Performance of Delayed-Enhancement Magnetic Resonance Imaging With Gadoversetamide Contrast for the Detection and Assessment of Myocardial Infarction

An International, Multicenter, Double-Blinded, Randomized Trial

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Background—The identification and assessment of myocardial infarction (MI) are important for therapeutic and prognostic purposes, yet current recommended diagnostic strategies have significant limitations. We prospectively tested the performance of delayed-enhancement magnetic resonance imaging (MRI) with gadolinium-based contrast for the detection of MI in an international, multicenter trial.

Methods and Results—Patients with their first MI were enrolled in an acute (≤16 days after MI; n=282) or chronic (17 days to 6 months; n=284) arm and then randomized to 1 of 4 doses of gadoversetamide: 0.05, 0.1, 0.2, or 0.3 mmol/kg. Standard delayed-enhancement MRI was performed before contrast (control) and 10 and 30 minutes after gadoversetamide. For blinded analysis, precontrast and postcontrast MRIs were randomized and then scored for enhanced regions by 3 independent readers not associated with the study. The infarct-related artery perfusion territory was scored from x-ray angiograms separately. In total, 566 scans were performed in 26 centers using commercially available scanners from all major US/European vendors. All scans were included in the analysis. The sensitivity of MRI for detecting MI increased with rising dose of gadoversetamide (P<0.0001), reaching 99% (acute) and 94% (chronic) after contrast compared with 11% before contrast. Likewise, the accuracy of MRI for identifying MI location (compared with infarct-related artery perfusion territory) increased with rising dose of gadoversetamide (P<0.0001), reaching 99% (acute) and 91% (chronic) after contrast compared with 9% before contrast. For gadoversetamide doses ≥0.2 mmol/kg, 10- and 30-minute images provided equal performance, and peak creatine kinase-MB levels correlated with MRI infarct size (P<0.0001).

Conclusions—Gadoversetamide-enhanced MRI using doses of ≥0.2 mmol/kg is effective in the detection and assessment of both acute and chronic MI. This study represents the first multicenter trial designed to evaluate an imaging approach for detecting MI. (Circulation. 2008;117:629-637.)

Key Words: imaging ■ magnetic resonance imaging ■ myocardial infarction

The diagnosis of myocardial infarction (MI) is one of the most important and common clinical issues that face medical practitioners. MI is a leading cause of mortality among adults in most industrialized countries,1 and even for survivors, the condition has important prognostic and therapeutic implications. For instance, patients with nonfatal MI have a chance of illness and premature death up to 15 times higher than that of the general population,2 and it is clear that medications such as aspirin and β-blockers can improve prognosis substantially.3

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According to the American College of Cardiology and European Society of Cardiology consensus document on the redefinition of MI, the cornerstone tests for the diagnosis are biomarkers such as troponin I and T and creatine kinase-MB (CK-MB) and the ECG.4 Unfortunately, these tests have limitations. Biomarkers are insensitive for infarcts more than a few days old,4 do not provide information on infarct location, and are only moderately accurate in determining...
infarct size.\textsuperscript{5} Likewise, the ECG is insensitive for chronic non-Q-wave infarcts (because by definition Q waves are required for the diagnosis), and the specificity may be poor in the setting of other cardiopulmonary disorders.\textsuperscript{6} Imaging techniques such as echocardiography and single-photon emission computed tomography may assist in the diagnosis of MI, but small infarcts may be missed, and infarction may be difficult to distinguish from ischemia.\textsuperscript{4} Importantly, no data on the performance of any imaging approach to diagnosing MI have been directly validated in a multicenter trial.

Delayed-enhancement magnetic resonance imaging (DE-MRI; also known as delayed-enhancement cardiovascular magnetic resonance) with gadolinium contrast media is a relatively new technique that may overcome some of these limitations. Studies in animal models demonstrate an excellent match of infarcted regions by DE-MRI to histopathology.\textsuperscript{7,8} Studies in humans demonstrate that DE-MRI is effective in determining the presence, location, and extent of MI in both the acute and chronic settings.\textsuperscript{9–11} Moreover, because a major advantage of DE-MRI is the high spatial resolution—more than 40-fold greater than that of single-photon emission computed tomography\textsuperscript{10,12,13}—even small infarcts can be detected in the absence of Q waves.\textsuperscript{10,12,13}

The available literature, however, is limited in that the patient investigations relative to DE-MRI involve small cohorts and are single-center studies. Moreover, the optimal dose of gadolinium contrast has not been established. Currently, none of the commercially available gadolinium agents that have been approved by the Food and Drug Administration for imaging the body and/or brain have been approved for imaging the heart. The goal of the present study was to prospectively test the performance of gadoversetamide DE-MRI for the detection and assessment of MI in an international, multicenter, double-blinded, randomized phase 2 trial.

Methods

Protocol and Randomization

Between January 2003 and May 2004, patients were prospectively enrolled at 26 centers: 13 in the United States, 8 in Europe, and 5 in South America. The protocol was approved by the institutional review board at each center. Written informed consent was obtained from all patients. The protocol was designed, conducted, and analyzed in accordance with Good Clinical Practice regulations.\textsuperscript{14}

The main inclusion and exclusion criteria and a flow diagram of the overall protocol are shown in Figure 1A. Briefly, patients with their first clinical presentation of MI and elevation in CK-MB to at least 3 times the upper limit of normal were enrolled. Because the performance of DE-MRI may be different in acute compared with chronic infarction, patients were enrolled into specific substudies depending on the age of the infarct. Only patients with first MI were included to prevent ambiguity in infarct age in patients with multiple infarcts. Although a protocol amendment on February 19, 2003, allowed patients with troponin I or T evidence of MI to be eligible for enrollment (to speed patient recruitment), >95% of enrolled patients had CK-MB data. To reduce the possibility that patients with biochemical evidence of necrosis but without MI were erroneously included (eg, patients with myocarditis), patients were required to have undergone x-ray coronary angiography documenting the infarct-related artery (IRA). Patients with significant coronary disease (\(\geq 70\%\) luminal narrowing) in multiple vessels were excluded to increase the likelihood that enrolled patients had only a single MI (ie, did not have prior clinically unrecognized MI). Patients with contraindications for MRI (eg, pacemaker or defibrillator), nonsinus rhythm (atrial fibrillation/flutter), dyspnea and an inability to hold breath for 10 to 15 seconds, known or suspected hypersensitivity to gadolinium, known or suspected end-stage renal disease, or a history of hemolytic anemia or other hemoglobinopathy and those who were pregnant or breast-feeding also were excluded.

Each patient was randomized to 1 of 4 doses of gadoversetamide: 0.05, 0.1, 0.2, or 0.3 mmol/kg body weight. Gadoversetamide was supplied by Mallinckrodt (Hazelwood, Mo) in a commercially available form (20-mL vials at 0.5 mmol/mL). Dose preparation and administration (peripheral vein bolus injection at 1 to 2 mL/s, followed by 10-mL saline flush) were done by a blinded third party; thus, DE-MRI was performed in a double-blinded fashion in that neither the patient nor the investigative team was aware of the dose given.

DE-MRI Studies

Standard DE-MRI was performed as detailed previously.\textsuperscript{7,15,16} Briefly, a cardiac gated inversion-recovery gradient-echo sequence was used. Short-axis views were obtained every 10 mm throughout the entire left ventricular (LV) myocardium. Two- and 4-chamber long-axis views were also obtained. Slice thickness was 6 mm; typical in-plane resolution was 1.9×1.4 mm.\textsuperscript{10,12,13} DE-MRI was performed before and at 0 and 30 minutes after gadoversetamide administration for 3 complete sets of images (Figure 1A). The inversion time was adjusted to null normal myocardium\textsuperscript{15,16} for each acquisition. Participating centers used commercial available scanners (1.5 T) and sequences from all major US/European vendors (12 from Siemens [Malvern, Pa], 6 from General Electric [Milwaukee, Wis], and 8 from Philips [Andover, Mass]). At the start of patient enrollment, participating centers had various degrees of experience with DE-MRI; 38% of centers were performing ≤2 studies per week. These less experienced centers enrolled 26% of the study cohort.

Data Management and Analysis

The 3 sets of MRI images from each patient were separated, and then all image sets from all patients were randomized and interpreted 1 at a time. Three independent physicians performed the blinded read. None of the readers had any affiliation with Mallinckrodt or any of the participating centers. The readers were provided no knowledge of the protocol design, patient identity, gadoversetamide dose, or any associated clinical information. The blinded read was conducted at an independent location not affiliated with Mallinckrodt or any of the participating centers.

DE-MRIs were scored for the presence, location, and extent of enhanced myocardium using a 17-segment model and a 5-point scale for each segment (0=no delayed enhancement, 1=1% to 25%, 2=26% to 50%, 3=51% to 75%, 4=76% to 100%).\textsuperscript{16} Because precontrast images were randomly interspersed among postcontrast images for analysis, on all images, bright myocardial regions were assumed to depict enhanced myocardium and were considered to represent infarction.\textsuperscript{17} Global infarct size as a percentage of LV myocardium was calculated by summing the segments with delayed enhancement (each weighted by the midpoint of the range of enhancement for the given segmental score; ie, 1=13%, 2=38%, 3=63%, 4=88%) and dividing by 17.\textsuperscript{17}

The x-ray coronary angiograms were analyzed at a separate core laboratory blinded to identity, gadoversetamide dose, MRI results, and any associated clinical information. The presence of significant disease (\(\geq 70\%\) luminal narrowing) in only 1 epicardial artery territory (ie, no multivessel disease) was verified. Then, the infarct was localized to less than half of the LV myocardium by selecting up to 8 segments on the 17-segment model that were most likely to include the IRA perfusion territory.\textsuperscript{17} This method was used rather than assigning fixed territories for coronary arteries (ie, left anterior descending, right coronary, and left circumflex arteries) to account for variations in left/right dominance, IRA vessel size, and small misregistrations between angiography and MRI reads.

Twelve-lead ECGs performed at the time of MRI were transmitted electronically to a core laboratory for blinded interpretation. Q-wave MI was defined using the American College of Cardiology/European Society of Cardiology consensus document definition.\textsuperscript{4} Prespecified Diagnostic Performance End Points and Design of Controls

The primary objective was to test the performance of DE-MRI for diagnosing both the presence and location of MI across the dose
range of gadoversetamide (Figure 1B). For each assessment, a direct comparator was designed to allow each patient to serve as his or her own control. Specifically, for the assessment of infarct presence, the MRIs obtained before gadoversetamide administration served as the control. For the assessment of infarct location, the perfusion territory of the IRA as determined by x-ray angiography served as the control. A secondary end point was infarct size. The comparator for this end point was the peak CK-MB level expressed in multiples of the upper limit of normal at each site.

Safety
Data were collected on potential effects of gadoversetamide contrast at 2 and 24 hours after administration, including vital signs, 12-lead ECGs, and blood chemistries. The complete methodology and results will be reported separately. Preliminarily, however, the data indicate that no significant changes occurred in vital signs, prolongation of ECG QTc intervals, or blood chemistries after gadoversetamide injection. Of a total of 3 serious adverse events (1 chronic, 2 acute cohorts), none were considered to be related to the administration of gadoversetamide.

Statistical Analysis
Continuous data are presented as mean±SD except when noted. Comparisons of characteristics between the acute and chronic cohorts were made through the use of 2-sample t tests for continuous variables and χ² tests for discrete variables. Infarction was recorded as a binary variable (present/absent) on the basis of the 17-segment model reading of delayed enhancement. An enhancement score >0 in at least 1 segment was considered to represent infarction.17 The sensitivity of DE-MRI for infarct detection was calculated by standard methods for each observer. Results from separate observers were then averaged. Comparisons among dose groups and time points and a dose-response evaluation were assessed with a generalized linear mixed model (SAS macro %GLIMMIX, SAS Institute Inc, Cary, NC) incorporating the binomial error distribution and a logit link. The variables included in the model were patient, reader, gadoversetamide dose, and imaging time points (baseline, 10 minutes, 30 minutes).

Location of infarction was categorized as correct or incorrect on the basis of the 17-segment model readings of enhancement and IRA territory. The number of segments within the IRA territory was considered to be correct if the number of segments with enhancement was greater than or equal to the number of segments outside the IRA territory. Scans with no enhancement identified were considered to be incorrect (ie, if infarction was not detected, the location was deemed incorrect). The accuracy of DE-MRI for identifying infarct location was calculated by standard methods. A generalized linear
mixed model as described above was used for comparisons among dose groups and time points and for an evaluation of a dose response.

Interrater agreement for the presence and location of infarction was calculated by averaging the percentage of exact agreement from the 3 sets of pairwise readers according to study cohort, dose group, and scan time point. Because the $\kappa$ statistic is influenced by trait prevalence, which may lead to paradoxical behavior (high levels of observer agreement with low $\kappa$ values), the $\kappa$ statistic was not used. All statistical tests were 2 tailed, and values of $P<0.05$ were regarded as significant.

All authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Population

A total of 303 acute and 297 chronic patients were enrolled. Twenty-three patients (16 acute, 7 chronic) did not receive gadoversetamide, typically because of clinical instability or withdrawal of consent; they were excluded from the analysis. Among the remaining 287 and 290 patients, respectively, who received gadoversetamide, 11 (1.9%) were excluded for protocol violations (eg, previous MI, multivessel coronary artery disease) or early scan termination resulting from clinical instability or patient request. Thus, the final populations consisted of 282 (acute) and 284 (chronic) patients in whom diagnostic performance was tested. Fifty-two patients (9%) were enrolled in both the acute and chronic substudies. All of the 566 patient scans that were completed (282 + 284 = 566) were included in the analysis (ie, none was removed because of image quality). Thus, the population included all patients who met the protocol-specified inclusion/exclusion criteria, received gadoversetamide, and completed the MRI.

Demographic and clinical characteristics of the patients are listed in the Table. MRI was performed a median of 6 and 59 days after hospital admission for MI in the acute and chronic groups, respectively. Q waves were present on the day of MRI in 66% and 56% of acute and chronic groups, respectively. Q waves were present on the day of MRI in 66% and 56% of acute and chronic groups, respectively.

Overall Sensitivity and Localization Accuracy

The sensitivity of DE-MRI for detecting infarction stratified by gadoversetamide dose group and imaging time point is shown in Figure 2A. In both acute and chronic patients, a significant dose-response relationship was seen 10 and 30 minutes after injection (both $P<0.0001$), with sensitivity increasing with rising gadoversetamide dose. Conversely, for precontrast images (control), no differences in sensitivity were found between dose groups ($P=0.93$ acute, $P=0.11$ chronic). Sensitivity reached 99% (acute, 0.3-mmol/kg dose) and 94% (chronic, 0.3-mmol/kg dose) after contrast compared with 11% before contrast (11% represents data pooled from all dose groups). At the highest doses (0.2 and 0.3 mmol/kg), 10- and 30-minute images appeared to have equal performance (all comparisons $P>0.41$). Accuracy reached 99% (acute, 0.3-mmol/kg dose) and 91% (chronic, 0.3-mmol/kg dose) after contrast compared with 9% before contrast. Accuracy was limited primarily by the readers’ inability to detect infarction (because if infarction was not detected, by definition the location was considered incorrect) rather than scoring infarction in the wrong territory (not matched to IRA perfusion territory). With regard to the latter, when infarction was identified after contrast, it was scored in the wrong location in only 2%, 6%, 2%, and 1% of cases for the 0.05-, 0.1-, 0.2-, and 0.3-mmol/kg dose groups, respectively, in acute patients (data from 10- and 30-minute scans together), and 1%, 3%, 1%, and 3% for chronic patients.

### Table. Patient Data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Acute MI (n=282)</th>
<th>Chronic MI (n=284)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ± SD, y</td>
<td>54.0±11.4</td>
<td>53.6±11.3</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>215 (76)</td>
<td>218 (77)</td>
</tr>
<tr>
<td>Risk factors, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>51 (18)</td>
<td>45 (16)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>130 (46)</td>
<td>149 (52)</td>
</tr>
<tr>
<td>Cigarette smoker</td>
<td>93 (33)</td>
<td>103 (36)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>162 (57)</td>
<td>178 (63)</td>
</tr>
<tr>
<td>Time from admission to MRI, d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>6 (3–10)</td>
<td>59 (41–102)</td>
</tr>
<tr>
<td>Twelve-lead ECG at time of MRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q waves present, n (%)</td>
<td>184 (66)</td>
<td>159 (56)</td>
</tr>
<tr>
<td>Cardiac biomarkers at initial hospitalization, multiples of ULN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak CK-MB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>20.5 (8.7–50.8)†</td>
<td>14.2 (7.7–33.9)‡</td>
</tr>
<tr>
<td>Peak troponin T</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>67 (37–120)§</td>
<td>69 (26–134)¶</td>
</tr>
<tr>
<td>Peak troponin I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>159 (49–333)¶¶</td>
<td>136 (36–318)¶¶</td>
</tr>
<tr>
<td>IRA, n (%)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>120 (43)</td>
<td>120 (44)</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>112 (40)</td>
<td>99 (36)</td>
</tr>
<tr>
<td>Left circumflex artery</td>
<td>50 (18)</td>
<td>55 (20)</td>
</tr>
<tr>
<td>Gadoversetamide dose group, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.05 mmol/kg</td>
<td>74 (26)</td>
<td>75 (26)</td>
</tr>
<tr>
<td>0.10 mmol/kg</td>
<td>70 (25)</td>
<td>73 (26)</td>
</tr>
<tr>
<td>0.20 mmol/kg</td>
<td>71 (25)</td>
<td>66 (23)</td>
</tr>
<tr>
<td>0.30 mmol/kg</td>
<td>67 (24)</td>
<td>70 (25)</td>
</tr>
</tbody>
</table>

ULN indicates the upper limit of normal at each site.

*Fifty-two patients enrolled in the acute substudy were subsequently also enrolled in the chronic substudy.
†Data were available for 270 patients.
‡Data were available for 269 patients; levels obtained during the index event.
§Data were available for 51 patients.
¶Data were available for 62 patients; levels obtained during the index event.
¶¶Data were available for 171 patients.
**Based on core laboratory analysis of the x-ray coronary angiograms. The IRA could not be identified in 10 chronic MI patients.
A significant dose effect was not observed in either acute or chronic patients (P=0.12 and P=0.21, respectively). Figure 3A shows typical postcontrast images in 9 patients arranged by scanner manufacturer and the IRA. Figure 3B shows multiple images in 1 patient who was enrolled in both the acute and chronic substudies. The inferolateral wall infarct is easily detected in both the acute and chronic stages, and 10- and 30-minute images appear nearly identical.

The mean percentage agreement among blinded readers for low-dose (≤0.1 mmol/kg) and high-dose (≥0.2 mmol/kg) postcontrast images were 87% and 96% for detecting the presence of MI in the acute setting and 83% and 92% in the chronic setting; 87% and 96% for identifying the location of MI in the acute setting, and 83% and 93% in the chronic setting, respectively.

**Stratification by CK-MB and Presence or Absence of Q-Waves**

Figure 4 demonstrates high-dose (≥0.2 mmol/kg) postcontrast DE-MRI findings stratified by tertiles of peak CK-MB (left column). In acute patients, the sensitivity and localization accuracy of DE-MRI were excellent (90% to 97%) for all tertiles. In chronic patients, both sensitivity and localization accuracy were reduced for the lowest tertile at 76% and 73%, respectively, compared with ≥96% for higher tertiles (P<0.01 for both). Peak CK-MB levels correlated with infarct size determined by postcontrast DE-MRI in both acute and chronic patients (both P<0.0001; Figure 4b). No correlation existed with precontrast (control) images (P=0.48 for acute, P=0.29 for chronic). Overall, infarct size by postcontrast DE-MRI was smaller in chronic than in acute patients (14.0±10.7% versus 17.7±11.6% LV; P<0.009).

Similar findings were observed when patients were stratified by the presence or absence of Q waves (Figure 4, right column). Although the sensitivity of DE-MRI was excellent for both non–Q-wave and Q-wave MI in acute patients (91% and 99%, respectively), sensitivity was reduced for non–Q-wave MI in chronic patients (79%). Overall, a total of 223 patients had non–Q-wave MI (98 acute, 125 chronic), and test
sensitivity in this group was quite good at 85% (pooled acute and chronic), even though mean infarct size was relatively small at 8.3% of LV (6.8% of LV in chronic).

Discussion
In this first international, multicenter DE-MRI trial, we found that imaging after appropriate doses of gadoversetamide is highly effective in the detection and assessment of both acute and chronic myocardial infarction. Test sensitivity reached 99% for detecting acute MI and 94% for detecting chronic MI. Moreover, when infarction was detected after 0.2 or 0.3 mmol/kg gadoversetamide, it was identified in the correct location (ie, matched to the IRA perfusion territory) in 97% to 100% of cases.

These results confirm and extend the findings of published single-center studies evaluating the sensitivity of DE-MRI for detecting infarction in patients with acute or chronic MI.\textsuperscript{9–11} Unlike earlier reports that involved sample sizes of 20 to 50 patients, the present study is 10- to 25-fold larger. Whereas single-center experience often is difficult to translate into general clinical practice because of site-specific hardware, software, or scanning protocols, the results from the present study should reflect the clinical value of DE-MRI more accurately. Participating centers used commercially available scanners (1.5 T) and sequences, and all major US/European vendors were represented. The delayed-enhancement technique used was a standard basic implementation that has been described thoroughly in the literature.\textsuperscript{7,15,16} Furthermore, despite the fact that 26% of the study cohort were enrolled from centers with only modest experience with DE-MRI and all 566 completed scans were included in the analysis (ie, none was removed because of image quality), the agreement between independent readers was high for both the detection and localization of MI (92% to 96% agreement for doses \(\geq 0.2 \text{ mmol/kg}\)). We believe that these findings indicate that

![Figure 3. Typical MRI. A, Typical post-contrast images from 9 different patients. Image quality was robust independently of the location of infarction and scanner vendor. B, Images in 1 patient who was enrolled in both the acute and chronic substudies and was randomized to the same dose of contrast (0.20 mmol/kg). The inferolateral wall infarct (arrows) is easily visible during the acute and chronic stages. Images 10 minutes after contrast appear virtually identical to those obtained 30 minutes after contrast. LAD indicates left anterior descending artery; RCA, right coronary artery; and LCx, left circumflex coronary artery.](http://circ.ahajournals.org/content/circulation/117/5/634/F2.large.jpg)
DE-MRI is a robust technique that can be implemented easily on scanners that are commonly available worldwide with an effectiveness that rivals the best available techniques for the detection and assessment of myocardial infarction.

The current consensus criteria for the diagnosis of MI, which are fundamentally based on cardiac enzymes and the 12-lead ECG, have important limitations. Although enzymes such as troponins are highly sensitive and can detect even minute amounts of necrosis, levels are elevated for only a few days after an acute event. Importantly, many patients do not have classic symptoms and do not seek medical attention within the time window when biomarkers may be elevated. By design, all patients in our study had a prior record of elevated enzymes because the study required an unequivocal truth standard for the diagnosis of MI. However, the implication is that if these patients had not had enzymes drawn at the time of the acute event but instead only at the time of MRI, many of those in the acute subcohort (MRI done up to 16 days after admission) and nearly all in the chronic subcohort (MRI done 17 days to 6 months after admission) would have had negative enzymes, whereas DE-MRI would have correctly detected MI.

The ECG, of course, is helpful, and incident Q waves have been the basis for diagnosing “silent” MI in population studies. By definition, however, all non–Q-wave infarcts will be missed, and even if Q waves are present initially, they may disappear at a later time point. Moreover, an imaging approach for the assessment of MI could offer additional value, even in those with obvious Q waves. The accurate measurement of infarct size may provide valuable information on ventricular remodeling, arrhythmic potential, and prognosis and is an attractive surrogate end point for the evaluation of new therapies for acute MI. Although cardiac enzyme levels and ECG changes can offer some information on the extent of infarction, both have limited ability to resolve small or moderate differences in infarct size. Precise information on infarct location also may be important. In many patients, the IRA cannot be identified during x-ray

Figure 4. Performance of MRI stratified by tertiles of CK-MB and the presence or absence of Q waves. Patients were categorized as having small, medium, or large infarcts according to tertiles of peak CK-MB (left column) or small or large infarcts according to the absence or presence of Q waves (right column). A, Sensitivity and localization accuracy of MRI along these categories. B, Corresponding infarct sizes as measured by MRI. The median peak CK-MB expressed in multiples of the upper limit of normal at each site for lower, middle, and upper tertiles were 6.8 (IQR, 4.6 to 8.7), 20.5 (IQR, 15.8 to 29.2), and 77.0 (IQR, 50.6 to 279.3) in acute patients and 5.9 (IQR, 3.9 to 7.8), 14.2 (IQR, 11.5 to 19.1), and 55.5 (IQR, 33.9 to 137.8), respectively, in chronic patients. A total of 223 patients had non–Q-wave MI and 343 had Q-wave MI. MRI data were pooled from 10- and 30-minute scans at the most effective doses (0.2 and 0.3 mmol/kg). Error bars represent 95% confidence intervals. See text for further details.
coronary angiography because either multivessel obstructive disease without an obvious culprit lesion is present or minimal nonobstructive disease exists.\(^23\) In this situation, infarct imaging may help to identify the IRA and/or confirm the diagnosis of MI.

Unfortunately, a paucity of data is available from multicenter trials on the accuracy of noninvasive imaging approaches for the detection and assessment of MI. Although several multicenter trials have used infarct size measurements by radionuclide imaging as a surrogate end point to assess the efficacy of an investigative therapy,\(^3\) these trials were not designed to evaluate radionuclide imaging. Not surprisingly, these studies present little or no data on the sensitivity or accuracy of radionuclide imaging for the detection or localization of MI. Rarely, however, some information can be gleaned indirectly. In the recently completed European and Australian Multicenter Evaluative Research on Atrial Fibrillation Dofetillide (EMERALD) study\(^24\) on distal embolic protection in acute MI patients undergoing percutaneous coronary intervention, one of the primary end points was infarct size measured by technetium sestamibi imaging. This randomized, multicenter trial reported that the interquartile range (IQR) of infarct size was 0% to 23% in the control group. Because an infarct size of 0% was the 25th percentile point, this result indicates that the sensitivity of sestamibi imaging for detecting acute MI was at most 75% in this cohort of patients who were selected to have large infarcts because only those with ST-segment elevation MI were enrolled. In contrast, the sensitivity for detecting MI was much higher in the present study, and patients were not limited to only those with ST-segment elevation MI. Moreover, the sensitivity of imaging was evaluated for both acute and chronic MI. This is important because there are virtually no clinical trial data on the detection of chronic MI, and chronic infarcts are generally more difficult to detect than acute infarcts because substantial infarct shrinkage can occur during the healing process when necrotic myocardium is replaced with collagenous scar.\(^7\) Notably, we believe the present study is the first multicenter trial that was expressly designed to evaluate an imaging approach for the detection and assessment of MI.

The results of this study highlight some practical issues on the performance of DE-MRI. First, 10- and 30-minute images after appropriate doses of gadoversetamide (≥0.2 mmol/kg) were equally effective (see Figure 2 and 3B). A set of images through the entire LV myocardium can be obtained in ≈5 minutes, which indicates that a relatively long time window (10 to 30 minutes after contrast) is available to complete DE-MRI after a single administration of contrast, with ample leeway built in. Second, only a few patients were unable to complete imaging because of clinical instability. Given that in the acute cohort, a quarter of the patients were scanned within the first 3 days after admission for MI and that our imaging protocol was more extensive (3 complete sets of images) than what would be required clinically, these results bode well for the use of DE-MRI in the early days after acute MI from a logistical standpoint. Third, higher doses of gadoversetamide clearly had better performance compared with lower doses. Although it is somewhat arbitrary to define a threshold level of performance that is necessary for clinical purposes, we note that the accuracy of DE-MRI for identifying the correct infarct location was 91% for the 0.2-mmol/kg dose (10-minute scan; Figure 2B), was mildly better at 95% for the 0.3-mmol/kg dose, and dropped rather precipitously to 79% for the 0.1-mmol/kg dose. This finding provides some evidence that gadoversetamide doses of ≥0.2 mmol/kg should be used when DE-MRI is performed in general clinical practice. This recommendation, however, should be tempered by the fact that intermediate doses between 0.1 and 0.2 mmol/kg were not tested. Additionally, because careful adjustment of imaging parameters such as inversion time is more important at lower doses,\(^15,16\) centers with experienced scanner operators may find superior levels of performance than that observed in the present trial at the lower doses. Moreover, we point out some limitations with higher doses of gadolinium, including cost, a brighter blood pool that may obscure subendocardial infarcts,\(^16\) and an increased concern for rare side effects such as nephrogenic systemic fibrosis in those with severe renal impairment.\(^25\)

In summary, these results indicate that DE-MRI with gadoversetamide in appropriate doses is effective in the detection and assessment of both acute and chronic myocardial infarction. Our study may have implications for patients who present with clinical symptoms or signs that suggest prior MI but in whom cardiac biomarkers and the ECG are negative or equivocal. However, there are several caveats. First, the very early diagnosis of acute MI (first minutes to hours) was not addressed in this study; results should not be extrapolated to that situation. Second, not all infarcts proven in the acute phase by enzyme elevations were detected later in the chronic phase; there are some diagnostic limitations in the setting of small chronic infarcts. Third, patients in this study were considered to have definitive MI on the basis of elevated CK-MB levels to at least 3-fold normal. Given this enrollment requirement, the diagnostic performance of DE-MRI may be lower when more borderline cases of MI are included. Fourth, similar to cardiac enzymes, DE-MRI can detect irreversible myocardial damage,\(^7\) but the presence of damage does not indicate its mechanism. Therefore, an abnormal DE-MRI scan in the absence of clinical evidence of ischemia should prompt a search for other causes of cardiac damage such as myocarditis. One potential advantage of DE-MRI is that the pattern of delayed enhancement, rather than simply the presence or extent, may offer important information on the origin of myocardial damage.\(^26,27\) For instance, enhancement that involves only the epicardial half of a myocardial region would point to a nonischemic origin because damage in the setting of coronary artery disease almost always involves the subendocardium.\(^27\) This aspect of DE-MRI was not evaluated in the present report because this topic was beyond the scope of the trial. Further study of this issue, however, and the potential role of DE-MRI in the clinical assessment of patients with known or suspected myocardial infarction is clearly warranted.

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**Disclosures**

Drs Kim and Judd have been consultants to Tyco Healthcare/Mallinckrodt, Inc, and are inventors of a US patent on DE-MRI that is owned by Northwestern University. Dr Allen, Dr Lee, Dr Witte, and A. Napoli are employees of Tyco Healthcare/Mallinckrodt, Inc. The other authors report no conflicts.
The identification and assessment of myocardial infarction (MI) are important for therapeutic and prognostic purposes, yet the current tools for diagnosing MI, which is based fundamentally on cardiac enzymes and the ECG, have significant limitations. For instance, cardiac enzymes are insensitive for infarcts more than a few days old, do not provide information on infarct location, and are only moderately accurate in determining infarct size. Likewise, the ECG is insensitive for non-Q-wave infarcts, and specificity may be poor in the setting of other cardiopulmonary disorders. In this study, we used delayed-enhancement magnetic resonance imaging (MRI) with various doses of gadoversetamide contrast to diagnose and assess infarction in 566 patients with either acute or chronic MI. The study involved 26 centers throughout the United States, Europe, and South America. We observed that the sensitivity of MRI for detecting MI increased with rising dose of gadoversetamide, reaching 99% in patients with acute MI and 94% in those with chronic MI. For gadoversetamide doses of ≥0.2 mmol/kg, when MI was identified, it was localized to the correct part of the heart in >97% of patients; i.e., it matched the perfusion territory of the coronary artery that was occluded by x-ray angiography. Thus, the results indicate that delayed-enhancement MRI with gadoversetamide doses of ≥0.2 mmol/kg is effective in the diagnosis of both acute and chronic MI. This study may have implications for patients who present with clinical symptoms or signs that suggest prior MI but in whom cardiac enzymes and the ECG are negative or equivocal.
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