Characterization of the Peri-Infarct Zone by Contrast-Enhanced Cardiac Magnetic Resonance Imaging Is a Powerful Predictor of Post–Myocardial Infarction Mortality

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Background—Accurate risk stratification is crucial for effective treatment planning after myocardial infarction (MI). Previous studies suggest that the peri-infarct border zone may be an important arrhythmogenic substrate. In this pilot study, we tested the hypothesis that the extent of the peri-infarct zone quantified by contrast-enhanced cardiac magnetic resonance (CMR) is an independent predictor of post-MI mortality.

Methods and Results—We studied 144 patients with documented coronary artery disease and abnormal myocardial delayed enhancement (MDE) consistent with MI. A computer-assisted, semiautomatic algorithm quantified the total infarct size and divided it into the core and peri-infarct regions based on signal-intensity thresholds (>3 SDs and 2 to 3 SDs above remote normal myocardium, respectively). The peri-infarct zone was normalized as a percentage of the total infarct size (%MDEperiphery). After a median follow-up of 2.4 years, 29 (20%) patients died. Patients with an above-median %MDEperiphery were at higher risk for death compared with those with a below-median %MDEperiphery (28% versus 13%, log-rank P<0.01). Multivariable analysis showed that left ventricular systolic volume index and %MDEperiphery were the strongest predictors of all-cause mortality (adjusted hazard ratio [HR] for %MDEperiphery, 1.45 per 10% increase; P=0.002) and cardiovascular mortality (adjusted HR, 1.51 per 10% increase; P=0.009). Similarly, after adjusting for age and left ventricular ejection fraction, %MDEperiphery maintained strong and independent associations with all-cause mortality (adjusted HR, 1.42; P=0.005) and cardiovascular mortality (adjusted HR, 1.49; P=0.01).

Conclusions—In patients with a prior MI, the extent of the peri-infarct zone characterized by CMR provides incremental prognostic value beyond left ventricular systolic volume index or ejection fraction. Infarct characteristics by CMR may prove to be a unique and valuable noninvasive predictor of post-MI mortality. (Circulation. 2006;114:32-39.)

Key Words: magnetic resonance imaging • myocardial infarction • prognosis

Although left ventricular ejection fraction (LVEF) is currently the most robust clinical parameter in post–myocardial infarction (MI) risk stratification and in guidance of critical treatment decisions such as prophylactic implantation of cardioverter-defibrillators,1,2 current risk assessment remains suboptimal, and the need for other accurate predictors of outcome is evident.3,4 Despite the high success rate of coronary revascularization in recent years, life-threatening ventricular arrhythmias remain an important cause of post-MI mortality.5,6 Although dense, fibrous scars in the infarcted myocardium incapable of depolarization cannot alone cause arrhythmias, when surrounded by distorted bundles of surviving myocytes capable of depolarization in the infarct border zone, arrhythmogenic substrates for slow conduction and reentry phenomena may arise.7–13

Cardiac magnetic resonance imaging (CMR) represents a valuable noninvasive tool in the assessment and risk stratification of patients with MI. CMR can not only accurately assess LV volumes and function14 but also detect and quan-

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tify the extent of both acute and chronic MI. Furthermore, infarct characterization by CMR may have prognostic implications. With high spatial resolution and contrast-to-noise ratio, CMR may allow detailed characterization of infarcts by differentiating the core and peripheral regions. Using necrosis-specific mesoporphyrin and nonspecific, extracellular, gadolinium-DTPA contrast agents in animal studies, Saeed et al demonstrated CMR characterization of the peri-infarct zone that was speculated to contain viable myocardium. Recent preliminary clinical studies with contrast-enhanced CMR have reported the associations of infarct size and the peri-infarct zone with inducible ventricular arrhythmias. However, the prognostic significance of the peri-infarct zone has not been assessed. Accordingly, the objective of this pilot study was to examine the relation between morphological infarct characteristics, determined by contrast-enhanced CMR, and post-MI mortality. We hypothesized that the extent of the peri-infarct border zone is associated with mortality in post-MI patients, independent of LV functional parameters such as LVEF and LV volume indices.

**Methods**

**Patient Population**

We enrolled 167 consecutive patients with a history of coronary artery disease who were found to have abnormal myocardial delayed enhancement (MDE) on CMR performed at our institution. A history of coronary artery disease included documented previous MI, coronary artery stenosis >70% on angiography, prior percutaneous coronary intervention, or coronary artery bypass graft surgery. The primary indications for CMR examination were as follows: assessment of myocardial viability and infarct size (n=65), ischemia (n=66), LV function and morphology (n=6), and others (n=3). In addition, 27 patients with reperfused acute MI underwent CMR for assessment of microvascular dysfunction according to a research protocol that included delayed enhancement imaging. No patient had an implanted cardioverter-defibrillator or pacemaker at the time of imaging. Twenty-three patients (14%) were excluded because of atypical MDE (epicardial or midwall; n=5) suggesting myocardial scar due to noncoronary etiologies or technical problems in quantifying the peri-infarct zone of MDE (n=18; mostly due to motion artifacts or poor nulling of the normal myocardium). There were no other specific study exclusion criteria, and the remaining 144 patients constituted the study cohort. Medical history was obtained before the CMR examination through patient interview and chart review. We ascertained follow-up vital status by telephone interview, mailed questionnaire, hospital chart review, and query of the National Social Security Death Index. The local institutional ethics review board approved the study.

**CMR Protocol**

All CMR examinations were performed with a 1.5-T scanner (Signa CV/i, General Electric, Milwaukee, Wis) with the patient in the supine position and a 4- or 8-element phased-array coil placed over the chest. Images were acquired during breath-holds with ECG gating. We used a segmented k-space steady-state free-precession sequence (repetition time, 3.4 ms; echo time, 1.2 ms; in-plane spatial resolution between 1.5×1.8 mm and 1.8×2.1 mm, depending on the field of view) for cine imaging in parallel short-axis (contiguous views per segment and trigger delay according to the patient’s heart rate to minimize any image blurring.

**CMR Image Analysis**

All images were reviewed and analyzed off-line with specialized postprocessing software (Cinetool version 3.9.8, General Electric Healthcare). Collection and interpretation of all imaging data were blinded to the clinical data and outcome. We manually traced the LV endocardial boundary on all short-axis cine images at the end-diastolic and end-systolic frames to determine the end-diastolic and end-systolic volumes, respectively. LV mass was calculated by subtracting the endocardial volume from the epicardial volume at end diastole and then multiplying by the tissue density (1.05 g/mL). The endocardial and epicardial contours on delayed enhancement images were also outlined manually. Using a semiautomated detection algorithm, we applied a signal-intensity threshold of ≥2 SDs above a reference remote myocardial region on the same slice to quantify the total infarct mass (MDEtotal), which was partitioned into the strongly enhanced core infarct mass (MDEcore) and the infarct periphery mass (MDEperiphery) based on signal-intensity thresholds of ≥3 SDs and 2 to 3 SDs above the remote reference segment, respectively (Figure 1). These thresholds were specified a priori. We also determined the mean transmural extent of the infarct, as previously described. Areas of microvascular obstruction, defined as subendocardial hyperenhanced regions surrounded by hypoenhancement, were included as part of the core infarct (MDEcore). In some cases, manual adjustments were necessary to include the area of microvascular obstruction in the MDEcore. Infarct size (%MDEcore) was expressed as a percentage of LV mass. We also normalized MDEperiphery and MDEcore as percentages of the MDEcore according to the following equations:

\[
%\text{MDE}_{\text{core}} = \left(\frac{\text{MDE}_{\text{core}}}{\text{LV mass}}\right) \times 100\%
\]

\[
%\text{MDE}_{\text{periphery}} = \left(\frac{\text{MDE}_{\text{periphery}}}{\text{MDE}_{\text{core}}}\right) \times 100\%
\]

\[
%\text{MDE}_{\text{total}} = \left(\frac{\text{MDE}_{\text{total}}}{\text{MDE}_{\text{core}}}\right) \times 100\%
\]

The results of %MDEperiphery and %MDEcore measurements were not communicated to the referring physicians and therefore did not influence any subsequent treatment decision.

**Statistical Analysis**

Continuous variables are summarized as mean±SD and were compared by the t test. We used Spearman’s rank correlation to examine correlations. Categorical variables are presented as frequency or percentage and were compared by the χ² test (or Fisher exact test, where appropriate). The primary outcome was all-cause mortality; the secondary end point was cardiovascular mortality, which included death due to heart failure, fatal MI, and sudden death. Survival curves were estimated by the Kaplan-Meier method and compared by the log-rank test. Multivariable Cox proportional-hazards models were developed to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). We constructed 2 separate multivariable models to critically assess the incremental prognostic value of %MDEperiphery, which was analyzed as a continuous variable. First, we considered %MDEperiphery and all of the baseline characteristics associated with mortality by univariable analyses by using forward stepwise selection (P<0.10 for entry and P<0.05 for removal) criteria to arrive at a parsimonious model. Second, we incorporated %MDEperiphery into a multivariable model containing age and LVEF because of their well-established prognostic importance. We examined the regression coefficients for quintiles of %MDEperiphery and found no violation of the linearity assumption. The proportional-hazards assumption was verified for all of the explanatory variables in the models. A 2-sided probability value <0.05 was considered statistically significant. All statistical analyses were conducted with SAS version 9.1 (SAS Institute, Cary, NC).

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscripts as written.
Results

Table 1 summarizes the clinical characteristics and CMR findings of the study population. The mean age was 62 years, and the majority of patients were male. All patients in the study cohort had abnormal MDE consistent with MI and clinical and/or angiographic evidence of coronary artery disease. Thirty-six patients (25%) had acute MI (defined as ischemic symptoms with an elevated troponin level within 7 days), 84 (58%) had a history of chronic MI and/or coronary revascularization (percutaneous coronary angioplasty or coronary bypass surgery), and 24 (17%) did not have any clinical history of MI or coronary artery disease but had evidence of MI by abnormal MDE and angiographically significant (>70%) coronary stenosis. The median age of chronic MI was 2.4 years (range, 5 months to 12 years), and nonacute MI–related coronary revascularization was performed at a median of 3.2 years (range, 9 months to 9 years) before CMR. Patients with %MDEperiphery above the median had significantly smaller infarcts and a lower prevalence of abnormal Q waves compared with the group with a %MDEperiphery below the median. %MDEperiphery was inversely correlated with %MDEtotal (Spearman rho=-0.50, P<0.0001). There were no significant correlations between %MDEperiphery and LVEF, LV end-diastolic volume index, or LV end-systolic volume index (all P=NS). Furthermore, %MDEperiphery did not demonstrate any significant positive correlation with heart rate (r=-0.14, P=NS), indicating that it was not related to image blurring due to inadequate temporal resolution.

Follow-up vital status was available for all patients. After a median follow-up of 2.4 years (range, 6 to 53 months), 29 (20%) patients had died. Of these patients, 19 had cardiovascular death; the immediate cause of death in the remaining 10 patients could not be ascertained (4 patients had a history of severe heart failure, 1 had documented ventricular tachycardia, and 5 had cancer). Figure 2 illustrates the Kaplan-Meier survival curves stratified by median %MDEperiphery. The risk of death was significantly higher among patients with a %MDEperiphery above the median compared with those with a %MDEperiphery below the median (28% versus 13%, respectively; HR, 2.74; 95% CI, 1.05 to 0.65; P=0.01). When %MDEperiphery was analyzed as a continuous variable, the HR for death per 10% increase in %MDEperiphery was 1.31 (95% CI, 1.06 to 1.63; P=0.01). Similarly, a greater MDEperiphery (absolute mass in grams) was associated with a higher risk of death (HR, 1.06; 95% CI, 1.00 to 1.11; P=0.035). Although there was an inverse correlation between infarct size (%MDEtotal) and LVEF (r=-0.48, P<0.001), there was no significant association between infarct size and mortality (all-cause or cardiovascular). There was also no significant relation between mean infarct transmural extent and mortality (all-cause or cardiovascular).

Table 2 lists the univariable predictors of mortality with P<0.10. When all of the clinical and imaging parameters associated with mortality on univariable analysis were considered in the multivariable model by stepwise forward...
selection, \%MDE_{periphery} and LV end-systolic volume index emerged as the 2 strongest independent predictors of all-cause mortality (Table 2) and cardiovascular mortality. The adjusted HRs for all-cause mortality and cardiovascular mortality were 1.45 (95% CI, 1.15 to 1.84; \(P = 0.002\)) and 1.51 (95% CI, 1.11 to 2.06; \(P = 0.009\)), respectively, per 10% increase in \%MDE_{periphery}. When patients with acute MI were excluded from the analysis (n = 108), \%MDE_{periphery} and LV end-systolic volume index remained the 2 strongest independent predictors of all-cause mortality and cardiovascular mortality by stepwise forward selection. Adjusted to the effects of LV end-systolic volume index, \%MDE_{periphery} maintained a strong, independent association with all-cause mortality (adjusted HR, 1.32 per 10% increase in \%MDE_{periphery}; 95% CI, 1.03 to 1.69; \(P = 0.03\)) and cardiovascular mortality (adjusted HR, 1.37 per 10% increase in \%MDE_{periphery}; 95% CI, 1.01 to 1.86; \(P < 0.05\)). Similarly, in the multivariable analysis after adjusting for age and LVEF, \%MDE_{periphery} remained a powerful, independent predictor of all-cause mortality (adjusted HR, 1.42 per 10% increase; 95% CI, 1.11 to 1.81; \(P = 0.005\); Table 2) and cardiovascular mortality (adjusted HR, 1.49 per 10% increase; 95% CI, 1.09 to 2.03; \(P = 0.014\)).

**Discussion**

The principal finding in this pilot study is that the extent of the peri-infarct zone defined by delayed-enhancement CMR (\%MDE_{periphery}) is an independent predictor of post-MI all-cause and cardiovascular mortality, after adjusting for LV volumes or LVEF. To the best of our knowledge, this study

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics and CMR Findings</th>
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<tbody>
<tr>
<td>All Patients (n=144)</td>
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<tr>
<td>Demographic and clinical characteristics</td>
</tr>
<tr>
<td>Age, y*</td>
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<tr>
<td>Female, %</td>
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<tr>
<td>Hypertension, %</td>
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<tr>
<td>Diabetes, %</td>
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<tr>
<td>Infarct location, %†</td>
</tr>
<tr>
<td>Anterior/septal</td>
</tr>
<tr>
<td>Inferior</td>
</tr>
<tr>
<td>Lateral</td>
</tr>
<tr>
<td>Acute infarct (within 7 days), %</td>
</tr>
<tr>
<td>Previous percutaneous coronary intervention, %</td>
</tr>
<tr>
<td>Previous coronary bypass surgery, %</td>
</tr>
<tr>
<td>Abnormal stress test, %</td>
</tr>
<tr>
<td>Heart rate, bpm*</td>
</tr>
<tr>
<td>Medication use</td>
</tr>
<tr>
<td>Acetylsalicylic acid, %</td>
</tr>
<tr>
<td>β-Blocker, %</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor, %</td>
</tr>
<tr>
<td>Statin, %</td>
</tr>
<tr>
<td>Amiodarone, %</td>
</tr>
<tr>
<td>ECG</td>
</tr>
<tr>
<td>Normal sinus rhythm, %</td>
</tr>
<tr>
<td>QRS duration &gt;120 ms, %</td>
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<tr>
<td>Left bundle-branch block, %</td>
</tr>
<tr>
<td>Corrected QT &gt;440 ms, %</td>
</tr>
<tr>
<td>Abnormal Q waves, %</td>
</tr>
<tr>
<td>CMR measurements</td>
</tr>
<tr>
<td>LV mass, g*</td>
</tr>
<tr>
<td>LVEF, %*</td>
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<tr>
<td>LV end-diastolic volume index, mL/m²*</td>
</tr>
<tr>
<td>LV end-systolic volume index, mL/m²*</td>
</tr>
<tr>
<td>Infarct size, %MDE_{total}*</td>
</tr>
<tr>
<td>Mean infarct transmural extent, %</td>
</tr>
</tbody>
</table>

*Mean±SD.
†Not mutually exclusive; some patients had >1 infarct.
is the first to demonstrate that infarct characterization by CMR after the acute phase of MI confers incremental prognostic information for post-MI mortality. Therefore, CMR not only may prove to be a valuable noninvasive tool to improve the risk stratification of post-MI patients but also may provide important insights into the pathophysiological determinants of post-MI risk.

The optimal management of post-MI patients has evolved rapidly during the past few years. Randomized clinical trials have established the efficacy of implantable cardioverter-defibrillator therapy in high-risk patients. Although we observed a significant relation between infarct size and LVEF, as reported in previous studies, infarct size per se was not associated with all-cause mortality. Although this lack of association may reflect the heterogeneous chronicity of MI of the study population or limited study power owing to the relatively small sample size, myriad neurohormonal factors beyond infarct size can mediate ventricular remodeling, arrhythmias, and impact on post-MI clinical outcomes.

Consistent with previous studies, we found that LVEF and LV volumes were stronger predictors of all-cause mortality than was infarct size. Although reduced LVEF is frequently used as an eligibility criterion, it has only limited ability to discriminate patients who would benefit from invasive and costly treatments, such as implantable cardioverter-defibrillators. Therefore, supplemental strategies to refine risk assessment are necessary to maximize the benefit-risk ratio and the cost-effectiveness of this potentially life-saving therapy. Our findings suggest that CMR characterization of the peri-infarct zone of less dense MI provides incremental predictive value for survival beyond LV functional parameters. We speculate that this predictive value may reflect the presence and extent of a potentially arrhythmogenic heterogeneous zone of viable and nonviable peri-infarct myocardium.

Animal studies have furnished valuable insights into the potential role of tissue heterogeneity in the development of arrhythmias after MI. Electrical remodeling occurs in the border zone of the infarct, leading to slow conduction that promotes reentrant ventricular tachycardia. Importantly, these experimental observations have been corroborated by pathological studies in humans. Smaller patchy infarcts, which might facilitate the development of complex 3-dimensional reentry circuits, have been documented in patients with chronic infarcts complicated by ventricular tachycardia. Histological examination of myocardial specimens from patients with chronic MI and medically refractory ventricular tachycardia revealed isolated bundles of surviving myocytes interwoven with strands of fibrous tissue at the apparent arrhythmic focus. These findings lend credence to the

![Figure 2. Kaplan-Meier survival curves for all-cause mortality, stratified by median %MDE\textsubscript{periphery}.](image)

### TABLE 2. Univariable and Multivariable Associations With All-Cause Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable Analysis</th>
<th>Multivariable Analysis 1</th>
<th>Multivariable Analysis 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted HR (95% CI)</td>
<td>P</td>
<td>Adjusted HR (95% CI)</td>
</tr>
<tr>
<td>Age*</td>
<td>1.37 (0.96-1.97)</td>
<td>0.09</td>
<td>...</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.21 (1.05-4.66)</td>
<td>0.04</td>
<td>...</td>
</tr>
<tr>
<td>Previous percutaneous coronary intervention</td>
<td>0.37 (0.16-0.88)</td>
<td>0.02</td>
<td>...</td>
</tr>
<tr>
<td>Previous coronary bypass surgery</td>
<td>2.39 (1.08-5.30)</td>
<td>0.03</td>
<td>...</td>
</tr>
<tr>
<td>QRS duration &gt;120 ms</td>
<td>2.29 (0.98-5.38)</td>
<td>0.06</td>
<td>...</td>
</tr>
<tr>
<td>Left bundle-branch block</td>
<td>3.21 (1.22-8.44)</td>
<td>0.02</td>
<td>...</td>
</tr>
<tr>
<td>Corrected QT &gt;440 ms</td>
<td>2.37 (1.14-4.93)</td>
<td>0.02</td>
<td>...</td>
</tr>
<tr>
<td>LV end-diastolic volume index†</td>
<td>1.13 (1.04-1.22)</td>
<td>0.004</td>
<td>...</td>
</tr>
<tr>
<td>LV end-systolic volume index†</td>
<td>1.13 (1.05-1.23)</td>
<td>0.002</td>
<td>1.16 (1.07-1.26)</td>
</tr>
<tr>
<td>LVEF‡</td>
<td>1.36 (1.08-1.72)</td>
<td>0.01</td>
<td>...</td>
</tr>
<tr>
<td>%MDE\textsubscript{periphery}§</td>
<td>1.31 (1.06-1.63)</td>
<td>0.01</td>
<td>1.45 (1.15-1.84)</td>
</tr>
<tr>
<td>MDE\textsubscript{periphery}§</td>
<td>1.06 (1.00-1.11)</td>
<td>0.035</td>
<td>...</td>
</tr>
</tbody>
</table>

For model 1, predictors on univariable analysis (P<0.10) were evaluated in this multivariable model by forward stepwise selection (P<0.10 for entry and P>0.05 for removal) criteria. For model 2, age, LVEF, and %MDE\textsubscript{periphery} were all entered into this multivariable model.

*HR per decade increase.
†HR per 10-mL/m² increase.
‡HR per 10% decrease.
§HR per 10% increase.
concept that the reentry pathway is defined by bands of surviving myocytes bordered by dense fibrosis that is often present in the infarct border.\textsuperscript{9–13} Collectively, these data strongly implicate a heterogeneous peri-infarct zone in the pathogenesis of arrhythmias after MI. Theoretically, the excellent spatial resolution afforded by CMR may permit noninvasive evaluation of this critical infarct region.

The heterogeneity of signal intensities within the infarct after gadolinium administration observed in the present study may correspond to different infarct zones with variable relative amounts of fibrosis and myocytes. This notion is supported by several lines of evidence. Although the threshold of remote +2 SDs has been validated against triphenyl-tetrazolium chloride (TTC) staining,\textsuperscript{16,17} it is noteworthy that TTC staining may not detect microscopic foci of surviving myocytes in nonhomogeneous infarcts, where necrotic and viable myocytes intermingle.\textsuperscript{30} Because such patchy infarcts are not expected to contribute to functional recovery after revascularization, practically they are considered to be nonviable. Although the transmural extent of delayed hyperenhancement is useful in predicting functional recovery after successful revascularization in clinical practice, it does not exclude the presence of surviving myocytes in a patchy infarct that may serve as an important arrhythmogenic substrate. These “islands” of myocytes may also be at risk for ischemia or reinfarction. Consistent with these postulates, an early study also showed that up to 10% of the hyperenhanced myocardium was viable.\textsuperscript{15} Saeed et al\textsuperscript{20,21} found that the gadolinium-enhanced region was larger than the true infarct as delineated by TTC staining, which was identical to regions enhanced by the necrosis-specific contrast agent mesoporphyrin. The difference in enhancement regions demarcated by the 2 contrast agents was considered the peri-infarct zone.\textsuperscript{21} Using a rabbit model, Kim et al\textsuperscript{16} demonstrated that differential image intensities were primarily related to regional differences in contrast wash-in and wash-out time constants. Of note, the time constants at the infarct rim were significantly different from and intermediate to those in the normal regions and in the infarct core. Finally, in the reperfused myocardium of rat hearts subjected to variable durations of ischemic injury, the fractional distribution of volume of gadodiamide in the peri-infarct rim was significantly greater than that in normal myocardium but lower than that in the infarct core.\textsuperscript{31} Therefore, the totality of experimental data strongly suggests the existence of a gradient of changes in contrast kinetics and volume of distribution from the normal myocardium to the infarct center,\textsuperscript{15,16,20,21,31} which likely reflects an increasing proportion of necrotic myocytes. Because the signal intensities before gadolinium administration are similar across the normal and infarcted myocardium, delayed enhancement is thought to arise from regional differences in tissue gadolinium concentration and T1. We therefore postulate that myocardium demonstrating intermediate signal intensity (between 2 SDs and 3 SDs above remote regions) on delayed imaging observed in the present study represents the peri-infarct zone, where the gadolinium concentration was higher than in the normal nulled myocardium but lower compared with the infarct core. Notably, this peri-infarct zone is not necessarily confined to the border of the infarct (Figure 3), but heterogeneous signal intensity can be seen in more central locations, consistent with surviving myocyte bands in central, subendocardial, and subepicardial locations in infarcts associated with ventricular tachycardia.\textsuperscript{9,11,13}

Partial-volume effect may also have contributed to the intermediate signal intensity in the periphery of the infarct. In an animal model, a similar intermediate signal intensity was reported along the periphery of the hyperenhanced zone due to partial-volume effect of the complex 3-dimensional structure of the infarct.\textsuperscript{17} Because the views per segment was adjusted according to heart rate, which was not correlated with %MDE\textsubscript{periphery}, the intermediate signal intensities that we observed probably represented a simple 3-dimensional complexity of the infarct structure rather than edge blurring due to limited temporal resolution. In a recent study by Bello et al,\textsuperscript{23} infarct surface area and mass defined by CMR delayed enhancement were better predictors of inducible ventricular tachycardia during electrophysiological study than LVEF. These authors did not assess the heterogeneity of delayed hyperenhancement. It should also be recognized that although electrophysiological study detects the presence of the relatively fixed reentry substrate, it may not predict arrhythmias that depend on autonomic and neurohormonal modulating factors or myocyte ischemia in the peri-infarct region. By demonstrating that %MDE\textsubscript{periphery} is an independent predictor of mortality incremental to LVEF, our results extend previous

Figure 3. An example of CMR in a 64-year-old male patient with an inferior MI (white arrows), preserved LV systolic function (LVEF, 61%), and normal LV systolic volume index (54 mL/m²). The MI of this patient was characterized by a substantial peri-infarct zone (yellow region) with a %MDE\textsubscript{periphery} measuring 27%. The patient died 11 months after undergoing the CMR examination.
work and provide further support that morphologically complex infarcts may portend a worse outcome. Although we recognize that partial-volume effect is a limitation of voxel resolution to maintain an adequate signal-to-noise ratio, delayed enhancement intensity may be used as a unique surrogate marker of infarct complexity pending further advances in CMR technology.

Limitations
Several study limitations should be considered in the interpretation of our findings. First, this pilot study included only a relatively small number of patients enrolled in a single-center setting. Our results require confirmation by larger, prospective studies. The relatively high mortality rate may also reflect potential selection bias influenced by the local CMR referral pattern. Therefore, the generalizability of our findings to less-selected post-MI patient populations needs to be established. Second, because the time of MI could not be ascertained in a minority of patients in this pilot cohort, any potential relation between infarct age and the characteristics of the peri-infarct zone by CMR cannot be determined. Third, we used a prespecified, arbitrary signal-intensity threshold (remote +3 SDs) to delineate the core infarct on delayed-enhancement imaging, although the chosen cutoff of remote +2 SDs for the entire infarct has been previously validated in animal models.15,17 and applied in various clinical studies.18,19,23 Future studies should determine the optimal signal-intensity thresholds for more accurate infarct characterization. Finally, we do not know the immediate cause of death or whether death was sudden or arrhythmic for some patients. It is recognized, however, that details about immediate cause of death are often inherently inaccurate, and all-cause mortality is a more robust end point that has been widely accepted, even in clinical trials of implantable cardioverter-defibrillators.1,2

Study Implications
Although this study does not provide insights into the exact histological basis of different infarct characteristics on CMR (isolated strands of surviving myocytes within the infarct border or complex 3-dimensional infarct morphology) or the pathophysiological mechanisms leading to adverse clinical outcomes, our study raises several important questions that may have profound therapeutic implications and deserve further investigations. For instance, the existence of viable myocytes in a large peri-infarct zone may raise the interesting hypothesis that revascularization could be beneficial by reducing arrhythmogenic triggers, despite the apparent lack of measurable improvement in contractile function. Alternatively, implantable cardioverter-defibrillator therapy may be warranted in such high-risk patients identified by CMR owing to the potential for multiple reentry circuits in the peri-infarct zone, even if LV function is preserved.

Conclusions
In conclusion, this pilot study demonstrates that the extent of the peri-infarct region detected by contrast-enhanced CMR is an independent predictor of all-cause mortality after MI, even after adjustment for LV systolic volume index or LVEF. If these results are confirmed, CMR may become a valuable noninvasive risk-stratification tool to guide the optimal use of therapies tailored to individual post-MI patients. Further studies are warranted to elucidate the histological basis of the peri-infarct zone, the pathophysiological links to unfavorable outcome, and their therapeutic implications.

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References

**CLINICAL PERSPECTIVE**

Accurate cardiac risk stratification techniques beyond global left ventricular function can benefit ≈500,000 patients who experience a clinical myocardial infarction (MI) in the United States alone each year. With high tissue contrast and spatial resolution, contrast-enhanced cardiac magnetic resonance (CMR) can characterize the components of an MI, including the core infarct and the peri-infarct regions. An early clinical study has demonstrated a relation between the peri-infarct region and inducible ventricular arrhythmias. In this study of 144 post-MI patients, we used a semiautomated, computer-assisted algorithm to quantify the CMR extent of the peri-infarct (percentage myocardial delayed enhancement [%MDEperiiphery]) and the core infarct (%MDEcore) regions adjusted to infarct size and followed up their subsequent clinical course for a median of 2.4 years. We found that %MDEperiiphery and left ventricular end-systolic volume index were the strongest predictors of all-cause and cardiovascular post-MI mortality in this study cohort. In addition, the strong associations of %MDEperiiphery with all-cause and cardiovascular mortality were independent of left ventricular end-systolic volume index and of age and left ventricular ejection fraction combined. This clinical study provides pilot evidence of the prognostic impact of infarct characterization by CMR and again raises the potential pathophysiological significance of the peri-infarct zone. Future prospective studies will be necessary to establish the histological validation of the peri-infarct zone and explore any utility of contrast-enhanced CMR in treatment planning, including the use of implantable cardioverter-defibrillator therapy, incremental to current risk-stratifying strategies.
Characterization of the Peri-Infarct Zone by Contrast-Enhanced Cardiac Magnetic Resonance Imaging Is a Powerful Predictor of Post–Myocardial Infarction Mortality

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