Magnetic Resonance Characterization of the Peri-Infarction Zone of Reperfused Myocardial Infarction With Necrosis-Specific and Extracellular Nonspecific Contrast Media

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Background—Because ischemically injured myocardium is frequently composed of viable and nonviable portions, a method to discriminate the two is useful for clinical management.

Methods and Results—Ischemically injured myocardium was characterized with extracellular nonspecific (Gd-DTPA) and necrosis-specific (mesoporphyrin) MR contrast media in rats. Relaxation rates (R1) were measured on day 1 and day 2 by inversion-recovery echoplanar imaging. Spin-echo imaging was used to define contrast-enhanced regions and regional wall thickening. Gadolinium concentration, area at risk, and infarct size were measured at postmortem examination. \( \Delta R1 \) ratio (\( \Delta R1_{\text{myocardium}}/\Delta R1_{\text{blood}} \)) after administration of Gd-DTPA was greater in ischemically injured myocardium (1.20 ± 0.15) than in normal myocardium (0.47 ± 0.05, \( P < 0.05 \)), which was attributed to differences in gadolinium concentration and water content. The Gd-DTPA–enhanced region on day 2 was larger (32.8 ± 0.9%) than true infarction as demonstrated by triphenyltetrazolium chloride (TTC) (24.6 ± 1.4%, \( P < 0.001, r = 0.21 \)). Bland-Altman analysis revealed that the Gd-DTPA–enhanced region overestimated true infarct size by 7.8 ± 5.9%. On the other hand, the mesoporphyrin-enhanced region (26.9 ± 1.8%, \( P = \text{NS}, r = 0.87 \)) and true infarct size were identical. The difference in the areas demarcated by the 2 agents is the peri-infarction. Systolic and diastolic MR images revealed no wall thickening in the mesoporphyrin-enhanced region (0.3 ± 3.3%) but reduced thickening in the Gd-DTPA–enhanced rim (8.5 ± 5.5%, \( P < 0.05 \)).

Conclusions—The Gd-DTPA–enhanced region encompasses both viable and nonviable portions of the ischemically injured myocardium. The Gd-DTPA–enhanced area overestimated infarct size, but the mesoporphyrin-enhanced area matched true infarct size. The salvageable peri-infarction zone can be characterized with double-contrast–enhanced and functional MR imaging; the mismatched area of enhancement between the 2 agents shows residual wall thickening. (Circulation. 2001;103:871-876.)

Key Words: magnetic resonance imaging ■ myocardial infarction

Timely coronary artery reperfusion reduces infarct size and improves left ventricular (LV) function.\(^1,2\) It has been suggested that preservation of the rim of injured myocardium might be sufficient to prevent or lessen infarct expansion and LV remodeling.\(^3,4\) Therefore, detection of residual viability in ischemically injured myocardium and accurate sizing of nontransmural infarction are critical for management decisions.

MR contrast media have been used for detection and characterization of myocardial injuries.\(^5-14\) Extracellular MR contrast media such as Gd-DTPA are passively distributed into the interstitium from intact capillaries in normal myocardium. Disruption of cellular membrane, expansion of interstitium, and increased blood volume provide an expanded distribution volume for these agents. Several studies\(^12-14\) have indicated that nonspecific extracellular contrast media overestimate infarct size, suggesting that the enhanced region encompasses both viable and nonviable portions. Until recently, the peri-infarction zone has not been mapped and characterized with a single technique because of spatial or contrast-resolution constraints of available imaging techniques.

A new contrast-enhanced MR imaging method has been described recently for sizing the peri-infarction zone.\(^14\) Paramagnetic metalloporphyrins, represented by mesoporphyrin, are known to be tumor-specific MR contrast media.\(^15\) Ni et
al\textsuperscript{16} have converted metalloporphyrins from tumor-seeking agents into markers of necrotic myocardium. Mesoporphyrin provides accurate sizing of occlusive and reperfused infarctions.\textsuperscript{17–19}

The purpose of this study was (1) to characterize the peri-infarction zone in moderately injured myocardium by use of the combination of Gd-DTPA and mesoporphyrin MR contrast media and (2) to determine the function (wall thickening) of regions enhanced by Gd-DTPA and mesoporphyrin. The major hypothesis of this study is that the difference in the areas demarcated by the 2 agents is the salvageable border zone with reduced but residual contractile function.

Methods

MR Contrast Media
The nonspecific gadopentetate dimeglumine (Gd-DTPA) and necrosis-specific bis-gadolinium-mesoporphyrin (mesoporphyrin) were synthesized by Schering AG. T1 and T2 relaxivities of mesoporphyrin are higher (8.9 and 8.9 mmol \textsuperscript{-1} \textcdot s \textsuperscript{-1}) than Gd-DTPA (3.7 and 5.6 mmol \textsuperscript{-1} \textcdot s \textsuperscript{-1}). The molecular weights of Gd-DTPA and mesoporphyrin are 938 and 1697 Da, respectively.\textsuperscript{20,21}

Experimental Protocol
Animal care and use was in accordance with the Guide for the Care and Use of Laboratory Animals. Sprague-Dawley rats were purchased from Simonsen Laboratory (Modesto, Calif). Anesthetized rats (n=20) were subjected to 30 minutes of coronary occlusion followed by reperfusion. Four rats died immediately after coronary occlusion due to ventricular arrhythmia. Ischemically injured myocardium after 30 minutes of occlusion is expected to contain viable and nonviable portions.\textsuperscript{22} Two groups were studied (n=8 rats per group). Group 1 animals received 0.3 mmol/kg Gd-DTPA on day 1 (2-hour reperfusion) and on day 2 (24-hour reperfusion) and were imaged after each injection. Group 2 animals received 0.05 mmol/kg mesoporphyrin on day 1 (2-hour reperfusion) and were imaged after each injection. Mesoporphyrin on day 1 (2-hour reperfusion) and were imaged on day 2 (24-hour reperfusion); then, 0.3 mmol/kg Gd-DTPA was administered, and another set of images was acquired. To directly compare the size and extent of the enhanced regions, the following steps were taken: (1) mesoporphyrin- and Gd-DTPA–enhanced areas were determined in a single imaging session on day 2 without removal of the animal from the magnet; (2) identical imaging parameters were used to measure the enhanced areas and wall thickening; and (3) MR images were acquired at identical times after the contrast injection.

MR Imaging
ECG-triggered MR images were acquired with a 2.0-T system (Bruker Instruments). Inversion-recovery echo-planar (IR-EPI) MR images were used to monitor regional changes in T1. Each T1 value was obtained from a set of 20 images. The imaging parameters have been described previously.\textsuperscript{23} Regional T1 (normal, ischemically injured myocardium and LV blood) was measured every 5 minutes for 30 minutes at 2 and 24 hours of reperfusion in group 1 rats and at 24 hours of reperfusion in group 2 animals. A relaxation rate (R1) value was derived from 1/T1. The \( \Delta R1 \) ratio (\( \Delta R1_{\text{myocardium}}/\Delta R1_{\text{blood}} \)) provides an approximation of partition coefficients and fractional distribution volume (fDV) of Gd-DTPA.\textsuperscript{10,11} We calculated fDV using the formula \( fDV = \Delta R1_{\text{myocardium/blood}} \times (1 - \text{hematocrit}) \).\textsuperscript{10,11,22}

T1-weighted spin-echo images were acquired after IR-EPI (30 minutes after Gd-DTPA). A single imaging sequence was used to measure regional signal intensity (SI) and contrast (SI ischemically injured/SI normal myocardium), determine the size of the differentially enhanced myocardium, and measure wall thickening between end-diastolic (QRS complex) and end-systolic images (~45% R-R interval time). The imaging parameters have been described previ-ously.\textsuperscript{14} SI values were normalized to SI of Gd-DTPA phantom (T1=1.1 seconds), which was included in each image acquisition. Heterogeneity in vascular distribution resulted in a high degree of intersubject variability in the injured area after coronary occlusion. Therefore, measurements of wall thickening were done in accordance with the extent of enhanced regions with Gd-DTPA and mesoporphyrin. LV wall thickening was determined in the mesoporphyrin-enhanced region and rim of the Gd-DTPA–enhanced region and in the remote region represented by the centers of the posterior and septal walls.

Postmortem Measurements
After imaging, the coronary artery was reoccluded. Phthalamoycine blue dye was injected intravenously to demarcate the area at risk. The LV was sliced into 2-mm-thick sections corresponding to MR images and scanned with a flatbed scanner (LaCie Limited) connected to a computer (Apple Computer). Slices were incubated in 2% triphenyltetrazolium chloride (TTC) and rescanned, and the infarcted region was traced with National Institutes of Health image-analysis software. Regional Gd-DTPA concentration was measured by inductive coupled plasma mass spectrometry (Schering AG), and myocardial water content was determined with the wet/dry weight ratio.

Statistics
Data were presented as mean±SEM. Measurements were compared between the 2 groups by ANOVA and Scheffé’s F test. Linear regression and Bland-Altman analysis were used to determine correlation and agreement between MR and histomorphometry. The null hypothesis was rejected for P<0.05.

Results

Characterization of Gd-DTPA–Enhanced Region (Group 1)
On baseline IR-EPI, T1 values were higher in ischemically injured myocardium (1.15±0.03 seconds) than in normal myocardium (1.05±0.03 seconds, P<0.05). Gd-DTPA caused greater reduction in T1 of ischemically injured myocardium (0.20±0.04 seconds) than that of normal myocardium (0.40±0.03 seconds, P<0.05). Peak reduction in T1 was noted 5 minutes after Gd-DTPA. \( \Delta R1 \) ratio was greater in ischemically injured myocardium (1.20±0.15) than in normal myocardium (0.47±0.05, P<0.05) and was almost constant after 10 minutes (Figure 1), indicating near-equilibrium distribution of Gd-DTPA between blood and myocardium. Because a near-equilibrium condition was
reached, fDV could be estimated from the ΔR1 ratio.\textsuperscript{10,11,22} fDV of Gd-DTPA was identical on day 1 and day 2 in normal (0.21±0.02) and ischemically injured (0.62±0.08) myocardium. Ischemically injured myocardium was discernible as a bright zone (SI=0.64±0.12 arbitrary units [AU]) compared with normal myocardium (0.42±0.09 AU, P<0.05) after Gd-DTPA but was not discriminated on precontrast spin-echo images (Figure 2). Prolonged reperfusion (22 hours) resulted in no significant change in contrast (1.58±0.06 on day 1 versus 1.61±0.06 on day 2) on Gd-DTPA–enhanced images. However, the Gd-DTPA–enhanced region was smaller on day 2 (32.8±0.9% of LV surface area) than on day 1 (37.0±0.5%, P<0.0001) (Figure 3). Linear regression analysis showed poor correlation between true infarct size demarcated by TTC and the Gd-DTPA–enhanced region on day 1 (Y=36.6±0.013X, r=0.04, P=NS) and on day 2 (Y=29.7±0.19X, r=0.21, P=NS). On day 1, Bland-Altman analysis revealed an overestimation of infarct size (12.4±4.1% of LV surface area) on the Gd-DTPA–enhanced region compared with true infarct size as defined by TTC (24.6±1.4%). The overestimation of infarct size by Gd-DTPA (8.3±4.1% of LV surface area) was less on day 2. On both days, the Gd-DTPA–enhanced region was smaller than the true area at risk defined at postmortem examination (49.6±1.9% of LV surface area, P<0.001) (Figure 3).

Gadolinium concentration in ischemically injured myocardium (487±145 nmol/g) was greater than that in normal myocardium (252±73 nmol/g, P<0.05). Similarly, wet/dry weight ratio was greater (4.70±0.17) in ischemically injured than in normal myocardium (4.33±0.11, P<0.05).

Characterization of Mesoporphyrin-Enhanced Region (Group 2)
On mesoporphyrin-enhanced IR-EPI, T1 values were shorter in ischemically injured myocardium (0.65±0.03 seconds) than in normal myocardium (0.90±0.01 seconds, P<0.001). T1 values of LV blood (1.23±0.15 seconds) and normal myocardium (0.91±0.01 seconds) were identical to the baseline T1 values in group 1 animals (1.21±0.15 and 1.05±0.03 seconds, P=NS), indicating that mesoporphyrin was completely cleared from the blood and normal myocardium.

Ischemically injured myocardium appeared as a homogeneously bright region on mesoporphyrin and Gd-DTPA–enhanced spin-echo images (Figure 4). The homogenous enhancement of ischemically injured myocardium suggests that the contrast medium is delivered and homogeneously distributed in this region. After mesoporphyrin, SI of normal myocardium (0.42±0.06 AU) was significantly lower than SI of ischemically injured myocardium (0.67±0.09 AU, P<0.001). On day 2, the contrast was 1.63±0.07 after mesoporphyrin and 1.96±0.09 (P<0.01) after mesoporphyrin plus Gd-DTPA.

The size of the mesoporphyrin-enhanced region (mean 26.9±1.8%, range 15.7% to 36.4% of LV surface area) was identical to the true infarct size as demarcated by TTC (mean 26.9±1.6%, range 18.7% to 38.4%, P=NS). Strong correlation was found between the mesoporphyrin-enhanced region and true infarct size as defined by TTC (r=0.87, slope=0.98, intercept=0.49, P>0.0001). Bland-Altman analysis also showed close agreement (0.0±2.87%) between the 2 measurements.
Demarcation of the Peri-Infarction Zone
Figure 5 shows examples of the size of the mesoporphyrin and Gd-DTPA–enhanced MR regions, as well as TTC-defined true infarct size and area at risk. Images and stained sections were obtained from corresponding slice. "Crescent bright area represents slowly flowing blood in LV cavity, suggesting poor contraction in adjacent wall.

The Gd-DTPA–enhanced region covered 70% of the true area at risk defined at postmortem examination (48.5±1.9%, P<0.001). There was no difference in area at risk between group 1 animals (49.6±1.9%) and group 2 animals (48.5±1.9%, P=NS). The size of the Gd-DTPA–enhanced region on day 2 was similar in group 1 (32.8±0.9%) and group 2 (34.7±0.7%, P=NS).

LV Wall Thickening
Short-axis images acquired at the midventricular level during systole and diastole revealed substantial reduction in regional function in contrast-enhanced regions (Figure 6A). Posterior and septal walls, which were remote from the ischemic region, demonstrated a 22.0±5.5% and 26.0±3.5% thickening (Figure 6B). There was no wall thickening at the mesoporphyrin-enhanced region (0.3±3.3%) or the center of the Gd-DTPA–enhanced region (0.3±3.3%, P=NS). However, there was reduced but residual wall thickening at the rim of the Gd-DTPA–enhanced region (8.5±5.5%). There a significant difference in wall thickening between the periphery of the Gd-DTPA–enhanced region and the mesoporphyrin-enhanced region (P<0.05).

Discussion
The present study describes a strategy for the use of a combination of nonspecific and necrosis-specific MR contrast media for mapping the potentially salvageable peri-infarction zone. The double-contrast–enhanced MR technique was performed in 1 imaging session on day 2. Gd-DTPA alone was not accurate in sizing infarcted myocardium. Unlike mesoporphyrin, Gd-DTPA overestimated infarcted myocardium by putatively including the peri-infarction zone. Overestimation of the infarct size by Gd-DTPA confirms previously published data in occlusive and reperfused infarctions.12–14 The difference in the enhanced regions demarcated by the agents may represent the peri-infarction zone. Functional MR imaging confirmed that the outer rim of the Gd-DTPA–enhanced zone (peri-infarction zone) is hypokinetic rather than akinetic, whereas the mesoporphyrin-enhanced region is entirely akinetic. Correlation between regional contrast enhancement and contractile function in ischemically injured myocardium may be important for assessment of viability in patients.

Sizing of Peri-Infarction Zone
Subtraction of the size of the Gd-DTPA–enhanced region from the mesoporphyrin-enhanced region provided quantitative estimation of the potentially salvageable peri-infarction zone. The following findings support the notion that the...
peri-infarction zone is viable: (1) Gd-DTPA overestimated infarct size determined by the gold standard of staining TTC; (2) a significant diminution in the size of Gd-DTPA–enhanced region was observed over the course of 22-hour reperfusion; and (3) residual wall thickening was found in the Gd-DTPA–enhanced rim. The peri-infarction zone has been characterized previously by invasive and noninvasive techniques.24–27 Using histopathological methods, Reimer et al27 reported that the peri-infarction zone develops less cellular necrosis than the core of the infarction. Using autoradiography, Arheden et al22 found that the fDV of 99mTc-DTPA is enlarged in the peri-infarction zone compared with normal myocardium but is significantly less than in completely infarcted myocardium. Bogaert et al24 combined positron emission tomography with tagged MR imaging to verify viability in a peri-infarction zone with reduced contractile function.

The double-contrast approach used in this study for mapping the peri-infarction zone takes advantage of both the specific and prolonged binding properties of mesoporphyrin in necrotic myocardium and the nonspecific distribution of Gd-DTPA in infarcted and peri-infarcted myocardium. The practical advantages of the double-contrast approach are as follows: (1) it has the potential to document both the infarcted zone, which will not recover function, and the peri-infarction zone, which may recover function; (2) when contrast-enhanced images are combined with functional images, the enhanced zone of infarction provides a landmark for relating improvement in wall thickening; and (3) accurate sizing of infarcted and peri-infarcted zones will improve the prediction of infarct expansion and LV remodeling.

Characterization of Ischemically Injured Myocardium

Coronary occlusion and reperfusion initiate a progression of changes in myocardium at both cellular (membrane damage) and microvascular (increase in intracapillary blood volume) levels that cause a significant increase in regional TI. TI changes were clearly demonstrated on unenhanced IR-EPI imaging but not on TI-weighted spin-echo imaging, because the IR-EPI sequence is more TI sensitive than the spin-echo sequence.22 The loss of cellular integrity and edema in ischemically injured myocardium have been reported previously in rats and pigs.30,31 Further studies are needed to explore the difference in Gd-DTPA concentration between viable and nonviable portions within the ischemically injured myocardium. The distribution of 99mTc-DTPA has been used recently as a surrogate agent for Gd-DTPA to study viable and nonviable portions within the ischemically injured myocardium by autoradiography.22

Clinical studies have drawn attention to the enhancement pattern of nonspecific MR contrast media to characterize ischemically injured myocardium. These studies have indicated that enhancement of ischemically injured myocardium is associated not only with necrosis but also with edema. Dendale et al7 and Rogers et al8 found 3 patterns of enhancement: (1) hypoenhancement (HYPO) on first-pass images; (2) isointense enhancement on first-pass and hyperenhancement on delayed images (HYPER); and (3) hypoenhancement on first-pass and hyperenhancement on delayed images (COMB). Regions characterized as HYPER exhibited improvement in function between weeks 1 and 7, signifying viability; HYPO regions showed no functional improvement; and COMB regions exhibited mixed improvement. These protocols may prove useful for the assessment of potentially salvageable myocardium in patients by Gd-DTPA alone.

In contrast to a previous report,14 the present study used moderate myocardial injury to create a sizable peri-infarction zone. Multiphase spin-echo MR imaging was used to characterize regional wall thickening. MR images were acquired in 1 session with identical spin-echo parameters for contrast enhancement and function to directly compare the enhanced areas of mesoporphyrin and Gd-DTPA, eliminate differences in spatial resolution of different techniques, and eliminate the effect of cardiac geometry or slice thickness. Therefore, the overestimation of the infarction by Gd-DTPA is not likely attributable to differences in spatial resolution, cardiac geometry, or slice thickness.

Choi et al15 claimed that mesoporphyrin produced maximum enhancement 1 to 3 hours after intravenous injection in cats with reperfused myocardial infarction. It is certainly true that greater myocardial enhancement by mesoporphyrin occurs early after the agent is administered. However, in the present study, imaging was done 22 hours after administration of mesoporphyrin to ensure that mesoporphyrin was completely cleared from plasma (plasma half-life = 90 minutes) and did not contribute to any nonspecific contrast enhancement in the injured region. Certainly, the proposed method (double-contrast and functional MR imaging) can be used with a shorter postinjection delay than 22 hours to improve clinical acceptability.

Study Limitations

The Gd-DTPA–enhanced region was significantly smaller than the true area at risk measured by postmortem histomorphometry. This finding may be attributed to washout of Gd-DTPA from the rim of the area at risk during the 30 minutes of elapsed time between contrast administration and spin-echo MR imaging, and/or the 30 minutes of coronary occlusion was insufficient to produce detectable edema in the...
rim of the area at risk by spin-echo imaging. The concentration of Gd-DTPA and water content were not measured in viable and nonviable portions within the ischemically injured myocardium.

In conclusion, the Gd-DTPA–enhanced region encompasses viable (peri-infarction zone) and nonviable portions. Nonspecific extracellular Gd-DTPA overestimated the infarct size, but the necrosis-specific mesoporphyrin did not. The difference between the 2 enhanced regions may represent the peri-infarction zone. Functional MR imaging confirmed that the peri-infarction zone was viable. The complementary use of double-contrast–enhanced and functional MR imaging can precisely characterize the peri-infarction zone.

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