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Exercise training response according to baseline ferrokinetics in heart failure with preserved ejection fraction: A substudy of the TRAINING-HF trial

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Abstract

Background Iron deficiency (ID) is associated with impaired functional capacity in patients with heart failure (HF), even in those with preserved ejection fraction (HFpEF). This study aimed to evaluate the effect of baseline ferrokinetics on peak oxygen consumption (peakVO_2) improvement after a 12-week physical therapy programme in patients with stable HFpEF.

Methods This study is a post-hoc sub-analysis of a randomized clinical trial in which 59 stable patients with HFpEF were randomized to receive a 12-week programme of inspiratory muscle training (IMT), functional electrical stimulation (FES), IMT + FES or usual care (UC) to evaluate change in peakVO_2 (NCT02638961). Serum ferritin and transferrin saturation (TSAT) determinations were assessed at baseline. ID was defined as ferritin <100 ng/mL and/or TSAT <20% if ferritin was within 100–299 ng/mL. We used a linear mixed regression model to analyse between-treatment changes in peakVO_2 across ferrokinetics status at 12 and 24 weeks.

Results The mean age was 74 ± 9 years, and 36 (61%) had ID. The mean of peakVO_2 was 9.9 ± 2.5 mL/kg/min. The median of ferritin and transferrin saturation (TSAT) was 91 (50–181) ng/mL and 23% (16–30), respectively. A total of 52 patients completed the trial (13 patients per arm). Compared with those patients on UC, patients allocated to any of the active arms showed less improvement in peak VO_2 when they showed ID (*P*-value for interaction <0.001), lower values of ferritin (*P*-value for interaction <0.001), or TSAT (*P*-value for interaction <0.001).

Conclusions Ferrokinetics status plays an essential role in modifying the aerobic capacity response to physical therapies in patients with HFpEF. Further studies are required to confirm these findings.

Keywords Aerobic capacity; Heart failure with preserved ejection fraction; Iron deficiency; peakVO_2; Physical therapies

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Introduction

In heart failure (HF), iron deficiency (ID) is a highly prevalent and multifactorial condition,[1–10] and it is associated with impaired functional capacity[6,8,9,11] and poor prognosis[3,5,10] irrespective of left ventricular ejection fraction (LVEF). Although intravenous iron replacement in patients with HF with reduced ejection fraction (HFrEF) resulted in exercise capacity and quality of life improvement and risk hospitalization for worsening HF reduction,[12–14] there is limited and

inconclusive evidence regarding the effects of iron replacement in patients with preserved ejection fraction (HFpEF).[15]

Less is known about the influence of baseline ferrokinetics status on response to exercise-based cardiac rehabilitation (EBCR) programmes where iron homeostasis and stores are essential for adequate oxygen availability and myocardial and skeletal muscle function.[16] Accordingly, this study aimed to evaluate the influence of the baseline ferrokinetics status on responsiveness to a 12-week inspiratory muscle training (IMT), functional electrical stimulation (FES), or IMT + FES programme over usual care (UC) on maximal functional capacity in patients with stable HFpEF included in the TRAINING-HF open-label randomized clinical trial.[17] Additionally, we assessed the inspiratory muscle strength response to IMT across ferrokinetics.

Methods

Study design

This is a post-hoc subanalysis of the TRAINING-HF trial, whose study protocol, rationale, design and primary outcomes were registered (http://clinicaltrials.gov, NCT02638961) and published previously.[17,18] The TRAINING-HF was an open-label randomized controlled trial assessing the effect of a 12-week programme of three physical therapy interventions (IMT, FES, or IMT + FES) over UC on peakVO_2 at 3-month and 6-month. This study was conducted at Hospital Clínic Universitari de València from September 2015 to December 2016. The inclusion criteria were (a) New York Heart Association functional class ≥II); (b) left ventricular ejection fraction >50% by Simpson method and end-diastolic diameter <60 mm; (c) structural heart disease (left ventricle hypertrophy/left atrial enlargement) and/or diastolic dysfunction estimated by two-dimensional echocardiography according to the 2012 European Society of Cardiology (ESC) Guidelines[19]; and (d) clinical stability, without HF decompensations in the past 3 months.

All patients provided informed consent, and the local research ethics committee approved the protocol following the principles of the Declaration of Helsinki and national regulations.

Training intervention

Participants were allocated to one of four study arms in the TRAINING-HF trial. The UC arm served as the control arm and did not receive physical therapy. In contrast, the IMT arm participated in a 12-week home-based programme focusing on enhancing inspiratory muscle strength, with weekly monitoring by a physiotherapist. The FES arm engaged in leg muscle training sessions involving functional electrical stimulation, conducted twice a week. Lastly, the IMT + FES arm underwent a combined intervention, concurrently targeting inspiratory and leg muscle function. All patients underwent regular maximal inspiratory pressure (MIP) assessments during each visit.

Laboratory analysis and iron deficiency definitions

Serum ferritin and transferrin saturation (TSAT) were evaluated at the initial visit. An immunoturbidimetric assay measured serum ferritin. Colourimetric methods were used to measure serum iron concentration and unsaturated iron-binding capacity (UIBC). The total iron-binding capacity (TIBC) was indirectly determined using serum iron concentration and UIBC. TSAT was calculated by dividing the serum iron concentration by the TIBC and multiplying it by 100. According to the European Society of Cardiology (ESC), ID was defined as ferritin <100 ng/mL (absolute ID) and/or TSAT <20% if ferritin was within 100–299 ng/mL (functional ID).

Haemoglobin concentration was measured at the initial visit by fluorescent flow cytometry. Anaemia was defined as a haemoglobin level of <12 g/dL in women and <13 g/dL in men, according to the World Health Organization (WHO) definition.[20]

Cardiopulmonary exercise testing

Maximal functional capacity was evaluated with incremental and symptom-limited cardiopulmonary exercise testing (CPET) on a bicycle ergometer, beginning with a workload of 10 W and gradually increasing in a ramp protocol of 10 W increments every 1 minute. We defined maximal functional capacity as the point when the patient stopped pedalling because of symptoms, and the respiratory exchange ratio (RER) was ≥1.[21]

Statistical analysis

Continuous variables are expressed as means (±1 SD) or medians (p25–p75) and discrete ones as percentages. Baseline variables were compared among treatment groups with unpaired t-test, Wilcoxon rank sum test, or chi-square test as appropriate. Due to a significant departure from a normal distribution, ferritin and TSAT were transformed to their natural logarithms (ln).

We used a linear mixed regression model (LMRM) to analyse between-treatment changes in peakVO_2. Visits at 3 and 6-month periods were the model's time variable. Baseline age, sex, haemoglobin, body mass index and the interaction between treatment and visits were included as covariates; due to ANCOVA design, the baseline values of the longitudinal endpoint—peakVO_2 at baseline—were also included as

a covariate. A similar approach was used for evaluating the association between ferrokinetics and response to active strategies regarding inspiratory muscle strength. For the markers' stratified analyses, we create a triple interaction that includes the treatment variable, the trial visits, and the markers' baseline variable. The decision between raw or logarithm-transformed variables was based on the model's AIC criteria. LMRM results are presented as least square means with 95% confidence intervals (CIs) and *P*-values.

All analyses were performed with STATA 17.0 [StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.].

Results

A total of 59 patients were randomly allocated to one of the four study arms. The mean age was 74 ± 9 years, and 43 (58%) were women. Most patients showed ischemic aetiology (62.3%). The mean of LVEF was 67 ± 10%, and the median of NT-proBNP was 912 (302–1826). The mean value of haemoglobin was 12.9 ± 1.5 g/dL, and the medians of ferritin and TSAT were 91 ng/mL (50 to 181), and 23% (16 to 30), respectively. The mean peakVO_2 at baseline was 9.9 ± 2.5 mL/kg/min, and most participants were on stable NYHA class II (69.5%). The rate of patients with ID and anaemia was 36 (61%) and 24 (40.7%), respectively. There were no significant baseline differences across treatment arms,[17] including body mass index [UC: 32.9 kg/m2 (30.4–38.8) vs. IMT: 32.2 (28.6–33.6) vs. FES: 31.2 (29.1–35.0) vs. IMT + FES: 31.7 (29.3–38.0), $p = 0.502$].

Baseline characteristics across ID are presented in Table 1. ID patients were older and showed higher heart rates and lower peakVO_2. We did not find differences in ischemic aetiology, echocardiographic parameters, medical treatment, or chronotropic response to exercise.

A total of 52 patients completed the study and performed a maximal CPET (RER $\geq$ 1) at baseline, 3 and 6-month.

Baseline ferrokinetic status and changes in peakVO_2 following physical therapies

Compared with patients on UC, we found a differential effect on peakVO_2 across different proxies of ID in the three active arms.

Baseline ferritin

Figure 1 shows the between-treatment differences in 3 and 6-month peakVO_2 along the continuum of ferritin at baseline. The *P*-value for the between-treatment effect was highly significant (omnibus *P*-value for interaction <0.001), showing a stepwise increase in peakVO_2 when moving from lower to higher values of ferritin (Figure 1) in the three active arms, more evident in those allocated to FES.

Baseline transferrin saturation

Between-treatment effect on 3 and 6-month peakVO_2 also showed a differential effect along the continuum of TSAT at baseline (omnibus *P*-value for interaction<0.001). Compared with UC, those on physical therapies showed a significantly greater improvement in peakVO_2 in those with higher values of baseline TSAT (Figure 2).

Iron deficiency (European Society of Cardiology definition)

Compared with those on UC, patients allocated to any active arms showed a less increase in peakVO_2 if they showed ID at baseline (between-treatment omnibus *P*-value<0.001), as shown in Figure 3. Overall, the magnitude of this improvement was stronger at the 3-month visit (time-dependent *P*-value<0.001).

Functional response to physical therapies: The role of anaemia and iron deficiency

Patients with anaemia had less functional improvement when compared with those without anaemia at baseline (Figure S1). By combining baseline anaemia and ID into three categories [1: anaemia and ID ($n = 14$), 2. ID without anaemia or ID ($n = 28$), and 3: no anaemia and no ID ($n = 10$)], we found a greater improvement in peakVO2 in response to physical therapies when moving from 1 to 3 categories (between treatment omnibus *P*-value<0.001). Thus, we found a greater functional improvement following physical therapies in those patients without ID and no anaemia (Figure 4). In contrast, the worse response was found in those with ID and anaemia, (Figure 4). This effect was stronger at a 3-month visit (time-dependent interaction *P*-value = 0.027).

Inspiratory muscle strength response across iron deficiency

Between-treatment comparisons revealed a greater inspiratory muscle response to training in those patients without ID. However, the improvement was blunted in those with ID (Figure 5).

Discussion

To our knowledge, this post-hoc substudy of TRAINING-HF is the first study that evaluated the effect of ID on maximal functional capacity response to physical therapies in a subset of patients with HFpEF. We found that baseline ferrokinetic was associated with maximal aerobic capacity response to

Table 1 Baseline characteristics of the patients stratified by ferrokinetics status

Variables	All patients	No ID	ID	*P*-value
n (%)	59 (100)	23 (40)	36 (61)	
Demographic and medical history				
Age, years	74 ± 9	71 ± 11	75 ± 8	0.048
Women, *n* (%)	34 (58)	10 (43.5)	24 (66.7)	0.079
Caucasian race	52 (100)	26 (100)	26 (100)	1.000
Body mass index, kg/m^2	31.9 (29.2–35.4)	31.6 (29.9–35.3)	32.0 (28.9–35.7)	0.952
Previous admission for AHF, *n* (%)	52 (100)	26 (100)	26 (100)	1.000
Hypertension, *n* (%)	53 (89.8)	21 (91.3)	32 (88.9)	0.765
Diabetes mellitus, *n* (%)	26 (44)	12 (52.2)	14 (38.9)	0.316
Dyslipidaemia, *n* (%)	48 (81.4)	21 (91.3)	27 (75)	0.117
Current smoker, *n* (%)	4 (6.8)	1 (4.3)	3 (8.3)	0.553
Prior history of IHD, *n* (%)	19 (32.2)	9 (39.1)	10 (27.8)	0.363
Prior history of atrial fibrillation, *n* (%)	36 (61)	13 (56.5)	23 (63.9)	0.571
Clinical examination				
NYHA III/IV, *n* (%)	18 (30.5)	6 (26.1)	12 (33.3)	0.555
Rest heart rate, b.p.m.	70 ± 15	64 ± 9.7	73.9 ± 16	0.011
Systolic blood pressure, mmHg	128 ± 15	129 ± 17	127 ± 13	0.658
Diastolic blood pressure, mmHg	71 ± 9	69 ± 10	72 ± 8	0.290
Atrial fibrillation, *n* (%)	25 (42)	9 (40.9)	16 (44.4)	0.792
Echocardiographic parameters				
Left ventricular ejection fraction	67 ± 10	67.3 ± 9.9	66.6 ± 9.8	0.801
Left atrial volume index, mL/m^2	41 ± 14	42.3 ± 15	40.7 ± 12.8	0.665
Septal E/E' ratio	16.8 (12.5–23.6)	15.3 (12.3–20.5)	17.1 (13.8–25.5)	0.152
Laboratory values				
Haemoglobin, g/dL	12.9 ± 1.5	13.1 ± 1.9	12.7 ± 1.1	0.370
Ferritin, pg/mL	91 (50–181)	180 (129–441)	54 (31–81)	<0.001
TSAT, %	23 (16–30)	29.9 (26–38)	18 (13.6–22.7)	<0.001
Anaemia, *n* (%)	24 (40.7)	10 (43.5)	14 (38.9)	0.726
NT-proBNP, pg/mL	912 (302–1826)	998 (515–1,583)	833(290–2,194)	0.309
Cardiopulmonary exercise testing and quality of life variables				
peakVO_2, mL/kg/min	9.9 ± 2.5	10.8 ± 2.8	9.4 ± 2.1	0.036
VE/VCO_2 slope	37 (34–42)	37 (35–39.5)	36.1 (33.2–41.8)	0.624
Heart rate at exercise peak, b.p.m.	92 ± 18	87 ± 14	96 ± 19	0.062
Chronotropic index	0.29 (0.19–0.38)	0.25 (0.18–0.33)	0.32 (0.21–0.39)	0.187
MLHFQ	42 (24–54)	34 (25–57)	44 (24–54)	0.678
Treatment				
Loop diuretics, *n* (%)	51 (86.4)	19 (82.6)	32 (88.9)	0.496
RAASi, *n* (%)	37 (62.7)	14 (60.9)	23 (63.9)	0.815
Beta-blockers, *n* (%)	50 (84.7)	19 (82.6)	31 (86.1)	0.715
MRA, *n* (%)	20 (33.9)	11 (47.8)	9 (25)	0.072

Continuous variables are presented as median (interquartile range), categorical variables as percentages.
AHF, acute heart failure; IHD, ischaemic heart disease; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association functional class; NT-proBNP, N-terminal pro B-type natriuretic peptide; peakVO_2, peak oxygen uptake; RAASi, renin-angiotensin-aldosterone system inhibitors; TSAT, transferrin saturation; VE/VCO_2 slope, ventilatory efficiency.

exercise training by showing that patients with surrogates of ID showed lower improvement in aerobic capacity in response to physical therapies. In the present work, all the estimates were adjusted by important potential confounders, including the effect of haemoglobin. The association between ferrokinetic status and functional response to therapy was greater at 3 months, a fact that may be attributable to the restriction of physical intervention to a period of 3-month.

Ferrokinetic and functional status in heart failure with preserved ejection fraction

Iron is an essential element in the body and is crucial in several physiological pathways for proper oxygen transport, delivery, and utilization to cardiac and musculoskeletal striated muscle cells.[1,22] Accordingly, a prior study showed that in subjects with unexplained dyspnea, ID was associated with lower functional capacity, peripheral oxygen extraction, and biventricular contractile reserve.[23] Furthermore, regarding patients with HFpEF, previous observational studies[6,8,9] using cross-sectional approaches have found that ID was consistently associated with reduced exercise capacity.

While ID has shown a negative effect on functional capacity in patients with HF, previous randomized studies demonstrated that intravenous iron replacement improved functional capacity in HFrEF.[12,13] However, little is known about the effect of ID on the response to physical therapies in HF. This is the first study suggesting lower ferritin and TSAT may help to identify those symptomatic HFpEF patients without a relevant, beneficial response to physical therapies in terms of maximal functional capacity. These findings should

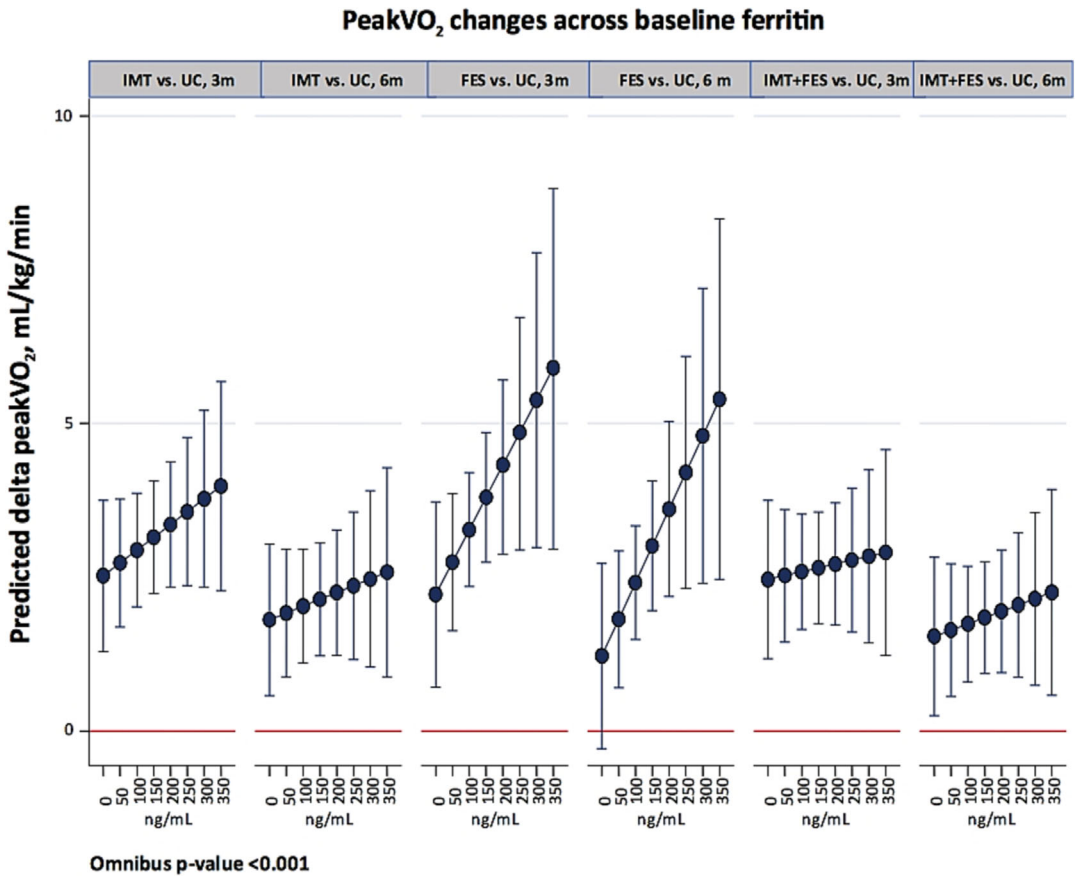

Figure 1 PeakVO_2 changes across baseline ferritin. FES, functional electrical stimulation; ID, iron deficiency; IMT, inspiratory muscle training; peakVO_2, peak oxygen consumption.

be replicated in larger studies and, more importantly, evaluate whether iron replacement may improve functional response to exercise or other physical therapies in symptomatic HFpEF. Along this line of thought, current trials evaluating intravenous iron replacement's impact on functional capacity in HFpEF are ongoing (NCT03074591 and NCT03833336).

Mechanisms behind iron status and response to physical therapies in heart failure

Data endorsing the clinical role of ID in peripheral muscle efficiency following exercise in HF is scarce. Skeletal and respiratory muscle dysfunction is a common pathophysiological finding in HF, contributing to the progression of the disease.[24] In experimental studies, ID is associated with skeletal and respiratory myopathy.[16,24] The histomorphological changes observed in the patient with HF include fibre atrophy, fatty infiltration, and changes in fibre composition with an increased number of type II fibres (anaerobic) over Type I fibres (aerobic).[25] Along this same line, a study conducted by Tkaczyszyn et al.[26] that enrolled 53 patients with HFrEF reported that inspiratory muscle weakness was more severe in those patients with ID.

From a mechanistic perspective, Melenovsky et al.[27] designed a study aiming to determine the impact of ID and the effects of short-term intravenous iron replacement in skeletal muscles bioenergetics of patients with HF by using 31-P magnetic resonance spectroscopy (an established non-invasive technique to evaluate muscle bioenergetic) of the calf muscle at rest and during exercise (in 44 patients with HF and 25 healthy volunteers). This study showed that the combination of HF and ID was associated with muscle myopathy by showing lower muscle strength, larger phosphocreatine depletion, and more intracellular acidosis with exercise. Furthermore, short-term intravenous iron replacement improved muscle strength without changes in muscle energy metabolism evaluated by magnetic resonance spectroscopy. In a more recent study, Charles-Edwards et al.[28] randomized 40 patients (50% anaemic) with chronic HF (50% with ischemic aetiology), NYHA class ≥II, LVEF ≤45%, and ID to receive a single sitting of iron isomaltoside or saline placebo. At 2-week after the intervention, those allocated to the active arm showed an improvement in phosphocreatine recovery half-time (−6.8 s [95% confidence interval 11.5–

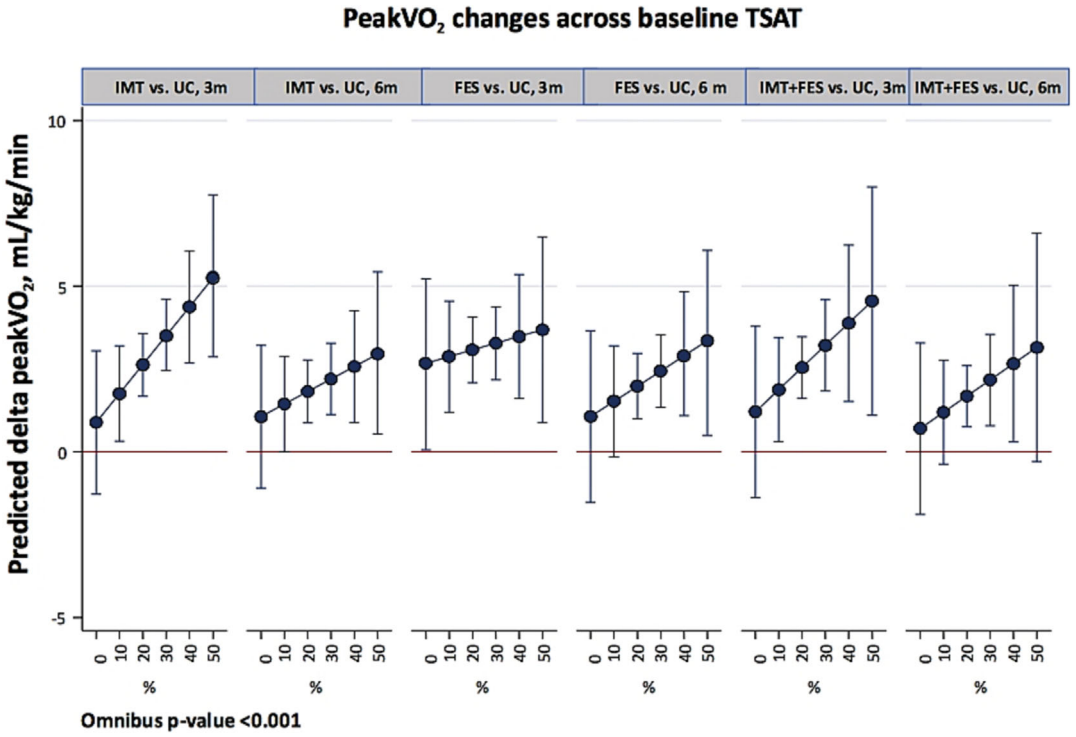

Figure 2 PeakVO$_2$ changes across baseline TSAT. FES, functional electrical stimulation; ID, iron deficiency; IMT, inspiratory muscle training; peakVO$_2$, peak oxygen consumption; TSAT, transferrin saturation.

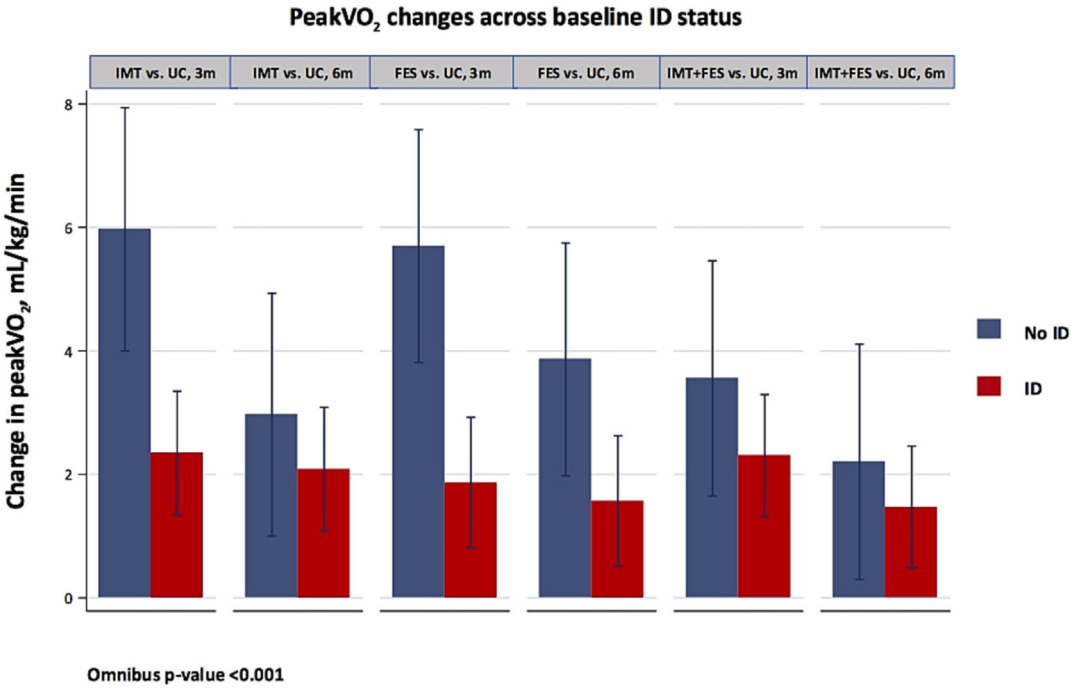

Figure 3 PeakVO$_2$ changes across baseline ID status. FES, functional electrical stimulation; ID, iron deficiency; IMT, inspiratory muscle training; peakVO$_2$, peak oxygen consumption.

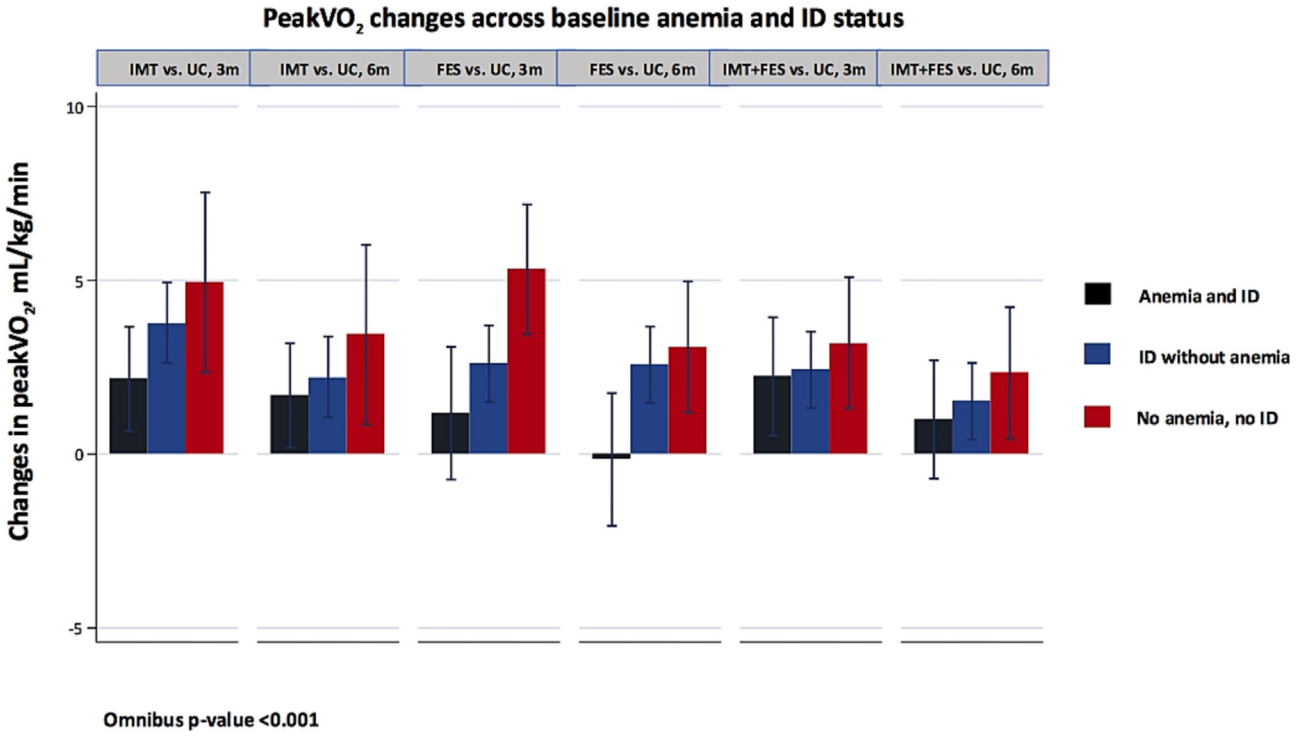

Figure 4 PeakVO_2 changes across baseline anaemia and ID status. FES, functional electrical stimulation; ID, iron deficiency; IMT, inspiratory muscle training; peakVO_2, peak oxygen consumption.

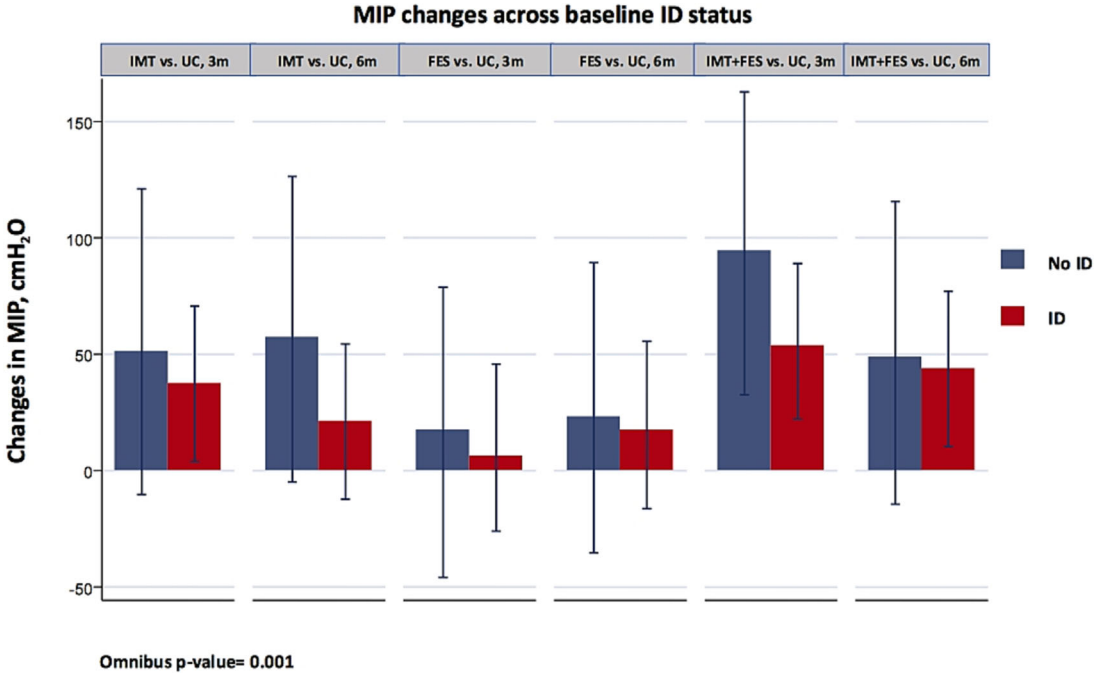

Figure 5 Inspiratory muscle strength response across ID. FES, functional electrical stimulation; ID, iron deficiency; IMT, inspiratory muscle training; MIP, maximal inspiratory strength.

2.1], P = 0.006) together with improvement in surrogates of HF severity such as Borg dyspnea score and NYHA class. The current work adds evidence in HFpEF corroborating the close relationship between inspiratory muscle function and maximal functional capacity response and ID status.

Clinical implications and future lines of research

Under the premise that our findings need further validation with prospective trials, we believe that our findings will help us to understand better the mechanisms underlying the heterogeneity of the HFpEF syndrome and support the need for further studies analysing the effect of iron replacement on aerobic capacity response to exercise in patients with HFpEF and ID.

Due to so many uncertainties in the diagnosis and management of HFpEF, future studies in this field should look into (a) a better understanding of the pathophysiological mechanisms of ID; (b) the impact of iron replacement on maximal aerobic capacity response; (c) the additive effect of iron replacement in predicting a better clinical response to exercise; (d) the role of HF aetiology in predicting response to iron replacement[29] and (e) define the clinical utility of intravenous iron replacement regarding major adverse outcomes. It is worth noting that current trials are evaluating intravenous iron replacement's impact on exercise capacity in HFpEF (NCT03074591 and NCT03833336).

Study limitations

Some limitations must be addressed. First, as a single-centre study, the generalizability of our results to other populations may be limited. Second, the current findings applied only to patients with symptomatic stable HFpEF. They cannot be extrapolated to other clinical scenarios or milder syndrome forms. Third, the current study did not evaluate nutritional and inflammatory status that may influence response to therapy. Finally, we acknowledge that this is a post-hoc analysis; the original TRAINING-HF study was not designed to evaluate the current hypothesis.

Conclusion

In this post hoc analysis of the TRAINING-HF trial on patients with symptomatic HFpEF, ID was associated with poorer aerobic capacity improvement after a 12-week programme of physical therapies. Further studies are needed to confirm these results and evaluate their clinical implications.

Conflict of interest

The authors have no conflict of interest to declare.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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