# Increased iron absorption in patients with chronic heart failure and iron deficiency

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## ABSTRACT

**Background:** Iron deficiency (ID) is common in patients with chronic heart failure (CHF), but the underlying causes are not fully understood. We investigated whether ID is associated with decreased iron absorption in patients with CHF.

**Methods and Results:** We performed an oral iron-absorption test in 30 patients and 12 controls. The patients had CHF with reduced (n = 15) or preserved (n = 15) ejection fraction and ID, defined as s-ferritin < 100 μg/L, or s-ferritin 100−299 μg/L and transferrin saturation < 20%. The controls had no HF or ID and were of similar age and gender. Blood samples were taken before and 2 hours after ingestion of 100 mg ferroglycin sulphate. The primary endpoint was the delta plasma iron at 2 hours. The delta plasma iron was higher in the group with HF than in the control group (median increase 83.8 [61.5;128.5] μg/dL in HF vs 47.5 [30.7;61.5] μg/dL in controls, $P = 0.001$), indicating increased iron absorption. There was no significant difference between the groups with preserved or reduced ejection fraction ($P = 0.46$).

**Conclusion:** We found increased iron absorption in patients with CHF and ID compared to controls without ID and HF, indicating that reduced iron absorption is not a primary cause of the high prevalence of ID in patients with CHF.

**Clinical Trial Registration:** EudraCT 2017-000158-21 (*J Cardiac Fail 2020;26:440−443*)

**Key Words:** Iron deficiency, heart failure, iron absorption.

## Background

Iron deficiency (ID) is common in patients with heart failure (HF) and is associated with adverse prognosis,[1,2] but the underlying causes of ID remain undetermined. Suggested causes include malnutrition, reduced iron absorption, blood loss from the gastrointestinal (GI) tract, and chronic inflammation leading to functional ID. The proposed reduced iron absorption[3,4] is part of the rationale for the intravenous (IV) iron treatment advocated by several guidelines.[5,6] These guidelines are based on clinical trials that have shown beneficial effects of IV iron treatment,[7,8] whereas 1 trial with oral iron treatment did not reach significant results.[9] Animal and histologic studies have shown impaired bowel function in HF,[10,11] suggesting altered iron absorption, but the degree of oral iron absorption in patents with HF has yet not been determined.

## Aims

We sought to test the hypothesis that ID in patients with chronic heart failure (CHF) is associated with decreased iron absorption. We performed an oral iron absorption test (OIAT)[12,13] in patients with CHF and compared the results with controls without ID and HF.

## Methods

We enrolled patients with ID and known and stable CHF, objectively defined as below and with no hospitalization because of HF or need for IV diuretics within the previous 3 months. ID was defined as s-ferritin < 100 μg/L, or s-ferritin 100−299

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Manuscript received February 17, 2020; revised manuscript accepted March 5, 2020.

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1071-9164/$ - see front matter



https://doi.org/10.1016/j.cardfail.2020.03.004

$\mu$g/L and transferrin saturation < 20%.[5] Patients were divided into those with HF with reduced ejection fraction (HFrEF) and those with HF and preserved ejection fraction (HFpEF). Patients with left ventricular ejection fraction < 45% were considered to have HFrEF, and patients with left ventricular ejection fraction ≥ 45% with structural and/or functional abnormalities and N-terminal proB natriuretic peptide (NT-proBNP) > 125 ng/L were considered to have HFpEF. This definition was used because some patients were included from the ongoing epidemiologic PREFERS study cohort.[14] Major exclusion criteria were known causes for ID, such as GI disease, bleeding or previous GI operation, chronic inflammatory disease, and renal impairment with estimated glomerular filtration rate < 30 mL/min/1.73m$^2$. The controls were recruited mainly from a seniors' gym and had no ID and no history, symptoms or signs of HF, had normal electrocardiograms and NT-proBNP levels < 125 ng/L indicating high negative predictive values to rule out CHF,[5] in addition to previously mentioned exclusion criteria.

Subjects were instructed to fast from midnight onward and to abstain from medications known to interact with ferroglycin sulphate (ie, antacids, calcium supplements) until the test was finished. In the morning, they were given 1 enterocapsule of ferroglycin sulphate complex containing 100 mg $Fe^{2+}$ (ATC code B03AA01, Niferex, Erol, Sweden), and venous blood samples were taken before and 2 hours after administration. Previous validation studies of OIAT have shown that delta iron at 2 hours is as informative and valid as, for example, area under the curve and concentration max[12]; therefore, the absolute increase of P-iron after 2 hours compared to baseline was chosen as the primary efficacy endpoint. We calculated that a sample of 15 patients, including 20% dropouts, in each group would provide 80% power to detect a difference of 50 $\mu$g/dL, assuming a common within-group standard deviation of 40 $\mu$g/dL. Descriptive statistics are presented as median with interquartile range (IQR) because the sample size was small, and normality could not be assumed. The nonparametric Mann-Whitney U test was used for hypothesis testing, and the Kruskal-Wallis test was used to compare differences among the 3 groups in baseline characteristics. A 2-sided overall $\alpha$ < 0.05 was considered to be significant. Analyses were performed with the use of SPSS Statistics 25 (IBM, Armonk, NY, USA).

The study was conducted according to principles outlined in the Declaration of Helsinki and was approved by the regional Ethics Committee in Stockholm and the Swedish Medical Products Agency (EudraCT 2017-000158-21). All subjects gave their written informed consent prior to any study-specific action was made.

## Results

Patient screening and selection is described in Fig. 1 Baseline characteristics are presented in Table 1. The median age of the patients was 72 years, and of controls 70 years ($P$= 0.23). Gender distribution was similar in the HF (63% men) and the control (67% men) groups. The majority of patients were in the New York Heart Association category II (70%); patients with HFrEF had a median NT-proBNP of 1070 ng/L, and patients with HFpEF had a median NT-proBNP of 747 ng/L. There was no significant difference in renal function among the 3 groups.

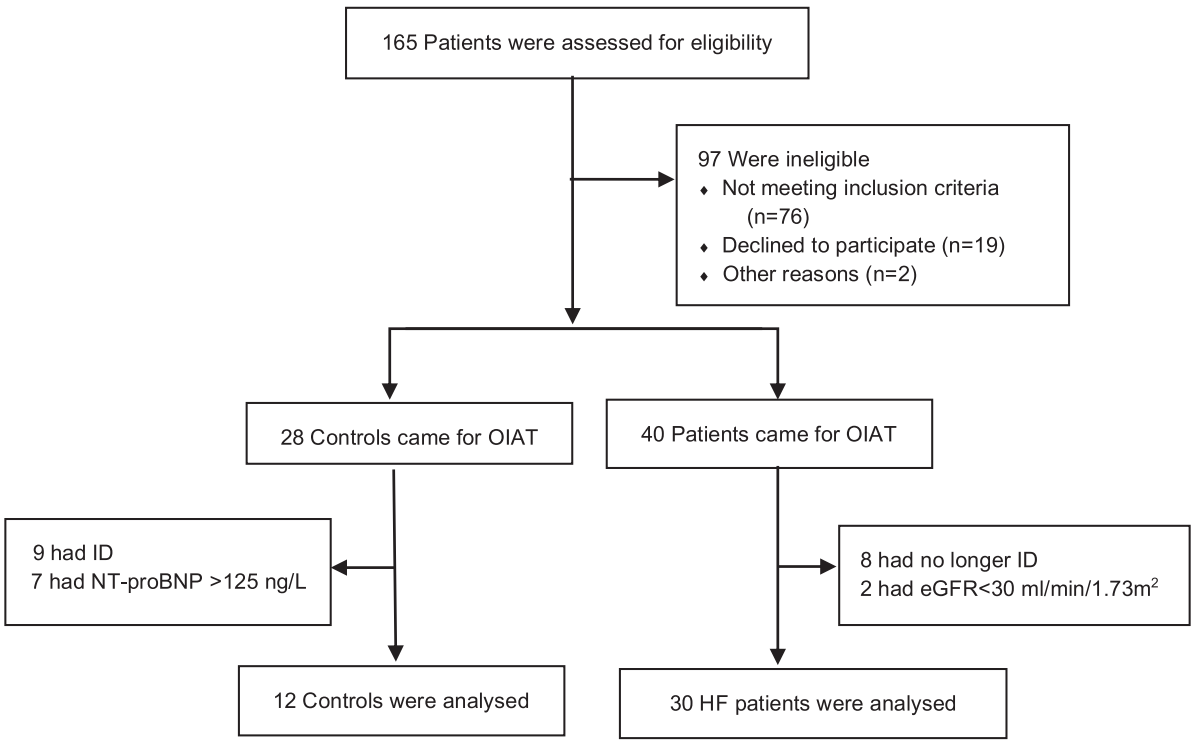


**Fig. 1.** Flow chart of patient screening and selection. ID, iron deficiency; OIAT, oral iron absorption test.

Plasma (P)-iron at baseline was lower in patients with HF and ID (median 78 $\mu$g/dL) compared to controls (115 $\mu$g/dL). The absolute increase of P-iron after 2 hours was higher in patients with HF (median increase 83.8 [IQR 61.5;128.5] $\mu$g/dL) compared to controls (47.5 [30.7;61.5] $\mu$g/dL; $P = 0.001$ (Fig. 2). There was no significant difference in delta P-iron between the HFrEF and HFpEF groups (78.2 [61.5;128.5] and 111.7 [61.5;150.8], respectively; $P = 0.46$). Seven patients (3 HFrEF and 4 HFpEF) did take proton pump inhibitors on the morning of the test. Their results did not deviate from those of the rest of the group with HF, and eliminating these patients from the analysis did not change the result.

**Table 1.** Baseline Characteristics

| | Control n = 12 | HFrEF n = 15 | HFpEF n = 15 |
|---|---|---|---|
| Age, years | 70 (67;72) | 73 (68;69) | 71 (66;78) |
| Sex, male | 8 (67%) | 10 (67%) | 9 (60%) |
| NYHA class | n.a. | | |
| I | | 2 (13%) | 1 (7%) |
| II | | 9 (60%) | 12 (80%) |
| III | | 4 (27%) | 2 (13%) |
| IV | | 0 | 0 |
| LVEF (%) | n.a. | 35 (27;41) | 55 (48;57) |
| E/é average | n.a. | n.a. | 10.9 (10.0;13.2) |
| LAVI (mL/m$^2$) | n.a. | n.a. | 46.4 (42.5;51.1) |
| AFib | 0 | 11 (73%) | 9 (60%) |
| Diabetes | 0 | 2 (13%) | 3 (20%) |
| IHD | 0 | 4 (27%) | 6 (40%) |
| Hypertension | 2 (17%) | 10 (67%) | 10 (67%) |
| Stroke | 1 (8%) | 3 (20%) | 3 (20%) |
| ACEi/ARB/ARNI | 2/0/0 (17%) | 5/7/3 (100%) | 5/8/0 (80%) |
| Beta-blocker | 0 | 14 (93%) | 14 (93%) |
| MRA | 0 | 10 (67%) | 2 (13%) |
| Diuretics | 1 (8%) | 10 (67%) | 11 (73%) |
| Antiplatelet | 2 (17%) | 3 (20%) | 5 (33%) |
| OAC | 0 | 11 (73%) | 9 (60%) |
| NOAC | | 8 | 6 |
| Warfarin | | 3 | 3 |
| Digoxin | 0 | 4 (27%) | 1 (7%) |
| PPI | 0 | 3 (20%) | 4 (27%) |
| Statin | 1 (8%) | 9 (60%) | 12 (80%) |
| B-Hb (g/L) | 142 (132;150) | 141 (131;152) | 131 (128;142) |
| Plasma creatinine ($\mu$mol/L) | 82 (74;99) | 86 (73;99) | 90 (76;111) |
| eGFR (mL/min/1.73m$^2$) | 69 (61;73) | 63 (54;70) | 57 (51;72) |
| Plasma CRP (mg/L) | 2 (2;2) | 2 (1;4) | 1 (1;5) |
| P-NTproBNP (ng/L) | 57 (31;83) | 1070 (597;1490) | 747 (584;1180) |
| S-ferritin ($\mu$g/L) | 171 (148;223) | 85 (62;93) | 47 (35;73) |
| Plasma TSAT | 0.35 (0.29;0.38) | 0.24 (0.17;0.29) | 0.18 (0.14;0.23) |
| Plasma iron ($\mu$g/dL) | 115 (92;131) | 89 (78;106) | 67 (56;78) |
| Plasma transferrin (g/L) | 2.3 (2.0;2.6) | 3.0 (2.3;3.3) | 2.7 (2.4;2.9) |

Note: Continuous variables are displayed as median (IQR), categorical variables as number (percent).

ACEi, angiotensin-converting enzyme inhibitor; AFib, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CRP, C-reactive protein; E/é average, ratio of the mitral inflow E wave to the tissue Doppler é wave average of the septal and lateral wall; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; IHD, ischemic heart disease; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NOAC, nonvitamin K antagonist oral anticoagulants; n.a., not available; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OAC, oral anticoagulant; PPI, proton pump inhibitor; TSAT, transferrin saturation.

## Conclusion

Our findings showed that symptomatic patients with CHF and ID had higher increases of P-iron evaluated with OIAT, likely reflecting increased iron absorption compared to controls without HF and ID. The results of this study of oral iron absorption in patients with HF do not support the hypothesis that reduced iron absorption is a contributing cause of the high prevalence of ID in patients with HF. The normal physiologic response to ID in otherwise healthy individuals is increased absorption,[15] and this study indicates that patients with CHF exhibit the same pattern, in contrast to previous speculations about the causes of ID in patients with HF.[4] The magnitude of the difference in delta-P-iron between patients with HF and controls in our study is in line with the results shown by Kobune et al,[13] in which patients with severe ID anemia (mean Hb 8.5 g/dL, ferritin 6.1 ng/mL) had approximately 2.8 times higher delta-P-iron at 2 hours compared to healthy volunteers. In contrast, patients with anemia and chronic inflammatory diseases had significantly lower delta-P-iron than controls. Our patients did not have anemia or signs of inflammation and had normal C-reactive protein values.

Limitations of the study include a small sample size; nevertheless, the increased iron absorption, as reflected by the higher peak levels attained in patients with HF, was highly significant. Another limitation is that study participants were fasting and abstaining from medications known to interact with ferroglycin sulphate during the test. In general, food intake and concurrent medication can affect iron absorption in patients with CHF. A third limitation is that only patients with stable CHF were included in the study, possibly affecting the generalizability of the results because patients with newly diagnosed or decompensated HF might have altered iron absorption.

Considering that clinical trials have shown beneficial results with IV iron treatment, the results from this study are of great interest. However, the present study was designed to test the hypothesis that HF was associated with reduced oral iron absorption and does not give evidence as to whether oral iron treatment could improve clinical outcomes in these patients. Further trials, including patients with HFpEF and with adequate clinical endpoints and long-time follow up, are needed to asses this.

To summarize, we found signs of increased iron absorption in patients with CHF compared to controls, irrespective of ejection fraction. Our study indicates that reduced iron absorption is not a cause of ID in these patients and suggests that further studies with clinical endpoints investigating the possible effect of oral iron therapy in patients with HF should be encouraged.

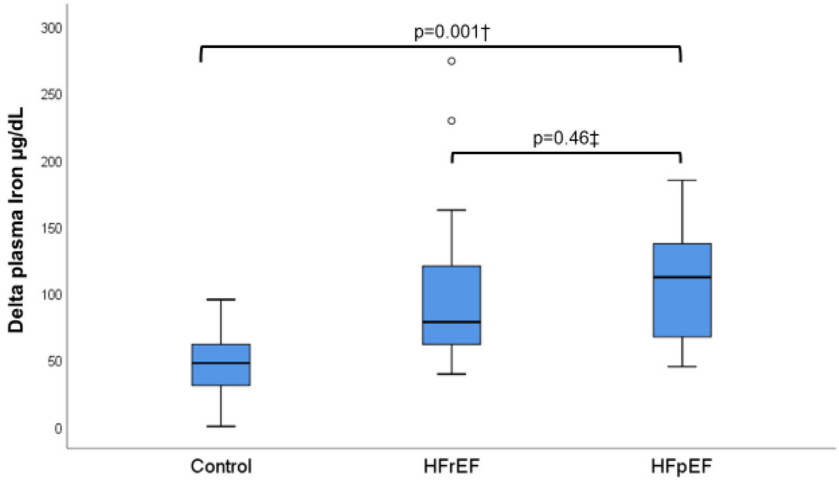


**Fig. 2.** Comparison of absolute increase of plasma iron after 2 hours in study groups.
†Control vs HFpEF and HFrEF.
‡HFpEF vs HFrEF. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

## Funding

This work was supported by the County of Stockholm (Stockholms Läns Landsting) and Karolinska Institutet (ALF). It was also supported by a collaborative grant to Karolinska Institutet [grant number 1377] from Astra Zeneca, Mölndal, Sweden, within the framework of the PREFERS study (Preserved and Reduced Ejection Fraction Epidemiological Regional Study).

## Conflicts of interest

None declared

## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2020.03.004.

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