Early Contrast-Enhanced MRI Predicts Late Functional Recovery After Reperfused Myocardial Infarction

Walter J. Rogers, Jr, MS; Christopher M. Kramer, MD; Gennady Geskin, MD; Yong-Lin Hu, PhD; Therese M. Theobald, RDCS; Diane A. Vido, MS; Susan Petruolo, RN; Nathaniel Reichek, MD

Background—We have observed 3 abnormal patterns on contrast-enhanced MRI early after reperfused myocardial infarction (MI): (1) absence of normal first-pass signal enhancement (HYPO), (2) normal first pass signal followed by hyperenhanced signal on delayed images (HYPER), or (3) both absence of normal first-pass enhancement and delayed hyperenhancement (COMB). This study examines the association between these patterns in the first week after MI and late recovery of myocardial contractile function by use of magnetic resonance myocardial tissue tagging.

Methods and Results—Seventeen patients (14 men) with a mean age of 53±12 years were studied after a reperfused first MI. Contrast-enhanced images were acquired immediately after bolus administration of gadolinium and 7±2 minutes later. Tagged images were acquired at weeks 1 and 7. Circumferential segment shortening (%S) was measured in regions displaying HYPER, COMB, or HYPO contrast patterns and in remote regions (REMOTE) at weeks 1 and 7. At week 1, %S was depressed in HYPER, COMB, and HYPO (9±8%, 7±6%, and 5±4%, respectively) and were less than REMOTE (18±6%, P<0.003). However, in HYPER, %S improved at week 7 from 9±8% to 18±5% (P<0.001 versus week 1). In contrast, HYPO did not improve significantly (5±4% to 6±3%, P=NS) and COMB tended to improve 7±6% to 11±6% (P=0.06).

Conclusions—HYPER has partially reversible dysfunction and represents predominantly viable myocardium. COMB shows borderline improvement and likely contains an admixture of viable and necrotic myocardium. HYPO shows little functional improvement at 7 weeks, presumably because of irreversible myocardial damage. (Circulation. 1999;99:744-750.)

Key Words: magnetic resonance imaging ■ reperfusion ■ contrast media

Prompt reperfusion salvages myocardium at risk after coronary artery occlusion.1,2 Significant improvement in mortality and morbidity may be achieved even when reperfusion occurs up to 6 to 12 hours after acute myocardial infarction (MI).3 However, protracted ischemia may produce an admixture of necrotic and viable myocardium. Although stunned viable myocardium differs structurally and metabolically from irreversibly injured myocardium, both may display similarly depressed mechanical function at rest early after MI.

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Recently, a number of studies have investigated the potential value of T1-shortening contrast agents, combined with rapid MRI, in the characterization of regional myocardial perfusion, ischemia, and infarction with and without reperfusion.4-10 Normal myocardium displays signal enhancement immediately after passage of the contrast bolus through the left ventricle (LV) because of the T1 shortening effect of the contrast material. Previously ischemic, reperfused myocardium has been shown to display 2 different types of contrast “defects”: first-pass regions of reduced signal enhancement and regions with relatively increased signal intensity on delayed images.6,7 The relationship between these 2 patterns and subsequent regional recovery of mechanical function has not been determined. In addition, most previous studies have used only delayed imaging, but it is now possible to image dynamically through the first-pass period. Thus, the goals of the present study were to combine first-pass and delayed image data to assess contrast abnormalities and to quantify the relationship between changes in regional mechanical function between 1 and 7 weeks after MI in regions with abnormal contrast patterns by use of myocardial tissue tagging.

Methods

Subject Population
Twenty-seven subjects, 10 normal (from medical history and age) control subjects who underwent contrast imaging only (4 men; mean age, 37±6 years) and 17 patients (14 men) with a mean age of 53±12 years were included. Patients were studied after a reperfused first MI. Average time from initial cardiac symptoms to initiation of reperfusion therapy was 280±170 minutes. Table 1 summarizes the
clinical parameters associated with each patient. All patients had TIMI grade 3 flow in the infarct-related artery after therapy and before week 1 contrast MRI.

**Image Acquisition**

The normal control group underwent first-pass and delayed contrast-enhanced imaging to establish normal values for contrast kinetics and regional signal variability. In patients, MRI was performed 1 (5±2 days) and 7 (7±2 weeks) weeks after MI. We used a Siemens 1.5-T clinical scanner with patients in the prone position using an elliptical surface receiver coil. Scout images in the coronal and parasagittal long axis were used to identify the LV short and long axes. End systole was timed on the basis of minimum cavity area from a rapid midlevel short-axis cine with a time of resistance of 40 ms and a matrix of 64×128.

Tagged short-axis cine-segmented k-space MRI allowed data to be gathered during breath-hold periods of 16 to 18 cardiac cycles. Contiguous 7-mm short-axis slices were acquired from the LV apex to base at weeks 1 and 7. Seven phase lines were acquired for every cardiac cycle. A 280×280-mm field of view was imaged, including 112 to 126 phase lines and 256 frequency lines. Two sets of periodically oriented tags, with 7-mm interstripe spacing, were generated by use of binomial radiofrequency pulses immediately before image acquisition. Images were acquired at 5 points across the cardiac cycle, with interphase delay adjusted to ensure timing of an image at end systole.

To position the contrast image plane, tagged short-axis images at multiple levels were reviewed in cine format to locate the region of mechanical dysfunction in each patient. On the basis of this information, a tagged long-axis cine was acquired in the center of the region of dysfunction in the short axis to verify dysfunction in the same plane that would be used for the contrast-enhanced images. Contrast-enhanced images were acquired at week 1 with 0.1 mmol/kg nonionic gadolinium (Gadoteridol, Bracco Diagnostics) as described by Atkinson et al.11 A venous line was positioned in the antecubital vein, and a contrast bolus was injected by hand over 4 to 6 seconds. TI-weighted, inversion-prepared Turboflash images were then sequentially acquired at a single location immediately after contrast injection (repetition time=1.12 ms, flip angle=25°, slice thickness=10 mm, and field of view=30 cm) in the center of the dysfunctional region. A sufficient number of images were acquired before contrast arrival in the LV to allow magnetization to reach steady state. The delay from the 180° inversion pulse to image acquisition was adjusted to maximize steady-state myocardial signal. Thus, images were acquired in diastole. A complete image was acquired in 360 ms during each of 64 sequential cardiac cycles. A delayed set of 10 inversion recovery images was acquired in the same orientation 7±2 minutes after contrast administration.

**Image Analysis**

First-pass and delayed contrast images were reviewed in cine format and used in combination to define 2 types of abnormal contrast pattern qualitatively. On the first-pass images, regions were classified by 2 experienced, blinded observers as either normal in intensity or hypointense. On the delayed images, regions were characterized as normal in intensity or hyperintense. Regions displaying first-pass hyperenhancement without delayed hyperenhancement were defined as HYPO. Regions displaying no first-pass HYPO but delayed hyperenhancement were defined as HYPER. Regions displaying combined first-pass hyperenhancement and delayed hyperenhancement were defined as COMB. Normal-appearing regions remote from either functional or contrast abnormalities were defined as REMOTE.

Contrast images were reviewed by 2 blinded reviewers for determination of location and transmurality of contrast patterns. Defects were defined as being limited to the endocardial half of the LV wall (ENDO), the epicardial half of the wall (EPI), or transmural (TRANS).

Matching between week 1 tagged short- and long-axis perfusion images was accomplished with a custom computer program. The 3-dimensional coordinates defining the tagged short-axis image plane locations were graphically superimposed on the long-axis contrast image that best represented HYPO and HYPER in the first-pass and delayed postcontrast images, respectively (Figure 1). Intersections between contrast defects and short-axis tagged image locations were used to select the tagged short-axis image planes that would be used for analysis of segment shortening (%S). In addition, the circumferential location and transmural extent (EPI, END0, or TRANS) of the contrast abnormality were matched to the tagged images to assign %S loci to HYPO, HYPER, COMB, or REMOTE. The transmural and circumferential locations used to compute %S at

**TABLE 1. Patient Characteristics**

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CPK = creatine phosphokinase; EF, ejection fraction; Site, location of LV ischemia; Ant, anterior; Inf, inferior; Time, days from infarction to MRI; Lytic, use of thrombolytic agent to restore coronary flow; and PTCA, use of PTCA to restore coronary flow.
Results

Contrast Kinetics

Normal Control Subjects

Normal myocardium displayed rapid, uniform first-pass signal enhancement and a lack of delayed regional hyperenhancement. The coefficients of variation for the 5 ROIs evenly distributed within the long-axis contrast enhanced images were 12.7% at peak enhancement and 15.2% on delayed images. The mean signal intensity relative to a reference ROI was 1.02±0.1, resulting in a ±2-SD range of 0.82 to 1.22 at peak enhancement. On delayed images, the mean relative signal intensity was 0.98±0.15 of the reference ROI, resulting in a ±2-SD range of 0.68 to 1.28. These values were used to verify HYPO and HYPER in the patient group.

Patients

Contrast imaging in the 17 patients identified 5 HYPO, 13 HYPER, 10 COMB, and 17 REMOTE for a total of 28 regions. It was possible to have >1 abnormal contrast region in each patient. HYPO and HYPER were validated by comparison with quantitative data from the 10 normal control subjects. In regions visually identified as HYPO or COMB, 15 of 15 (100%) had relative signal intensity >2 SD below mean normal values on first-pass images. In regions identified as HYPER, 11 of 13 (85%) had relative signal intensity >2 SD above mean normal values on delayed images; the remaining 2 (15%) had signal intensity >1 SD above delayed mean normal. Of 10 regions defined as COMB, 6 (60%) had relative signal intensity on delayed imaging >2 SD above normal delayed values, 3 (30%) were >1 SD above normal, and 1 (10%) was <1 SD above the mean normal delayed value.

Figure 2 shows time-intensity curves for ROIs positioned in the LV blood pool, REMOTE, and HYPO regions for a sample patient during myocardial contrast transit. After a rapid increase in blood pool signal intensity, there is an early and persistent difference in myocardial signal intensity between HYPO and REMOTE. HYPO is seen as a subendocardial region of hypointense signal in the apical-septum in a first-pass, 4-chamber long-axis image of the same patient (Figure 3). In contrast, in HYPER (Figure 4), the early signal increase is similar between HYPER and REMOTE. However, the signal intensity in HYPER continues to increase, whereas REMOTE reaches a plateau. This produces hyperintense myocardium on the delayed postcontrast image shown in Figure 1.

Quantitative Analysis of First-Pass Signal Intensity

in Patients

During the first pass of the contrast bolus, signal enhancement in HYPO was 52±27% of that seen in REMOTE.
whereas the signal intensity in HYPER was similar to REMOTE (91±31%). In delayed contrast imaging, HYPER increased to 139±38% of REMOTE (P<0.003). Signal enhancement in HYPO normalized in delayed images (80±38% of REMOTE, P=NS). COMB showed first-pass signal hypoenhancement (36±24%), which was different from both REMOTE and HYPER (P<0.001) but not from HYPO. Delayed-imaging hyperenhancement in COMB was 159±5% remote (P<0.001), whereas the change in %S within HYPO to 76±6% was not significant. There was borderline improvement in %S in COMB from 7±6% to 11±5% (P=0.06). REMOTE %S increased to 21±4%.

**Table 2.** \( \kappa \) Statistic for Interobserver Agreement

<table>
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<th>Transmurality</th>
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<td>Inferior</td>
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<tr>
<td></td>
<td>Inferior</td>
<td>†</td>
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The \( \kappa \) statistic measures the agreement between the evaluation of 2 raters when both are rating the same object. \( \kappa = 1.0 \) denotes perfect agreement; \( \kappa > 0.75 \) denotes excellent reproducibility; \( 0.4 < \kappa < 0.75 \) denotes good reproducibility; and \( 0 < \kappa < 0.4 \) denotes marginal reproducibility.

* \( \kappa \) statistic could not be computed because the table was nonsymmetrical.
† \( \kappa \) statistic could not be computed because 1 variable upon which measures of association are computed is a constant.
that reperfused myocardial regions displaying a HYPER MRI contrast pattern show significant recovery of mechanical function at 7 weeks after MI. In contrast, HYPO does not show significant mechanical improvement, and there is a borderline improvement in COMB.

Our data and those from previous studies that used delayed imaging to identify HYPO (as defined in the present study) suggest that HYPO represents predominantly necrotic myocardium. Reduced signal intensity on first-pass MRI contrast images has been shown to be associated with reduced blood flow, although this relationship may not be linear when higher doses of extravascular gadolinium-based MRI contrast agents are used. In infarct regions, however, microvascular myocardial blood flow may not return to normal even after epicardial revascularization, the so-called no-reflow phenomenon. In 2-day-old reperfused canine MI, Judd et al reported a blunted and delayed increase in signal intensity in regions of infarcted myocardium. Hypointense regions correlated closely with regions delineated by thioflavin-S, a no-reflow marker. Regions of hypoenhancement have also been reported in patients with the use of a similar technique in healed infarcts after edema and other transient postischemic sequelae have likely resolved. Saeed et al also demonstrated hypointense regions in a rat model after 3.5 hours of occlusion without reperfusion using gadodiamide and T1-weighted spin-echo images. Thus, the lack of normal, first-pass signal enhancement after a bolus injection of MRI contrast has been shown to identify myocardium with reduced blood flow and in the present study is associated with little late functional recovery.

A number of interrelated factors, including reduced regional blood flow, increased capillary permeability, and increased interstitial volume, may produce HYPER within viable but previously ischemic myocardium. In the present study, HYPER differed in both contrast enhancement pattern and late myocardial function compared with HYPO, COMB, or REMOTE. The presence of regions with delayed hyperenhancement by use of extravascular contrast agents has been
previously described.\textsuperscript{7,8} Using an isolated rabbit heart preparation, Kim et al\textsuperscript{15} quantified MRI contrast uptake and washout after reperfused MI. They concluded that hyperintense and hypointense contrast patterns are due primarily to alterations in wash-in/washout time constants that in turn result from differences in capillary density. Three different regions were analyzed: infarct center, infarct rim, and remote. These regions differed in extent and severity of ischemic damage and are roughly comparable to regions defined as HYPO, HYPER, and REMOTE in the present study. In the Kim et al\textsuperscript{15} study, signal-to-intensity ratios compared with REMOTE during the early wash-in phase were $40.4 \pm 2.1\%$ and $84.9 \pm 3.6\%$ (mean $\pm$ SEM) for infarct center and infarct rim, respectively. These were similar to our values of $52 \pm 27\%$ and $91 \pm 31\%$ for HYPO and HYPER, respectively. Kim et al\textsuperscript{15} also reported infarct core and infarct rim signal intensity ratios of $95.9 \pm 6.6\%$ and $114.8 \pm 2.7\%$, respectively, on delayed images. These are not dissimilar to our HYPO and HYPER values of $80 \pm 38\%$ and $139 \pm 38\%$, respectively. We have shown that exclusively HYPER displays significant week 7 improvement and therefore must represent at least partially viable myocardium.

In a study evaluating MRI contrast patterns in patients after reperfused MI, Lima et al\textsuperscript{6} found that there was a good correlation between fixed $^{201}$Tl defect size and delayed contrast-enhanced MRI when both hyperintense and hypointense regions were combined but did not assess recovery of mechanical function. Fixed $^{201}$Tl defects are often associated with nonviable myocardium. Thus, these data may seem to be at odds with the results of the present study. However, Lima et al\textsuperscript{6} did not perform first-pass imaging. Furthermore, in the present study, all vessels had TIMI grade 3 flow before imaging, whereas the population studied by Lima et al included TIMI 0 to 3 flow. Incomplete reperfusion may account for such apparent reduced viability in HYPER. Another possibility may be that regions identified on stress-redistribution $^{201}$Tl imaging as “fixed” may contain both viable and nonviable myocardium. Recently, Diltszian et al\textsuperscript{18} showed that $^{201}$Tl reinfusion identifies a significant volume of viable myocardium within “fixed” defects by stress-redistribution reinfusion $^{201}$Tl scintigraphy. Judd et al\textsuperscript{7} reported in a canine contrast MRI study that the hyperintense regions on delayed images were generally smaller than the risk region but larger (12\%) than regions of necrosis as defined by triphenyltetrazolium chloride staining. This would indicate that at least part of the delayed hyperintense regions contain viable myocardium.

Yokota et al\textsuperscript{6} used T1-weighted nonsegmented spin-echo imaging 5 to 10 minutes after Gd-DTPA administration in patients with nonreperfused myocardial infarction. They qualitatively compared contrast MRI results to peak creatine phosphokinase levels, wall motion, and coronary angiography and concluded that subendocardial or transmural hyperenhancement may reflect the existence of viable myocardium, whereas subendocardial hyperenhancement was associated with necrotic myocardium.

In the present study, there was a significant number (10 of 28) of abnormal regions that displayed both first-pass hyperenhancement and delayed hyperenhancement. It is likely that this group contains an admixture of viable and nonviable myocardium. There was a trend for improvement from week 1 to 7 in COMB ($P=0.12$) and for a difference in %S between COMB and HYPO in week 7 ($P=0.06$).

\section*{Study Limitations}

%S measurements were repeated over time. This required matching of regions within the LV between weeks 1 and 7. Intrinsic cardiac landmarks were used to maintain registration as previously reported by Kramer et al\textsuperscript{19} However, changes in LV shape or volume between imaging sessions could affect the precision of the match. Technical constraints limited MRI contrast imaging to a single image plane. Thus, care in positioning of the contrast plane in the center of the MI was essential. Given the limited spatial resolution of perfusion imaging, a conservative approach was assigning the transmural extent of contrast patterns as limited to EPI, the ENDO, or TRANS. There was a trend for greater week %S in COMB versus HYPO ($P=0.12$). Power analysis (independent-samples t test) indicated that analysis of an additional 12 subjects would result in a significant difference. Thus, the present study may be limited in detecting differences in %S between these 2 groups.

\section*{Conclusions}

Myocardium displaying hypoenhanced signal (HYPO) during first-pass transit, regardless of delayed contrast pattern, shows limited recovery of mechanical function by week 7 and is likely to be predominantly infarcted. In contrast, regions displaying hyperenhancement of delayed images in the absence of initial hypoenhancement show substantial functional late recovery and likely represent predominantly viable myocardium. Therefore, combining the information from first-pass and delayed contrast-enhanced MRI may predict late functional recovery in reperfused MI. Advances in MRI acquisition speed should permit imaging of all the LV during contrast first-pass and the delayed period, allowing clinically relevant application of the present study.

\section*{References}


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