



# Positive effect of intravenous iron-oxide administration on left ventricular remodelling in patients with acute ST-elevation myocardial infarction – A cardiovascular magnetic resonance (CMR) study

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## ABSTRACT

**Objectives:** This study investigated the safety profile and potential “therapeutic” effect of intravenous ultrasmall superparamagnetic iron-oxide (USPIO)-based iron administration regarding infarct healing in patients with ST-elevation myocardial infarction (STEMI). USPIO-administration was recently shown to enable an improved characterization of myocardial infarct pathology in acute STEMI patients.

**Materials and Methods:** Seventeen study patients (IRON,  $54 \pm 9$  yrs, 88% male) and 22 matched controls (CONTROL,  $57 \pm 9$  yrs, 77% male) both with primary reperused STEMI underwent multi-parametric CMR studies in the first week and three months after acute MI. Only IRON patients received a single intravenous bolus of 510 mg elemental iron as ferumoxytol (Feraheme™) within four days following acute MI.

**Results:** Three months later, all patients were alive and there were no adverse cardiac events. Significant improvement in left ventricular (LV) ejection fraction (IRON:  $53 \pm 10\%$  to  $59 \pm 9\%$ ,  $p = 0.002$ ; CONTROL:  $54 \pm 6\%$  to  $57 \pm 10\%$ ,  $p = 0.005$ ) as well as shrinkage of infarct size were seen in both groups at follow-up. There was a more pronounced decrease in infarct size in the IRON group (IRON:  $-10.3 \pm 5.4\%$  vs. CONTROL:  $-7.0 \pm 8.4\%$ ,  $p = 0.050$ ) in addition to a significant decrease in both endocardial extent and prevalence of transmural infarctions in IRON but not in CONTROL patients. A significant decrease in LV end systolic volume was only seen in the IRON group ( $71 \pm 25$  mL to  $59 \pm 25$  mL,  $p = 0.002$ ).

**Conclusions:** Intravenous iron administration in acute STEMI patients seems to be associated with an improved infarct healing and a beneficial global left ventricular remodelling. These findings together with the good safety profile make USPIO-based iron administration a promising future candidate as a “diagnostic” and “therapeutic” adjunctive solution in acute MI management.

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## 1. Introduction

Primary reperfusion by percutaneous coronary intervention (PCI) has become the standard treatment in ST-segment elevation myocardial infarction (STEMI). Successful PCI reduces infarct size, preserves left ventricular (LV) function and improves survival [1–3]. Nevertheless,

despite early recanalization of obstructed coronaries, subsequent adverse LV remodelling with progressive LV dilation and decrease in LV function remains an important clinical and prognostic issue. Up to two thirds of STEMI patients treated with primary PCI present with LV dilation at four months and approximately one third of them continue to show progressive dilation at six months [3,4]. In such patients, infarct mass was the best predictor of adverse remodeling [3]. Therefore, intensive efforts are currently made in order to find new adjunctive therapies to PCI aiming at reducing infarct size and improving ventricular remodeling following acute MI [5].

In the last decades, the role of iron metabolism in cardiovascular disease has been extensively explored [6–11]. Treatment with intravenous iron in patients demonstrating iron deficiency and suffering from ischemic as well as non ischemic chronic heart failure did not only improve symptoms, but also functional capacity and quality of life – even in the absence of anemia [12]. On the other hand, in the acute setting of STEMI, changes in iron status – with a decline in circulating levels and

**Abbreviations:** BfArM, German Federal Institute for Drugs and Medical Devices; CAD, coronary artery disease; ceCMR, contrast-enhanced CMR; CMR, cardiovascular magnetic resonance imaging; LGE, late-gadolinium-enhancement; MI, myocardial infarction; MVO, microvascular obstruction; NIMINI-MMRI, Non-invasive myocardial inflammation imaging based on new molecular magnetic resonance imaging contrast agents and methods; PCI, percutaneous coronary intervention; SE, spin-echo; SPIO, superparamagnetic iron oxide nanoparticles; SSFP, steady-state free precession; STEMI, ST-elevation myocardial infarction; STIR, short tau inversion recovery; USPIO, ultrasmall superparamagnetic iron oxide nanoparticle.

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rise in iron stores as expressed by serum Ferritin – are documented but their exact role and clinical significance is still to be elucidated [7,11]. So far, there are no data available regarding the safety and potential therapeutic or detrimental effect of iron administration in patients with acute MI.

Recently, ferumoxytol (Feraheme™), an ultrasmall superparamagnetic iron oxide (USPIO) with a particle diameter of ~30 nm, was approved for iron-replacement therapy in patients with anemia due to chronic renal failure by the FDA. As described previously, iron-oxide nanoparticles accumulate in lysosomes (following cellular internalization), in which the low pH breaks the iron oxide core down into iron ions. These ions are then incorporated back into the hemoglobin pool [13]. Interestingly, ferumoxytol is also attractive as a magnetic resonance imaging (MRI) contrast agent because of its magnetic relaxivity properties and because it can be given as a bolus. Moreover, in contrast to gadolinium-based contrast agents, there is no renal elimination of ferumoxytol. Recently, ferumoxytol was investigated as MRI contrast agent to detect cellular inflammation [14,15]. Preliminary results suggest that ferumoxytol enables a detailed characterization of acute MI pathology by detecting infiltrating macrophages and altered perfusion kinetic [6,16].

The present study (Non-invasive myocardial inflammation imaging based on new molecular magnetic resonance imaging contrast agents and methods, NIMINI-3) was performed in order to investigate a) the safety profile and b) the potential “therapeutic” effect of intravenous USPIO-based iron administration regarding infarct healing and short-term ventricular remodeling in patients with STEMI.

## 2. Methods

### 2.1. Study population

The present NIMINI-3 study was based on the follow-up of those patients that participated in the previous NIMINI-2 study [17]. NIMINI-2 was a prospective, non-randomized, non-blinded, single agent phase III clinical trial that investigated whether CMR using ferumoxytol allows improved characterization of infarct pathology compared to conventional gadolinium-based necrosis/fibrosis imaging in patients with acute MI [16,17]. Seventeen patients who had experienced recent acute STEMI were included into the NIMINI-2 study between June 2010 and December 2011 and represented the study group (IRON) of the present NIMINI-3 study. The control group (CONTROL) consisted of 22 age-, gender- and cardiovascular risk factor matched STEMI patients that were enrolled between April 2010 and July 2012. Patients were diagnosed according to the universal definition of myocardial infarction and all underwent successful primary PCI with stent placement (within 12 hours of symptom onset) [18]. Exclusion criteria were: prior documented MI, cardiovascular compromise (Killip class  $\geq$  III), severe kidney or liver failure, contraindications to CMR and, for the IRON group, known allergy to iron-containing compounds. The German Federal Institute for Drugs and Medical Devices (BfArM) and the ethics committee of the University of Tübingen approved the study protocol, and all participating patients provided written informed consent.

### 2.2. CMR data acquisition

ECG-gated CMR studies were performed in the first week after reperfusion (baseline) and at three months after the acute event (follow-up) on a 1.5-T Aera (Siemens Medical Solutions, Erlangen, Germany) using commercially available cardiac software, electrocardiographic triggering, and cardiac-dedicated surface coils. CMR included steady state free precession cine imaging, T2-weighted STIR “edema” imaging and T1-weighted late gadolinium enhancement (LGE) imaging after intravenous contrast administration (0.15 mmol/kg Magnevist®) as previously described in detail [16,17].

### 2.3. Iron administration

Within 24 hours following the baseline CMR scan, IRON patients received a single intravenous bolus (as recommended by the manufacturer) of 17 mL ferumoxytol (Feraheme™) containing 510 mg elemental iron. Throughout iron infusion, all patients were clinically and electrocardiographically monitored. All IRON patients underwent a multi-parametric CMR study 48 h after intravenous administration of ferumoxytol as part of the NIMINI-2 study protocol as described elsewhere [16,17].

### 2.4. CMR data analysis

CMR analysis was performed off-line by two experienced readers blinded to the clinical data. Ventricular volumes, ejection fraction and left ventricular mass were derived by contouring endo- and epicardial borders on the short-axis cine images. On the short-

axis LGE images, the number of left ventricular segments with positive LGE was first quantified using a standard left ventricular 17-segment model. Classification of myocardial segments with respect to the presence of myocardial damage was made dichotomously based on visual identification of LGE. In addition, the extent of LGE was planimetrically on the short-axis contrast images with the use of ImageJ software (National Institutes of Health, Bethesda, Md, USA). Infarct transmural extent was assessed on the LGE images using a model dividing each short-axis slice into 12 sectors and each sector into 3 equal circumferential segments (subendocardial, midmyocardial, subepicardial; in total 36 segments per slice). An infarct was considered transmural if all three segments were LGE positive in at least one sector. Endocardial extent of infarction was calculated by counting the number of endocardial segments with positive LGE for each short-axis slice, by summing them up and expressing this sum as percentage from the total number of endocardial segments (12 per slice). Microvascular obstruction (MVO) was defined as the dark area within the infarcted myocardium. In order to evaluate in-plane myocardial salvage after reperfusion, the area at risk (AAR) was determined on one T2-weighted STIR “edema” short-axis slice at the level of maximal edema using the same 36 segment per slice model. Corresponding in-plane baseline infarct size was obtained for the respective LGE short-axis slice. Salvage index was calculated as the difference between AAR and baseline infarct size normalized to AAR.

### 2.5. Statistical analysis

Continuous variables were expressed as mean  $\pm$  SD. Skewed variables were expressed as median and interquartile range. Categorical variables were expressed as frequency with percentage. *t*-Student test was used for the between group comparison of patient characteristics and CMR parameters expressed as continuous variables, at the two time points. Paired samples *t*-Student test was used to assess timely changes in CMR parameters within patient groups. Levene's test was used for testing equality of variances. Non-parametric tests were used for not normally distributed variables (Mann-Whitney U test and Wilcoxon signed rank test for repeated measurements). Pearson correlation (*r*) was used to assess the relationship between different CMR parameters at different time points and their timely change ( $\Delta$  values). The chi-square test with Yate's correction was used to compare non-continuous variables expressed as proportions. Statistical analysis was performed using SPSS software for Windows (version 18, SPSS, Chicago Illinois, US). A *p*-value  $\leq$  0.05 was considered statistically significant.

## 3. Results

### 3.1. Patient characteristics

Baseline demographic, clinical and infarct-related patient characteristics for the total study group as well as the IRON and CONTROL groups are presented in Table 1. There were no significant differences in demographic parameters and in the prevalence of cardiovascular risk factors between both groups. In addition, there were no significant differences regarding infarct-related characteristics and extent of myocardial necrosis as measured by the maximum plasma troponin T level between the IRON and CONTROL group. As for iron deficit laboratory tests, no patient demonstrated anemia (hemoglobin levels  $<$  130 g/L) on admission and all patients had red cell mean corpuscular volumes within normal range (80–96  $\mu^3$ ). Moreover, systemic inflammatory response quantified by maximum C-reactive protein levels did not differ significantly between groups. The ferumoxytol bolus was infused at 3 (IQR 2.5 – 4) days after admission and was well tolerated in all patients without any adverse events.

### 3.2. Baseline CMR findings

The baseline CMR scan was performed at a median of 3 (IQR 2–3) days from admission. Average LV ejection fraction was  $53 \pm 10\%$  (IRON) and  $54 \pm 6\%$  (CONTROL), respectively. As shown in Table 2, there were no significant differences in functional CMR parameters, i.e. baseline LV volumes, ejection fraction and myocardial mass between the IRON and CONTROL patients. On LGE images, all patients showed characteristic enhancement patterns for ischemic myocardial damage. Infarcted tissue comprised on average 27% of the total LV myocardium with 33% circumferential extent from total endocardial surface in both groups. All IRON patients and 77% of CONTROLS had transmural MI at baseline. No significant differences in infarct size, endocardial extent and prevalence of MVO or transmural extent of MI were seen at baseline between both groups (Table 2). Moreover, the (in-plane) area-at-risk was similar in both groups ( $45 \pm 14\%$  in IRON and  $44 \pm 12\%$  in CONTROL; *p* = NS).

**Table 1**  
Baseline patient characteristics.

	Total (N=39)	IRON (N=17)	CONTROL (N=22)	P-Value
Male (%)	32 (82)	15 (88)	17 (77)	0.438
Age, years	56±9	54±9	57±9	0.442
BSA, m <sup>2</sup>	2.0±0.2	2.0±0.2	2.0±0.2	0.404
<i>Cardiovascular risk factors</i>				
Hypertension, (%)	22 (56)	11 (65)	11 (50)	0.517
High cholesterol, (%)	26 (67)	13 (77)	13 (59)	0.314
Diabetes, (%)	4 (10)	1 (6)	3 (14)	0.407
Smoking, (%)	25 (64)	9 (53)	16 (73)	0.318
Obesity, (%)	7 (18)	4 (24)	3 (14)	0.677
<i>Infarct characteristics</i>				
Culprit artery, LAD/RCA/Cx, %	59/36/5	53/41/6	64/31/5	0.865
Time to reperfusion, min	180 (133–405)	240 (150–555)	165 (125–323)	0.188
Reperfusion to CMR, days	3 (2–3)	2 (2–3)	3 (2–4)	0.190
Max. troponin T, pg/mL	2843			
(1820–6161)	2700			
(1392–4481)	3555			
(1856–7447)	0.315			
Max. CRP, mg/L	2.0 (0.9–5.2)	2.3 (0.9–4.8)	1.8 (0.9–5.6)	0.519
TIMI flow grade before PCI, %				
0/1	82	71	91	0.314
2/3	18	29	9	
<i>Treatment at baseline admission</i>				
Aspirin, n (%)	5 (13)	1 (6)	4 (18)	0.363
Clopidogrel, n (%)	1 (3)	0 (0)	1 (5)	1.000
Beta-blocker, n (%)	8 (21)	3 (18)	5 (23)	1.000
ACEi/ARB, n (%)	3 (8)	1 (6)	2 (9)	1.000
Statin, n (%)	6 (15)	2 (12)	4 (18)	0.679
<i>Treatment at 3 months follow up</i>				
Aspirin, n (%)	38 (97)	17 (100)	21 (95)	1.000
Clopidogrel, n (%)	39 (100)	17 (100)	22 (100)	1.000
Beta-blocker, n (%)	39 (100)	17 (100)	22 (100)	1.000
ACEi/ARB, n (%)	37 (95)	15 (88)	22 (100)	0.184
Statin, n (%)	39 (100)	17 (100)	22 (100)	1.000
Rehabilitation program after discharge, n (%)	36 (92)	16 (84)	20 (91)	1.000

BSA, body surface area; Hb, blood hemoglobin concentration; MCV, mean corpuscular volume; CRP, C-reactive protein; LAD, left anterior descending coronary artery; RCA, right coronary artery; Cx, circumflex coronary artery; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction; ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin-receptor-blocker.

### 3.3. Follow-up CMR findings

All study patients underwent a follow-up CMR study three months after the acute episode (Tables 2 and 3). During the follow-up period,

**Table 2**  
CMR parameters at baseline and follow-up.

	Group	Baseline	3 Months	P-Value
<b>LV-EDV, mL</b>	Iron	153±39	143±36	0.152
	Control	143±38	145±49	0.690
<b>LV-ESV, mL</b>	Iron	71±25	59±25	<b>0.002</b>
	Control	68±27	65±36	0.396
<b>LV-EF, %</b>	Iron	53±10	59±9	<b>0.002</b>
	Control	54±6	57±10	<b>0.005</b>
<b>LV mass, g</b>	Iron	132 (118–172)	109 (100–118)	<b>&lt;0.001</b>
	Control	127 (100–189)	116 (94–159)	<b>&lt;0.001</b>
<b>Infarct size, %</b>	Iron	27±8	17±9	<b>&lt;0.001</b>
	Control	27±12	20±11	<b>&lt;0.001</b>
<b>Endocardial extent, %</b>	Iron	33±8	28±9	<b>0.002</b>
	Control	33±10	31±11	0.126
<b>MVO, (%)</b>	Iron	6 (35)	–	–
	Control	12 (55)	–	–
<b>Transmural MI, (%)</b>	Iron	17 (100)	7 (41)	<b>&lt;0.001</b>
	Control	17 (77)	10 (46)	0.070
<b>Area at risk, %</b>	Iron	45±14	–	–
	Control	44±12	–	–
<b>Salvage index</b>	Iron	0.27±0.16	–	–
	Control	0.32±0.15	–	–

LV, left ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; FUP, follow up; EF, ejection fraction; MVO, microvascular obstruction; MI, myocardial infarction.

none of the patients experienced major cardiac events. A significant decrease in LV end-systolic volume was observed in the IRON group (from 71 ± 25 ml to 59 ± 25 ml;  $p = 0.002$ ) but not in the CONTROL group at follow-up. This was accompanied by a substantial (but non-significant) decrease in LV end-diastolic volume in the IRON group only (from 153 ± 39 ml to 143 ± 36 ml). In both groups, significant increases in LV ejection fraction were observed from baseline to follow-up with a trend towards higher increases in the IRON group (from 53 ± 10% to 59 ± 9%;  $p = 0.002$ ). Left ventricular mass significantly declined in both groups at follow-up, however, again with a more pronounced trend in the IRON group (from 132 mg to 109 mg;  $p < 0.001$ ).

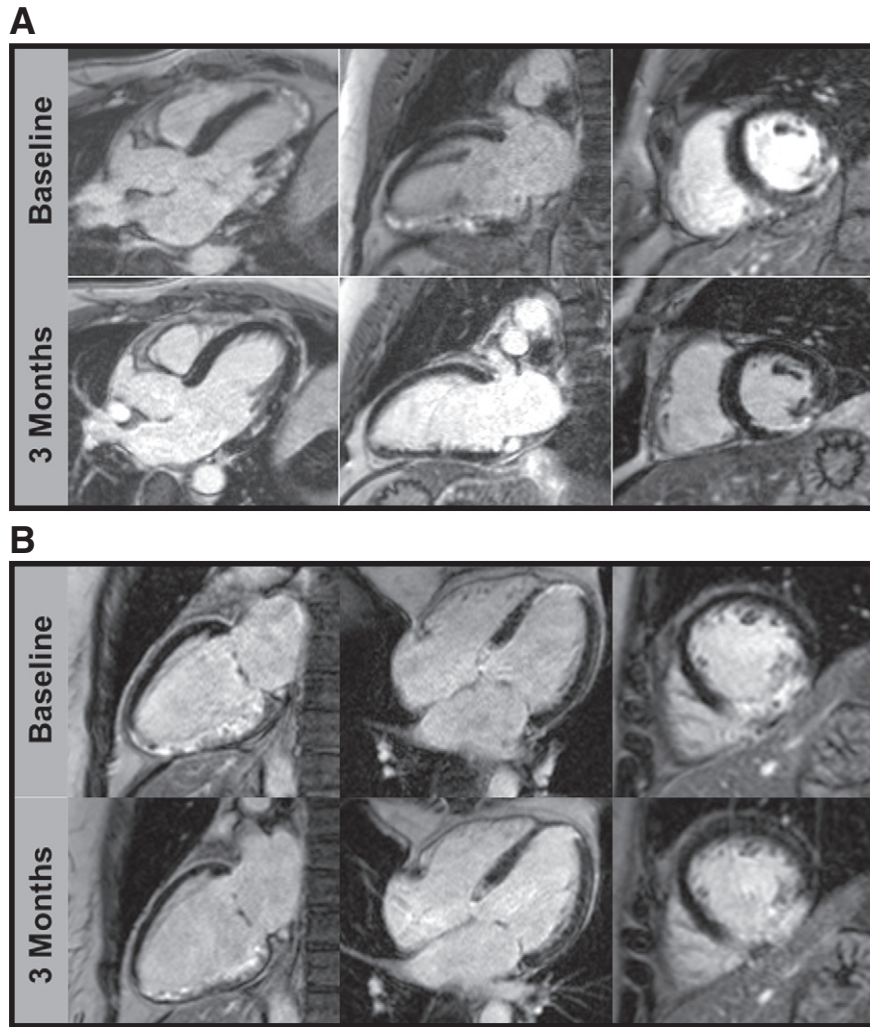
In all patients, persistence of at least some LGE was documented at follow-up suggesting chronic scarring. Infarct size significantly decreased in both groups at follow-up (IRON: from 27 ± 8% to 17 ± 9%;  $p < 0.001$  vs. CONTROL: from 27 ± 12% to 20 ± 11%;  $p < 0.001$ )

**Table 3**  
Change of CMR parameters from baseline to follow up.

Δ Values	IRON (N=17)	CONTROL (N=22)	P-Value
LV-EDV, mL	−10.1 ± 27.7	1.8 ± 20.6	0.132
LV-ESV, mL	−12.1 ± 13.8	−2.9 ± 15.8	0.066
LV mass, g	−27.1 ± 20.7	−20.9 ± 17.9	0.326
LV-EF, %	+5.2 ± 5.7	+3.7 ± 5.6	0.442
Infarct size, %	−10.3 ± 5.4	−7.0 ± 8.4	<b>0.050</b>
Endocardial extent, %	−4.9 ± 5.2	−1.8 ± 5.6	0.080

LV, left ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction.





**Fig. 1.** Exemplarily CMR images of an IRON and CONTROL patient. Late gadolinium enhancement (LGE) images in an IRON group patient (male, 39-year old) with infero-lateral STEMI by RCA occlusion showing typical enhancement in the inferior and lateral walls (A) and in a CONTROL group patient (female, 47-year old) with inferior STEMI by RCA occlusion showing typical enhancement in the inferior wall and inferior septum (B). An important decrease in infarct size from baseline to 3 months was only observed in the IRON group patient (25 to 11%) but not in the CONTROL group patient (29 to 26%).

with a substantially more pronounced decrease in IRON patients (IRON:  $-10.3 \pm 5.4\%$  vs. CONTROL:  $-7.0 \pm 8.4\%$ ;  $p = 0.050$ ) (Fig. 1A–B). The extent of the decrease in infarct size was positively associated with LV end systolic volume at follow-up only in the IRON group ( $r = 0.484$ ;  $p = 0.049$ ), but not in the CONTROL group ( $r = 0.020$ ;  $p = 0.928$ ). The average endocardial extent of infarcted myocardium significantly decreased in the IRON group (from  $33 \pm 8\%$  to  $28 \pm 9\%$ ;  $p = 0.002$ ), but not in the CONTROL group. In addition, there was a significant decrease in the number of transmural infarctions in the IRON group (from 100% to 41%;  $p < 0.001$ ), but not in the CONTROL group.

#### 4. Discussion

To the best of our knowledge, this is the first clinical study that evaluated the safety and therapeutic value of an USPIO-based iron compound (ferumoxytol, Feraheme™) in patients with acute MI. The present clinical trial NIMINI-3 was designed as a pilot study and comprised 17 patients who received single-dose (510 mg) iron within the first days after acute MI and underwent multi-parametric CMR studies in the acute setting (baseline) and at three months after MI. Comparison of the CMR results obtained from the IRON group to those of the matched CONTROL group of 22 STEMI patients who underwent similar

CMR studies without iron administration revealed some intriguing and promising results: The administration of a single-dose of ferumoxytol in the first week after STEMI resulted in a substantially larger decrease in infarct size when compared to the matched controls at three months. Moreover, this decrease in infarct size was associated with improved LV remodelling at follow-up, as expressed by significant LV end systolic volume reduction in the IRON group only. Noteworthy, an excellent safety profile was observed regarding ferumoxytol administration in the acute MI setting.

##### 4.1. Evolution of LV function and infarct size after STEMI

It is well documented that primary PCI in STEMI patients reduces infarct size, preserves LV function and improves survival [1,2]. Furthermore, in the short-term (three to six months) after primary reperfused STEMI, published CMR studies report heterogeneous results ranging from non-significant changes to improvements in LV volumes and ejection fraction [4,19–21]. A first finding of the current study is the significant increase in LV ejection fraction at three months after MI in both study groups. This is probably explained by the inclusion of relatively low risk MI patients (first MI, Killip class I and II) with only mildly impaired LV systolic function at baseline; hence, such MI patients

are probably the most likely ones to recover following adequate treatment [3].

Secondly, there was a significant decrease in infarct size in both groups at follow-up. This result is in accordance with previous data that describe “infarct shrinkage” up to four months after the acute event [22]. While earlier studies in the pre-PCI era attributed “infarct shrinkage” purely to volume loss, recent reports suggest that LGE early after MI does not necessarily reflect irreversibly damaged myocardium that will entirely transform into late scar [19,23–25].

The most notable finding of the present study is that although infarct size decreased significantly in both groups at follow-up, there was a substantially more pronounced decrease in the IRON patients (Fig. 1A–B). Furthermore, this change in the extent of infarct size was associated with significant decreases in both endocardial extent and transmural extent of infarcted segments. These results are in line with the finding of a significant decrease in LV systolic volume, a major predictor of survival after MI, “only” in the IRON patients (at three months) [26,27]. In addition, the extent of the decrease in infarct size was positively associated with a decreased LV end systolic volume at follow-up only in the IRON group, but not in the CONTROL group.

The current results are promising as intensive research is performed to find adjunctive interventions to standard therapy that would reduce infarct size and improve remodeling in acute MI. Several trials revealed minimal impact of bone marrow cells infused after primary PCI for STEMI on LV function and infarct size [5]. For example, the study of Wöhrle et al. included 42 primary reperfused STEMI patients with similar characteristics and baseline CMR findings to the present study (baseline LV ejection fraction  $55 \pm 7\%$  vs.  $53 \pm 9\%$  and infarct size  $28 \pm 10\%$  vs.  $27 \pm 12\%$  in the study and placebo groups, respectively). The authors reported no differences in LV ejection fraction, volumes and infarct size change from the acute phase to three months after intracoronary infusion of bone marrow cells when compared to placebo [28].

#### 4.2. Potential pathophysiological concepts

At first glance, the association between intravenous iron administration and improved infarct healing as well as beneficial global left ventricular remodeling in acute STEMI patients (compared to matched controls) seems to be surprising and even paradoxical. Indeed, parenteral iron administration was shown to be associated with increased myocardial oxidative stress – at least in hemodialysis patients [29]. Moreover, oxidative stress in case of acute MI is characterized by the generation of reactive oxygen species (ROS) in the ischaemic myocardium (especially after reperfusion) and ROS are known to directly injure the cell membrane of cardiomyocytes and cause cell death [30]. However, ROS do not only cause detrimental effects on the injured myocardium, but may also stimulate both the accumulation of leukocytes and activation of signal transduction pathways to elaborate inflammatory cytokines and various interleukins (IL) in both the ischaemic region and the surrounding non-ischaemic myocardium as a host reaction [30]. For example, significant up-regulation of IL-10 mRNA and protein was demonstrated both in the ischemic and reperfused myocardium [31]. By suppressing the degree of myocardial inflammation in acute MI, increased IL-10 availability leads to improved LV function and remodeling by inhibiting myocardial fibrosis [32]. Therefore, increased availability of specific inflammatory cytokines (such as IL-10) may also result in cell survival and positive LV remodelling as a consequence of ROS generation and macrophage/lymphocyte infiltration. Hence, ROS generation per se in response to intravenous iron administration does not need to be harmful and may even positively modulate the inflammatory response in acutely injured myocardium.

Furthermore, it is known that iron modulates the expression of the critical citric acid cycle enzyme aconitase via a translational mechanism involving iron regulatory proteins. In particular, iron supplementation results in increased formation of reducing equivalents by the citric

acid cycle, and thus in increased mitochondrial ATP formation via oxidative phosphorylation. This in turn leads to downregulation of glucose utilization. In contrast, all these metabolic pathways are reduced upon iron deficiency, and thus glycolysis and lactate formation are significantly increased in order to compensate for the decrease in ATP production. However, increased mitochondrial metabolism (e.g. following iron administration) may elicit an adaptive response and activate protective mechanisms which can possibly counteract cardiotoxic and/or ischemic stress and promote survival of cardiomyocytes.

#### 4.3. Immunomodulatory effects of USPIO on macrophages?

Preclinical small animal studies demonstrated that USPIO (such as ferumoxytol) are directly absorbed by macrophages infiltrating the infarcted myocardium during myocardial repair [33,34]. Recently, we could demonstrate for the first time in humans that a substantial drop in absolute  $T2^*$ -values in the (peri-) infarct zone occurred already 6 h after ferumoxytol administration [15–17]. Considering additional ex vivo data that demonstrated substantial uptake of ferumoxytol by activated macrophages, this drop in  $T2^*$ -values is expected to be caused by macrophages which had infiltrated the (peri-) infarct zone. This drop in  $T2^*$ -values remained rather constant for the first 2d after ferumoxytol administration and disappeared only 4d after ferumoxytol administration (corresponding in the median to day 8 after MI) which is in line with data from a recent study by Leuschner et al. in which the monocyte/macrophage resident time in the infarcted myocardium was shown to be only 20 h and the exit rate of macrophages from infarcted tissue between 5% and 13% within 24 h [35]. Intriguingly, a substantial drop in absolute  $T2^*$ -values was not only observed in the area of MI, but also (to a smaller extent) in the non-infarcted remote myocardium suggesting that infiltration of macrophages does not only take place in the (peri-) infarct zone but also in the non-infarcted remote myocardium – which is in line with recent data from Lee et al. [36]. Hence, considering a) the fact that ferumoxytol particles are taken up by macrophages accumulating in the infarcted (as well as non-infarcted) myocardium and b) the evidence that the immunological profile of macrophages is shifted towards an anti-inflammatory phenotype in response to internalization of USPIO by (amongst others) enhancing IL-10 expression, one can hypothesize that USPIO (such as ferumoxytol) may have potential beneficial immunomodulatory effects on macrophages resulting in improved infarct healing and beneficial global left ventricular remodeling in case of acute MI. Therefore, our current research is focusing on the exploration of these immunomodulatory effects of USPIO on macrophages [37].

#### 4.4. Potential clinical implications

As shown recently, USPIO-based contrast agents (such as ferumoxytol) enable an improved MRI-based characterization of myocardial infarct pathology by detecting infiltrating macrophages and altered perfusion kinetics [17]. Such an USPIO-based approach to image the infarcted myocardium may be of great clinical value, since a) USPIO may also be used in patients with contraindications to conventional gadolinium-based contrast agents such as in those with advanced renal insufficiency, b) USPIO may help to differentiate acute myocardial infarction from chronic myocardial fibrosis and c) further modification of the coating properties of USPIO (e.g. coupling with specific antibodies) may allow targeted molecular imaging. Considering these “diagnostic” properties of USPIO (such as ferumoxytol) regarding myocardial inflammation imaging in addition to its potential “therapeutic” effects on infarct healing and ventricular remodelling (as demonstrated in the present study), ferumoxytol could become a safe “diagnostic” and “therapeutic” adjunctive solution in acute MI management [6,16,17].

#### 4.5. Study limitations

Obviously, an important limitation of this study is the small number of patients as this was just a hypothesis-generating pilot study. The small study size could be one of the reasons for the non-significant/borderline-significant changes in the between group analysis for LV ejection fraction and end-diastolic volume. Despite this limitation, the current results can be regarded as promising pilot work that guarantees the need for additional future research. The second limitation is represented by the mode of patient enrollment in the two groups which was not performed randomly. Obviously, the current methodology of recruiting patients for this study may entail potential biases that may have influenced the results. Nevertheless, we achieved excellent matching between groups in baseline patient and infarct characteristics. Finally and unfortunately, comprehensive information regarding iron-metabolism parameters was not available in this hypothesis-generating study and we did not perform any serum screening regarding cytokine or interleukin profiles, nor did we perform endomyocardial biopsy (due to ethical reasons) in order to study myocardial tissue data. However, this will be the focus of future studies.

#### 5. Conclusion

Intravenous USPIO-based iron administration in acute STEMI patients seems to be associated with an improved infarct healing and a beneficial global left ventricular remodelling. These findings together with the good safety profile make USPIO-based iron administration a promising future candidate as a “diagnostic” and “therapeutic” adjunctive solution in acute MI management.

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