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CLINICAL RESEARCH | Clinical Trial

Effect of Intravenous Iron Sucrose on Exercise Tolerance in Anemic and Nonanemic Patients With Symptomatic Chronic Heart Failure and Iron Deficiency

FERRIC-HF: A Randomized, Controlled, Observer-Blinded Trial

Darlington O. Okonko, BSc, MRCP,* Agnieszka Grzeslo, MD,† Tomasz Witkowski, MD,† Amit K. J. Mandal, MRCP,‡ Robert M. Slater, MBBS,‡ Michael Roughton, MSc,* Gabor Foldes, MD, PhD,* Thomas Thum, MD,*§ Jacek Majda, MD,† Waldemar Banasiak, MD, PhD,† Constantinos G. Missouris, MD,‡ Philip A. Poole-Wilson, MD, FMedSci,* Stefan D. Anker, MD, PhD,*‖ Piotr Ponikowski, MD, PhD†

London and Slough, United Kingdom; Wroclaw, Poland; and Würzburg and Berlin, Germany

Objectives We tested the hypothesis that intravenous iron improves exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure (CHF) and iron deficiency.

Background Anemia is common in heart failure. Iron metabolism is disturbed, and administration of iron might improve both symptoms and exercise tolerance.

Methods We randomized 35 patients with CHF (age 64 ± 13 years, peak oxygen consumption [pVo_2] 14.0 ± 2.7 ml/kg/min) to 16 weeks of intravenous iron (200 mg weekly until ferritin >500 ng/ml, 200 mg monthly thereafter) or no treatment in a 2:1 ratio. Ferritin was required to be <100 ng/ml or ferritin 100 to 300 ng/ml with transferrin saturation <20%. Patients were stratified according to hemoglobin levels (<12.5 g/dl [anemic group] vs. 12.5 to 14.5 g/dl [nonanemic group]). The observer-blinded primary end point was the change in absolute pVo_2.

Results The difference (95% confidence interval [CI]) in the mean changes from baseline to end of study between the iron and control groups was 273 (151 to 396) ng/ml for ferritin ($p < 0.0001$), 0.1 (−0.8 to 0.9) g/dl for hemoglobin ($p = 0.9$), 96 (−12 to 205) ml/min for absolute pVo_2 ($p = 0.08$), 2.2 (0.5 to 4.0) ml/kg/min for pVo_2/kg ($p = 0.01$), 60 (−6 to 126) s for treadmill exercise duration ($p = 0.08$), −0.6 (−0.9 to −0.2) for New York Heart Association (NYHA) functional class ($p = 0.007$), and 1.7 (0.7 to 2.6) for patient global assessment ($p = 0.002$). In anemic patients ($n = 18$), the difference (95% CI) was 204 (31 to 378) ml/min for absolute pVo_2 ($p = 0.02$), and 3.9 (1.1 to 6.8) ml/kg/min for pVO_2/kg ($p = 0.01$). In nonanemic patients, NYHA functional class improved ($p = 0.06$). Adverse events were similar.

Conclusions Intravenous iron loading improved exercise capacity and symptoms in patients with CHF and evidence of abnormal iron metabolism. Benefits were more evident in anemic patients. (Effect of Intravenous Ferrous Sucrose on Exercise Capacity in Chronic Heart Failure; http://www.clinicaltrials.gov/ct/show/NCT00125996; NCT00125996) (J Am Coll Cardiol 2008;51:103–12) © 2008 by the American College of Cardiology Foundation

Exercise intolerance is a cardinal feature of chronic heart failure (CHF), related to a poor quality of life and a heightened risk of morbidity and mortality (1,2). Therapeutic options for increasing functional capacity are limited, and additional strategies are urgently required (3–6). A hallmark feature of exercise in CHF is the early onset of anaerobic metabolism

From *Clinical Cardiology, NHLI, Imperial College London, London, United Kingdom; †Cardiac Department, Military Hospital, Wroclaw, Poland; ‡Department of Cardiology, Wexham Park Hospital, Slough, United Kingdom; §Department of Cardiology, Julius-Maximilians University, Würzburg, Germany; and the ‖Division of Applied Cachexia Research, Department of Cardiology, Charité Campus Virchow-Klinikum, Berlin, Germany. Drs. Ponikowski and Anker contributed equally to this article. Drs. Okonko, Anker, Poole-Wilson, and Ponikowski designed and/or oversaw the study. Dr. Okonko drafted the study protocol, case report forms and manuscript. Drs. Okonko and Grzeslo monitored the trial. All authors were involved in data acquisition, data analysis, and review of the manuscript. Drs. Poole-Wilson and Okonko are supported by the British Heart Foundation, London, United Kingdom (FS/03/104/16341). Intravenous iron was supplied by Vifor International (St. Galen, Switzerland). An unrestricted grant was provided by Vifor International to Imperial College London. Drs. Ponikowski and Anker are consultants to Vifor International and have spoken at symposia. Dr. Poole-Wilson has attended Vifor advisory meetings.

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Abbreviations and Acronyms

CHF = chronic heart failure
Hb = hemoglobin
IV = intravenous
NYHA = New York Heart Association
TSAT = transferrin saturation
pVo_2 = peak oxygen consumption

as a consequence of impairments in skeletal muscle oxygenation and oxidative capacity that are unrelated to central hemodynamics (7,8). Targeting abnormalities that plausibly hinder oxygen transportation and/or utilization may confer functional benefits.

Iron is critical for oxidative metabolism, being an obligate component of hemoglobin (Hb; oxygen transport), myoglobin (oxygen storage), and the cytochromes and iron-sulphur proteins of the Krebs cycle and electron transport chain (oxidative phosphorylation) (9–13). Anemia due to iron deficiency impairs oxygen-carrying and tissue oxidative capacity, resulting in a diminished peak oxygen consumption (pVO_2) and ability to endure submaximal exertion (14–17). Even in the absence of anemia, iron deficiency can attenuate exercise performance (18,19). In both anemic and nonanemic iron-deficient but otherwise healthy cohorts, iron repletion has been shown to promptly correct functional deficits. The magnitude of benefit often exceeds the erythropoietic response (9,14–16,19,20).

Anemia is common in patients with CHF, but distinguishing iron-deficiency anemia (absolute iron deficiency) from the anemia of chronic disease (relative iron deficiency) is notoriously difficult (12,21–24). Nanas et al. (22) found that 73% of patients with advanced heart failure and anemia had depleted iron stores on bone marrow aspiration. In a recent observational study, Bolger et al. (25) reported that intravenous (IV) iron sucrose alone increased exercise capacity and reduced symptoms in CHF. Treatment with recombinant erythropoietin and adjuvant IV iron sucrose increases exercise capacity in patients with CHF and anemia (26,27).

We designed and undertook a randomized controlled trial (FERRIC-HF [Ferric Iron Sucrose in Heart Failure]) to test the hypothesis that iron repletion alone would improve exercise tolerance in anemic and nonanemic patients with symptomatic CHF and iron deficiency.

Methods

Study design. The FERRIC-HF trial was a prospective, randomized, open-label, observer-blinded, parallel, controlled trial conducted at 2 centers: Wexham Park Hospital, Slough, United Kingdom, and Fourth Clinical Military Hospital, Wroclaw, Poland. The study consisted of a 2-week initial assessment period and a 16-week treatment phase, with final assessments made 2 weeks later at week 18. The trial was performed in compliance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. The relevant ethics and research governance committees approved the protocol. Written informed consent was obtained from all patients before enrollment.

Study patients. Eligibility criteria were age ≥21 years; symptomatic CHF (New York Heart Association [NYHA] functional class II or III); exercise limitation as evidenced by a reproducible pVO_2/kg ≤18 ml/kg/min during screening; average of 2 screening Hb concentrations <12.5 g/dl (anemic group) or 12.5 to 14.5 g/dl (nonanemic group); ferritin <100 μg/l or between 100 g/l and 300 μg/l with a transferrin saturation (TSAT) <20%; left ventricular ejection fraction ≤45% measured within the preceding 6 months using echocardiography or magnetic resonance imaging; use of maximally tolerated doses of optimal CHF therapy for at least 4 weeks before recruitment and without dose changes for at least 2 weeks; resting blood pressure ≤160/100 mm Hg; and normal red cell folate and vitamin B_{12} (according to local laboratory reference ranges).

Exclusion criteria included the use of erythropoietin, iron (oral or IV), or blood transfusion within the previous 30 days; a history of acquired iron overload or hemochromatosis (or a first relative with hemochromatosis); earlier hypersensitivity to parental iron preparations or a history of allergic disorders; active infection, bleeding, malignancy, or hemolytic anemia; presence of any condition that precluded exercise testing, such as decompensated heart failure, significant musculoskeletal disease, unstable angina pectoris, obstructive cardiomyopathy, severe uncorrected valvular disease, or uncontrolled brady- or tachyarrhythmias; concurrent immunosuppressive or renal replacement therapy; and chronic liver disease (alanine transaminase >3 times the upper limit of the normal range).

Randomization. Qualifying patients were randomly assigned in a 2:1 ratio to receive 16 weeks of IV iron sucrose or to the control group. All patients continued to receive optimal conventional treatment for CHF. Computer-generated randomization was within each center, using random permuted blocks of 6 within each Hb strata. Patients were stratified according to Hb levels (<12.5 g/dl vs. 12.5 to 14.5 g/dl). Treatment allocation was concealed from the investigators involved in cardiopulmonary exercise testing and echocardiography.

Study drug and dosing schedule. Iron sucrose (Venofer; Vifor International, St. Gallen, Switzerland) was provided as a solution for IV infusion in 5-ml ampules (20 mg iron/ml). The treatment group received iron weekly (therapeutic phase) unless ferritin was ≥500 ng/ml and then at weeks 4, 8, 12 and 16 (maintenance phase). The total dose of iron was estimated as body weight (kg) × 2.4 × (15 − patients' Hb [g/dl]) + 500 mg (for stores) (25). Each dose was administered as 200-mg aliquots in 50 ml normal saline infused over 30 min. A test infusion (10 ml over 10 min) was performed before the first treatment. Patients were observed for drug reactions for up to 1 h after all visits. Blood pressures were monitored before and 15 and 30 min after the initiation of infusions.

Patient follow-up. All patients were scheduled to be seen at 1, 4, 8, 12, 16, and 18 weeks after randomization. At all visits, a clinical examination was undertaken and blood taken to measure Hb, urea, creatinine, alanine transaminase, C-reactive protein, serum iron, total iron binding capacity, ferritin, and transferrin. The TSAT was calculated (100 × serum iron/total iron-binding capacity). Iron therapy was withheld if ferritin was ≥500 ng/ml, or Hb was ≥16.0 g/dl, or TSAT was ≥45% at any stage. Treatment was reinstituted 2 weeks later if ferritin was <500 ng/ml, Hb was <16.0 g/dl, and TSAT was <45%. At baseline and end of study, levels of soluble transferrin receptor (Dade Behring, Marburg, Germany) and malondialdehyde (Pharmacia LKB, Freiburg, Germany), a marker of lipid peroxidation, were quantified (28). Patients were formally referred to a gastroenterologist who decided on the appropriateness of further diagnostic tests. Patients randomized to the control group were offered IV iron therapy at the end of the study if clinically appropriate.

End points. The primary end point for efficacy was the change in absolute pVO_2 (ml/min) from baseline to week 18. Prospectively defined secondary efficacy outcomes included changes from baseline to week 18 in pVO_2 (ml/kg/min) adjusted for body weight, exercise duration, Hb, ferritin, TSAT, soluble transferrin receptor, left ventricular ejection fraction, changes from baseline to week 8 to 18 in NYHA functional class, patient global assessment on a 7-point scale (4), Minnesota Living With Heart Failure Questionnaire (MLHFQ) score, and fatigue score (assessed using a 10-point visual analog fatigue scale, ranging from 1 for no fatigue to 10 for very severe fatigue) (20).

Exercise testing was performed on a treadmill using a modified Naughton or modified Bruce protocol depending on the physician's judgement (2,3). During screening, each patient underwent a minimum of 2 tests separated by a week. Ventilation, oxygen uptake, and carbon dioxide production were monitored on a breath-by-breath basis and averaged over 15-s intervals. Peak VO_2 (ml/min) was measured as an average of the last 15 s of exercise. Maximal exercise capacity was attained if the respiratory exchange ratio had reached >1.00 or had increased by a minimum of 0.15 from the resting value.

End points for tolerability included all adverse events, serious adverse events (including deaths and hospitalizations >24 h in duration), changes in mean arterial blood pressure at 15 and 30 min after IV iron infusion, episodes of anaphylaxis or symptomatic hypotension during IV iron infusion, episodes of hyperferritemia (>500 ng/ml), and changes in vital signs (systolic and diastolic blood pressure, heart rate), alanine transaminase, urea, creatinine, C-reactive protein and malondialdehyde from baseline to week 18. All serious adverse events were reported to an independent safety officer and the appropriate research governance committee within 24 h of occurrence.

Statistics. The statistical analyses were pre-specified and followed the intention-to-treat principal using the last observation carry-forward method for imputing missing data. Sample size estimates assumed an average baseline pVO_2/kg of 15 ml/kg/min, with a standard deviation (SD) of difference in pVO_2/kg of 2.0 ml/kg/min (4) and a desired treatment effect of 2.1 ml/kg/min. Adjusting for unequal sampling (2:1) and a 10% rate of attrition, we calculated that 36 patients (24 IV iron group, 12 control group) were needed (alpha = 0.05; beta = 83%).

The primary analysis was an unpaired comparison of the changes in absolute pVO_2 (ml/min) between the treatment arms using the Student *t* test. Paired changes from baseline to week 18 were assessed using paired *t* tests. Data are presented as mean ± SD. Summary statistics include the point estimates of week 18 pVO_2, the change from baseline to week 18, and the estimates and 2-sided 95% confidence intervals (CI) for the difference between least-squares means of the 2 treatment arms. All other continuous end points were analyzed in a similar fashion. Categoric variables were evaluated using a chi-square or Fisher exact test. The relations between variables were evaluated using Pearson correlation coefficient. Adjusted analyses were performed by analysis of covariance modeling including, where appropriate, interaction terms in the model. All statistical tests were 2 sided, and we judged a p value of <0.05 to be significant. All analyses were carried out using Stata 9.2 (Stata Corp., Dallas, Texas) and Statview 4.5 for Windows (Abacus Concepts, Berkeley, California).

Results

Patients and iron treatment. Between July 2004 and October 2005, we randomized 35 (14 British and 21 Polish) patients to IV iron (n = 24) or control (n = 11) (Fig. 1). Baseline characteristics were similar between groups (Table 1). In the control group, 8 were male and 3 female. In the group receiving IV iron, 17 were male and 7 female. Of the 18 classified as anemic, 11 were male and 7 female. In the nonanaemic group, 14 were male and 3 female.

Four treated patients (16%) terminated the study early because of death (n = 1) or withdrawal of consent (n = 3). One control patient (9%) withdrew consent early. Consequently, 14% of the data analyzed was imputed. Sensitivity analyses conducted without imputation for missing values yielded consistent results.

The mean weight at baseline in the control group was 84.3 ± 14.9 kg and in the treated group 75.9 ± 17.4 kg (p = 0.18). During the trial weight significantly increased by 2.7 kg in the control group and decreased by 1.8 kg in the treated group (p = 0.004) (Table 2).

The mean iron repletion dose was 928 ± 219 mg in the overall population, 1,051 ± 219 mg in anemic patients, and 781 ± 94 mg in nonanemic patients. The total dose of IV iron administered was 1,433 ± 365 mg in the overall population, 1,583 ± 366 mg in anemic patients, and 1,269 ± 297 mg in nonanemic patients.

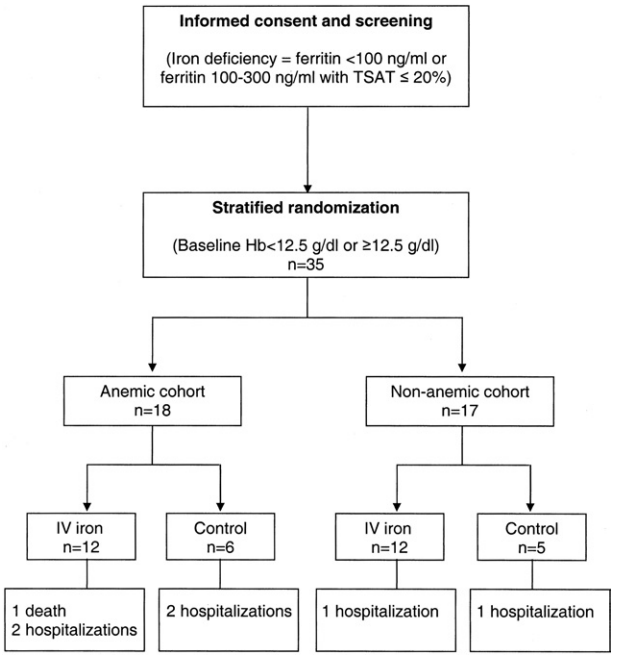

Figure 1 Trial Profile

Hb = hemoglobin; IV = intravenous; TSAT = transferrin saturation.

Effect of IV iron on iron status and hemoglobin. ALL PATIENTS. Ferritin and TSAT significantly increased only in the IV iron group (Table 2). Soluble transferrin receptor levels did not change significantly in either the control or the treated group. Iron therapy resulted in a significant treatment effect (95% CI) on ferritin (273 [151 to 396] ng/ml; $p < 0.001$), TSAT (11% [5% to 17%]; $p < 0.001$) and soluble transferrin receptor (−0.3 [−0.6 to −0.01] mg/l; $p = 0.046$). The Hb levels significantly increased from baseline in the iron group. The treatment effect (95% CI) was 0.1 [−0.8 to 0.9] g/dl ($p > 0.2$). Adjustment for center had no impact ($p > 0.50$) for all end points. Adjustment for center and Hb strata together did not alter the results ($p > 0.12$ for all interactions).

ANEMIC AND NONANEMIC SUBGROUPS. In anemic and nonanemic patients, ferritin and TSAT significantly increased in the iron group and remained unchanged in the control group (Table 3). There were no changes in Hb or soluble transferrin receptor levels in either of the subgroups.

Effect of IV iron on exercise tolerance. ALL PATIENTS. In patients receiving IV iron there was a trend toward an improvement in exercise tolerance as measured by absolute pVo_2 ($p = 0.08$) (Table 2). The mean treatment effect (95% CI) from baseline to week 18 between the iron and control groups was 96 [−12 to 205] ml/kg. Absolute pVo_2 significantly increased in the iron group and remained unchanged in the control group (Fig. 2A).

Similarly, pVo_2/kg (Fig. 2B) and exercise duration increased in the iron group and remained unchanged in the control group. The treatment effect (95% CI) was significant for pVo_2/kg (2.2 [0.5 to 4.0] ml/kg/min; $p = 0.01$). There was a trend toward an improvement in absolute exercise duration (60 [95% CI −6 to 126] s; $p = 0.08$) and the percentage change in exercise duration from baseline (17% [95% CI −3% to 36%]; $p = 0.09$) was shown. Caution is needed in interpreting exercise duration data, because 2 different exercise protocols were used as appropriate. Post-exercise respiratory exchange ratios were similar in treated and control patients (1.10 ± 0.16 vs. 1.04 ± 0.12; $p = 0.26$).

Significant interactions between treatment allocation and Hb strata (all $p < 0.03$), but not center (all $p > 0.50$), were evident for pVo_2 and pVo_2/kg. Adjustment for Hb strata and center together did not alter exercise duration findings ($p > 0.55$ for all interactions).

Changes in pVo_2 did not relate to changes in Hb (Fig. 3A) but to increases in TSAT in iron-treated ($r = 0.45$; $p = 0.03$) but not control ($r = 0.04$; $p = 0.90$) patients (Fig. 3B).

ANEMIC AND NONANEMIC SUBGROUPS. Iron significantly improved absolute pVo_2 (204 [95% CI 31 to 378] ml/min; $p = 0.02$) and pVo_2/kg (3.9 [95% CI 1.1 to 6.8] ml/kg/min; $p = 0.009$) in anemic but not in nonanemic patients (Table 3). Adjustment for baseline pVo_2 or pVo_2/kg did not alter the results ($p > 0.44$ for all interactions). Iron had no significant effects on exercise duration in either of these subgroups. Changes in pVo_2 were related to changes in TSAT (but not Hb) in anemic patients ($n = 18$; $r = 0.62$; $p = 0.006$).

Table 1 Baseline Characteristics

	Control (n = 11)	IV Iron (n = 24)
Demographics and clinical, n (%)		
Age (yrs), mean ± SD	62 ± 11	64 ± 14
Male gender	8 (73)	17 (71)
Caucasian race	10 (91)	21 (88)
Body mass index (kg/m^2)	28 ± 5	26 ± 5
Ischemic etiology	8 (73)	18 (75)
NYHA functional class		
II	6 (55)	13 (54)
III	5 (45)	11 (46)
Comorbidities		
Coronary artery disease	8 (73)	19 (79)
Hypertension	5 (45)	12 (50)
Diabetes	4 (36)	8 (33)
Hyperlipidemia	5 (45)	7 (29)
Treatment		
Diuretics	8 (73)	17 (71)
ACE inhibitors	8 (73)	18 (75)
Angiotensin II antagonists	2 (18)	5 (21)
Beta-blockers	11 (100)	20 (83)
Spironolactone	6 (55)	11 (46)
Digoxin	2 (18)	6 (25)

Data are presented as number of patients (%).
ACE = angiotensin-converting enzyme; IV= intravenous; NYHA = New York Heart Association.

Table 2 End Points for Total Population

	Baseline		End of Study		Change ± SD			
	Control (n = 11)	IV Iron (n = 24)	Control (n = 10)	IV Iron (n = 20)	Control	IV Iron	Treatment Effect (95% CI)	p Value
Primary end point								
Absolute peak Vo_2 (ml/min)	1,201 ± 330	1,053 ± 321	1,180 ± 320	1,128 ± 303	−21 ± 120	75 ± 156*	96 (−12 to 205)	0.08
Secondary end points								
Peak Vo_2/kg (ml/kg/min)	14.2 ± 3	13.9 ± 2.7	13.5 ± 2.5	15.4 ± 3.5	−0.7 ± 1.4	1.5 ± 2.7*	2.2 (0.5 to 4.0)	0.01
Exercise duration (s)	501 ± 179	476 ± 185	486 ± 193	521 ± 186	−15 ± 109	45 ± 84*	60 (−6 to 126)	0.08
Transferrin saturation (%)	21 ± 9	20 ± 8	23 ± 9	33 ± 10	2 ± 7	13 ± 9‡	11 (5 to 17)	0.001
Ferritin (ng/ml)	88 ± 62	62 ± 37	139 ± 122	386 ± 208	51 ± 85	324 ± 189‡	273 (151 to 396)	<0.001
Soluble transferrin receptor (mg/l)	1.6 ± 0.6	1.4 ± 0.4	1.8 ± 0.8	1.3 ± 0.4	0.2 ± 0.6	−0.1 ± 0.3	−0.3 (−0.6 to −0.01)	0.046
Hemoglobin (g/dl)	12.2 ± 1	12.6 ± 1.2	12.6 ± 1.1	13.2 ± 1.1	0.4 ± 0.9	0.5 ± 1.2*	0.1 (−0.8 to 0.9)	0.87
Jugular venous pressure (cm)	1.4 ± 2.0	1.5 ± 1.7	2.1 ± 2.2	1.4 ± 1.7	0.7 ± 1.4	−0.1 ± 0.7	−0.8 (−1.5 to −0.1)	0.03
Weight (kg)	84.3 ± 14.9	75.9 ± 17.4	87.0 ± 16.0	74.1 ± 16.1	2.7 ± 4.0*	−1.8 ± 3.9*	−4.6 (−7.5 to −1.6)	0.003
NYHA functional class	2.4 ± 0.5	2.5 ± 0.5	2.6 ± 0.8	2.1 ± 0.5	0.2 ± 0.4	−0.4 ± 0.6*	−0.6 (−0.9 to−0.2)	0.007
Patient global assessment	—	—	—	—	−0.2 ± 1.6	1.5 ± 1.2	1.7 (0.7 to 2.6)	0.002
MLHFQ score	46 ± 18	41 ± 22	49 ± 28	31 ± 25	3 ± 19	−10 ± 18*	−13 (−26 to 1)	0.07
Fatigue score	6 ± 1	6 ± 1	6 ± 2	4 ± 2	0 ± 2	−2 ± 2*	−2 (−3 to −1)	0.004
Left ventricular ejection fraction (%)	29 ± 6	30 ± 7	30 ± 9	32 ± 10	1 ± 5	2 ± 5	1 (−3 to 4)	0.66
Safety end points								
Systolic blood pressure (mm Hg)	116 ± 18	120 ± 22	115 ± 19	119 ± 20	−1 ± 17	−1 ± 12	0 (−10 to 10)	0.98
Diastolic blood pressure (mm Hg)	70 ± 9	69 ± 9	71 ± 12	69 ± 8	1 ± 15	0 ± 9	−1 (−8 to 6)	0.73
Heart rate (beats/min)	67 ± 6	74 ± 10	75 ± 10	75 ± 11	8 ± 7†	1 ± 11	−7 (−14 to 1)	0.08
Urea (mmol/l)	8.3 ± 3.1	9.1 ± 3.5	9 ± 5.4	8.5 ± 2.6	0.7 ± 5.3	−0.6 ± 2.5	−1.3 (−4.0 to 1.3)	0.32
Creatinine (μmol/l)	104 ± 39	109 ± 42	121 ± 61	110 ± 39	17 ± 49	1 ± 29	−16 (−43 to 11)	0.23
Alanine transaminase (iU/l)	22 ± 16	22 ± 13	22 ± 12	27 ± 14	0 ± 10	5 ± 17	5 (−6 to 16)	0.34
C-reactive protein (mg/l)	3 ± 2	6 ± 7	7 ± 10	6 ± 8	4 ± 9	0 ± 8	−4 (−10 to 2)	0.24
Malondialdehyde (μmol/l)	0.5 ± 0.3	0.5 ± 0.2	0.5 ± 0.3	0.5 ± 0.2	0 ± 0.3	0 ± 0.2	0 (−0.2 to 0.1)	0.76

Values are expressed as mean ± SD. Treatment effect = changes in IV iron group − changes in control group. The p value represents unpaired comparison of the changes between control and intravenous iron using the Student *t* test. *p < 0.05; †p < 0.01; and ‡p < 0.001 within-group differences compared with baseline.

IV = intravenous; MLHFQ = Minnesota Living With Heart Failure Questionnaire; NYHA = New York Heart Association; Vo_2 = oxygen consumption.

Effect of IV iron on symptoms and quality of life. ALL PATIENTS. Patients treated with IV iron had a significant improvement in NYHA functional class at week 18 (Table 2) (Fig. 4B). The NYHA functional class improved in 8 patients (44%) in the iron group versus 0 patients in the control group (p = 0.03). A consistent improvement in patient global assessment, fatigue score, and MLHFQ score from baseline to weeks 8 and 18 was observed only in the iron group (Figs. 4A, 4C, and 4D).

ANEMIC AND NONANEMIC SUBGROUPS. In anemic patients, iron significantly improved NYHA functional class at week 18 (Table 3). In nonanemic patients, a trend toward an improvement in NYHA functional class was observed.

Tolerability and adverse events. Adverse event profiles were similar between the treatment arms (Table 4). Ten (42%) and 7 (64%) adverse events occurred in the iron and control groups, respectively. All events were unrelated (76%) or unlikely to be related (24%) to the study. Three hospitalizations (12%) occurred in the iron group for cardiac decompensation, severe abdominal pain, and poorly controlled hyperthyroidism. Three (27%) hospitalizations occurred in the control group due to cardiac decompensation (n = 2) and cardioverter-defibrillator implantation. One death, due to intractable cardiac pump failure, that was judged to be unrelated to study drug, occurred in an anemic treated patient (Fig. 1).

Reductions in mean arterial blood pressure occurred 15 min (−3 [95% CI −4 to −1] mm Hg; p = 0.003) and 30 min (−2 [95% CI −4 to 0] mm Hg; p = 0.01) after IV iron infusion, but no episodes of symptomatic hypotension or anaphylactic reactions occurred. Nineteen episodes of transient hyperferritemia were recorded. Iron did not significantly alter renal and liver function tests or C-reactive protein and malondialdehyde levels (Table 2). In anemic patients, a significant increase in heart rate occurred in control but not iron-treated subjects and was associated with a significant treatment effect (Table 3).

Discussion

The major finding of this study is that, in symptomatic patients with CHF and abnormal indices of iron metabolism suggestive of possible iron deficiency, treatment with IV iron was well tolerated and associated with significant improvements in maximal exercise capacity as quantified by pVo_2/kg. Trends for an increase in absolute pVo_2 and exercise duration were found. Functional benefits were paralleled by significant improvements in symptoms and iron status. Changes in Hb levels were small. Benefits were

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Table 3 End Points for Anemic and Nonanemic Subgroups

	Baseline		Week 18		Change		Treatment Effect (95% CI)	p Value
	Control	IV Iron	Control	IV Iron	Control	IV Iron		
Anemic patients								
Absolute peak Vo_2 (ml/min)	1,224 ± 314	880 ± 259	1,178 ± 269	1,038 ± 324	−46 ± 116	158 ± 182*	204 (31 to 378)	0.02
Peak Vo_2/kg (ml/kg/min)	14.7 ± 3.6	12.9 ± 2.8	13.6 ± 2.9	15.7 ± 4.5	−1.1 ± 0.9*	2.8 ± 3.2†	3.9 (1.1 to 6.8)	0.009
Exercise duration (s)	506 ± 71	441 ± 188	526 ± 169	504 ± 214	20 ± 114	63 ± 97	43 (−66 to 153)	0.41
Transferrin saturation (%)	18 ± 4	18 ± 6	20 ± 4	32 ± 11	2 ± 7	14 ± 9‡	12 (3 to 22)	0.01
Ferritin (ng/ml)	91 ± 58	44 ± 33	132 ± 88	343 ± 199	41 ± 79	299 ± 187‡	258 (87 to 429)	0.006
Hemoglobin (g/dl)	11.4 ± 0.7	11.7 ± 1.0	12.0 ± 1.0	12.5 ± 1.0	0.6 ± 1.1	0.8 ± 1.5	0.2 (−1.3 to 1.7)	0.78
NYHA functional class	2.5 ± 0.5	2.4 ± 0.5	2.7 ± 0.8	2.1 ± 0.5	0.2 ± 0.4	−0.3 ± 0.5*	−0.5 (−1.0 to 0)	0.048
Heart rate (beats/min)	66 ± 8	77 ± 8	75 ± 10	73 ± 10	9 ± 5†	−4 ± 12	−13 (−24 to −2)	0.02
Nonanemic patients								
Absolute peak Vo_2 (ml/min)	1,174 ± 382	1,226 ± 288	1,183 ± 409	1,218 ± 262	9 ± 132	−8 ± 54	−17 (−110 to 76)	0.71
Peak Vo_2/kg (ml/kg/min)	13.6 ± 2.4	14.9 ± 2.2	13.3 ± 2.1	15.0 ± 2.1	−0.3 ± 1.9	0.1 ± 0.8	0.4 (−0.9 to 1.7)	0.53
Exercise duration (s)	492 ± 270	510 ± 180	438 ± 228	534 ± 162	−55 ± 98	27 ± 66	83 (−3 to 169)	0.06
Transferrin saturation (%)	26 ± 11	23 ± 10	27 ± 12	33 ± 10	1 ± 8	10 ± 8†	9 (0 to 19)	0.046
Ferritin (ng/ml)	86 ± 72	81 ± 32	148 ± 166	430 ± 217	62 ± 100	349 ± 197‡	287 (87 to 487)	0.008
Hemoglobin (g/dl)	13.1 ± 0.3	13.6 ± 0.6	13.3 ± 1	13.8 ± 0.9	0.2 ± 0.8	0.2 ± 0.7	0 (−0.9 to 0.8)	0.96
NYHA functional class	2.4 ± 0.5	2.6 ± 0.5	2.6 ± 0.9	2.2 ± 0.6	0.2 ± 0.4	−0.4 ± 0.7*	−0.6 (−1.3 to 0.1)	0.08
Heart rate (beats/min)	69 ± 4	70 ± 11	75 ± 11	76 ± 12	6 ± 9	6 ± 8	0 (−9 to 10)	0.97

Values are expressed as mean ± SD. Treatment effect = changes in IV iron group − changes in control group. The p value represents unpaired comparison of the changes between control and intravenous iron using the Student *t* test. *$p < 0.05$; †$p < 0.01$; and ‡$p < 0.001$ within-group differences compared with baseline.

Abbreviations as in Table 2.

more evident in anemic subjects, who demonstrated significant increases in both absolute pVo_2 and pVo_2/kg. Increments in pVo_2 did not correlate to increments in Hb (blood oxygen content) but to increases in TSAT (circulating iron status).

Iron metabolism in heart failure. Defective iron supply for erythropoiesis is an emerging feature of CHF (21), but defining iron deficiency in this cohort is notoriously difficult. Ferritin is the major iron storage protein, and in the absence of inflammation, serum ferritin levels are the best noninvasive estimates of body iron stores (9). However, heart failure is a state of chronic immune activation, and proteins such as ferritin are increased in the anemia of chronic disease (12). Thus, the use of biochemical markers and conventional cut-offs derived from noninflammatory cohorts to identify iron deficiency in CHF patients is questionable. Recently, Nanas et al. (22) measured the iron content of bone marrow biopsies in patients with advanced heart failure and anemia; 73% of patients had reduced iron stores. The mean ferritin levels were 75 ng/ml in those who were iron deficient and 211 ng/ml in those not iron deficient. Bolger at al. (25) reported a mean value of 87 ng/ml. These values are far above the 15 to 20 ng/ml cutoffs that are usually regarded as indicative of iron-deficiency anemia. Consequently, we used higher ferritin cutoffs for iron deficiency to address its impact on exercise and symptoms in CHF.

Effect of IV iron in anemic patients. In this trial, iron therapy led to an absolute mean increase of 204 ml/min (23%) and 3.9 ml/kg/min (30%) in pVo_2 and pVo_2/kg, respectively. This represents a substantial benefit. In a single-blind study of 26 anemic CHF patients, Mancini et al. (3) reported an absolute mean increase of 2.2 ml/kg/min after recombinant erythropoietin and oral iron and folate therapy. In the MIRACLE (Multicenter In-Sync Randomized Clinical Evaluation) and PATH-CHF (Pacing Therapies for Congestive Heart Failure) studies, cardiac resynchronization conferred absolute median increases in pVo_2/kg of 0.9 and 1.7 ml/kg/min, respectively (4,5). In trials evaluating exercise training, percentage increases from baseline in pVo_2/kg have ranged from 12% to 31% (6).

The effect of IV iron on exercise performance likely reflects its critical role in multiple facets of exercise physiology and is corroborated by earlier analyses. Studies in animals and otherwise healthy human subjects have now firmly established that iron-deficiency anemia attenuates indices of work capacity such as pVo_2/kg by 10% to 50% (14,16,29). Such impairments are proportional to the severity of iron deficiency and improve with iron repletion, but the magnitudes of benefit are often unrelated to the increases in Hb (16).

Increments in pVo_2 can be partly ascribed to an increase in tissue iron delivery. Anemia due to iron deficiency triggers excessive dyspnea (9), impairs neurotransmission (10,11), diminishes the oxygen-carrying capacity of both blood (reduced Hb) and skeletal muscle (reduced myoglobin), and attenuates mitochondrial oxygen utilization (reduced aerobic enzyme activity) (13–15). The mechanism of functional benefit with iron might involve the alleviation of any or all of these features. Elegant animal experiments have suggested that during iron repletion, improvements in Hb and pVo_2 evolve in parallel, whereas enhancements in submaximal (endurance) capacity track the increase in aerobic enzyme activity (14,30). This has not been a consistent

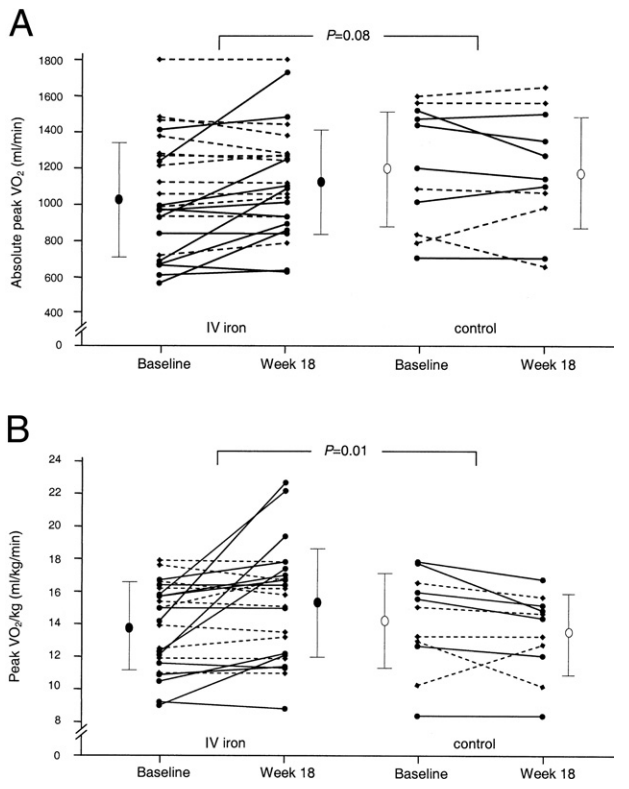

Figure 2 **Individual Changes in Exercise Tolerance With Iron Therapy**

Treatment effect of intravenous (IV) iron on **(A)** absolute peak oxygen consumption (Vo_2) and **(B)** peak Vo_2/kg in anemic **(bold lines)** and nonanemic **(dashed lines)** subjects. **Bars** correspond to mean ± SD.

finding in humans (16), and in the present analysis we found no correlation between changes in Hb and changes in pVo_2. Although limited power may account for this, it is tenable that mechanisms unrelated to oxygen delivery (Hb levels) were operative. Data accrued over the last 3 decades have now firmly established that, in CHF, pVo_2 at maximal exercise is not immediately limited by defects in central hemodynamics but by muscle atrophy, signals from stretch and metabolic receptors, near-normal glycolytic but attenuated Krebs cycle enzyme activity, accelerated phosphocreatinine depletion, and early skeletal muscle acidosis on exertion (7,8). Because skeletal muscle dysfunction in rats rendered iron deficient mirrors these abnormalities (14,15), it is plausible that IV iron mediates functional effects at the tissue level by augmenting aerobic metabolism and muscle oxidative phosphorylation (13). Consistent with this, we found a significant correlation between changes in TSAT and changes in pVo_2. The pilot nature of the present study precludes definitive mechanistic inferences from being made.

Iron triggered early improvements in NYHA functional class, patient global assessment (8), and fatigue score (20). This rapid onset of symptomatic benefit is an established feature of iron therapy and is thought to have a neurologic basis (9–11). Additionally, iron was associated with significant reductions in body weight. This may have been due to improvements in hemodynamic and/or neurohormonal status and may have contributed to exercise benefits. In contrast, the Hb response was surprisingly suboptimal. Iron deficiency is a continuum which, at its extreme, manifests as anemia. If low Hb levels follow from isolated iron store depletion (absolute iron deficiency), a 2-g/dl mean increase in Hb would be expected after 3 to 6 weeks of iron repletion (9). In the present study, the mean increase in Hb was 0.8 g/dl. In the study by Bolger et al. (25) the increase was greater, but the patients were more anemic at baseline. Pharmacokinetic analyses have shown that after IV injection, iron preparations are initially

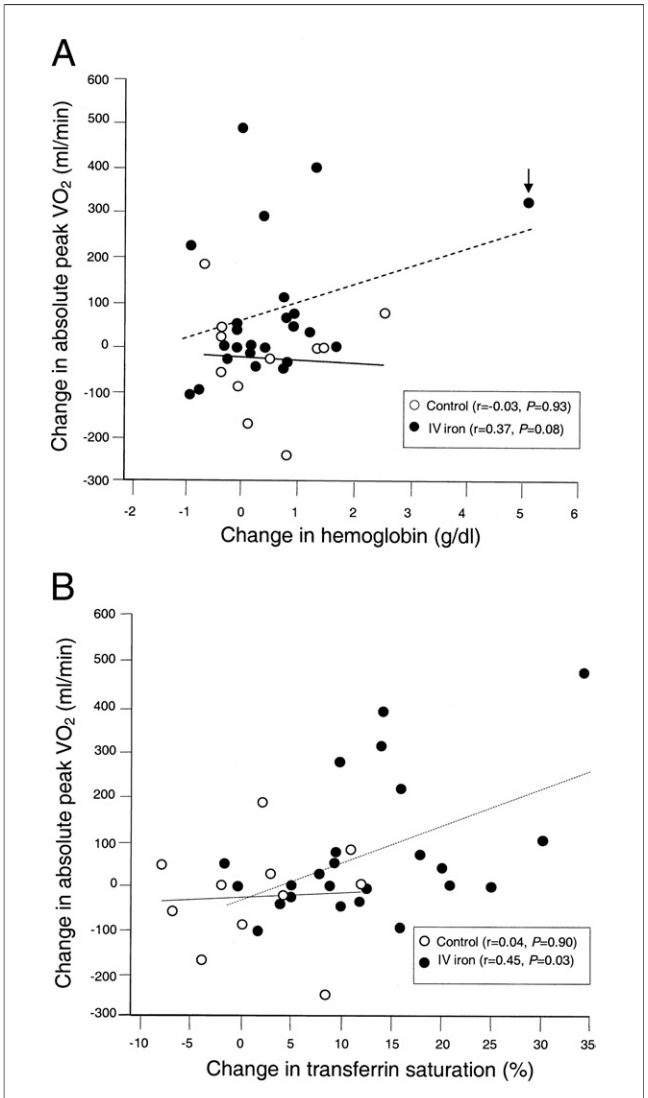

Figure 3 **Correlates of Exercise Performance**

Relation between changes in absolute peak oxygen consumption (Vo_2) and **(A)** changes in hemoglobin concentration (r = 0.17; p = 0.43 for intravenous [IV] iron group on removal of outlier **[arrow]**) and **(B)** changes in transferrin saturation in the total population.

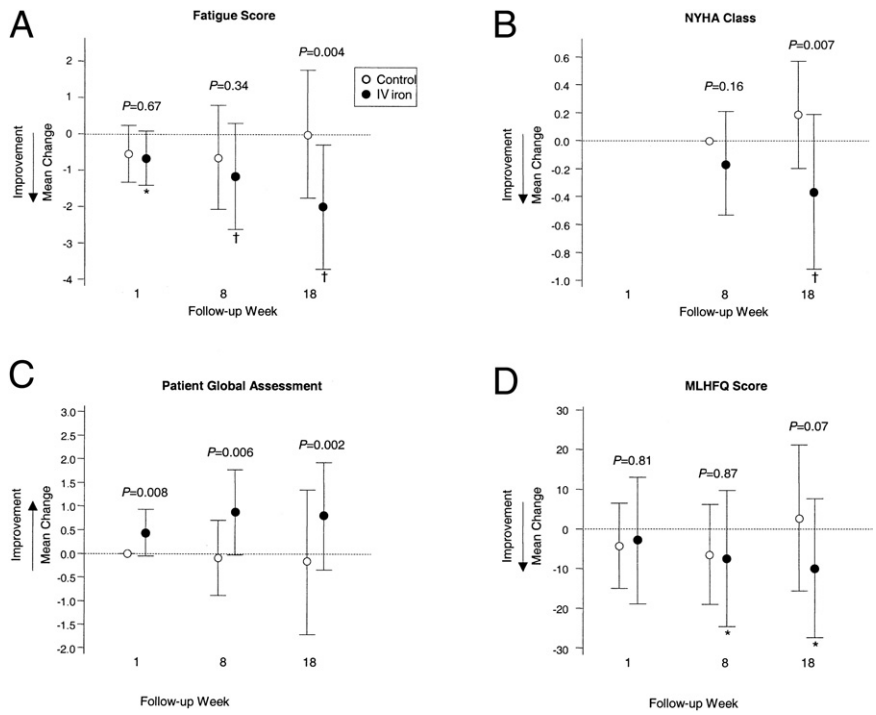

Figure 4 **Effect of Iron Therapy on Symptoms and Quality of Life**

Effect of treatment on **(A)** visual analog fatigue score, **(B)** New York Heart Association (NYHA) functional class, **(C)** patient global assessment, and **(D)** Minnesota Living With Heart Failure Questionnaire (MLHFQ) score in the total population. Data are shown as mean ± SD. *p < 0.05; †p < 0.01 compared with baseline.

cleared from the plasma by macrophages, and in the presence of inflammation the donation of infused iron from macrophages to the erythroid marrow is blunted (31–33). Thus, chronic low-grade inflammation and our inclusion of patients with mild anemia were possibly responsible for the suboptimal Hb response.

Effect of IV iron in nonanemic patients. Nonanemic patients derived no functional benefits from iron, but some favorable trends on symptoms were observed. Lower Hb levels are a surrogate for greater reductions in aerobic enzyme activity that are difficult to quantify noninvasively (9). Thus, anemic patients would be expected to derive greater functional benefits than their nonanemic counterparts irrespective of the erythropoietic response. Impairments in oxygen utilization in nonanemic patients might have been sufficient to limit submaximal, but not maximal, exertion. Indeed, substantial evidence suggests that iron confers inconclusive or no effects on pVO_2 but improves various indices of submaximal endurance capacity and quality of life in nonanemic iron-deficient subjects (18–20,29).

Tolerability of IV iron. Iron repletion with IV iron sucrose was well tolerated, without any clinical evidence of anaphylaxis. The incidence of adverse events was similar between the treatment arms. During 165 infusions, only 10 adverse events occurred in the iron group. The majority were minor and did not interrupt treatment. Although frequent mild hypotensive episodes occurred during iron infusions, none were associated with symptoms or tachycardia. Iron significantly reduced elevated heart rates in anemic patients, possibly by attenuating the stimulatory effects of iron-deficiency anemia on catecholamine synthesis (9). Iron therapy did not increase markers of inflammation or renal/hepatic dysfunction. Importantly, 16 weeks of IV iron sucrose did not escalate levels of malondialdehyde, a marker

Table 4 **Adverse Events Profile**

	Control (n = 11)	IV Iron (n = 24)
Patients with 1 or more adverse events, n (%)	7 (64)	10 (42)
Nonserious adverse events, n (%)		
Abdominal pain	0 (0)	2 (8)
Coryzal symptoms	1 (9)	2 (8)
Cough	2 (18)	0 (0)
Gout	0 (0)	1 (4)
Transient ischemic attack	0 (0)	1 (4)
Heartburn	0 (0)	1 (4)
Pneumonia	1 (9)	0 (0)
Internal cardiac defibrillator implantation	1 (9)	0 (0)
Decompensated heart failure (nonhospitalized)	1 (9)	0 (0)
Serious adverse events, n (%)		
Decompensated heart failure (hospitalized)	1 (9)	1 (4)
Symptomatic hyperthyroidism (hospitalized)	0 (0)	1 (4)
Death	0 (0)	1 (4)

IV = intravenous.

of lipid peroxidation. The adverse event rates seen in the present trial are similar to those listed in the medication's package insert (34). However, the present study was small and relatively short, restricting the ability to detect adverse events.

Study limitations. The small sample size limits the power to detect small differences between treatment groups. Although the open adjudication of secondary and safety end points escalates the risk of subject and/or investigator bias, our primary end point was objective, resistant to bias, and blindly ascertained. Our ferritin cutoff for iron deficiency (<100 ng/ml) was higher than that advocated by the World Health Organization (<12 ng/ml). Chronic heart failure is a chronic inflammatory state, and higher ferritin cutoffs, even as high as <200 ng/ml, provide optimal sensitivity and specificity for the detection of depleted iron stores in inflammatory cohorts (9).

We used the last observation carry-forward method for handling missing data. Stringent sensitivity analyses confirmed that the results were robust and not influenced by imputation. Because anemia is associated with edema formation and its correction can lead to significant weight reductions, absolute pVO_2 was chosen as the primary end point to minimize the attribution of functional benefits to weight changes. Owing to the lack of an appropriate placebo for IV iron, control patients in the United Kingdom received no treatment. The Ethics Committee in Poland required that control patients receive IV saline. Adjustment for center in statistical analyses did not affect the results. Nevertheless, the benefit of iron treatment did seem to be larger in the patients in the United Kingdom.

Conclusions

The FERRIC-HF trial has shown that 16 weeks of IV iron sucrose therapy is well tolerated and associated with improvements in exercise capacity and symptom status in patients with heart failure and iron deficiency. Benefits were more evident in anemic patients. Such outcomes, if replicated in larger and longer studies in CHF cohorts, may render anemic and possibly nonanemic iron deficiency a therapeutic target in this population. At present, this idea remains unproven.

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Reprint requests and correspondence: Dr. Darlington O. Okonko, Clinical Cardiology, NHLI, Dovehouse Street, London SW3 6LY, United Kingdom. E-mail: d.okonko@imperial.ac.uk.

REFERENCES

1. Szlachic J, Massie BM, Kramer BL, Topic N, Tubau J. Correlates and prognostic implications of exercise capacity in chronic congestive heart failure. Am J Cardiol 1985;55:1037–42.
2. Francis DP, Shamim W, Davies LC, et al. Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from VE/VCO_2 slope and peak VO_2. Eur Heart J 2000;21:154–61.
3. Mancini DM, Katz SD, Lang CC, LaManca J, Hudaihed A, Androne AS. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. Circulation 2003;107:294–9.
4. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845–53.
5. Auricchio A, Stellbrink C, Sack S, et al. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. J Am Coll Cardiol 2002;39:2026–33.
6. Pina IL, Apstein CS, Balady GJ, et al. Exercise and heart failure: a statement from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention. Circulation 2003;107:1210–25.
7. Clark AL, Volterrani M, Piepoli M, Coats AJ. Factors which alter the relationship between ventilation and carbon dioxide production during exercise in normal subjects. Eur J Appl Physiol Occup Physiol 1996;73:144–8.
8. Massie BM, Conway M, Rajagopalan B, et al. Skeletal muscle metabolism during exercise under ischemic conditions in congestive heart failure. Evidence for abnormalities unrelated to blood flow. Circulation 1988;78:320–6.
9. Fairbanks V, Beutler E. Iron deficiency. In: Beutler E, editor. Williams Hematology. 6th edition. New York, NY: McGraw-Hill, 2001:295–304, 447–440.
10. Dallman PR. Iron deficiency: does it matter? J Intern Med 1989;226:367–72.
11. Scrimshaw NS. Functional consequences of iron deficiency in human populations. J Nutr Sci Vitaminol (Tokyo) 1984;30:47–63.
12. Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med 2005;352:1011–23.
13. Dunn LL, Rahmanto YS, Richardson DR. Iron uptake and metabolism in the new millennium. Trends Cell Biol 2007;17:93–100.
14. Davies KJ, Maguire JJ, Brooks GA, Dallman PR, Packer L. Muscle mitochondrial bioenergetics, oxygen supply, and work capacity during dietary iron deficiency and repletion. Am J Physiol 1982;242:E418–27.
15. Maguire JJ, Davies KJ, Dallman PR, Packer L. Effects of dietary iron deficiency of iron-sulfur proteins and bioenergetic functions of skeletal muscle mitochondria. Biochim Biophys Acta 1982;679:210–20.
16. Ohira Y, Edgerton VR, Gardner GW, Senewiratne B, Barnard RJ, Simpson DR. Work capacity, heart rate and blood lactate responses to iron treatment. Br J Haematol 1979;41:365–72.
17. Davies CT, Chukweumeka AC, Van Haaren JP. Iron-deficiency anaemia: its effect on maximum aerobic power and responses to exercise in African males aged 17–40 years. Clin Sci 1973;44:555–62.
18. Zhu YI, Haas JD. Altered metabolic response of iron-depleted nonanemic women during a 15-km time trial. J Appl Physiol 1998;84:1768–75.
19. Brownlie T, Utermohlen V, Hinton PS, Haas JD. Tissue iron deficiency without anemia impairs adaptation in endurance capacity after aerobic training in previously untrained women. Am J Clin Nutr 2004;79:437–43.
20. Verdon F, Burnand B, Stubi CL, et al. Iron supplementation for unexplained fatigue in nonanaemic women: double blind randomised placebo controlled trial. Br Med J 2003;326:1124.
21. Opasich C, Cazzola M, Scelsi L, et al. Blunted erythropoietin production and defective iron supply for erythropoiesis as major causes of anaemia in patients with chronic heart failure. Eur Heart J 2005;26:2232–7.
22. Nanas JN, Matsouka C, Karageorgopoulos D, et al. Etiology of anemia in patients with advanced heart failure. J Am Coll Cardiol 2006;48:2485–9.
23. de Silva R, Rigby AS, Witte KK, et al. Anemia, renal dysfunction, and their interaction in patients with chronic heart failure. Am J Cardiol 2006;98:391–8.

24. Okonko DO, van Veldhuisen DJ, Poole-Wilson PA, Anker SD. Anaemia of chronic disease in chronic heart failure: the emerging evidence. Eur Heart J 2005;26:2213–4.
25. Bolger AP, Bartlett FR, Penston HS, et al. Intravenous iron alone for the treatment of anemia in patients with chronic heart failure. J Am Coll Cardiol 2006;48:1225–7.
26. Silverberg DS, Wexler D, Blum M, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. J Am Coll Cardiol 2000;35:1737–44.
27. Silverberg DS, Wexler D, Sheps D, et al. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. J Am Coll Cardiol 2001;37:1775–80.
28. Wong SH, Knight JA, Hopfer SM, Zaharia O, Leach CN Jr., Sunderman FW Jr. Lipoperoxides in plasma as measured by liquid-chromatographic separation of malondialdehyde-thiobarbituric acid adduct. Clin Chem 1987;33:214–20.
29. Haas JD, Brownlie T. Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. J Nutr 2001;131:676S–88S.
30. Davies KJ, Donovan CM, Refino CJ, Brooks GA, Packer L, Dallman PR. Distinguishing effects of anemia and muscle iron deficiency on exercise bioenergetics in the rat. Am J Physiol 1984;246:E535–43.
31. Grimes AJ, Hutt MS. Metabolism of 59Fe-dextran complex in human subjects. Br Med J 1957;2:1074–7.
32. Beshara S, Lundqvist H, Sundin J, et al. Pharmacokinetics and red cell utilization of iron(III) hydroxide-sucrose complex in anaemic patients: a study using positron emission tomography. Br J Haematol 1999;104: 296–302.
33. Beshara S, Lundqvist H, Sundin J, et al. Kinetic analysis of 52Fe-labelled iron(III) hydroxide-sucrose complex following bolus administration using positron emission tomography. Br J Haematol 1999; 104:288–95.
34. American Regent. Venofer (iron sucrose injection) package insert. Shirley, NY: American Regent, 2005.