

Prognostic Significance of Microvascular Obstruction by Magnetic Resonance Imaging in Patients With Acute Myocardial Infarction

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Background—The extent of microvascular obstruction during acute coronary occlusion may determine the eventual magnitude of myocardial damage and thus, patient prognosis after infarction. By contrast-enhanced MRI, regions of profound microvascular obstruction at the infarct core are hypoenhanced and correspond to greater myocardial damage acutely. We investigated whether profound microvascular obstruction after infarction predicts 2-year cardiovascular morbidity and mortality.

Methods and Results—Forty-four patients underwent MRI 10±6 days after infarction. Microvascular obstruction was defined as hypoenhancement seen 1 to 2 minutes after contrast injection. Infarct size was assessed as percent left ventricular mass hyperenhanced 5 to 10 minutes after contrast. Patients were followed clinically for 16±5 months. Seventeen patients returned 6 months after infarction for repeat MRI. Patients with microvascular obstruction (n=11) had more cardiovascular events than those without (45% versus 9%; $P=.016$). In fact, microvascular status predicted occurrence of cardiovascular complications ($\chi^2=6.46$, $P<.01$). The risk of adverse events increased with infarct extent (30%, 43%, and 71% for small [n=10], midsize [n=14], and large [n=14] infarcts, $P<.05$). Even after infarct size was controlled for, the presence of microvascular obstruction remained a prognostic marker of postinfarction complications ($\chi^2=5.17$, $P<.05$). Among those returning for follow-up imaging, the presence of microvascular obstruction was associated with fibrous scar formation ($\chi^2=10.0$, $P<.01$) and left ventricular remodeling ($P<.05$).

Conclusions—After infarction, MRI-determined microvascular obstruction predicts more frequent cardiovascular complications. In addition, infarct size determined by MRI also relates directly to long-term prognosis in patients with acute myocardial infarction. Moreover, microvascular status remains a strong prognostic marker even after control for infarct size. (*Circulation*. 1998;97:765-772.)

Key Words: prognosis ■ microcirculation ■ magnetic resonance imaging

Patient prognosis after acute myocardial infarction relates directly to the extent of myocardial injury produced during coronary occlusion.^{1,2} Postinfarction electrocardiography, echocardiography, and contrast ventriculography are often used to indirectly assess the degree of myocardial damage,^{1,3,4} whereas radionuclide studies with ^{99m}Tc sestamibi and contrast-enhanced fast MRI can measure infarct size directly.⁵⁻⁹ Recently, in addition to the extent of infarcted myocardium, the magnitude of microvascular obstruction sustained during acute infarction has been related to clinical outcome.^{10,11}

Experimentally, the territory injured by prolonged ischemia is composed primarily of nonviable myocardial tissue in which myocytes perish first, followed eventually by necrosis of the endothelial cells that line intramyocardial capillaries.^{12,13} At the center of the infarcted segment, however, myocytes and capillaries may undergo necrosis simultaneously because of

profound and sustained ischemia. In that situation, capillaries become occluded by dying blood cells and debris, to the degree that even with restoration of epicardial blood flow, the infarct core will not promptly reperfuse. This area of microvascular obstruction has been called the “no-reflow” or “low-reflow” region.^{12,13} The presence of microvascular obstruction immediately after acute infarction correlates with greater myocardial damage by electrocardiography and echocardiography⁶ and thus poorer global ventricular function in the early postinfarction phase.^{10,14} However, the long-term prognostic significance of microvascular obstruction in patients with acute myocardial infarction remains unknown. In addition, the mechanisms linking microvascular obstruction to a greater risk of postinfarction complications are unclear.

Infarct expansion with subsequent scar formation and ventricular remodeling also contributes significantly to the prog-

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TABLE 1. Patient Characteristics

Characteristic	Value
Age, y	57.7±9.4
Male, %	33 (75)
Infarct type, n (%)	
Q-wave	26 (59)
Non-Q-wave	18 (41)
Infarct location, n (%)	
Anterior	15 (34)
Inferior	25 (57)
Lateral	4 (9)
Creatine phosphokinase	1449±1100
Thrombolytics, n (%)	32 (73)
Rescue angioplasty, n (%)	7 (16)
Direct angioplasty, n (%)	3 (7)
MRI microvascular obstruction present, n (%)	11 (25)
Infarct size by MRI, %	25.7±10.7

nosis of patients surviving acute myocardial infarction.^{15–17} Left ventricular dilatation and volume-overload hypertrophy of noninfarcted myocardium are the consequences of the remodeling process.^{18–20} These changes in ventricular architecture partly reflect infarct extent^{16,19,21} but also depend on the rate of infarct healing and the material properties of the infarcted segment during the healing process.^{16,22,23} The benefit of reperfusion, even without myocardial salvage, in limiting infarct expansion and remodeling has been demonstrated.^{24–26} However, despite patent epicardial vessels by coronary angiography, myocardial reperfusion may not occur at the microvascular level.^{10,11,27} Previous studies indicate that the presence of microvascular obstruction adversely affects early left ventricular remodeling,¹⁴ perhaps by impeding the beneficial effects of myocardial reperfusion on the material properties of infarcted tissue, leading to greater infarct expansion.

Contrast-enhanced MRI techniques allow the *in vivo* visualization of regions of profound microvascular obstruction in patients with acute myocardial infarction.⁶ These regions appear as dark, subendocardial zones surrounded by hyperenhanced infarcted or injured myocardium and correspond to experimentally produced no-reflow regions.⁷ We conducted this study to determine whether the presence of MRI microvascular obstruction within human infarcts is a marker for long-term cardiovascular complications. In addition, we measured infarct extent by MRI and examined whether its interaction with infarct core microvascular status had additional prognostic value. Finally, in a subgroup of patients who had repeat imaging 6 months after infarction, we tested the hypothesis that microvascular obstruction relates to eventual transmural myocardial damage and late ventricular remodeling.

Methods

Study Patients

Forty-four patients were enrolled (Table 1). Entry criteria included typical symptoms of acute infarction with ECG changes, creatine phosphokinase (CPK) elevation more than twice the upper limits of normal, and >5% myocardium-specific bands. All patients gave

informed consent according to the Johns Hopkins Hospital Joint Committee for Clinical Investigation standards. All but 2 received thrombolytics or direct angioplasty: 1 had colon cancer; the other presented for care >24 hours after infarction. Data from 22 patients were published in a previous study characterizing postinfarction MRI myocardial enhancement patterns.⁶ Seventeen patients returned 6 months after infarction for repeat MRI; these patients composed the long-term follow-up group.

All subjects had coronary angiography by standard techniques 4±4 days (range, 0 to 11 days) after infarction. Two independent observers, blinded to clinical outcome, classified the angiograms according to Thrombolysis in Myocardial Infarction (TIMI) study group criteria.²⁸ ECGs taken at this time were also analyzed by two blinded, independent observers for Q-wave presence and infarct location, defined by leads demonstrating Q waves and/or ST-segment changes. “Acute” MRI occurred 10±6 days after infarction. “Chronic” MRI studies were performed 180±51 days after infarction.

MRI Protocol

Images were acquired during multiple breath-holds on a 1.5-T whole-body magnet (Signa, General Electric). Details of the pulse sequence used in this study have been published previously.²⁹ It resembles inversion-recovery turboFLASH³⁰ in that pixel intensity is heavily T1-weighted but minimizes T2 contamination by spoiling *xy* plane magnetization. Use of a very short TE minimizes T2* effects. Within each RR interval, 60 nonselective dummy radiofrequency pulses are transmitted before imaging to drive magnetization to a steady state. Thirty-two image phase encoding steps immediately follow, acquired with TR of 6.5 ms, TE of 2.3 ms, and flip angle of 45°. Ninety-six phase-encoding steps per image are acquired, such that each image is completed in three cardiac cycles. K-space lines 1, 4, 7 . . . etc; 2, 5, 8 . . . etc; and 3, 6, 9 . . . etc are obtained during the first, second, and third beats, respectively. Matrix size was 256×96, field of view was 36 cm, and voxel size was 1.4×3.7×10.0 mm. The imaging protocol included four base-to-apex short-axis cross sections acquired with prospective ECG gating during 12 heartbeat breath-holds. For the acute studies, a bolus of Gadoteridol (ProHance, Squibb, 0.1 mmol/kg) was administered by fast hand injection. Immediately after contrast, images were acquired every 30 seconds for 5 minutes, then each minute for the next 10 minutes. All perfusion images were obtained late in diastole (diastasis). Studies lasted ≈45 minutes, with no adverse contrast reactions. A similar pulse sequence was used to obtain short-axis and long-axis image planes at end diastole and end systole to obtain functional and anatomic indices for both acute and chronic MRI studies.

MRI Data Analysis

Acute Studies

Signal-intensity curves were generated with the aid of the software package NIH IMAGE. The methodology has been described.^{6,7} Regions of interest were defined within the infarcted region, represented as an area of hyperenhanced plus hypoenhanced signal in the territory perfused by the angiographically determined infarct-related artery. Regions of interest were also defined inside the noninfarcted myocardium and the left ventricular cavity. In patients with hypoenhanced subendocardium at the infarct core (Fig 1), the central region of interest was defined within the dark zone, whereas other sample regions were taken from areas of increased signal intensity surrounding the dark zone. The pulse sequence produces dark, homogeneous precontrast cardiac images.^{6,7,29} Signal intensity over time from each image was quantified, and the curves generated for each patient were expressed as the percent increase in signal intensity (SI) over baseline precontrast signal intensity: normalized SI (%) = 100×(SI–baseline SI)/baseline SI (Fig 1B).

The hyperenhanced areas (Fig 2) from the four base-to-apex short-axis images obtained 5 to 10 minutes after contrast were planimetered, with hypoenhanced regions included when present.⁷ All hypoenhanced regions were smaller than and circumscribed by hyperenhanced regions. Infarct size, expressed as percent total LV

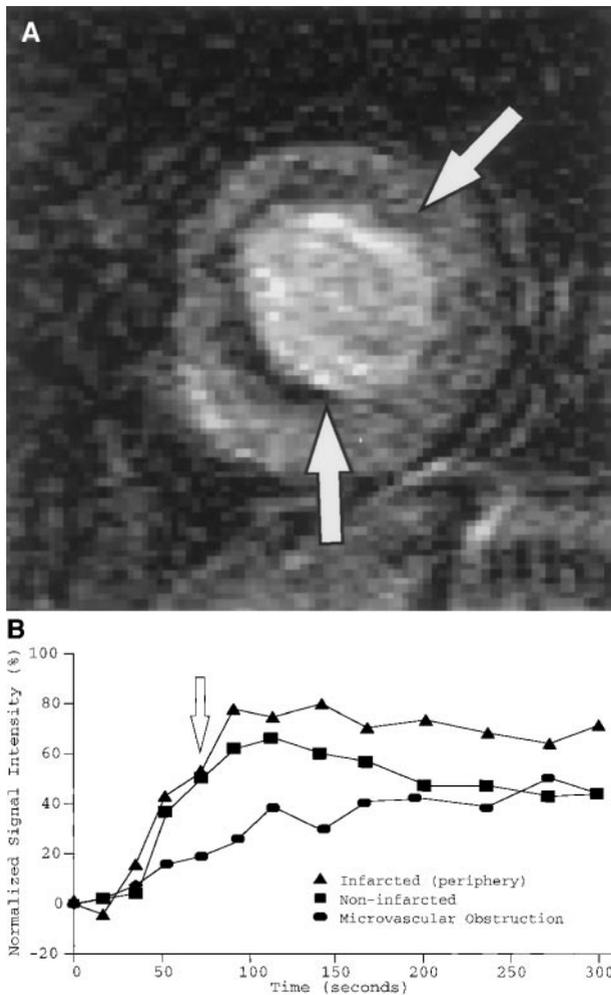


Figure 1. MRI (A) and time-intensity curve (B): microvascular obstruction. A is from patient with anteroseptal infarct and extensive subendocardial microvascular obstruction (between arrows). B, Corresponding time-intensity curves. Microvascular obstruction (●) is characterized by low signal intensity early after contrast followed by a gradual rise. Images 1 to 2 minutes after contrast (arrow) best delineate such regions because of maximal signal intensity differences between normal, noninfarcted myocardium (■) and infarct core microvascular damage. In infarct periphery (▲), signal intensity resembles that of noninfarcted myocardium initially but then diverges, reflecting eventual hyperenhancement.

mass, was then calculated from the percentage of hyperenhancement plus hypoenhancement in each slice, weighted according to slice cross-sectional area.⁷ Thus, for all slices, infarct size = $\sum(\% \text{ hyperenhanced plus hypoenhanced}) \times (\text{cross-sectional area}) / \sum(\text{cross-sectional area})$. Two observers blinded to clinical outcome determined microvascular status visually from scans obtained 1 to 2 minutes after contrast (Fig 1A). The presence of microvascular obstruction was corroborated by a characteristic time-intensity curve (Fig 1B). There was complete consensus as to the MRI presence or absence of microvascular obstruction. Infarct size was measured by two blinded observers with good interobserver ($y=0.9x$, $r=.8$) and intraobserver ($y=0.99x$, $r=.9$) variability. Although 6 patients had technically limited studies precluding accurate delineation of infarct extent, in all patients, microvascular status could be determined because image quality was preserved at the earlier time points (up to 2 to 5 minutes after contrast).

Chronic Studies

On the 6-month scans, scar was defined according to published criteria based on autopsy data.³¹ If the myocardial segment shown to be

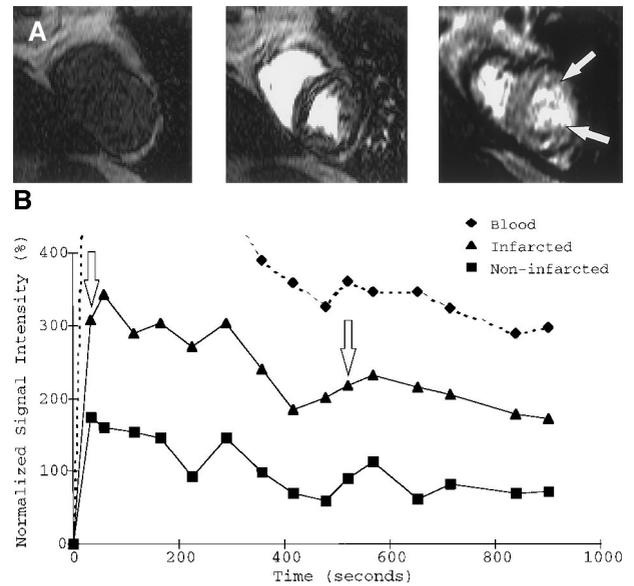


Figure 2. MRI (A) and time-intensity curve (B): hyperenhancement. A is from patient with anterolateral infarct. First image, precontrast, shows homogeneous signal from myocardium and intracavitary blood. Second image, taken immediately after contrast (first arrow, B), shows bright ventricular cavities before myocardial contrast penetration. Third image was taken 520 seconds after contrast (second arrow, B), at which time, intensity of infarcted area (between arrows) resembles that of blood and is most discernible from noninfarcted myocardium. B, Corresponding signal intensity curves.

hyperenhanced on the acute study was thinned on the chronic images (end-diastolic wall thickness <6 mm in three or more adjacent image planes), transmural scar formation was diagnosed (Fig 3).

Acute and Chronic Studies

MRI studies were also analyzed for left ventricular end-diastolic and end-systolic volume, mass, and ejection fraction by standard methods.³² Of the acute studies, 8 were technically limited, precluding calculation of functional indices.

Clinical Study Outcomes

Patients were followed clinically for 16 ± 5 months. Follow-up was conducted through telephone interviews with the patient and/or his or her physician and medical records review. Clinical end points included cardiac death, defined by sudden death or death preceded by typical chest pain; nonfatal myocardial reinfarction as determined by typical chest pain with ECG changes and CPK elevation to more than twice the upper limit of normal; congestive heart failure secondary to left ventricular systolic dysfunction, diagnosed by history and physical examination; ischemic cerebrovascular accident corroborated by clin-



Figure 3. MRI: fibrous scar formation. First image (acute study), taken immediately after contrast, shows bright ventricular cavities with homogeneous myocardium. Second image (acute study), obtained 570 seconds after contrast, delineates inferior wall hyperenhanced region. Six-month follow-up scan of same patient (third image) depicts thinning of myocardial segment that was initially hyperenhanced.

ical criteria and neuroimaging; and unstable angina requiring hospitalization, defined as typical chest pain with ECG changes but no CPK elevation. For statistical purposes, we defined permanent events as consisting of cardiac death, reinfarction, congestive heart failure, or stroke. In every analysis, all events were considered equivalent, and only the first event was included in the calculation.

Statistical Analysis

For the acute studies, patients were grouped by MRI microvascular status and by MRI-determined infarct size: "small" infarcts had <18% hyperenhancement; "intermediate," between 18% and 30%; and "large," >30%. To compare complication rates after infarction, the groups with and without microvascular obstruction were analyzed with two-tailed Fisher's exact tests; χ^2 tests for trends were used for the three infarct-size groups and the three ejection fraction groups.³³ The Kaplan-Meier technique was used to compare time from acute infarct to clinical complication occurrence.³³ To examine individual and combined effects of acute MRI microvascular perfusion pattern, MRI extent of hyperenhancement, infarct-related artery patency, and MRI functional indices on clinical outcome, logistic regression analysis was used.³³ The correlation between ejection fraction and infarct size was assessed with linear regression analysis.³³

For the chronic studies, changes in functional and anatomic indices over time were assessed by paired *t* tests or ANOVA.³³ Logistic regression was used to determine predictors of fibrous scar formation.³³ To evaluate the relationship between MRI extent of hyperenhancement and changes in functional and anatomic indices, linear regression was used.³³

Data are expressed as mean \pm SD. Values of $P < .05$ were considered significant.

Results

Study Population Clinical Characteristics and Follow-up

Table 1 summarizes the patients' characteristics. Excluding the 10 who underwent rescue or direct angioplasty, patients had coronary catheterizations ≥ 48 hours after infarction, at which time, 20 had coronary angioplasty. Patients were followed for 16 ± 5 months (range, 6 to 25 months). Although 6 patients had multiple events, only the first event was considered. Index clinical events occurred 14 ± 6 months after infarction (range, 0.3 to 25 months). These index events consisted of cardiac death in 1 patient (2.3%); nonfatal reinfarction in 4 (9.1%); congestive heart failure in 2 (4.5%); embolic stroke in 1 (2.3%); and unstable angina requiring hospitalization in 11 (25%).

Clinical Significance of MRI-Defined Microvascular Obstruction

Eleven patients had microvascular obstruction on their acute MRI scan; 33 did not. Of the 11 patients with microvascular obstruction, 5 (45%) experienced at least one permanent postinfarction complication (cardiac death, reinfarction, congestive heart failure, or stroke) versus only 3 (9%) of the 33 without obstruction ($P = .016$; odds ratio for patients with obstruction, 5.7; 95% CI, 1.84 to 51) (Fig 4). Moreover, univariate regression analysis showed that microvascular status predicted whether or not untoward permanent events occurred after infarction ($\chi^2 = 6.46$, $P < .01$).

MRI microvascular obstruction was a more potent marker for postinfarction cardiovascular complications than patency status of the infarct-related epicardial artery (assessed from the most recent angiogram preceding MRI). Although infarct-related artery status correlated with microvascular status ($P < .05$), 5 of the 11 patients with MRI microvascular ob-

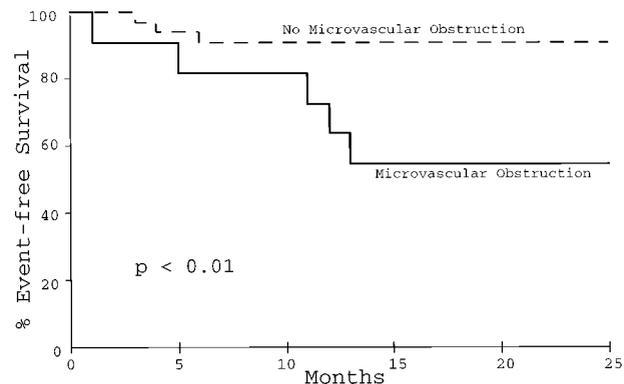


Figure 4. Event-free survival (clinical course without cardiovascular death, reinfarction, congestive heart failure, or stroke) for patients with and without MRI microvascular obstruction.

struction in fact had TIMI 3 flow (Table 2). Furthermore, by regression analysis, the relationship between TIMI flow and the rate of postinfarction complications was of only borderline statistical significance ($\chi^2 = 2.69$, $.05 < P < .1$).

Clinical Significance of MRI-Defined Infarct Size

Infarct size as determined by the extent of MRI hyperenhanced tissue relative to total myocardium ranged from 4% to 54%. Ten patients had small (<18%), 14 had midsize (18% to 30%), and 14 had large (>30%) infarcts. The risk of sustaining one of the following complications increased with infarct size ($P < .05$) (Fig 5): cardiac death, reinfarction, congestive heart failure, stroke, or unstable angina requiring hospitalization. Events occurred in 30% of the patients with small infarcts, in 43% with medium infarcts, and in 71% with large infarcts (Fig 5). When unstable angina was eliminated, a trend toward a higher rate of permanent events with increasing infarct size persisted (small, 10%; midsize, 14%; and large, 36%; $.05 < P < .1$). No differences were found when the rate of revascularization (angioplasty and bypass surgery) or unstable angina was considered independently. Infarct size did not correlate with peak CPK or infarct-related artery patency.

Experimentally, large reperfused infarcts are more often associated with regions of "no-reflow" produced by microvascular obstruction than are small infarcts.¹³ In this study, MRI microvascular obstruction and larger infarct sizes were clearly related: patients with microvascular obstruction had an average infarct size of $32.6 \pm 9.6\%$ versus $22.9 \pm 10.0\%$ in those without ($P < .005$). By multiple regression analysis, the presence of MRI microvascular obstruction remained a prognostic marker of untoward permanent events when infarct size was controlled for ($\chi^2 = 5.17$, $P < .05$). In addition, the predictive value of microvascular obstruction tended to vary with infarct size.

TABLE 2. Infarct-Related Artery Status Grouped by MRI Microvascular Obstruction

	TIMI 0, 1, 2	TIMI 3	Total
Microvascular obstruction present	6	5	11
Microvascular obstruction absent	4	25	29
Total (% with microvascular obstruction)	10 (60)	30 (17)	
	$P < .05$		

In the large-infarct group, the permanent event rate was 67% (4 of 6) in patients with obstruction versus 13% (1 of 8) in those without ($P=.09$). Although no patients with small infarcts had microvascular obstruction, among the mid-sized-infarct group, patients with obstruction had a permanent event rate of 20% (1 of 5) versus 11% (1 of 9) in those without ($P=NS$).

Prognostic Significance of Acute MRI Functional Indices

When grouped by left ventricular ejection fraction obtained in the acute postinfarction period, patients developed permanent events at the following rates: 3 of 9 (33%) for the $\leq 40\%$ group; 1 of 7 (14%) for the 40% to 55% group; and 4 of 20 (20%) for the $>55\%$ group ($\chi^2=0.92$; $P=NS$). If all events, including unstable angina requiring hospitalization, are considered, complication rates are 7 of 9 (78%) for the $\leq 40\%$ group; 4 of 7 (55%) for the 40% to 55% group; and 8 of 20 (40%) for the $>55\%$ group ($\chi^2=3.78$; $.05 < P < .1$). Left ventricular volumes and masses could not predict clinical outcome. The correlation between ejection fraction and infarct size was of borderline significance ($F=3.60$; $P=.067$).

MRI Predictors of Transmural Myocardial Infarction and Ventricular Remodeling

Microvascular status in the acute period predicted the occurrence of transmural myocardial damage with eventual scar formation 6 months after infarction ($\chi^2=10.0$, $P<.01$). Five (62.5%) of the 8 patients with microvascular obstruction in the acute postinfarction period had ventricular wall thinning consistent with scar formation at 6 months, whereas none (0%) of the 9 patients without microvascular obstruction developed fibrous scar ($P<.03$). Furthermore, the presence of microvascular obstruction was associated with greater increases in left ventricular volumes 6 months after infarction. In patients with microvascular obstruction, end-diastolic volumes rose by $89.0 \pm 77.8\%$ versus $9.8 \pm 26.8\%$ in patients without obstruction ($P<.02$). Similarly, end-systolic volumes increased by $165.5 \pm 199.6\%$ in patients with microvascular obstruction compared with $3.0 \pm 19.8\%$ in those without ($P<.04$). Microvascular obstruction at 1 week was also associated with a greater rise in left ventricular systolic mass over 6 months (from 131.2 ± 63.8 to 195.1 ± 57.3 g) compared with patients without obstruction (from 151.3 ± 29.2 to 164.1 ± 47.6 g) ($P<.05$). Left ventricular ejection fraction was similar in the two groups acutely ($48.8 \pm 20.0\%$ for patients with microvascular obstruction versus $54.3 \pm 12.0\%$ for those without, $P=NS$) and at 6 months ($43.3 \pm 14.1\%$ for patients with microvascular obstruction versus $55.0 \pm 15.0\%$ for those without, $P=NS$).

Acute infarct size, indexed as the extent of myocardial hyperenhancement, also predicted eventual scar formation ($\chi^2=5.9$, $P<.02$). Patients with MRI fibrous scars at 6 months after infarction had larger acute infarct sizes than those who did not develop fibrous scar ($36.5 \pm 12.4\%$ versus $21.9 \pm 9.6\%$, $P<.03$). More importantly, the presence of microvascular obstruction remained predictive of fibrous scar formation even when adjusted for infarct size ($\chi^2=10.85$, $P<.02$). Finally, acute infarct size was related to 6-month left ventricular volumes. Chronic end-diastolic volumes ($P=.02$) and chronic

end-systolic volumes ($P=.044$) correlated with infarct size acutely.

Discussion

This study is the first to demonstrate the relationship between MRI contrast defects, which most likely reflect severe microvascular obstruction, and long-term prognosis after infarction. The presence of MRI microvascular obstruction correlates with a higher rate of cardiovascular events in the first 2 years after acute myocardial infarction. Infarct size, determined by MRI, is also predictive of the risk of postinfarction complications. Although the development of microvessel occlusion during coronary thrombosis is related to infarct size, its presence remains a strong predictor of adverse cardiovascular events even after the extent of total myocardial damage is controlled for.

MRI hypoenhanced areas correspond to experimentally produced no-reflow regions and reflect myocardial microvascular obstruction.^{7,34} The evidence corroborating this is substantial. The pattern of hypoenhancement seen in our study patients is identical to that produced in experimental animals in terms of both spatial location and temporal occurrence after contrast injection, as shown by time-intensity curves.⁷ Myocardial biopsies taken from regions of hypoenhancement in experimental animals have demonstrated profound microvascular damage at the infarct core, with microvascular obstruction by red blood cells and necrotic debris.³⁴ In the canine model, MRI hypoenhanced regions are characterized by profoundly reduced blood flow, as measured by radioactive microspheres.⁷ These areas also correspond to regions that do not take up the vital stain thioflavin.⁷ Both of these characteristics further support the close correlation between MRI hypoenhancement and microvascular obstruction. Recent work investigating the time course of MRI hypoenhancement development has further corroborated this association with microsphere flow measurements.³⁵

This study demonstrates that early after infarction, patients with MRI microvascular obstruction have larger regions of injured myocardium than those without it, again correlating well with previous experimental data.¹³ Our results also concur with studies supporting the clinical importance of profound

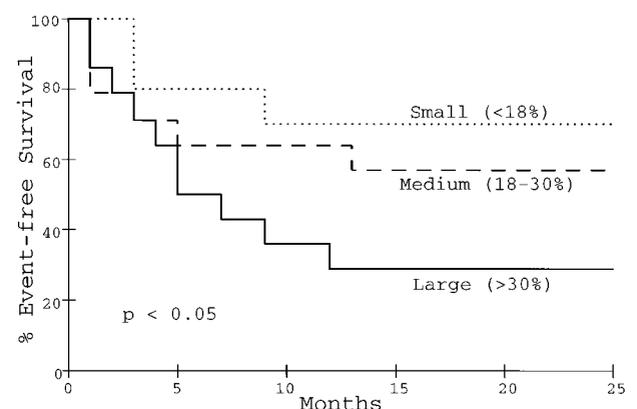


Figure 5. Event-free survival (clinical course without cardiovascular death, reinfarction, congestive heart failure, stroke, or unstable angina requiring hospitalization) for patients grouped by MRI infarct size.

alterations in microvascular integrity after coronary occlusion.^{6,14} We have previously shown that microvascular obstruction is associated with greater echocardiographic regional dysfunction acutely, ECG Q waves, and occluded infarct-related arteries by angiography.⁶ The present study demonstrates that such an MRI pattern predicts subsequent cardiovascular complications, including cardiac death, reinfarction, heart failure, and stroke. Although the prognostic value of microvascular obstruction may arise partly because it reflects a larger infarct, our findings suggest that its presence may independently predict long-term cardiovascular complications.

Other imaging modalities have been used to demonstrate postinfarction alterations in microvascular integrity after reperfusion. Myocardial contrast echocardiography^{10,11,14} has correlated the presence of contrast defects with poor functional recovery of postischemic myocardium despite restored infarct-related artery flow.^{10,11} Unlike MRI, however, it currently requires intracoronary injection of microbubbles, necessitating cardiac catheterization. Furthermore, infarct size definition is unfeasible with contrast echocardiography once flow in the infarct-related artery is reestablished. In vivo microvascular integrity has also been studied with techniques that use such radioactive tracers as ²⁰¹Tl and ⁸²Rb.^{36,37} However, no echocardiographic or nuclear studies have related those alterations to postinfarction long-term prognosis. Although our results agree with those obtained by such techniques, we demonstrate the clinical importance of microvascular obstruction by relating it to a greater probability of cardiovascular complications after acute infarction.

Another finding of our study is the direct relationship between MRI-determined infarct size and the risk of developing cardiovascular complications after infarction. Patients with larger infarcts had worse clinical outcomes. MRI myocardial hyperenhancement results from myocardial injury and/or necrosis and correlates well with infarct size clinically and experimentally.⁶⁻⁹ It also closely approximates ²⁰¹Tl fixed perfusion defect size.³⁸ Like ours, previous studies have correlated larger thallium perfusion defects with increased cardiovascular complications.³⁸ Likewise, predischARGE infarct size by ^{99m}Tc sestamibi appears to predict long-term left ventricular function better than predischARGE left ventricular ejection fraction.³⁹ Our range of MRI-determined infarct sizes was comparable to that obtained by ^{99m}Tc sestamibi.³⁹ However, because sestamibi is a relatively pure perfusion agent, direct comparisons with gadolinium may not be possible.

This study highlights the merits of a method that directly assesses myocardial injury after acute coronary artery occlusion. The ability of MRI perfusion patterns to predict clinical outcome was stronger than that of left ventricular function assessed during the acute postinfarction period. The decreased predictive value of early postinfarction ejection fraction can be explained by several factors. Significant myocardial stunning can occur after infarction, leading to an initial underestimation of left ventricular ejection fraction.⁴⁰ Conversely, hyperkinesis of noninfarcted myocardium may occur, thereby preserving overall ejection fraction in the face of significant myocardial loss due to infarction.⁴¹ Finally, the ability of ejection fraction to accurately reflect the extent of myocardial damage early after acute infarction is also limited by its dependence on global

afterload conditions.⁴² For these reasons, Califf et al⁴³ have suggested that left ventricular ejection fraction alone should not be used as a clinical trials outcome, particularly in the acute postinfarction period.

One limitation of our study was the small sample size, which necessitated that we combine multiple clinical end points for statistical analysis. Nonetheless, we were able to demonstrate significant differences in clinical outcome in only 44 patients. To maximize and highlight the value of our MRI parameters as surrogates for clinical outcome, we chose to include not only conventional postinfarction complications, such as cardiac death, reinfarction, and heart failure, but also clinically relevant outcomes, such as embolic cerebrovascular accident and unstable angina requiring hospitalization. Embolic stroke complicates the early postinfarction course of 0.7% to 4.7% of patients.^{44,45} The risk of stroke is directly proportional to left ventricular dysfunction in postinfarction patients.⁴⁶ Furthermore, the devastating morbidity associated with such events led us and others⁴⁷ to identify stroke as an end point after myocardial infarction. Nonetheless, even when stroke is eliminated as a permanent clinical end point, the difference between post-MI complication rates in patients with and without MRI microvascular obstruction remains statistically significant. By including only cardiac death, reinfarction, and congestive heart failure, the event rates become 4 of 11 (36.4%) for patients with microvascular obstruction versus 3 of 33 (9.1%) for those without ($\chi^2=4.09$, $.02 < P < .05$). When stroke is removed from the analysis examining the predictive value of MRI-determined infarct size on clinical outcomes, statistical significance is not reached ($\chi^2=2.79$, $.05 < P < .1$). Nevertheless, the difference in event rates remains high: 3 of 10 (30%) for patients with small infarcts, 6 of 14 (42.9%) for the medium-infarct group, and 9 of 14 (64.3%) for the large-infarct group. We also chose to include unstable angina requiring hospitalization as a clinical end point because of its impact on patient outcome. All but 1 patient with such an episode required revascularization to control the ischemic event: 8 had coronary angioplasty and 2 had coronary artery bypass surgery during the same hospital admission as their unstable angina. Therefore, these hospitalizations not only were significant in terms of patient morbidity but also led to costly diagnostic and therapeutic interventions.

Other methodological limitations of this study should be discussed in light of the potential advantages of MRI in examining postinfarction patients. One potential limitation was using only four base-to-apex short-axis cross sections to quantify infarct size. However, infarct size can, in fact, be adequately assessed with three base-to-apex short-axis slices.⁴⁸ Current MRI technical limitations precluded the attainment of useful scans for infarct size determination in 6 patients. However, in all patients, images during the first minutes after contrast were preserved, allowing the assessment of microvascular integrity for the entire group. This limitation related to difficulties in sustaining multiple breath-holds combined with claustrophobia, an apparently more prevalent phenomenon in postinfarction patients. Wider magnet designs⁴⁹ and solutions to the obstacles associated with motion artifacts⁵⁰ and the need for breath-hold imaging⁵¹ will certainly minimize patient apprehension and discomfort during the examination. More-

over, the possibility of combining detailed studies of myocardial function,⁵² perfusion,⁶ and sodium metabolism⁵³ with the noninvasive assessment of coronary anatomy⁵⁴ and epicardial coronary artery blood flow⁵⁵ highlight the diagnostic potential of MRI in coronary artery disease.

The exact mechanisms whereby microvascular obstruction determines postinfarction prognosis remain unknown. One potential explanation is the relationship between presence of microvascular obstruction and infarct size, documented previously in a canine model¹³ and confirmed in this study. However, controlling for infarct size did not eliminate the power of microvascular obstruction to predict the occurrence of adverse postinfarction events. Theoretically, early obstruction of microvessels after reperfusion could result in altered material properties locally relative to regions receiving adequate reperfusion. This concept is supported by previous studies that related the presence of microvascular obstruction documented by contrast echocardiography to left ventricular remodeling early in the postinfarction period.¹⁴ In addition, other investigators have shown that myocardial reperfusion limits postinfarction ventricular remodeling²⁴ and improves patient prognosis even without salvaging myocardium.²⁴⁻²⁶ Similarly, in our study, the presence of microvessel obstruction in the acute postinfarction period was associated not only with a greater rate of fibrous scar formation but also with greater ventricular remodeling, in terms of both increased left ventricular volumes and masses. Moreover, altered myocardial material properties as a mechanism of worse ventricular remodeling should theoretically be most important in patients with large infarcts who are already at risk for greater postinfarction remodeling and heart failure.^{17,19,56} In this regard, our results support the notion that there may be an interaction between infarct size and the presence of microvascular obstruction, resulting in greater left ventricular enlargement and worse prognosis after infarction. However, given the small sample size of the patient group who underwent repeat MRI, our findings linking microvascular obstruction to long-term left ventricular remodeling require confirmation by future clinical or experimental studies. Finally, it is possible that other mechanisms may predispose a patient to developing microvascular obstruction over and above the contribution of infarct size. The importance of platelet function in coronary syndromes has recently been demonstrated.⁵⁷ Whether or not hematologic alterations lead to more prolonged or extensive coronary thrombosis and/or reperfusion injury¹³ also needs further investigation. In any case, mechanistic possibilities linking microvascular occlusion to postinfarction prognosis are important to consider because they could lead to the development of new strategies that limit myocardial damage after therapeutic myocardial reperfusion in patients with acute infarction.

In conclusion, the presence of MRI microvascular obstruction acutely predicts long-term prognosis in patients with myocardial infarction. In addition, the extent of total myocardial ischemic injury assessed by MRI also directly relates to the risk of cardiovascular complications after infarction. Moreover, microvascular status remains a strong prognostic marker even after infarct size is controlled for. The ability to combine microvascular perfusion studies with direct measurements of

infarct extent illustrates the potential of MRI to study the heart after acute coronary thrombosis.

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Prognostic Significance of Microvascular Obstruction by Magnetic Resonance Imaging in Patients With Acute Myocardial Infarction

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