Cardiac magnetic resonance imaging: long term reproducibility of the late enhancement signal in patients with chronic coronary artery disease

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Objective: To determine long term reproducibility of the late enhancement (LE) signal in contrast enhanced magnetic resonance imaging (MRI) and potential changes of the signal after revascularisation.

Methods: 33 patients (29 men, mean (SD) 61 (11) years) with coronary artery disease (CAD) and left ventricular dysfunction (ejection fraction 30 (7)%) underwent two contrast enhanced MRI procedures within 9 (3) months. Fifteen patients (group A: 14 men, 59 (12) years) had no interventions between the two studies. Eighteen patients underwent revascularisation after MRI 1 (group B: 15 men, 62 (9) years). Changes in the LE signal between the first and second MRIs were investigated in both groups as well as intraobserver and interobserver variabilities for delineation of the signal.

Results: The LE signal was highly reproducible in groups A and B for segmental analysis (concordance 86% v 82%, respectively; κ = 0.70 v 0.67) and summed scores (group A: r = 0.97, p < 0.001; group B: r = 0.93, p < 0.001). The LE signal was quantified as 27 (27) cm³ in group A versus 30 (16) cm³ in group B in the first MRI and 26 (25) cm³ versus 30 (16) cm³, respectively, for the second MRI (both not significant). Moreover, low intraobserver and interobserver variabilities were observed in segmental analysis (κ = 0.86 and 0.74, respectively, for group A, and κ = 0.87 and 0.82, respectively, for group B).

Conclusion: In patients with chronic CAD, the LE signal in contrast enhanced MRI is very stable over an extended time period. These results further characterise contrast enhanced MRI as a useful tool for myocardial viability assessment. Low intraobserver and interobserver variabilities promise robustness of the method for clinical application.

METHODS

Patients
Fifty four patients with angiographically proven CAD and impaired LV function were initially enrolled in the study. Of the 54 patients, 15 declined a follow up MRI, three patients underwent implantation of a cardioverter-defibrillator, and three patients died before the follow up. The remaining 33 patients (29 men, mean (SD) age 60.7 (10.6) years) were studied twice with MRI within an interval of 9 (3) months (range 3–15 months). Four of the 33 patients had single vessel disease, three had double vessel disease, and 26 had triple vessel disease. Mean (SD) LV ejection fraction (LVEF) was 30 (7%). Twenty one patients had a history of prior myocardial infarction and 22 patients had undergone revascularisation procedures (bypass graft surgery, 13 patients; percutaneous coronary intervention, 13 patients), neither of which had occurred within two months before the first MRI. In the time interval between both scans, 15 patients (group A: 14 men, mean (SD) age 59.3 (12.3) years) were treated medically only, with no patients undergoing any coronary intervention or having a cardiac event before the
second MRI. The other 18 patients (group B: 15 men, mean (SD) age 61.8 (9.2) years) were revascularised within five weeks after the first MRI. Fifteen patients underwent bypass graft surgery (six patients had two bypass grafts, five patients had three bypass grafts, three patients had four bypass grafts, and one patient had one bypass graft) and three patients had a percutaneous coronary intervention (one native vessel/ bypass graft each). After revascularisation, one patient had a coronary reintervention (percutaneous transluminal coronary angioplasty of one native vessel) three months before the second MRI. For all patients of group B, the time interval between revascularisation and the second MRI was at least three months. In between the scans, no patient of this group had a cardiac event. Written informed consent was obtained from all patients after approval by the local ethics committee.

**Magnetic resonance imaging**

MRIs were recorded with two 1.5 T scanners (Gyroscan ACS 1.5T, Philips Medical Systems, Best, the Netherlands (22 patients) and Magnetom Sonata Maestro Class, Siemens Medical Solutions, Erlangen, Germany (11 patients)) with a dedicated cardiac phased array surface coil. For comparison, both scans for each patient were recorded with the same scanner and by the same physician (H B). Ten to 13 consecutive cine short axis views and one, two, and four chamber view, each acquired during one breath hold, were recorded for evaluation of wall motion (WM) and LVEF in a steady state free precession technique (Gyroscan ACS: echo time 1.4 ms, repetition time 2.9 ms, slice thickness 8 mm, spatial resolution 1.4 × 1.2 mm², flip angle 60°, temporal resolution 42 ms; Magnetom Sonata: echo time 1.5 ms, repetition time 2.6 ms, slice thickness 8 mm, spatial resolution 2.2 × 1.3 mm², flip angle 65°, temporal resolution 35 ms). The LE signal was evaluated by two techniques 15–20 minutes after intravenous injection of Gd-diffitylenetri-minepentaacetic acid (DTPA) 0.2 mmol/kg body weight (Magnesi; Schering AG, Berlin, Germany): an inversion recovery three dimensional turbo gradient echo technique with echo planar readout (Gyroscan ACS: echo time 3.3 ms, repetition time 5.4 ms, echo planar imaging factor 11, slice thickness 5 mm, spatial resolution 1.2–1.2 mm², flip angle 15°, acquisition window per heart beat 284 ms, inversion time varied visually to achieve complete nulling of normal myocardium between 225–300 ms for MRI 1 and kept constant for MRI 2); or a T1 weighted two dimensional inversion recovery true fast imaging technique with steady state precession sequence (Magnetom Sonata: echo time 1.4 ms, repetition time 2.4 ms, slice thickness 8 mm, spatial resolution 2.8 × 1.4 mm², flip angle 60°, acquisition window 156 ms/heart beat, inversion time varied between 225–300 ms for MRI 1 and kept constant for MRI 2). Both inversion recovery sequences were acquired at end diastole, covering the whole LV (in short axis views and part of the LV in two and four chamber views).

**Data analysis**

MRIs were evaluated with either a commercially available software (Mass 4.0; Medis, Leiden, the Netherlands for WM and LE data; Gyroscan ACS, Argus, Siemens Medical Solutions for WM data; Magnetom Sonata) or an in-house developed software (Munich Heart for LE data; Magnetom Sonata). Analysis of cine short axis views yielded LVEF and LE data; Gyroscan ACS, Argus, Siemens Medical Solutions (Mass 4.0; Medis, Leiden, the Netherlands) or a three point system (0, none; 1, non-transmural, defined arbitrarily as containing less than 50% of a transmural signal; and 2, transmural enhancement, defined arbitrarily as containing at least 50% of a transmural signal). All myocardial segments were evaluated according to this grading system and a summed score of LE and WM was calculated for each patient. The size of the LE signal (in cubic centimetres) was quantified from the regions of interest including the area of the LE signal on each short axis slice covering the LV.

Two independent observers determined interobserver variability of visual LE signal analysis by reading MRI 1 of the first 22 patients and were blinded to each other and to clinical data. To analyse intraobserver variability of the contrast enhanced MRI, one observer evaluated MRI 1 of the first 22 patients at two times at an interval of three months and was blinded to clinical data and results of the first evaluation.

**Statistical analysis**

Cardinal and ordinal variables were expressed as mean (SD) or range, where appropriate. Discrete variables are shown as absolute and relative frequencies. For evaluation of differences between groups A and B and between the two dimensional and three dimensional imaging sequences Mann-Whitney U test was applied, and for changes between MRI 1 and MRI 2 the Wilcoxon test was performed. Summed scores and the amount of LE signal were compared by Spearman correlation coefficients. Bland-Altman plots were created to evaluate agreement in the LE score and quantification of the LE signal between MRI 1 and MRI 2. Time course and interobserver and intraobserver agreements of the LE signal on a segmental basis were assessed by κ statistics. Bonferroni adjustment was used to account for multiple testing. Computed p values were two sided and p < 0.05 was
considered significant. Data were analysed with SPSS 11.5 (SPSS Inc, Chicago, Illinois, USA).

RESULTS
Segmental LE signal analysis
Tables 1 and 2 list the results of segmental LE signal analysis for both MRIs in patient groups A and B. Both scans were highly concordant in group A (concordance in 86% (424 of 495) of segments) but also in group B (82% (486 of 594)). Kappa statistics indicated close agreement (group A: $\kappa = 0.70$; group B: $\kappa = 0.67$), being highly significant ($p < 0.001$ each). Analysis of a subgroup of group B of only patients with improved LV function (15 patients) showed concordance in 82% (407 of 495) of segments and $\kappa = 0.68$, therefore not different from group A and group B as a whole.

Analysis of the LE summed scores for each patient showed a close correlation between MRI 1 and MRI 2 for both patient groups (group A: $r = 0.99$, $p < 0.001$; group B: $r = 0.98$, $p < 0.001$) and the Bland-Altman plot showed good agreement (fig 1). The two imaging sequences did not differ significantly according to the LE summed scores (group A: $p = 0.87$; group B: $p = 0.86$). Figures 2 and 3 show examples from three patients of group A and group B, respectively.

Intraobserver and interobserver variability in LE signal evaluation
Analysis of intraobserver and interobserver variabilities in the segmental evaluation of MRIs from the first 22 patients (group A: 13 patients; group B: nine patients) showed agreement in 93% (398 of 426 segments) and 88% (375 of 426), respectively, for group A and 92% (274 of 297) and 89% (265 of 297), respectively for group B. The corresponding $\kappa$ values were 0.86 ($p < 0.001$) and 0.74 ($p < 0.001$), respectively, for group A and 0.87 ($p < 0.001$) and 0.82 ($p < 0.001$), respectively, for group B. All agreements were highly significant with no significant differences between group A and B.

Quantification of the LE signal
The mean (SD) LE signal area in MRI 1 was quantitatively assessed to be 27 (27) cm$^3$ in group A and 30 (16) cm$^3$ in group B. The corresponding values for MRI 2 were 26 (25) cm$^3$ and 30 (15) cm$^3$, respectively. For both patient groups, no significant changes were observed between the first and second scans (group A: MRI 1 $\text{vs}$ MRI 2, $p = 0.311$; group B: $p = 0.879$). The quantitative amount of LE signal in MRI 1 and MRI 2 correlated closely in both patient groups (group A: $r = 0.99$, $p < 0.001$; group B: $r = 0.98$, $p < 0.001$). Furthermore, the Bland-Altman plot indicated good agreement between the absolute amount of LE signal in both scans (fig 4), with the majority of values falling within $\pm$ 2SD of the mean difference. A comparison between both imaging sequences (two versus three dimensional) showed no significant differences (group A: $p = 0.22$; group B: $p = 0.50$). The quantitative LE signals of both sequences in both MRIs were well correlated.

Analysis of LE signal in relation to LV function
Between the baseline and follow up scans the LVEF, indicating global LV function, did not change significantly in group A (31 (8)% $\text{vs}$ 32 (8)% in the first and second MRIs, respectively, $p = 0.20$) but improved non-significantly in group B (28 (6)% $\text{vs}$ 32 (8%), $p = 0.052$). For both MRIs, no significant differences in LVEF were found between patient groups A and B.
Table 3 shows the relation between LE score and WM score on a segmental basis. Either severe hypokinesis or akinesis/dyskinesis (WM score 2 or 3) was observed in 88% of segments containing transmural contrast enhancement (LE score 2) but in only 36% of segments with no LE signal. Table 4 lists the mean segmental LE score for each degree of WM score in both MRIs and both patient groups. A significant correlation between the WM score and the mean segmental LE score was found in both patient groups and both MRIs (group A, MRI 1 and 2: $r = 0.51$ and $r = 0.52$, respectively, $p < 0.001$ each; group B, MRI 1 and 2: $r = 0.55$ and $r = 0.51$, $p < 0.001$ each).

Table 5 shows the observed changes of WM score between MRI 1 and 2 according to LE score. With increasing LE score the percentage of segments with no change in WM score increased (LE score 0: 62%; LE score 1: 74%; and LE score 2: 90%). Conversely, the lower the LE score, the higher the percentage of segments with improving WM score, especially in group B (LE score 0: 19% v 27%; LE score 1: 18% v 18%; and LE score 2: 7% v 3% in group A v group B, respectively). Of 213 dysfunctional segments containing no LE signal (LE score 0) at MRI 1, 94 (44%) improved functionally after revascularisation. Segments with transmural enhancement (LE score 2) had a worsening (5% of segments) or improved WM score (5%). Seventy one per cent of these had only minor changes at the dysfunctional edge of the WM scale (changes between WM score 2 and 3). The mean summed WM score for patient group A did not change significantly between the two scans ($51 \pm 51$, $p = 0.40$), whereas it tended to improve, though not significantly, in group B ($46 \pm 50$, $p = 0.15$).

**DISCUSSION**

The results of this study show that, in patients with chronic CAD and impaired LV function, the extent and location of the LE signal are highly reproducible over an extended time. Furthermore, the LE signal was stable regardless of whether patients had undergone conservative treatment or revascularisation.

Analysis of the LE signal, together with regional WM, showed increasing regional dysfunction with increasing...
transmurality of contrast enhancement. In addition, improvement in WM decreased with increasing transmurality of the LE signal. This is in concordance with results of several studies describing a relation between the degree of myocardial contrast enhancement and the probability of functional recovery after revascularisation.

Concerning possible temporal changes of the LE signal, there are only few data published. One recent study by Mahrohld and colleagues evaluated short term reproducibility of contrast enhanced MRI in 20 patients with chronic myocardial infarction. They found high reproducibility of the LE signal 10 and 25 minutes after one injection of a gadolinium based contrast agent and repositioning of the patients between the two scans. In contrast, patients in our study underwent two MRIs with a mean time interval of 9 (3) months, therefore addressing biological and a lesser degree methodological reproducibility. Previous studies investigating LE signal changes at different time points focused mainly on the time course after acute and subacute myocardial infarction. In a canine model, Kim and colleagues studied seven dogs three days and eight weeks after acute infarction. They found a decrease in the extent of hyperenhancement by a factor greater than 3, which was explained by shrinkage of scar tissue. This is in accordance with a histological study in a canine model by Reimer and colleagues, who described a decrease of infarct size in the subacute phase by a factor of 4. In a porcine study, however, van Dijkman and colleagues found little change in contrast enhancement between one and three weeks after coronary occlusion. According to their medical records, none of our patients had an acute myocardial infarction within two months before the first or in between the two MRIs. Thus, no significant changes in infarct size based on shrinkage of infarcted myocardium could be expected, as the results confirmed.

In patients undergoing bypass graft surgery or percutaneous coronary intervention, several studies reported an increase of CK-MB and troponin T, suggesting myocardial injury. Furthermore, Regenfus and colleagues showed that 20 of 48 (42%) patients with successful coronary artery bypass surgery had an increase in LE signal, averaging 5% of the LV mass. Selvanayagam and colleagues found a new LE signal in about 40% of patients undergoing bypass graft surgery. In contrast to these authors, we detected no significant changes in the amount of LE signal in our study, suggesting absence of myocardial injury during or after revascularisation in this patient cohort. However, since we do not have information on serum markers (CK-MB, troponin) for these patients, we have no proof that no further myocardial injury had occurred.

Table 5 Segmental LE score (MRI 1) and changes in WM score (MRI 1 vs MRI 2) for patient groups A and B

<table>
<thead>
<tr>
<th>LE score</th>
<th>No change</th>
<th>Worsened</th>
<th>Improved</th>
<th>Total</th>
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<td>1</td>
<td>54</td>
<td>8</td>
<td>14</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>4</td>
<td>5</td>
<td>76</td>
</tr>
<tr>
<td>Total</td>
<td>342</td>
<td>69</td>
<td>84</td>
<td>495</td>
</tr>
<tr>
<td>Group B</td>
<td>208</td>
<td>48</td>
<td>94</td>
<td>350</td>
</tr>
<tr>
<td>0</td>
<td>132</td>
<td>10</td>
<td>32</td>
<td>174</td>
</tr>
<tr>
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<td>61</td>
<td>128</td>
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</table>

In conclusion, the results of this study show that the LE signal in patients with chronic CAD and LV impairment is highly biologically and methodologically reproducible over a prolonged time period. This further helps to characterise...
contrast enhanced MRI as a useful tool for myocardial viability assessment. Low intraobserver and interobserver variabilities prove that this method is sufficiently robust for clinical application. Quantitative LE signal assessment may provide an accurate measurement of infarct size as an end point for studies evaluating new treatments.

We thank all technicians in the MRI unit for their excellent support acquiring the studies.

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