MINIREVIEW

The Developing Role of Magnetic Resonance Contrast Media in the Detection of Ischemic Heart Disease (43852C)

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Abstract. **Recent developments in magnetic resonance (MR) imaging have opened up new avenues in the investigation of cardiovascular physiology. Inherent signal intensity of any tissue on MR images depends largely on proton concentration as well as longitudinal (T1) and transverse (T2) relaxation times. Myocardial contrast can be manipulated by using specific MR pulse sequences which are selectively sensitive to differences in any one of these parameters. Paramagnetic metal complexes are used as contrast media in MR imaging to enhance the inherent contrast. Contrast media in MR imaging are not directly visible but change the magnetic properties of other nuclei in close proximity, such as those of the water hydrogen. The signal of water can be altered by the contrast medium in different ways, either by changing the relaxation times or through bulb susceptibility effects, or both.**

The role of MR contrast media for quantitative characterization of ischemic heart disease has advanced considerably in the past 10 years. Conventional MR imaging techniques following the administration of contrast media are useful for identifying and sizing myocardial infarctions and for distinguishing between occlusive and reperfused myocardial infarctions as well as reversible (stunned) and irreversible injuries. Recent results suggest that contrast-enhanced MR imaging can also be used to identify dead cells in reperfused ischemically injured myocardium.

The recently developed fast MR imaging techniques, with the aid of MR contrast media as a perfusion indicator, may be useful in estimating regional myocardial perfusion and blood volume. The assessment of capillary circulation or myocardial perfusion may be used for evaluating the extent of hypoperfusion and treatment efficacy. Experimental and clinical perfusion studies indicate that perfusion-sensitive MR imaging detects compromised myocardium (area at risk). Combining myocardial perfusion imaging with the anatomic and functional information provided by other MR imaging sequences could make MR imaging a comprehensive noninvasive technique for the evaluation of ischemic heart disease. [P.S.E.B.M. 1995, Vol 208]

The recognition of the importance of magnetic materials and their effects on the relaxation times of resonating protons occurred almost simultaneously with the discovery of the magnetic resonance (MR) process in 1946 (1). Solomon in 1955 (2) and Bloembergen in 1957 (3) outlined the framework of the effect of paramagnetic transition metals. Lauterbur

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0037-9727/95/2083-0238$10.50/0

(4) was responsible not only for the seminal development of magnetic resonance imaging technique, but also for the conception and subsequent development of MR contrast media. In 1978, Lauterbur *et al.* demonstrated the first use of manganese ions as an MR agent in canine models of myocardial infarction (5). The development of the first commercial contrast medium, gadopentetate dimeglumine (gadolinium diethylenetriamine-pentaacetic acid-dimeglumine [Gd-DTPA]), commenced in 1981, and its first reported use in humans occurred in 1984. This agent received U.S. Food and Drug Administration (FDA) approval in 1988 (6, 7, 8).

Attempts to develop MR contrast materials for tissue enhancement have included the use of a wide range of magnetic materials, such as manganese (II), gadolinium (III), dysprosium (III), and iron (III). MR contrast materials are paramagnetic, meaning they have unpaired electrons. The number of unpaired electrons directly influences the potency of the contrast medium. In most cases, the mechanism of their action is dipolar interaction between proton nuclear spins and unpaired electrons. Other mechanism of action depends on the compartmentalization of these compounds, rather than direct interaction of tissue water with the unpaired spins. Unlike radiographic contrast media, MR contrast media are not directly measurable on MR images but alter the magnetic properties of other adjacent nuclei.

Although one of the great advantages of MR imaging is the high degree of intrinsic myocardial contrast, there has been increased interest in the use of MR contrast agent to improve detection and characterization of myocardial injuries (6–12, 14, 15, 17–25, 27–30), and recently to assess myocardial perfusion (6–13, 28–55). The major goals of using MR contrast media in the heart are (i) to delineate jeopardized area in the territory of a fixed coronary stenosis (hypoperfusion) or total occlusion (ischemia); (ii) to differentiate between occlusive and reperfused myocardial infarctions; (iii) to qualify regional myocardial perfusion; and (iv) to discriminate between viable (stunned) and dead cells in reperfused ischemically injured myocardium.

Myocardial Contrast

Water distribution is almost homogeneous and moves almost freely across the capillary wall and cellular membrane in normal myocardium. The extraction fraction of water is close to unity and is slightly sensitive to flow changes (56). In infarcted myocardium, edema (increase in interstitial volume) prolongs tissue relaxation times (longitudinal [T1] and transverse [T2]), resulting in higher signal intensity in infarcted regions than in normal myocardium (14, 15, 19). Thompson *et al.* monitored the evolution of myocardial signal intensity (edema) in patients with myocardial infarction. They found that changes in signal intensity of the infarcted region continued over a period of 3 months on unenhanced T2-weighted spin echo images (15).

Myocardial contrast can be manipulated by combining the administration of MR contrast media possessing the desired contrast properties (such as relaxivity or susceptibility) with the MR pulse sequences (such as spin echo, gradient echo, or echo planar imaging) which are sensitive to the contrast mechanism (16, 58–60). Each of the various imaging techniques has a different relationship between signal-to-noise or contrast:noise ratio and inherent MR tissue properties. For example, gadolinium chelates at low doses are potent relaxivity (T1) enhancing agents and cause myocardial signal enhancement on T1-sensitive sequences (inversion recovery or short TR/TE [repetition time/echo time]), whereas at higher doses susceptibility effects become dominant and can be detected as signal loss on either T2*- or T2-sensitive sequences (17, 18, 57, 58) (Fig. 1 and 2). Replacement of gadolinium with dysprosium in the same chelate increases the susceptibility effect (T2*) by 1.8-fold (21, 60, 61).

Multiple contrast enhancing strategies for cardiac imaging have been examined. These have included using (i) a single contrast medium for T1 (19–21), T2, or T2* enhancement (21–23, 62); (ii) a single MR contrast medium for T1, T2, and T2* (susceptible) enhancements (17, 57, 58); and (iii) combination of two MR

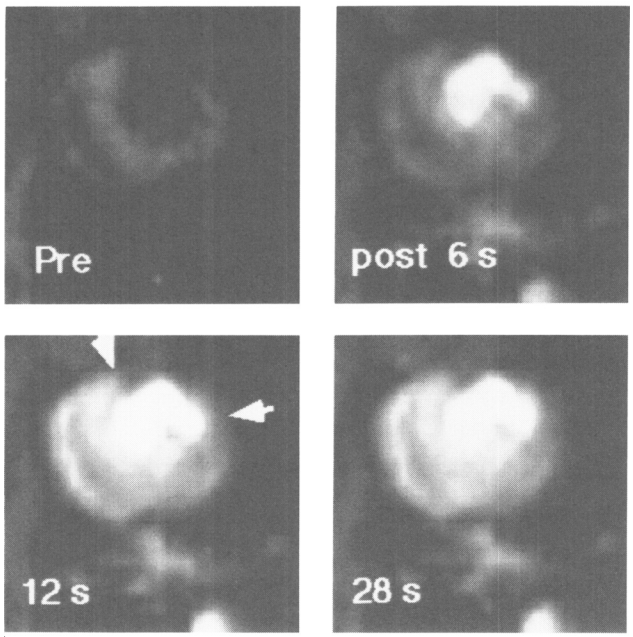

Figure 1. Selected inversion recovery echo planar MR images (TR/TE/TI = 2000/10/700 msec) were acquired prior to (top left) and during the transit of 0.05 mmol/kg GdDTPA-BMA through the heart of a rat subjected to 2 hr coronary artery occlusion. Note that the infarcted region (arrows) is shown as a region of low signal intensity (cold-spot).

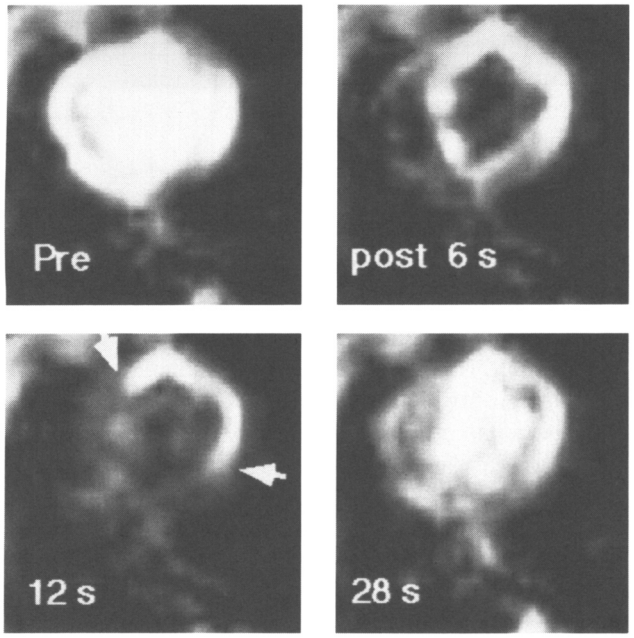

Figure 2. Selected gradient recalled echo planar MR images (TR/TE = 2000/10 msec) obtained from the same animal shown in Figure 1. These images were acquired during the transit of 0.2 mmol/kg GdDTPA-BMA through the heart. Note that the ischemic region (arrows) is shown as a hyperintense region on this type of pulse sequence (hot-spot).

contrast media (16, 18, 24–36). Other strategies to develop MR contrast media targeted to specific tissues or cells are under investigation (27, 63).

Types of MR Contrast Media. MR contrast media can be categorized according to their pharmacokinetic properties (biodistribution, local concentration as a function of time) or predominant action on proton relaxation (8–10, 64). The distribution of those media can be intravascular (macromolecular media), intravascular and extravascular (low molecular media), or to all compartments including intracellular spaces.

Intravascular or macromolecular MR contrast media (>50,000 daltons). Distribution to the intravascular space of both T1 and T2* agents can be achieved by conjugating the paramagnetic ligand to proteins, lipids, polysaccharides, and synthetic polymers, which prevent leakage through the capillary wall for some period of time (8, 29, 38, 64). This type of media has less distribution volume (5%–10% = myocardial blood volume) (65, 66) than extravascular media (30%–40% intravascular plus interstitial volumes) (31), because they are too large to escape through the small capillary pores in normal myocardium. Intravascular media demonstrate high T1 relaxivity than extravascular media (8, 29, 64), which is due to the multiplicity of paramagnetic ions attached to each polymeric molecule and to slowing of molecular rotational correlation times of each paramagnetic subunit (8, 64). These media are being developed to specifically enhance the blood pool (8). The prolonged intravascular retention and absence of extraction during the first pass of these media may permit measurements of relative blood volume and estimation of tissue perfusion (8, 30, 39, 64, 67), as well as detection of abnormal capillary leakage (8, 64, 67). Gadolinium-DTPA-albumin and Gadolinium-DTPA-polylysine have been used experimentally for characterization and assessment of myocardial injuries (8, 29, 68, 69). Gadolinium-DTPA-albumin and Gadolinium-DTPA-polylysine have not yet been clinically tested.

Extravascular or low molecular MR contrast media (<1000 daltons). In the heart, most extravascular agents equilibrate throughout the extracellular space, but they are excluded from the intracellular space. On the first pass through the capillary bed, 50% of circulating GdDTPA diffuses from the intravascular compartment into the extravascular compartments (8). Because these compounds have larger distribution volume, they are more potent than those confined to the intravascular space. Extravasation of these agents into the extravascular space relaxed extravascular water. Extravascular agents improve the contrast between normal and injured regions in the presence of edema and/or cellular necrosis. As detailed latter, this type of MR contrast agent is the most wildly studied and clinically used.

Intracellular MR contrast media, such as manganese chloride, have the largest distribution volume (~100% intravascular plus interstitial plus intracellular volumes), because they enter inside the cell via the same transporter as calcium (70). These agents are intended to reflect cellular transport processes (70). Paramagnetic ions are toxic, therefore they have been discarded from consideration as useful clinical agents.

Mechanism of Action. MR contrast media designated with regard to their predominant effect are either relaxivity- or susceptibility-enhancing media (8–10, 64, 71, 72).

Relaxivity contrast. The interactions between relaxivity MR contrast media and tissue have been studied extensively (72–74). The mechanism of action for these paramagnetic compounds is dipolar interaction between water protons and unpaired electrons within the compounds. Contrast molecules require direct contact with interstitial water. The presence of MR contrast media in the myocardium alters the T1 and T2 relaxation times by creating local magnetic fields that fluctuate with appropriate frequency components. In order for interstitial water molecules to be affected, they must rapidly approach and leave the vicinity of the paramagnetic field (70–74). In most tissues, their dominant effect is on longitudinal relaxation time (T1). As a result, image contrast is most apparent on T1-sensitive images (spin echo, gradient echo, and inver-

sion recovery echo planar). The varying field experienced by nearby protons depends on several characters of the contrast agent, such as magnetic moment, electron spin relaxation time, molecular interaction, and diffusional translation (8, 70–74).

Relaxivity-enhancing agents produce significant signal enhancement in the areas with blood supply. This class of agents is mostly used for delineation of acute myocardial infarction and for discrimination between occlusive and reperfused ischemically injured myocardium, and between reversible and irreversible myocardial injuries (9–12, 75–78).

Susceptibility contrast. Magnetic susceptibility is the proportionality constant between the applied magnetic field strength and the resultant magnetization established with ions with unpaired electrons, such as dysprosium or iron oxide. Variations in tissue magnetic susceptibility can substantially affect MR images (79–87). Susceptibility contrast media, or so-called T2*-enhancing agents cause signal loss on T2-sensitive images (spin echo, gradient echo, and echo planar). These agents disturb the local magnetic field, and protons rapidly lose their coherent precession after the radiofrequency pulse is applied to rotate their magnetic vector into the transverse plane. Spin dephasing is caused by microscopic field gradients in the tissue close to regions or compartments which contain contrast agent. The potency of the contrast agent is a function of its magnetic susceptibility and its distribution within the tissue, with the greater effect being associated with a more compartmentalized or heterogeneous distribution (82, 83).

Thulborn *et al.* were the first to demonstrate the susceptibility phenomenon in intact red cells using deoxyhemoglobin (82). Later, certain metals with susceptibility phenomenon have been tested in the heart. Dysprosium-chelates have been shown to provide substantial signal loss in the areas with blood supply, but not in regions supplied by occluded vessels (16, 18, 22, 23, 25). In these studies, the ischemic region was shown as a "cold-spot" region. This pattern of a bright region on a darkened field may be more unambiguously identified than the converse enhancement pattern. Another experimental magnetic susceptibility agent used for delineation of ischemic myocardium is iron oxide (84, 85). This contrast medium can also be utilized as a T1-enhancing agents in the detection of reperfused infarction (81).

Toxicity. Free paramagnetic ions exhibit poor solubility (except manganese), efficacy, and high toxicity when administered intravenously. The most suitable method to improve the biological tolerance and efficacy of the paramagnetic ions is to link them chemically to chelates, such as DTPA, BOPTA, or DOTA. The chelation approach has culminated in the development of several FDA-approved gadolinium chelate complexes, including gadopentetate dimeglumine (GdDTPA), gadodiamide injection (gadolinium diethylenetriaminepentaacetic acid-bis methylamide [GdDTPA-BMA]), gadoteridol injection (gadolinium 10-[2-hydroxypropyl]-1,4,10,-tetraazacyclododecane-1,4,7-triacetic acid [GdHP-DO3A]), and gadoterate meglumine (gadolinium tetraazacycliclodode-canetetraacetic acid [GdDOTA]—approved in Europe).

MR contrast media exhibit very high thermodynamic stability in aqueous solution. Some of these agents, such as GdDTPA and gadolinium (4RS)-4-carboxy-5,8,11-tris(carboxymethy10-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oicacid) (GdBOPTA/Dimeg), are called ionic because they have excess negative charges in their complexes. This results in an increase of the osmolality of the formulation so that these compounds are hyperosmolar at the concentrations used in MR imaging. In order to decrease the osmolality of these compounds to the osmolality of plasma (~250 mOsmol/kg water), neutral analogs of these ligands have been synthesized. For example, GdDTPA-BMA is a neutral analog of GdDTPA, while GdHP-DO3A is analog of GdDOTA. The clearance and excretion of low molecular weight MR contrast media are analogous to the well-documented excretion route of technetium-99m DTPA. Clinically approved MR contrast media are rapidly cleared from the intravascular space and undergo early renal excretion (more than 95% in the first 72 hr).

Slow intravenous infusion of MR contrast media has been used clinically at the recommended dose of 0.1 mmol/kg without any significant side effects. Cardiotoxicity and osmotoxicity are minor complications of MR contrast media because of peripheral injection, small volume, and slow infusion. The overall incidence of adverse reactions to these agents after slow infusion ranges between 0.9% and 2.4% (86), which is relatively low compared with iodinated contrast media (3% for nonionic and 12.6% for ionic) (87).

Because central rapid (bolus) administration of MR contrast media is a requisite for myocardial perfusion MR imaging, the potential hemodynamic effects of bolus injection must be considered. Bolus injection of MR contrast media is necessary for perfusion studies in order to obtain pure first-pass transit without the effect of recirculation (33) (the time between the first and second pass of the contrast medium is ~20 sec). Previous studies (63, 88, 89) in rats have indicated that bolus administration of ionic MR contrast agents causes transient depression in cardiac performance and hypotension. Figure 3 demonstrates the effects of bolus administration of the ionic GdDTPA on heart rate, peripheral, central, and LV pressures and dP/dt.

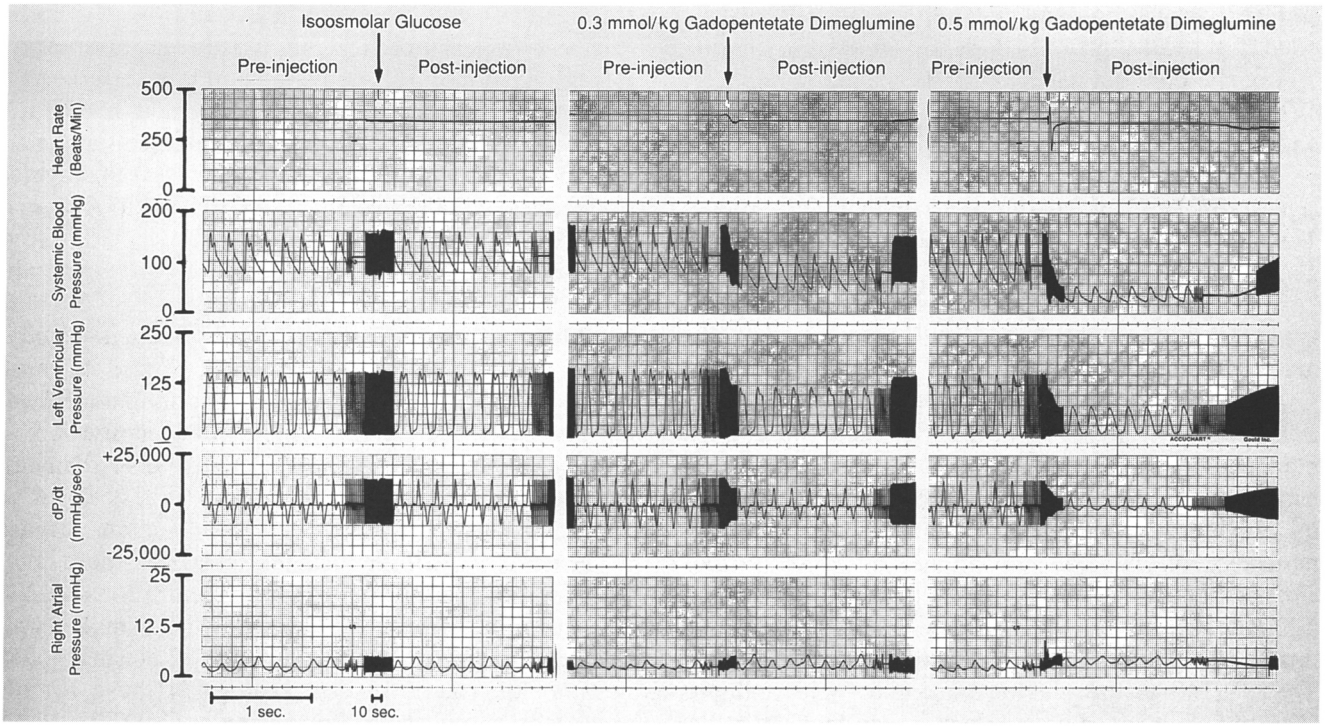

Figure 3. Representative cardiovascular response to bolus administration of ionic MR contrast medium, gadopentetate dimeglumine (GdDTPA) in rats. Bolus administration of this agent caused transient decrease in heart rate, peripheral blood pressures, left ventricular pressures, and ±dP/dt.

A relatively high doses of 0.3 and 0.5 mmol/kg, but not 0.1 mmol/kg, caused substantial reduction in heart rate, peripheral arterial pressures, systolic LV pressure, and both positive and negative dP/dt. Nonionic contrast media were found to produce no significant effects at the same dose levels (70, 71). The absence of negative inotropic, chronotropic effects and hypotension following bolus administration of nonionic media is believed to be related to the lower osmolality, superior physical properties (namely, the presence of balanced caldiamide-sodium in the formulation), and nonionic nature (64). The criteria that distinguish clinically available MR contrast media from one another include relaxivity, stability, and safety index (8).

Characterization of Myocardial Injuries

Acute Myocardial Ischemia. It has been shown that the major ultrastructural changes in acutely ischemic myocardium (viable but ischemic) consist of mild edema of the sarcoplasm and mitochondrial swelling without interstitial edema. For an ischemic area to have the potential of being detected on MR images, absence of flow, interstitial edema, and/or necrosis are required. Therefore, in the early stage of ischemia, there is no differential contrast between normal and ischemic myocardium on unenhanced MR images (7, 22). This problem is being overcome by the use of MR contrast media, which enhance the differences in signal intensities between normal and ischemic myocardium and thereby allow earlier detection of acute ischemia. Following the administration of GdDTPA-BMA, signal intensity of normally perfused myocardium increases on T1-weighted spin echo images, while signal of the ischemic region remains unchanged early after administration (3–15 min) (17). Later, the contrast medium redistributes into the ischemic region and the contrast between normal and ischemic myocardium is lost (Fig. 4) (17). This limitation would be less important using fast perfusion MR imaging. Perfusion studies for detection of regional ischemia have been accomplished using multiple low doses of MR contrast media (21, 57, 59) and multi-slice measurements along different axes of the heart (54, 55). Recently, contrast-enhanced echo planar and gradient echo imaging have been used to detect regional ischemia in experimental models (21, 30, 39, 43, 57, 59) and in humans (32, 34, 50–54, 62). In a rat model of ischemia examined with inversion recovery and gradient recalled echo planar imaging, there was no change in signal intensity in the territory of the occluded vessel after the administration of gadolinium chelate and the ischemic region was identified as a zone of either low "cold-spot" or high "hot-spot" signal, respectively (21, 57, 59). Similar results were obtained in dogs subjected to regional ischemia by acute occlusion of LAD coronary artery using inversion recovery (30, 39, 43, 45, 90) and driven equilibrium gradient recalled sequences (90). In patients with chronic coronary ar-

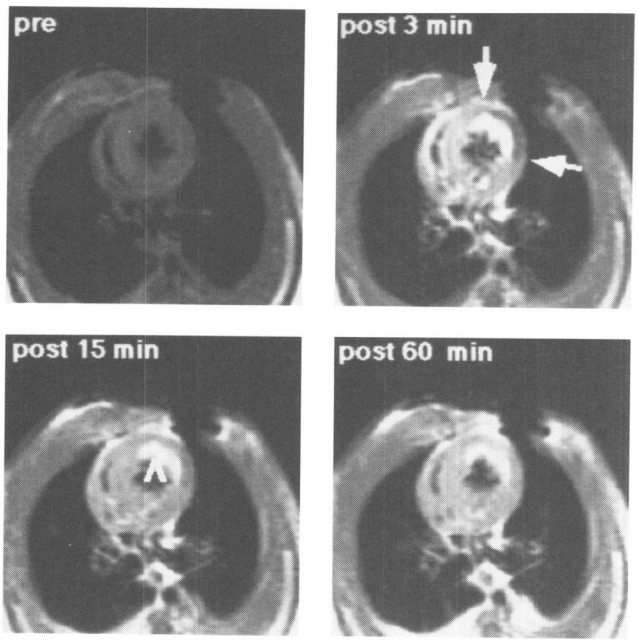

Figure 4. ECG-gated T1-weighted spin echo images (TR/TE = 300/20 mesc) obtained before and after the administration of GdDTPA-BMA. The rat was subjected to brief coronary occlusion of 30-min coronary artery occlusion prior to imaging. Images were acquired before (top left) and after 3 [top right], 15 [bottom left], and 60 [bottom right] min the injection of 0.3 mmol/kg GdDTPA-BMA. At early images (3 and 15 min), the ischemic region was depicted as region of low signal (cold-spot) (top right and bottom left images). Later (60 min), the contrast medium redistributes into the ischemic region and the contrast between normal and ischemic myocardium is lost (bottom right image). (^) Shows the static blood (bright area) inside LV chamber.

tery disease, detection of the ischemic myocardium is much more difficult because the gradual growth of collateral vessels causes rapid redistribution of contrast media and high variability in identifying ischemic myocardium. For this reason, small ischemic regions in many cases are not easily identified using contrast-enhanced T1-weighted spin echo images (75, 76).

Occlusive Myocardial Infarctions. Myocardial infarction is a complex and dynamic process. The progression of myocardial cell death may go to completion in a matter of hours, but the process of repair requires 4–6 weeks. The formation of edema in the infarcted region requires several hours to days to develop in humans (91). Thompson *et al.* (15) followed the healing process in patients with myocardial infarction over the course of 3 months using MR imaging. They found that signal intensity of the infarcted region evolved with the age of the infarction. A number of clinical and experimental studies have shown that acute, subacute, or chronic myocardial infarction can be detected as a bright region on unenhanced T2-weighted spin echo imaging (77, 78, 91, 92). The origin of the increase in signal intensity in the infarcted region is not well defined. However, several investigators have attributed the increase in signal intensity in the infarcted region to interstitial edema (i.e., shift of water between compartments), alterations in vascular permeability, and motion.

Several studies have suggested that administration of MR contrast media can improve the contrast between the normal and acutely infarcted myocardium, reduce the time for detection, and increase the contrast:noise ratio (9–11, 17, 75–78). In experimental animal models contrast-enhanced images of acute and subacute infarctions showed a bright peri-infarction zone; a doughnut pattern of enhancement (Fig. 5). Such peri-infarction enhancement has been noted as early as 3–5 hr (Fig. 5) and acute (1-day-old) (69) and subacute (10-day-old) myocardial infarctions in rats (69, 77). The cause for this peri-infarction enhancement is unknown but could represent local hyperemia and/or edema. In patients with acute and subacute infarctions, gadolinium-chelates (0.1–0.2 mmol/kg) produce greater increase in signal intensity of the infarcted region than normal myocardium on T1-weighted spin echo images (77, 78). Unlike in animal models of occlusive infarction, the infarcted regions can be visualized as a bright region, without a peri-infarction zone. Anatomic causes may be responsible for the difference in the pattern of enhancement of occlusive infarctions.

Magnetic susceptibility media have also proven to

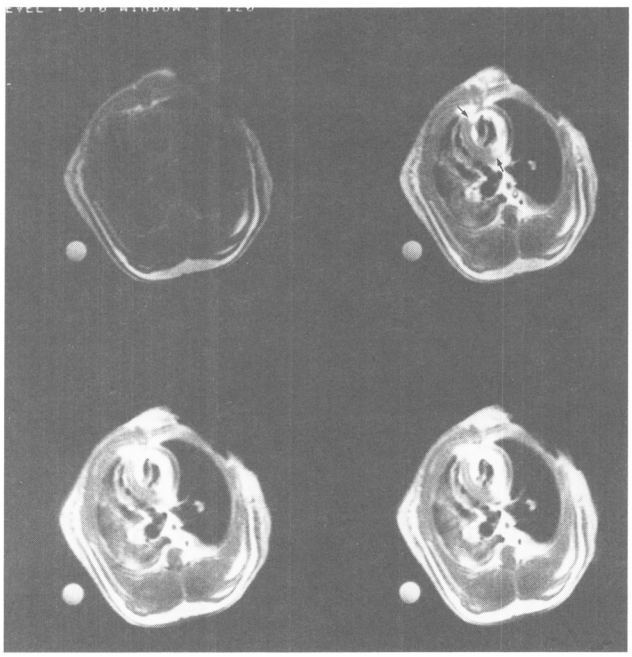

Figure 5. ECG-gated T1-weighted spin echo MR images (TR/TE = 300/20 msec) obtained from a rat subjected to 3½ hr coronary occlusion. MR images were acquired before (top left) and after (3 [top right], 30 [bottom left], and 60 [bottom right] min) the administration of 0.2 mmol/kg GdDTPA-BMA. The infarcted region appears as a dark region (cold-spot). Unlike acute ischemia, a doughnut pattern of enhancement (peri-infarction region) is shown at the periphery of the infarcted region (arrows). A crescent area of high signal intensity adjacent to the endocardial layer of the infarcted wall represents slowly flowing blood in the cavity of the LV.

be useful for demarcation of occlusive infarctions in experimental models (21–23). On T2-weighted spin echo images, DyDTPA-BMA (0.3–0.5 mmol/kg) induced a marked decrease in signal intensity of normal myocardium associated with a small decrease in signal of the infarcted region. The infarcted region can be visualized as a region of high signal intensity "hot-spot" (21, 23).

The dual utility of GdDTPA-BMA and GdBOPTA/Dimeg as a T1- or T2-enhancing agent was investigated in rats (57–59). Contrast-enhanced T1-weighted spin echo or inversion recovery echo planar images showed clear delineation of the infarcted region as an area of low signal intensity (cold-spot) after the injection of low dose (0.05 mmol/kg) of gadolinium-chelate (Fig. 1). At a higher dose (0.2 mmol/kg), the infarcted region was recognized as an area of high signal (hot-spot) (on driven equilibrium echo planar images) (14, 16, 23) (Fig. 2).

Characteristic Features of Occlusive and Reperfused Infarctions on MR Imaging. Discrimination between occlusive and reperfused myocardial infarctions has been a topic of considerable interest with implications for the noninvasive imaging of patients undergoing reperfusion procedures, such as balloon angiography or thrombolytic therapy.

It is well recognized that after coronary occlusion, ischemic cells do not die instantaneously or simultaneously. Hypoperfused myocardium in the jeopardized area may survive indefinitely. However, total coronary occlusion for a long period of time causes an intracellular osmotic load of accumulated catabolites which could cause substantial cell swelling when reperfusion provides an effectively unlimited supply of plasma water. This osmotic swelling, coupled with an already weakened membrane, could result in cellular membrane rupture (93, 94). With loss of cellular integrity of infarcted cells, there is no barrier between extracellular and intracellular compartments, consequently, the distribution volume of MR contrast media is expanded from 30–40% to 100%. The volumes of distribution of MR contrast media have been measured in normal and reperfused ischemically injured myocardium (25). Concentrations of gadolinium or dysprosium in the reperfused infarcted region were 2.5-fold greater in the infarcted than in normal myocardium, as measured by means of inductively coupled plasma mass spectrometry (25).

The appearance of occlusive and reperfused infarctions on contrast-enhanced images is different (Fig. 5 and 6) (95–98). Occlusive infarctions showed significantly greater enhancement of the peripheral zone (peri-infarction region) than the normal myocardium or the center of infarction in rats (20, 27) (Fig. 5), while reperfused infarction enhanced homogeneously following the administration of gadolinium- or manganese-chelate (20, 95, 96). Reperfused infarction showed no peri-infarction zone (97, 98), because this zone enhanced almost to the same degree as the center of the infarction (Fig. 6).

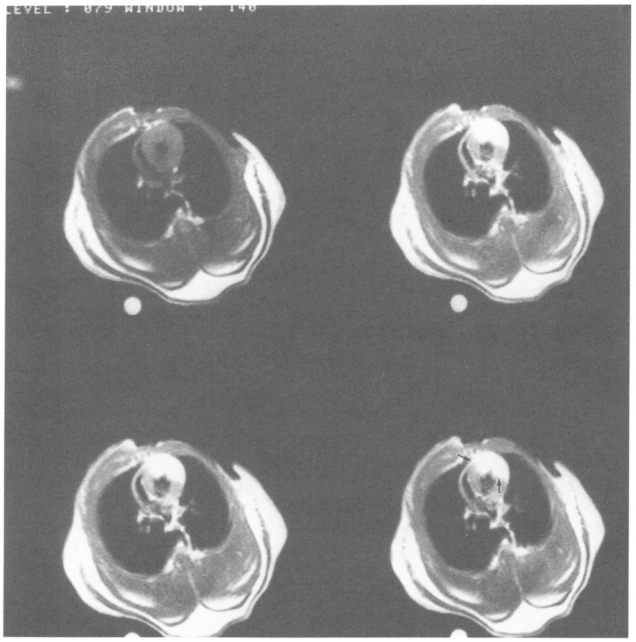

Figure 6. ECG-gated T1-weighted spin echo MR images (TR/TE = 300/20 msec) obtained from a rat subjected to 2 hr coronary occlusion followed by 1½ hr reperfusion. MR images were acquired before (top left) and after (3 [top right], 30 [bottom left], and 60 [bottom right] min) the administration of 0.2 mmol/kg GdDTPA-BMA. The reperfused ischemically injured region was depicted as region of high signal intensity (hot-spot) (arrows). Over the course of 60 min, a prominent increase in signal intensity of reperfused myocardium (antero-lateral LV wall) is demonstrated.

The findings of van Rossum *et al.* (35) in patients were in agreement with the experimental animal data. After the administration of GdDTPA, they were able to discriminate occlusive from reperfused infarctions at early images (8–10 min), suggesting that the difference was due to decreased delivery of GdDTPA to the territory of the occluded artery. Therefore, van Rossum *et al.* (35) suggested that fast MR imaging may be an appropriate technique for discriminating occlusive from reperfused myocardial infarctions. de Roos *et al.* were unable to confirm these findings in patients with acute myocardial infarctions (75). They found that GdDTPA produced greater and heterogeneous enhancement in occlusive infarcted regions compared with normal myocardium (75, 76). A similar pattern of enhancement was observed in patients with acute (5-day-old) and subacute (12- to 20-day-old) infarctions (77, 78, 92).

Recently, ultrafast echo planar imaging has been employed to discriminate between occlusive and reperfused myocardial infarctions during bolus transit of GdBOPTA/Dimeg. In rats subjected to occlusive infarction, inversion recovery echo planar images exhibited no change in signal intensity of the infarcted

region, while normally perfused myocardium showed rapid signal enhancement during the first passage of the contrast agent (cold-spot). Reperfused infarcted myocardium was affected very differently. The reperfused region showed delayed signal enhancement and a subsequent gradual signal intensity increase. By 2 min after injection, signal of reperfused infarction had increased (hot-spot) to a greater degree than that of normal myocardium at the peak of the bolus effect (36).

MR Imaging for Quantification of Area in Jeopardy and Infarction. Contrast-enhanced MR imaging offers certain attractions of physiological and anatomical parameters to be assessed in a single study. Since MR imaging is a noninvasive tool, dose- and time-dependent changes can be evaluated in individual subjects over a long period of time. A previous study has indicated that MR imaging is a valuable technique for assessing the development of left ventricular hypertrophy (99). Recent studies from our laboratory have suggested that contrast-enhanced MR imaging is a suitable technique to assess conditions accentuating ischemic injury in hypertrophied hearts. T1-weighted spin echo imaging with the aid of MR contrast media accurately depicted the higher incidence of myocardial injury among rats with left ventricular hypertrophy as compared with normal rats after 25 min of coronary occlusion followed by 1 hr reperfusion (100). Additionally, contrast-enhanced MR imaging proved to be useful in evaluating the effect of a calcium blocker designed to preserve myocardium at risk and reduce myocardial injury size in hypertrophied hearts (101).

Accurate sizing of the area in jeopardy and infarction can potentially provide valuable information for guiding therapeutic interventions aimed at limiting infarction size and ventricular remodeling (102). MR imaging has been effective for sizing regions of acute and subacute infarctions (103–108). de Roos *et al.* (108) used GdDTPA-enhanced imaging to estimate occlusive and reperfused infarction size in 21 patients. They found that the infarction size was significantly ($P < 0.05$) reduced in patients with reperfusion than in patients without reperfusion.

The accuracy of quantification of acutely reperfused infarction, determined histochemically, has been documented using gadolinium-enhanced MR imaging (16). Yu *et al.* (18) found a close correlation between unenhanced and dysprosium-enhanced T2-weighted images and the area in jeopardy measured by thallium-201 autoradiography. They concluded that DyDTPA-BMA-enhanced T2-weighted imaging has the potential to accurately quantify the area in jeopardy after acute coronary occlusion. In patients, the infarction size measured on unenhanced and contrast-enhanced images correlated well with thallium-201 and indium-111 antimyosin scans, respectively (105, 106). Johns *et al.* evaluated the capability of MR imaging to measure the size of 9 ± 3 days old infarction in patients. They found that the infarction size correlated well with the region of severe hypokinesa on contrast ventriculography (107). In the future, contrast-enhanced MR imaging may be used as a noninvasive technique for measurement of acute myocardial infarction size following reperfusion therapy (108).

MR Evaluation of Myocardial Perfusion

The most widely available clinical method for assessment of regional myocardial perfusion deficits is radionuclide scintigraphy with thallium-201 (84) or 99m-labeled technetium perfusion agents. Positron emission tomography (PET) is also useful for assessing myocardial perfusion, metabolism, and viability (109). Contrast-enhanced MR perfusion studies have recently been developed to allow noninvasive assessment of myocardial perfusion. Compared with the radionuclide techniques, myocardial MR perfusion techniques have advantages, including higher spatial resolution, no radiation exposure, and no attenuation problem related to overlying breast shadow, elevated diaphragm, or obesity.

Fast gradient recalled echo and echo planar imaging are the techniques currently used for myocardial perfusion. Fast gradient recalled echo imaging has the potential to acquire tomographic images at 1–3 sec intervals, whereas echo planar imaging needs 30–50 msec. With small modification in MR pulse sequence, these techniques can either be T1- (inversion recovery pulse) or T2-sensitive (driven equilibrium). It follows that appropriate MR contrast media for these studies are T1-enhancing agents and magnetic susceptibility agents, respectively.

At the present time, MR perfusion imaging research (28, 30, 31, 39, 40, 43, 49, 67) makes several assumptions: (i) myocardial water is freely diffusible between the compartments (intravascular, interstitial, and intracellular); (ii) extravascular gadolinium agents enhance myocardial signal monoexponentially; (iii) MR contrast media behave as a blood component of physiologic interest in its flow patterns; (iv) MR contrast agents do not perturb the physiologic parameters being measured; and (v) the measured parameters are constant in the MR images used for calculation. Accordingly, it has been suggested that the assessment of blood volume and perfusion deficits could be easily derived from signal intensity changes (30, 31, 39, 67).

However, MR perfusion imaging measurement differs from the original indicator-dilution method because MR techniques cannot measure an absolute quantity of the contrast medium in myocardium or blood, but can measure signal intensity which is not

necessarily proportional to the concentration of the agent (37, 38, 109–113). The original formulation of indicator-dilution method was based on the ability to measure directly the indicator content at the entry and exit from the myocardium. On contrast-enhanced MR images, the relaxation times (T1 and T2) of nearby water hydrogen in the capillaries can be lowered in the presence of contrast medium. The T1 value in other compartments (intracellular or interstitial) may then be lowered as a result of exchange of water between different compartments or because contrast medium can leak into these compartments. Accordingly, the indicator-dilution technique should be reviewed before it is used for MR perfusion imaging. Since the purpose of contrast-enhanced study is to probe myocardial perfusion, it is important that the contrast medium be confined within the intravascular compartment and not be allowed to diffuse through the capillary wall.

Quantification of blood flow (perfusion) and volume is complicated by the fact that an ideal bolus of MR contrast agent is difficult to achieve and the measured time dependence of signal intensity changes is a complex paradigm of organ transit function superimposed on arterial input function (30, 32, 34, 62, 109). Previous studies have indicated that when MR contrast medium is distributed throughout the extravascular space, enhanced T1 relaxation is not monoexponential (37, 109, 110). Any attempt to calculate myocardial flow from MR contrast transit time or image pixel intensity must take into account the interdependence of transit time and blood volume. It is necessary to determine the contrast concentration in the aorta, the amount of the contrast agent retained in myocardium during the first pass, the complete transit time of the contrast medium through the capillary bed, changes in intravascular volume and interstitium, and the width of the contrast input function. The precise form of $\Delta R1$ function depends, however, not only upon the integrity of local perfusion, but also upon the dilution and dispersion of the contrast medium bolus itself within the blood stream (111). If an arterial input function is added to signal intensity change over time, deconvolution analysis can then be used to find tissue clearance, the mean transit time through the capillary network, and ultimately the regional blood flow (112).

Experimental Models

Atkinson *et al.* (41) used inversion recovery prepared fast gradient recalled imaging to monitor the first pass of GdDTPA through Langendorff perfused hearts subjected to regional ischemia. Contrast-enhanced images provided differential contrast between normal and ischemic myocardium. The first pass of gadolinium and dysprosium chelates through hearts *in situ* was monitored in normal dogs (42, 90) and rats (21, 58, 59) as well as in dogs (43, 45, 90) and rats (21, 58, 59) subjected to coronary artery occlusion. In our laboratory, dogs were studied using a combination of inversion recovery prepared and driven equilibrium prepared fast gradient recalled sequences, while in rats inversion recovery and driven equilibrium echo planar images were used. On inversion recovery echo planar images and gradient echo images, administration of low dose of gadolinium chelates caused substantial enhancement in normal myocardium, while signal intensity of ischemic region was unchanged and this region was well defined as a cold-spot. On gradient recalled echo planar images and driven equilibrium prepared fast gradient recalled sequences, administration of dysprosium chelates or high dose of gadolinium-chelates caused substantial decrease in signal in normally perfused myocardium, while signal intensity of the ischemic region was less affected and the ischemic region was visualized as an area of relatively high signal (hot-spot) (21, 58, 59).

In a similar model of total coronary occlusion in dogs, Saeed *et al.* (90) imaged regions of myocardial ischemia using fast inversion recovery and driven equilibrium gradient recalled imaging. Inversion recovery gradient recalled imaging with gadolinium chelates produced substantial enhancement of normally perfused myocardium while the signal of the ischemic region remained unchanged (Fig. 7). On fast driven equilibrium gradient recalled images, dysprosium chelate produced signal loss in normally perfused myocardium while the signal of the ischemic region showed slight changes (Fig. 8). Scanning with echo planar imaging appears to offer higher sensitivity to T2* weighting compared with spin echo or gradient recalled sequences (17, 57, 58).

Kantor *et al.* (42) monitored myocardial signal intensity reduction associated with an intravenous bolus of DyDTPA or high dose of GdDTPA using echo planar imaging in normal dogs. They found that after dipyridamole infusion the magnitude of signal reduction was more profound and occurs earlier than in baseline state. Using dipyridamole-MR perfusion imaging, investigators have demonstrated the feasibility of detecting hypoperfused myocardium under conditions of mild, moderate, and severe coronary stenosis (39, 43). Wilke *et al.* (39) demonstrated in a canine heart a positive correlation between the alteration of myocardial signal intensity induced by GdDTPA and absolute myocardial blood flow assessed by radiolabeled microspheres. In another study by the same group (43), it has been shown that myocardial blood flow and volume can be measured using fast gradient recalled sequence with macromolecular MR contrast media such as GdDTPA-polylysine. Furthermore, GdDTPA-polylysine produced heterogeneous transmural en-

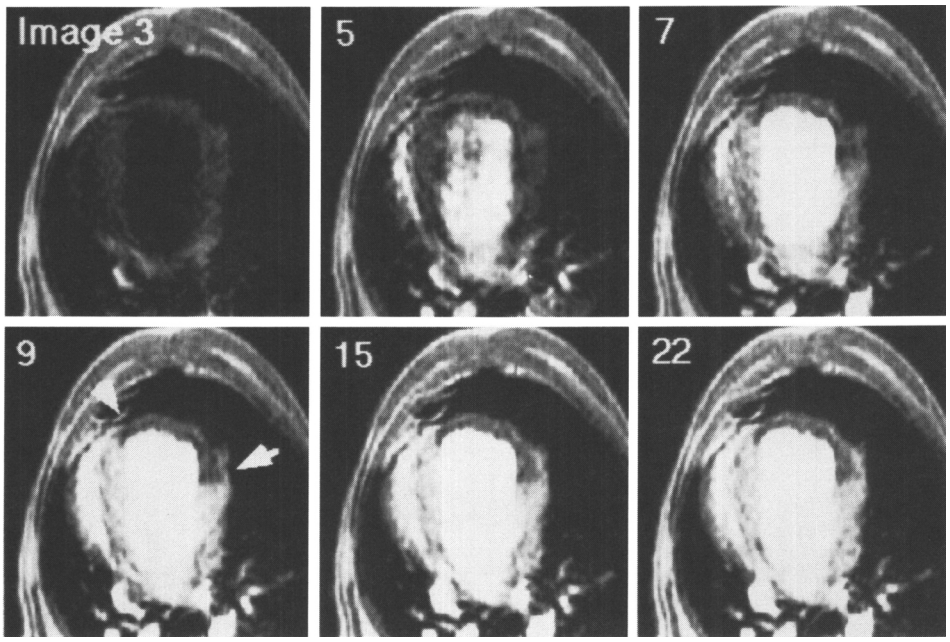

Figure 7. Inversion recovery prepared gradient recalled images (TI/TR/TE = 700/7.0/2.9 msec, and a flip angle = 7 degree) during the transit of 0.05 mmol/kg GdDTPA-BMA through the heart of a dog subjected to 10 min LAD coronary artery occlusion. Note that the ischemic region (arrows) is shown as a region of low signal intensity.

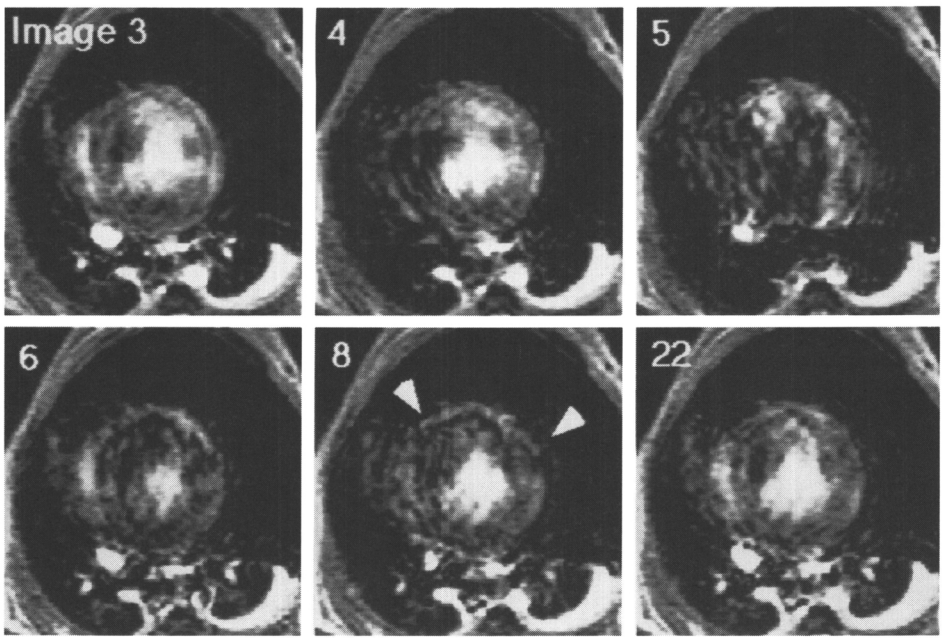

Figure 8. Driven equilibrium prepared gradient recalled images (DE delay/TR/TE = 60/10.2/4.2 msec, flip angle = 12 degree) during the transit of 0.4 mmol/kg DyDTPA-BMA through the heart of a dog subjected to 15 min LAD coronary artery occlusion. Note that the ischemic region (arrows) is shown as a region of relatively high signal intensity.

hancement (epi-, mid-, subendo-cardium) on fast gradient recalled images. This heterogeneous distribution of the agent may be attributed to variability in myocardial perfusion across the wall or capillary size and ordering.

On contrast-enhanced spin echo images, Miller *et al.* found that the signal intensity of the territory supplied by stenotic coronary artery was less enhanced than that of nonstenotic artery following the infusion of dipyridamole (44). Schaefer *et al.* (45) claimed that the hypoperfused region distal to coronary stenosis in a dog model can be detected in basal state (without the need of coronary vasodilator) during the first pass of manganese gluconate/calcium gluconate, indicating that the stenosis was severe. In recent studies in our laboratory, the use of dipyridamole has provided definition of hypoperfused regions during the first pass of gadolinium-based chelates. In the presence of critical

stenosis (abolishment of reactive hyperemic response) the hypoperfused region was not evident during the first pass of gadolinium chelate in the basal state. When the flow was challenged by dipyridamole infusion, the hypoperfused region became visible during the first pass of GdBOPTA/Dimeg (Fig. 9). This finding is in agreement with the well-established concept that hemodynamically significant stenosis is present when coronary reserve cannot be induced by vasodilatory stimulus (114). Yeon *et al.* (47) and Taeymans *et al.* (46) used elegant techniques to evaluate the spatial relationship between signal enhancement defects due to impaired perfusion and spatial modulation of magnetization (SPAMM) for assessment of function. They found that myocardial regions of perfusion deficit detected from the first pass of MR contrast corresponded to regions with contractile abnormality. Accordingly, fast MR imaging coupled with myocardial tagging techniques may allow noninvasive evaluation of myocardial perfusion, torsion, and regional wall stress and strain.

Ogawa *et al.* have shown in the brain that decreased blood oxygenation during apnea or anoxia causes decline in signal intensity on T2*-sensitive images (115). The cause of signal loss was that heme iron which is diamagnetic (low spin) in oxyhemoglobin became paramagnetic (high spin) in deoxyhemoglobin (116). In the heart, deoxyhemoglobin has also been used as endogenous MR contrast agent for demonstration of myocardial perfusion (47, 117). It has been found that during apnea, deoxyhemoglobin has the potential to significantly reduce myocardial signal Intensity by altering the T2* relaxation rate (47, 117–119). More recently, this phenomenon has been tested to determine whether reperfused myocardial infarction could be identified (119). It has been shown that significant signal loss in uninjured myocardium combined with no change in signal of the reperfused infarction allowed identification of the injured region as a bright region. The hyperintense region depicted during apnea was similar to that noted during a follow-up perfusion-sensitive scan in which the first pass of a bolus of dysprosium-based MR contrast medium was measured (119) (Fig. 10).

Human Studies

Pharmacologically induced coronary vasodilation with thallium-201 imaging, radionuclide angiography, or two dimensional echocardiography is routinely used for detection of coronary artery stenosis and impairment of contractile function in myocardial segment distal to stenosis in patients. Recently, the clinical potential of myocardial perfusion MR imaging has been extended to include healthy subjects (48, 62) and patients with coronary artery disease (32, 34, 44, 48–52). These studies were executed with bolus injection of MR contrast media and coronary vasodilators (such as dipyridamole, adenosine, or dobutamine infusion) or without pharmacological stress. Preliminary data in patients with coronary artery disease have indicated

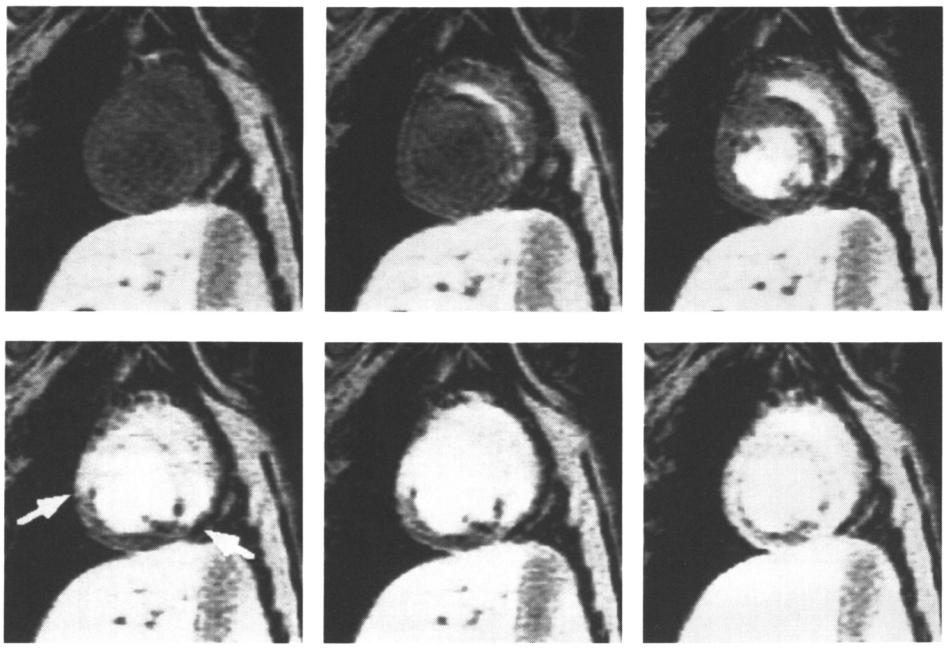

Figure 9. Inversion recovery prepared gradient recalled MR images (TI/TR/TE = 700/7.0/2.9 msec, and a flip angle = 7 degree) during the transit of 0.05 mmol/kg GdBOPTA/Dimeg through the heart of a dog subjected to nonocclusive left circumflex coronary artery stenosis (absence of reactive hyperemic response) following the infusion of 0.1 mg/kg/min dipyridamole for 5 min. Images were acquired every third heart beat (1.5–2 msec). Note that the area in jeopardy (posterior wall of the left ventricle) is shown as a region of lower signal intensity (arrows) compared to normal myocardium (anterior and septal walls). The territory of stenotic left circumflex coronary artery could not be defined prior to the infusion of dipyridamole.

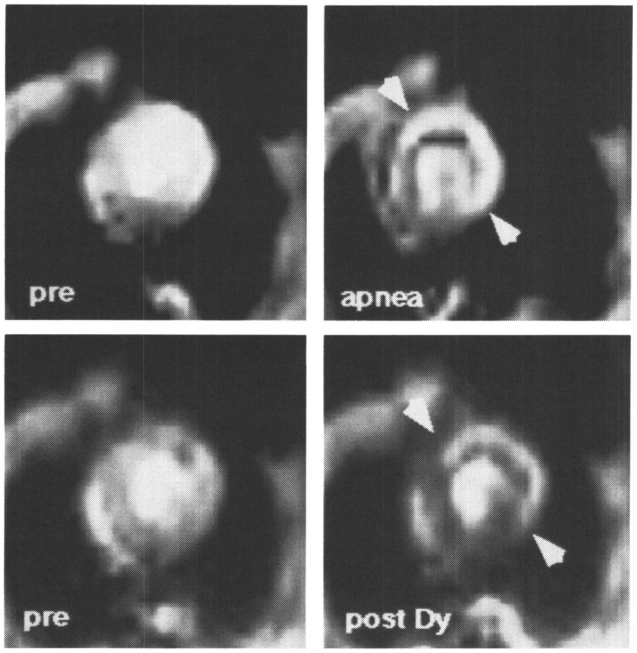

Figure 10. Transaxial gradient recalled echo planar imaging (TR/TE = 5 sec/10 msec) prior to and during apnea (top two images, respectively), and prior to and during bolus injection of 0.2 mmol/kg DyDTPA-BMA (bottom two images, respectively) in a rat subjected to 1 hr coronary occlusion followed by 1 hr reperfusion. Apnea caused substantial declines in signal from left ventricular chamber blood and myocardium but no change in signal of reperfused myocardium, allowing the depiction of reperfused infarction as a region of relatively high signal intensity (arrows). Bolus injection of DyDTPA-BMA caused greater reduction in signal of normal myocardium and allowed depiction of the infarcted zone as a region of high signal intensity that was similar to that evident during apnea.

that bolus administration of GdDTPA produces differential contrast between normal and ischemic myocardium on fast gradient recalled imaging (32, 34, 48, 49, 51). Wilke *et al.* (49) found a delay in the enhancement of the area in jeopardy, whereas Manning *et al.* (32) found reduction in the peak enhancement and diminution in up-slope of the intensity-time curve in the area in jeopardy. Eichenberger *et al.* (50) and Schaefer *et al.* (51) also demonstrated the difference between normally perfused and hypoperfused myocardium in patients with coronary disease following the infusion of dipyridamole. These results suggest that contrast-enhanced fast MR imaging has the potential to detect hypoperfused areas in patients with coronary disease.

Lombardi *et al.* (55) studied eight patients with acute myocardial infarction using contrast-enhanced fast gradient recalled imaging and echocardiography. They found close correlation between regional myocardial perfusion and contractility abnormalities after dobutamine infusion. Another group (52) used perfusion MR imaging in patients with myocardial infarction. This study has generated findings similar to those observed in different animal models of infarctions (57, 59, 90), with myocardial regions perfused by occluded vessels displaying weak signal enhancement compared with normally perfused myocardium.

The use of the contrast-enhanced fast gradient recalled imaging technique to provide an estimation of relative changes in myocardial perfusion has one potential limitation. Fast gradient recalled imaging technique provides only one image per cardiac cycle, thus limiting the number of slices as well as the temporal resolution. Recently, Edelman and Li (54) were the first who demonstrated the feasibility of using ultrafast inversion recovery echo planar MR imaging in normal hearts of humans. Grist *et al.* (54) studied 10 patients with known coronary artery disease on rest/stress SPECT thallium-201 or Tc-99mm MIBI. They found that fixed and reversible perfusion defects can be identified following the infusion of dipyridamole contrast-enhanced multi-slice echo planar MR imaging. The results correlated with areas of abnormal perfusion detected on SPECT perfusion study.

Further validations are necessary before definitive quantification of myocardial blood flow (ml/min) can be obtained using MR perfusion imaging in patients. Although it is too early to predict whether the use of MR contrast media and MR imaging techniques will be synergistic for the measurement of blood volume/flow in myocardium, the potential exists.

Myocardial Viability. Viability is of concern in patients with myocardial dysfunction because functional restoration may or may not be achieved following reperfusion. The ability to noninvasively discriminate reversible from irreversible myocardial injuries, following the administration of thrombolytic therapy, has assumed considerable clinical significance. Stress thallium-201 scintigraphy has been proposed as a method of assessing myocardial viability. Diminished uptake of thallium-201 with stress and absent redistribution at 4 hr has been called scar, while a reduction in thallium-201 uptake followed by redistribution is considered a marker of myocardial viability (120). PET also has the potential to differentiate between reversible and irreversible myocardial injuries in regions subjected to ischemia (109). Another fascinating method now in progress is the use of contrast-enhanced MR images for assessment of myocardial viability. This method uses susceptibility MR contrast media (16, 25).

Susceptibility enhancing (T2*) contrast media can be used to determine the integrity of cell membrane in red cell suspension (82). This idea has been recently adapted in the heart for characterizing the viability of myocardium in a model of reperfused ischemically injured myocardium. The hypothesis was that myocardial signal loss induced by DyDTPA-BMA is related to the cell viability (i.e., cellular exclusion of DyDTPA-BMA is compromised as cell viability is lost) (Fig. 11). In normal myocardium, cell membranes act as a barrier and limit the distribution of the contrast agent to

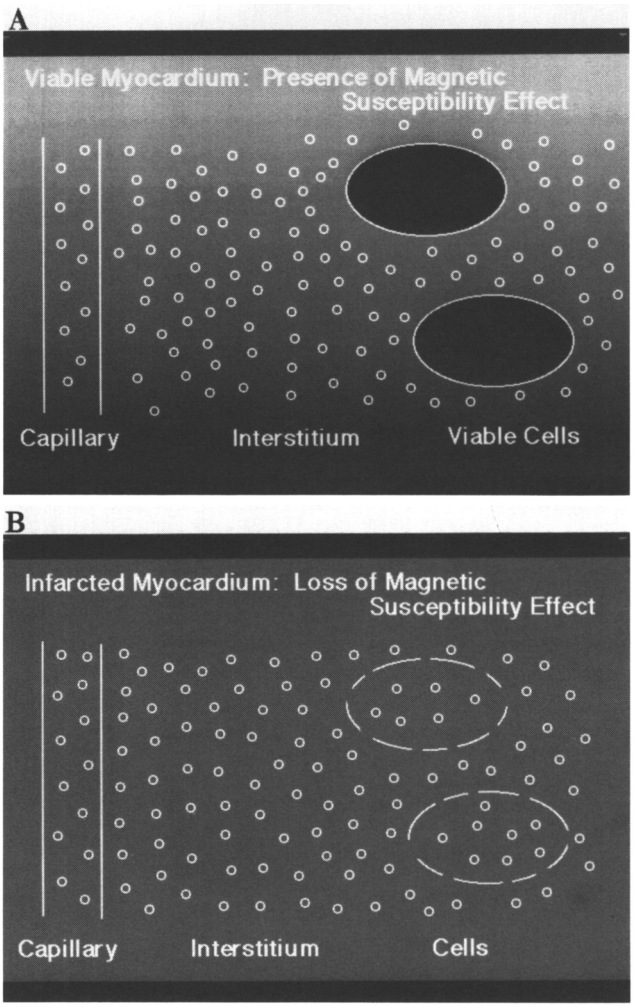

Figure 11. Schematic of concept of the mechanism of action of DyDTPA-BMA in normal (A) and infarcted myocardium (B). (A) After administration of DyDTPA-BMA, the signal is decreased in normal cells (dark cells). (B) In infarcted myocardium, administration of DyDTPA-BMA caused no change in signal intensity of dead cells because they lost their membrane integrity.

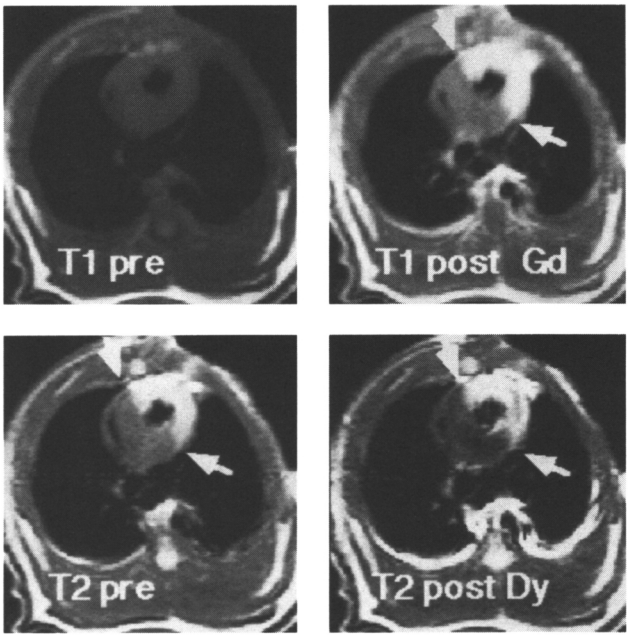

Figure 12. Transaxial spin echo images, acquired before and after the administration of GdDTPA-BMA and DyDTPA-BMA in a rat subjected to 2 hr coronary occlusion followed by 2½ hr reperfusion. Top left image is unenhanced T1-weighted spin echo images (TR/TE = 300/20 msec). Top right image is GdDTPA-BMA-enhanced T1-weighted image acquired 15 min after the administration of 0.2 mmol/kg GdDTPA-BMA. Bottom left image is unenhanced T2-weighted spin echo image (TR/TE = 1500/60 msec). The infarcted region is shown as a bright region on this type of imaging sequence due to the presence of myocardial edema. Bottom right image is DyDTPA-BMA-enhanced T2-weighted image acquired 20 min after injection of 1.0 mmol/kg DyDTPA-BMA. Reperfused infarcted myocardium is substantially enhanced following the administration of the GdDTPA-BMA compared with normal myocardium. In contrast, administration of DyDTPA-BMA caused great reduction in signal intensity of normal myocardium, while that of reperfused infarction was more moderately reduced, providing depiction of the infarction as a visible area of relative hyperintensity (arrows). The absence of signal loss in the reperfused region might be attributed to the loss of cellular compartmentalization; a component required for this agent to exert its effect.

intracellular space, and thereby cause signal reduction (Fig. 11A). Equilibrium distribution of the T2* contrast agent between extra- and intracellular compartments results in a net loss of its effect (Fig. 11B). This effect is evident on T2*-sensitive images, such as spin echo (T2) and gradient echo (T2*) images (16, 25) (Figures 12, 13). Since loss of cellular homeostasis is an indicator of cell death, alterations in the potency of susceptibility-dependent signal loss can be related to cell viability. In a recent study (16) we found that DyDTPA-BMA causes less signal loss in reperfused ischemically injured myocardium than normal myocardium (Fig. 12). The results of another study in excised hearts confirmed this finding using spin echo and gradient echo imaging (25) (Fig. 13). In both studies, GdDTPA-BMA was used to document the delivery of contrast agent and the restore of flow in the reperfused region, whereas DyDTPA-BMA was employed to probe myocardial viability (16, 25). Results suggest that DyDTPA-BMA can be used to define the collapse of cellular membrane integrity and GdDTPA-BMA as a marker of successful reperfusion. Whether dysprosium exclusion predicts functional recovery, especially in stunned myocardium, will need to be addressed in future experiments. In a canine model of reperfused ischemically injured myocardium, Piereira *et al.* confirmed our findings in rats (55). They found inverse correlation between the distribution volume of GdDTPA (using MR imaging) and myocardial viability (using thallium-201). Certainly, more studies are needed to confirm these exciting findings.

Conclusion

The recent development of rapid MR imaging techniques enables physiological events to be studied in real time. Information obtained from contrast-enhanced MR imaging will have a tremendous impact

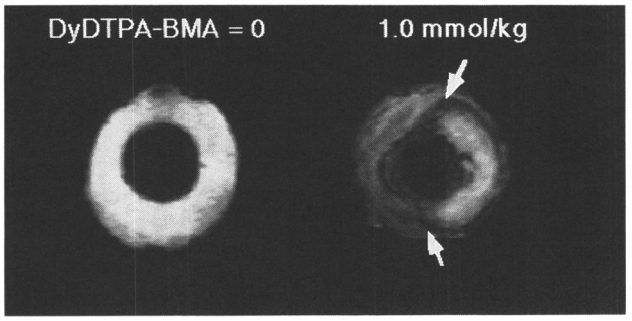

Figure 13. Short axis gradient recalled echo images (TR/TE = 600/15 msec) of two hearts subjected to ischemia (1 hr) followed by reperfusion (1 hr). The images were obtained from excised hearts: on the left is unenhanced and on the right DyDTPA-BMA-enhanced image. Note that the reperfused infarction (white arrow) is clearly visualized as a hyperintense region compared with normal myocardium, as a result of greater signal loss in normal myocardium. This finding is consistent with the hypothesis that the failure of necrotic myocardial cells, but viable cells, to exclude the dysprosium chelate is responsible for the diminished potency of dysprosium to cause MR signal loss in reperfused infarction.

on the understanding of myocardial physiology and pathology. The ongoing progress in MR contrast media research and MR imaging techniques will provide a unique and exclusive method for the evaluation of patients with ischemic heart disease.

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