Background—Previous animal studies have demonstrated that the transmural extent of acute myocardial infarction defined by contrast-enhanced MRI (ceMRI) relates to early restoration of flow and future improvements in contractile function. We tested the hypothesis that ceMRI would have similar predictive value in humans.

Methods and Results—Twenty-four patients who presented with their first myocardial infarction and were successfully revascularized underwent cine and ceMRI of their heart within 7 days (scan 1) of the peak MB band of creatine kinase. Cine MRI was repeated 8 to 12 weeks later (scan 2). The transmural extent of infarction on scan 1 and wall thickening on both scans were determined using a 72-segment model. A total of 524 of 1571 segments (33%) were dysfunctional on scan 1. Improvement in segmental contractile function on scan 2 was inversely related to the transmural extent of infarction on scan 1 ($P=0.001$). Improvement in global contractile function, as assessed by ejection fraction and mean wall thickening score, was not predicted by peak creatine kinase-MB ($P=0.66$) or by total infarct size, as defined by MRI ($P=0.70$). The best predictor of global improvement was the extent of dysfunctional myocardium that was not infarcted or had infarction comprising $<25\%$ of left ventricular wall thickness ($P<0.005$ for ejection fraction, $P<0.001$ for mean wall thickening score).

Conclusion—In patients with acute myocardial infarction, the transmural extent of infarction defined by ceMRI predicts improvement in contractile function. (Circulation. 2001;104:1101-1107.)

Key Words: magnetic resonance imaging ■ contrast media ■ myocardial infarction

Myocardial salvage is the hallmark of successful reperfusion therapy and results in long-term reestablishment of myocardial contractile function and improved prognosis.1-6 Ventricular wall motion at rest cannot be used to quantify salvage early after infarction because both necrotic and viable myocardium can have impaired contractile function.7-9 The distinction between reversible and irreversible dysfunction early after infarction, therefore, is an important and challenging clinical question. Wall motion during exercise or pharmacological stress may be used to distinguish between infarcted and stunned myocardium,10 but this approach can be problematic if residual stenosis is present in the infarct-related artery.11 Some indication of the extent of necrosis can be obtained on the basis of serum enzymes, but the time course and peak of serum enzymes can be influenced by the patency of the infarct-related artery12 and are of limited utility in patients presenting late after the onset of symptoms.

Previous studies have demonstrated that the transmural extent of hyperenhancement by contrast-enhanced MRI (ceMRI) corresponds to the transmural extent of infarction13,14 (TEI). Moreover, in a separate animal study, we found that reductions in TEI defined by ceMRI were associated with early restoration of flow and future improvements in contractile function.15 The current study was designed to test the hypothesis that TEI in humans within the first week after an event can predict improvement in contractile function 2 to 4 months later.

Methods

Patient Population

This study was approved by the Institutional Review Board of Northwestern University. Thirty-one consecutive patients (24 men and 7 women) admitted to the coronary care units at Northwestern Memorial hospital and Veterans Affairs Lakeside hospital with the diagnosis of myocardial infarction, as defined by cardiac enzymes (creatine kinase [CK]-MB $>9\,\mu$g/L), were prospectively enrolled. Patients were included if they had no prior history of myocardial infarction, were reperfused (thrombolitics or angioplasty), were clinically stable, had no contraindications to MRI, and could be scanned within 7 days (scan 1).

The study population consisted of the 24 patients who had a second MRI scan 2 to 4 months later (scan 2). Of the 7 patients without a second scan, 2 were lost to follow-up, 3 refused to return, and 2 had coronary artery bypass grafting and were excluded. No
patient was excluded for technical or image quality reasons. The time between peak CK-MB and second scan was 110±44 days (range, 55 to 225 days). No patient had clinical evidence of a new myocardial infarction between the first and second scans.

**MR Imaging**
Patients were placed supine in a clinical 1.5-T scanner (Siemens Sonata). All images were acquired using a phased-array receiver coil during breath-holds (~8 s) and were gated to the ECG. Cine images were acquired every 10 mm throughout the entire left ventricle (LV; 6 to 8 slices) using 6-mm-thick slices to minimize the effects of partial volume. The contrast agent was then administered intravenously (Gd-HP-DO3A, 0.15 mmol/kg), and contrast-enhanced images were acquired using a segmented inversion-recovery sequence. Typical voxel size was 1.9×1.4×6 mm.

**Data Analysis**

**Image Registration**
Images were registered as previously described. In brief, registration of cine MRI views acquired during scans 1 and 2 was done by the consensus of 2 observers using anatomical landmarks such as papillary muscles and the right ventricular insertion site.

**Definition of Segments**
Cine and contrast-enhanced images were analyzed using a 72-segment model (6 slices; 12 segments per slice) as previously described.

**Scoring**
Cine images from scan 1 and 2 were randomized and interpreted by 2 observers who were blinded to patient identity, contrast enhancement, and the chronological order of the 2 sets of images for each patient. Similarly, contrast-enhanced images from scan 1 were randomized and interpreted by two observers who were blinded to the patient identity and the results of scan 2.

Segmental wall thickening was scored by the consensus of 2 observers according to the following scheme: 0, normal; 1, mild-to-moderate hypokinesis; 2, severe hypokinesis; and 4, dyskinesis. TEI was scored by the consensus of 2 observers on the basis of the transmural extent of hyperenhanced tissue according to the following scheme: 0, no infarction; 1, TEI of 1% to 25% of LV wall thickness; 2, TEI of 26% to 50% LV wall thickness; 3, TEI of 51% to 75% of LV wall thickness; and 4, TEI of 76% to 100% LV wall thickness. Subendocardial hyperenhanced regions surrounded by hyperenhancement were included as part of the infarct territory. Note that a TEI score of 1 represents a small, subendocardial infarction but that the segment is classified as viable because >75% of the segment is not infarcted.

**Ejection Fraction**
An observer blinded to the contrast-enhanced images outlined the LV borders from the short-axis cine images. Papillary muscles were considered myocardium. Ejection fraction was calculated as follows: (volume at end-diastole−volume at end-systole)/volume at end-diastole.

**Statistical Analysis**
Continuous data are expressed as mean±SD. Both the χ² test for trend and logistic regression analysis using a nonlinear mixed effects model (S-PLUS 2000 software®) were used to assess the relationship between TEI immediately after myocardial infarction and improvement in wall thickening. Mixed effect modelling was used because of the non-independence of multiple segments per patient. The relationships between the change in ejection fraction, the change in mean wall thickening score, and various clinical and MR characteristics were evaluated using linear regression analyses. All statistical tests were 2-tailed; P<0.05 was regarded as statistically significant.

**Results**

**Patient Characteristics**
Table 1 summarizes the clinical data of the patient population.

**Segmental Analysis**
A total of 157 of the 1728 segments (9%; 24 patients × 72 segments = 1728) were within the left ventricular outflow tract or could not be visualized on both MRI scans. Of the remaining 1571 segments, 1047 (67%) had normal wall thickening and 524 (33%) were dysfunctional. Of the 524 segments showing dysfunction, 316 (60%) improved on scan 2 (change in wall thickening score of ≥1) and 208 (40%) did not improve.

**Infarct Size**
Figure 1 shows typical results of ceMRI on scan 1. The TEI and viable myocardium varied from patient to patient. Within each patient, the TEI varied both circumferentially (within each short-axis image) and longitudinally (among the 6 base-to-apex image locations). Of the 23 patients with hyperenhancement on scan 1, 20 had hyperenhancement on scan 2 and all 20 had hyperenhancement in the same territory compared with scan 1. The 3 patients without hyperenhancement on scan 2 had a peak CK-MB <38 µg/L.

Figure 2 relates peak CK-MB to infarct size by MRI on scan 1. Infarct size defined by MRI was strongly correlated with peak CK-MB values (r=0.90, P<0.001). Peak CK-MB was also related to absolute infarct mass (r=0.83, P<0.001).

**Regional Contractile Function**
Figure 3 shows 2 patient examples of how the TEI within dysfunctional segments on scan 1 predicted long-term improvement on scan 2. During the acute phase (scan 1) both patients had profound wall thickening abnormalities. The TEI observed in scan 1, however, was very different for these 2 patients, with nearly transmural infarction for patient D and nearly none for patient E. Approximately 3 months later (scan 2), abnormal wall thickening persisted in patient D, but the wall thickening in patient E significantly improved. Full-motion cine images for Figure 3 can be found as a Data Supplement at http://www.circulationaha.org.

Figure 4 shows the percentage of improved segments on scan 2 as a function of the TEI on scan 1. The percentage of improved segments decreased with increasing TEI (P<0.001). For example, 213 of 275 segments (77%) without any infarction and 56 of 84 segments (67%) with 1% to 25% TEI on scan 1 improved by Scan 2. Conversely, only 21 of 60 segments (35%) with 51% to 75% TEI and 3 of 64 segments (5%) with 76% to 100% TEI improved. When the dysfunctional segments were analyzed using the mixed-effects model, which takes into account the multiple measurements from the same patient and a variable number of segments...
from each patient, TEI remained the best predictor of improvement \((P<0.001)\). Multivariate analysis using the mixed-effects analysis revealed there were no models in which more than one predictor was statistically significant.

**Global Contractile Function**

Figure 5A shows the relationship between the change in mean wall thickening score per patient and that of the percent of dysfunctional but viable LV. There was a high correlation between future improvement in global contractile function (mean wall thickening score) and the percent of LV that was dysfunctional but viable \((r=0.87)\).

Figure 5B is similar to Figure 5A but examines the change in ejection fraction. There was again a correlation between future improvement in global contractile function (ejection fraction) and the percent of LV that was dysfunctional but viable \((r=0.65)\).

### Univariate Predictors of Improvement in Global Contractile Function

Table 2 summarizes the univariate predictors for global improvement in contractile function. For both change in mean wall thickening score and change in ejection fraction, the only statistically significant predictive variables were the dysfunctional region by MRI \((P=0.0002\) and \(P=0.037\), respectively) and the dysfunctional but viable region by MRI \((P<0.0001\) and \(P=0.0022\), respectively). The best single predictor of global improvement was the dysfunctional but viable region by MRI.

![](image1.png)

**Figure 1.** Representative results of ceMRI in 3 patients on scan 1. The transmural extent of infarcted (black arrows) and viable (white arrows) myocardium varied from patient to patient and with circumferential location.

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All (mean\(\pm SD\)) 54\(\pm 2\) NA 2.3\(\pm 0.3\) 16Y NA 1544\(\pm 314\) 191\(\pm 47\) 11.5\(\pm 2.5\) 3.6\(\pm 1.7\) 4.2\(\pm 1.8\)

IRA indicates infarct-related artery; M, male; F, female; Y, yes; N, no; LCX, left circumflex artery; RCA, right coronary artery; LAD, left anterior descending artery; and NA, not applicable.
Multivariate Predictors of Improvement in Global Contractile Function

There were no models in which more than one predictor was significant at \( P < 0.05 \).

Discussion

This is the first study to relate long-term improvement in contractile function to the TEI in patients with acute myocardial infarction. We found that within dysfunctional regions, a decrease in the TEI was associated with greater long-term improvement in contractile function.

Study Limitations

The range of time to follow-up (55 to 225 days) should be considered when interpreting the data. Patients with a short follow-up time may not have had full recovery of all dysfunctional segments.

Transmural Extent of Infarction

After coronary artery occlusion, the spatial extent of the region “at risk” is established by the perfusion territory of the occluded artery.\(^9,20\) Within the region at risk, necrosis begins first in the subendocardium and then progresses in a wavefront\(^9,20\) toward the epicardium with increasing occlusion time. This wavefront of necrosis could explain our observa-

<table>
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<th>TABLE 2. Statistical Analysis of Global Improvement</th>
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Abbreviations as in Table 1.

\(^*\) \( P < 0.05 \).
tion that the TEI predicts future improvement in contractile function. For the first several days after reperfusion (scan 1), most if not all of the region at risk would be dysfunctional, either because it was necrotic or stunned.7–9 Within this dysfunctional region, patients with shorter occlusion times and/or a more extensive collateral circulation would have smaller infarcts, which, due to the wavefront phenomenon, would be associated with a smaller TEI. Dysfunctional segments with a smaller TEI (Figure 4) would have a significant proportion of stunned myocardium that would recover contractile function by the time of scan 2. Conversely, dysfunctional segments with a larger TEI (Figure 4) would be predominantly necrotic and would not improve.

Comparison With Previous Studies
Although our study is the first to examine the role of infarct transmurality on contractile improvement, previous studies have related contrast enhancement by MRI early after acute myocardial infarction to contractile function several weeks later. Studies by Rogers et al21 and Kramer et al22 both defined myocardial segments as “hyper” if hyperenhancement was observed, but neither of these studies examined the effect of the transmural extent of hyperenhancement. Interestingly, the authors of both studies reported that myocardial segments fitting the definition of hyper improved contractile function 2 months later. Similarly in our study, segments with a transmural extent of hyperenhancement of 26% to 50% and 51% to 75% exhibited some improvement in contractile function (Figure 4). Unlike our study, however, Rogers et al21 and Kramer et al22 excluded dysfunctional segments with no hyperenhancement. We found that these were the most likely to exhibit contractile improvement (Figure 4).

Rogers et al21 used the observation that segments classified as hyper improved contractile function as the basis for their conclusion that hyperenhancement represents viable myocardium. The observation of improvement, however, could be explained by the fact that the population of hyper segments reported by Rogers et al21 contained a spectrum of infarct transmurality that improved as a group due to resolution of stunned myocardium located predominately toward the epicardium. The study designs of Rogers et al21 and Kramer et al22 were similar to those used in SPECT,23 echocardiographic,24 and PET25 studies of myocardial viability in that each myocardial segment was classified as either “viable” or “nonviable.” This study design excludes the possibility that individual segments contain both necrotic (endocardial) and viable (epicardial) regions and that such segments can experience some degree of contractile improvement. For SPECT, echocardiographic, and PET studies, neglecting the TEI is unavoidable because none of these modalities can define infarct transmurality. The studies by Rogers et al21 and Kramer et al22 may have had a limited ability to define transmural extent due to the use of an older MRI technique that did not null signal from normal myocardium after contrast and acquired the entire image in a single heartbeat,17 suggesting that direct comparison to the present study may be inappropriate. The data of the current study demonstrate that the TEI plays an important role in the prediction of improvement (Figure 4 and Table 2). In light of these data, it seems that viability should not be defined in a binary fashion.

Myocardial Enzymes
We found a strong correlation between infarct size as defined by MRI and peak CK-MB (Figure 2). Some relationship between these parameters would be expected considering that peak CK-MB relates to infarct size.26–30 Neither infarct size by MRI nor peak CK-MB were predictive of improvement, however (Table 2). One explanation for this is that 2 infarcts of similar size may be associated with different-sized regions at risk. Another possibility, however, is that a subendocardial infarct with a large circumferential extent may have an infarct mass similar to a transmural infarct with a small circumferential extent within the dysfunctional region on scan 1 (arrows) and had minimal improvement in contractile function in this region on scan 2. Note the subendocardial hypoenhanced region surrounded by hyperenhancement in this patient, indicating “no-reflow” at the infarct core (white arrow). Patient E, conversely, had a TEI <25% of LV wall thickness within the dysfunctional region on scan 1 (arrows) and had significant improvement in contractile function on scan 2. The full-motion cine images can be found Online at http://www.circulationaha.org.
ential extent. Despite similar infarct mass, the first shape would be expected to exhibit more improvement in contractile function. Further studies will be required to test the hypothesis that infarct shape plays an independent role in contractile improvement.

**Clinical Relevance**

The data of the current study establish that ceMRI performed early after infarction can be used to distinguish between reversible and irreversible dysfunction. The technique does not require exercise or pharmacological stress testing and, unlike existing techniques, allows direct visualization of the TEI. Myocardial salvage has been related to prognosis by a number of investigators

Further investigation will be required to test the hypothesis that reversible dysfunction defined by MRI early after infarction provides prognostic information for individual patients and provides a new end point for clinical trials.

**Acknowledgments**

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**References**

9. Reimer KA, Jennings RB. The “wavefront phenomenon” of myocardial ischemic cell death. II: transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. Lab Invest. 1979;40:633–644.

**Figure 5. Results of global analysis.** The size of the dysfunctional but viable region was the best predictor of both ejection fraction (EF) and mean wall thickening score. See Table 2.
Transmural Extent of Acute Myocardial Infarction Predicts Long-Term Improvement in Contractile Function
Kelly M. Choi, Raymond J. Kim, George Gubernikoff, John D. Vargas, Michelle Parker and Robert M. Judd

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