Acute Myocardial Infarction: Serial Cardiac MR Imaging Shows a Decrease in Delayed Enhancement of the Myocardium during the 1st Week after Reperfusion[1]

Tareq Ibrahim, MD
Thomas Hackl, MD
Stephan G. Nekolla, PhD
Martin Breuer, MD
Michael Feldmair, MD
Albert Schömig, MD
Markus Schwaiger, MD

Purpose: To evaluate the time course of delayed gadolinium enhancement of infarcted myocardium by using serial contrast agent–enhanced (CE) cardiac magnetic resonance (MR) images obtained during the acute, subacute, and chronic stages of infarction.

Materials and Methods: The study protocol was reviewed and approved by the local ethics committee, and written informed consent was obtained. Seventeen patients with reperfused acute myocardial infarction (AMI) underwent cine and CE cardiac MR a median of 1, 7, 35, and 180 days after reperfusion. Infarct size determined on the basis of delayed enhancement MR imaging at different times was compared by using nonparametric tests and Bland-Altman analysis. Extent of myocardial enhancement was compared with single photon emission computed tomographic (SPECT) measures of infarct size with Spearman correlation. Regional myocardial enhancement extent and contractility were analyzed with nonparametric tests.

Results: Infarct size was 18.3% of total myocardial LV volume on day 1 after AMI and decreased to 12.9% on day 7, 11.3% on day 35, and 11.6% on day 180 (all $P < .001$). Estimated infarct size on day 7, as compared with day 1 enhancement size, declined by 57.1% within the epicardium and by 6.3% within the endocardium (both $P < .001$). Infarct size on day 7 showed only minor changes at subsequent imaging and yielded a high correlation with SPECT measurements of infarct size ($r = 0.84$). Infarct size on day 7 inversely correlated with long-term wall thickening ($P < .0001$) and allowed prediction of contractile function.

Conclusion: In patients with AMI and successful coronary reperfusion, the size of delayed gadolinium enhancement at CE cardiac MR imaging significantly diminished during the 1st week after infarction. Thus, timing of CE cardiac MR imaging is crucial for accurate measurement of myocardial infarct size early after AMI.

[1] From the Department of Cardiology, Klinikums Rechts der Isar and German Heart Centre Munich, (T.I., M.B., A.S.) and Department of Nuclear Medicine (T.H., S.G.N., M.F., M.S.), Technische Universität München, Lazarettstrasse 36, 80636 Munich, Germany. Received April 15, 2009; revision requested May 18; revision received June 25; accepted July 6; final version accepted July 16. **Address correspondence to** T.I. (e-mail: *T.Ibrahim@lrz.tu-muenchen.de*).

Coronary reperfusion substantially reduces mortality in patients with acute myocardial infarction (AMI) (1). The principle mechanism by which patients benefit from reperfusion is salvage of the myocardium at risk, leading to a smaller infarct size (2,3). Since using mortality as an end point requires an extremely large number of patients to achieve adequate statistical power, investigators who are assessing the effectiveness of reperfusion therapies are increasingly using infarct size as a surrogate end point, which allows a substantial reduction in the required sample size (4).

Delayed contrast agent–enhanced (CE) cardiac magnetic resonance (MR) imaging with gadolinium-based contrast agents can depict both acute and chronic myocardial infarctions (5–16). The underlying mechanism of myocardial tissue enhancement with nonspecific extracellular contrast agents is generally owing to an increased distribution volume for these molecules within the infarct region, which is associated with a delayed washout as compared with healthy myocardium (6,8). In chronic myocardial infarction, delayed gadolinium enhancement is closely related to scar-tissue formation (9,12). However, its value in acute and subacute infarction following reperfusion is less clearly defined because the myocardium undergoes a complex healing process consisting of acute edema, inflammation, and replacement of necrotic cardiomyocytes at that time.

Advances in Knowledge

- Delayed gadolinium enhancement size on contrast agent–enhanced cardiac MR images significantly decreases between days 1 and 7 after reperfusion of acute myocardial infarction (AMI), particularly within the epicardial region.
- Myocardial contrast enhancement 7 days after reperfusion is in close agreement with that at imaging performed after 35 or 180 days and allows measurement of the final infarct size early after the acute event.

While some investigators (9) support the notion that delayed enhancement exclusively reflects necrotic myocardium, researchers in several experimental studies (5,6,10,11,17) have indicated that myocardial contrast enhancement may overestimate the size of true infarction when imaging is performed early (<48 hours) after reperfusion. Moreover, the findings of an animal study (11) of serial CE cardiac MR performed during the acute setting of infarction have shown that the size of delayed gadolinium enhancement may significantly change during the 1st 2 days after reperfusion, suggesting that the enhanced region encompasses not only nonviable tissue but also viable portions of ischemically injured myocardium.

Findings of human studies (18–22) in which CE cardiac MR was performed during the acute (<1 week) and chronic (several months later) stages of infarction have indicated that contrast enhancement diminishes over a period of time. However, to our knowledge, no clinical studies that systematically examine the myocardial infarct region with serial MR imaging during the acute setting of infarction are available. The purpose of our study was to evaluate the time course of delayed gadolinium enhancement of infarcted myocardium by using serial CE cardiac MR imaging performed during the acute, subacute, and chronic stages of infarction. We hypothesize that delayed gadolinium enhancement assessed early after AMI will be reduced at subsequent CE cardiac MR imaging.

Implications for Patient Care

- To properly estimate infarct size in patients with AMI, contrast-enhanced cardiac MR imaging should be performed about 7 days after reperfusion therapy.
- Timing of imaging should be considered in the design of AMI reperfusion trials that use infarct size on cardiac MR images as a surrogate end point.

Materials and Methods

Patient Population

The study protocol was reviewed and approved by the local ethics committee. Written informed consent was obtained prior to inclusion of a patient in our study. We included patients with AMI who successfully underwent percutaneous coronary reperfusion by implantation of a bare metal stent within 12 hours of the onset of symptoms. Diagnosis of AMI was established on the basis of the presence of chest pain lasting at least 20 minutes associated with electrocardiographic changes (eg, ST-segment elevation, new left bundle branch block). Patients with a history of prior infarction or contraindications to cardiac MR were excluded from our study.

Twenty patients with AMI were evaluated for study entry. One patient with myocardial reinfarction and two patients with claustrophobia were excluded. Seventeen patients who met the inclusion criteria were enrolled. All patients successfully underwent cardiac MR imaging 1, 7, 35, and 180 days after infarction. Additionally, single photon emission computed tomographic (SPECT) imaging at rest was also performed in all patients 7 days after infarction. No patient had any clinical evidence of recurrent myocardial infarction during the study period. All patients had normal renal function and received therapy consisting of

Published online
10.1148/radiol.09090660

Radiology 2010; 254:88–97

Abbreviations:
AMI = acute myocardial infarction
CE = contrast agent enhanced
LV = left ventricle

Author contributions:
Guarantor of integrity of entire study, T.I.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, all authors; clinical studies, T.I., T.H., S.G.N., M.B., M.F., M.S.; statistical analysis, T.I., T.H., S.G.N., A.S.; and manuscript editing, T.I., T.H., M.B., M.F.

Authors stated no financial relationship to disclose.

aspirin, clopidogrel, a β-blocker, an angiotensin-converting enzyme inhibitor, and statins.

Imaging Protocols

Cardic MR imaging was performed with a 1.5-T imager (Sonata; Siemens Medical Solutions, Erlangen, Germany) equipped with a cardiac phased-array surface coil. Images were obtained with electrocardiographic gating in contiguous short-axis and representative long-axis sections during repeated breath holds. For cine cardiac MR imaging, we used a steady-state free precession sequence (repetition time msec/echo time msec, 35/1.5; flip angle, 80°; section thickness, 8 mm; voxel size, 1.5 × 1.5 mm). CE cardiac MR was performed 20 minutes after injection of 0.2 mmol per kilogram of body weight gadopentetate dimeglumine (Magnevist; Schering, Berlin-Wedding, Germany) with a three-dimensional segmented inversion-recovery turbo fast low-angle shot T1-weighted sequence (4.0/1.5; flip angle, 30°; section thickness, 4 mm; voxel size, 1.5 × 1.5 mm). This technique allowed us to acquire between 20 and 30 sections during three to four breath holds in every patient. The inversion time was individually chosen to nullify healthy myocardium.

SPECT with technetium 99m sestamibi was performed by using a camera system (MultiSPECT 3; Siemens) equipped with low-energy parallel-hole collimators. Images were acquired with electrocardiographic gating in a 64 × 64 data matrix with an acquisition time of 40 seconds per projection. Data were reconstructed over 180°, from a 45° right anterior oblique angle to a 45° left posterior oblique oblique, by using a Butterworth filter.

Image Analysis

Serial cardiac MR studies of all patients were analyzed (T.I., T.H., M.B., and M.F., with >10, 5, 5, and 3 years experience with cardiac MR, respectively) in a randomized order. The size of delayed enhancement was quantified (T.I.) by using computer-assisted planimetry software (MunichHeart; *http://www.munichheart.de/*) (13). To facilitate the manual infarct definition, the data were scaled, with the minimum value set to zero and the maximum value manually adjusted to provide optimal image contrast. Endo- and epicardial contours and myocardial enhancement, if present, were manually drawn on every short-axis image, and enhancement size was calculated as the percentage of total left ventricular (LV) myocardial volume. Moreover, the transmural extent of enhancement was assessed on the basis of a 34-segment model applied on basal (12 segments), midventricular (12 segments), and distal (eight segments) short-axis images, as well as on a vertical long-axis image (two-chamber view) to assess the apex (two segments). Each segment was defined visually by two observers (T.H. and M.B.) in consensus by using a five-point scale: 0 = no enhancement, 1 = 1%–25% enhancement extent according to the segmental wall thickness, 2 = 26%–50% enhancement extent, 3 = 51%–75% enhancement extent, and 4 = 76%–100% enhancement extent (23). Endo- and epicardium were defined as the inner 50% (score ≤ 2) and outer 50% (score ≥ 3), respectively, of the segmental wall thickness. For transmurality assessment, the summed enhancement score was calculated within both regions.

LV volumes and ejection fraction derived from cine cardiac MR imaging were analyzed by another observer (M.F.), who was unaware of the CE cardiac MR results, by using a software package (Syngo Argus Ventricular Function; Siemens Medical Solutions). On the basis of these endo- and epicardial tracings, regional percentage systolic wall thickening was calculated on short-axis images from the same location and segmentation as were used for the determination of CE cardiac MR enhancement extent, by using the following equation: $[(W_{es} - W_{ed})/W_{ed}] \cdot 100$, where W_{es} is end-systolic wall thickness and W_{ed} is end-diastolic wall thickness.

SPECT images were analyzed in the scintigraphic core laboratory at our institution by operators who were blinded to the MR imaging results. The myocardial perfusion defect was quantified as a percentage of the LV by using a 50% threshold, as described previously (24).

Statistical Analysis

All data are expressed as medians, with ranges in parentheses. Categorical variables at multiple times were compared by using the McNemar test and Bonferroni adjustment for multiple hypothesis testing. Continuous variables at multiple times were first compared by using the Friedman test. In cases of statistical significance, further comparison with the Wilcoxon signed rank test was performed. Enhancement size on cardiac MR images at different times during the study was also compared by using Bland-Altman analysis. The relation of MR enhancement size and SPECT perfusion defect was examined by using the Spearman correlation coefficient. A *P* value of less than .05 was considered to indicate a significant difference.

Results

Patient characteristics of the study population are shown in Table 1.

Serial Cardiac MR Imaging

All patients successfully underwent cardiac MR imaging. The first imaging session was performed a median of 19.0 hours (range, 11.5–24.0 hours) after reperfusion. Cardiac MR imaging was repeated at a median of 7 (range, 5–9 days), 35 (range, 21–63 days), and 180 (range, 150–210 days) days. Delayed myocardial contrast enhancement was detectable in all patients at all times throughout the study. Images from a representative patient are shown in Figure 1. Microvascular obstruction was seen in one patient with anterior infarction on days 1 and 7, but a homogeneous enhancement pattern was observed at later studies.

Size of Myocardial Enhancement

The quantitative measurements of the infarct sizes at each time are shown in Table 2. Absolute enhancement volume and total LV myocardial volume significantly changed throughout follow-up ($P < .001$). On the basis of these

measurements, infarct size significantly ($P < .001$) decreased between days 1 and 7 after infarction but was stable at subsequent imaging (Fig 2). Patient-by-patient analysis demonstrated that, compared with enhancement size on day 1, enhancement size was reduced by 34.2% (range, 4.4–84.8) on day 7, by 33.3% (range, 8.8–80.4) on day 35, and by 34.8% (range, 14.1–94.8) on day 180 (all $P < .001$). Enhancement size on day 1 systematically overestimated that on day 7 by a mean of 6.9% ± 13.4% (2 standard deviations) (Fig 3a). However, enhancement size on day 7 showed close agreement with that at subsequent MR imaging (Fig 3b, 3c) and yielded a high correlation with other measures of infarct size, such as peak troponin T levels ($r = 0.74$) and myocardial perfusion defect at SPECT imaging ($r = 0.84$) (Figs 4, 5).

Table 1

Characteristics of 17 Patients

Characteristic	Datum
Age (y)*	56 (46–86)
Sex	
Female	1 (5.9)
Male	16 (94.1)
Arterial hypertension	14 (82.4)
Diabetes	3 (17.6)
Current smoker	8 (47.1)
Hypercholesterolemia	13 (76.5)
Prior angioplasty	1 (5.9)
Electrocardiographic abnormality	
ST-segment elevation	16 (94.1)
New left bundle branch block	1 (5.9)
Killip class	
1	15 (88.2)
2	1 (5.9)
3	0
4	1 (5.9)
Peak creatine kinase level (U/L)*	1316 (254–7158)
Peak troponin T level (ng/mL)*	4.5 (0.5–15.6)
Creatinine level (mg/dL)*†	0.9 (0.5–1.3)
Time from symptom onset to intervention (h)*	5.0 (1.8–15.0)
Glycoprotein IIb/IIIa receptor inhibitor	10 (58.8)
Severity of coronary artery disease	
Single vessel	3 (17.6)
Two vessels	7 (41.2)
Three vessels	7 (41.2)
Infarct-related artery	
Left anterior descending artery	8 (47.1)
Left circumflex artery	6 (35.3)
Right coronary artery	3 (17.6)

Note.—Unless otherwise specified, data are numbers of patients, with percentages in parentheses.

* Data are medians, with ranges in parentheses.

† Multiply by 88.4 to convert to Système International units of micromoles per liter.

Extent of Myocardial Enhancement

The total number of segments that displayed contrast enhancement was significantly higher on MR images obtained on day 1 after AMI as compared with those obtained subsequently ($P < .0001$) (Table 3). More than half (96 of 180)

Figure 1

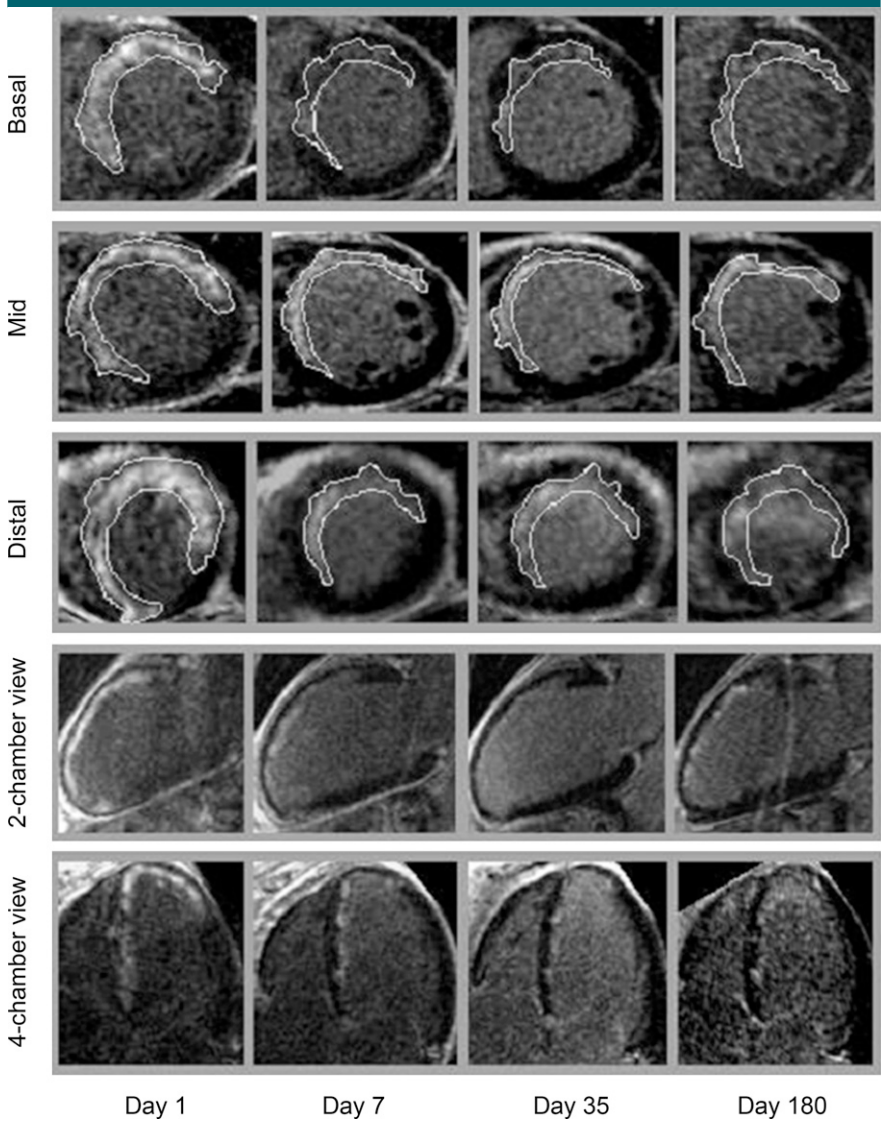

Figure 1: Serial contrast-enhanced cardiac MR images in a patient with anteroseptal infarction. Day 1 contrast enhancement revealed a nearly transmural anterior wall extent, which demonstrated a circumferential and epicardial decrease at follow-up. Day 1 enhancement size (area within white border) was 45% of LV; day 7, 24%; day 35, 21%; and day 180, 27%. *Mid* = midventricular.

Table 2

Quantitative Analysis of Serial MR Imaging

Measurement	Day 1	Day 7	Day 35	Day 180
	Enhancement at CE MR Imaging			
Absolute enhancement volume (mL)	20.6 (1.1–58.5)	14.2 (0.8–50.1)*	12.0 (0.6–52.1)*	11.1 (0.5–45.3)*
Total LV myocardial volume (mL)	112.7 (71.6–167.6)	110.2 (65.3–175.2)	101.9 (60.0–142.7)*	97.5 (55.3–135.6)*
Enhancement size (%)†	18.3 (1.5–45.2)	12.9 (1.3–37.4)*	11.3 (1.0–40.5)*	11.6 (0.9–37.3)*
	LV Function from Cine MR Imaging			
End-diastolic volume (mL)	160.1 (95.8–204.8)	158.1 (115.2–206.4)	151.6 (107.2–237.2)	150.4 (99.0–254.1)
End-systolic volume (mL)	77.1 (47.9–133.4)	76.3 (41.3–152.7)	76.4 (39.1–170.5)	69.9 (29.5–186.6)
Ejection fraction (%)	48.2 (31.3–61.9)	50.2 (24.5–65.3)	52.9 (28.1–65.0)	53.7 (26.6–70.2)
Myocardial mass (g)	128.2 (74.6–191.7)	126.4 (81.6–182.4)	118.1 (77.6–163.6)‡	115.1 (69.2–152.2)‡

Note.—Data are medians, with ranges in parentheses.

* $P < .001$ for comparison with day 1.

† Enhancement size given as a percentage of total LV myocardial volume.

‡ $P < .01$ for comparison with day 1.

Figure 2

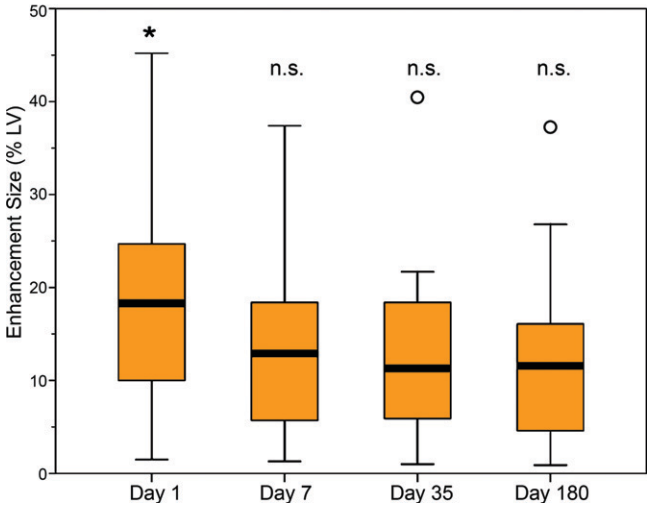

Figure 2: Box and whisker plot of serial measurements of enhancement size as a percentage of total LV myocardial volume *(% LV)*. Enhancement size on day 1 was significantly (* = $P < .001$) larger than that at subsequent imaging. *n.s.* = not significant, ○ = outlier.

of the segments with enhancement on day 1 showed a decrease in the transmural extent of enhancement on later MR images. While the majority of segments with enhancement on day 1 displayed transmural or nearly transmural (>50%) enhancement, myocardial contrast enhancement at follow-up was more often defined as nontransmural (≤50%). The major decrease of myocardial enhancement after day 1 occurred within the epicardium, and enhancement also decreased, to a lesser extent, in the endocardium (Fig 6). On the basis of a patient-by-patient analysis, epicardial enhancement on day 1 was reduced by 57.1% (range, 0%–100%) on day 7, by 71.4% (range, 0%–100%) on day 35, and by 66.7% (range, 0%–100%) on day 180 (all $P < .001$). Endocardial enhancement on day 1 decreased by 6.3% (range, 0%–91.3%) on day 7, by 18.5% (range, 0%–69.6%) on day 35, and by 13.3% (range, 0%–100%) on day 180 (all $P < .005$).

Myocardial Function

LV function of the entire patient population is summarized in Table 2. Although ejection fraction showed stepwise improvement throughout the study, these changes were not significant. Regional myocardial function in segments that displayed contrast enhancement was significantly reduced compared with that in segments without enhancement (Table 4). Enhanced segments demonstrated a trend toward improvement of regional wall thickening throughout the study; however, this was not significant. Transmural extent of myocardial contrast enhancement at day 7 showed an inverse relation to myocardial wall thickening assessed at day 180 (Fig 7).

Discussion

The major findings of our study are that serial gadolinium-enhanced cardiac MR images in patients with AMI demonstrate significantly decreased enhancement within the infarcted region between days 1 and 7 after coronary reperfusion and that the extent of myocardial contrast enhancement seen on day 7 is in close agreement with that at subsequent MR imaging on days 35 and 180 and with scintigraphic measures of infarct size.

Coronary occlusion and reperfusion initiate a progression of changes within the myocardium that result in signal intensity increases on T1-weighted gadolinium-enhanced cardiac MR images. It is generally thought that delayed gadolinium enhancement within ischemically injured myocardium is related to an increase in interstitial space caused by the loss of cellular integrity in necrotic myocytes and/or by the development of tissue edema. Owing to the nonspecific properties of gadolinium-based contrast agents, some authors (5,6,10,17) have

Figure 3

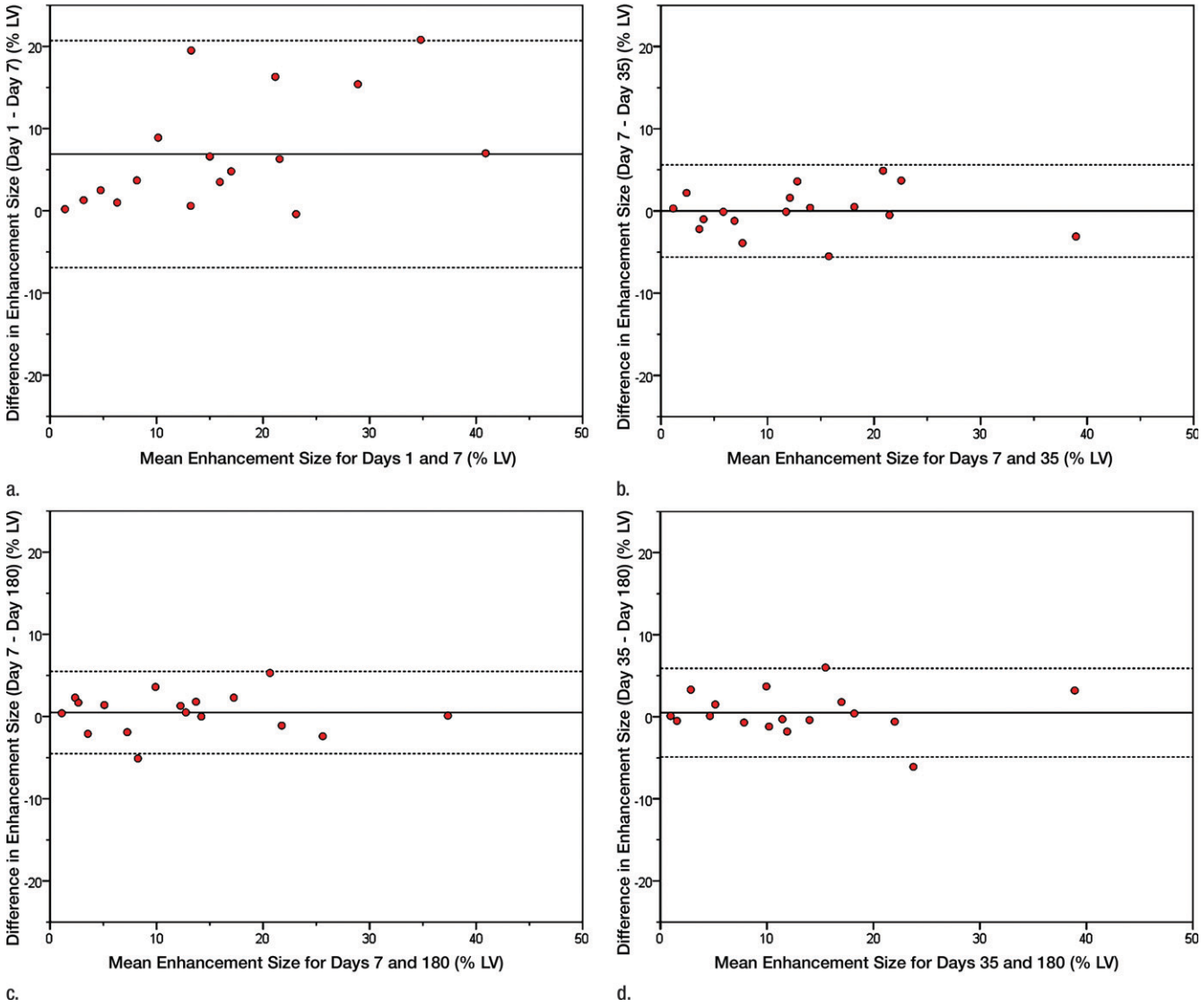

Figure 3: Bland-Altman plots for the comparison of enhancement size as measured on MR images at various times after reperfusion. **(a)** Enhancement size on day 1 systematically overestimated that on day 7, but **(b–d)** measurements after 1 week were in close relation with subsequent imaging. Dashed line = 2 standard deviations, solid line = mean difference, *% LV* = percentage of total LV myocardial volume.

suggested that the gadolinium-enhanced region may overestimate the true infarct size when CE cardiac MR imaging is performed soon after reperfusion of an AMI. Moreover, dynamic imaging has demonstrated that the size of the region with delayed enhancement may vary with the time imaging is performed after gadopentetate dimeglumine injection, and overestimation can be particularly observed with early (<10 minutes after injection) acquisition (13,25). Serial CE cardiac MR data in animals have indicated a noticeable decline in the size of gadolinium enhancement within the 1st 2 days following infarction (11). Likewise, our serial MR measurements in humans reveal a substantial decrease in gadolinium enhancement during the 1st week after reperfusion, suggesting overestimation of the true infarct size with CE cardiac MR imaging 1 day after reperfusion. Because all MR imaging in our patients was performed with a sufficient and constant time of 20 minutes after gadolinium injection, it is unlikely that these observations may be caused by inappropriate timing of imaging. The diminishing tissue enhancement may be explained by a resolution of interstitial edema in reversibly injured myocardium within the periinfarction zone, which leads to overestimation of the true infarct size at early CE MR imaging. This is supported by audioradiographic examinations in a rat model

Figure 4

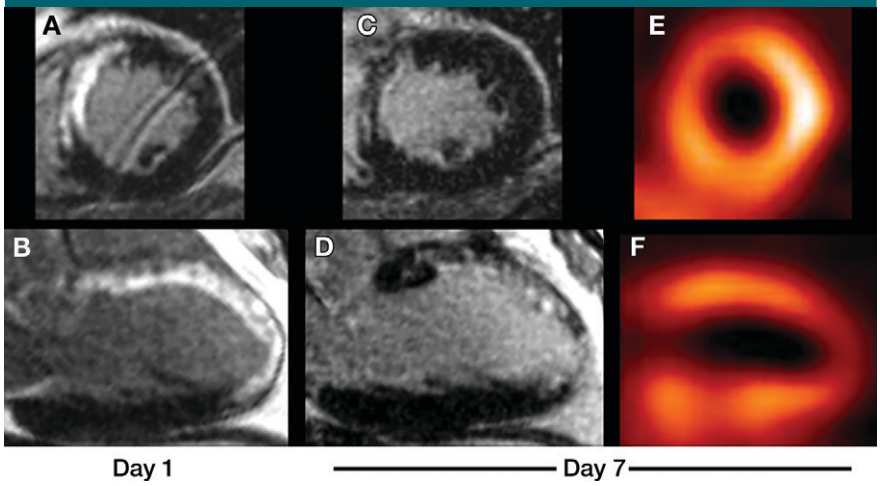

Figure 4: Short-axis (top) and long-axis (bottom) **(a–d)** CE MR and **(e,f)** SPECT perfusion images in a patient with anteroseptal infarction demonstrate enhancement decrease within subepicardium between days **(a,b)** 1 and **(c,d)** 7 and close agreement on day 7 between MR and SPECT imaging.

Figure 5

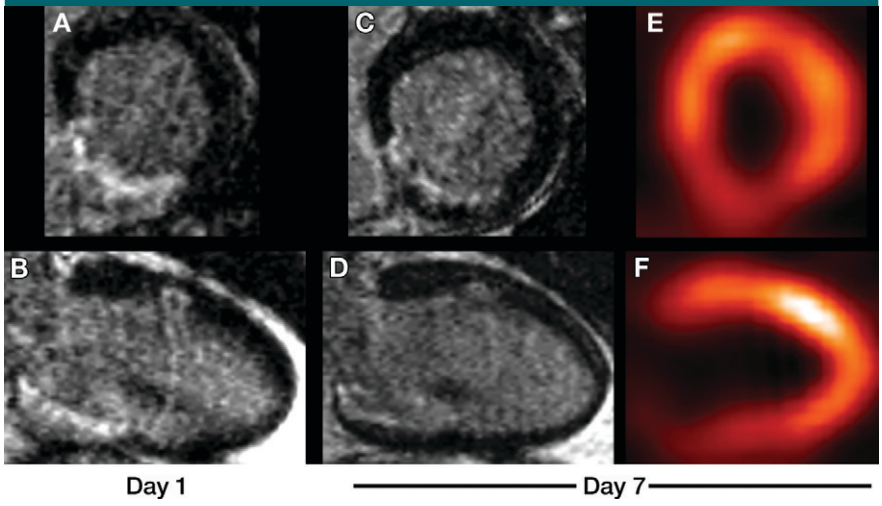

Figure 5: Short-axis (top) and long-axis (bottom) **(a–d)** CE MR and **(e,f)** SPECT perfusion images in a patient with inferoseptal infarction demonstrate enhancement decrease within subepicardium between days **(a,b)** 1 and **(c,d)** 7 and close agreement on day 7 between MR and SPECT imaging.

(26), in which the distribution volume of technetium 99m sestamibi–pentetic acid in the periinfarcted zone is significantly larger than in healthy myocardium but significantly smaller than in the core of the infarcted myocardium.

Previous studies (18–22,27) of serial MR imaging in humans have indicated that gadolinium enhancement may change over time following myocardial infarction. Because researchers in all these studies examined patients just twice, during AMI (<1 week) and several months later, multiple mechanisms, including infarct shrinkage, partial volume effects, and overestimation owing to early imaging, have to be considered for the interpretation of their findings. In contrast, we systematically examined the time course of gadolinium enhancement at multiple defined times, and our findings demonstrated a reduction in enhancement during the 1st week after reperfusion of an infarction.

In our study, several different lines of evidence support the hypothesis that early CE MR imaging results in overestimation of the true infarct size owing to gadolinium enhancement within viable myocardium of the periinfarction zone. First, the major enhancement decline was noted within the subepicardium, the region where salvage of at-risk myocardium is to be expected. Irreversible ischemic injury begins in the subendocardium and progresses as a "wave front" of necrosis moving toward the epicardium. Histopathologic characterization of salvaged myocardium within the subepicardial zone of ischemic but viable myocardium has shown that cellular necrosis develops less frequently there than in the subendocardial core of the infarction (28). Second, coronary reperfusion was performed in our patients with a median time interval of less than 6 hours after symptom onset. Investigators in previous studies (24,29) have shown that coronary stent placement is highly effective for the rescue of at-risk myocardium if it is performed less than 12 hours after the onset of AMI. Therefore, a high likelihood for substantial amounts of ischemically injured but salvageable myocardium is to be expected in our population. We can only speculate whether the decline of enhancement in patients with large and transmural infarction owing to a limited benefit from reperfusion may be as high as that in our patients. Finally, there was a nonsignificant trend toward better prediction of long-term contractility on the basis of enhancement extent assessed at day 1 imaging as compared with that at subsequent imaging, suggesting the presence of viable myocardium.

CE MR imaging performed 1 week after AMI provided accurate estimation of the final infarct expansion. The extent of myocardial gadolinium enhancement at that time showed a close association with various clinical measurements of infarct size, including peak troponin T release (20) and SPECT perfusion defect (7,13,30). Infarct sizing with MR imaging yielded the best correlation with measures with SPECT; however, myocardial enhancement was systematically larger than the scintigraphic perfusion defect.

Table 3

Segmental Analysis of Serial CE MR Imaging

Variable	Day 1	Day 7	Day 35	Day 180
No. of segments with enhancement	180 (31.1)	156 (27.0)*	149 (25.8)*	151 (26.1)*
Transmural extent of enhancement				
1%–25%	10 (1.7)	15 (2.6)	21 (3.6)	15 (2.6)
26%–50%	44 (7.6)	76 (13.1)	75 (13.0)	80 (13.8)
51%–75%	67 (11.6)	38 (6.6)	36 (6.2)	41 (7.1)
76%–100%	59 (10.2)	27 (4.7)	17 (2.9)	15 (2.6)

Note.—Data are numbers of segments, with percentages in parentheses. All percentages were calculated for 578 segments analyzed.

* $P < .0001$ for comparison with day 1.

Table 4

Percentage of Regional Systolic Wall Thickening on Serial CE MR Images

Segment	Day 1	Day 7	Day 35	Day 180
No enhancement	57.0 (−1.7–165.6)	61.2 (7.0–152.3)	60.0 (6.2–158.2)	67.3 (8.3–186.0)
Enhancement	18.0 (0.7–127.0)	21.9 (−7.9–125.7)	29.3 (−0.3–139.1)	31.7 (−12.4–167.6)

Note.—Data are given as median, with ranges in parentheses. $P < .0001$ for comparison of segments with and those without enhancement on each day.

Figure 6

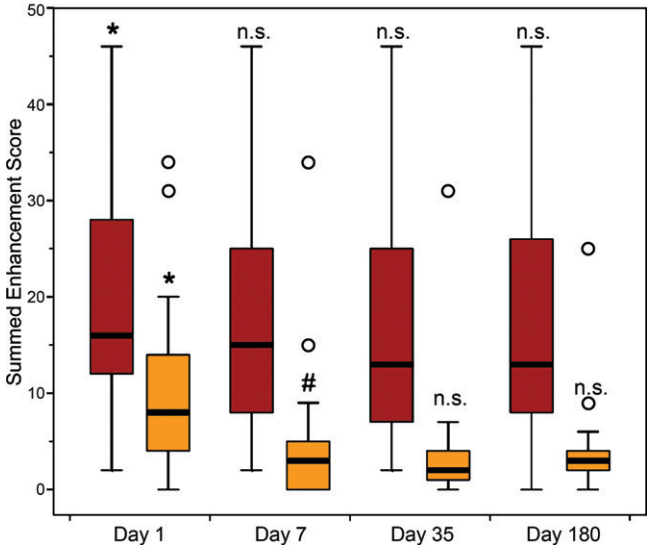

Figure 6: Box and whisker plot of changes of myocardial enhancement extent, as assessed with summed ehancement score for serial CE MR imaging, in endocardium (purple) and epicardium (orange) after AMI. * = $P < .01$ for comparison of day 1 and follow-up, # = $P = .03$ for comparison of days 7 and 35, ○ = outlier, *n.s.* = not significant.

This difference may be explained by the intrinsically higher spatial resolution of MR as compared with SPECT imaging, enabling a more sensitive detection of even small and nontransmural infarction (15,16). As previously described (4) for SPECT with technetium 99m sestamibi, timing of imaging early after reperfusion is crucial for the precise estimation of the final myocardial infarct size. In most clinical reperfusion studies (24,31) in which SPECT infarct size was used as an end point, therefore, acquisition was performed 5–9 days after reperfusion to permit the demarcation of irreversibly injured myocardium. Our findings with CE MR imaging of a major decrease in enhancement during the 1st week may be similarly explained by the dissociation of necrotic tissue from the periinfarction zone and emphasize the importance of delaying MR imaging after AMI reperfusion. Compared with early (<1 week) CE MR imaging, the extent of gadolinium enhancement 1 week after reperfusion demonstrated only minor changes at subsequent imaging, and these changes may be related to infarct shrinkage (28).

Enhancement extent on day 7 after reperfusion was closely associated with future development of regional contractility, thus indicating the registration of the final infarct expansion after 1 week. Results of an experimental study (32) showed that coronary reperfusion initiated before infarction is complete is associated with increased myocardial salvage and stronger recovery of future contractility. Since reperfusion therapy was highly effective and all patients received optimal pharmacologic treatment (eg, angiotensin-converting enzyme inhibitor, β-blocker), global LV function was relatively preserved in our population, and severe adverse ventricular remodeling did not occur.

CE MR imaging performed 1 week after reperfusion is a valuable and attractive imaging tool for measuring the final infarct size in patients with AMI, which can be used as a surrogate end point in clinical trials in which the effect of reperfusion therapies is evaluated. Moreover, assessment of the periinfarction zone with CE MR imaging may

Figure 7

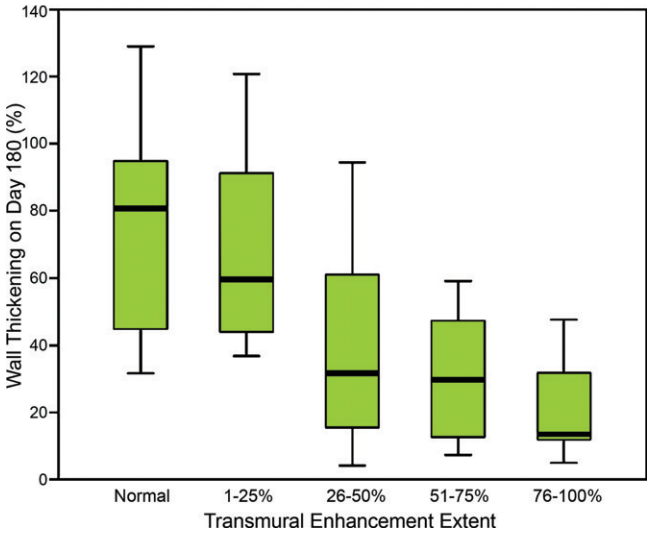

Figure 7: Box and whisker plot shows inverse relationship ($P < .0001$) of regional wall thickening on day 180 and transmural enhancement extent on day 7.

provide important prognostic information concerning future mortality (33). Other MR techniques, such as T2-weighted imaging, have been shown to characterize the at-risk area early after infarction (34). Combining T2-weighted and CE MR imaging data has demonstrated the potential to define the amount of salvaged myocardium after reperfusion of AMI (35). Further studies are warranted to clarify whether the enhancement decrease at serial CE MR imaging during AMI may be used to identify and measure myocardial salvage.

Our study had limitations. Although the overall patient population was relatively small, we could demonstrate a significant decrease in contrast enhancement during the 1st week after AMI. We cannot rule out whether a larger sample size would have affected findings during the chronic stage of infarction; however, this factor was not the primary concern of our study. Because we only examined stable patients with successful coronary intervention (<12 hours after symptom onset), we cannot comment on the situation in patients with prolonged or unsuccessful reperfusion therapy.

Delayed enhancement imaging was performed with a high-spatial-resolution three-dimensional segmented inversion-recovery turbo fast low-angle shot sequence, which has been clinically validated in comparison to SPECT imaging (16). Because we used an identical imaging protocol and contrast agent dose in all patients at all acquisitions, it is unlikely that the observed enhancement decrease may be related to technical reasons, particularly since this phenomenon has also been described in studies in animals (5,6,10,11,17) with the use of spin-echo sequences with what are usually lower image contrast and spatial resolution.

The size of gadolinium enhancement was analyzed with computer-assisted planimetry. Despite studies (9,13,36,37) documenting automated detection methods by using signal intensity–threshold techniques, no standardized approach has been established and generally recommended for the quantification of contrast enhancement. Researchers in previous studies (20,22) who used CE MR imaging to evaluate enhancement size used a quantitative approach similar to that used in our study, and moreover, we additionally performed a semiquantitative analysis by using a widely accepted score (15) that similarly showed the decline in enhancement.

Our findings demonstrate that the extent of delayed myocardial gadolinium enhancement as assessed with MR imaging may significantly diminish during the 1st week after infarction and successful reperfusion therapy. To accurately measure the final infarct expansion during the acute phase of infarction, it is necessary to perform CE cardiac MR imaging with an adequate interval following the acute event.

Acknowledgments: The authors thank the MR imaging and SPECT technicians of the Technische Universität München.

References

1. Gersh BJ, Anderson JL. Thrombolysis and myocardial salvage: results of clinical trials and the animal paradigm—paradoxic or predictable? Circulation 1993;88:296–306.
2. Braunwald E. Myocardial reperfusion, limitation of infarct size, reduction of left ventricular dysfunction, and improved survival: should the paradigm be expanded? Circulation 1989;79:441–444.
3. Ndrepepa G, Mehilli J, Schwaiger M, et al. Prognostic value of myocardial salvage achieved by reperfusion therapy in patients with acute myocardial infarction. J Nucl Med 2004;45:725–729.
4. Gibbons RJ, Valeti US, Araoz PA, Jaffe AS. The quantification of infarct size. J Am Coll Cardiol 2004;44:1533–1542.
5. Judd RM, Lugo-Olivieri CH, Arai M, et al. Physiological basis of myocardial contrast enhancement in fast magnetic resonance images of 2-day-old reperfused canine infarcts. Circulation 1995;92:1902–1910.
6. Schaefer S, Malloy CR, Katz J, et al. Gadolinium-DTPA-enhanced nuclear magnetic resonance imaging of reperfused myocardium: identification of the myocardial bed at risk. J Am Coll Cardiol 1988;12:1064–1072.
7. Lima JA, Judd RM, Bazille A, Schulman SP, Atalar E, Zerhouni EA. Regional heterogeneity of human myocardial infarcts demonstrated by contrast-enhanced MRI: potential mechanisms. Circulation 1995;92:1117–1125.
8. Kim RJ, Chen EL, Lima JA, Judd RM. Myocardial Gd-DTPA kinetics determine MRI contrast enhancement and reflect the extent and severity of myocardial injury after acute reperfused infarction. Circulation 1996;94:3318–3326.
9. Kim RJ, Fieno DS, Parrish TB, et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. Circulation 1999;100:1992–2002.

10. Rochitte CE, Lima JA, Bluemke DA, et al. Magnitude and time course of microvascular obstruction and tissue injury after acute myocardial infarction. Circulation 1998;98:1006–1014.

11. Saeed M, Lund G, Wendland MF, Bremerich J, Weinmann H, Higgins CB. Magnetic resonance characterization of the peri-infarction zone of reperfused myocardial infarction with necrosis-specific and extracellular nonspecific contrast media. Circulation 2001;103:871–876.

12. Klein C, Nekolla SG, Bengel FM, et al. Assessment of myocardial viability with contrast-enhanced magnetic resonance imaging: comparison with positron emission tomography. Circulation 2002;105:162–167.

13. Ibrahim T, Nekolla SG, Hörnke M, et al. Quantitative measurement of infarct size by contrast-enhanced magnetic resonance imaging early after acute myocardial infarction: comparison with single-photon emission tomography using Tc99m-sestamibi. J Am Coll Cardiol 2005;45:544–552.

14. Mahrholdt H, Goedecke C, Wagner A, et al. Cardiovascular magnetic resonance assessment of human myocarditis: a comparison to histology and molecular pathology. Circulation 2004;109:1250–1258.

15. Wagner A, Mahrholdt H, Holly TA, et al. Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial myocardial infarcts: an imaging study. Lancet 2003;361:374–379.

16. Ibrahim T, Bülow HP, Hackl T, et al. Diagnostic value of contrast-enhanced magnetic resonance imaging and single-photon emission computed tomography for detection of myocardial necrosis early after acute myocardial infarction. J Am Coll Cardiol 2007;49:208–216.

17. Saeed M, Bremerich J, Wendland MF, Wyttenbach R, Weinmann HJ, Higgins CB. Reperfused myocardial infarction as seen with use of necrosis-specific versus standard extracellular MR contrast media in rats. Radiology 1999;213:247–257.

18. Nishimura T, Kobayashi H, Ohara Y, et al. Serial assessment of myocardial infarction by using gated MR imaging and Gd-DTPA. AJR Am J Roentgenol 1989;153:715–720.

19. van Dijkman PR, van der Wall EE, de Roos A, et al. Acute, subacute, and chronic myocardial infarction: quantitative analysis of gadolinium-enhanced MR images. Radiology 1991;180:147–151.

20. Ingkanisorn WP, Rhoads KL, Aletras AH, Kellman P, Arai AE. Gadolinium delayed enhancement cardiovascular magnetic resonance correlates with clinical measures of myocardial infarction. J Am Coll Cardiol 2004;43:2253–2259.

21. Ichikawa Y, Sakuma H, Suzawa N, et al. Late gadolinium-enhanced magnetic resonance imaging in acute and chronic myocardial infarction: improved prediction of regional myocardial contraction in the chronic state by measuring thickness of nonenhanced myocardium. J Am Coll Cardiol 2005;45:901–909.

22. Baks T, van Geuns RJ, Biagini E, et al. Effects of primary angioplasty for acute myocardial infarction on early and late infarct size and left ventricular wall characteristics. J Am Coll Cardiol 2006;47:40–44.

23. Kim RJ, Wu E, Rafael A, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med 2000;343:1445–1453.

24. Schömig A, Kastrati A, Dirschinger J, et al. Coronary stenting plus platelet glycoprotein IIb/IIIa blockade compared with tissue plasminogen activator in acute myocardial infarction. Stent versus Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction Study Investigators. N Engl J Med 2000;343:385–391.

25. Oshinski JN, Yang Z, Jones JR, Mata JF, French BA. Imaging time after Gd-DTPA injection is critical in using delayed enhancement to determine infarct size accurately with magnetic resonance imaging. Circulation 2001;104:2838–2842.

26. Arheden H, Saeed M, Higgins CB, et al. Reperfused rat myocardium subjected to various durations of ischemia: estimation of the distribution volume of contrast material with echo-planar MR imaging. Radiology 2000;215:520–528.

27. Britten MB, Abolmaali ND, Assmus B, et al. Infarct remodeling after intracoronary progenitor cell treatment in patients with acute myocardial infarction (TOPCARE-AMI): mechanistic insights from serial contrast-enhanced magnetic resonance imaging. Circulation 2003;108:2212–2218.

28. Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischemic cell death. I. Myocardial infarct size vs duration of coronary occlusion in dogs. Circulation 1977;56:786–794.

29. Kastrati A, Mehilli J, Dirschinger J, et al. Myocardial salvage after coronary stenting plus abciximab versus fibrinolysis plus abciximab in patients with acute myocardial infarction: a randomised trial. Lancet 2002;359:920–925.

30. Lund GK, Stork A, Saeed M, et al. Acute myocardial infarction: evaluation with first-pass enhancement and delayed enhancement MR imaging compared with ^{201}Tl SPECT imaging. Radiology 2004;232:49–57.

31. Miller TD, Christian TF, Hopfenspirger MR, Hodge DO, Gersh BJ, Gibbons RJ. Infarct size after acute myocardial infarction measured by quantitative tomographic ^{99m}Tc sestamibi imaging predicts subsequent mortality. Circulation 1995;92:334–341.

32. Hillenbrand HB, Kim RJ, Parker MA, Fieno DS, Judd RM. Early assessment of myocardial salvage by contrast-enhanced magnetic resonance imaging. Circulation 2000;102:1678–1683.

33. Yan AT, Shayne AJ, Brown KA, et al. Characterization of the peri-infarct zone by contrast-enhanced cardiac magnetic resonance imaging is a powerful predictor of post-myocardial infarction mortality. Circulation 2006;114:32–39.

34. Aletras AH, Tilak GS, Natanzon A, et al. Retrospective determination of the area at risk for reperfused acute myocardial infarction with T2-weighted cardiac magnetic resonance imaging: histopathological and displacement encoding with stimulated echoes (DENSE) functional validations. Circulation 2006;113:1865–1870.

35. Friedrich MG, Abdel-Aty H, Taylor A, Schulz-Menger J, Messroghli D, Dietz R. The salvaged area at risk in reperfused acute myocardial infarction as visualized by cardiovascular magnetic resonance. J Am Coll Cardiol 2008;51:1581–1587.

36. Amado LC, Gerber BL, Gupta SN, et al. Accurate and objective infarct sizing by contrast-enhanced magnetic resonance imaging in a canine myocardial infarction model. J Am Coll Cardiol 2004;44:2383–2389.

37. Schuijf JD, Kaandorp TA, Lamb HJ, et al. Quantification of myocardial infarct size and transmurality by contrast-enhanced magnetic resonance imaging in men. Am J Cardiol 2004;94:284–288.