Accuracy of Contrast-Enhanced Magnetic Resonance Imaging in Predicting Improvement of Regional Myocardial Function in Patients After Acute Myocardial Infarction

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Background—Contrast-enhanced (CE) MRI demonstrates a pattern of hypoenhancement early after contrast injection in acute myocardial infarction (MI) and a pattern of hyperenhancement late after contrast injection. Because the significance of these CE patterns for myocardial viability remains debated, we evaluated their diagnostic accuracy to quantitatively predict late functional improvement of regional contractility.

Methods and Results—Twenty patients underwent CE and tagged MRI at 4 days and again at 7 months after acute MI. Resting circumferential shortening strain (Ecc) was analyzed in 24 segments per patient, and its improvement was correlated with the presence or absence of the CE patterns. Immediately after MI, 389 segments were considered dysfunctional because of having less than mean ± 2 SD Ecc of the remote region (−18 ± 4%). At follow-up, significant improvement of Ecc occurred in 170 dysfunctional segments with normal CE (from −4 ± 7% to −12 ± 7%, P < 0.001) but not in 60 segments with early hypoenhancement (from −2 ± 6% to −6 ± 9% Ecc, P = NS). In 240 dysfunctional segments with delayed hyperenhancement, the improvement of Ecc (from −2 ± 6% to −5 ± 8%, P < 0.001) decreased with increasing transmural extent of hyperenhancement. Receiver operating characteristic analysis demonstrated that absence of delayed hyperenhancement, compared with absence of early hypoenhancement, had better sensitivity (82% versus 19%, respectively; P < 0.001) and accuracy (74% versus 49%, respectively; P < 0.001) in predicting recovery of Ecc to any given level.

Conclusions—Compared with lack of early hypoenhancement, lack of delayed hyperenhancement has better diagnostic accuracy in predicting functional improvement in dysfunctional segments. The early hypoenhanced regions, which represent only the fraction of infarcted tissue with concomitant microvascular obstruction, greatly underestimate the amount of irreversibly injured myocardium present after acute MI. (Circulation. 2002;106:1083-1089.)

Key Words: magnetic resonance imaging ▪ myocardial infarction ▪ hibernation ▪ myocardial stunning

Contrast-enhanced (CE) MRI can characterize acute myocardial infarction (MI) with 2 well-defined CE patterns as follows: (1) First-pass images performed immediately after contrast injection often demonstrate areas of reduced CE MRI or hypoenhancement in the endocardial core of the infarct, corresponding to microvascular obstruction.1,2 (2) Delayed images (10 to 20 minutes after contrast injection) demonstrate regional signal hyperenhancement, corresponding to myocardial necrosis. It has been hypothesized that a combination of CE perfusion MRI with functional data might be useful for the identification of myocardial viability, allowing one to distinguish permanently dysfunctional myocardium from dysfunctional segments bound to recover contractile function and contribute to left ventricular (LV) stroke volume after MI.1-4 However, previous studies have provided conflicting data regarding the interpretation of these perfusion patterns for the identification of viable and nonviable myocardium in patients after MI.

Kim et al5 reported that in patients with chronic MI, the increasing transmural extent of delayed hyperenhancement is correlated with poor recovery of contractile function after revascularization. This suggests that hyperenhanced tissue would be an accurate marker for nonviable myocardium in these patients.5 However, that analysis relied on the visual assessment of wall thickening and not on the quantitative measurement of regional contractility. Also, that study did not report on the presence of regions with early hypoenhancement, because this pattern is not identified in chronic MI patients. On the other hand, in patients with acute MI, Rogers et al6 demonstrated that hyperenhanced but not hypoenhanced segments could spontaneously improve contractility, suggesting that only tissue with early hypoenhanced tissue would
represent nonviable myocardium, whereas tissue with delayed hyperenhancement would represent partially viable myocardium. However, in that study, the diagnostic accuracy of both CE patterns in predicting spontaneous improvement of dysfunctional segments at follow-up was not quantified in detail.

The aim of the present study was to clarify the value of both CE MRI patterns for the detection of myocardial viability in patients with acute MI. We examined the accuracy of both early hyperenhanced and delayed hyperenhanced regions in quantitatively predicting improvement in local myocardial function, and we used receiver operating characteristic (ROC) analysis to perform these comparisons independent of cutoff values chosen to define functional recovery and myocardial necrosis by MRI.

Methods

Patient Population
We studied 20 patients (13 male, aged 61±14 years) hospitalized for a first acute MI, diagnosed by acute chest pain, increased creatine phosphokinase levels, characteristic ECG changes, and angiographically demonstrated partial or complete occlusion of the infarct related artery. To be included, patients had to be hemodynamically stable and to have no contraindication to MRI. All participants gave written informed consent to the study protocol, which was approved by the Institutional Review Board of the Johns Hopkins Hospital.

Study Protocol
Patients were studied twice. Baseline MRI, consisting of tagged and perfusion images, was performed ±2 days after acute MI. Improvement of resting regional contractile function was assessed by a follow-up tagged MRI study 7±2 months later.

MRI Protocol
MRI was performed with a 1.5-T magnet (Signa CV, GE) by using a phased-array coil wrapped around the chest. After localization of the heart, 5 contiguous tagged short-axis cine images of the LV were prescribed to cover the entire heart from base to apex. Tagged images were acquired by using an ECG-gated segmented k-space gradient echo pulse sequence with spatial modulation of magnetization. Image parameters were as follows: repetition time (TR) 5.8 ms, excitation time (TE) 2.3 ms, image matrix 256×128, field of view 36 cm, slice thickness 10 mm, spacing 2 to 4 mm, flip angle 12°, and k-space/ cardiac cycle 8 to 12 lines. Images were acquired during short breath-holding (12 to 15 seconds) at end expiration.

After tagged images were acquired, the patients received an intravenous bolus of 0.1 mmol/kg Gadodiamide (Omniscan, Nycomed) at a rate of 5 mL/s by means of an infusion pump. A first-pass perfusion scan was acquired simultaneously with the bolus injection for 40 to 50 heartbeats. First-pass images were acquired by using an ECG-gated saturation recovery interleaved gradient echo planar imaging pulse sequence, with a temporal resolution covering the entire heart (5 slices) every other heart beat. Imaging parameters were as follows: TR 6.2 ms, TE 1.2 ms, echo train length 4, image matrix 128×128 interpolated to 256×256 pixels, flip angle 20°, saturation pulse 90°, bandwidth 125 kHz, and inversion time 160 ms. After completion of the first-pass images, a second bolus of 0.1 mmol/kg Gadodiamide was given. Ten minutes after the second bolus, delayed images were acquired by using an inversion-recovery prepared gated fast-gradient echo-pulse sequence, similar to that recently described by Simonetti et al. Imaging was performed with the following parameters: TR 6 ms, TE 2 ms, image matrix 256×192, flip angle 20°, inversion pulse 180°, and inversion time 200 to 250 ms. Both the first-pass and delayed-image prescriptions had the same slice thickness and spacing as the tagged short-axis images.

Figure 1. A, Segmental model. Ecc and perfusion patterns were analyzed on 5 slices, which were segmented into 8 sectors by using anterior-septal right ventricular insertion as a landmark. Remote segments for anterior infarcts are shown in red; remote segments for inferior infarcts, in blue. B, Characterization of CE patterns. Baseline, first-pass, and late images were automatically segmented. Segments were considered to be hyperenhanced if they had less than mean−2 SD PSIC of remote segment on first-pass images. Segments were defined to be hyperenhanced when they had more than mean+2 SD SI of remote segment on late images. Late images were thresholded to compute extent of hyperenhancement in each sector.

MRI Data Analysis
To accurately correlate perfusion and contractile function at baseline and follow-up, a mesh consisting of 40 sectors was used. By use of the anterior-septal insertion of the right ventricular wall as a landmark, each of the 5 prescribed short-axis slices was subdivided into 40 radially spaced segments. In each patient, 9 segments (3 inferior-posterior segments on 3 basal levels for patients with anterior infarction, and 3 anterior segments on 3 apical levels for patients with inferior-posterior infarction; Figure 1A) were defined as representing remote myocardium.

Tagged images were analyzed quantitatively by using harmonic phase imaging analysis.7 Eulerian circumferential shortening strain (Ecc) was computed at the midventricular level within each of the 40 sectors. Ecc was expressed as a fractional change of length of the myocardium between end diastole and end systole and, by convention, was defined as having a negative sign representing shortening (active contraction) and a positive sign representing stretching (passive deformation).

Perfusion data were analyzed quantitatively by the user interactive program MEDIMAN.10 Circumferential profiles of signal intensity
Percent SI increase (PSIC) was computed in each of the 40 segments as follows:

\[
\text{PSIC} = \frac{\text{SI}_{\text{early}} - \text{SI}_{\text{late}}}{\text{SI}_{\text{remote}}} \times 100
\]

where SI, is SI at peak myocardial contrast enhancement, and SI<sub>late</sub>, is SI before injection of the contrast agent. Early hypoenhancement was defined as being present if PSIC was lower than mean ±2 SD of the 9 remote segments at peak myocardial contrast enhancement. Delayed hyperenhancement was defined as being present if SI on late images was higher than mean ±2 SD of the 9 remote normal segments 10 minutes after contrast injection. Images were thresholded to these levels, and the extent of both regions was planimetric and expressed as percent LV area. The transmural extent of hypoenhancement was computed within each of the 40 segments on these thresholded images as the percentage of the segmental area, which was hyperenhanced (Figure 1B).

Statistical Analysis

All values are mean ± SD. Two-way ANOVA with repeated measurements with planned comparisons was used to compare strains in remote segments, in dysfunctional segments with different CE patterns, and in different segments between the baseline and follow-up study. ROC curves were used to compare predictive accuracy of hypoenhanced and hyperenhanced segments with different cutoff values to predict improvement of strain at follow-up. Areas under the ROC curves were compared by use of the 2-tailed McNemar test. Individual sensitivities and specificities were compared by using the McNemar test. All tests were 2-sided, and a value of \(P < 0.05\) was considered indicative of statistical significance.

Results

Study Population and CE Patterns

Eleven patients had acute anterior MI, and 9 had inferior MI. Seventeen patients had Q-wave MI, and the remaining 3 patients had non–Q-wave MI. The peak creatine phosphokinase level was 2380 ± 2854 (range 209 to 12 000) U/mL. Six patients were successfully revascularized by direct angioplasty. Twelve patients received thrombolysis; 8 of them received angioplasty (first or second post-MI days). Two patients did not undergo infarcted artery revascularization because they already had Thrombolysis in Myocardial Infarction (TIMI) III flow on angiography. The infarct-related artery was angiographically patent in all but 1 patient at the baseline study. Between the baseline and the follow-up study, 4 patients underwent coronary artery bypass surgery. None of the patients developed angina pectoris or reinfarction during the follow-up period. Immediately after MI, all 20 patients had regions of delayed myocardial hyperenhancement. In addition, 13 of the 20 patients presented with a region of early hypoenhancement.

Myocardial Strains in Infarcted and Remote Myocardium Immediately After Infarction

The magnitude of circumferential shortening in remote non–infarcted segments (−18 ± 4%, Figure 1) was similar to that of circumferential shortening in 8 normal volunteers (−18 ± 4%). Using these remote normal values, we defined abnormal regional contraction as those segments with Ecc of the remote region (389 of the total 800 segments) of less than mean−2 SD. The 389 dysfunctional segments were further classified according to their contrast enhancement pattern. One hundred forty-nine segments presented no early hypoenhancement or late hyperenhancement. Two hundred forty segments displayed delayed hyperenhancement, and of these, 60 also had early hypoenhancement. The remaining 180 segments with delayed hyperenhancement had no early hypoenhancement on the first-pass MRI perfusion study. An example of a CE MRI study and corresponding Ecc maps are shown in a patient immediately and late after MI (Figure 2). At baseline, mean strain values were similar in dysfunctional segments with normal enhancement, delayed hyperenhancement, and early hypoenhancement (Figure 3).

Ecc Changes at Follow-Up in Relation to CE Patterns

Changes in circumferential shortening in dysfunctional myocardium between the baseline study 4 days after MI and the follow-up study 7 months later are shown in Figure 3. There were no significant changes of circumferential shortening in remote nondysfunctional myocardium. Dysfunctional myocardium with normal contrast enhancement (neither early hypoenhancement nor delayed hyperenhancement) displayed significant improvement of circumferential shortening (from −4 ± 7% to −12 ± 7%, \(P < 0.001\)). In contrast, early hypoenhanced regions showed no improvement of midventricular circumferential shortening at follow-up (from −2 ± 6% to −6 ± 9%, \(P = \text{NS}\)). However, dysfunctional myocardium with delayed hyperenhancement, but without early hypoenhancement, presented some improvement of circumferential shortening at follow-up (from −2 ± 6% to −5 ± 8%, \(P < 0.001\)). This improvement of Ecc was significantly smaller than in dysfunctional normally enhanced segments (−3 ± 10% versus −9 ± 10%, respectively; \(P < 0.001\)). Moreover, the improvement of circumferential shortening in segments with delayed hyperenhancement was dependent on its transmural extent (Table). When the transmural extent of hyperenhancement was categorized into 4 categories (<25%, 25% to 49%, 50% to 74%, and >75%), a significant relationship between the transmural extent and quantitative improvement in circumferential shortening was observed. Improvement was most prominent in segments with the least amount of hyperenhancement, and it decreased for each category of increasing transmural extent, until becoming absent when the transmural extent of myocardial hyperenhancement reached >75%.

Accuracy of CE Patterns in Predicting Recovery of Regional Contractile Function by ROC Analysis

Diagnostic accuracy of early hypoenhancement was compared against that of delayed hyperenhancement in predicting recovery of Ecc 7 months after MI. Sensitivity and specificity were computed by using different cutoff values of SI for the definition of delayed hyperenhancement and early hypoenhancement (ranging from mean ± 1 SD to mean + 10 SD SI relative to the remote region of each individual patient) and by using 4 different qualitative cutoff values of Ecc (−5%, −7.5%, −10%, and −12.5% Ecc) to define normal and abnormal contractile function. Results are reported in the form of ROC curves in Figure 4. As illustrated by the significantly larger area \((P < 0.001\) for all curves) under the ROC curve, for every cutoff
point of Ecc, absence of delayed hyperenhancement was more accurate in predicting recovery of Ecc to the specified level than any combination of CE MRI patterns.

For example, if a cutoff value of mean $-2 \text{ SD}$ (lower boundary of the CI in remote myocardium and in normal volunteers) is used to define dysfunction at baseline and at follow-up, of the 389 dysfunctional ($< -10\%$ Ecc) segments at baseline, 170 (44%) would normalize circumferential shortening (to $> -10\%$) at follow-up. The remaining 219 (56%) segments would remain dysfunctional ($< -10\%$ Ecc at follow-up). The probability of improvement for dysfunctional segments with early hypoenhancement and late hyperenhancement is demonstrated in Figure 5A and 5B. All but 19 of the 60 dysfunctional segments with early hypoenhancement remained dysfunctional at follow-up. Therefore, the presence of early hypoenhancement had a high positive predictive value of 68% (41 of 60) and a high specificity of 89% (151 of 170) in forecasting persistent dysfunction. However, because 178 dysfunctional segments without early hypoenhancement also remained dysfunctional at follow-up, the absence of early hypoenhancement had a negative predictive value of 46% (93 of 329) and a low sensitivity of 19% (41 of 219) in predicting persistent dysfunction. Overall accuracy was 49% (192 of 389). Because only 40 of 149 dysfunctional segments without delayed hyperenhancement remained dysfunctional (Figure 5B), the presence of delayed hyperenhancement had a better negative predictive value, 73% (109 of 149), and a higher sensitivity, 82% (179 of 219), in predicting persistent dysfunction. Its absence was 64%
specific in predicting the recovery of dysfunction, and its overall accuracy was better (74% [288 of 389], \( P < 0.001 \)) than that of early myocardial hypoenhanced regions. Figure 6 shows the sensitivity, specificity, and accuracy of early hypoenhanced region and delayed hyperenhanced region in predicting improvement of Ecc to \(< -10\%\) in dysfunctional segments at baseline.

Discussion

The principal findings of the present study can be summarized as follows: (1) Improvement of segmental circumferential shortening late after infarction can be predicted by CE patterns early after MI. Regions with normal CE pattern display the most improvement in circumferential shortening, whereas regions with early hypoenhancement do not improve regional contractility. In regions with delayed hyperenhancement, improvement in circumferential shortening is inversely related to the degree of transmural involvement. (2) ROC analyses indicate that the presence or absence of late hyperenhancement has better diagnostic accuracy than does the presence or absence of early hypoenhancement in predicting respective failure or success of functional improvement after MI.

CE MRI for Prediction of Segmental Functional Recovery

There is ongoing debate regarding the significance of CE MRI in predicting the recovery of contractile function clinically. Recent clinical studies\(^6,7\) suggest that normally enhanced dysfunctional myocardium can improve contractility after MI, whereas hypoenhanced myocardium remains dysfunctional. This has been demonstrated in the present study in a quantitative manner and is in agreement with pathological findings, which indicate that normally enhanced myocardium is noninfarcted,\(^4\) whereas hypoenhanced myocardium represents necrotic tissue with microvascular damage and obstruction.\(^1,2\) Reversible dysfunction in noninfarcted myocardium is most commonly caused by myocardial stunning,\(^1,2\) whereas irreversible dysfunction is most commonly due to necrotic myocardium.

By contrast, the significance of delayed hyperenhancement in predicting improvement of contractile function after MI remains debated. Experimental studies have demonstrated excellent spatial correlation between the presence of Gd-DTPA hyperenhancement and regional myocardial necrosis on ex vivo imaging.\(^2,4\) Yet, by imaging performed in vivo, infarct size by MRI with delayed hyperenhancement may overestimate infarct size (according to triphenyltetrazolium chloride surface staining) because of partial volume effects in the slice thickness requirements that are inherent to current in vivo MRI.\(^4\)

As a result, it has been postulated that hyperenhanced myocardium detected clinically could also include significant amounts of damaged noninfarcted tissue and, thus, would reflect viable rather than nonviable myocardium.\(^6,11,14\) In support of this, Dendale et al\(^15\) reported inotropic response in
41% of hyperenhanced segments, suggesting viability. Rogers et al also reported that regions presenting delayed hyperenhancement alone or in combination with early hyperenhancement improved circumferential shortening between 1 and 7 weeks after acute MI and would, therefore, be viable.

**Accuracy of Contrast Enhancement Patterns for Predicting Viability**

To resolve the issue of which CE pattern is most useful in predicting recovery of function after acute MI, the present study used ROC analysis and objective operator-independent measurements with quantitative thresholds for the definition of CE patterns and functional recovery. This analysis demonstrated that an absence of delayed hyperenhancement has higher accuracy in predicting improvement of function than does an absence of early hyperenhancement for any threshold chosen to define these CE patterns and functional recovery. Indeed, although early hyperenhancement was highly specific for irreversible dysfunction, its absence was not sensitive, because its extent greatly underestimates the amount of irreversibly dysfunctional myocardium in the human infarcted LV. On the other hand, the absence of hyperenhancement had superior sensitivity in predicting functional recovery. These findings correlate well with previous experimental and clinical studies, which demonstrate that regions with early hypo-enhancement reflect only that part of the necrotic tissue afflicted by microvascular obstruction, excluding the reperfused necrotic area with patent microvasculature, which is included in the delayed hyperenhanced region.

**Complex Relationship Between Myocyte Viability and Recovery of Contractile Function**

Despite the higher sensitivity of the delayed hyperenhanced region in predicting functional recovery, the previously reported findings of functional improvement in these regions were confirmed in the present study. Such an improvement of contractility in hyperenhanced regions suggests a discrepancy between metabolic viability, as indicated by myocardial hyperenhancement, and segmental function improvement. To clarify this issue, we determined the relationship between the transmural extent of hyperenhancement and the quantitative improvement of contractility measured as changes in circumferential shortening 7 months after MI. We could demonstrate that the magnitude of long-term functional recovery measured quantitatively is inversely related to the transmural extent of hyperenhancement: In the infarcted human heart, the magnitude of segmental function recovery decreases with increasing degrees of transmural extent, being completely absent in segments showing >75% transmural extent of hyperenhancement.

This complex relationship between the transmural extent of necrosis and quantitative functional improvement can be explained by findings from recent experimental studies. These studies document that improvement of subendocardial strains in nontransmural infarcts can occur through passive deformation created by the improved contractility of noninfarcted subepicardial segments. This concept has been proposed in previous experimental studies and is also supported by prior clinical investigations that use less quantitative techniques. The present study documents the complexity of this relationship between function and extent of necrosis at a local level. Therefore, improvement in passive deformation despite the absence of metabolic viability likely explains the functional improvement of hyperenhanced segments in previous clinical and MRI studies.

**Clinical Implications**

The present study underscores the contribution of CE MRI to our current understanding of myocardial viability after MI. It demonstrates the potential of CE MRI to predict functional recovery in patients with acute MI. CE MRI is superior to other techniques because it allows the precise assessment of the transmural extent of myocardial necrosis and microvascular occlusion. MRI also allows the quantitative assessment of functional recovery by using tagged MRI. Our results demonstrate that both the transmural extent of myocardial necrosis and the extent of microvascular damage influence regional recovery of contractility. They indicate the importance of these parameters in predicting the likelihood of myocardial functional recovery after acute MI.

**Conclusions of the Study**

The present study demonstrates that CE MRI can quantitatively predict the recovery of resting regional function and, thus, myocardial viability early after acute MI. It also demonstrates that the presence or absence of delayed hyperenhancement, which reflects myocardial necrosis, is a more accurate parameter for predicting persistent dysfunction than is early hyperenhancement alone, which reflects microvascular obstruction. In addition, the present study quantifies the magnitude of local contractile functional recovery and its dependence on the transmural extent of CE patterns in myocardial segments in which infarcts are nontransmural. These observations clarify and corroborate the value of CE MRI in the clinical detection of myocardial viability in humans.

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