MINIREVIEW

New Concepts in Characterization of Ischemically Injured Myocardium by MRI

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New concepts regarding the assessment of ischemic myocardial injuries have been addressed in this Minireview using magnetic resonance imaging (MRI). MRI, with its different techniques, brings not only anatomic, but also physiologic, information on ischemic heart disease. It has the ability to measure identical parameters in preclinical and clinical studies. MRI techniques provide the ideal package for repeated and noninvasive assessment of myocardial anatomy, viability, perfusion, and function. MR contrast agents can be applied in a variety of ways to improve MRI sensitivity for detecting and assessing ischemically injured myocardium. With MR contrast agents protocol, it becomes possible to identify ischemic, acutely infarcted, and peri-infarcted myocardium in occlusive and reperfused infarctions. Necrosis specific and nonspecific extracellular contrast-enhanced MRI has been used to assess myocardial viability. Contrast-enhanced perfusion MRI can explore the disturbances in large (angiography) and small coronary arteries (myocardial perfusion) as the underlying cause of myocardial dysfunction. Perfusion MRI has been used to measure myocardial perfusion (ml/min/g) and to demonstrate the difference in transmural myocardial blood flow. Information on no-reflow phenomenon is derived from dynamic changes in regional signal intensity after bolus injection of MR contrast agents. Another development is the near future availability of blood pool MR contrast agents. These agents are able to assess microvascular permeability and integrity and are advantageous in MR angiography (MRA) due to their persistence in the blood. Noncontrast-enhanced MRI such as cine MRI at rest/stress, sodium MRI, and MR spectroscopy also have the potential to noninvasively assess myocardial viability in patients. Futuristic applications for MRI in the heart will focus on identifying coronary artery disease at an early stage and the beneficial effects of new therapeutic agents such as intra-arterial gene therapy. MR techniques will have great future in the drug discovery process and in testing the effects of drugs on myocardial biochemistry, physiology, and morphology. Molecular imaging is going to **bloom in this decade.** [Exp Biol Med Vol. 226(5):367–376, 2001]

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Ischemic heart disease is the leading cause of death in the Western world (1, 2). The diagnosis of this disease requires a precise and accurate diagnostic method due to the high surgical mortality rate and complication rate for revascularization. Thrombotic occlusion of an epicardial coronary artery causes acute myocardial infarction. Management of patients with acute myocardial infarction is based, in most cases, on the patency of the major vessels. The importance of microvessels status in ischemic heart disease has been recently emphasized in patients with patent epicardial coronary arteries. Therefore, the focus has been shifted to include microvessels and their role in ischemic myocardial injury (3–7). Table I shows the current imaging modalities used in the characterization of ischemically injured myocardium.

In recent years, magnetic resonance imaging (MRI) techniques have emerged as a powerful and robust tool for characterizing ischemic heart disease. Unlike two-dimensional X-ray angiography, MRI is a volumetric (three-dimensional) technique. MRI is the process of localizing the radio signal from relaxing nuclei and displaying the signal as an image. Images are constructed from a number of lines of data in (frequency) or (K) space as opposed to (image) space. In MRI, each line is acquired from the same part of successive cardiac cycles; therefore, ECG-gatting of the acquisition is critical. The number of lines determines the resolution of the image, but also directly influences the duration of the acquisition.

Several MRI techniques have been proposed and experimentally implemented to address the issue of characterization of myocardial injury. Until now, the utilization of MRI in characterization of myocardial injury has been limited, primarily due to clinical reliance upon nuclear scintigraphy and echocardiography. Administration of MR contrast

Table I. The Imaging Modalities Used in the Detection and Characterization of Ischemic Heart Disease

Imaging modality	LV morphology	Myocardial viability	Coronary angiography	Myocardial blood flow/perfusion
X-ray cine catheterization			X	X
Electron bean CT	X			
Echocardiography	X	X		
Nuclear scintigraphy		X		X
PET	X	X		X
Doppler ultrasound				X
MRI	X	X	X	X

agents increases the sensitivity of MRI. MR contrast agents have similar physiological properties as the iodinated contrast agents. One problem encountered with contrast-enhanced MRI compared with other imaging modalities in radiology or nuclear medicine is that the effect of the contrast agent on water is being measured rather than the contrast agent itself. Since the presence of MR contrast agent in the tissue is only evident indirectly from its effect on tissue water, the influence of the water movement inside and outside of the capillaries and the myocytes should also be considered in the measurement of myocardial perfusion, along with the physical distribution of the contrast agent. Accordingly, restricting the contrast agent to the intravascular space does not necessarily restrict the contrast agent's effect to the intravascular space, because the excited water in the intravascular space diffuses freely into the interstitial space of the tissue.

In a recently published article, Runge (8) reviewed the safety of clinically approved MR contrast media. It was found that worldwide clinical trials and subsequent standard practice have shown that gadolinium chelates are safe and well tolerated in both adult and pediatric patients. Intravenous administration of gadolinium chelates is associated with adverse reaction, although this is infrequent. For example, minor adverse reactions such as nausea (1%–2%) and hives (<1%) were observed in few patients. The manganese chelate Mn-DPDP (magafodipir trisodium) and superparamagnetic iron oxide particles ferumoxides are also safe, but have relatively higher percentage of adverse reactions; 7% to 17% with Mn-DPDP and 15% with ferumoxides. MR contrast agents can be administered in patients with renal failure and anaphylactic reaction. Therefore, MRI with MR contrast media has clear advantage over conventional angiography that requires administration of nephrotoxic iodinated contrast media. The following properties are needed in a MR agent: nontoxic, nonreactive, and rapidly (several hours) and completely cleared from the body. The present Minireview highlights the results of laboratory animal investigations and clinical research in the area of myocardial injuries using MRI and MR contrast agents.

Myocardial Relaxation Times and MR Contrast Agents

The appearance of a tissue on MRI depends on both the physical characteristics of the tissue (such as viscosity, temperature, and flow through the area being examined) and the chemical characteristics (of MR contrast agents) that influence spin density, spin-lattice relaxation (T1), spin-spin relaxation (T2), and magnetic susceptibility of the tissue (T2*) (9–12). Although relaxation times in injured myocardium are generally prolonged in comparison with normal myocardium, there is considerable overlap in T1 and T2 relaxation times of surrounding tissues on unenhanced MRI. For example, the blood has longer T1 (1222 ± 228 msec) than that of normal myocardium (956 ± 158 msec) (13), but the T1 of edematous infarcted myocardium (1200 ± 150 msec) is close to that of the blood.

MR contrast agents enhance the difference between normal and infarcted myocardium on MRI and reduce blood signal loss due to saturation or dephasing of magnetization on MR angiography (MRA). The efficacy of MR contrast agents to affect proton relaxation rate (1/T1 and 1/T2) in myocardium or blood is related to the magnetic moment of unpaired electron, electron spin relaxation rate of the metal ion, and number of coordination sites available for water ligation (9–16).

The fractional distribution volume (FDV) of a contrast agent in normal and ischemically injured myocardium is exceedingly important because it determines the magnitude of regional enhancement. The molecular weight and shape of MR contrast agents play important roles in the distribution and elimination of these agents in the body. Furthermore, the physiologic environment of MR contrast agents also gives these agents different applications, analysis opportunities, and physiological inferences. Accordingly, the classification of MR contrast agents is based on their distribution in normal tissues and their effects on signal intensity.

Positive (T1-enhancing) contrast agents increase signal intensity of myocardium and blood on T1-weighted MR sequences. Most of the available MR contrast agents are positive (T1-enhancing) agents. Negative (susceptibility, T2*-enhancing) MR contrast agents decrease signal intensity of myocardium and blood on T2-weighted MR sequences. This group of agents alters signal intensity by reducing the homogeneity of the local magnetic field. Magnetic susceptibility agents must be compartmentalized to exert their susceptibility effect (17–19). The susceptibility effect is the proportionality constant between the applied

magnetic field strength and magnetization established with ions with unpaired electron. It should be noted that all efficient T1-enhancing MR contrast agents have a high magnetic susceptibility effect and can potentially be used to exert susceptibility under appropriate dose and imaging sequences.

The FDV of blood pool, extracellular, or intracellular MR contrast agents in normal myocardium during equilibrium phase (continuos infusion) are 5% to 10% (= myocardial blood volume during systole and diastole, respectively), 18% to 22% (= myocardial blood volume plus interstitial fluid volume), and 100% (= myocardial blood volume, interstitial fluid volume, and cellular fluid), respectively. An ideal MR contrast agent distributes only to the organ, tissue, or pathology of interest.

Seven MR contrast agents for intravenous administration are currently approved for clinical use in the United States. These include five gadolinium-chelates: gadopentetate dimeglumine was approved in 1988 (Gd-DTPA, Magnevist, Berlex Laboratories, USA and Schering AG, Germany), ProHance was approved in 1992 (Gd-HP-DO3A, Bracco Diagnostic), gadodiamide was approved in 1993 (Gd-DTPA-BMA, Omniscan, Nycomed-Amersham, USA), gadobenate dimeglumine was approved in a limited number of countries (Gd-BOPTA, Multihance, Bracco Diagnostics), and gadoterate meglumine was approved in many countries, but not USA (Gd-DOTA, Dotarem, Guerbet, France). The other two approved agents are manganese-chelate Mn-DPDP (Teslascan, Nycomed, Norway) and superparamagnetic iron particles. Several iron particles are also in various stages of clinical development.

Extracellular gadolinium-chelates have low molecular weights (650–2500 Daltons), therefore, after intravenous administration they rapidly equilibrate with the interstitial fluid. This group of agents has a relatively short plasma half-life of 20 min. Extracellular gadolinium-chelates produce greater enhancement in myocardium than intravascular agents do. They are highly effective agents with a high safety index. This group of agents can not be differentiated in terms of their enhancement effect. On the basis of osmolality and viscosity, clinically approved gadolinium-chelates can be differentiated; for example, gadodiamide and gadoteridol have the lowest osmolality (783 and 630 mOsmol/kg) and viscosity (1.4 and 1.3 cP at 37°C), respectively, in part since they are nonionic.

True blood pool MR contrast agents have higher molecular weight (>50,000 Daltons) than extracellular agents. Blood pool agents are also called intravascular, macromolecular, or nondiffusable agents. Distribution to intravascular space of extracellular agent can be achieved by conjugating the paramagnetic ligand to albumin, liposomes, or polymers, which prevent extravasation of these large molecules through the intravascular gaps for some period of time. Blood pool agents have greater T1 relaxivity than extracellular agents because they have multiple paramagnetic ions attached to each polymeric molecule, as well as slower molecular rotational correlation times of each paramagnetic subunit (13–16).

Intracellular MR contrast agents are free ions such as manganese (20, 21). Manganese ion distributes actively in the cellular compartment via voltage-operated calcium channels. Many organs, including the heart, are avid for manganese and appear to acquire it from chelates; e.g., Mn-DPDP. Manganese retention in normal myocardium and clearance from infarcted myocardium are comparable with features of widely used thallium (^{201}Tl) in SPECT imaging. Both ^{201}Tl and Mn^{2+} are characterized by a high uptake in the heart.

Table II shows recent applications of contrast-enhanced MRI in characterizing ischemically injured myocardium.

Assessment of Ischemically Injured Myocardium Using Contrast Enhanced MRI

After cessation of blood flow, phosphocreatine (PCr) and ATP are rapidly depleted in the ischemic region. The failure of the energy-dependent cell membrane allows influx of sodium and calcium and efflux of potassium, which are associated with cellular damage. Timely coronary artery reperfusion reduces cellular damage and improves left ventricular function. Functional improvement after reperfusion must be considered as the gold standard. Because ischemically injured myocardium is frequently compressed of both reversibly and irreversibly injured regions, accurate measurement of residual viability in postischemic myocardium or infarction size is critical for management decisions. Imaging modalities in radiology and cardiology are directed toward the depiction of myocardial function, perfusion, or metabolic abnormalities. Table I shows the current imaging modalities used and the potential of MRI in the characterization of ischemically injured myocardium.

MRI has several advantages over the other imaging modalities, including higher spatial resolution, no radiation exposure, no attenuation problem related to overlying breast shadow, elevated diaphragm, or obesity. The main se-

Table II. Applications of Contrast-Enhanced MRI in Characterization of Ischemic Heart Disease

1. Delineation of hypoperfused myocardium in patients with coronary artery stenosis.
2. Detection of acute, subacute, and chronic infarctions.
3. Differentiation between occlusive and reperfused infarctions and documentation of reperfusion at tissue level.
4. Assessment of myocardial viability and sizing of salvageable peri-infarcted border zone.
5. Assessment of microvascular integrity and detection of no-reflow zone.
6. Measurement of regional myocardial perfusion and transmural flow heterogeneity.
7. Coronary artery angiography to evaluate changes in the diameter of lumen and in plague morphology in major vessels.
8. Intervention-MRI, such as placement of stent, angioplasty, catheter tracking, and intra-arterial gene therapy.

quences that are widely used in MRI are shown in Table III. Administration of MR contrast agents improves the contrast between normal and ischemically injured myocardium, reduces the imaging time, and allows earlier depiction myocardial injury. Recently, contrast-enhanced MRI has emerged as an attractive approach for characterization of myocardial viability (20–34).

Since the effects of MR contrast agents are determined by physiologic factors within the tissue and physical/biophysical properties of the agent, it is often difficult to interpret contrast-enhancement patterns unambiguously in terms of pathologic state of tissue. The interaction between physiologic factors and physical/biophysical properties of extracellular, intracellular, and blood pool MR contrast agents in normal and infarcted myocardium has been extensively studied using regional T1-relaxation rate (R1) (33). The study illustrated that extracellular MR contrast agents have many properties that make them suitable markers of myocardial viability, including fast exchange between the intravascular and extravascular pools and lack of binding affinity to plasma albumin or necrotic cells. These properties are not available in blood pool or intracellular MR contrast agents. Table IV shows the main MR methods used in characterization of ischemically injured myocardium. These methods are discussed below.

Table III. Common MR Pulse Sequences Used in Imaging the Heart and Coronary Arteries

MRI Sequences	Measurements
Contrast-enhanced fast T1- and T2*-weighted gradient echo sequences	Detection and sizing of area at risk in nonocclusive coronary artery stenosis, measurement of myocardial perfusion, detection and sizing noreflow zone
Contrast-enhanced T1-weighted spin echo sequences	Sizing of infarction and peri-infarction border zone
Cine functional gradient echo (rest/stress), contrast-enhanced gradient echo and echo planar imaging	Myocardial viability
Contrast-enhanced inversion recovery echo planar, gradient echo, and spin echo sequences	Myocardial perfusion, sizing of infarction, and myocardial viability

Table IV. MR Methods Used in Characterization of Ischemically Injured Myocardium

1. Equilibrium state distribution of nonspecific extravascular MR agents to demonstrate the breakdown of cellular membranes.
2. Enhancement pattern (washin/washout) of postischemic myocardium using nonspecific extravascular MR contrast agents to predict regional viability.
3. Necrosis-specific MR contrast agents to define and size necrotic myocardium and, in conjunction with extracellular contrast agents, to measure the size of peri-infarction zone.
4. Specific intracellular MR contrast agents to probe ionic transport across functional cellular membranes.
5. Functional MRI to measure left ventricular wall thickness and thickening and LV chamber dimensions.

The Use of Equilibrium State Distribution of Nonspecific Extravascular MR Agents to Demonstrate the Breakdown of Cellular Membranes

Measurement of FDV from contrast-enhanced MRI rests upon the patency of the macro- (epicardial) and microcoronary arteries, the rapid exchange of the contrast agent between blood and tissue compartments, the constant T1 relaxivity of the extracellular MR contrast agent (i.e., no bonding to plasma proteins or debris of necrotic cells), the passive distribution of the agent in tissue, and the residual viability in postischemic myocardium (33). The relaxation rates (1/T1 or R1) of normal and infarcted myocardium exhibited a parallel decline with the central blood during the clearance of extracellular MR contrast agents (25), suggesting that the rate of exchange of MR contrast agents between myocardium and central blood is much faster than the clearance rate by the kidney. Under this condition, extracellular MR contrast media alone could estimate the FDV of these contrast agents simply from ΔR1 ratio of myocardium (R1 of the myocardium post-contrast media injection minus R1 of the myocardium pre-contrast media injection) to blood (R1 of the blood post-contrast media injection minus R1 of the blood pre-contrast media injection). The FDV of the extracellular contrast agent Gd-DTPA-BMA in normal and infarcted myocardium were 0.18 ± 0.01 and 0.85 ± 0.5, respectively using inversion recovery echo planar MRI (32–34). These values are in agreement with previously published data using different radioactive tracers and techniques (35, 36). The method of calculating FDV in normal and injured myocardium was validated using ^{99m}Tc-DTPA-autoradography (as a gold standard) (32). In this study it was confirmed that FDV values for Gd-DTPA are identical to ^{99m}Tc-DTPA in normal and infarcted myocardium. Normal myocardium was distinct from infarcted myocardium as a region of high count on ^{99m}Tc-DTPA images.

Arheden *et al.* (34) examined reperfused myocardial injuries produced by increasing duration of coronary artery occlusion from 20 to 60 min followed by 60 min of reperfusion. On autoradiography postischemic myocardium exhibited two regions of abnormally elevated count density—a core of high count density surrounded by a rim of moderately count density of ^{99m}Tc-DTPA. Animals subjected to 20 min of coronary artery occlusion exhibited only moderately count density of ^{99m}Tc-DTPA, but no sign of

infarction on histochemical staining. On electron microscopy, it was found that the moderate injury was comprised largely of viable cells, and that the distribution volume of GdDTPA-BMA and its surrogate (^{99m}TcDTPA) in the region is approximately 2-fold greater than normal myocardium, but one-half that of the infarction core in animals subjected to >30 min ischemia.

Saeed *et al.* (18) reported a somewhat different measure of breakdown of cellular membranes, using the unique properties of magnetic susceptibility MR contrast agent Dy-DTPA-BMA. These investigators found that reperfused infarction, while appearing hyperintense on GdDTPA-BMA-enhanced T1-weighted spin echo images, was also hyperintense on DyDTPA-BMA-enhanced T2-weighted spin echo images. Since the susceptibility agent causes signal loss when distributed heterogeneously in myocardium, the reduced signal loss evident in the infarcted region was hypothesized to result from a more even tissue (homogeneous) distribution, signifying that the agent penetrated the cellular spaces. This was further investigated in a subsequent report (19) in which excised hearts were imaged, using the same imaging parameters, shortly after administering of GdDTPA-BMA and DyDTPA-BMA. After imaging, the quantities of these agents present in the infarcted and normal myocardium were measured using analytical methods. It was found that the concentrations of both agents were significantly greater in infarcted than in normal myocardium (2.6 fold). Thus, it was postulated that the reduced effect exerted by DyDTPA-BMA was caused by a major decrease in the susceptibility potency of DyDTPA-BMA rather than by a reduced concentration in infarcted myocardium.

The Use of the Enhancement Pattern to Discriminate Infarcted from Noninfarcted Myocardium

The first pass approach has been widely applied in various ischemic animal models, as well as in patients with ischemic heart disease. Perfusion MRI with extracellular MR contrast agents has typically focused on the first pass of the contrast agent through the myocardium, following bolus intravenous injection (37–49). Two potential contrast mechanisms are offered for bolus tracking procedure, namely T1 (positive) and T2* (negative) enhancements of Gd-chelates alone or in combination with susceptibility-enhancing agents such as iron particles and dysprosium-chelates. We observed a delayed first pass arrival of MR contrast agents related to this effect followed by steady changes in signal to normal levels in acute reperfused infarction (49).

The first pass is of interest for measuring mean transit time, maximum signal intensity, upslope, downslope, and delay enhancement. Decreased perfusion to myocardium is manifest on T1-weighted images as less signal enhancement after bolus and thus relative hypointensity of the ischemic region. Qualitative estimation of the degree of hypoperfusion could be determined by comparison of the time-to-peak and mean transit time derived from the contrast-time curve with reference to normally perfused myocardium (37). Later, quantification of delays in the time of peak contrast agent arrival was suggested to allow delineation of area at risk (39, 40, 47). The applications of contrast-enhanced MR perfusion imaging extend beyond the detection of the area at risk and ischemia. It can help in the assessment and mapping of myocardial perfusion at baseline and in coronary stenosis and hyperemia based on signal intensity-time curve (46). Perfusion defects appear as only transient phenomenon on few images following the bolus administration of conventional extracellular MR contrast media. Gerber *et al.* (50) found that the intravascular Gadomer-17 provides more prolonged differentiation of perfusion defects in ischemically noninfarcted myocardium and in infarcted myocardium than the extracellular agent Gd-DTPA.

Recent clinical studies have indicated that the pattern of enhancement of postischemic myocardium varies from patient to patient during the first pass of MR contrast agents. This variation in enhancement is most likely related to the size of the area at risk, the stage of infarction (inflammatory or scar), the presence of collateral flow, the presence of intramyocardial hemorrhage, the dose of MR contrast agents, the imaging time after administration of contrast agents, and the acquisition time and pulse sequence used.

Recent studies have postulated that the enhancement of postischemic myocardium comes from dead myocardium (30, 51, 52). In some of these studies, a dobutamine-stress test was not used to determine whether the enhanced region is viable or nonviable. A dobutamine-stress test is useful in providing a more clear definition of viable myocardium than the enhancement by contrast agent. Lima *et al.* (30), using thallium scitigraphy and delayed MR contrast enhancement, found a close correlation between the enhanced-region and fixed-scintigraphic defects 10 min post-Gd-DTPA injection. In 21 of 22 patients, an abnormal MRI signal-time profile was observed for some regions. It was characterized by rapid initial signal rise followed by a slower continued rise, while normal regions exhibited rapid initial rise followed by decline. Importantly, in 10 of these patients, those with large infarctions, an additional abnormal subregion could be identified. It was typically located in the subendocardium, and it exhibited a much slower initial signal rise such that it appeared relatively hypointense in the first minutes after contrast administration. The hypointense regions were considered no-reflow zones.

Later, the clinical observations were confirmed by experimental findings (54). Similar to the patient study, three regions were identified on rapid T1-weighted postcontrast MRI in dogs subjected to reperfused infarction. Normal myocardium showed a modest signal rise followed by a slow decline, subendocardium of the injured region showed a delayed signal increase and was hypointense compared with normal myocardium for the initial 2 min postcontrast (designated "hypo" zone), and surrounding the hypointense

subendocardium was a region that exhibited rapid initial signal increase followed by an abnormal further signal increase and hyperintensity compared with normal myocardium by 2 min postcontrast (designated "hyper" zone). Further characterization revealed that both "hypo" and "hyper" zones corresponded to myocardial infarction defined by triphenyltetrazolium chloride (TTC) staining, that microsphere-determined blood flow in the "hypo" zone at 48 hr reflow was substantially decreased from baseline while blood flow in the "hyper" zone was not, and that the "hypo" zone matched the "no-reflow" zone defined by absence of fluorescence following administration of thioflavin-S, a putative marker of the "no-reflow" phenomenon (48, 54, 55). This phenomenon has been previously described by Kloner *et al.* (56). The "no-reflow" phenomenon was studied in two subsequent experimental MR studies. Rochitte *et al.* (48) prepared dogs with 90 min of occlusion of the LAD followed by reperfusion. MRI was performed 2, 6, and 48 hr later. It was found that the hypointense "no-reflow" zone progressively increased from 3.2% ± 1.8% of left ventricle at 2 hr to 9.9% ± 3.2% at 48 hr of reperfusion, while blood flow in the thioflavin-S-negative zone declined progressively. In another dog study, Wu *et al.* (57) examined reperfused infarction at 2 and 9 days of reperfusion and found no change in the size of the hypointense "no-reflow" zone or infarction on MRI, nor was there change in microsphere blood flows within the thioflavin-S-negative region or the triphenyltetrazolium chloride- (TTC) defined infarction. The infarction size on contrast-enhanced MRI was larger than TTC-defined infarction. From these studies it was concluded that augmentation in infarction size and in "no-reflow" zone occurred during the first 2 days of reperfusion, but not thereafter.

On the other hand, several studies (27, 28, 58–61) have suggested that early enhancement of postischemic myocardium by MR contrast medium is not necessarily a guarantee of necrosis. Investigators (27, 28, 58) have shown that rapid enhancement of injured myocardium constitutes a superior index of functional recovery than slow-delayed enhancement. Clinical studies have indicated that portions of enhanced myocardium contain viable myocardium (27, 28, 58). In a study of 28 patients in the first 2 weeks after reperfusion therapy for acute myocardial infarction, Dendale *et al.* (27) reported inotropic reserve in 41% of segments that showed transmural enhancement on postcontrast T1-weighted spin echo images, suggesting viability. Rogers *et al.* (28) examined 17 patients at 1 and 7 weeks after reperfusion by tagged images to evaluate regional function and at 1 week by monitoring of the first pass of Gd-DOTA with additional imaging at 7 min postinjection. Three distinct types of abnormal enhancement were observed; they are as follows: hypoenhancement during the first pass of the contrast agent without delayed hyperenhancement was termed HYPO, regions that were not hypointense during first pass and that showed delayed hyperintensity were termed HYPER, and regions that were hypointense during first pass, but hyperintense on delayed imaging, were termed COMB. Regions characterized as HYPER exhibited significant improvement in function between weeks 1 and 7, signifying viability; HYPO regions did not improve, and COMB regions exhibited mixed improvement. Kramer *et al.* (62) reported a similar result in patients after reperfusion. Inotropic reserve and improved function at follow-up examination, indicating viability, were observed in hyperenhanced and combined profiles, while regions exhibiting hypoenhancement did not improve.

The Use of Necrosis-Specific MR Contrast Agents to Accurately Detect Nonviable Myocardium

Differential contrast enhancement is a sensitive indicator of myocardial injury. Such a differential contrast enhancement that is seen after the administration of extracellular MR contrast agents results from the fractions of intravascular volume, interstitial volume, and intracellular volume of necrotic cells. Therefore, the mere presence of differential enhancement is not necessary necrosis specific and may not offer quantitative measurement of infarction size. Recent studies (27, 28, 58–61) have shown that differential enhancement by Gd-DTPA is derived from necrotic and viable myocardium, for example.

Therefore, a new strategy has been developed to detect and accurately size acute myocardial infarction using necrosis-specific MR contrast agents (63–66). The development of necrosis-specific MR contrast agents is analogous to the development of necrosis-specific radiotracers in nuclear medicine such as technectium-99m pyrophosphate and labeled monoclonal antibodies. MR contrast agents were linked to antibodies specific for intracellular components or to phosphonates or pyprohosphonate compounds. After intravenous injection, these agents interact with calcium deposits that accumulate in necrotic regions. These efforts did not persist due to concerns over agent toxicity (63). Molecular imaging may play an important role in characterizing myocardial viability, enzyme reaction, and oxidation-reduction of myocardium (67).

More recently, another necrosis-specific MR contrast agent, mesoporphyrin, has become available (64, 65). Several metalloporphyrins, including gadolinium, manganese, and iron chelates, have been investigated as potential tumor-specific MR agents. In 1996, Ni *et al.* (65) found that both gadolinium and manganese porphyrins have a marked and specific affinity for infarcted myocardium. In another study, Marschal *et al.* (64) reported that mesoporphyrin provides an accurate estimation of infarction size. The infarcted region was differentially and persistently (>24 hr) enhanced after administration of 0.05 mmol/kg mesoporphyrin, one-half of the recommended dose of extracellular MR contrast media. Pislaru *et al.* (66) studied the effect of mesoporphyrin in dogs subjected to reperfused infarction. Groups of dogs were given mesoporphyrin on 1, 2, and 6 days and were imaged 24 hr after contrast administration. Infarction size by contrast-enhanced MRI matched exactly the size

determined by TTC staining. Lim and Choi (68) found that the size of infarction did not change from 40 min to 12 hr after injection of mesoporphyrin. The persistent enhancement by mesoporphyrin can be used as a landmark for assessment of wall thickening around the infarcted region using functional MRI (60). Studies in our laboratory showed that the size of mesoporphyrin-enhanced region matched the true infarction defined by histochemical staining, while the Gd-DTPA overestimates infarction size. From the double contrast-enhanced MRI, the size of peri-infarction zone can be determined (Gd-DTPA-enhanced region – mesoporphyrin-enhanced region) (58–60). Measurement of regional wall thickening at the site of the mesoporphyrin-enhanced region revealed no wall thickening, while the rim of the Gd-DTPA-enhanced region (peri-infarction zone) showed moderate wall thickening at 24 hr of reperfusion, suggesting that the peri-infarction zone is viable. These MRI studies demonstrated that acute occlusion of the coronary artery followed by reperfusion produces infarcted core surrounded by viable but stunned myocardium.

The possibility of selective enhancement of infarcted myocardium and peri-infarcted zone has obvious diagnostic applications. Double contrast-enhanced MRI has been used for assessing the effects of new therapies designed to reduce infarction size and peri-infarction zone (69). It was found that the ATP-sensitive potassium channel opener nicorandil reduced the size of infarction and increased the size of viable peri-infarction zone. The role of cardiac MRI can be expected to expand with the availability of well-tolerated formulation of necrosis-specific MR contrast agents. Tolerance may improve with the adjustment of dose, slow infusion, or modification of the existing formulation of mesoporphyrin. Acute and chronic toxicity of mesoporphyrin must be addressed before this agent can be applied in clinical setting.

The Use of the Specific Intracellular MR Contrast Agents to Probe Ionic Transport across Viable Myocardium

Evidence of myocardial viability relies on the scintigraphic demonstration of uptake of various metabolic tracers such as thallium, carbon, or manganese. In analogue to ^{52m} manganese radionuclide for positron tomography method, a new method has been recently described for defining viable myocardium using manganese cation for MRI. This MR method is based on the released manganese from the MR contrast medium Mn-DPDP (20–22). Since the paramagnetic free manganese and the parent compound Mn-DPDP have distinct distribution and kinetic properties in the body, it was possible to obtain MR images on which contrast enhancement is primarily provided by free manganese. It has been shown that paramagnetic free manganese ($MnCl_2$) produces persistent enhancement of viable myocardium on heavily T1-weighted MR sequences (33). Useful enhancement of viable myocardium was achieved at 1 hr and persisted for several hours, providing ample opportunity for repeated image acquisition.

Mn-DPDP is metabolized and transmetallated with zinc, resulting in the release of manganese from the chelate. It was found that once manganese cation is released from the chelate, it is taken up by viable myocardium via voltage-dependent calcium channels and retained (20–22). Manganese ion binds to intracellular component. This mechanism explains the significant increase in relaxivity of manganese upon localization in tissue (20, 70–72). Consequently, if manganese released from the chelate can be imaged, it would be possible to relate the regional signal intensity (or R1) change to normal cellular function. This method demands a high T1-sensitive pulse sequence, such as inversion recovery spin echo images, to demonstrate the small change in T1 of viable myocardium. MnDPDP and Mn-TP were used for cardiac imaging 10 years ago (73, 74). At that time, they were used as nonspecific extracellular agents to delineate ischemic myocardium and to discriminate occlusive from reperfused myocardial infarctions. The immediate advantages of such agents for myocardial viability are, however, not so apparent.

Assessment of Myocardial Injuries by Noncontrast-Enhanced MRI

Noncontrast-enhanced MRI has been employed to assess myocardial viability using regional left ventricular wall thickening, thickness, stress, and strain during rest and pharmacologic-stress (dobutamine) (75–83). Sodium MRI has also been used to monitor the accumulation of sodium in necrotic myocardium (83, 84). MR spectroscopy techniques offer the capability to monitor the changes in myocardial energetics such as high-energy phosphates, PCr/ATP and pH at rest and during stress (85–91).

The detection of myocardial dysfunction during pharmacologic stress (dipyridamole and dobutamine infusion) has been used as a gold standard method for diagnosing ischemic heart disease. On nonenhanced MRI, the extent of systolic wall thickening has been shown to be more than 6 mm at the site of reversibly injured myocardium, while at the site of myocardial infarction the extent of systolic wall thickening was less than 2 mm. On functional MRI, a decreased wall thickening at rest and normal contraction after dobutamine characterized stunned myocardium, whereas infarcted myocardium is characterized by persistent dysfunction (76–78).

MR tagging is a technique unique to MRI (79–82) and is used to measure regional strain, motion, and thickening with excellent spatial resolution to distinguish the function in myocardial layers (epicardium versus endocardium). MR tagging allows identification and confirmation of myocardial ischemia that may otherwise be obscured by other imaging modalities. MR tagging has also characterized the contractile function of the peri-infarction zone.

Evaluation of ischemic myocardium using perfusion and ventricular function provides important diagnostic in-

formation. MRI represents accurate, safe, noninvasive, and inexpensive modality. Investigators found good correlation between MRI and other imaging modalities such as echocardiography, PET, or SPECT. Close correlation was also found between regional perfusion and function abnormalities after dipyridamole or dobutamine infusion (39, 42–46, 92–94).

In conclusion, MRI has the ability to measure identical parameters in preclinical and clinical studies. MRI in conjunction with different types of MR contrast media can characterize myocardial injuries. Extracellular and necrosis-specific MR contrast media are suitable agents to measure residual myocardial viability and infarction size, respectively, while blood pool agents can be employed in characterizing microvascular permeability, integrity, and no-reflow zone. Contrast-enhanced MRI can be used to noninvasively monitor the effects of new drugs designed to protect myocardium from injury. MR techniques will have great future in the drug discovery process and molecular imaging. MRI has not received, at the present time, the clinical acceptance to be referred to as a one-stop-shopping. However, it is the hope of the MR community that this will soon be achieved.

1. Lerner DJ, Kannal WB. Patterns of coronary heart disease mobility and mortality in the sexes: A 26-year follow up of the Framingham population. Am Heart J **111**:383–390, 1986.
2. American Heart Association. Heart and Stroke Facts. Dallas, TX: American Heart Association Press, pp1–2, 1992.
3. Ito H, Tomooka T, Sakai N, Yu H, Higashino Y, Fujii K, Masuyana T, Kitabatake A, Minamino T. Lack of myocardial perfusion immediately after successful thrombolysis: A predictor of poor recovery of left ventricular function in anterior myocardial infarction. Circulation **85**:1699–1705, 1992.
4. Topol EJ, Herskowitz A, Hutchins GM. Massive hemorrhagic myocardial infarction after coronary thrombolysis. Am J Med **81**:339–343, 1986.
5. Jeremy RW, Links JM, Becker LC. Progressive failure of coronary flow during reperfusion of myocardial infarction: Documentation of the no-reflow phenomenon with positron emission tomography. J Am Coll Cardiol **16**:695–704, 1990.
6. Asanuma T, Tanabe K, Ochiai K, Yoshitomi H, Nakamura K, Murakami Y, Sano K, Shimada T, Murakami R, Morioka S, Beppu S. Relationship between progressive microvascular damage and intramyocardial hemorrhage in patients with reperfused anterior myocardial infarction. Circulation **96**:448–453, 1997.
7. Garot P, Teiger E, Dupouy P, Aptecar E, Hittinger L, Dubois-Rande J-L. Coronary microcirculation and cardiovascular pathology. Drugs **58**:23–31, 1999.
8. Runge VM. Safety of approved MR contrast media for intravenous injection. J Magn Reson Imaging **12**:205–213, 2000.
9. Lauffer RB. Paramagnetic metal complexes as water proton relaxation agents for NMR imaing: Theory and design. Chem Rev **87**:901–923, 1987.
10. Keller KE, Henrichs PM, Spiller M, Koenig HS. Relaxation of solvent protons by solute Gd+3-chelates, revisited. Magn Reson Med **37**:730–735, 1997.
11. Fullerton GD. Physiologic basis of magnetic relaxation. In: Stark DD, WG Bradley, Eds. Magnetic Resonance Imaging. St. Louis, MO: Mosby Year Book, Inc., pp88 Magnetic Resonance Imaging 108, 1992.
12. Kowalewski J, Nordenskiold L, Benetis N, Westlund PO. Theory of nuclear relaxation in paramagnetic systems in solution. Prog NMR Spectroscopy **17**:141–185, 1985.
13. Taylor AM, Panting JR, Keegan J, Gatehouse PD, Amin D, Jhooti P, Yang GZ, McGill S, Burman ED, Francis JM, Firmin DN, Pennell DJ. Safety and preliminary findings with the intravascular contrast agent NC100150 injection for MR coronary angiography. J Magn Reson Imaging **9**:220–227, 1999.
14. Brasch RC. New directions in the development of MR imaging contrast media. Radiology **183**:1–11, 1992.
15. Wang SC, Wikstrom MG, White DL, Klaveness J, Holtz E, Rongved P, Moseley ME, Brasch RC. Evaluation of Gd-DTPA-labeled dextran as an intravascular MR contrast agent: Imaging characteristics in normal rat tissues. Radiology **175**:483–488, 1990.
16. Adam G, Neuerburg J, Spuntrup E, Muhler A, Scherer K, Gunther RW. Gd-DTPA-cascade-polymer: Potential blood pool contrast agent for MR imaging. J Magn Reson Imaging **4**:462–466, 1994.
17. Rosen BR, Belliveau JW, Vevea JM, Brady TJ. Perfusion imaging with NMR contrast agents. Magn Reson Med **14**:249–265, 1990.
18. Saeed M, Wendland MF, Masui T, Higgins CB. Reperfused myocardial infarctions on T1- and susceptibility-enhanced MRI: Evidence for loss of compartmentalization of contrast media. Magn Reson Med **31**:31–39, 1994.
19. Geschwind JF, Wendland MF, Saeed M, Lauerma K, Derugin N, Higgins CB. Identification of myocardial cell death in reperfused myocardial injury using dual mechanisms of contrast-enhanced magnetic resonance imaging. Acad Radiol **1**:319–325, 1994.
20. Bremerich J, Saeed M, Arheden H, Higgins CB, Wendland MF. Normal and infarcted myocardium: Differentiation with cellular uptake of manganese at MR imaging in a rat model. Radiology **216**:524–530, 2000.
21. Brurok H, Ardenkjaer-Larson JH, Hansson G, Skarra S, Berg K, Karlsson JO, Laursen L, Jynge P. Manganese dipyridoxyl diphosphate: MRI contrast agent with antioxidative and cardioprotective properties? Biochem Biophys Res Commun **254**:768–772, 1999.
22. Wendland MF, Saeed M, Lund G, Higgins CB. Contrast-enhanced MRI for quatification of myocardial viability. J Magn Reson Imaging **10**:694–702, 1999.
23. Diesbourg LD, Prato FS, Wisenberg G, Drost DJ, Marshall TP, Carroll SE, O'Neill B. Quantification of myocardial blood flow and extracellular volumes using a bolus injection of Gd-DTPA: Kinetic modeling in canine ischemic disease. Magn Reson Med **23**:239–253, 1992.
24. Tong CY, Prato FS, Wisenberg G, Le TY, Carroll E, Sandler D, Wills J, Drost D. Measurement of the extraction efficiency and distribution volume for Gd-DTPA in normal and diseased canine myocardium. Magn Reson Med **30**:337–346, 1993.
25. Wendland MF, Saeed M, Lauerma K Derugin N, Mintorovich J, Cavagna FM, Higgins CB. Alterations in T1 of normal and reperfused infarcted myocardium after Gd-BOPTA versus Gd-DTPA on inversion recovery EPI. Magn Reson Med **37**:448–456, 1997.
26. Harris PA, Lorenz CH, Holburn GE, Overholster KA. Regional measurement of the Gd-DTPA tissue partition coefficient in canine myocardium. Magn Reson Med **38**:541–545, 1997.
27. Dendale P, Franken PR, Block P, Pratikakis Y, de Roos A. Contrast-enhanced and functional magnetic resonance imaging for the detection of viable myocardium after infarction. Am Heart J **135**:875–880, 1998.
28. Rogers WJ, Jr., Kramer CM, Geskin G, Hu YL, Theobald TM, Vido DA, Petruolo S, Reichek N. Early contrast-enhanced MRI predicts late functional recovery after reperfused myocardial infarction [see comments]. Circulation **99**:744–750, 1999.
29. Wu KC, Zerhouni EA, Judd RM, Lugo-Olivieri CH, Barouch LA, Schulman SP, Blumental RS, Lima JA. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. Circulation **97**:765–772, 1998.
30. Lima JA, Judd RM, Bazille A, Schulman SP, Atalar E, Zerhouni EA. Regional heterogeneity of human myocardial infarcts demonstrated by

contrast-enhanced MRI: Potential mechanisms. Circulation **92:**1117–1125, 1995.
31. Pereira RS, Prato FS, Wisenberg G, Sykes J. The determination of myocardial viability using Gd-DTPA in a canine model of acute myocardial ischemia and reperfusion. Magn Reson Med **36:**684–693, 1996.
32. Arheden H, Saeed M, Higgins CB, Gao DW, Bremerich J, Wattynbach R, Dae MW, Wendland MF. Measurement of the distribution volume of gadopentatate dimeglumine at echo-planar MR imaging to quantify myocardial infarction: Comparison with 99mTc-DTPA autoradiography in rats. Radiology **211:**698–708, 1999.
33. Saeed M, Higgins CB, Geschwind JF, Wendland MF. T1-relaxation kinetics of extracellular, intracellular, and intravascular MR contrast agents in normal and acutely reperfused infarcted myocardium using echoplanar MR imaging. Eur Radiol **10:**310–318, 2000.
34. Arheden H, Saeed M, Higgins C, Ursell PC, Bremerich J, Wattenbach R, Dae MW, Wendland MF. Reperfused rat myocardium subjected to various duration of ischemia: Estimation of the distribution volume of contrast material using echoplanar MR imaging. Radiology **215:**520–528, 2000.
35. Polimeni PI. Extracellular space and ionic distribution in rat ventricle. Am J Physiol **227:**676–683, 1974.
36. Macchia DD, Page E, Polimeni PI. Interstitial anion distribution in striated muscle determined with [35S]sulfate and [3H]sucrose. Am J Physiol **237:**C125–C130, 1979.
37. Manning WJ, Atkinson DJ, Grossman W, Paulin S, Edelmann RR. First pass nuclear magnetic resonance imaging studies using Gadolinium-DTPA in patients with coronary artery disease. J Am Coll Cardiol **18:**959–965, 1991.
38. Wyttenbach R, Saeed M, Wendland MF, Geschwind JF, Bremerich J, Arheden H, Higgins CB. Detection of acute myocardial ischemia using first-pass dynamic of MN-DPDP on inversion recovery echo planar imaging. J Magn Reson Imaging **9:**209–214, 1999.
39. Schwitter J, Saeed M, Wendland MF, Sakuma H, Bremerich J, Canet E, Higgins CB. Assessment of myocardial function and perfusion in a canine model of non-occlusive coronary artery stenosis using fast magnetic resonance imaging. J Magn Reson Imaging **9:**101–110, 1999.
40. Saeed M, Wendland MF, Sakuma H, Geschwind JF, Derugun N, Cavagna FM, Higgins CB. Coronary artery stenosis: Detection with contrast-enhanced MR imaging in dogs. Radiology **196:**79–84, 1995.
41. van Rossum AC, Visser FC, Van Eenige MJ, Sprenger M, Valk J, Verheugt FW, Roos JP. Value of gadolinium-diethylene-triamine pentaacetic acid dynamics in magnetic resonance imaging of acute myocardial infarction with occluded and reperfused coronary arteries after thrombolysis. Am J Cardiol **65:**845–851, 1990.
42. Higgins CB, Saeed M, Wendland MF, Bourne M, Steffans J, Sakuma H. Evaluation of myocardial function and perfusion in ischemic heart disease. MAGMA **2:**177–184, 1994.
43. Klein MA, Collier BD, Hellman RS, Bamrah VS. Detection of chronic coronary artery disease: Value of pharmacological stressed, dynamically enhanced turbo-fast low-angle shot MR images. Am J Roentgenol **161:**257–263, 1993.
44. Bremerich J, Buser P, Bongartz G, Muller-Brand J, Graedel C, Pfistere M, Steinbrich W. Noninvasive stress testing of myocardial ischemia: Comparison of MRI perfusion and wall motion analysis to 99mTc-MIBI SPECT, relation to coronary angiography. Eur Radiol **7:**990–995, 1997.
45. Lauerma K, Virtanen KS, Sipila Lm, Hekali P, Aronen HJ. Multislice single-vessel proximal left anterior descending coronary artery disease before and after revascularization. Circulation **96:**2859–2867, 1997.
46. Szolar DH, Saeed M, Wendland MF, Sakuma H, Roberts TP, Stiskal MA, Derugin N, Higgins CB. MR imaging characterization of post-ischemic myocardial dysfunction ("stunned myocardium"): Relationship between functional and perfusion abnormalities. J Magn Reson Imaging **6:**615–624, 1996.
47. Saeed M, Wendland MF, Szolar D, Sakuma H, Geschwind JF, Globits S, Derugin N, Higgins CB. Quantification of the extent of area at risk with fast contrast-enhanced magnetic resonance imaging in experimental coronary artery stenosis. Am Heart J **132:**921–932, 1996.
48. Rochitte CE, Lima JA, Bluemke DA, Reeder SB, McVeigh ER, Furuta T, Becker LC, Melin JA. Magnitude and time course of microvascular obstruction and tissue injury after acute myocardial infarction. Circulation **98:**1006–1014, 1998.
49. Saeed M, Wendland MF, Yu KK, Lauerma K, Li HT, Derugin N, Cavagna FM, Higgins CB. Identification of myocardial reperfusion with echo planar magnetic resonance imaging: Discrimination between occlusive and reperfused infarctions. Circulation **90:**1492–1501, 1994.
50. Gerber BL, Bluemke DA, Chinn BB, Heldman A, Lima JA, Kraitchman DL. Comparison between Gadomer-17 and gadolinmium DTPA for the assessment of myocardial perfusion using first pass MRI in a swine model of single vessel coronary artery stenosis. Radiology **217:**130, 2000.
51. Kim RJ, Fieno DS, Parrish TB, Harris K, Chen EL, Simonetti O, Bundy J, Finn JP, Klocke FJ, Judd RM. Relationship of MRI delayed contrast enhancement to reversible injury, infarct age and contractile function. Circulation **100:**1992–2002, 1999.
52. Ramani K, Judd RM, Holly RA, Parrish TB, Rigolin VH, Parker MA, Callahan C, Fritzgerald SW, Bonow RO, Klocke FJ. Contrast magnetic resonance imaging in the assessment of myocardial viability in patients with stable coronary artery disease and left ventricular dysfunction. Circulation **98:**2687–2694, 1998.
53. Judd RM, Lugo-Olivieri CH, Arai M, Kondo T, Croisille P, Lima JA, Mohan V, Becker LC, Zerhouni EA. Physiological basis of myocardial contrast enhancement in fast magnetic resonance images of 2-day-old reperfused canine infarcts. Circulation **92:**1902–1910, 1995.
54. Gerber BL, Rochitte CS, Melin JA, McVeigh ER, Bluemke DA, Wu KC, Becker LC, Lima JA. Microvascular obstruction and left ventricular remodeling early after acute myocardial infarction. Circulation **101:**2734–2741, 2000.
55. Ambrosio G, Weisman HF, Mannisi JA, Becker LC. Progressive impairment of regional myocardial perfusion after initial restoration of postischemic blood flow. Circulation **80:**1846–1861, 1989.
56. Kloner RA, Ganote CE, Jennings RB. The "no-reflow" phenomenon after temporary coronary occlusion in the dog. J Clin Invest **54:**1496–1508, 1974.
57. Wu KC, Kim RJ, Bluemke DA, Rochitte CE, Zerhouni EA, Becker LC, Lima JA. Quantification and time course of microvascular obstruction by contrast-enhanced echocardiography and magnetic resonance imaging following acute myocardial infarction and reperfusion. J Am Coll Cardiol **32:**1756–1764, 1998.
58. Sandstede JJW, Lipke C, Ber M, Harre K, Pabst T, Kenn W, Neubauer S, Hahn D. Analysis of first and delayed contrast-enhancement patterns of dysfunctional myocardium on MR imaging: Use in the prediction of myocardial viability. Am J Roentg **174:**1737–1740, 2000.
59. Saeed M, Bremerich J, Wendland MF, Wyttenbach R, Weinmann HJ, Higgins CB. Reperfused myocardial infarction as seen with use of necrosis-specific versus standard extracellular MR contrast media in rats. Radiology **213:**247–257, 1999.
60. Saeed M, Lund G, Wendland MF, Weinmann HJ, Higgins CB. MR evaluation of the peri-infarction zone in postischemic myocardium using functional and contrast-enhanced MR imaging. Radiology **217:**241, 2000.
61. Stillman AE, Wilke N, Jerosch-Herold M. Myocardial viability. Radiol Clin North Am **37:**361–378, 1999.
62. Kramer CM. Integrated approach to ischemic heart disease: The one-stop shop. Cardiol Clin **16:**267–276, 1998.
63. Weissleder R, Lee A, Khaw B, Shen T, Brady T. Detection of myocardial infarction with MION-antimyosin. Radiology **182:**381–385, 1992.
64. Marchal G, Ni Y, Herijgers P, Flameng W, Petre C, Bosmans H, Yu J, Ebert W, Hilger CS, Pfeffer D, Semmler W, Baert AL. Paramagnetic metalloporphyrins: Infarct avid contrast agents for diagnosis of acute myocardial infarction by MRI. Eur Radiol **6:**2–8, 1996.
65. Ni Y, Marchal G, Herijgers P, Flameng W, Miao Y, Bogaert J, Dy-

markowski S, Semmler W, Markel W, van de Werf FJ. Paramagnetic metalloporphyrins: From enhancers of malignant tumors to markers of myocardial infarcts. Acad Radiol **3**(Suppl 2):S395–S397, 1996.
66. Pislaru SV, Ni Y, Pislaru C, Bosmans H, Miao Y, Boggert J, Dymarkowski S, Semmler W, Marchal G, van Frans J. Noninvasive measurements of infarct size after thrombolysis with a necrosis-avid MRI contrast agent. Circulation **99**:690–696, 1999.
67. Weissleder R. Molecular imaging: Exploring the next frontier. Radiology **212**:609–614, 1999.
68. Lim T-H, Choi SH. MRI of myocardial infarction. J Magn Reson Imaging 10:686-693, 1999.
69. Saeed M, Lund G, Wendland MF, Watziger N, Weinmann HJ, Higgins CB. The cardioprotective effects of nicorandil in ischemically injured myocardium depicted by necrosis-specific and standard extracellular MR contrast media. Radiology **217**:465, 2000.
70. Gallez B, Bacic G, Swartz H. Evidence for the dissociation of the hepatobiliry MRI contrast agent Mn-DPDP. Magn Reson Med **35**:14–19, 1996.
71. Brurok H, Schjott J, Berg K, Karlsson JO, Jynge P. Effects of Mn DPDP, DPDP, and MnCl2 on cardiac energy metabolism and manganese accumulation: An experimental study in the isolated perfused rat heart. Invest Radiol **32**:205–211, 1997.
72. Van der Elst L, Colet JM, Muller RN. Spectroscopic and metabolic effects of MnCl2 and MnDPDP on the isolated and perfused rat heart. Invest Radiol **32**:581–588, 1997.
73. Pomeroy OH, Wendland M, Wagner S, Derugin N, Holt WW, Rocklage SM, Quay S, Higgins CB. Magnetic resonance imaging of acute myocardial ischemia using a manganese chelate, Mn-DPDP. Invest Radiol **24**:531–536, 1989.
74. Saeed M, Wagner S, Wendland MF, Derugin N, Finkbeiner WE, Higgins CB. Occlusive and reperfused myocardial infarcts: Differentiation with Mn-DPDP-enhanced MR imaging. Radiology **172**:59–64, 1989.
75. Pennel DJ, Underwood RS, Ell PJ, Swannton RH, Walker JM, Longmore DB. Dipyridamole magnetic resonance imaging: A comparison with thallium-201 emission tomography. Br Heart J **64**:362–369, 1990.
76. Baer FM, Voth E, Schneider CA, Theissen P, Schicha H, Sechtem D. Comparison of low-dose dobutamine-gradient echo magnetic resonance imaging and positron emission tomography with [18F]fluorodeoxyglucose in patients with chronic coronary artery disease: A functional and morphological approach to the detection of residual myocardial viability. Circulation **91**:1006–1015, 1995.
77. Sechtem U, Baer FM, Voth E, Theissen P, Schneider CA. Stress functional MRI: Detection of ischemic heart disease and myocardial viability. J Magn Reson Imaging **10**:667–675, 1999.
78. Baer FM, Theissen P, Schneider CA, Voth E, Sechtem U, Schicha H, Erdmann E. Dobutamine magnetic resonance imaging predicts contractile recovery of chronically dysfunction myocardium after successful revascularization. J Am Coll Cardiol **31**:1040–1048, 1998.
79. Zerhouni EA, Parish DM, Rogers WJ, Yang A, Shapiro EP. Human heart: Tagging with MR imaging a method for noninvasive assessment of myocardial motion. Radiology **169**:59–63, 1988.
80. Axel L, Dougherty L. Heart wall motion: Improved method of spatial modulation of magnetization for MR imaging. Radiology **172**:349–356, 1989.
81. Young AA, Kramer CM, Ferrari L, Axel N, Reicheck N. Three-dimensional left ventricular deformation in hypertrophic cardiomyopathy. Circulation **90**:854–867, 1994.
82. Kramer CM, Lima JA, Reicheck N, Ferrari VA, Lianeras MR, Palmon LC, Yeh IT, Tallant B, Axel L. Regional differences in function within noninfarcted myocardium during left ventricular remodeling. Circulation **88**:1279–1288, 1993.
83. Reicheck N. MRI myocardial tagging. J Magn Reson Imaging **10**:609–616, 1999.
84. Cannon PJ, Maudsley AA, Hilal SK, Simon HE, Cassidy F. Sodium nuclear magnetic resonance imaging of myocardial tissue of dogs after coronary artery occlusion and reperfusion. J AM Coll Cardiol **7**:573–579, 1986.
85. Kim RJ, Lima JA, Chen EI, Reeder SB, Klocke FJ, Zerhouni EA, Judd RM. Fast 23Na magnetic resonance imaging of acute reperfused myocardial infarction: Potential to assess myocardial viability. Circulation **95**:1877–1885, 1997.
86. Saeed M, Wendland MF, Wagner S, Derugin N, Higgins CB. Preservation of high-energy phosphate reserves in a cat model of post-ischemic myocardial dysfunction. Invest Radiol **27**:145–152, 1992.
87. Higgins CB, Saeed M, Wendland MF, Chew WM. Magnetic resonance spectroscopy of the heart: Overview of studies in animals and man. Invest Radiol **24**:962–968, 1990.
88. Holt WW, Wendland MF, Derugin N, Wolfe C, Saeed M, Higgins CB. Effects of nicardipine, a calcium channel antagonist, on myocardial salvage and high energy phosphate stores in reperfused myocardial injury. J Am Coll Cardiol **16**:1736–1744, 1990.
89. Weiss RG, Bottomley PA, Hardy CJ, Gerstenblith G. Regional myocardial metabolism of high-energy phosphates during isometric exercise in patients with coronary artery disease. New Engl J Med **323**:1593–1600, 1990.
90. Bottomley PA, Weiss RG. Non-invasive magnetic resonance detection of creatine depletion in non-viable infarcted myocardium. Lancet **351**:714–718, 1998.
91. Pohost GM. Is 31P-NMR spectroscopic imaging a viable approach to assess myocardial viability? Circulation **92**:9–10, 1995.
92. Kraitchman DL, Wilke N, Hexeberg, H, Jerosch-Herold M, Wang Y, Parrish TB, Chang CN, Zhang Y, Bache RJ, Axel L. Myocardial perfusion and function in dogs with moderate coronary stenosis. Magn Reson Med **35**:771–780, 1996.
93. Kraitchman DL, Young AA, Bloomgarden DC, Fayad ZA, Dougherty L, Ferrari VA, Boston RC, Axel L. Integrated MRI assessment of regional function and perfusion in canine myocardial infarction. Magn Reson Med **40**:311–328, 1998.
94. Eichenberger AC, Schuiki E, Kochli VD, Amann FW, McKinnon GC, von Schulthess GK. Ishemic heart disease: assessment with gadolinium-enhanced ultrafast MR imaging and dipyridamole stress. J Magn Reson Imaging **4**:425–431, 1995.