Ultrasmall Superparamagnetic Particles of Iron Oxide in Patients With Acute Myocardial Infarction
Early Clinical Experience

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Background—Inflammation following acute myocardial infarction (MI) has detrimental effects on reperfusion, myocardial remodelling, and ventricular function. Magnetic resonance imaging using ultrasmall superparamagnetic particles of iron oxide can detect cellular inflammation in tissues, and we therefore explored their role in acute MI in humans.

Methods and Results—Sixteen patients with acute ST-segment elevation MI were recruited to undergo 3 sequential magnetic resonance scans within 5 days of admission at baseline, 24 and 48 hours following no infusion (controls; n=6) or intravenous infusion of ultrasmall superparamagnetic particles of iron oxide (n=10; 4 mg/kg). T2*-weighted multigradient-echo sequences were acquired and R2* values were calculated for specific regions of interest. In the control group, R2* values remained constant in all tissues across all scans with excellent repeatability (bias of −0.208 s−1; coefficient of repeatability of 26.96 s−1; intraclass coefficient 0.989). Consistent with uptake by the reticuloendothelial system, R2* value increased in the liver (84±49.5 to 319±70.0 s−1; P<0.001) but was unchanged in skeletal muscle (54±8.4 to 67.0±9.5 s−1; P>0.05) 24 hours after administration of ultrasmall superparamagnetic particles of iron oxide. In the myocardial infarct, R2* value increased from 41.0±12.0 s−1 (baseline) to 155±45.0 s−1 (P<0.001) and 124±35.0 s−1 (P<0.05) at 24 and 48 hours, respectively. A similar but lower magnitude response was seen in the remote myocardium, where it increased from 39±3.2 s−1 (baseline) to 80±14.9 s−1 (P<0.001) and 67.0±15.7 s−1 (P<0.05) at 24 and 48 hours, respectively.

Conclusions—Following acute MI, uptake of ultrasmall superparamagnetic particles of iron oxide occurs with the infarcted and remote myocardium. This technique holds major promise as a potential method for assessing cellular myocardial inflammation and left ventricular remodelling, which may have a range of applications in patients with MI and other inflammatory cardiac conditions.


Key Words: myocardial infarction • inflammation • magnetic resonance imaging • ultrasmall superparamagnetic particles of iron oxide

Inflammation occurs in the acutely infarcted myocardium in order to remove necrotic cellular debris and allow tissue remodelling. Excessive inflammation may follow reperfusion therapy and can have detrimental effects on healing and left ventricular (LV) remodelling.1 With the aim of improving outcomes following acute myocardial infarction (MI), novel drugs are increasingly focusing on the optimization of myocardial repair and regeneration, which include anti-inflammatory interventions.2–5 There is therefore a need for noninvasive methods to assess in vivo myocardial inflammation following MI, both to define the healing process and to measure the potential efficacy of novel therapeutic interventions.

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Magnetic resonance imaging (MRI) is ideally suited for the serial examination of the heart because it is noninvasive, does not involve ionizing radiation, and has excellent soft tissue contrast and spatial resolution. Cardiac magnetic resonance, using T2-weighted imaging, has previously been used to detect...
myocardial edema associated with MI because it may help delineate the area at risk from the infarcted region.4 However, there are major differences in the diagnostic performance of edema imaging and there have been conflicting results regarding its utility as a prognostic marker or guide to therapeutic intervention.5–6 One explanation for this is that MRI of edema does not directly assess the more dynamic cellular inflammatory processes.

Iron oxide particles can be used as a contrast medium in MRI because they alter the T2* relaxation time of tissues in which they accumulate. Ultrasound superparamagnetic particles of iron oxide (USPIO) are taken up by the cells of the liver, spleen, bone marrow, and lymph nodes. Because of their small size (≈30 nm), they extravasate freely through capillaries and are phagocytosed by tissue-resident inflammatory cells of the reticuloendothelial system.10 These cells are predominantly macrophages, but neutrophils may also take up USPIO.11,12 We have recently established that USPIO can be used to assess vascular cellular inflammation in patients with abdominal aortic aneurysms.13 Histological examination of aneurysm tissue confirmed the colocalization and uptake of USPIO in areas with macrophage infiltration, and mural uptake of USPIO was associated with a 3-fold increase in the rate of abdominal aortic aneurysm expansion.13 T2*-weighted MRI has been validated as a method for detecting hepatic and myocardial iron accumulation in patients with thalassemia and transfusion-related iron overload, and this method could be adapted for the detection of focal accumulation of USPIO.14,15

We hypothesized that we could use USPIO to track inflammatory cell infiltration within the myocardium of patients who had recently sustained an acute MI. The aims of the study were therefore to investigate the proof of principle that USPIO could be used to assess cellular myocardial inflammation following acute MI in humans.

Methods

Subjects

This study was an open-label pilot proof-of-concept study in 16 patients who suffered a recent MI. Inclusion criteria were age of 18 to 80 years, recent (within 48 hours) MI defined by the universal definition of MI, and plasma troponin I concentration in excess of 10 µg/L. 80 years, recent (within 48 hours) MI defined by the universal definition of MI, and plasma troponin I concentration in excess of 10 µg/L. Exclusion criteria were known critical stenosis (>90%) of left main stem, ongoing symptoms of unstable angina, atrial fibrillation, heart failure (Killip class >II), hepatic failure (Childs–Pugh grades B or C) or renal failure (estimated glomerular filtration rate <25 mL/min), contraindication to MRI, past history of systemic iron overload or hemochromatosis, and patients with known allergy to dextran- or iron-containing compounds.

All patients suffered an acute ST-elevation MI. One patient in each group received thrombolytic therapy with tenecteplase, followed by percutaneous coronary angioplasty and stent placement. One patient in the control group was treated by primary percutaneous coronary intervention. All patients were treated with aspirin, clopidogrel, and a statin. The median time from the onset of chest pain to hospital admission was 2 hours (interquartile range 1–4 hours).

All patients were assessed for the following clinical and laboratory variables: age, sex, body weight, body mass index, history of diabetes mellitus, hypertension, coronary artery disease, previous MI, peripheral arterial disease, peripheral venous cannula at a dose of 4 mg/kg at a rate of up to 1 mL/s. Hemodynamic and electrocardiographic monitoring was conducted throughout.

Magnetic Resonance Imaging

Sequential imaging was performed at baseline (24–72 hours after admission) and 24 and 48 hours thereafter. In 10 patients, USPIO were administered immediately after the baseline scan. Six patients received no infusion and acted as control subjects. MRI was performed using a combination of body matrix and spine coil matrix coil elements of a 3-tesla Verio scanner (Siemens Medical, Germany). Standard cardiac breath-hold ECG-gated true fast imaging with steady state precession (FISP) sequences were acquired to acquire vertical long-axis, horizontal long-axis, and short-axis views of the heart. Imaging of USPIO was performed using established T2*-weighted multigradient-echo sequences, breath-held and cardiac-gated after a volumetric shim had been applied over the entire heart volume. Standard cardiac slice widths (6 mm width with 4 mm gap) and echo times (2.1–17.1 ms range) with matrix size of 256×115 were acquired. The in-plane resolution differed as required for larger or smaller objects; generally, a field of view of 400×300 was used with an in-plane resolution of 2.6×1.6. Quantitative analysis of the accumulation of USPIO was achieved by calculation of T2* relaxation times before and after administration of USPIO.15 In order to optimize image analysis and prevent degradation because of T2*-blooming artefacts, images of USPIO were quantitatively analyzed using a susceptibility gradient mapping technique previously used in imaging of SPIO to quantify the accumulation of USPIO using changes in calculated T2* relaxation times.17

Immediately after the baseline T2*-weighted scan, breath-held inversion recovery sequences in the vertical long-axis, horizontal long-axis, and short-axis planes were used to acquire late-enhancement images 10 to 15 minutes following an intravenous administration of gadolinium contrast agent (0.2 mmol/kg; Gadovist, Bayer Plc, Germany). Optimal inversion time (TI) was determined on a slice-by-slice basis using standard late-enhancement protocols. The inversion-recovery late-enhancement short-axis slices were acquired with the same slice position as the short-axis T2*-weighted slices. The T2*-weighted short-axis acquisitions included views through the liver and spleen and allowed the quantification of uptake of USPIO within the reticuloendothelial system via changes in these tissues’ R2* values.

Image Analysis

Late-enhancement analysis was performed using QMass software (Medis Medical Imaging Systems, The Netherlands), allowing quantification of infarct size and location for correlation with signal changes related to USPIO.

Baseline and 24- and 48-hour T2*-weighted multigradient-echo images for each patient were spatially coregistered using ANALYZE software (AnalysisDirect Software, USA). The 4 echoes (Echo Time [TE]=2.13, 4.27, 6.41 and 8.55 ms) in a multiecho T2*-weighted sequence were combined to generate a T2* map, in which the data represented the T2* value (SI=SI0[(S0-T)/(T/T2*)]) for each voxel. This was achieved using in-house software developed in Matlab (Mathworks, USA). The T2* value is the decay constant for the exponential decay of signal intensity with time. In the presence of USPIO, the signal decays more rapidly because of local field inhomogeneities and the T2* value is reduced. A 3×3 voxel Gaussian filter was applied to the individual echoes to reduce noise. By minimizing the sum of the squares of errors between the data and an exponential function, the decay constant (ie, T2*) was obtained. An experimentally determined threshold for the coefficient of determination (r2>0.85) was used to exclude data that did not have an acceptable exponential decay when signal intensity (SI) was plotted against echo time. The inverse of T2*, R2*, was then calculated to assess the uptake of USPIO. In our laboratory, we have previously assessed the repeatability of the measurement of the R2* value by comparing data from 2 T2*W sequences (run 1 versus run 2) performed in quick succession without moving the patient. This was
performed on a voxel-by-voxel basis with a total of 32,936 data points, of which 1.2% were affected by artifact and discarded. Using the Bland and Altman method, there was no evidence of bias with a mean difference (0.99±21.9 s⁻¹) with a coefficient of repeatability of 42.9 s⁻¹.

The transformation matrix of the coregistration was then applied to the subsequent T2*-weighted echoes, and R2* value was calculated on a voxel-by-voxel basis to generate coregistered R2* maps at baseline and 24 and 48 hours. The late-enhancement short-axis images were also spatially coregistered with the R2* images for each visit in case of lack of reproducibility of patient breath-holding between scans. Regions of interests (ROIs) were selected on the late-enhancement images and applied to the coregistered R2* maps corresponding to (1) microvascular obstruction if present, (2) infarct area (defined by late gadolinium enhancement), (3) peri-infarct area (adjacent to late gadolinium enhancement), (4) myocardium remote from the infarct zone (distant from late gadolinium enhancement), (5) skeletal muscle, (6) blood pool, (7) liver, and (8) spleen (Figure 1). The ROIs were mapped to the first T2* echo before being applied to R2* maps to ensure there was coherence to the corresponding areas on all 3 scans and no overlap with the blood pool or extracardiac structures. Two investigators created and quantified ROIs for all scans independently in order to assess the reproducibility of the technique.

Statistical Analysis
All statistical analyses were performed with GraphPad Prism, version 4.00 (GraphPad Software, San Diego, CA), except the intraclass correlation, which was performed with SPSS (IBM Version 20.0.0, USA) using a 1-way random effects model. Repeatability was assessed by the method of Bland and Altman and coefficient of repeatability, defined as twice the SD of the mean of the differences. Patient characteristics (Table) were compared using unpaired nonparametric Mann–Whitney test. R2* values at baseline, 24, and 48 hours for each ROI were compared using repeated-measure 1-way ANOVA (Friedman test). If significant, Dunn’s multiple comparison post-test was performed comparing R2* value at baseline to that at 24 hours and to that at 48 hours. Statistical significance was defined as 2-sided \( P<0.05 \).

Results
All patients sustained an acute MI with a substantial area of myocardial necrosis (Table). All patients underwent 3 scans (baseline and at 24 and 48 hours), including T2*-weighted multigradient-echo sequences and late gadolinium enhancement. Late enhancement reconfirmed MI in all patients.

Repeatability
Data from patients who did not receive administration of USPIO were used to assess any potential changes in R2* attributable to acute MI alone. There were no changes in R2* value within the myocardium or the infarct zone itself (Figures 2 and 3; online-only Data Supplement Table I; \( P>0.05 \)). Similar findings were also observed in other organs such as the liver, spleen, and skeletal muscle. Moreover, we were able to demonstrate excellent repeatability for the assessment of R2* value with a mean bias of \(-0.208\ s^{-1}\), coefficient of repeatability of 26.96 s⁻¹, and intraclass coefficient of 0.989 (online-only Data Supplement Figure I).

Effect of Administration of USPIO
All patients tolerated the infusions well with no significant adverse events or arrhythmia. In the area of MI, R2* value increased from 41.0±12.0 s⁻¹ at baseline to 155±45.0 s⁻¹ \((P<0.001)\) and 124±35.0 s⁻¹ \((P<0.05)\) at 24 and 48 hours, respectively, following administration of USPIO (Figures 2 and 3). Intriguingly, although more modest, the remote noninfarcted myocardium also demonstrated an increase from a baseline of 39.0±3.2 s⁻¹ to 80.0±14.9 s⁻¹ \((P<0.001)\) and 67.0±15.7 s⁻¹ \((P<0.05)\) at 24 and 48 hours, respectively (Figures 2 and 3; online-only Data Supplement Table II).

To determine whether there was a nonspecific effect of USPIO enhancing R2* values in muscle, we assessed ROIs within skeletal muscle. We were able to confirm that there was no change in R2* value of skeletal muscle (Figures 2 and 3; online-only Data Supplement Table II). Given that USPIO are taken up by cells of the reticuloendothelial system, both the liver and spleen were expected to develop marked changes in R2* values and act as positive controls. In the liver, there was a large increase in R2* value from 84.0±49.5 s⁻¹ at baseline to 319±70.0 s⁻¹ \((P<0.001)\) and 243.0±63.6 s⁻¹ \((P<0.001)\) at 24 and 48 hours, respectively, following administration of USPIO. A similar pattern was also seen in the spleen (online-only Data Supplement Table II).

Figure 1. Object map (OM) creation. Following registration with late gadolinium enhancement (LGE) images, an OM was defined from ROIs of specific tissues and subsections: skeletal muscle (light blue), spleen (dark blue), liver (yellow), blood pool (iliac), and heart subdivided into areas of infarction (red), peri-infarction (white), and remote myocardium (green). The object map was spatially coregistered with the R2* map (R2*) to measure specific R2* values (R2*+OM). ROIs indicate regions of interest.
Discussion

For the first time, we have demonstrated that USPIO are taken up into the myocardium of patients with a recent MI. The increase of \( R^2* \) value after administration of USPIO was highest within infarcted tissue, although we did observe a more modest increase within myocardium remote from the site of infarction. This suggests early macrophage and inflammatory cell infiltration predominantly occurs within the infarcted myocardium but appears to be associated with a more global influx of these cells that extends beyond the area at risk. However, no histological quantification of macrophage infiltration was performed, and so the degree of inflammation cannot be correlated to MRI changes. Our preliminary findings need further confirmation in larger cohorts, but this technique does appear to hold major promise in the investigation of myocardial inflammation following MI and could be applied to other inflammatory cardiac diseases such as cardiac sarcoidosis, myocarditis, or transplant rejection.

USPIO are actively taken up by inflammatory phagocytic cells, especially macrophages. They have been used to explore a number of inflammatory conditions, including atherosclerotic plaques and abdominal aortic aneurysms. More specifically, preclinical models have demonstrated the uptake of magnetic nanoparticles into macrophages of infarcted myocardium by both fluorescence microscopy and immunohistochemistry. We were unable to obtain tissue confirmation of the uptake of USPIO into macrophages in our cohort of patients. It is possible that other cell types with phagocytic capacity, such as neutrophils, may contribute to the increase in \( R^2* \) value. However, we have no reason to believe that the uptake would differ from previous studies and, indeed, phagocytosis into macrophages is 4 to 6 times greater with ferumoxytol than with ferumoxtran-10, a previously used USPIO agent. Moreover, we have demonstrated that organs of the reticuloendothelial system, such as the liver and spleen, demonstrate marked increases in \( R^2* \) values uptake of USPIOs by monocytes and macrophages.

We found that there was an increase in \( R^2* \) value in the remote myocardium and this finding is intriguing. Recent data have also demonstrated increased numbers of macrophages in the myocardium remote from the area of infarction both in murine models and in autopsies of patients who have died from MI. Expression of cytokines is not confined to the infarct or peri-infarct zone, but is also expressed by colocalization of USPIO with macrophages.

### Table. Characteristics of Trial Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>USPIO Group</th>
<th>Control Group</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>10</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Age, y (range)</td>
<td>52 (38–65)</td>
<td>55 (48–65)</td>
<td>0.5622</td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
<td>5</td>
<td>0.1824</td>
</tr>
<tr>
<td>WBC count, ( \times 10^9/L )</td>
<td>9.3±2.6</td>
<td>12.7±3.9</td>
<td>0.0934</td>
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<tr>
<td>Risk factors</td>
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<td></td>
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<tr>
<td>Hypercholesterolemia</td>
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<td>2</td>
<td>0.5153</td>
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<tr>
<td>Hypertension</td>
<td>4</td>
<td>0</td>
<td>0.7897</td>
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<td>Family history of CAD</td>
<td>6</td>
<td>3</td>
<td>0.6963</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Current smoker (ex-smoker)</td>
<td>4 (2)</td>
<td>3 (1)</td>
<td>0.6963</td>
</tr>
<tr>
<td>MI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from symptoms to reperfusion, min (mean±SD)</td>
<td>300±218</td>
<td>181±92</td>
<td>0.2198</td>
</tr>
<tr>
<td>Plasma troponin I concentration (µg/L)</td>
<td>33.04±15.5</td>
<td>45.27±10.63</td>
<td>0.1120</td>
</tr>
<tr>
<td>Infarct volume, mL (95% CI)</td>
<td>35.1 (8.0–62.2)</td>
<td>43.2 (14.9–71.7)</td>
<td>0.1471</td>
</tr>
<tr>
<td>Site of infarction</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Anterior infarct</td>
<td>3</td>
<td>3</td>
<td>0.4237</td>
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<tr>
<td>Lateral infarct</td>
<td>1</td>
<td>3</td>
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<tr>
<td>Inferior infarction</td>
<td>6</td>
<td>0</td>
<td>0.0164</td>
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<tr>
<td>LV variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction, % (mean±SD)</td>
<td>54±15</td>
<td>48±11</td>
<td>0.5622</td>
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<tr>
<td>Myocardial mass, g (mean±SD)</td>
<td>76±19</td>
<td>67±15</td>
<td>0.3676</td>
</tr>
<tr>
<td>Timing of scanning</td>
<td></td>
<td></td>
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<tr>
<td>Reperfusion to baseline scan, h (mean±SD)</td>
<td>49±30</td>
<td>44±16</td>
<td>0.8749</td>
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<tr>
<td>Reperfusion to scan 2, h (mean±SD)</td>
<td>73±30</td>
<td>68±17</td>
<td>0.9578</td>
</tr>
<tr>
<td>Reperfusion to scan 3, h (mean±SD)</td>
<td>95±30</td>
<td>92±38</td>
<td>0.7925</td>
</tr>
<tr>
<td>USPIO infusion to scan 2, h (mean±SD)</td>
<td>22±2</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>USPIO infusion to scan 3, h (mean±SD)</td>
<td>44±3</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; MI, myocardial infarction; NA, not applicable; USPIO, ultrasmall superparamagnetic particles of iron oxide; LV, left ventricular; and WBC, white blood cell.
myocardium remote from the infarct. Furthermore, when MI is induced in an abdominal heterotopic transplanted rodent heart, the native heart demonstrates a decrease in LV fractional shortening and an increase in LV end-diastolic dimension accompanied by an increase in tumor necrosis factor-α levels. Thus, the postinfarct inflammatory process may induce cytokine production and inflammatory cell infiltration in remote normal myocardium. This is reflected by

Figure 2. Tissue R2* values. R2* value in ROIs from the different tissues in control patients (blue) and patients who received an infusion of USPIO (red). Asterisk denotes a significant increase from baseline. ROIs indicates regions of interest; and USPIO, ultrasmall superparamagnetic particles of iron oxide.

Figure 3. Comparison of R2* color maps in patients with MI at (i) baseline and (ii) 24 hours after no infusion (A, upper) or after an infusion of ultrasmall superparamagnetic particles of iron oxide (USPIO; B, lower). R2* values did not change in the liver (blue) or myocardium (remote myocardium, green; infarct, red; microvascular obstruction (MVO), purple) of the control patient (A iii) but did rise in the patient who received USPIO (B iii). MI indicates myocardial infarction.
our finding of an almost 3-fold increase in R2* value in remote myocardium. The magnitude of increase in macrophages reported in autopsy studies is similar to the increase in the signal of USPIO observed in this study. This suggests that increased macrophage infiltration is not a post- or perimortem artefact but a real pathophysiological phenomenon.24 Thus, our technique has the potential, pending histopathological confirmation, to study macrophage infiltration and myocardial inflammation not just in the area of infarction but throughout the heart. This has potential applications as a method for assessing and monitoring LV inflammation and remodelling following MI.

R2* value was decreasing in myocardial, splenic, and hepatic tissues by 48 hours postinfusion. The decrease in R2* value in the blood pool is to be expected given efficient USPIO phagocytosis by reticuloendothelial cells leading to rapid clearance.21 However, preclinical findings suggest that monocyte tissue residence in infarcted myocardium is brief despite high recruitment rates.27 Consistent with this study, we found evidence of high extramedullary activity in terms of high uptake of USPIO in the liver and spleen in contrast with minimal uptake in the bone marrow (online-only Data Supplement Figure II). The decrease in R2* value in the splenic tissues at 48 hours may represent mobilization of the splenic reservoir of monocytes.1,28 In addition, the decrease in tissue R2* will reflect clearance of extravasated particles by phagocytic cells through efflux of USPIO-laden inflammatory cells. The time course of monocyte and macrophage recruitment into the myocardium is unclear from our study and would require administration of USPIO at differing time points following MI. This would help define the peak influx and time course of macrophage trafficking into the myocardium.

We have applied this technique to patients who have recently sustained a MI. However, this approach could be applied to other cardiac conditions that involve intense inflammatory processes. This could include viral myocarditis, giant cell myocarditis, anthracycline-induced cardiotoxicity, and sarcoidosis. Indeed, it may also have a role in detecting cardiac transplant rejection in a noninvasive manner. However, this needs further careful validation in well-phenotyped clinical subgroups.

Limitations to our study included the lack of histopathological confirmation of macrophage uptake, the longer reperfusion time in the USPIO group potentially resulting in more inflammation and the injection of USPIOs at variable time points post-MI. However, given the previous evidence that USPIO are taken up by macrophages, our study provides proof of principle that cellular inflammation may be tracked post-MI.

In conclusion, we have demonstrated for the first time that USPIO is taken up by the infarct tissue in patients with recent MI and by the peri-infarct and remote myocardium to a lesser degree. Given previous preclinical and clinical studies, this is likely to correspond to cellular inflammation. This represents a novel noninvasive method to further study cardiac inflammation and therapeutic interventions. It may also provide prognostic information or a diagnostic tool for the investigation of inflammatory cardiac conditions such as myocarditis and transplant rejection, as well as a potential biomarker for therapeutic interventions targeted at improving LV remodelling following infarction.

Acknowledgments
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Disclosures
None.

References


**CLINICAL PERSPECTIVE**

In preclinical and clinical studies, ultrasmall superparamagnetic particles of iron oxide are taken up and concentrated by macrophages. This alters the T2* relaxation properties of the cells such that they can be detected by magnetic resonance imaging in order to identify areas of cellular inflammation within tissues. We have developed a technique that uses ultrasmall superparamagnetic particles of iron oxide and magnetic resonance imaging to identify areas of cellular inflammation following acute myocardial infarction. We demonstrate that it can detect cellular inflammation not only within the infarct and peri-infarct zone but also within the remote myocardium. This technique therefore has potential to be used as a tool to assess the effectiveness of new therapies or other interventions targeted at improving left ventricular remodelling after myocardial infarction. It also has the potential to diagnose other inflammatory cardiac conditions such as myocarditis or graft rejection following transplantation.
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Supplemental Table I. R2* value (s⁻¹) in infarct region of interest (ROI) of control patients.

<table>
<thead>
<tr>
<th>Region</th>
<th>Baseline</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Micro-Vascular Obstruction</strong></td>
<td>Mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(When present)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>S.D.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min, Max</td>
<td></td>
<td></td>
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<tr>
<td><strong>Infarct ROI</strong></td>
<td>Mean</td>
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<td>43.33</td>
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<tr>
<td></td>
<td>S.D.</td>
<td>13.78</td>
<td>8.17</td>
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<tr>
<td></td>
<td>Min, Max</td>
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<td>40, 60</td>
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<td><strong>Peri-Infarct ROI</strong></td>
<td>Mean</td>
<td>40.0</td>
<td>38.33</td>
</tr>
<tr>
<td></td>
<td>S.D.</td>
<td>6.33</td>
<td>7.53</td>
</tr>
<tr>
<td></td>
<td>Min, Max</td>
<td>30, 50</td>
<td>40, 50</td>
</tr>
<tr>
<td><strong>Remote Myocardium ROI</strong></td>
<td>Mean</td>
<td>43.33</td>
<td>41.67</td>
</tr>
<tr>
<td></td>
<td>S.D.</td>
<td>5.16</td>
<td>4.08</td>
</tr>
<tr>
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<td>Min, Max</td>
<td>40, 50</td>
<td>40, 50</td>
</tr>
<tr>
<td><strong>Liver ROI</strong></td>
<td>Mean</td>
<td>56.67</td>
<td>58.33</td>
</tr>
<tr>
<td></td>
<td>S.D.</td>
<td>10.33</td>
<td>9.83</td>
</tr>
<tr>
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<td>Min, Max</td>
<td>40, 70</td>
<td>40, 70</td>
</tr>
<tr>
<td><strong>Skeletal Muscle</strong></td>
<td>Mean</td>
<td>51.67</td>
<td>51.67</td>
</tr>
<tr>
<td></td>
<td>S.D.</td>
<td>75.28</td>
<td>75.28</td>
</tr>
<tr>
<td></td>
<td>Min, Max</td>
<td>40, 60</td>
<td>40, 60</td>
</tr>
<tr>
<td><strong>Spleen</strong></td>
<td>Mean</td>
<td>68.33</td>
<td>75.0</td>
</tr>
<tr>
<td></td>
<td>S.D.</td>
<td>28.58</td>
<td>37.82</td>
</tr>
<tr>
<td></td>
<td>Min, Max</td>
<td>40, 100</td>
<td>40, 120</td>
</tr>
</tbody>
</table>
Supplemental Table II. R2* value (s⁻¹) in infarct region of interest (ROI) of patients receiving ultrasmall superparamagnetic particles of iron oxide (USPIO).

<table>
<thead>
<tr>
<th>Microvascular Obstruction (When Present)</th>
<th>Baseline</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>66.67</td>
<td>173.3</td>
<td>143.3</td>
</tr>
<tr>
<td>S.D.</td>
<td>55.08</td>
<td>68.07</td>
<td>41.63</td>
</tr>
<tr>
<td>Min, Max</td>
<td>30, 130</td>
<td>120, 250</td>
<td>100, 190</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Infarct ROI</th>
<th>Mean</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>41.0</td>
<td>155.0</td>
<td>124.0</td>
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<tr>
<td>S.D.</td>
<td>11.97</td>
<td>45.03</td>
<td>35.02</td>
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<td>Min, Max</td>
<td>30, 70</td>
<td>110, 250</td>
<td>80, 180</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Peri-Infarct ROI</th>
<th>Mean</th>
<th>Day 2</th>
<th>Day 3</th>
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</thead>
<tbody>
<tr>
<td>Mean</td>
<td>43.0</td>
<td>130.0</td>
<td>95.0</td>
</tr>
<tr>
<td>S.D.</td>
<td>8.23</td>
<td>30.18</td>
<td>19.0</td>
</tr>
<tr>
<td>Min, Max</td>
<td>30, 60</td>
<td>100, 200</td>
<td>80, 140</td>
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</table>

<table>
<thead>
<tr>
<th>Remote Myocardium ROI</th>
<th>Mean</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>39.0</td>
<td>80.0</td>
<td>67.0</td>
</tr>
<tr>
<td>S.D.</td>
<td>3.16</td>
<td>14.91</td>
<td>15.67</td>
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<tr>
<td>Min, Max</td>
<td>30, 40</td>
<td>50, 100</td>
<td>50, 100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Liver ROI</th>
<th>Mean</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>84.0</td>
<td>319.0</td>
<td>243.0</td>
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<tr>
<td>S.D.</td>
<td>49.49</td>
<td>69.99</td>
<td>63.60</td>
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<tr>
<td>Min, Max</td>
<td>50, 220</td>
<td>230, 420</td>
<td>160, 370</td>
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</table>

<table>
<thead>
<tr>
<th>Skeletal Muscle</th>
<th>Mean</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>54.0</td>
<td>67.0</td>
<td>65.0</td>
</tr>
<tr>
<td>S.D.</td>
<td>8.43</td>
<td>9.49</td>
<td>14.18</td>
</tr>
<tr>
<td>Min, Max</td>
<td>40, 70</td>
<td>50, 80</td>
<td>50, 100</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Spleen</th>
<th>Mean</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>65.0</td>
<td>293.0</td>
<td>250.0</td>
</tr>
<tr>
<td>S.D.</td>
<td>23.69</td>
<td>172.1</td>
<td>162.6</td>
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<tr>
<td>Min, Max</td>
<td>20, 100</td>
<td>10, 500</td>
<td>10, 460</td>
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<table>
<thead>
<tr>
<th>Bone Marrow (Ribs)</th>
<th>Mean</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>247.0</td>
<td>276.0</td>
<td>274.0</td>
</tr>
<tr>
<td>S.D.</td>
<td>92.62</td>
<td>140.4</td>
<td>164.9</td>
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<td>Min, Max</td>
<td>80, 360</td>
<td>100, 500</td>
<td>60, 570</td>
</tr>
</tbody>
</table>
Supplemental Figure I.
Supplemental Figure II.
Supplemental Figure Legends

**Supplemental Figure I.** Bland-Altman plot - Differences versus average of R2* values in all patients.

**Supplemental Figure II.** Medullary and extramedullary R2* value post myocardial infarction - There is a significant increase in R2* value of hepatic and splenic tissues at 24 hours, that later fall. The R2* value of rib bone marrow does not increase significantly. *P<0.05 versus baseline.