

Utility of Fast Cine Magnetic Resonance Imaging and Display for the Detection of Myocardial Ischemia in Patients Not Well Suited for Second Harmonic Stress Echocardiography

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Background—Some patients referred for pharmacological stress testing with transthoracic echocardiography (TTE) are unable to undergo testing owing to poor acoustic windows. Fast cine MRI can be used to assess left ventricular contraction, but its utility for detection of myocardial ischemia in patients poorly suited for echocardiography is unknown.

Methods and Results—One hundred fifty-three patients (86 men and 67 women aged 30 to 88 years) with poor acoustic windows that prevented adequate second harmonic TTE imaging were consecutively referred for MRI to diagnose inducible myocardial ischemia during intravenous dobutamine and atropine. Diagnostic studies were completed in an average of 53 minutes. No patients experienced myocardial infarction, ventricular fibrillation, exacerbation of congestive heart failure, or death. In patients who underwent computer-assisted quantitative coronary angiography, the sensitivity and specificity for detecting a >50% luminal diameter narrowing were 83% and 83%, respectively. In the 103 patients with a negative MRI examination, the cardiovascular occurrence-free survival rate was 97%.

Conclusions—Fast cine cardiac MRI provides a mechanism to assess left ventricular contraction and diagnose inducible myocardial ischemia in patients not well suited for stress echocardiography. (*Circulation*. 1999;100:1697-1702.)

Key Words: magnetic resonance imaging ■ stress ■ ischemia

Detection of left ventricular (LV) contraction abnormalities induced during dobutamine stress echocardiography has proven clinical utility for the determination of inducible myocardial ischemia.^{1,2} Unfortunately, in patients with poor acoustic windows,³ particularly those with large body habitus, severe obstructive airway disease, or prior cardiothoracic surgery, LV segmental contractility cannot be adequately assessed with transthoracic echocardiography. A noninvasive method to detect myocardial contractile abnormalities indicative of ischemia in patients not suitable for pharmacological stress echocardiography would be useful.

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Cine gradient-echo MRI can be used to assess LV contraction without limitations imposed by body habitus.⁴ Although LV contractile abnormalities indicative of ischemia have been detected with MRI,^{4,5} the length of scans, perceptions of poor patient tolerance, and the lack of an accepted method to monitor patients for ischemia have hindered widespread clinical use.⁶ Recently, MRI visualization of LV wall motion

that is suitable for use during pharmacological stress has become available.⁷ The purpose of the present study was to assess the safety and clinical utility of fast cine MRI stress testing for the determination of inducible ischemia in patients not suitable for stress echocardiography.

Methods

Study Population

The study was approved by the Institutional Review Board of the Wake Forest University School of Medicine, and all participants gave written informed consent. The study population consisted of 163 subjects (89 men and 74 women aged 30 to 88 years) referred for diagnosis of ischemia with dobutamine echocardiography who did not have adequate endocardial visualization despite the use of second harmonic imaging⁸ in all subjects and the administration of 0.5 to 1.0 mL of octafluoropropane (Optison, Molecular Biosystems) in 10% (n=16) of subjects.⁹ Patients' images were scrutinized by 1 of 5 experienced echocardiography faculty who collectively interpret >2500 stress echocardiograms per year that have been performed by experienced sonographers by use of recent model instruments (Hewlett-Packard 5500). Ninety percent of referrals had ≥ 8 and 10%

Received May 6, 1999; revision received June 17, 1999; accepted June 23, 1999.

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TABLE 1. Guidelines for k-Space Segmentation (Views per Segment) and View Sharing During Stress-Induced Changes in Heart Rate

Heart Rate	VPS	VS
HR<50	10	5
50≤HR<65	8	4
65≤HR<105	6	3
105≤HR<125	4	2
125≤HR<150	2	1
150≤HR	1	1

VPS indicates views per segment; VS, view sharing; and HR, heart rate (in bpm).

had 5 to 8 of 16 endocardial segments (segment location as defined by the American Society of Echocardiography¹⁰) not visualized with echocardiography. The study population represented 0% to 20% of the patients referred for dobutamine echocardiography on a given day. Patients were ineligible for enrollment if they had a pacemaker, intracranial metal, claustrophobia, or a known contraindication to receiving dobutamine or atropine.

Study Protocol

Before study, a 12-lead ECG was performed outside of the magnet. After intravenous access was established, patients were positioned supine on the MR scanning table with a phased-array surface coil, ECG monitoring leads, respiratory gating belt, pulse oximetry monitor, and brachial blood pressure cuff attached. During testing, a registered nurse and physician continuously monitored heart rate and rhythm, blood pressure, oxygen saturation, and respiratory rate.

At baseline, single-slice, multiphase gradient echo images were obtained in 3 apical (horizontal, vertical, and apical long axis) views, similar to the 4-chamber, 2-chamber, and long-axis views acquired during transthoracic echocardiography, and 3 short-axis (the base, middle portion, and apex) views of the LV.¹¹ Images were acquired continuously during 5-minute intravenous dobutamine infusions of 5, 10, 20, and 40 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ that were designed to achieve 85% of the maximum predicted heart rate response (MPHRR) for age. If 85% MPHRR was not achieved, atropine was administered (0.3 mg/min increments) up to 1.5 mg. End points for protocol termination were a fall in systolic blood pressure >40 mm Hg, significant ventricular arrhythmias, development of a new wall motion abnormality, or achievement of 85% MPHRR for age. Additional images were obtained after 10 minutes of recovery to confirm that LV wall motion had returned to baseline. Once the patient was removed from the magnet, a repeat 12-lead ECG was obtained.

MRI Technique

MRI was performed with a 1.5-T GE Horizon 5.5 whole-body (bore size of 60 cm) imaging system (General Electric Medical Systems, Inc). All MR scans used prospective ECG gating. Acquisition parameters included a repetition time (TR) of 10 to 14 ms, an echo time (TE) of 5 ms, a flip angle of 30°, a receiver bandwidth of 31.5 kHz, a 32- to 48-cm field of view, and a slice thickness of 8 mm. Eight- to 12-second breathhold scans were performed with a fast gradient-echo sequence with k-space segmentation (views per segment) and view sharing.¹² As shown in Table 1, the views per segment and view sharing were adjusted throughout the procedure to increase the temporal resolution (50 to 14 ms) to identify the LV endocardium at end systole as the heart rate and velocity of endocardial thickening increased during stress. Because the k-space segmentation decreased (increasing scan time) as the heart rate increased (reducing scan time), the duration of the breathhold remained relatively constant throughout the procedure.

During stress testing, custom display software written in IDL (Interactive Data Language, Research Systems) permitted viewing of LV regional wall motion in an 8-panel display format on an adjacent Sun Microsystems workstation (Figure 1). The reconstruction, trans-

fer, and display of images were overlapped in time to visualize each slice within 20 to 30 seconds after acquisition.

Data Analysis

MRI data were interpreted at the time of examination by 1 of 2 investigators (W.G.H. or K.M.L.) without knowledge of any other cardiovascular study. During each study, 18 LV segments (apical, middle, and basal, from the 3 apical and short-axis views) were continuously assessed by a 4-point scoring system in which 1 was normal, 2 was hypokinetic, 3 was akinetic, and 4 was dyskinetic. Myocardial segments were identified as ischemic if the score incremented by 1 during infusion or a hypokinetic segment at rest failed to improve contractility or elicited a biphasic response.¹³

Computer-assisted, quantitative coronary angiography¹⁴ was performed without knowledge of patient characteristics or MRI results in all patients who underwent angiography within 6 months of MRI without an intervening cardiac event (myocardial infarction or cardiovascular death) or occurrence (exacerbation of congestive heart failure or unstable angina). The sensitivity and specificity of fast cine MRI and display for the determination of coronary arterial luminal narrowings of >50% and of >70% were determined. Patients with a negative MRI examination were contacted (by M.S.T.) to assess vital status and to determine whether they had experienced a cardiovascular event or occurrence.

All data were expressed as mean±SD; a *P* value of <0.05 was considered significant.

Results

Of the 163 referrals, 6 did not fit into the MR bore and 4 were not imaged because of anxiety. The remaining 153 subjects (86 men and 67 women aged 30 to 88 years) formed the study population. Their clinical characteristics are displayed in Table 2. Their mean heights and weights were 170 cm (range 140 to 196 cm) and 89 kg (range 39 to 135 kg). Ideal body weights¹⁵ (range 84% to 241%) were >120% and >150% in 79% and 41% of patients, respectively. At baseline, 97 patients had abnormal and 56 had normal LV regional wall motion. After baseline imaging, 10 subjects did not receive dobutamine owing to aortic dissection (n=1), large LV aneurysm (n=1), mobile LV thrombus (n=2), severe diastolic (>135 mm Hg) hypertension (n=2), marked ventricular ectopy (n=1), or intractable anxiety (n=3). No patients had ventricular fibrillation, myocardial infarction, or death during stress testing. The total duration of the MRI procedure (screening, preparation, testing, and recovery) averaged 114 minutes, and the scan time averaged 53 minutes.

Baseline and peak stress heart rates were 72±13 bpm (range 45 to 118 bpm) and 123±18 bpm (range 90 to 158 bpm), respectively. Baseline and peak blood pressures were 141/80 mm Hg (range 94/45 to 224/131 mm Hg), and 146/78 mm Hg (range 78/42 to 220/129 mm Hg), respectively. Forty-two subjects (27%) received atropine. The reasons for stress test termination are displayed in Table 3. Thirty-six patients had evidence of inducible myocardial ischemia, and 103 patients did not (examinations for 4 patients were terminated prematurely). Twenty-nine patients (19%) developed chest discomfort during the examination, but only 8% developed new wall motion abnormalities concomitant with their discomfort. Images from a positive and negative examination are shown in Figure 2.

Forty-one patients who received dobutamine underwent contrast coronary angiography without a coronary event or occurrence within 6 months (8 owing to the results of

One dose - all views

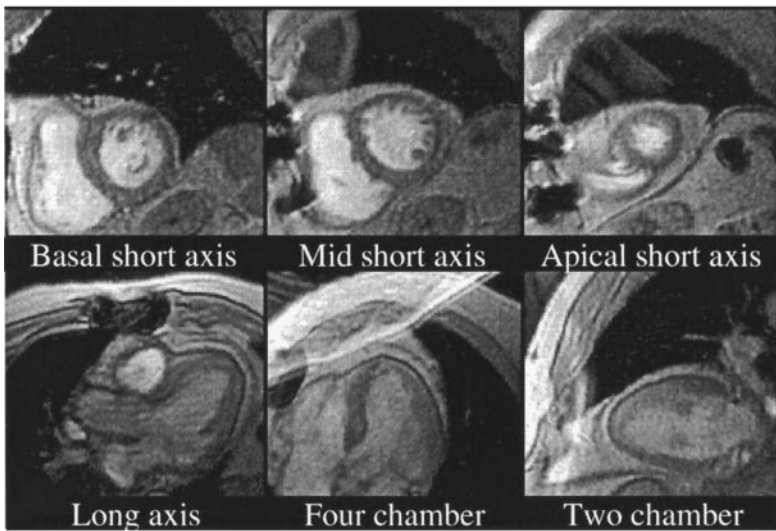
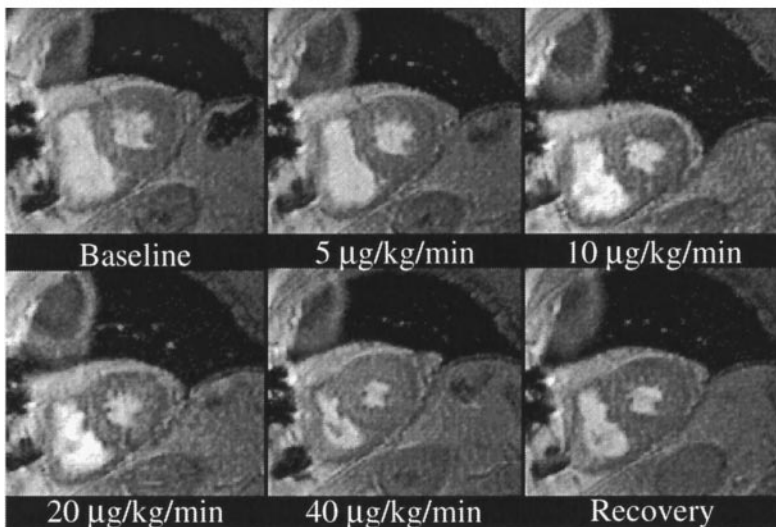


Figure 1. Selectable display format for viewing synchronized cine loops of LV during testing. Top, 3 apical and short-axis views of LV at end diastole from a single dose of dobutamine are shown; bottom, images from a single short-axis view acquired at end systole at multiple doses of drug infusion are displayed. In each view, LV myocardium appears gray and flowing blood appears white. Viewing format is selectable to provide rapid switching (<1 s) between display formats continuously during stress testing.

One view - all doses



noninvasive testing [4 MRI, 4 owing to results of another test], and 33 on the basis of clinical characteristics). In 22, 13, and 6 patients, the time between MRI and catheterization was <1 month, from 1 to 3 months, and from 3 to 6 months, respectively. The average time from MRI to catheterization was 35 days. The sensitivity and specificity for detecting a coronary arterial luminal narrowing >50% are shown in Table 4. The sensitivity of detecting an epicardial luminal narrowing >70% was 82% (1 vessel), 88% (2 vessel), and 100% (for 3 vessels or left main), respectively. The specificity of detecting a >70% narrowing was 58% (7 patients had a positive MRI scan and a luminal narrowing >60% but <70%).

One hundred three patients had no evidence of inducible ischemia with MRI. All living patients were contacted an average of 228 (range 75 to 442) days after MRI. The cardiovascular event and occurrence-free survival rates for these patients are displayed in Figure 3. Two patients experienced noncardiovascular deaths (1 of disseminated intravascular coagulation that occurred during surgery and 1 of pneumonia).

Discussion

Abnormalities of LV contraction during pharmacological stress echocardiography have proven utility for detecting inducible myocardial ischemia.^{1,2} Unfortunately, in patients with poor acoustic windows (owing to large body habitus, prior cardiac surgery, or obstructive airway disease), LV regional wall motion often cannot be assessed during stress testing.^{1,2} Because LV contraction can be assessed in multiple tomographic planes with MRI,⁵ it is an attractive alternative for patients with technically difficult echocardiograms. To date, the diagnostic accuracy of dobutamine/atropine MR stress testing has been shown in selected populations to be equivalent to stress echocardiography⁷ and radionuclide scintigraphy,^{4,6} but the widespread use of MRI stress testing has been limited by the inability to monitor ST segments during a scan, the inability to assess LV wall motion throughout all levels of pharmacological stress (particularly at 85% MPHRR for age), and perceptions of poor patient tolerance for the

TABLE 2. Characteristics of 153 Patients Undergoing Dobutamine MRI

	n	% of Patients
Clinical diagnoses		
Hypertension	92	60
Hypercholesterolemia	77	50
Diabetes mellitus	52	34
Current smoker	76	50
Obstructive airway disease	30	20
Prior myocardial infarction	52	34
Prior surgical coronary revascularization	49	32
Prior percutaneous coronary revascularization	39	25
Historical findings		
Angina	86	56
Atypical chest pain	10	7
Dyspnea on exertion	80	52
NYHA class I or II congestive heart failure	21	14
NYHA class III congestive heart failure	6	4
Family history of coronary artery disease	80	52
Twelve-lead ECG findings		
ST-segment and T-wave abnormalities	42	28
Q waves	41	27
Left bundle-branch block	9	6
Right bundle-branch block	6	4
Atrial fibrillation	2	1

NYHA indicates New York Heart Association.

procedure. With fast cine MRI and display, we were able to overcome these limitations. Our results indicate MRI can be used to assess LV contractility continuously during a stress test and to detect inducible ischemia in patients poorly suited for stress echocardiography.

Routine clinical performance of cardiac stress testing with MRI requires detection of malignant arrhythmia and inducible ischemia.¹⁶ Because the magnetic field alters the appearance of ST segments when patients are within the bore of the MR scanner,¹⁷ the ECG is used to monitor heart rate and

TABLE 3. Reasons for MRI Test Termination in the 143 Patients Receiving Dobutamine and/or Atropine Infusions

	Patients Using β -Blockers (n=53)	Patients Not Using β -Blockers (n=90)
Clinical Diagnoses		
Inducible ischemia	19 (36%)	15 (17%)
Anxiety	4 (8%)	6 (7%)
Nausea and vomiting	1 (2%)	5 (6%)
Severe hypertension	1 (2%)	1 (1%)
Atrial fibrillation (rapid response)	1 (2%)	0
Marked ventricular ectopy	2 (4%)	2 (2%)
Ventricular tachycardia	1 (2%)	1 (1%)
Mitral regurgitation	1 (2%)	0
Achieved 85% MPHRR for age	15 (28%)	57 (63%)
Maximal pharmacological stress	22 (42%)	7 (8%)

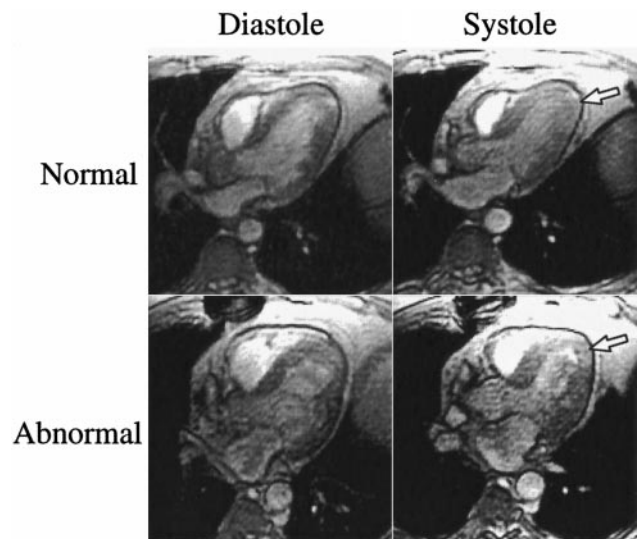


Figure 2. LV end-diastolic (left) and end-systolic (right) frames from an apical long-axis view of LV at peak stress in patient with normal contractile response (top) and with inducible ischemia (bottom). White arrows demarcate a region in the apex of the posterior wall that exhibits an appropriate (top right) or impaired (bottom right) contractile response. Also note that chamber dimensions in LV apex are increased in subject with inducible ischemia.

rhythm and not to diagnose ischemia. To detect ischemia, we used fast cine imaging and display to assess LV endocardial thickening throughout the stress test. This strategy is similar to that implemented with real-time echocardiography and follows the reasoning of Aroesty et al,¹⁸ who have demonstrated in pacing-induced myocardial ischemia that abnormalities of LV systolic dysfunction precede the onset of ST-segment depression on the ECG. Importantly, in 153 consecutively referred patients who could not undergo a stress echocardiogram, our results (inducible ischemia in 36 subjects and none with infarction, ventricular fibrillation, heart failure, or death) substantiate the safety profile of fast MR imaging and display during pharmacological stress.

Fast imaging/display enhances the clinical utility of MR stress testing in several respects. First, the synchronized cine display format (Figure 1) can be used to assess LV endocardial thickening throughout a pharmacological stress test. In stress echocardiography studies, the physician's diagnostic accuracy is significantly higher when images are reviewed

TABLE 4. Sensitivity and Specificity of Fast Cine MRI for Detecting Coronary Arterial Narrowings Assessed With Computer-Assisted Quantitative Coronary Angiography

	Number of Coronary Arteries With >50% Luminal Diameter Narrowing			
	0	1	2	3 or Left Main
MRI				
Positive	1	9	9	11
Negative	5	3	2	1
Sensitivity	...	75%	82%	92%
Specificity	83%

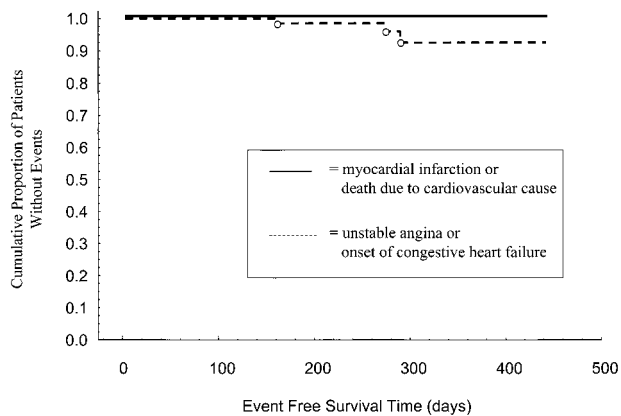


Figure 3. Kaplan-Meier curve indicating cardiovascular event (myocardial infarction or cardiovascular death) and occurrence-free (congestive heart failure or unstable angina) survival for 103 patients with a negative MRI examination. Circles indicate patients who developed unstable angina and underwent coronary arterial revascularization.

throughout the course of testing rather than at baseline and peak stress.¹⁹ Second, inducible ischemia can be detected when patients develop chest discomfort. In prior dobutamine MRI stress studies, the protocol was terminated once subjects experienced chest pain.^{5,6,20} Premature test termination reduces the diagnostic accuracy of stress testing with dobutamine. In 28 stress echocardiography studies involving 2246 patients,³ 20% of patients developed angina during dobutamine infusion, but only 2% to 4% of subjects developed wall motion abnormalities consistent with myocardial ischemia. Our results were consistent with these findings. Third, LV endocardial thickening can be visualized (Table 1) through modification of k-space segmentation parameters at 85% MPHRR for age (up to 158 bpm in our study). Achieving a target heart rate response of 85% MPHRR for age has been shown to improve the detection of myocardial ischemia with other forms of noninvasive testing.²¹ Finally, results are interpreted and reported immediately. This feature is particularly important for facilitating rapid patient management, such as same-day preoperative risk assessment.

Our results with fast MRI indicate the sensitivity and specificity for detecting a significant coronary stenosis are similar to that shown with echocardiography and radionuclide scintigraphy.^{1,22} Previous dobutamine MRI studies have reported a sensitivity of 50% to 92% and a specificity of 75% to 100% for detecting coronary arterial narrowings⁴⁻⁷; our results were similar (Table 4). Although the negative predictive value of a test is heavily influenced by the prevalence of disease in a population (which can vary widely between studies), the predictive value of a negative examination with fast MR imaging and display (Figure 3) is similar to that reported with echocardiography.^{23,24}

Fast cine MRI/display provides physicians with an alternative method to diagnose inducible ischemia in patients with inadequate echocardiograms. Our echocardiography laboratory uses personnel highly trained in the administration of microbubble contrast and is equipped with recently released ultrasound machines. All patients had very poor acoustic windows, even with second harmonic imaging (90% had ≥ 8 of 16 segments not

visualized), and many were markedly obese (41% of subjects with ideal body weight $>150\%$) and short in stature (height averaged 170 cm) and had prior bypass grafting (32%) or obstructive airway disease (21%). Ninety-seven of our patients had multiple LV wall motion abnormalities at rest (a patient population in which prior echocardiographic studies²⁵ have documented difficulty in assessment of endocardial thickening during stress testing), and 31% had a positive result in the apex of the posterolateral wall (an area not visualized well during transthoracic echocardiography [Figure 2]). Additional studies are needed to determine how stress MRI compares with echocardiography for diagnosis of inducible ischemia in these patient subgroups.

A potential alternative noninvasive stress test for patients with poor echocardiograms includes single photon emission computed tomography (SPECT).²⁶ MRI differs from nuclear scintigraphy in several respects. First, radioisotopes expose patients and workers to ionizing radiation; MRI does not. Second, the images generated with MRI can provide information regarding other structures within the chest that may influence patient management. In the present study, images of the aorta, LV, and valves changed the course of therapy for 6 (4%) of 153 patients. Third, our methodology was used to assess LV contraction, not perfusion. In general, techniques that are used to assess LV regional wall motion versus perfusion exhibit a lower sensitivity but higher specificity for detecting inducible ischemia,^{27,28} and in patients with LV dysfunction at rest, they are more accurate for predicting recovery of myocardial thickening after coronary arterial revascularization.^{29,30} Finally, MRI may be useful for patients not well suited for an intravenous vasodilator (owing to asthma) or with uncorrectable attenuation artifacts.^{31,32}

Fourteen percent of our patients exhibited findings or symptoms that required immediate medical attention before the administration of dobutamine (aortic dissection [n=1], mobile LV thrombus [n=2], large LV aneurysm [n=1], marked hypertension [n=2]) or during infusion (nausea/vomiting [n=6], severe hypertension [n=2], marked ventricular ectopy [n=4], ventricular tachycardia [n=2], rapid atrial fibrillation [n=1], and marked hypotension with systolic anterior motion of the mitral valve and mitral regurgitation [n=1]) (Table 3). The incidence of these complications and the hemodynamic responses of our patients were similar to data reported from other large trials of stress echocardiography.^{3,33} A trained team of individuals (technologists, physicians, and nurses) was essential for management of the patients during testing.

Our study has limitations. First, many of our patients were in sinus rhythm. Few had frequent ventricular ectopy (3%) or atrial fibrillation (2%). We are uncertain whether this technique provides reliable results in subjects with irregular rhythms. Second, because coronary angiography was not performed on all subjects, our sensitivity and specificity data for detecting coronary arterial luminal narrowings could be influenced by referral bias. Third, our patients possessed a relatively high pretest probability of coronary artery disease (Table 2). Application of our findings is appropriate for similar patients. Fourth, our specificity data are based on 6 patients; thus, an erroneous result in 1 patient would change the specificity by 17%. Fifth, total procedure time (114 minutes) was relatively long. Because our technique is new, it is likely that this

time can be reduced with protocol streamlining. Finally, our images were analyzed qualitatively; quantitative wall motion analyses may yield improved results.³³

In conclusion, fast MRI pharmacological stress testing can be used to diagnose inducible ischemia in patients unable to undergo stress echocardiography. The safety profile and clinical utility of dobutamine/atropine MRI compare favorably with other widely accepted noninvasive imaging modalities.

Acknowledgments

This research was supported in part by the North Carolina Baptist Hospital Technology Development Fund (BG96-302). The authors wish to thank David Carey, Joyce Crane, Debra Fuller, Sandy Kaminsky, Jani Lee, Gay Luebchow, Wendy Mabe, Karan Miller, Jenny Hagee, David Philips, Darrell Sloan, Cathy Smith, Lesa Smith, Cynthia Souder, Susan Tucker, and Tina Zuchowski for their assistance with the performance of the MRI examinations and Matella Drum for her expert assistance with the quantitative coronary angiography measurements.

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