Early Assessment of Myocardial Salvage by Contrast-Enhanced Magnetic Resonance Imaging

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Background—Myocardial salvage after acute myocardial infarction is defined clinically by early restoration of flow and long-term improvement in contractile function. We hypothesized that contrast-enhanced magnetic resonance imaging (MRI), performed early after myocardial infarction, indexes myocardial salvage. We studied the relationship between the transmural extent of hyperenhancement by contrast-enhanced MRI, restoration of flow, and recovery of function.

Methods and Results—The left anterior descending coronary artery was occluded in dogs (n = 15) for either 45 minutes, 90 minutes, or permanently. Cine and contrast-enhanced MRI were performed 3 days after the procedure; cine MRI was also done 10 and 28 days after the procedure. The transmural extent of hyperenhancement and wall thickening were determined using a 60-segment model. The mean transmural extent of hyperenhancement for the 45-minute occlusion group was 22% of the 90-minute group and 18% of the permanent occlusion group (P < 0.05 for both). The transmural extent of hyperenhancement on day 3 was related to future improvement in both wall thickening score and absolute wall thickening at 10 and 28 days (P < 0.0001 for each). For example, of the 415 segments on day 3 that were dysfunctional and had 25% transmural hyperenhancement, 362 (87%) improved by day 28. Conversely, no segments (0 of 9) with 100% hyperenhancement improved. The transmural extent of hyperenhancement on day 3 was a better predictor of improvement in contractile function than occlusion time (P < 0.0001).

Conclusions—A reduction in the transmural extent of hyperenhancement by contrast-enhanced MRI early after myocardial infarction is associated with an early restoration of flow and future improvement in contractile function. (Circulation. 2000;102:1678-1683.)

Key Words: Magnetic resonance imaging ■ contrast media ■ myocardial infarction ■ salvage therapy

Myocardial salvage is the hallmark of successful reperfusion therapy. The assessment of myocardial salvage is important clinically because significant salvage results in the long-term reestablishment of myocardial contractile function and is associated with improved prognosis and outcome.1-6 Ventricular wall motion at rest cannot be used to quantify myocardial salvage early after myocardial infarction because both necrotic and stunned myocardium will have impaired contractile function.7-9 Wall motion during exercise or pharmacological stress may be used to distinguish between infarcted and stunned myocardium,10 but this approach can be problematic if residual stenosis is present in the infarct-related artery.11 It would be advantageous to index myocardial salvage within regions exhibiting acute contractile dysfunction. In previous studies, we found that contrast-enhanced magnetic resonance imaging (ce-MRI) can distinguish between reversible and irreversible ischemic injury within the region at risk,12 independent of wall motion.13 Specifically, we found that nonviable myocardium was hyperenhanced, whereas viable myocardium was not. Because irreversible ischemic injury begins in the subendocardium and progresses as a “wavefront” of necrosis moving toward the epicardium,14 we hypothesized that the transmural extent of hyperenhancement can be used to index myocardial salvage early after infarction.

In this study, we produced a full range of salvage and necrosis by subjecting animals to 45 minutes, 90 minutes, and permanent coronary artery occlusion.1 We tested the hypothesis that ce-MRI can index myocardial salvage by relating the transmural extent of hyperenhancement observed early after injury to early restoration of flow and future improvement in contractile function.

Methods

Experimental Preparation
A total of 15 purpose-bred dogs weighing 20 kg were studied. The care and treatment of all animals was in accordance with the Position...
of the American Heart Association on Research Animal Use, which was adopted November 15, 1984. The animals were premedicated with 1 mL of intramuscular Innovar-Vet (0.4 mg/mL fentanyl and 20 mg/mL droperidol) followed by 11 mg/kg IV Brevital (methohexital); they were then intubated and ventilated with gas anesthesia (isoflurane and nitrous oxide). Using a sterile technique, a lateral thoracotomy was performed at the fourth left intercostal space to expose the heart, and the pericardium was opened. The proximal left anterior descending coronary artery was carefully dissected distal to the first major diagonal. In groups 1 (n = 5) and 2 (n = 5), the artery was occluded for 45 and 90 minutes, respectively, using a removable soft occluder, and then reperfusion was restored. In group 3 (n = 5), the artery was permanently occluded with a snare ligature. The chest was then sutured closed and the animals were allowed to recover.

MRI and Experimental Protocol
All animals were studied 3 days after the procedure by cine and Ce-MRI; cine MRI studies were also performed 10 and 28 days after the procedure. MRI was performed using a 1.5 Tesla clinical scanner (Siemens Sonata) using a flexible radiofrequency receiver coil. Each study day, the animals were tranquilized with 1 mL of Innovar and transported to the MRI facility. There, they were anesthetized with methohexital (11 mg/kg IV), intubated, ventilated under gas anesthesia (isoflurane); they were then intubated and ventilated with gas anesthesia (isoflurane and nitrous oxide). Using a sterile technique, a lateral thoracotomy was performed at the fourth left intercostal space to expose the heart, and the pericardium was opened. The proximal left anterior descending coronary artery was carefully dissected distal to the first major diagonal. In groups 1 (n = 5) and 2 (n = 5), the artery was occluded for 45 and 90 minutes, respectively, using a removable soft occluder, and then reperfusion was restored. In group 3 (n = 5), the artery was permanently occluded with a snare ligature. The chest was then sutured closed and the animals were allowed to recover.

MRI
MRIs were ECG-gated, and all images, which were prescribed as short-axis views of the heart, were acquired during repeated breath-holds. Both cine and Ce-MRIs were prescribed every 5 mm from base to apex (12 to 15 cine short-axis views and 12 to 15 corresponding contrast-enhanced views per heart). Cine-MRI was performed using a retrogated true-FISP (fast imaging with steady-state precession) sequence, which yielded 32 image frames throughout one RR cycle, with a heart rate–dependent temporal resolution of between 20 and 30 ms. All cine images were acquired before the administration of the contrast agent. Typical imaging parameters were the following: repetition time, 3.0 ms; echo time, 1.5 ms; flip angle, 50°; in-plane resolution, 1 x 1 mm; slice thickness, 5 mm. Ce-MRI was performed ~20 minutes after the intravenous administration of 0.3 mmol/kg Gd-HP-D03A (Prohance, Bracco Pharmaceuticals), T1-weighting was achieved using a segmented inversion-recovery fast low-angle shot (IR-FLASH) pulse sequence, which has been described in detail elsewhere. Typical parameters were as follows: repetition time, 8 ms; echo time, 4 ms; in-plane resolution, 1 x 1 mm; slice thickness, 5 mm; “typical inversion delay,” 250 ms; and k-space data segmented over 4 cardiac cycles (23 lines/cycle) with data acquired every other cardiac cycle. Ce-MR images were ECG-gated to end-diastole.

Data Analysis
Image Registration
Figure 1 summarizes the registration procedure. On the basis of the 12 to 15 short-axis cine views taken at 3 days, a single view was chosen in which the papillary muscles were most prominent (Figure 1). The angle required to rotate this view such that the anterior insertion of the right ventricle was located at 12 o’clock was recorded. Next, every other view (10 mm apart) moving apically from this view and distal to the occlusion site was selected for further analysis. This yielded ~5 short-axis views per animal distal to the site of occlusion. One additional view at the base of the heart was located proximal to the occlusion and was excluded from the analysis. Each of these 5 cine views located distal to the site of occlusion and the corresponding contrast-enhanced views were rotated by the prerecorded angle. For each pair of cine and Ce-MRI views, the center point of the heart was defined, and the myocardium was divided into 12 circumferential segments; this nominally yielded 60 segments per animal (12 segments/view x 5 views).

Registration of the cine views on days 10 and 28 with the views from day 3 was accomplished by a choice from the total of 12 to 15 views by a consensus of 3 observers using anatomical landmarks. The views at 10 and 28 days were rotated using the same procedure as that at 3 days. Using this approach, the registration between cine and contrast-enhanced views at 3 days would be precise because both were acquired in the same imaging session and that between cine images at 3 days and cine images at 10 and 28 days would be within 50% of the 5-mm slice thickness and 5-mm interslice separation.

Delayed MRI Contrast Enhancement
Cine-MRIs acquired at 3 days were analyzed by defining hyperenhancement as >3 SD above remote. On the basis of this definition, binary images were produced in which regions with image intensities >3 SD were white (hyperenhanced) and regions with image intensities ≤3 SD were black (non-hyperenhanced). Within each segment, the hyperenhanced area (HEA) and normal enhanced area (NEA) were outlined by hand in magnified views. The transmural extent of hyperenhancement within each segment was calculated as a percentage of the total segment area: HEA(%) = (HEA x 100)/(HEA + NEA). For each study group, the mean transmural extent of hyperenhancement was calculated by averaging the HEA for all dysfunctional segments at 3 days.

Wall Thickening
Wall thickening was analyzed qualitatively and quantitatively. For both analyses, cine MR images on days 3, 10, and 28 were
randomized and presented to observers who were blinded to animal group and the ce-MRI results. For the qualitative analysis, each myocardial segment was scored independently by 2 observers using the following system: 0, normal thickening; 1, mild to moderate hypokinesis; 2, severe hypokinesis; and 3, akinesis or dyskinesis. Wall thickening was first scored by the observers individually and then by consensus to resolve cases of disagreement. Remaining discrepancies were resolved by a third observer who was also blinded to animal group and the ce-MRI results. For dysfunctional segments on day 3, improvement was defined as normal thickening or a reduction in score of $\geq 2$ levels by days 10 and 28. For the quantitative analysis, wall thickening was determined by the modified centerline method and expressed as a percent of end-diastolic wall thickness. For this analysis, dysfunction at 3 days was defined as any segment with wall thickening $\geq 2$ SD below the mean of wall thickening in segments in the half of the heart opposite the wall motion abnormality.

Statistical Analysis
Continuous data are expressed as mean±SEM. Between-group comparisons in continuous data were made using ANOVA. The $\chi^2$ test for trend was used to assess the relationship between segmental hyperenhancement on day 3 and follow-up wall thickening. The data were also analyzed using a linear mixed effects model with a separate parameter for “dog” to eliminate the problem of nonindependence of segments. Receiver-operating characteristic (ROC) curves were generated for the prediction of wall thickening improvement based on day 3 hyperenhancement and occlusion time according to the method described by Metz. ROC curves were compared using the CORROC2 program of Metz. The Bonferroni method was used when making multiple between-group comparisons. All statistical tests were 2-tailed; $P<0.05$ was regarded as statistically significant.

Results
A total of 75 short-axis views (5 levels $\times$ 15 animals) were analyzed for contrast enhancement at 3 days and wall thickening at 3 days, 10 days, and 28 days. Four of the 75 short-axis views were excluded by the observers because they were located too apical to allow for accurate wall thickness determination (2 views in group 1 and 1 view in groups 2 and 3), thus yielding a total of 71 views ($\times$12 circumferential segments) and 852 segments.

Transmural Extent of Hyperenhancement
Figure 2 shows one representative contrast-enhanced short-axis view from each of the 15 dogs on day 3. Hyperenhanced regions were small and subendocardial in the 45-minute occlusion group. After 90 minutes of occlusion, hyperenhanced regions were larger and comprised $\approx 50\%$ of wall thickness. Hyperenhanced regions were even larger in animals with permanent occlusion and, in 3 of the 5 animals, the hyperenhanced region extended to the epicardial border. The mean transmural extent of hyperenhancement for the 45-minute group was 22% of the 90-minute group and 18% of the permanent occlusion group ($P<0.05$ for both; Figure 3).

Relationship Between the Transmural Extent of Hyperenhancement on Day 3 and Recovery of Function
A total of 201 of the 852 segments (24%) were hyperenhanced. For the qualitative analysis, 567 of the 852 segments (67%) were dysfunctional on day 3. By day 10, contractile function had improved in 347 segments (61%) and by day 28, contractile function had improved in 440 (78%). For the quantitative analysis, dysfunction at 3 days was defined as wall thickening $<12\pm 4\%$ ($<2$ SD below remote; see Methods). Using this criterion, 357 of the 852 segments (42%) were dysfunctional on day 3. Whether they improved is reflected by absolute wall thickening in these same segments at 10 and 28 days.

Figure 4 shows 3 examples of how the contrast enhancement observed on day 3 predicted long-term improvement. Each row in the figure shows a different dog, with contrast enhancement in the first column and the corresponding end-diastolic and end-systolic still frames on days 3 and 28 in the remaining four columns. For all 3 dogs, a severe impairment in wall thickening was observed in the cine images at day 3. Contrast enhancement on day 3, however, reveals essentially transmural hyperenhancement in the first dog, hyperenhancement extending to $\approx 50\%$ of wall thickness in the second dog, and no hyperenhancement in the third dog. On day 28, wall thickening minimally improved in the first

**Figure 2.** One representative ce-MR image from each of the 15 dogs on day 3. Top row, 45-minute occlusion group; middle row, 90-minute occlusion group; and bottom row, permanent occlusion group. Arrows indicate hyperenhanced regions.

**Figure 3.** Mean transmural extent of hyperenhancement in segments with baseline wall thickening abnormality on day 3 in each group.
dog, partially improved in the second dog, and significantly improved in the third dog.

Figure 5A shows the percentage of improved segments by days 10 and 28 on the basis of qualitative wall thickening as a function of the transmural extent of hyperenhancement on day 3. The percentage of improved segments decreased with increasing transmural extent of hyperenhancement at both 10 and 28 days ($P<0.0001$ for both). For instance, 321 of 368 segments (87%) without any hyperenhancement and 362 of 415 segments (87%) with $25\%$ transmural extent of hyperenhancement on day 3 improved by day 28. Conversely, only 2 of 17 segments (12%) with $76\%$ to $100\%$ hyperenhancement and 0 of 9 segments (0%) with $100\%$ hyperenhancement improved. Concordance between the 2 observers for improvement in contractile function was $83\%$ from 3 days to 10 days and $88\%$ from 3 days to 28 days.

Figure 5B shows quantitative wall thickening at 3, 10, and 28 days for the 357 dysfunctional segments at 3 days. Wall thickening at 3 days was $10\%$ on average for all categories of hyperenhancement. By 10 and 28 days, however, segments with little or no hyperenhancement improved wall thickening to $30\%$. Conversely, segments with increasingly large regions of hyperenhancement showed significantly less improvement by 10 and 28 days ($P<0.0001$ for both). Analysis of the wall thickening data by dog as opposed to by segment revealed a similarly strong dependence on the transmural extent of hyperenhancement ($P<0.0001$).

Predictive Value of Hyperenhancement Compared With Occlusion Time

Figure 6 shows ROC curves for the prediction of wall-thickening improvement by day 28 as a function of both occlusion time and transmural extent of hyperenhancement on day 3. Ce-MRI was a stronger predictor of wall thickening improvement than was occlusion time ($P<0.0001$).

Discussion

The data from this study demonstrate that the transmural extent of hyperenhancement by ce-MRI performed early after infarction is inversely related to the early restoration of flow and future improvement in contractile function. The relationships between ce-MRI and these clinical indices of myocardial salvage have not been previously shown.

Study Limitations

The extent to which the data from this article relate to the clinical setting in humans is unknown. The contrast dosage used in the present study (0.3 mmol/kg) is higher than that used clinically (0.1 to 0.2 mmol/kg), and the images were acquired $\approx 20$ minutes after contrast to improve the distinction between subendocardial hyperenhancement and blood in the left ventricular cavity. In addition, the extent to which partial volume effects may have caused the spatial extent of hyperenhancement to appear greater than true infarct size was not evaluated.
Hyperenhancement and Oclusion Time
In previous studies, we found that delayed hyperenhancement by ce-MRI was exclusively associated with irreversible ischemic injury, as defined histologically. Assuming that hyperenhancement indicates infarction, the increase in the transmural extent of hyperenhancement with increasing duration of coronary occlusion observed in the current study (Figure 3) could be explained by the “wavefront phenomenon” of infarct progression beginning in the endocardium and growing toward the epicardium.

Interestingly, however, considerable animal-to-animal variations in the transmural extent of hyperenhancement were also observed, even for those with identical occlusion times (Figure 2). Again, assuming that hyperenhancement indicates infarction, these animal-to-animal variations might be explained by additional factors that influence infarct progression, such as the degree of collateral flow. The assumption that hyperenhancement indicates infarction would suggest that the transmural extent of hyperenhancement would be a better predictor than occlusion time of future improvement in contractile function because it would represent a direct measure of the transmural extent of necrosis. The ROC curves shown in Figure 6 demonstrate that hyperenhancement was indeed a better predictor than occlusion time of future improvement in contractile function.

Hyperenhancement and Recovery of Function
We found that segments for which the transmural extent of hyperenhancement at 3 days was >75% were unlikely to exhibit improved wall thickening at 10 and 28 days (Figure 5). This finding would be expected on the basis of the interpretation that hyperenhancement indicates myocardial infarction.

Conversely, 87% of segments for which the transmural extent of hyperenhancement was <25% at 3 days exhibited improved thickening by 28 days (Figure 5). This finding could be explained on the basis of the data from our previous article, in which we found that hyperenhancement did not occur in regions subjected to severe but reversible ischemic injury, despite a persistent wall motion abnormality. The lack of hyperenhancement after the severe but reversible injury observed in our previous study, combined with our current finding that these regions eventually recover contractile function (Figure 5), strongly suggests that dysfunctional regions without hyperenhancement observed in the setting of acute ischemic injury represent stunned myocardium.

In addition to regions with nearly transmural hyperenhancement (>75%) and nearly absent hyperenhancement (<25%), however, a significant number of segments exhibited a transmural extent of hyperenhancement between 25% and 75% and were associated with intermediate likelihoods for contractile improvement (Figure 5). The presence of these segments underscores the fact that segmental viability defined by contrast MRI is not an “all-or-none” phenomenon; instead, the intrinsically high spatial resolution of the technique seems to allow direct visualization of the transmural extent of infarction and of residual viable tissue.

Our finding that 87% of segments with <25% hyperenhancement improved raises the question as to why the remaining 13% did not improve. It has been shown that wall motion recovery after myocardial infarction may last for several weeks or even months. Thus, improvement in additional segments may have been found if the animals had been imaged beyond 28 days. At the other end of the hyperenhancement range, we found that 2 of 17 segments (12%) with 76% to 100% hyperenhancement improved by day 28 (Figure 5). When these segments were reexamined, we found that they did indeed exhibit wall thickening but that these segments were located exactly at the border between hyperenhanced and non-hyperenhanced myocardium. One possible explanation for this finding would be tethering between actively contracting regions and scar. Another possible explanation relates to infarct shrinkage. In a previous study, we found that the spatial extent of hyperenhancement decreased between 3 days and 8 weeks as the acutely necrotic zone was replaced by collagenous scar. Infarct shrinkage may have caused misregistration of contrast-enhanced segments at 3 days and cine segments at 28 days for regions at the infarct border.

Mechanism of Hyperenhancement
The mechanism responsible for the hyperenhancement of acutely necrotic myocardium has not been established. Gadolinium-DTPA and Gd-HP-DO3A, with molecular weights of ≈800 daltons, are thought to be biologically inert and to passively diffuse throughout the extracellular space. Loss of sarcomere membrane integrity after acute cellular injury may allow the Gd chelate to enter the intracellular space, thereby increasing the myocardial concentration of Gd and resulting in hyperenhancement.

Clinical Implications
The data from the current study indicate that ce-MRI can be used to index myocardial salvage acutely within regions of contractile dysfunction. In addition, the technique does not require exercise or pharmacological stress testing, which may be of practical utility in the acute setting. Of potentially greater importance, however, is the observation that ce-MRI can be used to directly visualize nontransmural infarction, which is not possible using any other existing technique. Further investigation will be required to determine whether this physiological information is of additional clinical importance.

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