Rapid Initial Reduction of Hyperenhanced Myocardium After Reperfused First Myocardial Infarction Suggests Recovery of the Peri-Infarction Zone One-Year Follow-Up by MRI

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Background—The time course and magnitude of infarct involution, functional recovery, and normalization of infarct-related electrocardiographic (ECG) changes after acute myocardial infarction (MI) are not completely known in humans. We sought to explore these processes early after MI and during infarct-healing using cardiac MRI.

Methods and Results—Twenty-two patients with reperfused first-time MI were examined by MRI and ECG at 1, 7, 42, 182, and 365 days after infarction. Global left ventricular function and regional wall thickening were assessed by cine MRI, and injured myocardium was depicted by delayed contrast-enhanced MRI. Infarct size by ECG was estimated by QRS scoring. The reduction of hyperenhanced myocardium occurred predominantly during the first week after infarction (64% of the 1-year reduction). Furthermore, during the first week the amount of nonhyperenhanced myocardium increased significantly (P < 0.001), although the left ventricular mass remained unchanged. Left ventricular ejection fraction increased gradually, whereas the greater the regional transmural extent of hyperenhancement at day 1, the later the recovery of regional wall thickening. Regional wall thickening decreased progressively with increasing initial transmural extent of hyperenhancement (P_trend < 0.0001). The time course and magnitude of decrease in QRS score corresponded with the reduction of hyperenhanced myocardium.

Conclusions—The early reduction of hyperenhanced myocardium may reflect recovery of hyperenhanced, reversibly injured myocardium, which must be considered when predicting functional recovery from delayed contrast-enhanced MRI findings early after infarction. Also, the time course and magnitude for reduction of hyperenhanced myocardium were associated with normalization of infarct-related ECG changes. (Circ Cardiovasc Imaging. 2009;2:47-55.)

Key Words: electrocardiography • MRI • myocardial infarction • remodeling • reperfusion

Recovery of left ventricular function and normalization of infarct-related electrocardiographic (ECG) changes after acute myocardial infarction (MI) have previously been described.1,2 Until recently, however, it has been difficult to establish the anatomic correlate of these changes because of a lack of an accurate in vivo method for infarct visualization.

Clinical Perspective see p 55

It is now possible to noninvasively depict myocardial injury in great detail using delayed contrast-enhanced MRI (DE-MRI).3,4 This technique has been used to study the impact of infarct characteristics on functional recovery after acute infarction in animal models5,6 and in humans.7–9 Still, the pathophysiological basis for the hyperenhancement of myocardial tissue early after infarction remains somewhat controversial. It has been suggested that only irreversibly injured myocardium becomes hyperenhanced using the DE-MRI technique.3 Other studies related to the pathophysiological basis for hyperenhancement have indicated that reversibly injured myocardium in the peri-infarction zone might enhance early after acute infarction.10–13 If the recovery of this reversibly injured myocardium is incomplete the peri-infarction zone will consist of both viable and infarcted tissue, partly explaining its gray appearance with DE-MRI in healing MI. Presence of a gray peri-infarction zone in healing MI has been shown to be associated with risk of arrhythmias14 and increased mortality.15

It remains to be explored how the hyperenhanced myocardium changes during the first week after reperfused infarction in humans. Furthermore, the relationships between sequential changes of the hyperenhanced myocardium and sequential ECG changes after MI have not yet been studied. The aim of
the present longitudinal study was to explore the changes in hyperenhanced myocardium, recovery of global and regional left ventricular function, and sequential ECG changes at multiple points in time during the first year after infarction in patients with reperfused first-time MI treated with currently available pharmacological therapy.

Methods

Patient Population

The present study was approved by the local ethics committee, and all patients gave their written informed consent to participate in the study. Patients arriving at the Coronary Care Unit of Lund University Hospital with signs of acute MI were approached for enrollment. Patients were excluded from the study based on prior infarction, unstable condition, lost during follow-up, reinfection or cardiac intervention during follow-up, contraindications for MRI, or diagnosis other than acute MI. Ultimately, 22 patients were included in the study, all having significant ST-segment deviation, single vessel coronary occlusion, positive biochemical markers (creatine kinase isoenzyme MB mass >10 µg/L and cardiac troponin T level >0.05 µg/L), and symptoms suggestive of acute MI. All patients included underwent successful percutaneous transluminal coronary angioplasty with stenting (described as thrombolysis in myocardial infarction [TIMI] Grade 3 blood flow).

Study Design

On inclusion, patients were scheduled for MRI examination the day after admission and for follow-up examinations after 7, 42, 182, and 365 days. Standard 12-lead ECGs were recorded in each patient at admission, the day after admission, and when possible at the time of the follow-up MRI examination.

MR Imaging

MR imaging was performed on either of two 1.5-T systems: Magnetom Vision (Siemens) with a CP body array coil, or Philips Intera CV (Philips) with a cardiac synergy coil. All subjects were placed in supine position. Cine short-axis gradient-recalled echo images covering the left ventricle were acquired using either a turbo fast low-angle shot sequence (slice thickness = 10 mm, field-of-view = 380 mm, TR = 100 ms [echo sharing resulting in phases every 50 ms], TE = 4.8 ms) or a balanced turbo field echo sequence (slice thickness = 8 mm, field-of-view = 340 mm, TR = 3.14 ms, TE = 1.58 ms). Five patients were initially examined on the Siemens scanner and had 1 or more of the follow-up examinations performed on the Philips scanner because of scanner replacement during the ongoing patient follow-up. However, all patients had follow-up examinations using the same cine sequence, either turbo fast low-angle shot or balanced turbo field echo, at all time points. Twenty to 40 minutes after intravenous administration of a commercially available extracellular gadolinium-based contrast agent (gadoteric acid, Gd-DOTA, 0.2 mmol/kg, Guerbet, Gotthia Medical AB, Bilddal, Sweden) an inversion-recovery sequence was used to acquire contrast-enhanced images in the corresponding short-axis planes as for the cine images. Typical inversion-recovery sequence parameters were as follows: slice thickness = 10 mm, TR = 8 ms, TE = 4 ms, in-plane resolution = 1.4 × 1.4 mm, and flip angle = 25° with acquisition every other heartbeat for the Siemens scanner and slice thickness = 8 mm, TR = 3.9 ms, TE = 1.2 ms, in-plane resolution = 1.5 × 1.5 mm, and flip angle = 15° with acquisition every heartbeat for the Philips scanner. The inversion time, typically 200 to 350 ms, was manually adjusted to null the signal from remote myocardium.16

MR Analysis

The MR images were analyzed using freely available software developed and validated in-house (Segment 1.457, available at http://segment.heiberg.se).17

Global Left Ventricular Function and Hyperenhancement

The endocardial and epicardial borders were manually traced in each cine short-axis plane in both end-diastole and end-systole, enabling determination of left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV). The left ventricular ejection fraction was calculated as (EDV − ESV)/EDV. Left ventricular mass was calculated as left ventricular muscle volume multiplied by the myocardial muscle density (1.05 g/mL). The area of hyperenhancement was defined on the DE-MRI short-axis images and was quantified using a previously described semiautomatic method.19 In regions where the computer algorithm was clearly wrong, areas of hyperenhancement were manually adjusted. The absolute and relative (to left ventricular mass) amounts of hyperenhanced myocardium and mean transmural extent of hyperenhancement were obtained as previously described.19 In short, the transmural extent of hyperenhancement was determined using a centerline approach, assessing the radial extent of hyperenhancement at each 4.5° from the center of each short-axis slice. In addition, the endocardial extent of hyperenhancement was obtained by multiplying the circumferential endocardial extent of hyperenhancement in each short-axis slice by the thickness of each slice. The total endocardial extent of hyperenhancement was expressed as a percentage of the total left ventricular endocardial surface.

Regional Left Ventricular Function and Hyperenhancement

The left ventricle was divided into 72 segments (6 short-axis slices with 12 sectors in each) according to a previously described model.20 For each segment, wall thickening was calculated as (end-systolic wall thickness − end-diastolic wall thickness)/end-diastolic wall thickness. The transmural extent of hyperenhancement of each of the corresponding 72 segments was then determined independently of the wall-thickening analysis. The segments were divided into remote segments (no hyperenhancement), adjacent segments (no neighboring hyperenhanced segment), and hyperenhanced segments with increasing transmural extent of hyperenhancement (1% to 25%, 26% to 50%, 51% to 75%, and 76% to 100%).

The registration of corresponding segments at different time points was done using the anterior insertion site of the right ventricle at the insertion level of the anterior papillary muscle as guidance. The analyses of the cine MR images and the DE-MRI images were performed by 2 blinded observers, each with 7 years of experience with cardiac MRI.

MR Image Registration

Cine and DE-MRI images were obtained at the same MRI session for each time point. The registration of images acquired at different time points was aided by using the same acquisition protocol to identify the short-axis plane for all examinations. The left ventricular apex was used as the anatomic landmark for choosing the same level of short-axis planes at each MRI session.

ECG Recording and Analysis

A standard 12-lead ECG was recorded at admission and at 92% (98 of 106) of the MRI examinations using a MEGACART-R recorder (Siemens-Elema AB). To estimate infarct size from the infarct-related ECG changes, the 50-criteria/31-point Selvester QRS scoring system was used.21 In short, the QRS scoring system is a quantitative evaluation of infarct related QRS changes, enabling an ECG estimate of infarct size and location. Two experienced electrocardiologists, blinded to the MRI results, independently completed case report forms designating each point awarded on each of the series of ECGs. Differences in points awarded by the 2 observers were then adjudicated in conference for comparison with the MRI results.

Statistical Analysis

All statistical analyses were performed using SPSS version 12.0 (SPSS Inc.). Continuous variables were expressed as mean ± SD. The Wilcoxon signed-rank test was used to assess global changes in left
ventricular function and hyperenhancement characteristics over time (1 measurement per patient and time point). Mixed-effect modeling was used for 2 different types of regional segmental analyses, given the dependence of multiple segments per patient. First, at each of the 5 time points (days 1, 7, 42, 182, and 365), a linear mixed model was fitted with the relative wall thickening as dependent variable, a random intercept per patient, and a fixed overall intercept. The probability value of the fixed intercept was used to assess the trend of regional wall thickening over time. The Mann–Whitney test was used to assess global differences between infarct size by QRS score and the relative amount of hyperenhanced myocardium. Finally, linear regression analysis was used to assess the relationship between QRS score and the relative amount of hyperenhancement at each time point separately. A probability value of <0.05 was considered to indicate statistical significance.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Patient Characteristics

In all, 22 patients (21 men; aged 42 to 77 years) were enrolled. In one case, the 42-day MRI follow-up was missed, and in another case the patient did not return for the 365-day follow-up. Twenty patients had a repeat ECG recorded 7 days after admission; 15, after 42 days; 21, after 182 days; and 21 had repeat ECG recorded after 365 days. The 1-day, 7-day, 42-day, 182-day, and 365-day follow-up examinations occurred 1±1 days, 8±1 days, 44±4 days, 186±8 days, and 369±11 days after infarction, respectively.

Patient characteristics are shown in the Table 1. In conjunction with the percutaneous transluminal coronary angioplasty, all patients received a platelet glycoprotein IIb/IIIa inhibitor.

Hyperenhancement Characteristics

The absolute and relative amounts of hyperenhancement, transmural extent of hyperenhancement, and endocardial extent of hyperenhancement all decreased over time after infarction (Figure 1). For all variables, the decrease was most pronounced during the first week; almost two thirds of the total decrease in absolute and relative amounts of hyperenhancement (64% and 63%, respectively) over the 1-year follow-up had occurred during this time. The mean transmural extent and endocardial extent of hyperenhancement both followed the same pattern with a significant decrease at 1 week. One patient showed microvascular obstruction (hyperenhancement within the region of hyperenhancement) associated with expansion of the endocardial extent of hyperenhancement over time (Figure 1D). This patient also had the largest amount of hyperenhancement at baseline (42% of the left ventricular mass).

Table 1. Patient Characteristics

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1 IRA indicates infarct-related artery; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; PAI, platelet aggregation inhibitor; CK-MB, peak creatine kinase isoenzyme MB mass; cTnT, peak cardiac troponin T; LAD, left anterior descending coronary artery; pPTCA, primary percutaneous transluminal coronary angioplasty; RCA, right coronary artery; LCA, left circumflex artery; and rPTCA, rescue PTCA.
Figure 2 shows an example of sequential changes in wall thickening in relation to changes in hyperenhanced myocardium over the first year after infarction. Three patients had no signs of hyperenhancement by DE-MRI at any time point. These patients had the lowest levels of peak creatine kinase isoenzyme MB mass (Table 1).

Global Left Ventricular Function

Figure 3 shows the changes in left ventricular ejection fraction and mass, EDV, and ESV during the first year after infarction. Ejection fraction increased gradually (47±10% versus 56±8%; day 1 versus day 365, P<0.001) and was associated with an increase in EDV during the first week and a gradual decrease in ESV after the first week. Left ventricular mass remained relatively constant, whereas the nonhyperenhanced myocardial mass increased significantly during the first week (145±27 g versus 151±27 g; day 1 versus day 7, P<0.001). The patient with microvascular obstruction did not follow the general pattern of functional recovery. This patient showed only a slight improvement in ejection fraction (30%...
versus 36%; day 1 versus day 365), and both EDV and ESV increased progressively (248 mL versus 328 mL and 174 mL versus 211 mL; day 1 versus day 365).

Regional Left Ventricular Function

Figure 4 shows the relationship between regional transmural extent of hyperenhancement at day 1 and regional wall thickening over time. For all time points, there was a progressive decrease in regional wall thickening as the initial regional transmural extent of hyperenhancement increased. The time course for recovery of regional wall thickening varied with the initial regional transmural extent of hyperenhancement. Note the improvement in wall thickening in the remote left ventricular segments during the first week. For the adjacent segments and the segments with 1% to 25% transmural extent of hyperenhancement, the functional recovery occurred primarily between days 7 and 42. There was a gradual recovery of function over time for segments that had 26% to 75% transmural extent of hyperenhancement. Of the 149 segments with a transmural extent of hyperenhancement >50% at day 1, 48% (72 of 149) had <50% transmural extent of hyperenhancement at day 7.
A total of 628 segments were dysfunctional on the initial MRI examination (wall thickening $<30\%$). An improvement during the 1-year follow-up was observed in 83\% (115 of 138) of the remote segments and 68\% (55 of 81) of the adjacent segments. For segments with transmural extent of hyperenhancement of 1\% to 25\%, 26\% to 50\%, 51\% to 75\%, and 76\% to 100\%, improvement was observed in 69\% (108 of 155), 63\% (60 of 95), 42\% (37 of 91), and 30\% (9 of 30), respectively.

**ECG Infarct Size**

Figure 5 shows the relationship between relative infarct size estimated by QRS scoring of the ECG and relative amount of hyperenhancement by DE-MRI. Four patients were excluded because of right bundle-branch block or left anterior fascicular block. The time courses and magnitudes of decrease in relative infarct size by QRS scoring corresponded well with the reduction of hyperenhancement by DE-MRI. Both showed the most pronounced decrease during the first week and 1-year decreases of 35 and 40\% for QRS score and DE-MRI, respectively. The relative infarct size estimated by QRS scoring was persistently larger (about 5 percentage points) than the relative amount of hyperenhanced myocardium. QRS score correlated significantly with the amount of hyperenhanced myocardium at all time points, with $R^2$ values ranging from 0.36 to 0.59 (Table 2).

**Discussion**

The data in the present longitudinal study show that the reduction of hyperenhanced myocardium as assessed by DE-MRI occurs primarily during the first week in patients with reperfused first-time MI.

The reduction of hyperenhanced myocardium showed a 2-phase response: a rapid initial reduction during the first week, and a more gradual reduction from the second week on. From the second week and throughout the year, the gradual decrease of hyperenhanced myocardium was associated with a gradual normalization of infarct-related ECG changes. These gradual changes may be explained by resorption and scar replacement of infarcted myocardium in conjunction with simultaneous compensatory hypertrophy of the viable myocardium occurring throughout the year.

The basis for the rapid reduction of hyperenhanced myocardium during the first week, however, is more controversial. Reimer and Jennings have described the changing anatomic reference base of evolving MI early after acute infarction. They showed that swelling of the ischemic myocardium caused by acute inflammation, edema, and hemorrhage resulted in an overestimation of infarct size as assessed by histology. The rapid reduction of hyperenhanced myocardium found in the present study during the first week may be explained in 2 different ways. First, the rapid reduction may be attributable to resorption of the infarcted myocardium itself, which has been proposed by Kim et al. They showed a strong correlation between hyperenhancement on ex vivo MRI and necrosis by triphenyltetrazolium chloride (TTC) 1 day after infarction, suggesting that regions of reversibly injured myocardium do not hyperenhance. Thus, the early reduction would be explained by resorption of edema, hemorrhage, and irreversibly injured myocytes within the region of infarction. Second, the rapid reduction may be attributable to hyperenhancement of a viable peri-infarction zone surrounding the irreversibly injured core of myocytes early after infarction. Saeed et al showed that MRI with the extracel-
lular contrast agent gadopentetate dimeglumine overestimated the true infarct size measured by TTC 1 and 2 days after infarction. Others have shown similar results.\textsuperscript{10,12,13} Thus, the early reduction could partly be explained by resorption of edema and consequent loss of hyperenhancement in the viable peri-infarcted zone during the first week after infarction.

Enhancement of a viable peri-infarction zone is likely to play a role in the reduction of hyperenhanced myocardium observed during the first week in the present study, for several reasons. First, there was a significant increase in nonhyperenhanced myocardium, which is unlikely to be explained by a significant compensatory hypertrophy during this short period. Of note is that the total left ventricular mass did not change during this period. Second, almost half of the segments with >50% transmural extent of hyperenhancement at day 1 had <50% transmural extent of hyperenhancement at day 7. Third, 30% of the segments with 76% to 100% transmural extent of hyperenhancement on the initial MRI examination showed functional improvement after 1 year, which is difficult to explain if indeed all the hyperenhanced myocardium would be irreversibly injured. Furthermore, the reduction in QRS score found during the first week may be explained by recruitment of viable but electrophysiologically dysfunctional myocytes in the peri-infarction zone. Ursell et al.\textsuperscript{22} have shown a reversible electrophysiological dysfunction in surviving cells from the peri-infarction zone during the first 2 weeks after infarction. In addition, peri-infarction edema can cause conduction abnormalities,\textsuperscript{23} which might disappear as the edema is being resorbed. Similar to the findings in the present study, others have reported a marked decrease in QRS score early after infarction.\textsuperscript{24,25}

Thus, all of the different pathophysiological explanations above are valid for the reduction of hyperenhanced myocardium and normalization of infarct-related ECG changes found in the present study, although they might be of different importance for the short- and long-term infarct evolutionary process as discussed earlier.

Even though acute and chronic MI differs with myocardial necrosis in the former and scar tissue replacement in the later, the pathophysiological basis for hyperenhancement is similar. Both conditions are associated with an increased distribution volume compared to noninjured myocardium, which makes it possible to follow the infarct involution process using the same DE-MRI technique, shown to be reproducible both in the acute\textsuperscript{26} and the chronic state.\textsuperscript{4,26}

Aletras et al.\textsuperscript{27} recently showed that T2-weighted MR images can depict myocardial edema, which can be used to assess the myocardium at risk in dogs with experimentally induced MI. Thus, T2-weighted imaging can potentially be used to further explore the role of edema and reversible injured myocardium early after infarction in humans. This technique has recently been used to study reversibly injured myocardium and myocardium at risk in patients with reperfused acute MI\textsuperscript{28} and for risk assessment in patients with clinical symptoms suggestive of acute coronary syndrome.\textsuperscript{29}

Regional transmurality of hyperenhancement has been shown to affect the probability of regional functional recovery after acute infarction.\textsuperscript{8,9,30} The present study is, however, the first human study to explore the time course of this recovery relative to transmural extent of hyperenhancement from the first day after infarction. The early increase in wall thickening found during the first week in remote myocardial segments has been shown in animal models of early changes after reperfused infarction.\textsuperscript{31} Previous DE-MRI follow-up studies in humans have not revealed this early change in remote myocardium, probably because the initial examination was not undertaken until 4 to 7 days after the acute event.\textsuperscript{7–9} In the present study, the adjacent segments were found to recover primarily between 1 and 6 weeks after infarction. Kramer et al.\textsuperscript{32} showed similar results in an animal model in which the increase in regional function in the adjacent
myocardium occurred predominantly between 1 and 8 weeks. Potential mechanisms for the initial decrease in wall thickening in remote and adjacent segments are coronary vasodilator abnormalities in the nonoccluded arteries and increased systolic longitudinal wall stress because of acute alterations in left ventricular morphology.

Using DE-MRI, it has previously been shown that pathological Q waves are not predictive of MI transmurality. However, the Selvester QRS scoring system, used for MI quantification from the ECG in the present study, has been shown to be useful for estimating both size and transmurality of acute MI. The QRS score is based not only on presence of Q waves but also other infarct-related changes of the ECG complex such as loss of R- and S-wave amplitudes and durations as well as ratios between different waveforms.

Limitations
The findings in this study should be considered in light of some limitations. First, the study was conducted on a relatively small number of patients, predominantly men, all presenting with first-time MI and undergoing successful revascularization. Thus, the extent to which the results can be generalized to a larger clinical MI population is limited, because they reflect only the involution of reperfused first-time MI. However, when studying MI involution, it is advantageous not to include patients with multiple MIs or patients with different baseline interventions. Second, few patients had a large amount of hyperenhanced myocardium (>25% of the left ventricle) in the present study. Hence, the results predominantly reflect the time course of small to moderately sized MIs. Third, the success of reperfusion therapy was based on TIMI flow and no direct assessment of reperfusion at the myocardial level was performed. However, all patients received glycoprotein IIb/IIa inhibitor at the time of PCI, a combination which has previously been shown to decrease the risk of microvascular obstruction. Microvascular obstruction was found in only 1 patient in the present study. This patient, as discussed earlier, did not follow the pattern of the other patients with regard to infarct resorption and functional recovery. Hence, the findings in the present study do not apply to patients with signs of microvascular obstruction. Fourth, 2 different scanners were used, which might have introduced variability of the analysis because of nonidentical imaging sequences. However, the pattern of change in hyperenhanced myocardium observed over time did not differ between patients examined by different scanners. Finally, using fixed anatomic hallmarks for registration when comparing regional hyperenhancement and function of serial examinations has limited accuracy as the cardiac anatomy changes because of remodeling in the postinfarction period.

Conclusions
The reduction of hyperenhanced myocardium as assessed by DE-MRI after reperfused first-time MI occurs predominantly during the first week after infarction. This might reflect recovery of initially hyperenhanced but reversibly injured myocardium. Furthermore, the time course for recovery of regional wall thickening correlates with the initial regional transmural extent of hyperenhancement, and even nonhyperenhanced myocardium shows an early increase in regional wall thickening. Finally, the time course and magnitude of reduction of hyperenhanced myocardium as assessed by DE-MRI corresponds well with normalization of infarct-related ECG changes as assessed by QRS scoring.

Acknowledgments
The authors thank Jonas Björk and Nuray Güner at Lund University Hospital (Lund, Sweden) for providing biostatistical expertise.

Sources of Funding
This study was supported by grants from the Swedish Research Council, Stockholm, Sweden; the Swedish Heart Lung Foundation, Stockholm, Sweden; and the Medical Faculty at Lund University, Lund, Sweden.

Disclosures
None.

References
Temporal sequence of myocardial infarction by magnetic resonance imaging (MRI). Engblom et al. Time Course of Infarct Involution

CLINICAL PERSPECTIVE

Delayed contrast-enhanced MRI (DE-MRI) is currently considered the gold standard for myocardial infarct visualization in vivo. The present study shows that it is important to consider the timing of the first MR examination after reperfusion therapy, because there is a considerable decrease in the amount of hyperenhanced myocardium during the first week after acute myocardial infarction. Thus, to enable accurate comparison between patients examined during the first week after infarction, a narrow window of inclusion is desirable. This is important to consider when designing clinical trials using final infarct size, determined by DE-MRI, as a clinical end point. Furthermore, infarct characteristics such as infarct transmural may be overestimated if assessed early after reperfusion therapy, affecting the predicted prognosis of functional recovery and clinical decision making. In fact, 30% of the myocardial segments with 76% to 100% transmural extent of hyperenhancement the day after infarction, showed functional improvement at the 1-year follow-up in the present study.
Rapid Initial Reduction of Hyperenhanced Myocardium After Reperfused First Myocardial Infarction Suggests Recovery of the Peri-Infarction Zone: One-Year Follow-Up by MRI
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doi: 10.1161/CIRCIMAGING.108.802199
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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