Use of Gadolinium-DTPA as a Myocardial Perfusion Agent: Potential Applications and Limitations for Magnetic Resonance Imaging

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To establish the effect of the paramagnetic contrast agent gadolinium diethylenetriaminepentaacetic acid ([Gd]DTPA) on myocardial magnetic resonance relaxation parameters T1 and T2, and its relationship to myocardial perfusion, we administered [Gd]DTPA 0.2 mM/kg to two groups of dogs. Group I had severe, resting myocardial ischemia induced by coronary occlusion, followed in 2 min by [Gd]DTPA infusion and heart excision 1 min later. Group II had a variable reduction in blood flow. In Group II the coronary vasodilator dipyridamole was infused to enhance blood flow to the normal myocardium before [Gd]DTPA was given. In Group I [Gd]DTPA caused a significant difference in T1 between the normal and severely ischemic zones; changes in T2 correlated with the severity of myocardial ischemia. Although vasodilatation delivered more Gd-DTPA to the normal myocardium in Group II, the lack of further decrease in T1 suggested that it was cleared more rapidly. Thus, [Gd]DTPA permits the detection and characterization of severe, resting myocardial ischemia by magnetic resonance techniques. Using the experimental techniques described in this study, less severe flow differences caused by vasodilatation and resultant hyperemia are not detected.


Several studies have shown magnetic resonance imaging (MRI) to be a useful technique for the detection of recent myocardial infarction (1–4). Increased T1 and T2 result in enhanced tissue contrast on both T1- and T2-weighted magnetic resonance images. A portion of these changes is likely due to an increase in water content, although the exact mechanism remains to be elucidated. In contrast, brief periods of myocardial flow reduction not resulting in infarction have not been shown to alter T1 or T2 and therefore, are unlikely to be visualized by proton magnetic resonance imaging. Thus, the use of paramagnetic contrast agents to alter myocardial relaxation times may be necessary for detecting such reduction in blood flow. One such agent, gadolinium diethylenetriaminepentaacetic acid ([Gd]DTPA), has been used in animals to detect image contrast following coronary (5,6), renal, and splenic artery ligations (7). It has been used in humans without known toxic effects for the detection of brain tumors (8,9).

For MRI to be widely useful for the detection of chronic coronary artery disease, it will be necessary to detect relative flow differences such as those which occur with exercise in patients with fixed coronary lesions. Such flow differences can be produced by the administration of dipyridamole, a coronary vasodilator (10). Dipyridamole is currently used with thallium-201 (201Tl) for the diagnosis of coronary artery disease (CAD) in patients unable to exercise (11). However, in the evaluation of CAD, the limited spatial resolution of 201Tl images indicates a potential role for magnetic resonance imaging, a technique which produces high quality tomographic images.

Specific aims of this study were (a) to examine the effect of [Gd]DTPA on T1 and T2 myocardial relaxation times and rates (1/T1, 1/T2) following brief periods of coronary flow reduction, (b) to determine if changes in relaxation rates following a [Gd]DTPA infusion correlate with regional myocardial blood flow, thus characterizing the severity of flow reduction, (c) to assess whether maximizing regional flow differences by ad-
ministering a coronary vasodilator enhances the ability of magnetic resonance techniques to detect coronary artery lesions following a [Gd]DTPA infusion.

METHODS

Animal Preparation

Eighteen mongrel dogs were anesthetized with intravenous pentobarbital, entubated and ventilated with room air using a Harvard respirator. Procainamide was administered as a 1-g intramuscular injection. The heart was exposed through a left thoracotomy and suspended in a pericardial cradle. The chest remained open for the duration of the procedure with care being taken to keep the exposed heart covered to prevent drying. A 20-cm vinyl catheter (23 gauge) was placed into the left atrium and used to inject microspheres for regional myocardial blood flow determinations. A second vinyl catheter was inserted into the femoral artery for systemic arterial pressure monitoring and withdrawal of reference blood required for blood flow determination. Data was recorded on paper. The left anterior descending artery was isolated and an inflatable balloon occluder was positioned proximally. A 100-mg bolus of lidocaine was given followed by a constant infusion of 1 mg/min throughout the experiment. Myocardial blood flow was measured immediately after coronary flow reduction was established. Approximately 4.5 million ruthenium-103 or scandium-46, 14–16 micron microspheres (total dose 30 μCi) were injected over 20 sec into the left atrial line. A 2-min collection of arterial reference blood samples was made. Technetium 99m-labeled macroaggregated albumin (10 mCi) was then injected into the left atrium. Autoradiography of the excised heart provided a visual display of blood flow alterations and to aid in the identification of the tissue segments.

Study Protocol

Group I (coronary flow reduction at rest). Dogs were divided into two groups; Group I consisted of four dogs, each with a coronary occlusion so as to create maximal reduction in regional myocardial flow. Immediately following collection of the occlusion reference bloods, Group I dogs had a 20-sec infusion of [Gd]DTPA (0.2 mM/kg) into the left atrium; the heart was excised 60 sec later. Total duration of coronary occlusion in this group was ~3.5 min.

Group II (coronary flow reduction after dipyridamole). Group II consisted of ten dogs having a variable reduction in coronary flow. This allowed the assessment of T1 with flow reductions ranging from mild to complete occlusion. Dipyridamole, a coronary vasodilator, was infused to enhance regional myocardial blood flow (0.08 mg/kg/min × 4 min; total dose = 0.32 mg/kg). Eight dogs in Group II had a coronary stenosis created and two had a coronary occlusion. For the dogs with a coronary stenosis, two had the hyperemic flow response prevented without reducing resting flow, and two each had stenoses of 50%, 75%, and 90% reduction in resting flow. Severity of the stenosis was held constant throughout the procedure by using a magnetic flow probe placed proximal to the balloon occluder. A catheter was placed in the distal coronary artery for pressure monitoring and was used to confirm the flow measurements. Dipyridamole was diluted in 20 ml of normal saline and infused into a peripheral vein to enhance flow. Regional myocardial blood flow was measured with microspheres before and after infusion of dipyridamole. Technetium-99m- (99mTc) labeled macroaggregated albumin was given during maximal coronary vasodilation. Autoradiography was performed later on the excised, sliced heart. Immediately following collection of the second group of reference bloods, [Gd]DTPA 0.2 mM/kg was infused into the left atrium over 20 sec. The heart excised 60 sec after [Gd]DTPA. Total time of flow reduction for Group II was ~10 min. The extra time required when compared to Group I was due to the extra set of microspheres given and the need to infuse dipyridamole over 4 min.

Control (no [Gd]DTPA). Control animals for Group I (n = 4) and Group II (n = 4) underwent identical protocols, but did not receive [Gd]DTPA.

Magnetic Resonance Imaging

Excised hearts were imaged in a prototype magnetic resonance imaging system. This system consisted of an 8-cm horizontal bore, superconducting magnet operating at a field strength of 1.44 tesla corresponding to a proton resonance frequency of 61.4 MHz. The heart was placed on a Pyrex carrier in the magnet bore with the long axis of the left ventricle parallel to the magnetic field and the anterior wall facing superiorly. Tomographic magnetic resonance images were obtained along the short axis of the left ventricle. An image best demonstrating the mid-left ventricle was selected and repetitively imaged using various pulse sequences.

TR (pulse repetition time) values for T1-weighted spin echo imaging ranged from 100 to 500 msec for each heart; TR for T2-weighted spin echo imaging was 2,000 msec. TR for inversion recovery imaging was 1,100 msec plus TI (inversion time). Optimal TI varied somewhat for each heart and was chosen to produce the best contrast between the ischemic area and the adjacent normal tissue. The T1-weighted pulse sequences used in this study measured signal from rephased spin echoes, thus making the duration of TE (echo time) an important factor in determining T1 image contrast, since lengthening TE increases the influence of T2. A relatively short TE of 15 msec was used for the T1-weighted spin-echo and inversion recovery pulse sequences; TE = 60 msec was used for T2-weighted spin-echo imaging. A single acquisition T2-weighted spin-echo image required 5 min to obtain. Multiple signal acquisitions allowed equal imaging times for T1-weighted spin echo and inversion recovery imaging. Total imaging time for each heart was 1 hr. Images were acquired in a 128 × 256 pixel array and interpolated to a 256 × 256 pixel display. Tomographs were 3 mm thick and the in-plane resolution was <1 mm.

Tissue Preparation

The heart was sliced into 1-cm-thick slices at an angle parallel to the atrioventricular groove. A mid-ventricular segment was selected for further in vitro studies. This slice was wrapped in paraffin and placed directly on the surface of an undeveloped radiographic film. The exposed 99mTc-autoradiograph was removed after 10 min. After developing the autoradiograph, the tissue slice was restored to its previous position on the film and subdivided into 10–15 (depending on the size of the slice), 500–1,000 mg segments. A diagram of the subdivided slice was then drawn directly onto the film. Even though known differences exist in blood flow between ischemic epicardium and endocardium, a previous study from
our laboratory was unable to measure differences in regional $T_1$ and $T_2$ following the infusion of manganese chloride (2). Therefore, only transmural segments were examined in this study. Normal zone relaxation parameters and flow were represented by the mean value of three contiguous segments taken from the mid-region of high radioactive exposure on the autoradiograph. Ischemic zone relaxation parameters and flow were represented by three contiguous segments lying within the mid-region with no radioactive exposure. For the hearts without evidence of flow differences on the autoradiograph, the ischemic zone was estimated from visual inspection of the stenotic coronary distribution and the normal zone was chosen from the opposite wall. Throughout the study, care was taken to prevent drying of tissue samples.

**MR Spectroscopy**

$T_1$ and $T_2$ were measured using an International Business Machine 6 MHz minispectrometer (model PC-20) with ambient temperature controlled at 40°. Tissue specimens were placed into glass tubes, capped and heated at 40° in a water bath before being placed into the probe for measurement. The spectrometer frequency, 90° and 180° radiofrequency pulse widths and phase were calibrated for each sample. $T_1$ was obtained using an inversion recovery pulse sequence at eight different $T_1$ values ranging from 20 to 2,560 msec. The magnitudes of the magnetization vector for each $T_1$ value were automatically processed and $T_1$ calculated. $T_2$ values were obtained with the Carr-Purcell-Meiboom-Gill pulse sequence using ten echoes. $T_1$ and $T_2$ were measured twice for each specimen and an average value obtained.

**Regional Myocardial Blood Flow**

To calculate regional myocardial blood flow, blood, and tissue samples were placed in a well counter and ~10,000 counts for each isotope were collected. Scandium-46 was counted in a 180-1,200 keV window and ruthenium-103 was counted in a 440-600 keV window. A computer program was applied to correct for activity spilling from one window into another. Regional myocardial blood flow in ml/min/g was calculated from the sample activity and activity of the reference blood samples obtained during the administration of each isotope.

**Statistical Methods**

Differences within and among the different groups of dogs were analyzed using a multivariate analysis of variance with repeated measures (BMDP P4V statistical program, University of California at Los Angeles). Least squares exponential function fits (program fit function in RS/1, Bolt, Beranek and Newman, Cambridge, MA) of the form $T_1 = a + be^{-x}$ were used to describe the relationship between relaxation parameters and regional myocardial blood flow. Probability of 5% or less was considered significant. All values are mean ± s.e.m.

**RESULTS**

**Number of Samples Studied**

Forty-five tissue samples were obtained from Group I control dogs, 40 from Group II control dogs, 47 from Group I dogs and 133 from Group II dogs.

**Regional Myocardial Blood Flow**

**Group I (coronary flow reduction at rest).** Blood flow decreased (p < 0.001) from 0.92 ± 0.07 ml/min/g (mean ± s.e.m.) in the normal zone to 0.12 ± 0.04 ml/min/g in the ischemic zone. Control (no Gd-DTPA) flow was not significantly different (0.97 ± 0.08 ml/min/g and 0.03 ± 0.01 ml/min/g, respectively).

**Group II (coronary flow reduction after dipyridamole).** Before vasodilatation, blood flow decreased (p < 0.001) from 0.93 ± 0.06 ml/min/g in the normal zone to 0.45 ± 0.08 ml/min/g in the ischemic zone. Control (no [Gd]DTPA) flow was not significantly different (0.93 ± 0.07 ml/min/g and 0.14 ± 0.04 ml/min/g, normal and ischemic zones, respectively). After vasodilatation, normal zone flow increased threefold to 2.82 ± 0.40 ml/min/g, while the ischemic zone remained relatively unchanged at 0.67 ± 0.20 ml/min/g. Control flow after vasodilatation was lower for the ischemic zone (0.09 ± 0.07 ml/min/g), since all control dogs had a coronary occlusion as contrasted to Group II dogs where only two of the ten dogs had an occlusion. Control flow in the normal zone after vasodilatation (2.85 ± 0.07 ml/min/g) was not significantly different.

**Relaxation Values (Figures 1 and 2)**

**Group I.** Control $T_1$ was 637 ± 4 msec (mean ± s.e.m.) for the normal zone and 628 ± 6 msec for the ischemic zone. Gadolinium-DTPA caused normal zone

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**FIGURE 1**

Effect of [Gd]DTPA on $T_1$. Far right; Dipyridamole caused a slight increase (p < 0.05) in normal zone $T_1$ when compared with Group I normal zone $T_1$ (middle). This presumably was due to more rapid washout from the enhanced flow zone in group II. Values are mean ± s.e.m. *p < 0.001 ischemic zone versus normal zone. (□) Normal; (■) Ischemic.
The relaxation times $T_1$ and $T_2$ were converted to relaxation rates $1/T_1$ and $1/T_2$ in order to derive correlations with flow. A significant relationship existed between regional myocardial blood flow and $1/T_1$: $2.3 + 0.6e^{-1.5\text{Flow}}$, $p < 0.001$, $r = 0.68$, s.e.e. = 1.1 (Fig. 3) Thus, a decrease in blood flow was associated with a progressive decrease in $1/T_1$, or stated simply, $T_1$ was inversely proportional to blood flow. Inspection of the curve in Figure 3, however, showed that this relationship was relevant only for severe, resting ischemia, i.e., blood flow $< 0.5 \text{ml/min/g}$.

**Group II.** A significant relationship occurred between resting flow and $1/T_1$: $1.4 + 1.8e^{-0.06\text{Flow}}$, $p < 0.001$, $r = 0.51$, s.e.e. = 0.65. However, inspection of the curve in Figure 4 demonstrates no relationship between flow and $1/T_1$ when flow was $> 1.00 \text{ml/min/g}$ (i.e., hyperemic flow). Group II segments were analyzed according to eight sub-groupings spanning the range of flows. There were no significant differences in $1/T_1$ among the groups with hyperemic flow. Thus, regional flow differences induced by dipyridamole were not detected by measuring $1/T_1$.

**Magnetic Resonance Images**

The ischemic zone was readily visualized in Group I. For Group II, however, only the hearts which had severe resting ischemia (>50% stenosis) demonstrated

T$_1$ to decrease ($p < 0.001$ compared with control) to 239 ± 18 msec and ischemic zone T$_1$ to decrease ($p < 0.001$) to 363 ± 23 msec (Fig. 1). The difference between the two zones was significant ($p < 0.001$). The decrease in ischemic zone $T_1$ following [Gd]DTPA was most likely due to the delivery of [Gd]DTPA by collateral flow to the ischemic region. Control $T_2$ was 45 ± 1 msec for the normal zone and 48 ± 1 msec for the ischemic zone. Gadolinium-DTPA caused normal zone $T_2$ to decrease ($p < 0.001$ compared with control) to 40 ± 1 msec and ischemic zone $T_2$ to decrease ($p < 0.001$) to 43 ± 1 msec (Fig. 2). However, the difference between normal and ischemic zones was not significant.

**Group II.** Control $T_1$ was 642 ± 3 msec for the normal zone and 633 ± 5 msec for the ischemic zone. Gadolinium-DTPA caused normal zone $T_1$ to decrease ($p < 0.001$ compared with control) to 266 ± 5 msec and ischemic zone $T_1$ to decrease ($p < 0.001$) to 356 ± 19 msec. The difference between the two zones was significant ($p < 0.001$). Normal zone $T_1$ was slightly higher ($p < 0.05$) in Group II compared to Group I. These results would suggest that, although more [Gd]DTPA was delivered to the normal myocardium with hyperemic flow, it was cleared rapidly during the 1 min before heart excision. Control $T_2$ was 47 ± 1 msec for normal zone and 48 ± 1 msec for ischemic zone. Gadolinium-DTPA caused normal zone $T_2$ to decrease ($p < 0.001$ compared with control) to 41 ± 1 msec and ischemic zone $T_2$ to decrease ($p < 0.01$) to 43 ± 1 msec. As with Group I, however, there was no significant difference between normal and ischemic zones.

**Correlation Between Flow and Relaxation Rates**

For Group II, a significant relationship occurred between resting flow and $1/T_1$: $1.4 + 1.8e^{-0.06\text{Flow}}$, $p < 0.001$, $r = 0.51$, s.e.e. = 0.65. However, inspection of the curve in Figure 4 demonstrates no relationship between flow and $1/T_1$ when flow was $> 1.00 \text{ml/min/g}$ (i.e., hyperemic flow). Group II segments were analyzed according to eight sub-groupings spanning the range of flows. There were no significant differences in $1/T_1$ among the groups with hyperemic flow. Thus, regional flow differences induced by dipyridamole were not detected by measuring $1/T_1$.

**Magnetic Resonance Images**

The ischemic zone was readily visualized in Group I. For Group II, however, only the hearts which had severe resting ischemia (>50% stenosis) demonstrated
tissue contrast. The region of increased T1 in the ischemic zone demonstrated a decrease in signal intensity relative to the normal zone on both T1-weighted spin echo (Fig. 5A) and inversion recovery (Fig. 5B) images.

In keeping with the lack of T2 differences between normal and ischemic regions by spectrometer, the ischemic zone was not observed with T2-weighted spin echo imaging (Fig. 5C).

FIGURE 4
Relationship between 1/T1 and regional myocardial flow for Group II; r = 0.51, p < 0.001. Note that there is little correlation between flow and 1/T1 when flow is ~ > 1 ml/min/g, i.e., hyperemic flow.

FIGURE 5
Magnetic resonance images of an excised heart (Group I) following left anterior descending coronary artery occlusion. There was marked coronary flow reduction at rest. Imaging time was approximately the same for each pulse sequence. A: T1-weighted spin echo image obtained at TR/TE = 300/15 msec; B: Inversion recovery image obtained at TR/TI/TE = 1,450/350/15 msec; C: T2-weighted spin echo image obtained at TR/TE = 2,000/60 msec. The region of decreased myocardial signal intensity in the anterior wall of Figure 5A and 5B is the region of reduced myocardial flow. The lack of tissue contrast on the T2-weighted spin echo image was in keeping with the lack of spectrometer-measured T2 tissue differences.
DISCUSSION

Resting Flow Reduction Versus Flow Differences due to Hyperemia

The present study demonstrates the potential of [Gd]DTPA, a paramagnetic contrast agent, for detecting brief, severe reductions in resting myocardial flow using magnetic resonance techniques. Infusion of [Gd]DTPA induced a marked decrease of $T_1$ in normal myocardium, while causing significantly less decrease of $T_1$ in the ischemic region. The ability of [Gd]DTPA to further characterize the degree of myocardial blood flow reduction was demonstrated by the relationship between reduction in regional myocardial blood flow and $1/T_1$ in Group I, particularly when flow was reduced to $<0.5 \text{ ml/min/g}$.

Thus, this study demonstrated the potential for magnetic resonance imaging to assess severe, resting myocardial ischemia.

Our study also demonstrated some of the difficulties that will be encountered when magnetic resonance imaging is used to assess less severe myocardial ischemia. These difficulties are due to the extracellular behavior of [Gd]DTPA, which has a short, 20-min biologic half-life (13). Following i.v. infusion, distribution occurs throughout the intravascular space followed immediately by equilibration with the interstitium (14). These characteristics may have contributed to our failure to detect flow differences during hyperemia. Thus, in the 60 sec prior to heart excision in Group II dogs, we hypothesize that rapid washout of [Gd]DTPA from the hyperemic, normal myocardium caused $T_1$ to increase from a low immediate postinfusion value to a higher value by the time the heart was excised. One possible solution to imaging the less severe flow differences due to vasodilation and resultant hyperemia would be to provide a constant infusion of [Gd]DTPA during the period of time that images are being acquired.

Implications for Imaging

For hearts having a severe reduction in resting myocardial flow, a decrease in normal zone $T_1$ (relative to the ischemic zone) was associated with image contrast on $T_1$-weighted spin echo and inversion recovery images. In all likelihood, however, in vivo cardiac images will not be as good, since contractile motion of the heart and respiration tend to degrade image quality. This will be especially important for inversion recovery imaging, since tissue contrast with this pulse sequence is greatest near the null point when overall image signal is least (15). In the present study, we detected tissue contrast only when blood flow to the ischemic zone was markedly reduced. To visualize the less severe flow differences due to vasodilation and resultant hyperemia it will be necessary to obtain images before the dual effects of Gd-DTPA washout from the normal tissue and Gd-DTPA delivery to the ischemic zone causes equilibration of relaxation times. This will require very rapid sequences, since the normal zone flow is greatly increased during exercise or by dipyridamole infusion and washout will be accelerated.

Unlike the $T_1$-weighted images, $T_2$-weighted spin-echo images did not demonstrate tissue contrast and this was in keeping with the lack of spectrometer-measured $T_2$ tissue differences. Development of a paramagnetic contrast agent capable of preferentially altering $T_2$ would make $T_2$-weighted spin-echo imaging more attractive.

Using $T_2$-weighted spin-echo imaging of excised dog hearts, McNamara et al. (5) demonstrated myocardial perfusion abnormalities following 2 min of coronary occlusion (i.e., severe, resting ischemia). Gadolinium-DTPA 0.5 mmol/kg was infused after the first minute of occlusion. Signal intensity increased in the ischemic region in keeping with increased $T_2$ relative to the decreased $T_2$ of normal myocardium. Our inability to demonstrate image contrast with $T_2$-weighted spin echo imaging may have been due to our use of a smaller dose of [Gd]DTPA (0.2 mmol/kg versus 0.5 mmol/kg).

Using a lower dose, normal zone $T_2$ may not have been sufficiently altered to be significantly different from the ischemic zone.

The time required for a single, in vivo data acquisition during cardiac gating depends primarily on TR, which in turn is dependent on heart rate. Also, since TR is heart rate dependent, it would not be possible to preset TR for optimal $T_1$-weighted imaging. This, however, may not be critical for image contrast as demonstrated by a recent study from our laboratory (16). The findings of this study show that short TE is the most critical pulse parameter for $T_1$ image contrast, while contrast depends less strongly on optimizing TR. This factor may eventually be important in determining whether $T_1$ weighted gradient reversal echo imaging techniques will be useful in assessing myocardial perfusion following the infusion of $T_1$-altering paramagnetic contrast agents. With the exception of severe, resting ischemia, however, it is unlikely that one could acquire sufficient gated data following dipyridamole and a bolus dose of [Gd]DTPA before regional $T_1$ differences diminished.

Sampling of the heart more frequently than with each heart beat would permit imaging with short TRs, in the range of 200–300 msec. This may be achieved without gating to the QRS complex. The feasibility of this type of cardiac MR imaging has been previously demonstrated (17). Other techniques, such as single pulse (i.e., echo planar) imaging (18) may prove valuable when used with a paramagnetic contrast agent for detecting differences in myocardial flow. Development of paramagnetic contrast agents that remain longer in the region of myocardial distribution may provide more time to acquire images.

In summary, the use of [Gd]DTPA permits the detection of severe, resting myocardial flow reduction by
magnetic resonance techniques. Severity of flow reduction can be characterized in these hearts. Due to the extracellular characteristics of [Gd]DTPA, however, less severe flow differences resulting from dipyridamole-induced hyperemia are not readily detected using the techniques described in this study.

NOTES
1. H.A. Webster & Sons, Billerica, MA.
2. Harvard Apparatus, South Natick, MA.
6. Elins-Sinn, Inc., Cherry Hill, NJ.
8. Technicare Corporation, Solon, OH.
9. Danbury, CT.

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