Early detection of canine myocardial infarction by magnetic resonance imaging in vivo

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ABSTRACT This study was undertaken to assess the ability of proton magnetic resonance imaging (MRI) to detect myocardial ischemia shortly after coronary artery occlusion. Fifteen dogs were studied before and serially for up to 6 hr after anterior descending or circumflex coronary artery ligation in vivo by gated MRI with a 0.15 tesla resistive magnet (resonant frequency of hydrogen 6.25 MHz). Image acquisition was by single-spin echo, with echo times (TE) of 30 msec and TE 60 msec, and modified inversion recovery pulse sequences. Excellent anatomic definition was observed. By 4 hr after coronary artery occlusion the signal in the infarct zone increased to 36 ± 20% greater than that in the adjacent normal myocardium for the TE 30 msec sequence (p < .01) and to 116 ± 100% for the TE 60 msec sequence (p < .05). The most intense increase in signal was noted with the TE 60 msec pulse sequence and because normal myocardium is not well visualized by this technique, acutely ischemic myocardium was clearly delineated. Inversion recovery imaging did not show areas of ischemia. Changes seen on MR images correlated well with the location of ischemic changes noted on microscopic examination of the excised hearts. MRI thus provides a noninvasive means for detection of ischemia early in the course of myocardial infarction.


ENTHUSIASM for limiting the extent of myocardial necrosis associated with acute myocardial infarction has heightened in recent years with the appreciation that patient prognosis is to a large part dependent on the amount of myocardial destruction. It has been shown that reperfusion of ischemic myocardium early in the course of infarction is feasible, whether by intracoronary or intravenous streptokinase, transluminal coronary angioplasty, or by immediate surgical revascularization. Drugs such as β-blockers and nitrates have also been used early in the course of myocardial infarction in an attempt to limit infarct size. Whether these interventions do indeed salvage reversibly ischemic myocardium is currently a subject of extensive interest and investigation.

To demonstrate benefit from such interventions, it is necessary to employ a technique whereby myocardium at risk can be identified at a very early stage and infarct size can be accurately and reproducibly quantified. Creatine kinase analysis, multivariate electrocardiography, echocardiography, radionuclide wall motion analysis, and thallium scintigraphy are all practical tools that can estimate the extent of early myocardial injury, although each has its limitations.

Proton magnetic resonance imaging (MRI) is rapidly emerging as a high-resolution noninvasive technique that is potentially useful for cardiovascular imaging. Not only can MRI provide excellent anatomic definition of the heart, but it also may be able to clearly define regions of metabolic derangement such as those seen in patients with ischemia or infarction. Studies in vitro of excised hearts have demonstrated the ability to clearly visualize and accurately quantify the extent of 24-hr-old canine myocardial infarctions with MRI. Experience with imaging of early myocardial infarction in vivo has been limited and results have been conflicting. It was therefore the intent of the present study to further assess the ability of MRI to detect early regional myocardial ischemia. Cardiac MR images were obtained in vivo before and sequentially for up to 6 hr after anterior descending or circumflex coronary artery ligation in 15 dogs.

Methods

Canine infarction. Fifteen adult dogs of both sexes weighing from 5 to 15 kg were premedicated with 1 mg/kg xylazine and
0.3 mg atropine intramuscularly. Anesthesia was achieved by the administration of 20 to 30 mg/kg pentobarbital or 10 to 20 mg/kg thiopental followed by halothane, 1% to 2%. After endotracheal intubation, respirations were maintained by positive-pressure ventilation with use of oxygen-enriched room air.

A left thoracotomy exposed the heart and coronary arteries. A portion of the mid anterior descending artery or the proximal circumflex artery (dogs 4 to 6) was dissected free. A silk ligature was loosely placed around the artery, and the ends of the ligature were brought outside the chest cavity. The chest wound was then closed and the animal was transferred to the nuclear MRI facility. Control and subsequent imaging was done under continued pentobarbital or halothane anesthesia and positive-pressure ventilation was continued in all dogs.

Procainamide, 10 mg/kg im, and 2 to 3 mg/kg iv xylocaine were administered before coronary artery ligation. Coronary artery occlusion was accomplished by drawing the ends of the silk ligature taut. After stabilization of cardiac rhythm, sequential imaging was performed for up to 6 hr after the occlusion.

**MRI.** Images were obtained in the 29 cm diameter head coil of a Technicare Corporation prototype 0.15 tesla resistive imager. The resonant frequency of hydrogen in this magnetic field is 6.25 MHz.

Imaging pulse sequences were initiated by an electrocardiographic signal using a modified Honeywell TT-31 telemetry transmitter and receiver. This system provided a noise-free electrocardiographic signal during imaging without interfering with image quality.

All images were obtained in the interval immediately after the peak of the R wave. All studies were obtained as two-dimensional single slices in either the transverse, sagittal, or coronal planes and in single-spin echo and modified inversion recovery pulse sequences. Time required for acquisition of each image ranged from 5 to 15 min.

**Definitions.** TE (time to the echo) refers to the interval between the application of the first radiofrequency pulse of the sequence and activation of the radiofrequency receiver. TR (time to sequence repetition) refers to the interval between the sequence-initiating radiofrequency pulses and in gated cardiac imaging is necessarily limited to the R to R interval or a multiple thereof. The spin echo sequence consists of a 90 degree pulse followed by one refocusing 180 degree pulse at 15 msec in the case of a TE 30 msec study, or at 30 msec in the case of a TE 60 msec study. The inversion recovery sequence consists of a 180 degree pulse followed after time TI (inversion time) by a TE 30 msec spin echo pulse combination (figure 1).

Both spin echo TE 30 msec and TE 60 msec sequences were used with TR times ranging between 400 and 1200 msec. The inversion recovery sequence was used with TI between 400 and 500 msec and TR greater than 1 sec. A series of control images was obtained before coronary artery ligation in all but one dog in which intraoperative occlusion was necessary because of hemorrhage. A repeat series of images was obtained sequentially for up to 6 hr after occlusion.

**Pathologic examination.** Dogs 1 to 6 were killed on the day of imaging and their hearts were prepared for pathologic examination. Dog 11 died 120 min after coronary artery ligation and its heart was not studied. The remaining dogs were killed at 3 weeks after coronary ligation and their hearts were excised for examination.

The hearts were sectioned at 5 to 10 mm intervals in a plane approximating the MRI plane. After fixation in 10% formalin, whole microscopic mounts of each heart from a section most closely correlating with the MRI plane were made and stained with hematoxylin and eosin. The mounts were subsequently examined microscopically for evidence of ischemic changes.

**Data analysis.** For analysis, raw image data were transferred from the MRI computer to a Digital PDP 11/34 computer system in which custom-written software was used. For each animal several regions of interest were applied to the myocardium to derive signal-intensity data. Regions of interest were drawn in the section of myocardium supplied by the vessel to be occluded as well as for the "noninfarct" vessel before coronary artery ligation, as well as for myocardium in the distribution of the occluded vessel and for normal adjacent myocardium after coronary artery ligation. MR signal intensity within the zone at risk of infarction was examined as a percentage change from normal myocardium in the distribution of the nonoccluded vessels.

Because an insufficient number of animals was studied beyond 4 hr, data analysis only includes observations up to that point.

![FIGURE 1. Schematic representation of MRI pulse sequences used in the study. $\tau = TI =$ inversion time.](image-url)
Statistical analysis. Mean values are presented ± SD. An analysis of variance and Scheffé's test were used to test for significance in changes in signal intensity over time.

Results

Anatomic definition. MR images obtained with the TE 30 msec spin-echo sequence provided excellent anatomic detail. Both right and left ventricular chambers were clearly defined, as was the ventricular myocardium. Papillary muscles and the valvular apparatus as well as atria and the pulmonary veins could be visualized in the appropriate imaging plane (figure 2). With the TE 60 msec sequence normal myocardium was not well visualized, although epicardial and noncardiac structures could be seen (figure 3).

In dog 1 and to a lesser extent in dog 2 a reduction in signal from the anterior wall was noted before coronary artery ligation. In both instances, images were obtained in the transverse plane, in dog 1 at heart rates of 145 to 165 beats/min and dog 2 at heart rates of 80 to 105 beats/min. After coronary artery ligation the signal in this region increased.

A region of increased apical intraluminal signal was seen in four dogs and was assumed to represent stagnant flow adjacent to the infarct zone. Left ventricular chamber enlargement was also observed in several animals after coronary artery ligation.

Infarct visualization. Signal-intensity data are presented in table 1. Within 1 hr after coronary artery occlusion, MR signal within the infarct zone increased to 23 ± 13% greater than that in surrounding noninfarcted myocardium for the TE 30 msec sequence (p <
FIGURE 3. TE 60 msec images obtained before and sequentially after circumflex artery occlusion. a, Before occlusion little myocardial signal is seen. b, Fifty minutes after occlusion, signal has increased in the inferior wall. c, Seventy-five minutes after occlusion. d, Two hundred ten minutes after occlusion. PF = pericardial fat.

By 4 hr after occlusion the signal had increased to 36 ± 20% greater than that in adjacent myocardium (p < .01). In eight of 13 dogs after 1 hr and in 14 of 15 dogs by 4 hr an observable increase in signal in the infarct zone was seen (figure 4).

With the use of the TE 60 msec pulse sequence MR signal in the infarct zone increased to 35 ± 34% greater than that in normal myocardium by 1 hr and to 116 ± 100% by 4 hr (p < .05). An observable increase in signal was seen in four of 10 dogs by 1 hr and in 12 of 13 by 4 hr (figure 3).

Because of low signal intensity, normal myocardium was poorly visualized with the TE 60 msec pulse sequence. The resultant signal increase in the infarct zone was therefore clearly seen, providing a positive contrast image analagous to that obtained by infarct-avid radionuclide scanning (figure 5). Although it provided adequate anatomic definition, inversion recovery imaging demonstrated very little or no contrast between normal and ischemic myocardium.

Pathologic examination. All except one heart was examined pathologically. In dogs 1 to 6 the duration of ischemia was short and therefore only subtle changes resulting from myocardial injury were noted. Light-microscopic changes consisted of patchy eosinophilia, waviness of myocardial fibers, and contraction bands confined to the infarct zone; in dog 1 early neutrophil infiltration was noted.14 In all of the remaining hearts microscopy very clearly defined a region of myocardial fibrosis. The location of these changes correlated well with the abnormalities seen on the MR images (figure 6).

Discussion

Background. The application of MR technology to cardiology has evolved over the past half decade from spectroscopic analysis in vitro to high-resolution imaging in vivo. Investigation of changes in MR parameters associated with the early stages of myocardial infarction has received particular attention.

Studies in vitro, both spectroscopic and imaging,
have provided useful insights into the results of imaging experiments in vivo. Using spectroscopy, Frank et al.\textsuperscript{16} showed that a slight increase in the water content of myocardium subjected to 4 hr of ischemia resulted in a 10% to 20% increase in T1 in this region. They further demonstrated that by the administration of intravenous manganese, a paramagnetic element, T1 was selectively shortened in normal myocardium, resulting in enhanced contrast between normal and ischemic myocardium 90 min after occlusion of canine coronary arteries.\textsuperscript{17} Detailed spectroscopic work by Williams et al.\textsuperscript{18} has shown a significant increase in both water content and T1 in myocardium after only 30 min of ischemia. More recent work by Ratner et al.\textsuperscript{19} has demonstrated a 4% increase in T1, without an increase in T2, 30 min after coronary artery occlusion in dogs. After 15 min of reperfusion, however, T1 was noted to be increased 10% and T2 9% in the ischemic zone. Slutsky et al.\textsuperscript{20} have also shown a significant increase in water content, T1 and T2 of canine myocardium subjected to 3 hr of ischemia.

Imaging of myocardial infarction in vitro has provided further encouragement for the development of imaging techniques in vivo. Brady et al.\textsuperscript{21} showed that detailed images of the heart could be obtained in vitro. By using a T1-weighted steady-state free precession technique, they were able to visualize ischemic canine myocardium within 90 min of coronary artery occlusion, although only after the administration of manganese. The ischemic zone in this study was visible as a region of reduced MR signal. The same group further reported that 24-hr-old canine myocardial infarction could be accurately quantified by imaging in vitro with the use of the same T1-weighted pulse sequence after manganese administration.\textsuperscript{10} Higgins et al.\textsuperscript{11} have also demonstrated that 24-hr-old canine infarctions can be clearly visualized. However, by use of T2-weighted spin-echo pulse sequences (TE 56 msec, TR 1 sec, in a 0.35 tesla MR unit), the infarctions were seen as regions of increased MR signal without the need for paramagnetic contrast agents. Myocardial water content and T2 were found to be significantly increased in

FIGURE 4. Transverse (a) and sagittal (b) TE 30 msec images obtained before occlusion of the anterio-descending artery. c and d, TE 30 msec images in the same planes showing apical dilatation, thinning, and intracavitary signal suggestive of static blood. TE 30 msec images e and f show progressive signal enhancement in the infarct zone 30 and 150 min after coronary artery occlusion. g, TE 60 msec image at 1 hr; h, the inversion recovery image 4 hr after occlusion.
the infarct zone in their study, and although there was an increase in T1, this trend was not statistically significant.

Imaging in vivo. We have demonstrated that detection of myocardial ischemia in vivo is possible within 1 hr of coronary artery occlusion. In an earlier study, Selwyn et al.\textsuperscript{13} reported a reduction in MR signal and increased T1 in myocardium after 1 hr of ischemia by using T1-weighted free induction decay and inversion recovery pulse sequences. However, Pohost et al.\textsuperscript{12} who used a T1-weighted saturation recovery pulse sequence, did not observe any change in myocardial signal intensity 30 to 60 min after anterior descending artery occlusion in dogs. An enhanced spin echo signal has been observed by imaging in vivo in 2- to 7-day-old canine myocardial infarcts by Wesbey et al.\textsuperscript{24} In the present study, using a T2-weighted spin echo technique, we also observed signal enhancement rather than a reduction in signal. This may offer some advantage in that the extent of ischemic injury may be more easily delineating on visual inspection, particularly in the case of the TE 60 msec images in which normal myocardium is not well visualized and ischemic myocardium is markedly enhanced.

The signal intensity of inversion recovery images obtained by our system is given by the relationship

\[ S_{IR} \propto p (1 - 2e^{-T1/T1} + e^{-TR/T1}) e^{-TE/T2} \]

where \( p \) = proton density. Increases in T1 and T2 have opposing effects on signal intensity by this imaging technique and although these images are heavily T1 weighted, there is a contribution of T2. The lack of any
significant change in signal in the infarct zone by this technique in the present study suggests an unchanged or only slightly changed T1 or perhaps cancellation of the T1 effect (signal reduction) by an increased T2 (signal enhancement). Furthermore, we used a T1 value of 400 to 500 msec in our studies and have not explored the effect on the MR image of shortening or shortening this parameter.

The mechanisms of the increased nuclear MR signal observed with the use of the spin echo technique in this study are not entirely clear. MR signal intensity in spin echo images obtained by our system follows the relationship

\[ S_{SE} = \rho c^{T1/T2}(1 - e^{-T1/T2}) \]

Again, an increase in T1 will cause a reduction in signal, although not one as marked as with the inversion recovery sequence. Increases in T2 will lead to signal enhancement. By increasing TR, the expression 1 - e^{-TR/T1} approaches unity and the resultant image is largely T2 weighted. For this reason we set a TR as long as possible for our TE 60 msec images.

Although not inherent in this relationship, motion is a very significant determinant of the appearance of MR images. The most obvious example of this is the appearance of flowing blood. At high velocities, no signal is observed because stimulated protons have moved from the imaging plane before the resonant signal is returned. On the other hand, low velocity or stationary blood emits a strong signal because most protons remain in the imaging field. Motion likely influences the appearance of the myocardium on cardiac images in vivo and we believe that this is the cause of the reduced signal noted in the anterior myocardium of dog 1 before coronary artery ligation. After anterior descending artery ligation, the signal in this region increased despite the similar heart rates before and after ligation. This is presumably due in part to regional hypokinesia. At the same time, this effect does not entirely explain the absence of signal noted in normal myocardium when the TE 60 msec pulse sequence was used. With this sequence, epicardial structures such as pericardial fat and fat in the atrioventricular groove are distinctly visualized despite cardiac motion. Fat has a relatively long T2, suggesting that the inherent T2 of myocardium is considerably less and is thus visualized with a 30 msec spin echo sequence but poorly defined by a 60 msec spin echo.

A reduction in motion may have in part contributed to the signal enhancement in ischemic myocardium noted in this study. However, this is likely not a major factor since ischemic myocardium has been detected as an area of increased signal by other investigators using the spin echo technique and imaging in vitro the motionless heart. Also, since akineticis occurs in the infarct zones almost immediately on coronary artery occlusion one would not expect a progressive increase in signal, as we have noted, on this basis alone.

One factor likely to contribute substantially to the increased signal is the increase in water content in areas of myocardial ischemia. Williams et al. have shown that water content increases rapidly in the first 30 min after coronary artery ligation. With an increase in tissue water, proton characteristics change and magnetic relaxation times T1 and T2 increase, as has been shown by MR spectroscopy. As seen in the mathematical relationships above, these changes will substantially affect signal intensity to a degree that depends on the imaging sequence employed. Also, with an increase in proton density the signal will increase linearly.

Other possible causes of changes in relaxation rates and MR signal intensity include reduction in tissue oxygen and high-energy compounds in the ischemic zone, changes in regional pH, and potassium flux into the extracellular fluid causing a change in ionic hydration shells.

Using a Technicare 0.15 tesla resistive MR imager, we have demonstrated that spin echo imaging can be used to identify ischemic myocardium. One issue not addressed by this study, and one that requires investigation, is the ability of MRI techniques to distinguish

**FIGURE 6.** Pathologic specimen demonstrating extent of infarction in heart at 3 weeks after infarction shown by MRI in figure 4.
between reversibly ischemic myocardium and that committed to infarction. Such may be possible with the refinement of current imaging techniques or may come about in the future with the development of nontoxic paramagnetic flow tracers.

MRI is a noninvasive tool with no known adverse effects. If found to be sensitive for identifying acutely ischemic myocardium in humans, MRI could potentially be used to study the effects of efforts to limit the size of myocardial infarction and may be helpful in selecting patients to receive such interventions.

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