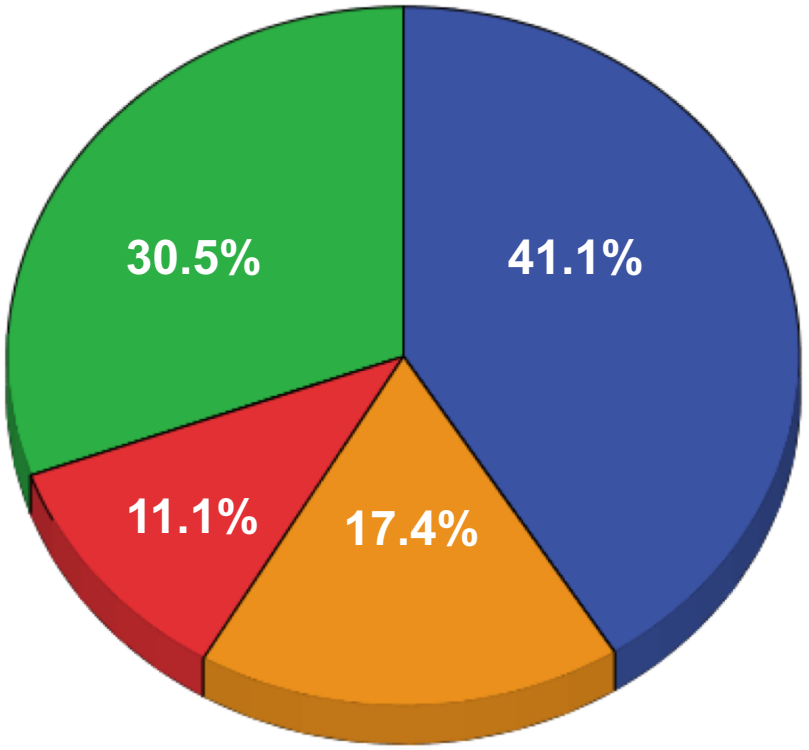

Figure 1b

No ID, no anemia

ID only

ID and anemia

Anemia only

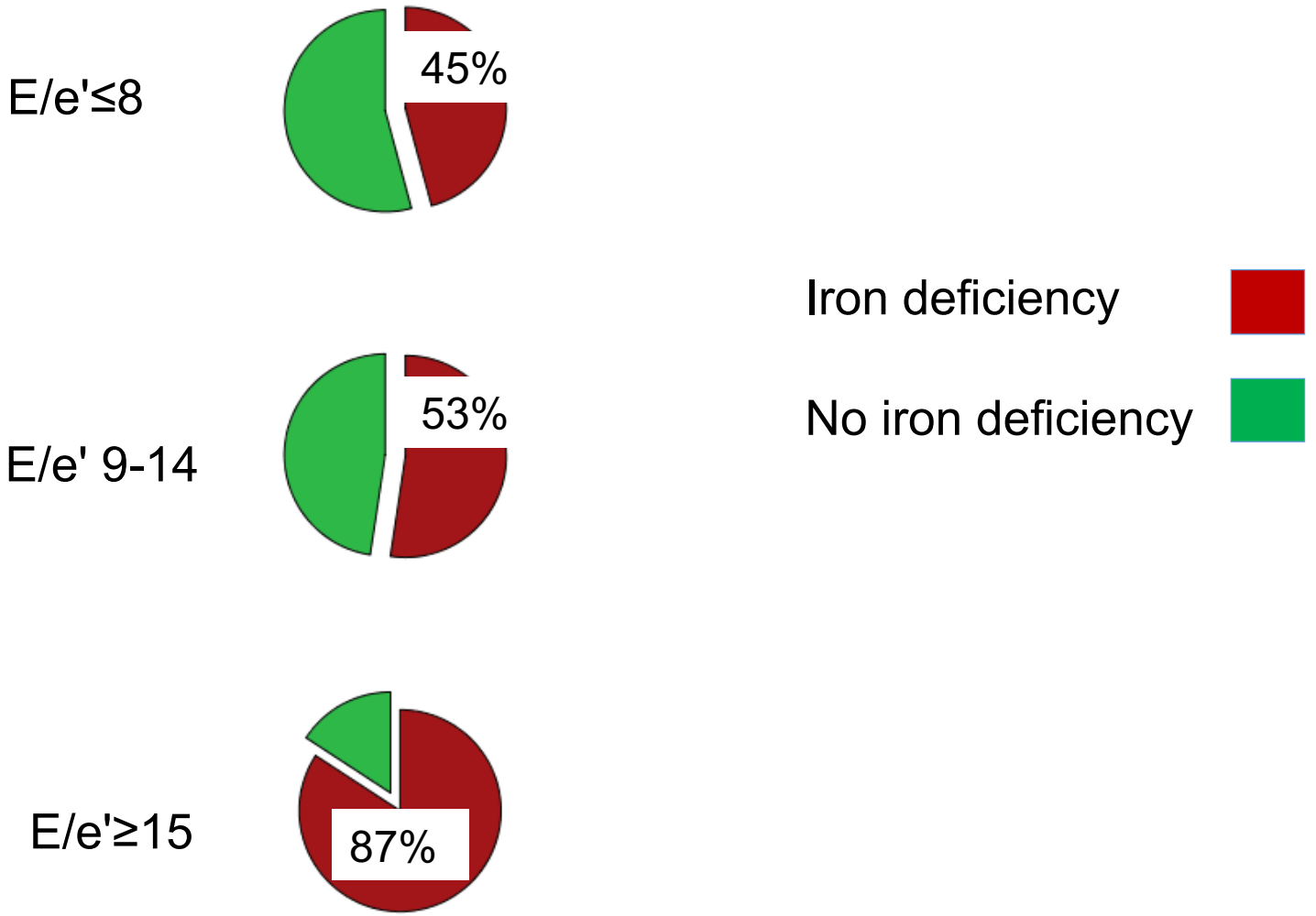

Figure 2

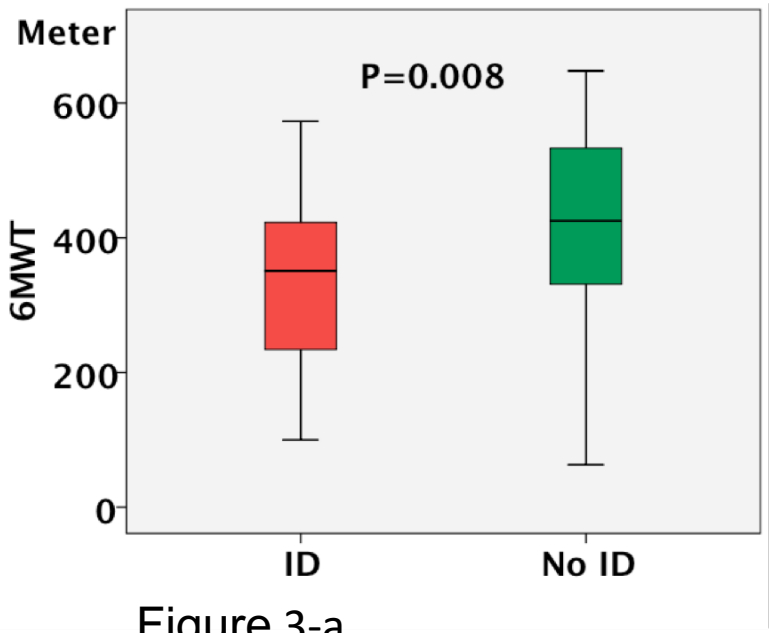

Figure 3-a

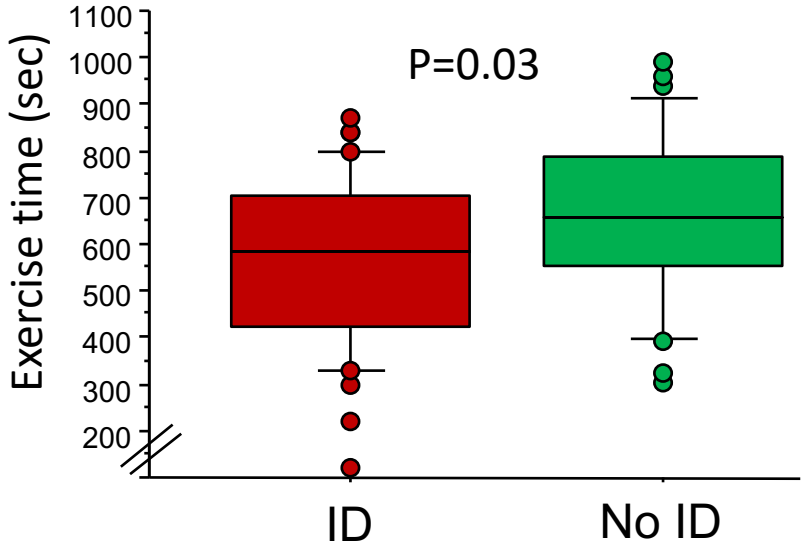

Figure 3-b

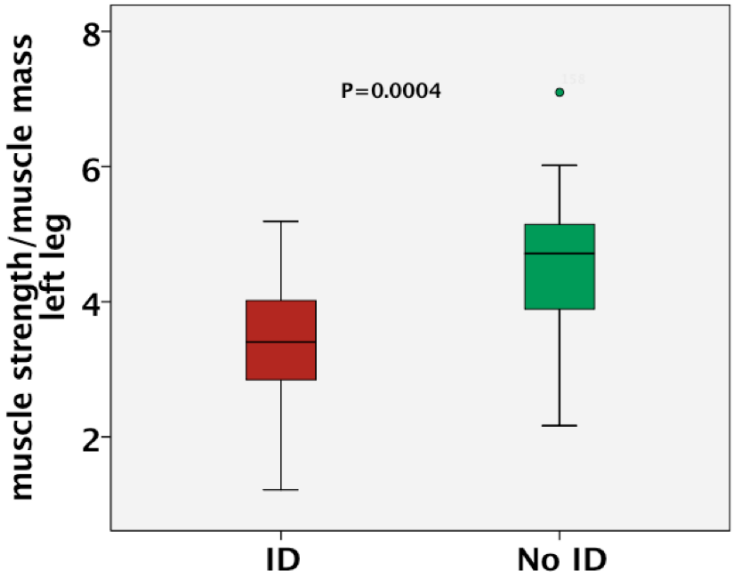

Figure 3-c

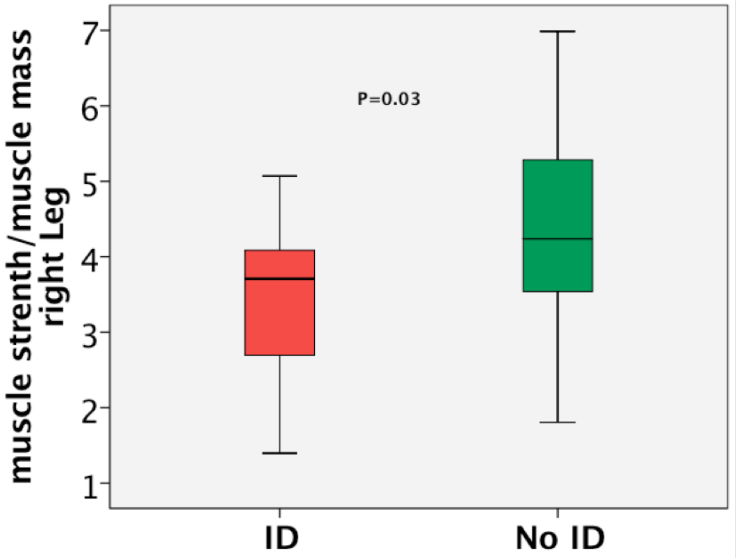

Figure 3-d

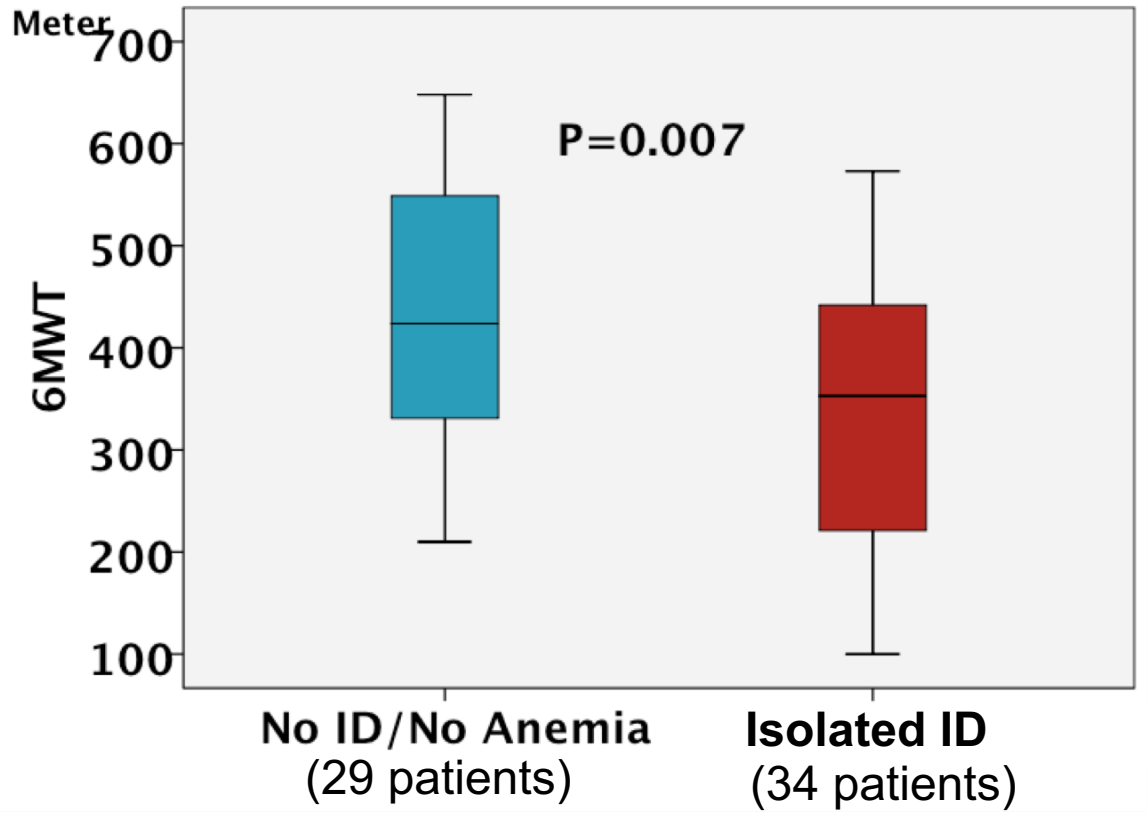

Figure 4

Isolated ID: ID only without anemia.

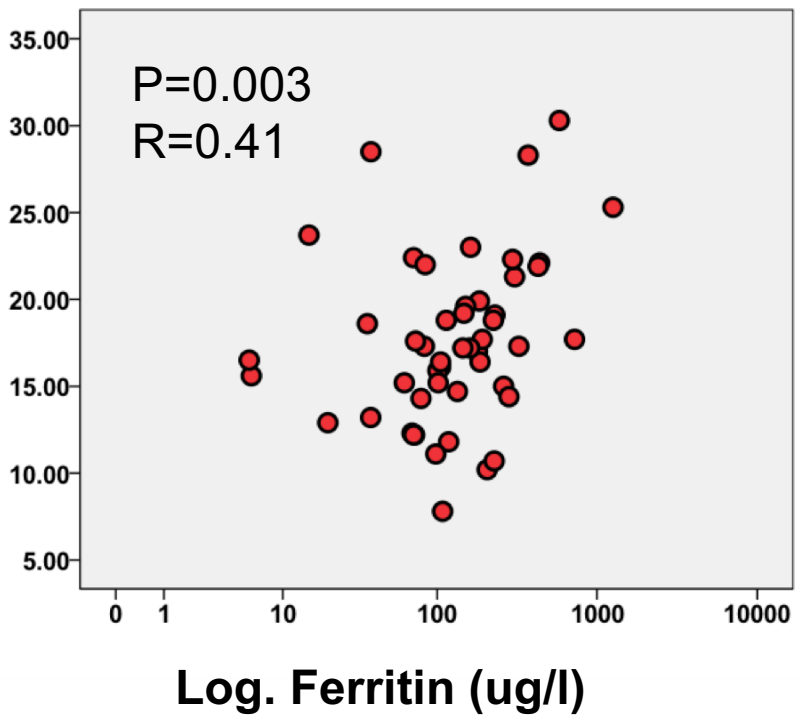

Figure 5a

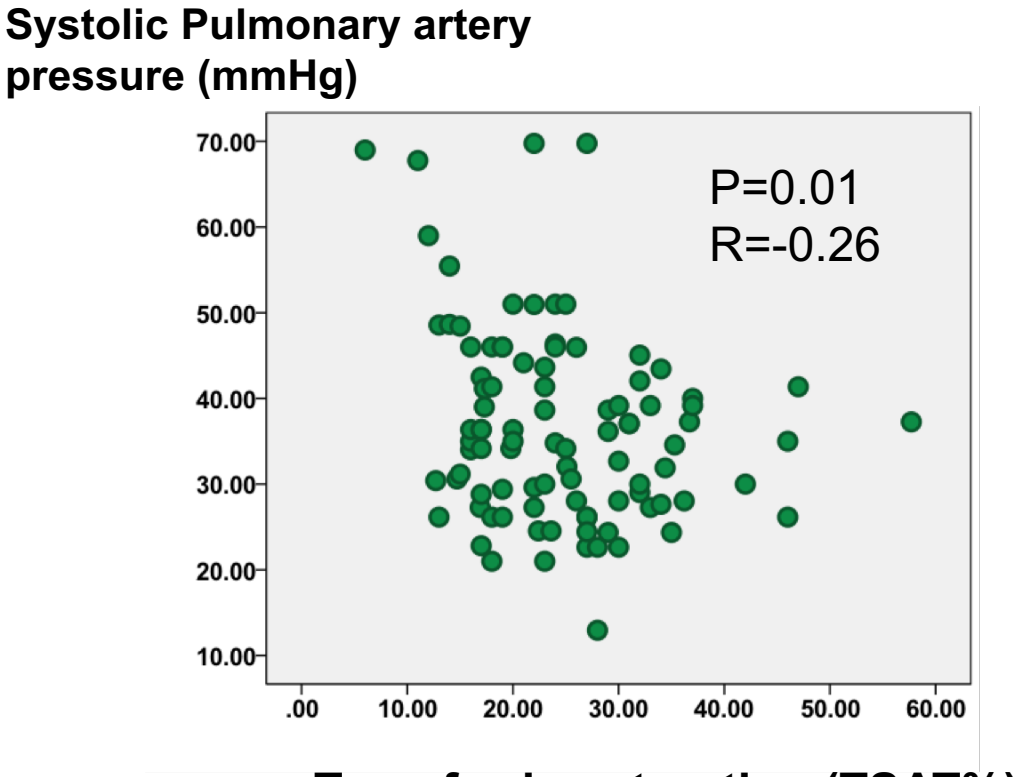

Figure 5b

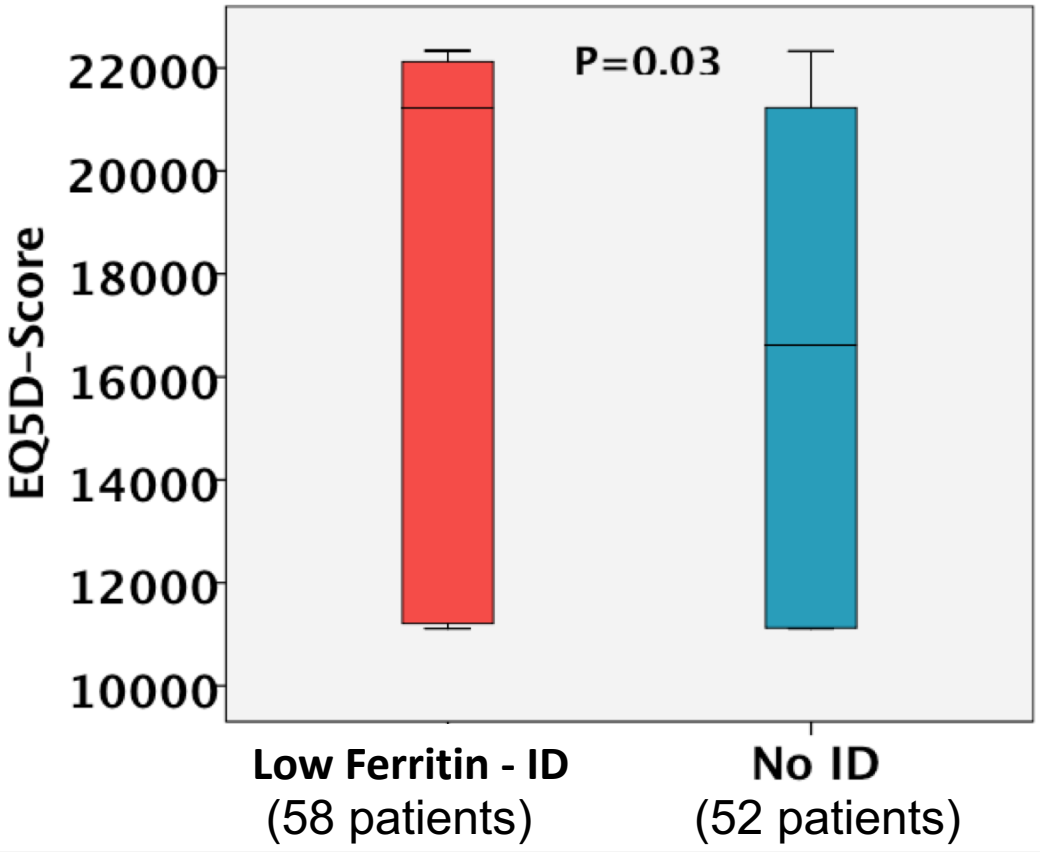

Figure 6-a

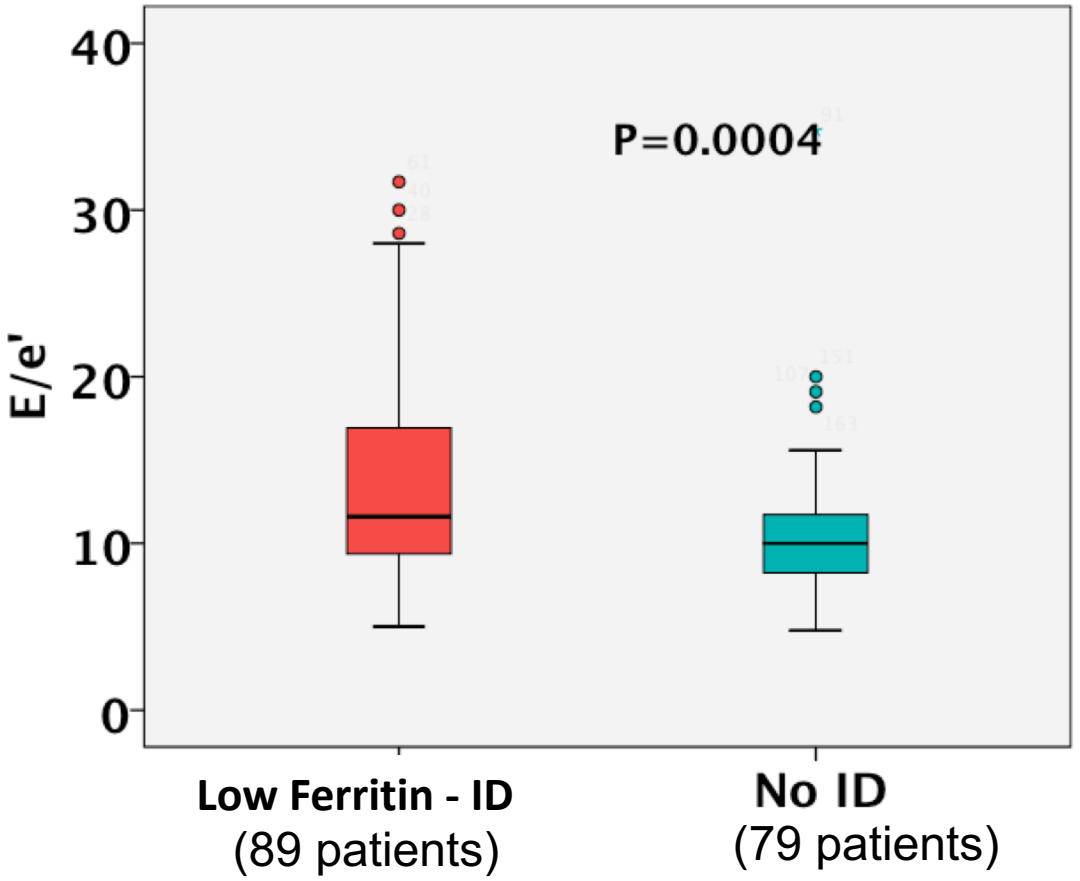

Figure 6-b

Low ferritin ID: Ferritin <100ug/l