

Magnetic Resonance and Computed Tomographic Imaging

Gadolinium Delayed Enhancement Cardiovascular Magnetic Resonance Correlates With Clinical Measures of Myocardial Infarction

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OBJECTIVES	The current study tested the hypothesis that gadolinium delayed enhancement assessment of infarct size correlates with clinical indices of myocardial infarction (MI) in humans. Acute infarct mass by cardiac magnetic resonance (CMR) was compared with peak troponin I, acute and chronic left ventricular (LV) systolic function, and chronic infarct mass in patients imaged after recent acute MI.
BACKGROUND	Cardiac magnetic resonance accurately determines myocardial viability in patients with chronic ischemic heart disease but is not well validated for recent MI.
METHODS	Patients with first acute MI (n = 33) or chronic MI (n = 10) underwent cine CMR followed by gadolinium delayed enhancement imaging. A follow-up CMR scan was performed on 20 of the 33 acute MI patients and all of the chronic MI patients.
RESULTS	In patients with acute percutaneous coronary intervention, acute MI mass correlated with peak troponin I (r = 0.83, p < 0.001, n = 23). In the 20 acute infarct patients with follow-up CMR scans, the acute infarct size correlated well with the follow-up LV ejection fraction (r = 0.86, p < 0.001). The transmural extent of delayed enhancement imaged acutely correlated inversely with wall thickening measured acutely (p < 0.001) and at follow-up (p < 0.001). Although chronic infarct size was reproducible (11 ± 4% vs. 12 ± 7%, p = NS), acute infarct size decreased from 16 ± 12% to 11 ± 9% (p < 0.003).
CONCLUSION	In humans imaged shortly after acute MI, gadolinium delayed enhancement acute CMR infarct size correlates with acute and chronic indices of infarct size but will appear to diminish in size on follow-up. (J Am Coll Cardiol 2004;43:2253-9) © 2004 by the American College of Cardiology Foundation

We hypothesized that gadolinium delayed enhancement myocardium correlates with clinical indices of myocardial infarction (MI) in humans and can differentiate infarcted from viable myocardium. To test this hypothesis, we studied the relationship between the mass of myocardium exhibiting delayed enhancement and other clinical indices of infarct size such as peak serum troponin I, ejection fraction, regional wall thickening, and recovery of wall thickening. Patients were imaged, on average, two days after documented acute MI, and the cardiac magnetic resonance (CMR) was repeated at least two months later. The mass of myocardium exhibiting gadolinium delayed enhancement was compared between the two CMR scans. A control group of patients with chronic MI was studied to test the reproducibility of measuring CMR infarct mass on scans performed at least two months apart.

METHODS

Patient population and subgroup definitions. Thirty-three consecutive patients with first-time MI were imaged zero to five days after acute MI. Studies were performed after obtaining written informed consent.

The 33 subjects were selected to analyze correlations with peak troponin I and further subdivided based on whether they received acute revascularization (n = 23), because it was postulated that reperfusion status might influence the dynamics of serum troponin I levels.

Temporal changes in MI mass and the relationship to acute and regional left ventricular (LV) function were studied in the subgroup of 20 patients that returned for a CMR scan more than two months after the acute study. The time span of two months was chosen to allow for recovery of function in stunned myocardium. To be eligible for follow-up, the patients could have no clinically recognized ischemic events in the interval time period.

To determine the reproducibility of the CMR analysis, a separate control group of 10 patients with known chronic MIs were imaged on two CMR scans more than two months apart. Only those patients with no documented interval MI were eligible for follow-up imaging.

Myocardial infarction was diagnosed by history, electro-

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Abbreviations and Acronyms

CMR	= cardiac magnetic resonance
Gd-DTPA	= gadolinium diethylenetriaminepentaacetic acid
LV	= left ventricle/ventricular
MI	= myocardial infarction

cardiographic changes, and cardiac enzyme abnormalities in accordance with the consensus of the American College of Cardiology and the European Society of Cardiology (1). Troponin I was measured, by emergency department protocol, every 4 h and continued for 8 h after acute interventions.

Acute percutaneous coronary interventions and subsequent revascularization procedures were based upon standard clinical indications as determined by the attending cardiologist. Acute percutaneous reperfusion was defined by coronary angioplasty or stenting within 6 h of presentation. Subacute revascularization was defined as occurring 6 h to one month after the initial event.

Functional CMR. The CMR was performed using a GE (General Electric Medical Systems, Waukesha, Wisconsin) CV/i 1.5-T scanner and a four-element cardiac phased array coil. Functional assessment of the LV was performed pre-contrast using cine CMR with either fast gradient echo (n = 6) or steady-state free precession imaging (n = 27). Imaging was performed in multiple short breath-holds. The in-plane resolution was approximately 2 mm (26 μ l/voxel), and the temporal resolution was 40 to 50 ms within the cardiac cycle. The heart was imaged in multiple parallel short-axis planes 8-mm thick separated by 3-mm gaps, as well as in the two-chamber, three-chamber, and four-chamber long-axis views.

Gadolinium delayed enhancement CMR. Myocardial infarction was imaged using an inversion recovery fast gradient echo sequence triggered every other heartbeat. Images were obtained approximately 20 min after intravenous injection of 0.2 mmol/kg gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA). Imaging was performed at end-expiration and lasted about 12 heartbeats. The in-plane image resolution was typically 2.5 mm, and each imaging voxel represented approximately 42 μ l of tissue. Volumetric coverage of the entire LV was obtained using a slice

thickness of 8 mm and a slice separation of 3 mm. The same slices were acquired for both functional imaging and delayed enhancement to ensure registration between cine CMR and infarct measurements.

Analysis and statistics. Ejection fractions were calculated on the basis of end-diastolic and end-systolic endocardial tracings manually drawn by a cardiologist using computer-assisted planimetry. Wall thickening was quantified from endocardial and epicardial tracings using a centerline analysis (2). The LV wall thickening was summarized using the 16-segment model of the American Society of Echocardiography (3). The change in wall thickening between the two CMR scans was analyzed on segments with <1 mm of wall thickening on the acute study. To minimize the influence of heterogeneous tissue within the relatively large segments of the 16-segment model, focal one-dimensional measurements of wall thickening were also made at the core of the MI. The core of the MI was defined as the location in which there was maximal transmural extent of delayed enhancement.

Delayed enhancement images were displayed with a gray scale to optimally show normal myocardium (dark) and the region of delayed enhancement myocardium (bright). Infarct size was quantified using computer-assisted planimetry and reported in units of grams of infarcted myocardium. Infarct size was also summarized as percent of LV mass that appeared infarcted. Qualitatively, the segments were categorized according to the transmural extent of delayed enhancement: 0%, 1% to 25%, 26% to 50%, 51% to 75%, and 76% to 100%.

Summary statistical indices were calculated using a paired *t* test and linear regression in SigmaStat for Windows v2.03 (SPSS Inc., Chicago, Illinois). Values of *p* > 0.05 were considered not significant.

RESULTS

The mean age of the 33 patients in the acute infarct group was 63 \pm 14 years. There were 23 males and 10 females. None had a previous history of MI (Table 1). Table 1 also summarizes characteristics of the subgroup of patients in the acute infarct group who returned for follow-up CMR studies (n = 20). The median time of follow-up for the

Table 1. Patient Characteristics

	Age (Mean \pm SD)	Gender	Peak Tn-I Median (ng/ml) (range)	Reperfusion and/or Revascularization	MI Location
First MI (n = 33)	63 \pm 14	10 Female 23 Male	42 (2-745)	23 Acute 3 Subacute 7 Not done	7 Anterior 21 Inferior 5 Lateral
Follow-up CMR (n = 20)	62 \pm 13	5 Female 15 Male	59 (9-745)	16 Acute 3 Subacute 1 Not done	5 Anterior 12 Inferior 3 Lateral
Chronic (n = 10)	65 \pm 13	10 Male	N/A	3 Acute 4 Subacute 3 Not done	4 Anterior 4 Inferior 2 Lateral

CMR = cardiovascular magnetic resonance; MI = myocardial infarction; N/A = not applicable; Tn-I = troponin-I.

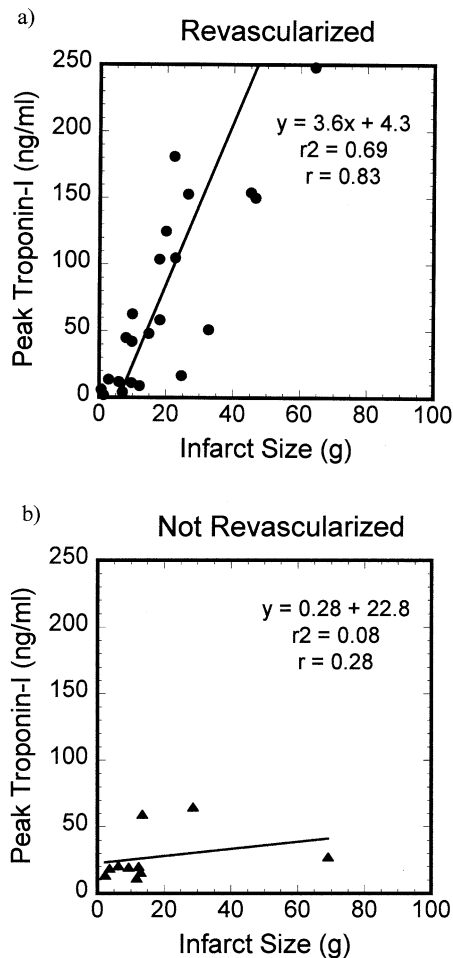


Figure 1. The cardiac magnetic resonance size of acute myocardial infarction correlates with peak troponin I. **Circles** indicate revascularized acute myocardial infarction (**a**); **triangles** indicate patients who did not undergo revascularization (**b**).

acute infarct group was five months. Of the 20 patients in the acute MI group with follow-up CMR, 17 were on an angiotensin-converting enzyme inhibitor, an angiotensin II receptor blocking agent, or a beta-blocker. The three patients who were on neither treatment had LV ejection fractions ranging from 56% to 68%. Of the 13 patients who did not return for a follow-up study, one patient had a pacemaker implanted, one patient had a defibrillator implanted, and one patient died in the interim. The other 10 patients either declined to return for follow-up or were unable to be contacted for follow-up.

In the control group (n = 10), the mean age was 65 ± 13 years, and all 10 subjects were males. The median time of follow-up for the chronic infarct group was 14 months, and the average time from infarction was 7 ± 5 years. Of the 10 patients in the control group with chronic MI, 9 were on an angiotensin-converting enzyme inhibitor, an angiotensin II receptor blocking agent, or a beta-blocker.

Correlation between infarct size and troponin I. Correlations between peak troponin I and CMR infarct size were studied in the 33 patients with first MI. Twenty-three

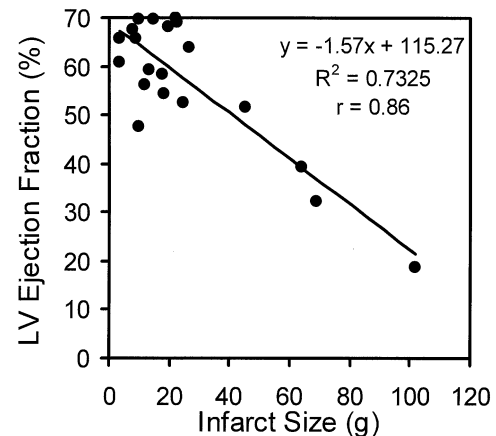


Figure 2. The cardiac magnetic resonance size of acute myocardial infarction predicts left ventricular (LV) ejection fraction at time of follow-up scan.

of these patients had acute percutaneous interventions and 10 did not. Median troponin I was 42 (range 2.0 to 745 ng/ml; where normal is 0.00 to 0.40 ng/ml). For reperfused infarcts (Fig. 1a), the correlation between troponin I and infarct size was r = 0.83 and p < 0.001 (excluding the 745 ng/ml point which was deemed an outlier that increased the correlation disproportionately). The linear correlation between troponin I and infarct size was not statistically significant for non-reperfused infarcts (p = 0.28).

Relationship between infarct size and ejection fraction.

In the 20 acute infarct patients with follow-up CMR scans, the acute infarct size correlated well with the follow-up LV ejection fraction (r = 0.86) (Fig. 2). The correlation between follow-up infarct size and follow-up ejection fraction was also good (r = 0.84). The correlation was weaker between acute infarct size and the acute ejection fraction (r = 0.66). Consistent with the possibility of dysfunctional but viable myocardium on the acute CMR scan, the ejection fraction in these patients averaged 52 ± 12% initially and increased to 57 ± 14% on the follow-up study (p < 0.002). Ejection fractions improved by >10% in seven patients and by >5% in two patients. One patient's ejection fraction decreased by 9%. Acute infarct size also correlated with acute left ventricular end-systolic volume (r = 0.79) and follow-up left ventricular end-systolic volume (r = 0.83).

Transmural extent of delayed enhancement predicts regional contractile function.

Based upon the 16-segment model, a total of 320 segments were quantitatively analyzed for wall thickening in the 20 acute infarct patients with follow-up studies. The transmural extent of delayed enhancement was graded 76% to 100% in 31 segments, 51% to 75% in 22 segments, 26% to 50% in 29 segments, and 1% to 25% in 20 segments. There were 218 segments with no delayed enhancement.

Figure 3 shows two time points in the recovery of wall thickening after acute MI. In the acute infarct group, there was an inverse relationship between the transmural extent of delayed enhancement and the measured wall thickening.

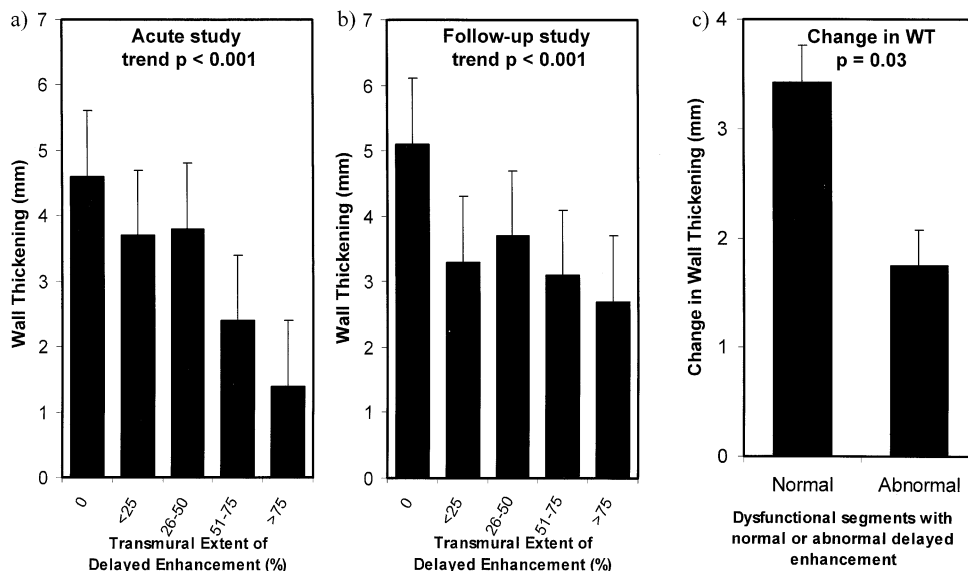


Figure 3. The transmural extent of delayed enhancement is inversely related to quantitative regional wall thickening (a: acute study, b: chronic study, $p < 0.001$ for both trends). For segments with <1 mm of wall thickening on the acute study, the improvement in wall thickening is much greater for segments that appear normal on delayed enhancement images compared with abnormal segments (c). There were too few segments with residual severe wall motion abnormalities on the acute study with $<50\%$ transmural extent of delayed enhancement to allow further stratification of the change in wall thickening (WT).

From segments with no delayed enhancement to segments with progressively greater CMR evidence of infarction, there was a stepwise worsening in regional wall thickening on the acute CMR scan (Fig. 3a) ($p < 0.001$ for trend). There was also an inverse relationship between the transmural extent of delayed enhancement on the acute CMR study and the regional wall thickening on the follow-up study (Fig. 3b) ($p < 0.001$ for trend).

As shown in Figure 3c, the change in wall thickening was much higher for segments that appeared normal on delayed enhancement images compared with abnormal segments. Perhaps because stunning had already resolved, only 5 of the 49 segments with $<50\%$ transmural extent of delayed enhancement had severe enough wall motion abnormalities on the acute scan to allow analysis of improvement in wall thickening. This precluded stratification of change in wall thickening by transmural extent of delayed enhancement.

Because the circumferential extent of segments can be large relative to the extent of infarction and infarcts may straddle segment borders, we also made one-dimensional measurements of wall thickening within the core of the MI. Wall thickening in the core of the infarct changed by 1 mm between the acute infarct study and the follow-up study (2.2 ± 2.3 mm vs. 3.2 ± 2.2 mm, $p = 0.05$). The transmural extent of delayed enhancement at the core of the infarct was $>75\%$ in 14 of the 20 acute infarctions. Similar measurements in the chronic infarct group did not change significantly (1.8 ± 4.4 mm vs. 2.0 ± 4.5 mm, $p = 0.29$).

CMR infarct size. The 20 acute infarct patients underwent CMR on average 1.7 ± 0.8 days post-MI for the acute study. They were imaged 22 ± 5 min post-contrast after the acute MI and 24 ± 5 min on the follow-up study ($p = \text{NS}$).

Eighteen of 20 patients demonstrated a decrease in the CMR infarct size (example shown in Fig. 4).

The average acute infarct size decreased from 26 ± 25 g to 17 ± 19 g ($p < 0.002$) (Fig. 5a). The percent of infarcted myocardium decreased from $16 \pm 12\%$ to $11 \pm 9\%$ ($p < 0.003$) (Fig. 5b). Total LV mass did not change significantly (152 ± 40 g vs. 152 ± 52 g, $p = \text{NS}$).

The 10 chronic infarct patients were imaged 22 ± 10 min post-contrast administration on the initial study and 20 ± 4 min on the second study ($p = \text{NS}$). Apparent infarct size was not statistically different between the paired studies (18 ± 8 g vs. 21 ± 13 g, $p = \text{NS}$) (Fig. 5c), and the percent of infarcted myocardium also demonstrated little change ($11 \pm 4\%$ vs. $12 \pm 7\%$, $p = \text{NS}$) (Fig. 5d).

DISCUSSION

In humans two days after the clinical event, the mass of myocardium exhibiting delayed enhancement correlates with clinical indices of infarct size. The CMR determined acute infarct size correlates both with peak serum troponin I in patients treated with acute percutaneous coronary interventions and with the LV ejection fraction seen in patients at follow-up. The acutely determined transmural extent of infarction predicts, in a graded fashion, LV regional function, as seen on both the acute and follow-up cine CMR studies. In fact, delayed enhancement shows better correlations with ultimate LV function than acutely imaged LV function—a finding most likely explained by the residual stunned but viable myocardium in an era of early percutaneous interventions. Thus, gadolinium delayed enhancement CMR may

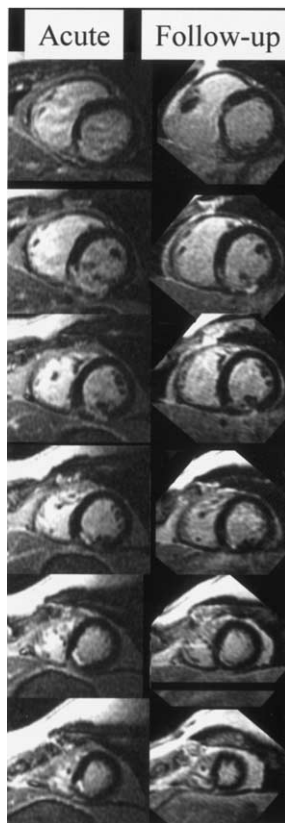


Figure 4. Images demonstrating a decrease in the size and transmural extent of myocardial infarction in a patient. The images in the left column were performed one day after successful percutaneous intervention on an occluded right coronary artery. The images in the right column show the corresponding infarct images on follow-up.

be a better prognosticator than subacute assessments of global or regional LV function.

Numerous studies in the literature have shown a correlation between troponin and histopathologic infarct size in canine (4,5) and murine (6) models. In patients, troponin has been correlated against ventriculography (7), thallium (8,9), and sestamibi (10).

This is the first study delineating the relationship between CMR infarct size and serum peak troponin I rather than the MB fraction of creatine kinase (11,12). Fifteen percent of our patients had troponin I levels of ≤ 9 ng/ml, which are small infarctions but of significant adverse prognostic value (13). The infarct was visualized on both CMR scans in all patients despite the fact that many had less than 1 g of infarcted myocardium per image. Thus, delayed enhancement can detect many of the smallest acute MIs recognized in humans (14).

Figure 5 raises important questions about the absolute accuracy of gadolinium delayed enhancement determined infarct size in humans. Whereas some studies show close agreement between CMR infarct size and standard measurements (11,12), others have suggested that gadolinium overestimates infarct size in rats (15) and humans (16). Six mechanisms should be considered: 1) involution of the scar tissue into a smaller volume than the original amount of

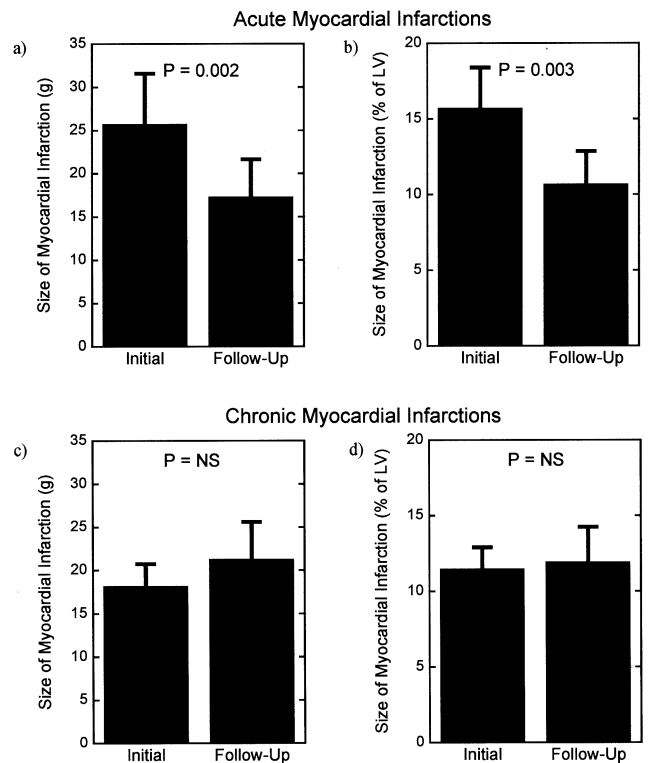


Figure 5. The cardiac magnetic resonance infarct size decreases between the acute and the follow-up cardiac magnetic resonance scan based on grams of myocardium with delayed enhancement (a) or percent of myocardium that showed delayed enhancement (b). For comparison purposes, similar measurements in patients with chronic myocardial infarction do not change significantly between serial cardiac magnetic resonance scans (c and d). LV = left ventricle.

myocardium (17); 2) partial volume effects; 3) through-plane motion errors in assessing wall thickening; 4) mismatch between segment size and infarct size; 5) possible regeneration of cardiomyocytes from primitive progenitor cells (18); and 6) overestimation of infarct size, perhaps as a result of peri-infarct edema (15). High-resolution x-ray spectroscopic analysis indicates that gadolinium closely correlates with sodium and potassium concentrations in the myocardium and suggests peri-infarct edema should not cause overestimation of infarct size by gadolinium-based contrast agents (19).

We believe a combination of involution of infarcted myocardium and partial volume effects can explain the apparent decrease in infarct size and even conversion from apparently transmural infarction to subendocardial infarction (Fig. 6). In our experiments, each imaging voxel represents an average of about 42 μ l of tissue. Consider a voxel that contains half normal and half infarcted cardiomyocytes. If the fibrous scar tissue that replaces the infarcted cardiomyocytes has 50% the volume of those cells and the normal cardiomyocytes undergo compensatory hypertrophy that increases their volume by 50%, the infarct could appear to decrease from 50% of the voxel to 25% by the follow-up scan. Because almost all of our patients were reperfused therapeutically or spontaneously, the possibility of mixed

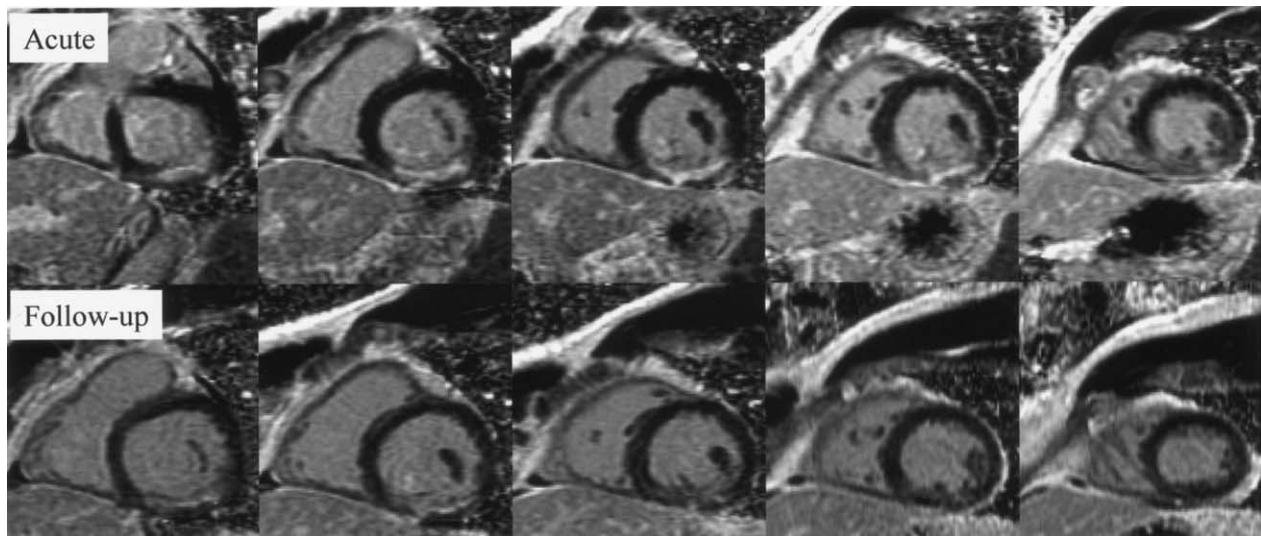


Figure 6. Changes in the amount of gadolinium delayed enhancement myocardium without net thinning of the left ventricular wall may represent partial volume effects as described in the “Discussion” section. Offsetting involution of the infarcted myocardium and hypertrophy of viable myocardium within pixels could explain serial changes on the delayed enhancement images. The first cardiac magnetic resonance scan (**top row**) was performed two days after acute percutaneous intervention on a circumflex coronary artery. The follow-up scan (**bottom row**) was performed two months later.

viable and nonviable myocytes needs to be considered. These effects will be most prominent in the borders of infarcts, particularly in the transmural direction across the LV wall. Hypertrophy of the viable cells in conjunction with involution of the infarcted cells would account for the relative stability of LV mass over time. Through-plane motion issues could further complicate wall thickening measures.

Techniques are important in obtaining accurate infarct size. The time interval between injection of Gd-DTPA and image acquisition could affect the size of infarct that showed delayed enhancement (20). We prospectively designed the imaging protocol to avoid issues related to inconsistent timing or doses and used the best validated inversion recovery methods (21) rather than older T₁-weighted sequences (22). Furthermore, we had full volumetric coverage of the LV to minimize chances of registration errors between scans. As demonstrated by the control group, the infarct appearance and size are quite reproducible.

We used regional wall thickening as the primary indicator of viability rather than a change in function because regional wall motion could not be evaluated before acute reperfusion therapy. In normal hearts wall thickening is relatively uniform. Myocardial infarction is the primary cause of regional wall thickening abnormalities, particularly in patients with first MI and full revascularization as in our population. Because there is a graded transmural extent of infarction, it is not unreasonable to expect a graded response in wall thickening for more severe infarctions. This is the basis of the data presented in Figures 3a and 3b. We found an inverse correlation between the transmural extent of delayed enhancement seen on the acute study and regional wall thickening on either scan.

The presence or absence of abnormal delayed enhance-

ment stratified the likelihood and extent of recovery of dysfunctional myocardium (Fig. 3c). Unlike viability studies where regional function can be measured before and after an intervention, differential measurements of wall thickening between the two CMR scans are not appropriate for evaluating viability because the first scan can be predicted to miss early recovery of function associated with mild stunning (23). Note that 44 of 49 segments with <50% delayed enhancement had mild enough wall motion abnormalities to preclude assessment of serial changes. The severity and duration of myocardial stunning generally increases with the severity of the ischemic episode (24–27). This can lead to the paradoxical observation that there is more improvement in myocardium that demonstrates the most delayed enhancement (Fig. 3). Regional contractile function improvement in regions with extensive delayed enhancement (Fig. 3) was also observed by Rogers *et al.* (22) and Choi *et al.* (11). To keep things in clinical perspective, regions with the most delayed enhancement remained the most dysfunctional segments and had 50% less wall thickening compared with “normal” segments. The amount of improvement in regional wall thickening was small and averaged about 1 mm on each of our quantitative analyses.

CONCLUSIONS

Despite the decrease in infarct size over time and statistically significant changes in regional wall thickening, overall we conclude that delayed enhancement CMR infarct imaging correlates well with standard clinical assessments of myocardial necrosis and LV function. Serum markers of infarction correlate with infarct size but are modulated by reperfusion status. Global and regional LV function acutely are complicated by myocardial stunning. Our best predictor

of ultimate cardiac function is the amount of myocardium exhibiting delayed enhancement on the acute CMR scan. For post-infarct risk stratification, CMR infarct size may prove to be a prognosticator with less variability than peak troponin I and acute ejection fraction.

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