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SHORT COMMUNICATION

Left ventricular ejection fraction recovery in patients with heart failure treated with intravenous iron: a pilot study

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Abstract

Aims In patients with heart failure with reduced ejection fraction (HFrEF) and iron deficiency, treatment with intravenous iron has shown a clinical improvement regardless of anaemic status. Cardiac magnetic resonance (CMR) T2* sequence has shown a potential utility for evaluating myocardial iron deficiency. We aimed to evaluate whether T2* sequence significantly changes after ferric carboximaltose (FCM) administration, and if such changes correlate with changes in left ventricle ejection fraction (LVEF).

Methods and results In this pilot study, we included eight patients with chronic symptomatic (New York Heart Association II–III) HFrEF and iron deficiency. A CMR, including T2* analysis, was performed before and at a median of 43 days (interquartile range = 35–48) after intravenous FCM administration. Pearson or Spearman correlation coefficient (r) was used for bivariate contrast as appropriate. A partial correlation analysis was performed between ΔLVEF and ΔT2* while controlling for anaemia status at baseline. Anaemia was present in half of patients. After FCM administration, T2* decreased from a median of 39.5 (35.9–48) to 32 ms (32–34.5), $P = 0.012$. Simultaneously, a borderline increase in median of LVEF [40% (36–44.5) to 48.5% (38.5–53), $P = 0.091$] was registered. In a bivariate correlational analysis, ΔT2* was highly correlated with ΔLVEF ($r = -0.747$, $P = 0.033$). After controlling for anaemia at baseline, the association between ΔT2* and ΔLVEF persisted [r(partial): −0.865, R^2(partial): 0.748, $P = 0.012$]. A median regression analysis backed-up these findings.

Conclusions In a small sample of patients with HFrEF and iron deficiency, myocardial iron repletion assessed by CMR was associated to left ventricular remodelling. Further studies are warranted.

Keywords Iron deficiency; Intravenous iron; Left ventricular ejection fraction; Systolic heart failure; Magnetic resonance imaging; T2* sequence

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Introduction

In patients with heart failure with reduced ejection fraction (HFrEF), treatment with intravenous iron has shown to improve symptoms, functional capacity, and quality of life regardless of anaemic status.[1,2] Experimental studies have shown that iron deficiency (ID) led to structural and functional abnormalities of the heart.[3] In humans, a small report showed a reduction in iron content of cardiomyocytes of patients with HFrEF compared with controls.[4] More recently, in a small clinical trial of patients with HFrEF, anaemia, and chronic kidney disease, intravenous iron treatment was

associated with improved myocardial function and cardiac dimensions.[5] Such findings led some authors to postulate that part of the beneficial effect of iron treatment in HFrEF is attributed to myocardial iron repletion.[6] Nevertheless, no study so far has evaluated the short-term effect of intravenous iron therapy on myocardial iron content and its correlation with simultaneous changes in left ventricular (LV) function. Cardiac magnetic resonance (CMR) T2* sequence has emerged as a reliable non-invasive technique for assessing myocardial iron overload.[7,8] Recently, this technique has also shown a potential utility for evaluating myocardial iron deficiency.[9,10]

Aims

We aimed to evaluate whether (i) T2* sequence significantly changes after intravenous iron administration in patients with ID with HFrEF, and (ii) if such changes correlate with simultaneous changes in CMR LV systolic function.

Methods

Study sample

In this observational pilot study, eight patients visited in the heart failure (HF) unit of a third-level hospital from 29 January 2015 to 26 October 2015 were included. All of them met the following inclusion criteria: (i) ID, defined as serum ferritin $<100\ \mu g/L$ or as ferritin 100–299 $\mu g/L$ with a transferrin saturation $<20\%$; (ii) New York Heart Association (NYHA) functional class $\geq$II; (iii) clinical stability during the last 3 months; and (iv) left ventricular ejection fraction (LVEF) $<50\%$ assessed by transthoracic echocardiography within the last 3 months. In addition, the patients were excluded if any of the following were documented: (i) severe to moderate primary valve heart disease; (ii) acute coronary syndrome, cardiac surgery, or revascularization within the previous 3 months; and (iii) patients with pacemakers, intracardiac defibrillators, and cardiac resynchronization devices. Informed consent was obtained from every patient, and the study protocol conforms to the Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Protocol

Clinical, laboratory, electrocardiographic, distance walked in 6 minutes (6MWT), Minnesota Living with Heart Failure Questionnaire (MLHFQ), and treatment characteristics were recorded in electronic forms. The patients enrolled underwent a CMR within the first 7 days after ID diagnosis. Following CMR, a single dose of 1000 mg of ferric carboximaltose (FCM) was administered to all patients. A second CMR, blood laboratory, clinical assessment, 6MWT, and MLHFQ were performed at a median of 43 days [interquartile range (IQR) = 35–48] after FCM administration. Anaemia was defined as haemoglobin (Hb) level <12 g/dL in women and <13 g/dL in men.

CMR

All CMR studies (1.5 T unit, Magnetom Sonata, Siemens, Erlangen, Germany) were performed by the same operator. Steady-state free precession cine sequences at rest were made, and the following were quantified: LV end-diastolic and end-systolic volumes (LVEDV and LVESV) (mL/m^2), LV end-systolic diameter, LVEF determined by the Simpson method (%), and LV mass (g/m^2) determined by manually outlining the endocardial borders in all short-axis cine slices.

The basic T2* pulse sequence was a single breath-hold, multi-echo, gradient echo T2* sequence. In brief, a six-element cardiac phased array coil and a chest saturation band were used to image a single 10 mm mid-ventricular short axis slice at eight echo times from ~2 to ~18 with 2.0 ms increments. Data were acquired every other cardiac cycle.

For T2* analysis, a region of interest was chosen in the mid-left ventricular septum. The mean signal intensities of region of interest were measured in the series of increasing echo time images to give an exponential decay curve. The monoexponential decay model and the nonlinear curve fitting algorithm were used to fit the curve to obtain T2* measurement. An example of T2* calculation is shown in *Figure S1*.

Endpoints

Absolute changes in LVEF (ΔLVEF) (%) were selected as the main endpoint. Secondary endpoints were absolute changes in LV mass (ΔLVmass) (g/m^2), LVEDV (ΔLVEDV) (mL/m^2), and LVESV (ΔLVESV) (mL/m^2). Reverse remodelling was defined as (i) LVEF increase $\geq$ 15%, or (ii) LVEF increase $\geq$10% + LV end-systolic diameter reduction $\geq$ 20%, or LVESV reduction $\geq$ 40%.

Statistical analysis

Continuous variables were expressed in alignment with their distribution, and discrete variables were expressed as percentages. The median was always presented with IQR = 25–75 percentiles as a measure of dispersion. The equality of each pair of pre–post observations was tested either with paired *t*-test or Wilcoxon matched-pair signed-rank test as appropriate.

Pearson or Spearman correlation coefficient (r) was used for bivariate contrast as appropriate. A partial correlation analysis was performed between ΔLVEF (dependent variable or Y) and ΔT2* (independent variable or X) while controlling for anaemia status at baseline (X2). Within the same framework, ΔLVmass, ΔLVEDV, and ΔLVESV were contrasted with ΔT2*. The partial correlation coefficient [*r*(partial)] reflects the degree of correlation between X and Y after removing the effect of X2 on Y and X2 on X. By the same token, the R^2(partial) is interpreted as the proportion of shared variance between Y and X controlling for X2. To add robustness to the correlational analysis, we also tested the relationship between ΔT2* and the median of ΔLVEF by using quantile regression analysis ($q = 0.5$). In this latter analysis, anaemia at baseline and changes in haemoglobin were used as covariates. A sensibility analysis assessing the relationship between inverse of T2* (R2*) and changes in left ventricular systolic function was also performed.

Results

The median (IQR) age was 81 (69–83) years; 62.5% patients were women, 62.5% displayed NYHA III, and 87.5% were of non-ischemic aetiology. Anaemia was present in half of patients. The median of LVEF, NT-proBNP, and estimated glomerular filtration rate were 40% (36–45), 3868 pg/mL (1680–4841), and 38 mL/min/1.73 m^2 (26–47), respectively. Baseline characteristics are summarized in *Table 1*.

Table 1. Baseline characteristics

Variable	*n*=8
Demographics and medical history	
Age, years[b]	81 (69-83)
Female, n (%)	5 (62.5)
Hypertension, n (%)	7 (87.5)
Diabetes Mellitus, n (%)	5 (62.5)
Dyslipidemia, n (%)	4 (50)
Active smoker, n (%)	2 (25)
Chronic renal disease, n (%)	5 (62.5)
Ischemic heart disease, n (%)	1 (12.5)
NYHA class III, n (%)	5 (62.5)
Atrial fibrillation, n (%)	4 (50%)
Vital signs and physical examination	
Systolic blood pressure, mmHg[b]	122 ± 14
Diastolic blood pressure, mmHg[b]	61 ± 10
Heart rate, bpm[b]	75 ± 13
Peripheral edema, n (%)	4 (50)
Laboratory data	
Hemoglobin, g/dL	12.2 ± 1.7
Anemia[a], n (%)	4 (50)
Ferritin, mg/dL	126 (32-210)
Transferrin saturation, %	17.7 (15.3-19.8)
Sodium, mEq/L[b]	140 ± 2
Potassium, mg/dL[b]	4.5 ± 0.5
Urea, mg/dL[b]	106 ± 44
Creatinine, mg/dL[b]	1.79 ± 0.62
eGFR, mg/dL/1.73 m^2	38 (26-47)
CA125, U/mL	20 (18-29.5)
NT-proBNP, pg/mL	3868 (1680-4841)
Cardiac magnetic resonance	
LVEF, %	40 (36-45)
LVEDV, mL/m^2	105.5 (90-129)
LVESV, mL/m^2	67 (49-81)
LV mass, g/m^2	92 (79.5-96.5)
Medical treatment	
Diuretics, n (%)	8 (100)
Loop diuretics dose, mg/day	60 (40, 80)
Betablockers, n (%)	8 (100)
Aldosterone blockers, n (%)	8 (100)
ACEI, n (%)	5 (62.5)
ARB, n (%)	1 (12.5)
Statins, n (%)	6 (75)

NYHA: New York Heart Association; eGFR: estimated glomerular filtration rate; CA125: antigen carbohydrate 125; NT-proBNP: amino-terminal pro-brain natriuretic peptide; LVEF: left ventricle ejection fraction; LVEDV: left ventricle end-diastolic volume; LVESV: left ventricle end-systolic volume; LV: left ventricle; ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers.
[a]Anemia was defined as hemoglobin lower than 13 mg/dL in men and 12 mg/dL in women. Values for continuous variables are expressed as median (interquartile range). Values for continuous variables are expressed as median (interquartile range) unless otherwise specified.
[b]Variable expressed as mean ± standard deviation.

Clinical, laboratory, and CMR changes after intravenous FCM

Clinical, laboratory, and CMR changes after intravenous FCM are shown in *Table 2*. Briefly, NYHA class improved in 50% of patients, and median 6MWT also showed a significant improvement. There was also an associated significant increase in the median of ferritin [126 μg/L (32 to 210) to 620 μg/L (535–814), $P = 0.012$] and transferrin saturation [17.7% (15.3–19.8) to 29.6% (28.1–31.4), $P = 0.012$]. The increase in Hb was borderline significant (12.2 ± 1.7 mg/dL vs. 12.8 ± 1.9 mg/dL, $P = 0.088$). Regarding CMR parameters, T2* decreased from a median of 39.5 ms (35.9–48) to 32 ms (32–34.5), $P = 0.012$ (*Figure 1a*). Likewise, R2* significantly increased after FCM (*Figure S2*). Simultaneously, a borderline increase in the median of LVEF [40% (36–44.5) to 48.5% (38.5–53) $P = 0.091$] and a decrease in the median of LVESV [67 mL/m^2 (49–81) to 55 mL/m^2 (48–68), $P = 0.093$] were registered (*Figure S1*). Reverse remodelling was observed in four patients (50%). No significant changes were found for LV end-diastolic volumes, LV mass, MLHFQ, or other biomarkers (*Figure S1* and *Table S1*).

Absolute changes in T2* and LVEF CMR parameters

In a bivariate correlational analysis, ΔT2* was highly correlated with ΔLVEF ($r = -0.747$, $P = 0.033$). After controlling for anaemia at baseline, the association between ΔT2* and ΔLVEF persisted [r(partial) = −0.865, R^2(partial) = 0.748, $P = 0.012$]. A median regression analysis backed-up these findings. Indeed, per decrease in 1 unit of ΔT2*, there

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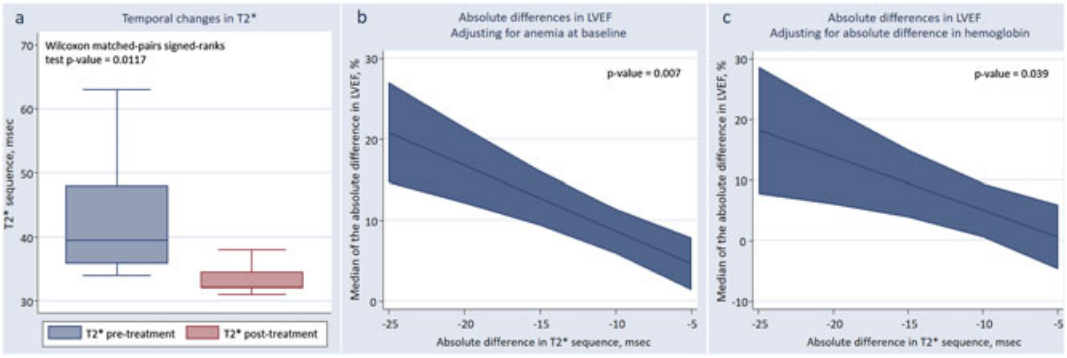
Table 2. Changes in patients' characteristics after FCM administration

Variable	First assessment	Second assessment	*P*-value
Laboratory data			
NT-proBNP, pg/mL	3868 (1680-4841)	3120.5 (1430-5788)	0.674
eGFR, mg/dL/1.73 m^2	38 (26-47)	44 (29-51)	0.123
Hemoglobin, g/dL[a]	12.2 ± 1.7	12.8 ± 1.9	0.088
Ferritin, mg/dL	126 (32-210)	620 (535-814)	0.012
Transferrin saturation, %	17.65 (15.3-19.8)	29.6 (28.05-31.35)	0.012
Vital signs			
SBP, mmHg[a]	122 ± 14	130 ± 24	0.134
DBP, mmHg[a]	61 ± 10	69 ± 18	0.136
Heart rate, bpm	72 (65.5-87)	68.5 (60-87)	0.205
Functional capacity			
NYHA class≥III	5 (63%)	1 (13%)	0.039
6MWT	198 (160-236)	276 (169-342)	0.011
Quality of life			
MLHFQ	55 (18-68)	27 (15-48)	0.293

FCM: ferric carboximaltose; NT-proBNP: amino-terminal pro-brain natriuretic peptide; eGFR: estimated glomerular filtration rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; 6MWT; 6-minute walk test; MLHFQ: Minnesota Living with Heart Failure questionnaire
Values for continuous variables are expressed as median (interquartile range) unless otherwise specified.
[a]Variable expressed as mean ± standard deviation.

Figure 1 (a) Temporal changes in median of cardiac magnetic resonance T2* sequence after intravenous ferric carboximaltose administration. (b) ΔLVEF and ΔT2*, adjusting for anaemia at baseline. (C) ΔLVEF and ΔT2* adjusting for changes in haemoglobin. CMR, cardiac magnetic resonance; FCM, ferric carboximaltose; ΔLVEF, changes in left ventricular ejection fraction; ΔT2*, changes in T2*.



was an associated increase in the median of LVEF by a factor of 0.81 ($P = 0.007$), having the sample adjusted by anaemia at baseline (*Figure 1b*). The results did not significantly change when absolute difference in pre–post Hb was used instead as covariate (per decrease in 1 unit of ΔT2* and increase in the median of LVEF of 0.88, $P = 0.039$), as shown in *Figure 1c*. Likewise, the correlation analysis also showed a borderline positive correlation between ΔLVEF and ΔR2* ($r = 0.65$; $R^2 = 0.421$; $P = 0.082$); after adjusting for anaemia at baseline, such association became significant ($r = 0.795$; $P = 0.0325$)

Absolute changes in T2* and other CMR parameters

ΔT2* was borderline correlated with ΔLVESV ($r = 0.663$, $P = 0.073$), but it was not with ΔLVEDV ($r = 0.052$, $P = 0.903$) nor ΔLVmass ($r = 0.436$, $P = 0.280$). After adjusting for anaemia at baseline, the association between ΔT2* and ΔLVESV became significant [r(partial) = 0.906, R^2(partial) = 0.821, $P = 0.005$]. Similarly, a quantile regression analysis showed that the associations with ΔLVESV were significant and in the same direction after adjusting either for anaemia at baseline or ΔHb (β-coefficient = 0.65, $P = 0.007$ and β-coefficient = 1.11, $P = 0.048$, respectively).

Discussion

This is the first study reporting a significant decrease in myocardial T2* sequence after intravenous FCM administration. In addition, we found a significant association between T2* changes and short-term improvement in LVEF and LVESV in a small group of elderly patients with chronic HFrEF of

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predominant non-ischemic aetiology and ID. Interestingly, the association persisted independent of Hb changes.

During the last decade, ID has become a well-recognized therapeutic target in HFrEF.[1,2,11] Two large randomized placebo-controlled trials have shown that intravenous iron administration was associated to improvement in symptoms, functional capacity, quality of life, and reduction in HF hospitalizations.[1,2] However, the pathophysiological mechanisms underlying the effect of iron administration in HF remain poorly understood, because clinical benefits have been observed irrespective of anaemia status.[1,2] Iron is a chemical element that plays a central role in the oxidative metabolism and muscle oxygen storage and transport.[12]

Despite the crucial role of iron in the physiology of cardiovascular system, this element remains understudied outside of the erythropoietic system. Experimental studies have shown that ID induced cardiac dysfunction[13] and cardiac hypertrophy, characterized by aberrant mitochondrial and irregular sarcomere organization.[14]

Given previous evidence, it seems plausible to speculate that ID may play a causative role in the pathophysiology of HF beyond anaemia.[4,6,11] Recently, Toblli *et al*., in a small randomized trial in patients with HFrEF, ID, and chronic kidney disease, showed that iron sucrose administration translated into a significant 6-month improvement in LVEF by echocardiography estimation (6.6 ± 3.8%).[5] More recently, findings from a cohort of 232 patients undergoing renal transplantation showed an increase of LVEF, particularly notorious in those with systolic dysfunction pretransplantation.[15] Because these changes were strongly and positively related to haemoglobin changes following transplantation, the authors speculated a potential causal link between ID-anaemia and HF progression in patients with chronic renal failure.[15] Interestingly, all patients included in the present study displayed concomitant renal dysfunction. In summary, our results corroborate the prior findings and add new evidence, suggesting that myocardial iron repletion may explain, at least partially, the beneficial effects of intravenous iron administration observed in prior studies.

There are important limitations that need to be acknowledged. First, this is small single centre observational study using one magnetic resonance imaging system. However, we believe that eight patients in a pre–post testing design provide enough statistical power to detect the obtained effect size in T2* with an alpha of 0.05. Second, T2* is a well-established sequence for quantification iron overload, but the reliability for assessing ID remains more debatable. Third, the magnitude of CMR changes may be explained in part because of the inherent variability of the technique. Further studies aiming to evaluate the reproducibility of T2* measurements are necessarily warranted.

Conclusions

In a small sample of patients with HFrEF, ID, and renal dysfunction, myocardial iron repletion, as assessed by CMR, was associated to left ventricular remodelling. Further studies are needed.

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Supporting information

Supporting information may be found in the online version of this article.

Figure S1. Example of T2* measurement before and after intravenous carboximaltose administration.

Figure S2. Cardiac magnetic resonance changes after intravenous carboximaltose administration. R2*: Inverse of T2*LVEF: left ventricle ejection fraction; LVEDV: left ventricle end-diastolic volume; LVESV: left ventricle end-systolic volume; LVM: left ventricular mass.

Table S1. Changes in patients' characteristics after FCM administration.

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