Imaging and characterization of acute myocardial infarction in vivo by gated nuclear magnetic resonance

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ABSTRACT Imaging by nuclear magnetic resonance (NMR) techniques has been shown to provide high-contrast resolution between soft tissues and characterization of normal and pathologic tissues by differences in magnetic relaxation times. The current study was designed to determine whether electrocardiogram (ECG)-gated NMR imaging of the canine heart in vivo could distinguish normal from infarcted myocardium without the use of intravenous paramagnetic contrast agents. Seven dogs were studied by ECG-gated NMR imaging in vivo (spin-echo technique) with a 0.35 Tesla superconducting magnet at 2 to 7 days after ligation of the left anterior descending coronary artery. In six of the seven dogs, signal intensity was increased in the anterior wall compared with the remainder of the left ventricle; this region of high signal intensity corresponded to the area of myocardial infarction demonstrated at postmortem examination. The signal intensity of the infarcted region was 66 ± 27% greater than that of normal myocardium (p < .01). The T2 (spin-spin) relaxation time was 69 ± 3% longer in the infarcted myocardium as compared with normal myocardium (p < .01). The NMR images from the seventh dog had uniform signal intensity throughout the myocardium of the left ventricle. An infarct was not evident on postmortem examination in this dog. Thus gated NMR imaging in vivo by the spin-echo technique displays acute myocardial infarctions as regions of high signal intensity without the use of contrast media. The infarct is characterized by a prolonged T2 relaxation time.

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TOMOGRAPHIC IMAGING of the hydrogen nucleus by proton nuclear magnetic resonance (NMR) techniques offers potential advantages for imaging the cardiovascular system. The lumen of blood vessels and the cardiac chambers display essentially no NMR signal by the spin-echo imaging technique because of the high velocity of the protons in blood. This allows a high degree of signal contrast between moving blood and the walls of blood vessels and cardiac chambers without the need for intravenous paramagnetic contrast media. NMR imaging also offers the potential for characterization of tissues and biological fluids by T1 and T2 relaxation times, spin (hydrogen) density, and possibly spin-diffusion constants.

Many pathologic processes, including acute myocardial infarction, are associated with an increased regional water content. Previous NMR spectrometric studies of tissue samples in vitro have demonstrated prolonged T1 relaxation times in infarcted myocardium relative to normal myocardium. Although an early report of experiments with hearts ex situ suggested that acute myocardial infarctions could be discriminated from normal myocardium only in the presence of a paramagnetic contrast medium, more recent reports suggest that infarcts can be detected without contrast media.

Previous investigations with proton NMR imaging in our laboratory have also demonstrated prolonged T1 and T2 relaxation times of acutely infarcted skeletal muscle in the rat (in vivo) and in excised canine hearts with acutely infarcted myocardium. Both of these studies used the spin-echo imaging technique and found that the NMR signal intensity was perceptibly increased in the infarcted muscle as compared with normal muscle.

The purposes of this study were to determine whether electrocardiogram (ECG)-gated proton NMR imaging could detect myocardial infarction without the use of contrast media.
of paramagnetic contrast media and whether infarcted myocardium could be uniquely characterized from normal myocardium by T2 relaxation times.

Methods

Seven adult mongrel dogs weighing 21 to 27 kg underwent operative ligation of the left anterior descending coronary artery (LAD) distal to the first septal branch. One dog underwent NMR imaging at 2 days after ligation; the other six dogs underwent NMR imaging at 7 days after ligation.

The dogs were preanesthetized with 1 mg/kg morphine sulfate administered subcutaneously 45 min before NMR imaging. General anesthesia was produced with pentobarbital sodium, 15 to 20 mg/kg. The animals were intubated with an endotracheal tube but were not mechanically ventilated. The metallic respirator could not be used in the immediate environment of the NMR imager because of the need to avoid proximity of ferromagnetic devices to the imager’s static magnetic field. NMR imaging was performed with a 0.35 Tesla superconducting magnet system previously described. At this field strength the hydrogen resonant frequency was 15 mHz.

Nonferromagnetic ECG leads were placed on the dog’s chest. An ECG-gating device was used to trigger data acquisition (radiofrequency and gradient pulsing) to begin 2 msec after the peak of the R wave. Five contiguous 7 mm thick anatomic slices were obtained during each imaging sequence. The gated data acquisition for each successively caudal slice was 100 msec later than the preceding slice, and consequently each of the five slices were obtained during a different interval of the cardiac cycle. The five slices obtained were from mid-LV to apex. Two spin-echo signals were routinely acquired at 28 and 56 msec (TE parameters) after the 90 degree RF pulse. The RF pulse repetition rate (TR parameter) was dependent on the dog’s heart rate (which ranged from 80 to 120 beats/min in this study). The TR was equivalent to the RR interval of the ECG. Repeated small intravenous doses of atropine (less than 0.1 mg) were used to maintain a regular heart rate above 80 and below 120 beats/min. A series of gated NMR images (consisting of five adjacent axial sections) was obtained in approximately 4.5 to 6.5 min.

The spin-echo signal intensity is related to the following NMR variables by the equation

\[
I = N(H)(v)\exp(-TE/T2)\left[1 - \exp(-(TR/T1))\right]
\]

where: \[I\] = NMR signal intensity, \[N(H)\] = spin density (hydrogen), \(v\) = proton velocity function, \(TE\) = time to reception of spin-echo signal (28 or 56 msec after 90 degree RF pulse), \(T2\) = spin-spin relaxation time, \(TR\) = RF pulse repetition rate (heart rate, gating sequence, dependent in this study), and \(T1\) = spin-lattice relaxation time.

With the spin-echo technique, focal signal intensity of the NMR image is increased with shortening of T1 relaxation time, lengthening of the T2 relaxation time, and increased proton (hydrogen) concentrations.

Data analysis. For each series of NMR images, spin-echo intensity values (in arbitrary units of magnitude in the frequency domain after Fourier transformation of the time domain data) were calculated for normal and infarcted myocardium by operator-defined regions of interest. Regions of interest consisted of more than 50 voxels for infarcted myocardium and more than 100 voxels for normal myocardium. Technically satisfactory first-echo images (\(TE = 28\) msec) and second-echo images (\(TE = 56\) msec) were both obtained in four of the seven dogs. In these four dogs, T2 relaxation times were calculated by computer from the values for NMR signal intensity of each voxel in the same region of interest of the two spin-echo images. In the other three dogs, only satisfactory first-echo images (\(TE = 28\) msec) were obtained. Thus T2 could not be calculated in these three animals. The T1 relaxation times could not be calculated in this study because this requires intensity data obtained at two different TR values with our spin-echo imaging technique. With gating the TR is defined by the RR intervals. In the current study only images gated to every heart beat were obtained.

The following formula was used to calculate the percent difference in spin-echo signal intensity (1) and T2 relaxation times between infarcted and normal myocardium:

\[
\text{percent difference} = \frac{I(\text{or } T2)_{\text{infarct}} - I(\text{or } T2)_{\text{normal}}}{I(\text{or } T2)_{\text{normal}}} \times 100%
\]

Twenty-four hours after imaging studies, the dogs were killed by an overdose of pentobarbital. After cardiecotomy, the hearts were cut into axial sections from apex to base at intervals of 10 mm. Each myocardial slice was placed onto clear film overlays. The inner and outer borders of the myocardium on each slice and the area of grossly visible infarction were drawn onto the film for correlation of the site of the infarction with the region of abnormal signal intensity on NMR images. Histochmical staining was not necessary to delineate the infarcts at this time after coronary arterial ligation. Moreover, the staining procedure would have precluded measurements of water content. The NMR images were compared with anatomic film overlays to correlate the NMR images with the actual site of the myocardial infarctions.

Tissue samples were cut from grossly infarcted and normal myocardium for determination of percent water content. Each sample was weighed (Metlar balance) initially (wet weight) and after drying to a constant weight (72 hr) in a desiccating oven. Percent water content was calculated by the formula

\[
\text{percent water content} = \frac{\text{wet weight} - \text{dry weight}}{\text{wet weight}} \times 100%
\]

Statistical analysis. All data are expressed as mean ± SD. The statistical significance of the difference between normal and infarcted myocardium for all variables was evaluated by the paired Student’s t test.

Results

Pathology. Grossly visible myocardial infarctions were observed in six of the seven dogs at postmortem examination. One dog (No. 1) had no evidence of infarction at postmortem examination. In each case, the infarct was located in the anterior segment of the left ventricle on every myocardial slice caudal to the ligature on the proximal LAD. Each infarct extended nearly to the full circumference at the level of the left ventricular apex. Extension of the infarcts to involve the anterior portions of the interventricular septum or the lateral wall of the left ventricle was also noted in some dogs. The percent water content of the infarcted myocardium (79.0 ± 0.9%) was significantly (p < .05) greater than that of the normal myocardium (75.9 ± 0.7%).

NMR imaging in vivo. An ECG-gated NMR image through a cross-sectional level of the left ventricle below the mitral valve of the dog that did not have an infarct is shown in figure 1. The NMR signal intensity was uniform in all regions of the left ventricular myo-
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FIGURE 1. ECG-gated first spin-echo NMR images (TE = 28 msec) at a heart rate of 120 beats/min. A 7 mm thick slice through the heart of a normal dog (No. 1) at the level of middle left ventricle is shown. Soft tissue adhesions are present between the left side of the heart and the thoracotomy site (right).

The ECG-gated NMR images of the hearts of the six dogs with postmortem evidence of infarction after LAD ligation showed regions of distinctly high signal intensity in the anterior segment of the left ventricle (figures 2 to 5). In each instance the region of high signal intensity conformed to the site of gross infarction at postmortem examination. This high intensity region was visible on both first (TE = 28 msec) and second (TE = 56 msec) spin-echo images (figures 2 and 5). The region of high signal intensity in infarcted myocardium was homogenous in two dogs (figure 2) and heterogeneous in four (figure 4). A “rim” of greater signal intensity was noted in the subendocardial region of the anterior segment of the left ventricle (figures 4 and 5).

In concordance with postmortem findings, the infarcts extended from the middle of the left ventricle to the apex (figure 4). At the apex the infarct involved most of the circumference of the left ventricle.

The effect of different spin-echo delays (TE) on the regional signal intensity of the infarct on the NMR image is shown in figure 5. There was an increase in contrast between infarcted and normal myocardium on images produced from the second echo (TE = 56 msec); the difference in signal intensity of the infarct compared with normal myocardium was even greater with this imaging parameter. From images of the same transverse slice with two echo delay times, a T2 image was calculated, which demonstrated a moderately prolonged T2 relaxation time throughout the infarct and an even longer T2 time in the subendocardial region compared with normal myocardium and the remainder of the infarct.

FIGURE 2. First-echo (TE = 28 msec, left) and second-echo (TE = 56 msec, right) gated NMR images (dog 2) displaying high signal intensity in the anterior infarct.
**NMR parameters.** The spin-echo intensity values and T2 relaxation times for normal and infarcted myocardium in vivo in the seven dogs are presented in tables 1 and 2. Signal intensity values in the region of the myocardial infarction (anterior segment) (4157 ± 1890 units) were significantly increased (p < .01) relative to normal myocardium (lateral segment) (2781 ± 1380 units) in all six dogs with infarcts. The T2 relaxation times were significantly prolonged (p < .01) in the infarct region (51.5 ± 4.4 msec) compared with normal myocardium (30.4 ± 2.9 msec) in the three infarcted dogs with satisfactory first and second spin-echo images. The signal intensity (on first echo images) of infarcted myocardium compared with normal myocardium was increased by 65.7 ± 27.0% SD (n = 6). The T2 relaxation times of infarcted myocardium compared with normal myocardium was increased by 69.2 ± 3.4% SD (n = 3).

**Discussion**

The current study shows that proton NMR imaging (spin-echo technique) in living dogs detects infarcted myocardium as clearly defined regions of increased signal intensity compared with normal myocardium.

**FIGURE 3.** First-echo gated NMR image (dog 3), showing increased signal intensity in the anterior region, with highest signal intensity in the subendocardial region. This is compatible with a gradient in myocardial edema toward the subendocardial layer.

**FIGURE 4.** Successive cranial-to-caudal, contiguous gated spin-echo NMR images (dog 7) depicting high signal intensity in this large anterior infarction that extended into the septum and lateral walls at caudal levels. Note the predominant subendocardial location of edema on the most cranial image (left).
Electrocardiographic gating provides diagnostic quality images of the beating heart; the normal and infarcted myocardium are sharply delineated from intracavity blood and surrounding structures without the need for contrast media. Regions of high spin-echo signal intensity in infarcted myocardium result from prolonged T2 relaxation times and probably from increase in hydrogen (spin) density. The T1 myocardium time has also been shown to be different for normal and infarcted myocardium in previous studies with tissue samples obtained from dogs with induced acute myocardial ischemia, from excised hearts, and from hearts in vivo during gated imaging. The use of only a single repetition rate (TR) in our study in vivo precluded the estimation of T1 time.

An earlier study with spin-echo NMR imaging of the whole heart within the first hour after death also demonstrated increased signal intensity of infarcted myocardium compared with normal myocardium. In each animal the T1 and T2 times of infarcted myocardium were prolonged as compared with normal myocardium. There was a close linear relationship between T2 relaxation time and percent water content of the myocardial regions. Despite the T1 prolongation in the infarct (which acts to decrease signal intensity on NMR images), high signal intensity in the infarct was found in the current study in vivo and in the previous study with the heart ex situ. This is likely because the T2 changes (lengthening in this case) predominate over T1 changes for the spin-echo technique, which is more heavily influenced by the T2 factor. The spin-echo NMR pulse sequences have the ability to display edematous tissue with prolonged T2 relaxation times.

**FIGURE 5.** First-echo (top left), second-echo (lower left), and calculated T2 (upper right) gated images of myocardial tissue from the same dog as in figure 4 (dog 7), illustrating the higher signal intensity at the site of the infarction on the second-echo image due to the long T2 relaxation time (arrow). The subendocardial high-intensity “rim” is depicted in the calculated T2 image as having a longer T2 relative to both the remainder of infarct and normal myocardium.

**TABLE 1**

<table>
<thead>
<tr>
<th>Dog</th>
<th>LV region of interest</th>
<th>Signal (ppm)</th>
<th>Intensity (SD)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td>3671</td>
<td>273</td>
</tr>
<tr>
<td>2</td>
<td>Normal</td>
<td>5331</td>
<td>516</td>
</tr>
<tr>
<td>3</td>
<td>MI</td>
<td>7764</td>
<td>1137</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>1384</td>
<td>227</td>
</tr>
<tr>
<td>4</td>
<td>MI</td>
<td>2549</td>
<td>389</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>2355</td>
<td>277</td>
</tr>
<tr>
<td>5</td>
<td>MI</td>
<td>4472</td>
<td>271</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>2152</td>
<td>287</td>
</tr>
<tr>
<td>6</td>
<td>MI</td>
<td>3390</td>
<td>469</td>
</tr>
<tr>
<td></td>
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<td>2945</td>
<td>610</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>3036</td>
<td>268</td>
</tr>
<tr>
<td>Group mean</td>
<td>MI</td>
<td>3823</td>
<td>358</td>
</tr>
</tbody>
</table>

LV = left ventricular; MI = region of myocardial infarction.

^Standard deviation for the intensity values of the pixels within the region of interest.

^Standard deviation for the intensity values among the animals in each group (normal and MI).

**TABLE 2**

<table>
<thead>
<tr>
<th>Dog</th>
<th>LV region of interest</th>
<th>T2 (msec)</th>
<th>Intensity (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td>34.3</td>
<td>3.9</td>
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<tr>
<td>2</td>
<td>Normal</td>
<td>32.2</td>
<td>6.4</td>
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<td>6</td>
<td>MI</td>
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<td>20.7</td>
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<tr>
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<td>MI</td>
<td>46.5</td>
<td>18.6</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>32.0</td>
<td>3.7</td>
</tr>
<tr>
<td>Group mean</td>
<td>MI</td>
<td>52.9</td>
<td>11.2</td>
</tr>
</tbody>
</table>

LV = left ventricular; MI = region of myocardial infarction.

^Standard deviation for the T2 values of the pixels within the region of interest.

^Standard deviation for the T2 values among the animals in each group (normal and MI).
as high signal intensity (T2 dominates), while T1 weighted pulse sequences (inversion-recovery and saturation recovery) should display edematous tissue as low signal intensity because of the prolonged T1 time. However, Pohost et al., in a preliminary report, found increased signal intensity in gated saturation-recovery imaging of three 72-hr-old canine myocardial infarctions, perhaps due to focally increased hydrogen spin density.

The prolonged T2 relaxation time in infarcted myocardium is probably related to an increase in the “free” or “unbound” fraction of water protons in the edematous tissue. Water content is increased in myocardial infarcts. Increasing the percentage of fast-tumbling, “free” protons (not bound to macromolecules) with shorter molecular correlation times makes both T1 and T2 relaxation less efficient, resulting in prolonged T1 and T2 times. This inefficiency results from the very-rapidly changing magnetic fields created by the tumbling proton magnetic dipoles. Only a small frequency component of these varying magnetic fields is effective in promoting T1 relaxation of adjacent water protons. Very little local magnetic field inhomogeneity results from the very-rapidly changing proton magnetic dipoles, causing spin-phase coherence to last longer. Thus T1 and T2 would be expected to be prolonged in edematous myocardium. Normal myocardium, with a higher percentage of macromolecular-bound water, probably has more efficient T1 and T2 relaxation because of the slower velocity of the tumbling proton dipoles and their associated magnetic fields.

In conclusion, the results of this study in vivo with gated proton NMR imaging demonstrated greater signal intensity of infarcted myocardium compared with normal myocardium, and good discrimination of infarcted from normal myocardium was possible without the need for paramagnetic contrast media. The infarcted tissue could be differentially characterized from normal myocardium by its T2 relaxation time.

References

Imaging and characterization of acute myocardial infarction in vivo by gated nuclear magnetic resonance.
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