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EXPERIMENTAL STUDIES

Distinguishing Viable From Infarcted Myocardium After Experimental Ischemia and Reperfusion by Using Nuclear Magnetic Resonance Imaging

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Early reperfusion has the potential for salvaging ischemic myocardium at risk for infarction. To test the ability of nuclear magnetic resonance (NMR) imaging to differentiate between stunned and infarcted myocardium early after reperfusion, 16 mongrel dogs underwent transient occlusion of the left anterior descending artery or a diagonal branch for 30, 60 or 180 min followed by reperfusion. To identify the area at risk for infarction and to assess the extent of hypoperfusion and reperfusion, two-dimensional and contrast echocardiography were performed at baseline study, during coronary occlusion and at three separate times during reperfusion (before NMR imaging, immediately after NMR imaging and 12 to 14 h later). Wall thickening in the control and ischemic zones and the circumferential extent of abnormal wall motion were analyzed at each time point using short-axis echocardiograms. Nuclear magnetic resonance imaging at 1.5 tesla was performed 2 to 3.5 h (mean 2.7 ± 0.5) after reperfusion. Short-axis, multislice spin-echo images (TE 26 and TE 60) were obtained. Signal intensity was measured in the control and ischemic areas and expressed as a percent difference compared with normal myocardium.

All dogs demonstrated a significant decrease in wall thickening and abnormal wall motion before and after NMR imaging. Seven of the eight dogs with infarction had an area of increased signal intensity on TE 60 images. The mean percent difference in signal intensity compared with adjacent normal myocardium was 127 ± 68% ($p = 0.002$). None of the eight dogs without infarction had a visually apparent change in signal intensity on TE 60 images (mean percent difference versus control area 13 ± 11%), despite regional systolic dysfunction documented by echocardiography at the time of imaging. The area of increased signal intensity correlated with infarct size ($r = 0.69$), although overestimation by NMR imaging occurred. The area of increased signal intensity did not correlate with the extent of echocardiographic contrast defect during coronary occlusion (risk area).

This study demonstrates that NMR imaging can be applied early after coronary reperfusion to assess the potential for recovery of dysfunctional myocardium. In addition, by using a TE 60 multislice spin-echo imaging sequence at 1.5 tesla, quantification of the extent of infarction also may be possible.

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Early reperfusion of ischemic myocardium has the potential for salvaging tissue at risk for infarction, thereby reducing infarct size, improving left ventricular function and altering outcome (1). Although reperfusion can be accomplished by a variety of methods, in most cases thrombolytic agents are initially utilized to restore blood flow to the ischemic zone. Determination of the success of such therapy soon after attempted reperfusion remains a difficult and important clinical issue. The myocardium may be dysfunctional but viable ("stunned") or dysfunctional and infarcted (2). Although subsequent clinical decisions may hinge on differentiating between these two states, currently available imaging modes often are incapable of providing the necessary information (3). Furthermore, if the duration of stunning is prolonged (4), techniques that measure regional systolic

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function (such as contrast ventriculography and two-dimensional echocardiography) may not detect evidence of viability for several days. Ideally, a method should be capable of providing reliable quantitative information regarding viability within a few hours of attempted reperfusion.

Nuclear magnetic resonance (NMR) imaging has been used to detect and quantify myocardial infarction in humans (5–7) and animals (8–17). By measuring prolongation of spin-lattice (T_1) and spin-spin (T_2) relaxation times (18,19) or the resulting changes in signal intensity, myocardial infarction can be detected within a few hours of coronary artery occlusion (9,12,17). The contrast between infarcted and normal myocardium is more striking and may be detected earlier when an infarct has been reperfused (20–22). However, if reperfusion occurs very early in the course of ischemia, no significant changes in relaxation times occur (23), presumably as a result of the absence of myocardial necrosis or tissue edema, or both. If a change in signal intensity occurs only in the presence of infarction, such an approach may be more useful than wall motion analysis to predict myocardial viability after reperfusion. Thus, the use of NMR imaging to measure signal intensity rather than regional systolic function may provide information on the success of therapies designed to salvage ischemic myocardium.

In the current study, cardiac-gated NMR imaging was performed in dogs subjected to coronary artery occlusion and reperfusion. The duration of occlusion was varied to simulate successful and unsuccessful myocardial reperfusion. Imaging was performed while regional systolic function remained depressed, because of either stunning or infarction. The purpose of the investigation was to 1) determine whether NMR imaging can distinguish reversibly ischemic (stunned) myocardium from infarcted tissue, and 2) examine the correlations between the extent of the zone of increased signal intensity, infarct size by tissue staining and area at risk by contrast echocardiography.

Methods

Twenty-six mongrel dogs of either gender, weighing 18 to 26 kg, were used in this study. Seven animals died before completion of the protocol. In three others, unsuccessful cardiac gating during nuclear magnetic resonance (NMR) imaging or images of unacceptable quality precluded data collection. Thus, 10 dogs were eliminated, leaving 16 for final analysis. This study was approved by the Indiana University School of Medicine Animal Care Committee, and all dogs were maintained in accordance with its guidelines for humane treatment of laboratory animals.

Experimental preparation. The 16 dogs were anesthetized with pentobarbital sodium, intubated and ventilated with use of a Harvard veterinary respirator. The heart was exposed by left thoracotomy, and a small incision was made in the pericardium. An adjustable ligature was placed around the left anterior descending coronary artery or a major diagonal branch. Variable occlusion sites were selected to provide a range of ischemic zone sizes. A 7F straight aortic catheter was introduced through the right femoral artery and advanced to the aortic root. The electrocardiogram (ECG) and arterial blood pressure were monitored throughout the study.

Echocardiography. Echocardiographic examinations were performed with use of a wide angle sector scanner (Mark 600, Advanced Technology Laboratories) with a 5.0 MHz mechanical transducer. With the animal lying on its right side, imaging was accomplished from below through a hole in the surgical table. Gain, reject and depth were optimally adjusted at baseline study and remained unchanged throughout. Short-axis images were recorded on 0.5 in. (1.27 cm) VHS tape at four levels (below the papillary muscles at the apex, low and high papillary muscle levels and above the papillary muscles at the chordae tendineae).

Contrast echocardiography was utilized during coronary artery occlusion to quantify the area at risk and during reperfusion to determine the extent of persisting hypoperfusion (24,25). Contrast echocardiograms were performed by injecting 3 ml of a hand-agitated 1:1 mixture of iohexol and saline solution into the aortic root.

Nuclear magnetic resonance imaging. In vivo cardiac-gated NMR imaging was performed with a Picker Vista 2055 system (Picker International) operating at 1.5 tesla. With the dog sedated and lying on its right side, multiple gated pilot scans were obtained. Short-axis multislice spin-echo images were then performed using echo times of 26 ms (TE 26) and 60 ms (TE 60). The repetition time of the TE 26 scans was equal to one RR interval on the ECG (approximately 500 ms) in all animals. Repetition time for the TE 60 images was manually set at a lower limit of 2,500 ms, with the gating circuitry triggering on the first R wave occurring after this point. All scans were run with four repetitions and 128 views in a 35 cm field of view. The final image matrix was 128 × 256 interpolated to 512 × 512. Slice thickness of all images was 10 mm.

Data collection for the first slice of the TE 26 multislice set was obtained after a delay of 100 or 150 ms after the R wave. Subsequent data collections occurred regularly throughout a manually supplied repetition time that was less than the RR interval. The time delay and manual repetition time were selected to define the temporal spacing of the slices within the cardiac cycle. The actual repetition time resulted from R wave detection by the imager.

Data collection for the first slice of the TE 60 multislice set was begun without programmed delay after the R wave. Subsequent data collections were obtained at approximately 80 ms intervals after this point. Initially, the sequence microcode was written to force all slices to be obtained

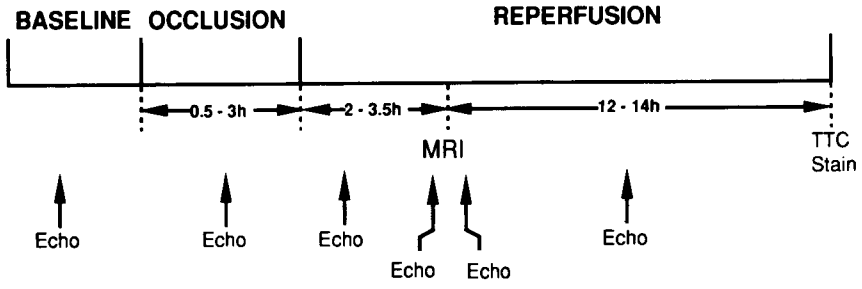

Figure 1. Schematic depiction of the experimental protocol. Nuclear magnetic resonance imaging (MRI) was performed a mean of 2.7 ± 0.5 h after reperfusion. Echocardiograms (Echo) were obtained at six time points as shown. TTC = triphenyltetrazolium chloride.

within one RR interval and with an 80 ms interval between data collections. Later, a feature in the scan software was altered to allow data collection for each slice to occur as rapidly as possible without distributing the slices over the entire repetition time. Both techniques ensured that data collection of all four slices would be obtained within one RR interval as near in time to each other as reasonably possible. Imaging times were approximately 4 min for TE 26 scans and 22 min for TE 60 scans.

Experimental protocol (Fig. 1). A two-dimensional echocardiogram was recorded at baseline study. A contrast echocardiogram was performed to confirm optimal position of the aortic root catheter and uniform contrast effect. Coronary artery occlusion was then performed for 30 (n = 5), 60 (n = 6) or 180 min (n = 5). Routine and contrast echocardiograms were recorded 5 min after occlusion and again just before reperfusion. At the end of occlusion, lidocaine (2 mg/kg) was given as a bolus injection before release of the ligature. If ventricular ectopic activity persisted, a lidocaine infusion (0.5 mg/min) was maintained during imaging. After release of the coronary artery ligature, the chest was closed in layers and a dressing was applied. The animal was weaned from the ventilator, but remained intubated and sedated throughout the imaging protocol.

Routine and contrast echocardiograms were again recorded approximately 2 h after reperfusion, just before NMR imaging. Immediately after completion of imaging, a routine echocardiogram was performed (approximately 4 h after reperfusion).

Dogs were allowed to recover for 12 to 14 h. They then were sedated and final routine and contrast echocardiograms were obtained. On completion of the studies, a large dose of pentobarbital sodium was administered and the heart was immediately excised, rinsed and sectioned for pathologic studies.

Tissue preparation. The freshly excised heart was sliced into 1 cm thick short-axis sections and incubated for 10 min in a buffered 1% triphenyltetrazolium chloride solution. This procedure stains viable myocardium dark red and infarcted tissue remains a pale tan color (26). Slices (including the apex) were positioned basal-side up and photographed for later analysis.

Data analysis. To ensure proper alignment of pathologic slices with echocardiographic and NMR images, the apex of the left ventricle was always used as a reference point to define the first slice. Three contiguous sections, each approximately 10 mm thick, were then identified to complete the four slices of the reconstruction. Within each section, proper alignment was achieved by using the papillary muscles and right ventricle as reference landmarks. A limitation of this approach was a failure to include the most basal parts of the left ventricle of the larger animals. Because the infarct zone never involved the base, no significant error was introduced by neglecting this region.

Routine and contrast echocardiograms were analyzed off-line by an investigator unaware of outcome using a computer-based image analysis system (MicroSonics). Systolic function was defined in two ways. Wall thickness was measured in control and ischemic areas at end-systole and end-diastole. Wall thickening was calculated and expressed as a percent according to: end-systolic thickness (cm) − end-diastolic thickness (cm)/end-diastolic thickness (cm) × 100%. Wall thickening was measured throughout the protocol in the same two locations (one ischemic area and one control area).

To provide an index of the functional extent of ischemia, the circumferential extent of abnormal wall motion was calculated. The endocardial perimeter was traced at end-diastole at each short-axis level and summed to provide a total endocardial length. The percent of the total endocardial length demonstrating abnormal wall motion was measured and expressed as: total abnormal endocardial segment length (cm)/total end-diastolic endocardial length (cm) × 100%.

Contrast echocardiography was performed during coronary artery occlusion and during early (2 h) and late (12 to 14 h) reperfusion. The extent of the contrast defect was measured by planimetry of end-diastolic images and expressed as a percent of the total left ventricular area of the four short-axis levels.

The TE 26 and TE 60 short-axis images were analyzed for the presence or absence of a zone of increased signal intensity. Signal intensity was measured by using image analysis software available on the NMR imaging system. Intensity was calculated in operator-defined regions of interest in both ischemic and control areas. The anterior free wall at the left midventricular level was designated as the ischemic area. The inferior wall represented the control area in all

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dogs. At least three regions in each zone were measured, and the results were averaged.

Relative changes in signal intensity were expressed as: signal intensity (ischemic) − signal intensity (control)/signal intensity (control) × 100%. Because signal intensity varies with repetition time, which is heart rate-dependent, comparison of absolute values between dogs and over time is inappropriate (11). By expressing intensity as a percent difference compared with adjacent normal myocardium, such comparisons can be made. The extent of the region of increased signal intensity was measured by planimetry and expressed as a percent of the total left ventricular area determined over the four short-axis levels.

Statistics. Data are presented as mean values ± SD. Differences between groups were compared by two-tailed *t* tests with Bonferroni's correction. Because of a large SD in one group, a Mann-Whitney U test (for nonparametric comparison) was used to assess differences in signal intensity. Changes over time were assessed by repeated measures analysis of variance. Correlation between measurements was made using linear regression analysis. A p value <0.05 was considered significant.

Results

Outcome as a function of duration of coronary occlusion. Outcome was defined by the presence or absence of pathologic evidence of infarction by triphenyltetrazolium chloride staining. Various durations of coronary artery occlusion were employed to simulate successful and unsuccessful reperfusion therapy. The dogs were killed, and the heart was stained approximately 18 h after the onset of ischemia and 12 to 14 h after nuclear magnetic resonance (NMR) imaging. Considerable disparity existed in the duration of occlusion among dogs with and without infarction.

At the time of death, myocardial infarction was present in eight dogs. Infarction developed in four dogs after 180 min of coronary occlusion, in three after 60 min of occlusion and in one after 30 min of occlusion. The remaining eight dogs had no infarction, including one dog that underwent 180 min of occlusion, three with 60 min of occlusion and four with 30 min of occlusion. The duration of coronary artery occlusion was 116 ± 69 min for the dogs with infarction and 51 ± 60 min for those without infarction (p = NS).

Time course of wall thickening and wall motion abnormalities (Fig. 2 and 3). All 16 dogs developed significant abnormalities of wall thickening and regional systolic function during the period of ischemia. Mean wall thickening declined from 36 ± 6% at baseline to 0 ± 5% during coronary artery occlusion in the ischemic zone. There was no difference in the degree of reduction of wall thickening induced by ischemia between the eight dogs with (−1 ± 5%) and the eight without (1 ± 4%) infarction (Fig. 2). The mean circumferential extent of abnormal wall motion was 29 ± 13%. Again, there was no difference in this variable between the dogs with (33 ± 12%) and without (28 ± 13%) infarction (Fig. 3).

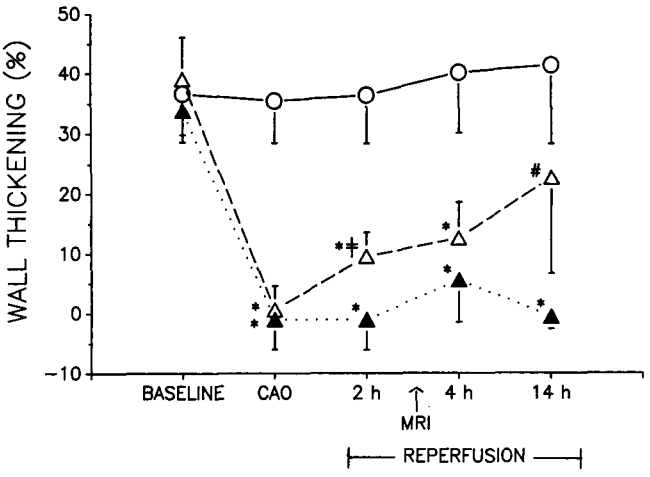

Figure 2. Changes in systolic wall thickening over time in control (**circles**) and ischemic (**triangles**) myocardial zones. **Open triangles** represent the eight dogs without infarction and **closed triangles** represent the eight dogs with infarction. Despite a trend toward improvement in wall thickening in regions with reversible ischemia, systolic function was significantly depressed at the time of NMR imaging (MRI) in both groups. Times refer to number of hours after reperfusion. Data are presented as mean values ± SD. *p < 0.001 versus baseline; ‡p < 0.001 versus infarct group; #p < 0.005 versus infarct group; CAO = coronary artery occlusion.

Regional systolic function remained abnormal before and after NMR imaging in both groups. Wall thickening was

Figure 3. Changes in circumferential extent of abnormal wall motion over time in the group without (**open triangles**) and the group with (**closed triangles**) infarction. Although the extent of abnormal wall motion diminishes over time in the animals with reversible injury, the extent of the abnormality before and after NMR imaging (MRI) was not significantly improved compared with coronary artery occlusion. Values are given as mean values ± SD. *p = NS versus coronary artery occlusion; #p = 0.008 versus coronary artery occlusion. LV = left ventricular; time points and other abbreviations as in Figure 2.

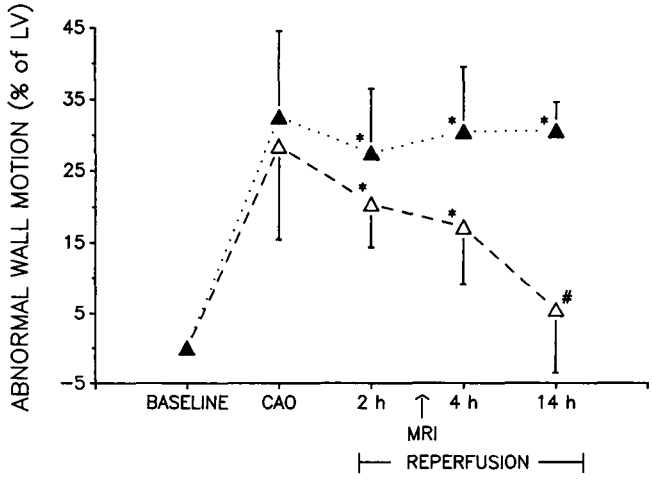

Table 1. Extent of Risk Area, Infarct Size and NMR Imaging Results in Eight Dogs With and Eight Without Pathologic Evidence of Infarction

Dog No.	Duration of Occlusion (min)	Contrast Defect (% of LV) CAO	Early Reperfusion	Late Reperfusion	Pathologic Stain +/−	% of LV	NMR Imaging +/−	% of LV	SI % Difference TE 26	TE 60
No infarction										
2	60	21	15	0	−	0	−	0	4	34
5	30	15	0	0	−	0	−	0	2	23
9	180	29	10	0	−	0	−	0	7	7
11	60	25	0	0	−	0	−	0	28	7
12	30	23	0	0	−	0	−	0	12	11
14	30	19	4	0	−	0	−	0	11	7
15	30	22	5	0	−	0	−	0	13	10
16	60	14	0	17	−	0	−	0	8	1
Mean ± SD	51 ± 60	21 ± 5	4 ± 6†	2 ± 6†		0		0	9 ± 5	13 ± 11
Infarction										
1	60	21	17	13	+	16	+	45	3	105
3	180	36	18	12	+	12	+	24	7	189
4	30	22	15	26	+	9	−	0	3	12
6	180	28	18	20	+	18	+	31	14	132
7	180	22	17	15	+	8	+	18	12	69
8	60	35	17	10	+	4	+	23	10	174
10	60	18	14	19	+	13	+	27	3	223
13	180	30	14	25	+	21	+	42	1	109
Mean ± SD	116 ± 69	27 ± 7	15 ± 4	18 ± 6		13 ± 6		26 ± 14	7 ± 5	127 ± 68*

*p = 0.002 versus no infarct group; †p < 0.001 versus infarct group. All data are in percent, with mean ± SD of the group. CAO = coronary artery occlusion; LV = left ventricle; SI = signal intensity; SI% Difference = (SI ischemic − SI control)/SI control × 100%; + = positive; − = negative.

significantly depressed compared with baseline values at 2 and 4 h of reperfusion (before and after NMR imaging; both $p < 0.001$). However, a trend toward improvement in the group with reversible injury resulted in a significant difference in mean wall thickening between groups ($p < 0.001$ at 2 h and $p < 0.05$ at 4 h after reperfusion).

As with wall thickening, the extent of abnormal wall motion was similar before and after imaging in the two groups. The extent of abnormal wall motion did not change significantly in either group at 2 and 4 h after reperfusion when compared with values after coronary artery occlusion. These findings document that regional systolic function remained depressed in both groups of dogs during NMR imaging. Although a trend toward a decrease in the size of the wall motion abnormality occurred in the dogs without infarction, the difference between the two groups was not significant.

At the time of death, 12 to 14 h after NMR imaging, the dogs with reversible injury demonstrated substantial improvement in both wall thickening and extent of abnormal wall motion. Mean wall thickening had increased to 23 ± 16%. Although this value was still reduced compared with baseline values, the difference was not statistically significant ($p = 0.052$). The extent of abnormal wall motion showed a similar trend ($p < 0.01$ versus occlusion and $p < 0.001$ versus the values in group with infarction). Wall motion was interpreted as normal in five dogs without infarction. In the remaining three dogs, some degree of abnormality persisted even though pathologic evidence of infarction was absent.

Neither wall thickening nor wall motion changed significantly over time in the group with infarction. Thus, by 14 h after reperfusion, the degree of improvement in regional systolic function in the dogs without infarction provided a clear separation between the two groups that did not exist at the time of NMR imaging.

Contrast echocardiography. During coronary artery occlusion, all dogs exhibited a contrast defect ranging from 14% to 36% of total left ventricular area (Table 1). The mean size of the defect was not different between the dogs with (27 ± 7%) and without (21 ± 5%) infarction. The size of the contrast defect decreased in all dogs during early reperfusion and completely disappeared in four (all of which were without infarction), confirming restoration of coronary blood flow. During early and late reperfusion, the extent of the defect was significantly greater in the group with compared with the group without infarction (both $p < 0.001$). Before death, contrast echocardiograms were normal in seven of the eight dogs without infarction and a defect remained in all eight dogs with infarction. Among the eight dogs with infarction, the correlation between the size of the contrast

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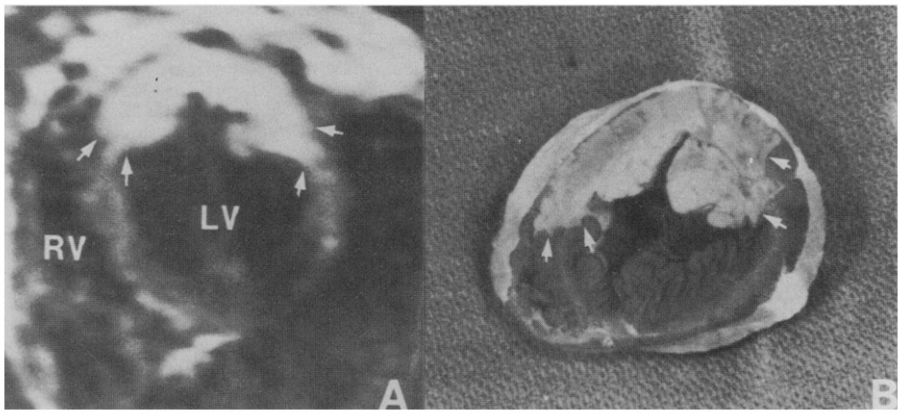


Figure 4. The TE 60 short-axis NMR image (**A**) and corresponding triphenyltetrazolium chloride-stained pathologic slice (**B**) from a dog with a large anterior transmural infarction. This dog underwent 3 h of coronary artery occlusion before reperfusion. The extent of the area of increased signal intensity correlated well with the size of the infarct (**arrows**). LV = left ventricle; RV = right ventricle.

echocardiographic defect and pathologic infarct size was not significant.

NMR imaging (Table 1). Imaging was performed 2 to 3.5 h (mean 2.7 ± 0.5) after the onset of reperfusion. Multislice TE 26 and TE 60 short-axis images were reviewed independently by two observers, both unaware of the echocardiographic and pathologic data. Agreement on the presence or absence of a region of increased signal intensity on the TE 60 scans occurred in all cases. With TE 60 scans, an area of increased signal intensity, corresponding to the region of myocardial ischemia, was detected in seven of the eight dogs with infarction (Fig. 4 and 5) and none of the remaining eight dogs without infarction (Fig. 6).

The mean increase in signal intensity in the ischemic (anterior) wall corrected for the control (inferior) wall was 127 ± 68% for the dogs with and 13 ± 11% for those without infarction ($p = 0.002$) (Fig. 7). With TE 26 images, signal intensity was unchanged in the anterior versus inferior wall irrespective of the presence or absence of infarction (Fig. 8).

In the seven dogs demonstrating increased signal intensity on the TE 60 images, the size of the zone of increased signal intensity ranged from 15% to 45% of the total left ventricle. The size of the region of increased signal intensity correlated with the pathologic extent of infarction ($r = 0.69$) (Fig. 4 and 9). Overestimation of infarct size by NMR imaging occurred in seven of eight dogs (Fig. 5); the degree of overestimation was approximately 4% of the total left ventricular area. However, if the single dog in the infarct group with a false-negative NMR imaging result was excluded, the degree of overestimation was even greater (approximately 12%). The size of the zone of increased signal intensity failed to correlate with the size of the contrast echocardiographic defect during occlusion ($r = 0.09$).

Discussion

The major finding of this study is that stunned but viable myocardium can be distinguished from acutely infarcted tissue. This determination can be made within a few hours of reperfusion at a time when contractile function is still impaired and the issue of viability remains unsettled. It was further demonstrated that using high field nuclear magnetic resonance (NMR) imaging, a TE 60 pulse sequence is useful in detecting reperfusion myocardial infarction early in its course. Infarcted myocardium appears as a region of increased signal intensity in high contrast to adjacent normal tissue. The approach described in this study does not require the use of paramagnetic contrast agents such as gadolinium-diethylenetriamine pentaacetic acid (DTPA). Finally, the area of increased signal intensity correlates with infarct size

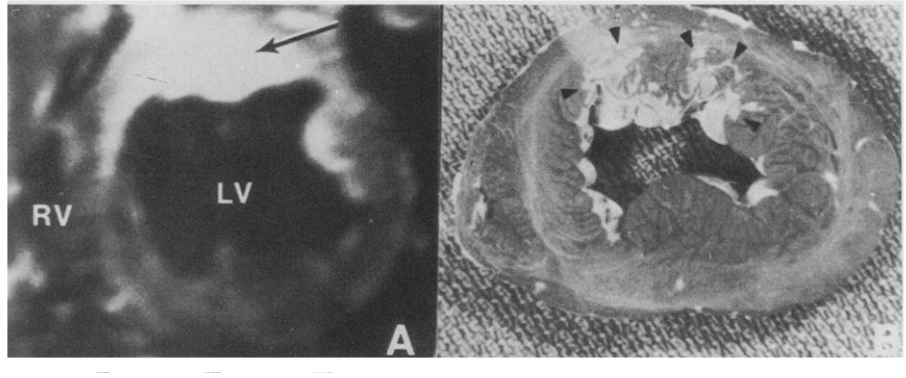


Figure 5. The TE 60 short-axis NMR image (**A**) and corresponding triphenyltetrazolium chloride-stained specimen (**B**) from a dog subjected to 3 h of coronary artery occlusion. Despite the duration of occlusion (similar to that in the dog in Fig. 4), the infarct was small, patchy and predominantly subendocardial (**black arrowheads**). The region of increased signal intensity on the NMR image (**large arrow**) was more transmural, leading to overestimation of infarct size. Abbreviations as in Figure 4.

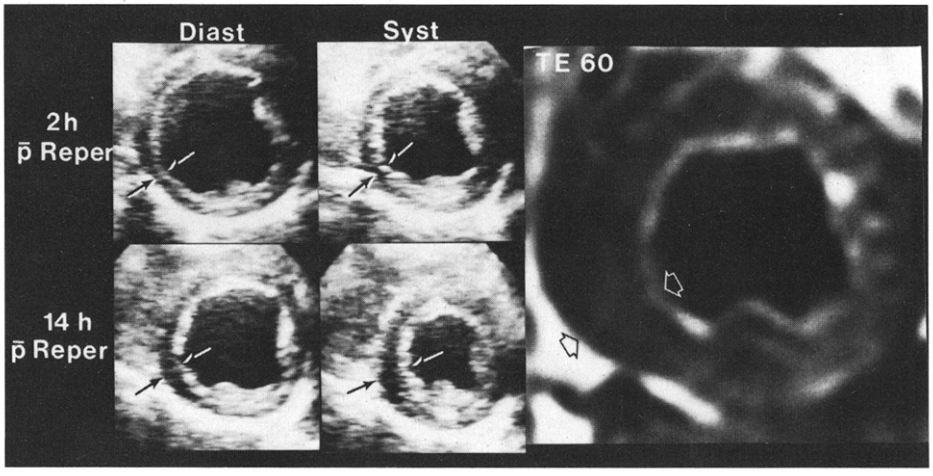
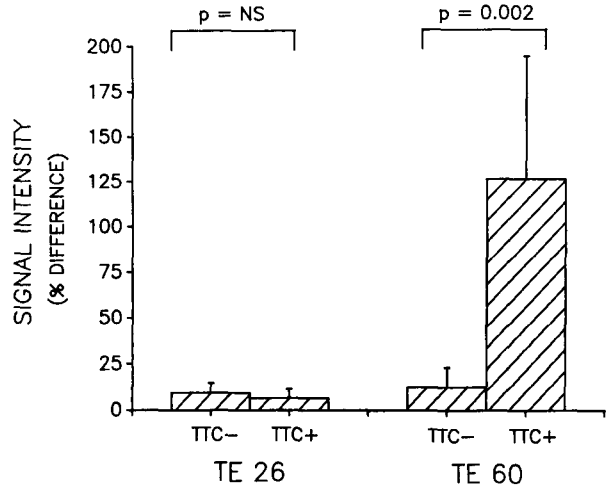


Figure 6. Short-axis echocardiograms at end-diastole (Diast) and end-systole (Syst) and the corresponding TE 60 NMR imaging from a dog that underwent 1 h of ischemia before reperfusion (p̄ Reper). At 2 h of reperfusion (just before NMR imaging), diastolic thinning and reduced systolic thickening were apparent in the ischemic zone (**arrows**). After 14 h of reperfusion (**bottom two images**), wall thickening had improved. The NMR image revealed no visually apparent change in signal intensity in the corresponding anterior region (**open arrows**).

and not risk area as delineated by contrast echocardiography. However, overestimation of infarct size by NMR imaging consistently occurred.

Comparison with other studies. These results are consistent with and extend the observations of other investigators. To assess viability after experimental myocardial ischemia, McNamara et al. (23) performed NMR imaging with and without gadolinium-DTPA on explanted dog hearts. In their study, animals were subjected to 15 or 60 min of ischemia, followed by 22 h of reperfusion, and then imaged at 0.35 tesla. The main difference between that study and ours is that we performed NMR imaging in vivo at 2 to 3.5 h (as opposed to 22 h) after reperfusion while contractility remained depressed and the question of reversibility remained. In the study by McNamara et al. (23), systolic function was not measured and imaging was performed ex vivo. It is quite likely, however, that with 15 min of ischemia followed by 22 h of reperfusion, wall motion had normalized at the time of imaging so that the issue of viability was no longer in doubt. Conversely, in the dogs with infarction, the persistence of a wall motion abnormality at 22 h would favor irreversible injury.

Figure 7. Bar graph demonstrating the percent difference in signal intensity in the ischemic zone (anterior wall) compared with the control zone (inferior wall). With a TE 26 pulse sequence (**left**), there was no significant difference in the change in signal intensity between the group with and without infarction (TTC+ and TTC−, respectively). Using a TE 60 pulse sequence (**right**), a marked increase in signal intensity (127 ± 68%) developed in the group with infarction (TTC+) compared with those animals with reversible injury (TTC−). This difference was highly significant ($p = 0.002$). TTC = triphenyltetrazolium chloride. Data are presented as mean values ± SD.



Johnston et al. (21) subjected a series of dogs to 3 h of coronary occlusion, followed by 1 h of reperfusion. In vivo NMR images were obtained during occlusion, and imaging after reperfusion was performed on the nonbeating, drained heart. All eight dogs with histochemical evidence of infarction demonstrated an area of increased signal intensity on TE 60 images of nonbeating hearts. As in our study, no increase in signal intensity was evident on T_1-weighted images. Of four dogs without infarction, only one demonstrated increased signal intensity on the TE 60 images. In contrast to our study, in vivo imaging after reperfusion was not done and the presence or absence of myocardial stunning at the time of imaging was not determined.

Tscholakoff et al. (22) assessed signal intensity and relaxation times of canine myocardium subjected to 1 h of ischemia, then reperfusion. In that study, systolic wall thickness was measured using NMR imaging to document a lack of thickening during occlusion and restoration of thickening with reperfusion. At autopsy, 7 of 10 surviving dogs had evidence of infarction. By 60 min of reperfusion, systolic wall thickness had partially normalized in dogs with or without infarction. The authors (22) concluded that a reperfused infarct could be detected as early as 30 min after reperfusion. Although the identification of stunned myocardium was not specifically addressed, their findings in the three dogs without infarction are consistent with our obser-

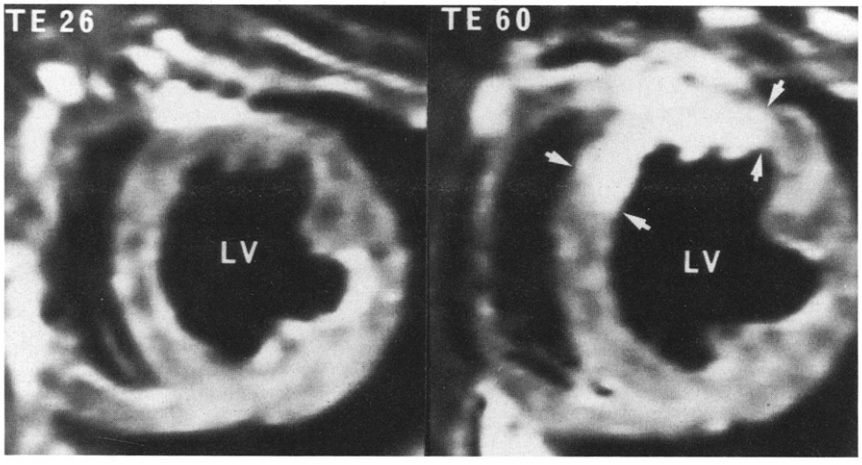
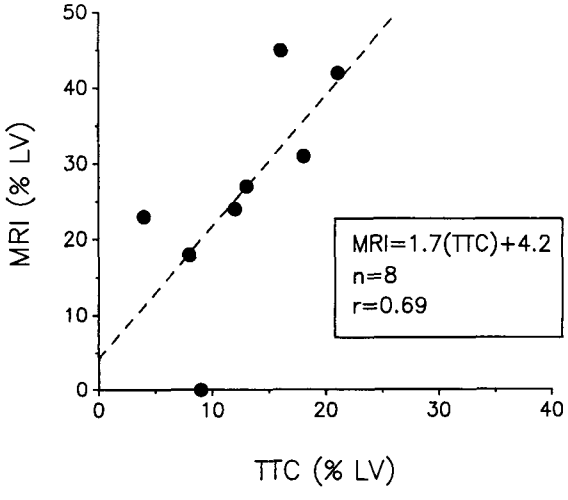


Figure 8. Corresponding short-axis NMR images are shown from a dog with myocardial infarction. The TE 26 pulse sequence (**left**) revealed no apparent change in signal intensity in the anterior wall. The TE 60 pulse sequence (**right**) demonstrated a large area of increased signal intensity (**arrows**) in the anteroseptal region of the left ventricle (LV).

vations. However, because regional systolic function was not directly measured and systolic wall thickness had partially normalized in both groups, it is not known whether the ischemic zone remained dysfunctional at the time of imaging.

Although similarities exist between these previous studies and ours, fundamental differences should be mentioned. Our study was specifically designed to assess viability early after reperfusion. Thus, in vivo imaging was performed soon after reperfusion at at time when abnormal regional function precluded an accurate determination of viability by standard echocardiographic criteria. Because the time course of recovery of systolic function is variable and unpredictable (27), depressed regional systolic function was confirmed both before and after NMR imaging. This documentation, unique to the current study, provides evidence that NMR imaging may be more useful in predicting myocardial salvage soon after attempted reperfusion than are techniques that depend on wall motion variables.

Figure 9. Infarct size versus extent of increased signal intensity. Infarct size is presented as percent of left ventricle (LV) determined by triphenyltetrazolium chloride (TTC) staining of short-axis slices. The size of the area of increased signal intensity was measured by planimetry of corresponding short-axis TE 60 images. Despite the positive correlation, significant overestimation by NMR imaging (MRI) is apparent. If the dog with the false-negative magnetic resonance imaging result is excluded, the degree of overestimation is approximately 12%.



Positron emission tomography has also been shown to identify viable myocardium. By detecting evidence of ongoing cellular metabolism, the technique can identify and localize regions of viable tissue. Such regions have been detected in association with reduced myocardial blood flow, decreased thallium uptake, ECG Q waves and localized asynergy (28,29). Although this method provides extremely useful information concerning tissue viability, widespread application is limited. To date, no studies have compared positron emission tomography with NMR imaging for predicting myocardial salvage after reperfusion.

Detection of myocardial infarction. Our study further demonstrated that NMR imaging can be used to detect evidence of myocardial infarction relatively early in its course. This finding is consistent with the results of several previous investigations (9,11–13,17). Areas of infarction are consistently identified after several hours and may be detected even earlier, particularly if coronary occlusion is followed by reperfusion or if gadolinium-DTPA is employed (20,23). In the current study, seven of eight infarcts were detected between 3 and 6 h after occlusion. The study was not designed to determine when the increased signal intensity first developed; other investigators (22) have shown that this may occur as early as 30 min after reperfusion.

Overestimation of infarct size by NMR imaging. The size of the zone of increased signal intensity correlated with but overestimated infarct size in our study. This finding is in agreement with most other reports (10,13,15), as well as our previous experience (30). In reperfused myocardial infarction, this overestimation may occur because NMR imaging reflects risk area rather than infarct zone. Recently, risk area

was accurately measured with NMR imaging when gadolinium-DTPA was administered 5 min after reperfusion and T_1-weighted scans of the explanted heart were obtained 1 to 2 h later (31). However, no such correlation could be demonstrated in our study, in which risk area was defined using contrast echocardiography. Although the true risk area is difficult to quantify in vivo (32), previous investigations (25) have confirmed that the extent of contrast defect during coronary occlusion as determined by contrast echocardiography correlates well with the percent of left ventricle "at risk" assessed by autoradiography. The lack of correlation between NMR imaging and risk area in our study may, in part, reflect the inherent difficulty in quantifying the zone at risk by any noninvasive technique. In addition, the protocol employed in our study may further explain the lack of correlation. Because NMR imaging was performed at a mean of 2.7 ± 0.5 h after reperfusion (rather than during occlusion), the failure of NMR imaging to reflect risk area should not be surprising.

Advantages of measuring signal intensity. In our study, tissue contrast was expressed as relative signal intensity rather than calculated relaxation times (T_1 and T_2). Values for T_1 and T_2 were not calculated because of the concern that, in the beating heart, relaxation times are sensitive to motion. Thus, differences in relaxation time values between normal and ischemic regions may be influenced by changes in regional cardiac motion resulting from ischemia, as well as by true changes in relaxation times. Likewise, absolute signal intensity values were not used for comparison because signal intensity is dependent on repetition time, which is also heart rate dependent. Thus, absolute intensity varies over time unless heart rate is controlled. We chose to report relative changes in signal intensity in which data are expressed as a percent change corrected for the level of intensity of nearby normal myocardium. This method facilitates comparison of changes in signal intensity within individual animals and among different animals over time (11,21,22).

Limitations. A limitation of this study is the comparison of multislice NMR images obtained throughout the cardiac cycle with corresponding echocardiographic images obtained at end-diastole. This is an inherent limitation of multislice spin-echo NMR imaging. The four slices are collected at uniform intervals after the R wave, all within a single cardiac cycle. A sufficiently long repetition time (>2,500 ms) is programmed to allow adequate recovery for T_2 weighing. Thus, each slice is collected at a different time within the cardiac cycle. Although this causes wall thickness (and slice area) to vary from one slice to the next, the error introduced is relatively small.

Within each image slice, the ratio of increased signal intensity area to total slice area should remain relatively constant over a cardiac cycle. For example, if at end-diastole the area of increased signal intensity was 30% of total slice area, the percent would be slightly less at end-systole because greater thickening of the normal zone would increase total area more than the infarct area. This unavoidable phenomenon would have an acknowledged impact on quantification of NMR images. The alternative would be to perform four sequential single slice TE 60 scans, all at end-diastole. This would cause unacceptable prolongation of total imaging time.

A second limitation of this study was our decision not to quantify myocardial blood flow. It is known that reduced blood flow during coronary artery occlusion can be qualitatively assessed using contrast echocardiography (24,25). This same approach can be used to demonstrate restoration of flow during reperfusion and, if necessary, to detect the "no reflow" phenomenon. Because our primary objective was to correlate changes in NMR images with functional variables of contractility and pathologic infarct size, quantification of myocardial blood flow itself was not deemed necessary. However, because flow was not quantified, the potential contribution of collateral flow during occlusion or reperfusion, or both, cannot be excluded.

Clinical implications. The determination of the success of interventions designed to salvage myocardium may be impossible early in the course of acute myocardial infarction. The difficulty stems from the inability of methods measuring regional systolic function to distinguish stunned from infarcted myocardium (2,3). Because transiently ischemic myocardium may remain stunned for days or weeks, patient management during this period is hampered by uncertainty about the fate of the myocardium. For example, if viability was demonstrated, strategies designed to prevent reinfarction could be vigorously implemented. Alternatively, if significant irreversible injury had already occurred, a more conservative approach might be undertaken. These same issues apply to the chronic setting when myocardial dysfunction may be secondary to either scar or "hibernating" myocardium. This differentiation is also difficult, but has considerable clinical significance.

In the usual clinical situation, myocardial salvage is rarely an "all or none" phenomenon. Some degree of myocardial necrosis usually accompanies even the most successful interventions. Therefore, a quantitative approach is necessary, and the ability to measure the fraction of the risk area that has suffered irreversible damage becomes critical to clinical decision making.

In the current study, the potential for NMR imaging to provide this clinically relevant information has been demonstrated. If these observations can be confirmed and extended to human studies, NMR imaging may prove useful in the management of patients after administration of thrombolytic therapy. In that setting, accurate quantitative information on the degree of myocardial salvage will have substantial impact on subsequent patient management. Although the practical concerns with regard to imaging critically ill patients

soon after myocardial infarction are acknowledged, greater clinical experience and technologic advances should enhance the feasibility of NMR imaging in this patient subset.

Conclusions. Nuclear magnetic resonance imaging can be applied early after reperfusion to determine the viability of dysfunctional myocardium. By using a TE 60 multislice spin-echo imaging sequence at 1.5 tesla, identification and quantitation of the extent of infarction may be possible. This approach warrants further study to determine its potential role in the management of patients with myocardial infarction who are subjected to interventions designed to salvage myocardium.

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