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ARTICLE

Exercise capacity, iron deficiency and depressive symptoms in patients with asymptomatic chronic systolic heart failure

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Abstract

Background: Iron deficiency (ID) is a common comorbidity in symptomatic heart failure (HF). It is associated with lower exercise capacity, anemia and poor quality of life and has proven to be a successful therapeutic target. In asymptomatic heart failure (NYHA 1) with reduced ejection fraction (HFrEF) however, prevalence of ID and its impact on exercise capacity, anemia and depressive symptoms are unknown.

Methods: We analyzed 364 asymptomatic HFrEF patients for ID, ID-associated impairment of exercise capacity, anemia, inflammation, ventricular overload and depressive symptoms. Exercise capacity was measured by 6-minute walk test (6 MWT), peak oxygen consumption per kg bodyweight (peak VO_2) and breathing efficiency (VE-VCO_2 slope). ID was defined as ferritin <100 µg/L or ferritin 100-299 µg/L with transferrin saturation (TSAT) <20% [European Society of Cardiology (ESC) guideline-recommended definition]. Iron status was also assessed by serum soluble transferrin receptor (sTfR). Inflammation was defined as serum C-reactive protein >5 mg/L. Depressive symptoms were diagnosed by Hospital Anxiety and Depression-Scale (HADS-D) score ≥11 and Patient Health Questionnaire 9 (PHQ-9) score≥10.

Results: Prevalences were 36.5% (29.3% absolute, 7.2% functional) for ID, 11% for anemia, 15.3% for inflammation and 6.5% (HADS-D) and 9.8% (PHQ-9) for depressive symptoms. The latter were similar in patients with/without ID (6.7% *vs*. 6.4%, p=0.46). Patients with ID had lower breathing efficiency (26.8±6.4 *vs*. 25.2±6.1, p=0.015), lower 6 MW distance (557 m±99 *vs*. 577 m±84, p=0.030), higher NT-pro BNP (545 ng/l [201; 1226] *vs*. 428 ng/L [195; 783], p=0.047), more often anemia (15.9% *vs*. 8.2%, p=0.015) and inflammation for functional ID (8/25 *vs*. 13/101, p=0.015). Patients with a TSAT<20% had lower 6 MW distance than those with a TSAT 20-25% or >25% (565±90 *vs*. 581±74 *vs*. 589±86 ms, p=0.003). In univariate regression models, we found higher sTfR to be associated with anemia (r=0.122, p<0.015), inflammation (r=0.118, p<0.02), ventricular overload (r=0.202, p<0.001) and lower exercise capacity in form of 6 MW distance (r=-0.138, p=0.007), which is similar to ID by ESC definition. In multivariable regression, only NT-pro BNP and in trend ID by ESC definition independently predicted lower breathing efficiency (p<0.001 and p=0.055, r=0.295). NT-pro BNP>1400 ng/L yielded 90% specificity for ID in ROC analysis.

Conclusions: ID is a common comorbidity already in asymptomatic HFrEF patients. In a multivariable model, NT-pro BNP and in trend ID independently predicted lower breathing efficiency. NT-pro BNP>1400 ng/L yielded 90% specificity for ID. An association of ID with worsening of breathing efficiency and transition to higher NYHA classes should be subject of further studies.

Key words: heart failure, NYHA 1, iron deficiency, depression, anemia, exercise capacity.

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Introduction

Iron deficiency (ID) is a common comorbidity in symptomatic chronic systolic heart failure (HF) with reduced ejection fraction (HFrEF).[1] It is associated with lower exercise capacity,[2] reduced quality of life and lower survival.[3,4] Symptomatic HF patients with ID show higher NT-pro BNP,[3] mild systemic inflammation and a higher prevalence of anaemia than non-ID patients.[2,5] ID has also been associated with depression in general population cohorts.[6] Intravenous iron therapy (IVIT) has proven to be a valid treating option for ID in symptomatic HFrEF, improving exercise capacity and out-of-hospital time.[7-9]

For asymptomatic heart failure, however, clinical data is scarce and mostly derives from small subgroup analyses. Therefore, we here analyzed patients with HFrEF in New York Heart Association (NYHA) class I and hypothesize that ID is a common comorbidity occurring in these patients already and is associated with lower exercise capacity, anemia, inflammation, higher NT-pro BNP (reflecting ventricular overload) and depressive symptoms.

ID is currently defined as serum ferritin <100 µg/L or ferritin 100-299 µg/L with low transferrin saturation (TSAT) <20% in European Society of Cardiology (ESC) guidelines.[10] It should be noted, however, that evidence from smaller studies suggests soluble transferrin receptor (sTfR) to reflect myocardial iron most accurately, while also holding strong prognostic value in HF patients.[11] We therefore decided to evaluate iron status in this cohort of asymptomatic HFrEF via both ESC guideline-recommended definition of ID and serum sTfR level.

Materials and Methods

We analyzed data of 364 patients with asymptomatic HFrEF from the German Center of Cardiovascular Research (DZHK) cohort study *Transition from asymptomatic to symptomatic chronic heart failure* (TransitionCHF). Asymptomatic HFrEF was defined as patients with asymptomatic systolic HF in NYHA class I with left ventricular ejection fraction (LVEF) ≤40%, diagnosed by transthoracic echocardiography. Participants were allowed a maximum of one hospitalization for HF or less within two years prior to baseline. Additionally, a 6-minute walk test (6 MWT) distance result of ≥80% of the age-adapted reference value was required for inclusion. We excluded patients with significant valvular disease (>2nd degree), severe lung disease, recovery of LVEF to ≥50% at baseline, life expectancy of less than a year, pericardial diseases, hypertrophic cardiomyopathy, myocardial infarction in the previous three months, planned cardio-surgical intervention within three months of study inclusion or loop diuretic therapy within four weeks prior to inclusion. Baseline assessment included echocardiography, electrocardiogram (ECG), blood testing, psychological questionnaires, spirometry, 6 MWT and spiroergometry.

All patients underwent clinical examinations and further diagnostics at University Medical Center Göttingen, Germany. The study was conducted in accordance with the Declaration of Helsinki principles and local/national regulations. Ethical approval has been obtained from the leading ethics committee (Institutional Ethics Committee of the University Medicine Göttingen, approval number 2/10/14). The diagnosis of chronic HF was based on documented left ventricular impairment in echocardiography (LVEF ≤40%) according to guidelines.[10]

Laboratory analyses

Venous blood samples were taken after a resting period of 15 minutes. Following cell counts, blood samples were aliquoted and stored at -80°C at the local biobank of Göttingen University Center of Medical Care until further analysis.

All parameters were measured with standard techniques at the certified central laboratory of University Medical Center Göttingen.

Serum sTfR was measured by immunoturbidimetry using the Quantilab sTfR (II) assay by Instrumentation Laboratory (Biokit, S.A., Werfen, Barcelona, Spain) on an Architect c 16000 by Abbott (Abbot Park, IL, USA).

Iron deficiency

Iron deficiency was defined as serum ferritin <100 µg/L or ferritin 100-299 µg/L with TSAT<20%, with the former indicating absolute ID and the latter indicating functional ID.

Iron status was furthermore assessed by serum sTfR. Serum sTfR was measured in 325 out of 364 patients.

Anemia

Anemia was defined as hemoglobin <12 g/dL for women and hemoglobin <13 g/dL for men according to the WHO-recommended definition.

Psychological assessment for depression

HADS-D is a part of the Hospital Anxiety and Depression Scale (HADS), that is commonly used to detect patients with depressive symptoms.[12] It consists of 7 question items which are scored from 0-3 and add up to a total score. For this analysis, we used a cutoff score of 11 or higher, to determine depressive symptoms, which has been validated in large populations and shown to have a high specificity of 95% with a sensitivity of 44%.[12] 332 out of 364 patients completed a HADS-D questionnaire.

The Patient Health Questionnaire 9 (PHQ-9) consists of 9 items, with each item scoring from 0-3 and adding up to a total score.[13] A cutoff of 10 or higher was shown to be specific (85%) and sensitive (88%) for depression,[13] and was thus used in this analysis to discriminate between *no depressive symptoms* (score <10) and *depressive symptoms* (score ≥10). Out of 364 patients, 337 filled out the PHQ-9 questionnaire.

Exercise capacity

All patients in this cohort completed the 6 MWT with at least 80% of their age-recommended distance (as per inclusion criteria of the cohort study).
All patients were asked to participate in spiroergometry, with 309 patients consenting [ZAN® 600 Spiroergometer by ZAN Austria e.U., software supplied by nSpire™ Health GmbH (Oberthulba, Germany)]. Out of 309 patients undergoing spiroergometry, 50 patients were excluded from peak VO_2 analyses, because they failed to reach a respiratory exchange rate (RER) of at least 1.05, indicating insufficient effort. We measured peak oxygen consumption (peak VO_2/kg bodyweight) and minute ventilation to CO_2 production slope (VE-VCO_2 slope), with a higher VE-VCO_2 slope indicating lower breathing efficiency.

Statistical analysis

ID was used as a categorial variable with subgroups *ID* and *non-ID*. Serum sTfR was used as a continuous variable. Continuous variables are presented as means with standard deviation when normally distributed and as medians with upper and lower quartiles when showing a skewed distribution (NT-pro BNP, CRP and sTfR). When subgroups had a normal distribution, student's t-test or Welch's t-test (in case of unequal variances) was used to compare differences in means. For variables with skewed distribution, log transformation (ln) was performed prior to testing via student's t-test, or the Mann-Whitney-U test was used. Associations between other clinical variables and sTfR were tested in univariate linear regression models. Categorial variables were compared by using χ^2-test. Independent influence of parameters was subsequently analyzed by using a multivariable linear regression model. For this model, all independent variables did not show collinearity between one another. All statistical tests were evaluated one-sided with a significance of $p \leq 0.05$.
All statistical analyses were performed on SPSS 27.0.0.0 (IBM, USA 2020).

Results

Prevalence of iron deficiency

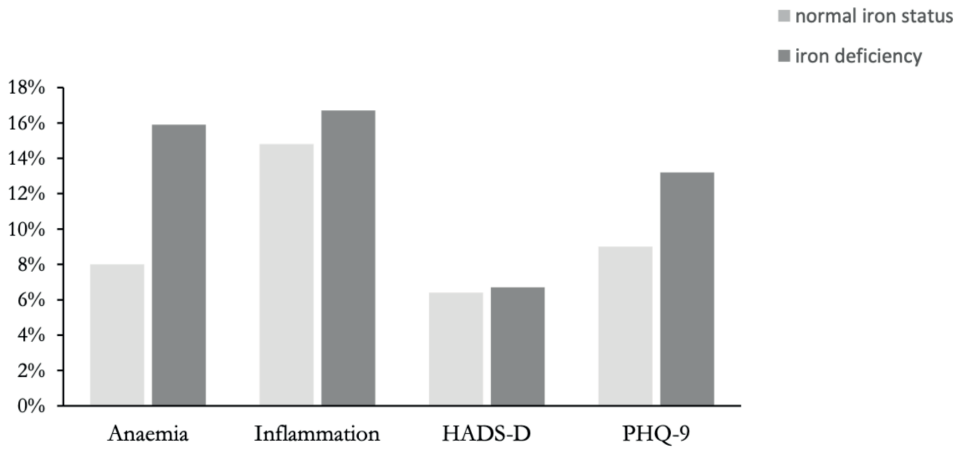
Prevalence of ID was 36.5% with 29.3% absolute ID and 7.2% functional ID. Baseline characteristics for patients with and without ID are shown in Table 1. Comorbidity prevalences for ID and non-ID subgroups are shown in Figure 1. Anemia was observed in 11% of all patients (37/364). Anemia was more common in ID patients compared to non-ID patients (15.9% *vs*. 8.2%, p=0.015) and in anemic patients, ID prevalence was 52.6%.

Inflammation

15.3% of patients (53/347) showed a serum CRP >5 mg/L, indicating inflammation.
Inflammation prevalence did not differ between ID and non-ID 16.7% *vs*. 14.8%, p=0.33, but patients with functional ID showed inflammation more often than patients with absolute ID (8/25 *vs*. 13/101, p=0.011).

Hemodynamic overload

NT-pro BNP was higher in ID patients than in non-ID patients [545 ng/L (201; 1226) *vs*. 428 ng/L (195; 783), p=0.047]. ROC-analysis for ID and NT-pro BNP is shown in Figure 2. NT-pro BNP cutoffs 430 ng/L, 780 ng/L and 1400 ng/L yielded 50%, 75% and 90% specificity for ID.



HADS-D, Hospital Anxiety and Depression-Scale; PHQ-9, Patient Health Questionnaire-9.

Figure 1. Anemia, inflammation and depressive symptoms according to HADS-D and PHQ-9 in patients with and without iron deficiency (ID). ID was defined as ferritin <100 µg/L or ferritin 100-299 µg/L with transferrin saturation <20% according to European Society of Cardiology guideline recommendations.

Depressive symptoms

HADS-D questionnaire: in the overall cohort, depressive symptoms were detected in 6.5% of patients with a similar prevalence in ID and non-ID patients (6.7% *vs*. 6.4%, p=0.46).
PHQ-9 questionnaire: in the overall cohort, depressive symptoms were found in 9.8% of patients. Prevalence of depressive symptoms again did not differ in ID *vs*. non-ID patients (13.2% *vs*. 9.0%, p=0.12).

Iron deficiency and impaired exercise capacity

6-MWT distance was lower in ID patients compared to non-ID patients (557 m ±99 *vs*. 577 m ±84, p=0.03). ID patients showed lower breathing efficiency indicated by higher VE-VCO_2 slope in spiroergometry (26.79±6.4 *vs*. 25.17±6.1, p=0.015), while peak VO_2/kg bodyweight did not differ (23.45 mL/kg ±7.3 *vs*. 22.91 mL/kg ±6.6, p=0.275).
In univariate regression models, we found higher sTfR to be as-

Table 1. Baseline characteristics for iron deficiency (ID) vs non-ID patients. ID was defined as ferritin <100 µg/L or ferritin 100-299 µg/L with transferrin saturation <20% according to European society of Cardiology guideline recommendations.

Parameter	Iron deficiency	Normal iron status	p
Age (years)	64.30±13.49	62.55±13.46	0.123
Female/male	35/91	27/192	<0.001
Body mass index	28.19±5.13	28.06±4.37	0.397
Left ventricular ejection fraction, %	36.69±4.58	36.17±5.89	0.181
Blood pressure (mmHg)			
Systolic	134.4±18.1	130.9±20.3	0.053
Diastolic	78.6±10.3	79.4±12.2	0.284
Pulse (bpm)	70.6±13.0	69.0±12.1	0.117
Cardiovascular risk factors, %			
Hypertension	69.0	62.6	0.287
Dyslipidemia	38.1	45.7	0.112
Diabetes mellitus	16.7	13.7	0.278
Atrial fibrillation	31.0	67.6	0.708
Smoking	65.1	61.2	0.175
Medical history, %			
Myocardial infarction	63.3	47.7	0.006
Coronary heart disease	74.8	63.9	0.039
Stroke	7.3	7.9	0.976
Laboratory measurements			
Hemoglobin (g/dL)	14.1±1.5	14.8±1.3	<0.001
Serum ferritin	69.0 {39.0; 92.5}	193.0 {142.0; 313.0}	<0.001
Transferrin saturation	20.0 {15.0; 27.0}	29.0 {25.0; 36.0}	<0.001
Soluble transferrin receptor	0.87 {0.71; 1.10}	0.78 {0.65; 0.88}	<0.001
C-reactive protein	1.55 {0.70; 3.40}	1.45 {0.70; 2.80}	0.169
Sodium	139.9±3.71	139.5±2.66	0.116
Potassium	4.56±0.50	4.51±0.39	0.210
Creatinine	0.95 {0.83; 1.10}	0.98 {0.87; 1.13}	0.243
eGFR	76.88±19.1	78.21±19.7	0.271
Concomitant treatment, %			
ACE-inhibitor	57.14	58.45	0.502
AR-antagonist	30.10	32.88	0.487
Beta-blocker	94.06	86.51	0.028
Aldosteron-antagonist	52.38	64.84	0.049
ASS	57.14	46.12	0.096
Statine	72.22	63.01	0.136
Other lipid-lowering	11.11	9.59	0.577
Cumarine	15.08	13.24	0.466
Direct oral anticoagulants	17.46	23.29	0.135
Insulin	4.76	3.67	0.663
Oral hypoglycemic agent	11.90	11.87	0.634
Thiazide diuretics	17.46	15.07	0.445
Digitalis glycoside	1.59	3.20	0.447

Iron deficiency is defined as serum ferritin <100 µg/L or serum ferritin 100-299 µg/L with transferrin saturation <20%. Stroke is defined as hemorrhagic or ischemic insult or transient ischemic attack. Smoking is defined as current smokers and ex-smokers.

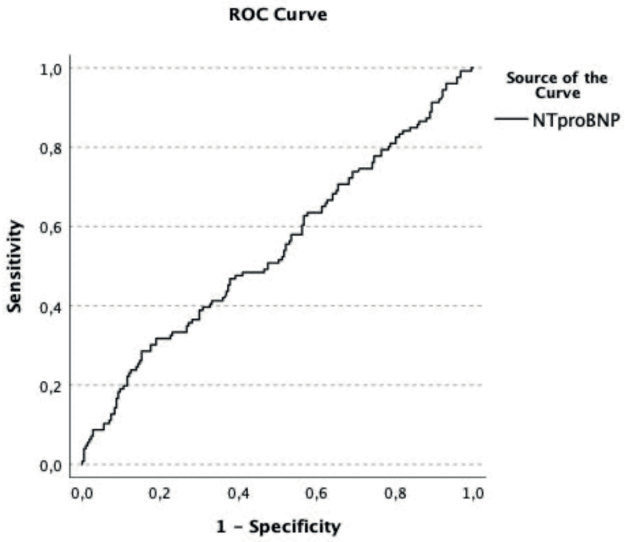


Figure 2. ROC-analysis for iron deficiency and NT-pro-B-type natriuretic peptide.

sociated with anemia, inflammation, ventricular overload and lower exercise capacity in form of 6MW distance, which is similar to ID by ESC definition. Results from univariate regression models are displayed in Table 2. Differences in 6MW distance according to the more widely used TSAT-based categorization are displayed in Table 3.

In a multivariable model with variables gender, BMI, age, anemia, LVEF, (ln)CRP, (ln)NT-pro BNP and ESC-D ID or ln(sTfR), 6 MW distance was predicted by gender, BMI, age, anemia and CRP (all p≤0.03, r=0.638 or 0.423, respectively). ID by ESC-D did not predict lower 6MW distance in this model (p=0.9) and neither did sTfR (p=0.7).

In a multivariable model with variables gender, BMI, age, anemia, LVEF, (ln)CRP, (ln)NT-pro BNP and ID (r=0.295), ID by ESC-D did in trend predict higher VE-VCO_2 slope (p=0.055). Furthermore NT-pro BNP predicted higher VE-VCO_2 slope (p=0.001). All other variables did not predict lower breathing efficiency in this model (all p≥0.24).

In the same model with (ln)sTfR (r=0.282) instead of ESC-D ID, only NT-pro BNP predicted higher VE-VCO_2 slope (p<0.001, standardized coefficient β=0.26, partial correlation coefficient=0.22), but not sTfR (p=0.6).

Results from multivariable regression models with ESC-D and (ln)sTfR are shown in Table 4.

Table 2. Results of univariate regression for soluble transferrin receptor.

Parameter	Standardized coefficient β	r	p
Gender	0.025	0.032	0.66
Age	0.126	0.126	0.02
Body mass index	-0.006	0.000	0.9
Anemia	0.122	0.122	0.014
Inflammation	0.118	0.118	0.017
Hospital anxiety and depression scale-D	0.012	0.000	0.8
Patient health questionnaire-9	-0.020	0.000	0.7
Left ventricular ejection fraction	-0.024	-0.032	0.7
(ln) NT-pro-B-type natriuretic peptide	0.203	0.202	<0.001
(ln) C-reactive protein	0.135	0.134	0.007
(ln) hemoglobin	-0.074	-0.071	0.2
Estimated glomerular filtration rate	-0.200	-0.200	<0.001
6-minute walk test	-0.138	-0.138	0.007
PeakVO_2 per kg body weight	-0.115	-0.106	0.038
Ventilation/carbon dioxide production slope	0.018	0.000	0.8

Table 3. Exercise capacity stratified by transferrin saturation (TSAT). Standard deviation is given for each TSAT level and indicated by ±.

Parameter	TSAT <20% (n=69)	TSAT 20-25% (n=92)	TSAT >25% (n=189)	ANOVAp	F
Peak VO_2, mL min-1 kg^{-1}	22.72±7.35	22.76±6.70	22.16±6.81	0.7	0.4
Ventilation/carbon dioxide production slope	26.71±7.42	25.20±5.63	25.84±6.04	0.5	0.7
6-minute walk test, m	565±90	581±74	589±86	0.003	5.9
Left ventricular ejection fraction, %	6.84±4.38	35.92±5.65	36.45±5.70	0.5	0.64
NT-pro-B-type natriuretic peptide, ng/L^{-1}	1079±1581	719±877	672±854	0.2	1.6

Discussion

This study shows for the first time in a large cohort of asymptomatic (NYHA 1) HFrEF patients that ID is a common comorbidity with a prevalence of 36.5% (29.3% absolute ID and 7.2% functional ID) already in this early stage of HF.

This prevalence is larger than previously assumed from data in small NYHA 1 subgroups.[2,4] In our cohort, ID was associated with ventricular overload, anaemia, inflammation and impaired exercise capacity, but not with depressive symptoms.

Iron deficiency and anemia

Anemia was a relevant comorbidity in this cohort with a prevalence of 11%. This prevalence is higher than the anemia prevalence in healthy patient cohorts,[14] and lower than anemia prevalence in symptomatic HF, where it ranges from 17.5% in NYHA class 2 to 27.5% in NYHA 3 and 4.[15] As anemia has been linked to lower peak VO_2,[2] more frequent hospitalizations, worsening of HF and lower survival in HF patients,[15] it is an important comorbidity with a relevant prevalence in NYHA 1 patients already and possibly could have prognostic value in these patients as well. Since more than half of anemic patients were also iron deficient (by ESC-D), IVIT might be a valuable therapeutic approach towards treating both ID and anemia in these patients. The impact of anemia in NYHA 1 patients and a possible contribution towards a transition to symptomatic HF should be subject to further studies.

Iron deficiency and inflammation

Inflammation prevalence was 15.3% in the whole cohort and 16.7% in all ID patients. However, inflammation was twice as prevalent in patients with functional ID as in patients with absolute ID (32.0% *vs*. 12.9%), with 80% of ID patients showing absolute ID and 20% of patients showing functional ID. Since inflammation was defined as CRP >5 mg/L in this cohort, it seems likely that more precise diagnostic measures of inflammatory status such as hs-CRP or IL-6 might yield even higher prevalences of inflammation.

ID has been linked to higher serum CRP in HF patients and was associated with increased mortality.[5] Although mild systemic inflammation is generally considered to be a cause of ID in HF patients, the impact of iron deficiency itself on the inflammatory status is uncertain.

Drug-based anti-inflammatory treatment approaches for inflammation in HF have been evaluated before, but did not yield promising results.[16] However, sodium glucose transporter 2 (SGLT-2) inhibitors have been thought to exert anti-inflammatory effects leading to a potential alleviation of a state of inflammation-related functional iron deficiency according to cytosolic iron repletion hypothesis.[17] Therefore, our cohort may serve as a relevant comparison group as all patients were SGLT-2 inhibitor-naive. The effect of ID repletion on inflammatory status remains understudied and could be subject to future studies.

Iron deficiency and ventricular overload

In this cohort, ID was associated with higher NT-pro BNP levels, indicating increased ventricular overload. This has also been shown in HF cohorts primarily consisting of patients in higher NYHA stages.[3] As higher levels of NT-pro BNP predict higher mortality in HF patients,[18] therapeutic success is often indicated by a decrease in NT-pro BNP levels in clinical practice.[19] As ID in this cohort was severely more prevalent in patients with higher NT-pro BNP levels, the results of ROC analysis within this study suggests assessing iron status in asymptomatic HFrEF patients with NT-pro BNP >1400 ng/L, which identified ID patients with a 90% specificity in our asymptomatic HFrEF cohort.

Iron deficiency and depressive symptoms

We detected depressive symptoms in 6.5% of the total cohort by HADS-D and 9.8% by PHQ-9. Depressive symptoms did not

Table 4. Multivariable regression model for iron deficiency and exercise capacity.

Determinant	Iron deficiency				ln (sTFR)	
	VE-VCO_2 slope**		6 MW distance***		6 MW distance****	
	Standardized β coefficient	Partial correlatory coefficient	Standardized β coefficient	Partial correlatory coefficient	Standardized β coefficient	Partial correlatory coefficient
Gender	0.069	0.068	-0.208*	-0.251	-0.201*	-0.250
Age	0.038	0.036	-0.477*	-0.487	-0.495*	-0.509
Body mass index	0.022	0.021	-0.233*	-0.261	-0.257*	-0.288
Anemia	0.055	0.054	-0.169*	-0.199	-0.162*	-
Left ventricular ejection fraction	-0.025	-0.025	0.060	0.073	0.046	0.056
(ln) C-reactive protein	-0.012	-0.012	-0.134*	-0.156	-0.133*	-0.156
(ln) NT-pro-B-type natriuretic peptide	0.220*	0.187	-0.77	-0.080	-0.082	-0.086
Iron deficiency	0.097	0.097	-0.021	-0.026	-0.014	-0.018

*p<0.05; **r=0.295; ***r=0.638; ****r=0.423.

sTFR, soluble transferrin receptors; VE-VCO_2, ventilation/carbon dioxide production; 6 MW, 6-minute walk.

Iron deficiency was defined as ferritin <100 µg/L or ferritin 100-299 µg/L with transferrin saturation <20% according to European society of Cardiology guideline recommendations.

differ between ID and non-ID patients for each questionnaire, and neither were associated with sTfR levels. In contrast to depression prevalence reaching up to 42% in higher NYHA classes,[20] the prevalence of depressive symptoms in our NYHA 1 cohort was actually closer to the prevalence of depression within the general population.[21] Iron plays a central role by contributing as a cofactor for the rate-controlling enzyme of monoamine synthesis,[22] which is a plausible pathophysiological mechanism for depression in ID. However, clinical manifestation of depressive symptoms is a multifactorial process. The low prevalence of depressive symptoms in our cohort could be related to a lesser impairment of daily life activities and better exercise capacity in NYHA 1 as compared to higher NYHA classes, which are commonly related to poor health-related quality of life.[3] Given the low prevalence of depressive symptoms in our cohort, a larger cohort might be necessary to detect an association between ID and depressive symptoms. This is supported by the fact that there has been evidence towards depressive patients showing lower ferritin than non-depressive patients in healthy cohorts.[6] However, as we have recently demonstrated that brain iron levels in patients of higher NYHA classes remain unchanged after iron repletion by IVIT,[23] it is implied that intravenous iron would not reach the brain and that brain iron homeostasis might be largely unaffected by systemic ID. An indirect effect of systemic iron repletion, which positively affects mental state (*e.g*. through improved physical performance and quality of life) seems plausible and should be investigated in further detail, especially since depression in HF is very resilient to conventional treatment for depression.[24]

Iron deficiency and exercise capacity

ID patients in our cohort showed lower 6MW distance and higher VE-VCO_2 slope (lower breathing efficiency) than non-ID patients, while peakVO_2 was similar in both groups. When assessing iron status by sTfR, we found lower 6 MW distance to be associated with higher sTfR. In a multivariable model, lower 6 MW distance was predicted by age, gender, BMI, anemia and (ln)CRP, but not by ID. When using the same multivariable model for lower breathing efficiency, a strong trend towards lower breathing efficiency in ID remained. Furthermore, NT-pro BNP also predicted lower breathing efficiency.

In other HF cohorts consisting of patients in higher NYHA classes, ID predicted not only lower breathing efficiency,[2] but also lower peak VO_2 independently of anemia and other confounders.

These findings appear to be less distinct than the findings in the current study, however the aforementioned study cohorts severely underrepresented NYHA 1 patients. Furthermore, as one of the inclusion criteria of our study was reaching at least 80% of the age-recommended 6MW distance, our cohort was intentionally selected for patients less affected by impaired exercise capacity. This is supported by the fact that our patients showed higher median peak VO_2, higher breathing efficiency and longer median 6MW distances than other HF cohorts and is therefore rather similar to the general population in regard to exercise capacity. A VE-VCO_2 slope above 33 is considered predictive for higher mortality and morbidity in HF,[25] yet only 9.1% of patients in our total cohort showed such a high slope. For peak VO_2, values ≤14 mL/kg bodyweight are related to higher mortality,[25] which were seen in only 6.7% of our cohort. This further indicates the generally well-preserved exercise capacity in our cohort. Therefore, it can be argued that NYHA 1 patients can tolerate the negative impact of ID to an extent, but are nonetheless affected, as demonstrated by the robust findings on lower breathing efficiency in our cohort.

In HF patients of higher NYHA classes, iron repletion has already been demonstrated to improve 6 MW distance and peak VO_2,[7,26] and leads to less hospitalizations.[8] It therefore seems likely that patients would benefit from extending the current range of effective intravenous iron repletion schemes,[27,28] from NYHA 2 and higher into NYHA 1. It is tempting to speculate whether iron repletion could prevent deterioration of breathing efficiency and the transition to higher NYHA classes, as this might preserve the patient's capability to perform regular exercise training. Such training has in turn been associated with decreased NT-pro BNP and increased peak VO_2,[29] higher quality of life and less hospitalizations.[30] A synergistic effect between these two therapeutic approaches seems plausible and should therefore be a target for future HF studies.

Conclusions

ID is a common comorbidity already in asymptomatic HFrEF patients. In a multivariable model, NT-pro BNP and in trend ID independently predicted lower breathing efficiency. NT-pro BNP >1400 ng/L yielded 90% specificity for ID. Therefore, the issue whether ID is associated with worsening of breathing efficiency and transition to higher NYHA classes should be subject of further studies.

Limitations

Patients in this cohort were acquired from a single hospital (Universitary Center of Medical Care Göttingen) as this is a sub study of the larger multicenter TransitionCHF study. Female gender is a known risk factor for iron deficiency; therefore, women were overrepresented in the iron deficiency group.

Conflict of interest

The authors declare no potential conflict of interest.

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