

Magnetic Resonance Imaging Determination of Cardiac Prognosis

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Background—Regional assessments of left ventricular (LV) wall motion obtained during MRI cardiac stress tests can be used to identify myocardial injury and ischemia, but the utility of MRI stress test results for the assessment of cardiac prognosis is not known.

Methods and Results—Two hundred seventy-nine patients referred (because of poor LV endocardial visualization with echocardiography) for dobutamine/atropine MRI for the detection of inducible ischemia were followed for an average of 20 months. After MRI stress testing, the occurrence of myocardial infarction, cardiac death, death attributable to any cause, coronary arterial revascularization, and unstable angina or congestive heart failure requiring hospitalization was determined. In a multivariate analysis, the presence of inducible ischemia (hazard ratio 3.3, CI 1.1 to 9.7) or an LV ejection fraction <40% (hazard ratio 4.2, CI 1.3 to 13.9) was associated with future MI or cardiac death independent of the presence of risk factors for coronary arteriosclerosis.

Conclusions—In patients with poor echocardiograms, the results of cardiac MRI stress tests can be used to forecast myocardial infarction or cardiac death. (*Circulation*. 2002;106:2328-2333.)

Key Words: magnetic resonance imaging ■ ischemia ■ prognosis

Selecting patients with cardiovascular disease who might benefit from a therapeutic intervention often depends on identifying the individuals at risk for sustaining a cardiac event. Regional assessments of left ventricular (LV) myocardial wall motion obtained during dobutamine/atropine MRI have been used to locate myocardial injury or ischemia in patients with coronary arteriosclerosis,¹⁻³ but the prognostic utility of these assessments is not known. We performed this study to determine if the presence of inducible ischemia identified during MRI stress tests could be used to identify those at risk of sustaining a future cardiac event.

Methods

Study Population and Design

The Institutional Review Board at the Wake Forest University School of Medicine approved this study, and all participants gave verbal (for performing follow-up questionnaire) and written (for MRI testing and review of patient records) informed consent. Patients with contraindications to MRI (implanted pacemakers or defibrillators or intracranial metal) or to receiving dobutamine or atropine were excluded from enrollment. Between April 1997 and June 1999, 338 consecutive patients were referred (owing to >6 of 16 LV endocardial segments not seen with second harmonics transthoracic echocardiography) for dobutamine/atropine MRI to diagnose inducible ischemia. The imaging and pharmacologic dosing methodology was described previously in 143 subjects receiving pharmacologic stress³; their outcomes are included in this study.

Patients' routine use of medications, including β -receptor antagonists, was not altered before testing. Of those referred, 12 did not undergo scanning because of large body habitus (n=3), uncontrolled hypertension (n=1), an inability to lie flat because of heart failure (n=7), or intoxication on presentation to the scanning facility (n=1). Of the 326 subjects who underwent baseline imaging, 31 did not receive intravenous dobutamine/atropine because of dissection or aneurysm of the aorta (n=6), large LV mobile thrombus (n=9), unsuspected malignancy (n=2), arrhythmia preventing adequate gating (n=6), severe hypertension (n=3), anxiety (n=2), or a new cardiac diagnosis (n=3). An occurrence of prior Q-wave myocardial infarction (MI)⁴ and risk factors for coronary arteriosclerosis, including the treatment or presence of blood pressure >140/90 mm Hg,⁵ total cholesterol \geq 6.4 mmol/L,⁶ fasting glucose \geq 7.8 mmol/L,⁷ and smoking, were recorded at the time of MRI testing.

Dobutamine/Atropine MRI Procedure

Single-slice gradient-echo images of the left ventricle were acquired on a Horizon 1.5T whole-body imaging system (General Electric Medical Systems) using a 256 \times 128 matrix, a 35- to 48-cm field of view, a 10-ms repetition time, a 4-ms echo time, a 20-degree flip angle, an 8-mm slice thickness, a 40-ms temporal resolution, and an 8- to 12-second breathhold. Eighteen LV myocardial segments (Figure 1) were identified at rest and during graded doses of dobutamine/atropine that were administered to achieve 80% of the maximum predicted heart rate response (MPHRR) for age. Images at peak stress were collected at all slice positions after the peak heart rate response occurred. Throughout stress MRI, LV segmental wall motion was assessed as normal, hypokinetic, akinetic, or dyskinetic. Inducible ischemia was defined as a deterioration in wall motion

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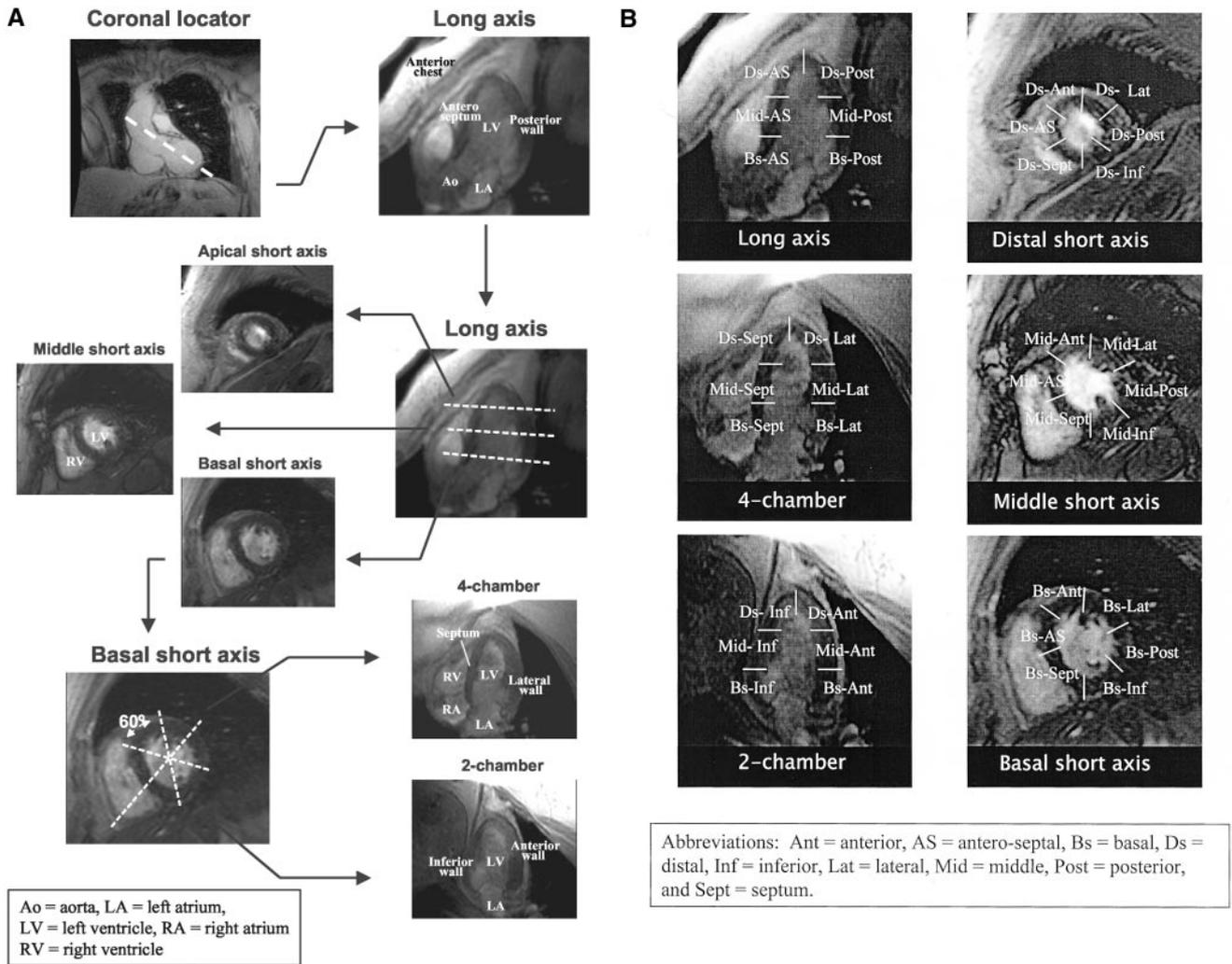


Figure 1. A, Strategy for obtaining 3 apical (long-axis, 4-chamber, and 2-chamber) and 3 short-axis (basal, middle, and apical) MRI views of the left ventricle. On each image the myocardium is gray and the blood pool white. The white dotted lines on the coronal locator, long-axis view, and basal short-axis view indicate the slice positions for obtaining the subsequent views demarcated by the black arrows. B, White lines demarcate the 18 myocardial segments.

within a myocardial segment during the course of testing observed in 2 orthogonal views by the investigator (K.M.L. or W.G.H.) performing the study. At rest, LV ejection fraction (LVEF) was measured using a biplane area-length technique.⁸

Follow-Up

Personnel unaware of the study design or stress testing results contacted each subject (or, if deceased, an immediate family member); the date of this contact was used for calculating follow-up times. Any change in physical state, medical condition, or medication was confirmed by review of the participant’s medical records. Hard events were defined as MI (angina of >30 minutes duration and either ≥2 mm ST segment elevation in 2 consecutive ECG leads or a rise in creatine kinase level and its MB fraction 2 times the upper limit of normal)⁹ or cardiac death (death in the presence of acute MI, significant cardiac arrhythmia, or refractory congestive heart failure).¹⁰ Other events determined included all-cause mortality, coronary arterial revascularization, and unstable angina or congestive heart failure warranting hospital admission. When available, ECG, enzymatic, or autopsy data were used to substantiate cardiac mortality. In the case of 2 simultaneous cardiac events, the worst event was chosen (cardiac death>MI>revascularization>unstable angina or congestive heart failure).

Statistical Analysis

Patients were categorized according to the presence, extent, and location of inducible ischemia during pharmacologic infusion, the presence of an improvement in wall motion in akinetic segments at rest (contractile reserve), the presence of persistent hypokinesis during testing, and whether their LVEF was <40% or ≥40%. All grouped data were expressed as mean±SD. Univariate and multivariate Cox proportional hazards regression models were used to identify independent predictors of events. The risk of a given variable was expressed by a hazard ratio (HR) with corresponding 95% CIs. Variables were considered significant if the null hypothesis of no contribution could be rejected at a probability value of <0.05. The probability of the presence or absence of cardiac events as a function of follow-up duration was estimated by the Kaplan-Meier method and compared between groups by use of the log-rank test.

Results

The amount of dobutamine infused during testing was 30±10 μg/kg per min; 105 participants required atropine administration, with 60% of subjects attaining >80% of the MPHRR for age and 58 subjects experiencing chest pain. Tests were terminated in those subjects not attaining 80% of the MPHRR

TABLE 1. Demographic Data and Summary of Events

	LVEF \geq 40% – Ischemia (n=164)	LVEF \geq 40% + Ischemia (n=71)	LVEF <40% – Ischemia (n=22)	LVEF <40% + Ischemia (n=22)
Patient characteristics				
Age, y	62 \pm 11	63 \pm 12	64 \pm 10	65 \pm 10
Range	35–84	36–84	43–83	45–88
Women:Men, n	85:79	30:41	4:18	5:17
Weight, kg	94 \pm 19	90 \pm 23	83 \pm 16	83 \pm 16
BSA, m ²	2.0 \pm 0.2	2.0 \pm 0.2	2.0 \pm 0.3	1.9 \pm 0.2
LVEF, %	60 \pm 8	52 \pm 9	29 \pm 6	32 \pm 5
Historical information				
Hypertension	115 (70)	62 (87)	18 (82)	16 (73)
Diabetes mellitus	54 (33)	32 (45)	9 (41)	9 (41)
COPD	44 (27)	26 (37)	4 (18)	3 (14)
Smoking	94 (57)	45 (63)	13 (59)	13 (59)
Hypercholesterolemia	105 (64)	47 (66)	13 (59)	19 (86)
Prior revascularization	33 (20)	36 (51)	4 (18)	15 (68)
Prior Q-wave MI	18 (11)	7 (10)	6 (27)	10 (45)
Medications				
β -Blocker	56 (34)	31 (44)	9 (41)	15 (68)
Calcium antagonist	50 (31)	21 (30)	5 (23)	6 (27)
ASA	70 (43)	44 (62)	13 (59)	16 (73)
Nitrate	55 (34)	40 (56)	11 (50)	10 (45)
ACE inhibitor	26 (16)	21 (30)	7 (32)	8 (36)
Diuretic	56 (34)	27 (38)	14 (64)	13 (59)
Events				
MI and CV death	3 (2)	8 (11)	3 (14)	4 (18)
Death (all causes)	7 (4)	6 (8)	2 (9)	5 (23)
Combined end points	38 (23)	34 (48)	14 (64)	11 (50)
Coronary revascularization	10 (6)	5 (7)	4 (18)	1 (5)
USA	26 (16)	20 (28)	6 (27)	6 (27)
CHF	2 (1)	9 (13)	4 (18)	4 (18)

Values are expressed as n (%) unless otherwise indicated.

BSA indicates body surface area; COPD, chronic obstructive pulmonary disease; ASA, aspirin; ACE, angiotensin-converting enzyme; CV, cardiovascular; USA, unstable angina; and CHF, congestive heart failure.

for age attributable to inducible ischemia (28%), ventricular or atrial arrhythmia (21%), abnormal hypertensive or hypotensive BP response (8%), nausea or vomiting (8%), or receipt of \geq 40 μ g/kg per min of dobutamine and 1.5 mg of atropine (27%). Ventricular fibrillation, MI, or death did not occur during stress testing.

Contact was made with all 295 patients. Sixteen subjects underwent coronary arterial revascularization within 60 days of their MRI stress tests; none experienced a subsequent hard event. To exclude the possibility that immediate revascularization prevented subsequent hard events, we excluded from additional analyses these 16 patients. The remaining 279 subjects formed the study population; their clinical data are displayed in Table 1. MRI evidence of inducible ischemia or a LVEF <40% was associated with MI and cardiac death independent of the presence of risk factors for coronary arteriosclerosis (Table 2). In patients with and without induc-

ible ischemia, coronary arterial revascularization before stress MRI was not associated with an increase in the HR of hard events. The hard event rate was higher (19% versus 5%) in those receiving <20 μ g/kg per minute of dobutamine; the hard event rate was not influenced by the peak rate pressure product.

The proportion of patients free of hard events is shown in Figure 2; for patients with a LVEF <40% at rest, the presence or absence of inducible ischemia did not significantly influence the 2-year incidence of hard events (25.6% versus 26.5%; $P>0.9$, respectively). Thirty-three of 279 subjects exhibited a resting LVEF \geq 60% and no evidence of inducible ischemia at 80% of the MPHRR for age; a MI or cardiac death did not occur in these subjects. The absolute number of hard events was greater in men than women; there were too few events in women with a LVEF <40% to determine if LVEF was an indicator of

TABLE 2. Predictors of Events Expressed as Hazard Ratio ($\pm 95\%$ CI)

	Univariate			Multivariate		
	CV Death/MI	All Death	CHF/USA/Revasc	CV Death/MI	All Deaths	CHF/USA/Revasc
+ Ischemia by MRI	4.9 (1.8 to 13.0)*	2.9 (1.2–6.9)*	2.0 (1.3–3.2)*	3.3 (1.1–9.7)*	2.8 (1.0–7.5)	1.6 (1.0–2.7)
LVEF <40% by MRI	3.7 (1.4–9.5)*	3.3 (1.3–8.2)*	1.7 (0.9–3.0)	4.2(1.3–13.9)*	4.2 (1.3–13.1)*	1.5 (0.8–2.9)
Age >65 y	2.5 (1.0–6.7)	3.9 (1.4–10.6)*	1.0 (0.6–1.5)	2.7 (1.0–7.6)	4.2 (1.5–11.9)*	1.0 (0.6–1.6)
Sex	0.6 (0.2–1.6)	0.6 (0.3–1.6)	1.1 (0.7–1.7)	1.1 (0.4–3.5)	1.2 (0.4–3.4)	1.2 (0.7–2.0)
Obesity (BMI >27)	1.0 (0.3–2.6)	0.7 (0.3–1.7)	1.2 (0.7–2.1)	1.3 (0.4–4.4)	0.8 (0.3–2.4)	1.1 (0.6–2.0)
Revasc. (before MRI)	2.3 (0.9–5.8)	1.2 (0.5–3.0)	1.9 (1.2–3.0)*	1.5 (0.5–4.3)	0.7 (0.3–2.1)	1.3 (0.8–2.2)
Prior Q-wave MI	1.6 (0.5–5.0)	1.0 (0.3–3.4)	1.1 (0.6–2.0)	0.9 (0.3–3.3)	0.4 (0.1–1.5)	1.0 (0.5–1.8)
Hypercholesterolemia	1.1 (0.4–2.9)	1.6 (0.6–4.4)	1.6 (0.9–2.7)	0.5 (0.2–1.7)	1.5 (0.5–4.9)	1.2 (0.7–2.2)
Hypertension	3.0 (0.7–13.2)	1.4 (0.5–4.2)	1.9 (1.0–3.6)	3.1 (0.6–15.6)	1.1 (0.3–3.8)	1.5 (0.8–2.9)
Diabetes mellitus	1.5 (0.6–3.9)	1.0 (0.4–2.4)	1.7 (1.1–2.7)*	1.3 (0.5–3.9)	0.7 (0.3–2.1)	1.5 (0.9–2.5)
COPD	1.8 (0.7–4.6)	1.8 (0.7–4.4)	1.1 (0.7–1.9)	1.8 (0.6–5.2)	1.9 (0.7–5.3)	1.1 (0.6–1.9)
Smoker	2.7 (0.9–8.1)	1.7 (0.6–4.4)	1.1 (0.7–1.8)	2.2 (0.7–7.1)	1.4 (0.5–4.0)	1.1 (0.7–1.9)

CV indicates cardiovascular, CHF, congestive heart failure; USA, unstable angina; Revasc, coronary artery revascularization; BMI, body mass index; and COPD, chronic obstructive airways disease.

*95% CI >1.0.

poor prognosis. A test for interaction between sex and LVEF was not significant.

Overall, 5022 segments were assessed during testing. Ischemia was identified in 120, 134, and 181 basal, middle, and apical segments, respectively; and in segments with resting akinesis, contractile reserve was identified in 52, 53, and 83 basal, middle, and apical segments, respectively. The HR of developing a hard event in relation to the number, the location, and the distribution of myocardial segments receiving blood from a major epicardial coronary artery (as defined by the American Heart Association) are displayed in Figure 3.¹¹ No significant difference in the HR of hard events existed between the location or number of the distal segments with ischemia. Sixty-six subjects, 50 with and 16 without inducible ischemia, displayed an improvement in wall motion in segments that were akinetic at baseline. Improvement in wall motion in segments akinetic at rest was associated with MI

and cardiac death (HR 4.9, CI 1.8 to 13.2, $P=0.001$) but not all-cause mortality (HR 2.4, CI 0.7 to 8.9, $P=0.19$) or other events (HR 1.8, CI 0.8 to 4.2, $P=0.16$). Together, improvement in wall motion in resting akinetic segments and ischemia (HR 4.8, CI 1.8 to 12.9, $P=0.002$) conferred no additional increase in the HR of hard or other events than the risk associated with each alone. Eighty-six subjects had persistent hypokinesis of a myocardial segment during testing (13 individuals with concomitant ischemia, 6 with concomitant improvement in wall motion in an akinetic segment, 37 with concomitant ischemia and improved wall motion in an akinetic segment, and 30 without myocardial ischemia or improved wall motion in an akinetic segment). The hard event rate ranged from 11% to 33% in those with persistent hypokinesis and concomitant ischemia, improved wall motion in an akinetic segment, or a combination of the two; the hard event rate was 3% in those without either of the two.

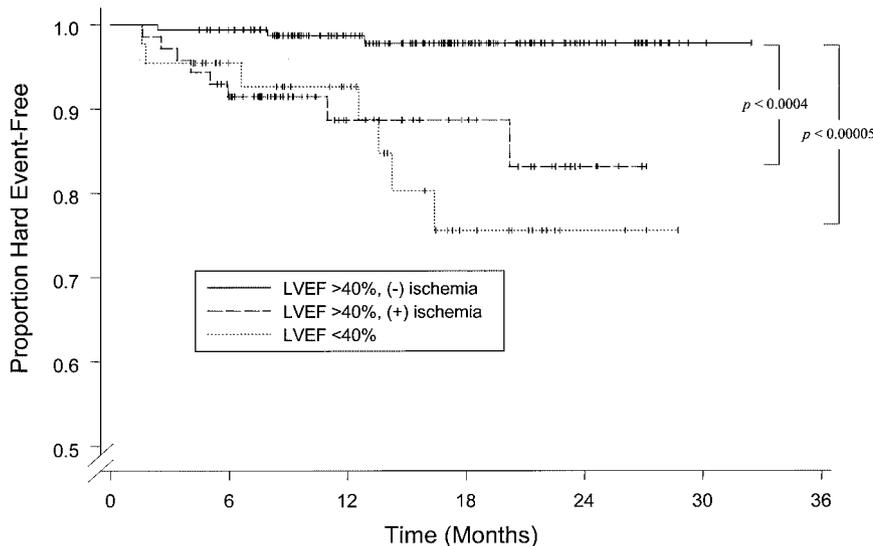


Figure 2. Kaplan-Meier event-free survival curves in patients with an LVEF <40% or $\geq 40\%$ with or without inducible ischemia. Compared with patients with a LVEF $\geq 40\%$ and no evidence of inducible ischemia, event-free survival was significantly lower in patients with inducible ischemia ($P < 0.0004$) or an LVEF <40% ($P < 0.00005$).

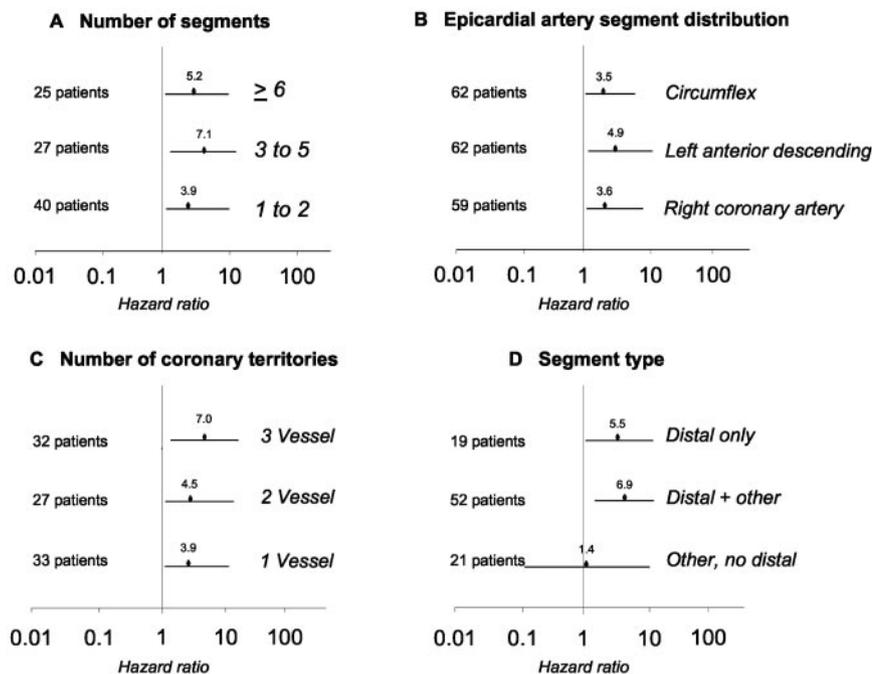


Figure 3. HRs ± 95% CIs (x-axis in all panels) for developing myocardial infarction or cardiac death versus the number of myocardial segments with ischemia (y-axis, A), the area of myocardium localized to a coronary territory (y-axis, B), the number of coronary territories containing myocardial segments with inducible ischemia (y-axis, C), and the base to apex location of segments with ischemia (y-axis, D). Ischemia in distal myocardial segments was associated with a significant increase in the HR of MI or cardiac death ($P < 0.003$).

The chronic use of a β -receptor antagonist was associated with the presence of inducible ischemia ($P=0.027$). A test for interaction between β -receptor antagonist use and a LVEF $<40\%$ in predicting a hard events was significant ($P=0.01$). The absence of β -receptor antagonist use was associated with MI and cardiac death in patients with a LVEF $<40\%$ ($P=0.04$) but not $>40\%$.

Discussion

The results of this study indicate the following: (1) in patients with an LVEF $>40\%$, evidence of inducible ischemia during MRI identifies those at risk of MI and cardiac death independent of the presence of conventional risk factors for coronary arteriosclerosis (Table 2); (2) an MRI-measured LVEF of $<40\%$ is associated with an increased risk of MI or cardiac death; (3) patients without ischemia and a LVEF $>40\%$ have an excellent cardiac prognosis in the 2 years after MRI stress testing (Figure 2); (4) the location of ischemia induced during a MRI stress test may be important for identifying those at risk of future MI and cardiac death (Figure 3); and (5) an improvement in wall motion in resting akinetic LV segments is associated with future cardiac death and MI.

The HRs associated with future MI and cardiac death trended higher for larger numbers of myocardial segments and coronary territories associated with inducible ischemia and in participants with ischemia in myocardial segments associated with the distribution of the left anterior descending coronary artery.¹¹ The number of redistribution defects indicative of inducible ischemia during radionuclide stress tests has been shown to correlate with the occurrence of MI and cardiac death.^{12,13} Although trends in our data suggest ischemia in larger territories may be associated with increased risk, in our study of 279 participants with a total of 18 events, these trends did not separate from one another statistically. Perhaps these trends would reach statistical significance if we studied

a larger population that sustained more events. Alternatively, larger ischemic territories may have been recognized if we had continued our pharmacologic infusion to higher levels used during stress tests that implement ST-segment monitoring. As a safety precaution, our infusion and imaging protocol was terminated at the earliest detection of a wall motion abnormality in 2 orthogonal views.³

Inducible ischemia in distal LV segments was associated with hard events; isolated basal or middle segmental ischemia was not (Figure 3). Studies incorporating dobutamine stress echocardiography have identified a relatively high rate of false-positive results for ischemia when isolated wall motion abnormalities occur in posterior and inferior basal or middle LV myocardial segments.^{14,15} Although abnormal wall motion in distal LV segments has been correlated with reduced exercise capacity and increased mortality in patients sustaining MI,^{16,17} to date, even though large ischemic territories often include distal LV segments, most stress radionuclide or echocardiography studies have not examined the relationship between ischemia in distal LV segments and cardiac prognosis. Perhaps the resulting shape or mechanical function of distal LV segments is an important determinant of prognosis. Alternatively, our finding may indicate that a large territory, such as a left anterior descending artery coursing over the LV apex, is at risk.

Several findings in this study are consistent with those reported using other noninvasive stress imaging techniques. First, our findings indicate that patients poorly suited for stress echocardiography, who demonstrate inducible ischemia on a stress MRI, exhibit a cardiac prognosis (a 10.6% 1-year event rate of cardiac death/MI) similar to patients with ischemia that are well suited for stress echocardiography or radionuclide scintigraphy (1-year event rates of 7% to 11%).^{18,19} Second, our hard event rates in patients without ischemia and a LVEF $>40\%$ (2% over 2 years) or $>60\%$ (0%

over 2 years) closely resemble those reported in patients with an LVEF >60% and no evidence of ischemia during stress nuclear or echocardiograms (0.5% to 0.85% per year).^{20,21} Third, a biplane MRI measured LVEF of <40% in patients with or without myocardial ischemia is associated with a 13% 1-year incidence of MI and cardiac death. This percentage is similar (11% to 34%) to that experienced by patients with a LVEF ≤35% either with or without coronary arteriosclerosis.^{22–25} Finally, similar to the presence of contractile reserve or viability described in the echocardiography literature, we found an improvement in wall motion in resting akinetic segments associated with MI and cardiac death.^{26,27}

Our study has the following limitations. First, we were unable to determine if inducible ischemia predicted hard events in the setting of an LVEF <40%. We had 44 subjects with a LVEF <40%, and we observed 7 hard events in this population. To determine with 80% power if inducible ischemia confers a 3-fold increase in the risk of sustaining a hard event, a study would need 27 events distributed among patients with a LVEF <40%. Second, because of an interaction in the subgroup of patients taking β -receptor antagonists with a severely reduced LVEF, we cannot determine the prognostic value of a MRI-determined LVEF of <40% when an individual is taking a β -receptor antagonist. Our results are consistent with other large studies, indicating a survival benefit for chronic β -receptor antagonist therapy in the setting of heart failure.^{28,29} Third, only 60% of our subjects attained >80% of the MPHRR for age during testing. Because the diagnostic accuracy of noninvasive stress tests is higher when participants achieve >80% of the MPHRR for age during testing, the utility of our methodology for identifying those at risk for future cardiac events could have been greater if a higher proportion of our participants had attained a higher heart rate response during testing.

Acknowledgments

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