Background: Quantitative measurement of wall motion is essential to assess objectively the functional significance of coronary artery disease. We developed a quantitative wall thickening analysis on stress magnetic resonance images. This study was designed to assess the clinical value of magnetic resonance imaging (MRI) during dobutamine stress for detection and localization of myocardial ischemia in patients with suspected coronary artery disease.

Methods and Results: Thirty-nine consecutive patients with clinically suspected coronary artery disease referred for coronary arteriography and 10 normal volunteers underwent gradient-echo MRI at rest and during peak dobutamine stress (infusion rate, 20 μg·kg⁻¹·min⁻¹). MRI was performed in the short-axis plane at four adjacent levels. Display in a cine loop provided a qualitative impression of regional wall motion (cine MRI). A modification of the centerline method was applied for quantitative wall motion analysis by means of calculation of percent systolic wall thickening. Short-axis cine MRI images were analyzed at 100 equally spaced chords constructed perpendicular to a centerline drawn midway between the end-diastolic and end-systolic contours. Dobutamine MRI was considered positive for coronary artery disease if the percent systolic wall thickening of more than four adjacent chords was <2 SD below the mean values obtained from the normal volunteers. The overall sensitivity of dobutamine MRI for the detection of significant coronary artery disease (diameter stenosis ≥50%) was 91% (30 of 33), specificity was 80% (5 of 6), and accuracy was 90% (35 of 39). The specificity for identifying one-vessel disease was 88% (15 of 17), for two-vessel disease 91% (10 of 11), and for three-vessel disease 100% (5 of 5). The sensitivity for detection of individual coronary artery lesions was 75% for the left anterior descending coronary artery, 87% for the right coronary artery, and 63% for the left circumflex coronary artery.

Conclusions: Dobutamine MRI clearly identifies wall motion abnormalities by quantitative analysis using a modification of the centerline method. Dobutamine MRI is an accurate method for detection and localization of myocardial ischemia and may emerge as a new noninvasive approach for evaluation of patients with known or suspected coronary artery disease.

Key Words: coronary disease • magnetic resonance imaging • ventricle • pharmacology • stress

Stress testing is the cornerstone in the diagnosis of patients with suspected coronary artery disease. Although exercise ECG has been the mainstay for evaluating patients with chest pain syndromes, its sensitivity and specificity are limited, and the exercise ECG does not provide detailed information about the localization and extent of coronary artery disease. With increasing availability of therapeutic interventions in salvaging jeopardized myocardial tissue at present, accurate localization and quantification of myocardial ischemia is essential.

Wall motion asynergy reflects the functional significance of coronary artery lumen narrowing, and some data indicate that wall motion abnormalities are early, sensitive, and reliable markers of myocardial ischemia. In current clinical practice, wall motion is classified subjectively by use of qualitative wall motion analysis. Few data are available regarding quantitative wall motion analysis by wall thickening measurements, which has been shown to be more precise than qualitative evaluation of wall motion in discriminating ischemic from nonischemic myocardium.

Recently, magnetic resonance imaging (MRI) has emerged as a new noninvasive imaging modality providing high-resolution images in any desired plane of the heart, combined with the potential to monitor regional left ventricular function. To detect latent myocardial ischemia, however, cardiovascular stress has to be induced pharmacologically because physical exercise with MRI is difficult because of space restriction and motion artifacts. The clinical usefulness of dobutamine stress testing has been demonstrated in previous echocardiographic and MRI studies. Improved temporal res-
olution of gradient-echo MRI sequences permits capture of end-diastolic and end-systolic time frames. Importantly, endocardial and epicardial interfaces are well defined because of intrinsic contrast, allowing quantification of chamber volumes and myocardial wall thickness. In a previous study, we studied 45 patients with documented coronary artery disease by dobutamine MRI using qualitative analysis of the MR images. Although visual assessment of the MR images was quite acceptable, the use of a quantitative approach should theoretically provide more accurate results. In the past decade, the centerline method has been advocated to determine the effect of interventions designed to salvage left ventricular function in patients with an acute myocardial infarction receiving thrombolytic therapy. A modification of the centerline method has been used for analysis of regional left ventricular wall thickening on echocardiographic images but has not been reported in MRI studies.

This study was designed to assess the clinical value of dobutamine stress MRI for detection and localization of myocardial ischemia in a subsequent population of patients with suspected coronary artery disease by quantitative wall motion analysis using a modification of the centerline method.

Methods

Characteristics of Volunteers and Patient Population

Before they entered the study, informed consent was obtained from each volunteer and each patient in accordance with the ethical standards on human research at our institution. Ten healthy volunteers (8 men and 2 women; mean age, 24 years; range, 21 to 26 years), all with normal physical examination, no history of heart or lung disease, and a normal ECG, served as a control group. According to tables designed by Diamond and Forrester, the likelihood of coronary artery disease for the control group was <5%.

Patients referred for diagnostic cardiac catheterization between November 1992 and May 1993 were screened for eligibility for the study. Patients with a history of myocardial infarction were excluded because of homogeneity of the patient population and the potentially difficult assessment and interpretation of wall motion abnormalities in infarcted areas. Other exclusion criteria were atrial fibrillation, heart failure, unstable angina, ventricular arrhythmias, hypertrophic cardiomyopathy, valvular heart disease, and uncontrolled hypertension. Patients with an implanted pacemaker, claustrophobia, or metallic cerebral vascular clips were also excluded from this study. The study population comprised 39 patients (32 men, 7 women; mean age, 60 years; range, 41 to 77 years). All patients had a history of exertional angina and were in sinus rhythm. One patient had previous coronary artery bypass graft surgery. Dobutamine MRI and cardiac catheterization were performed within 2 weeks of each other in random order. β-Adrenergic blocking agents were discontinued ≥48 hours before dobutamine MRI, and calcium antagonists were not taken the day of the test.

Cardiac Catheterization

Coronary arteriography and biplane cine ventriculography were performed according to the Judkins technique. Multiple views of each of the three major coronary arteries were obtained. Coronary cineangiograms were analyzed with a personal computer–based coronary analysis system with a manual caliper program in its basic configuration, routinely applied in our center. Significant coronary artery stenosis was defined as ≥50% luminal diameter narrowing of a major epicardial coronary artery or major branch vessel in two or more projections.

Magnetic Resonance Imaging

MRI was performed on a whole-body superconducting magnet operating at a magnetic field strength of 1.5 T (Gyroscope S15, Philips Medical Systems). The ECG signal was recorded simultaneously with a standard lead and transmitted by telemetry to a remote receiver to trigger the image acquisition according to the R wave. The shortest trigger delay was 8 milliseconds after the onset of the R wave. Coronal and sagittal scout images were obtained with a spin-echo sequence, with a repetition time equal to the RR interval and an echo time of 30 milliseconds. The short-axis plane of the heart was derived from these coronal and sagittal scout views followed by double angulation to determine the angulations and centers (Fig 1). Cine MRI was performed with a flow-compensated gradient-echo sequence (the repetition time within one RR interval was 30 milliseconds, the echo time was 13 milliseconds, and the flip angle was 30°). Four contiguous slices were taken with a thickness of 10 mm, starting at the basal level, and each slice was imaged separately. The acquisition matrix of 128×256 was interpolated to 256×256 for display purposes. The field of view was 350 mm, and four acquisitions were averaged to improve signal-to-noise ratio. The number of sequential frames per cardiac cycle corresponded with the number of 30° pulses delivered within one RR interval. Accordingly, given a heart rate of 60 beats per minute, the RR interval was 1000 milliseconds and composed of 30 time frames (RR interval/repetition time), since the final 100 milliseconds of the diastole could not be imaged. The MRI scan time for one slice was approximately 7 minutes at control state, depending on the RR interval, number of measurements (n=4), and phase-encoding gradients (128 steps). Accordingly, the imaging time for one complete baseline acquisition at four slices was 26±3 minutes. The increased heart rate during dobutamine infusion reduced the imaging time during stress to 12±6 minutes.

Dobutamine Infusion Protocol

Before the MRI procedure, an intravenous cannula was inserted into the antecubital vein of the right arm and flushed with heparin to prevent coagulation. Dobutamine was administered intravenously by a syringe pump that was placed outside the magnetic environment and connected via a long line with the cannula, which was primed with dobutamine solution. After the baseline MRI images were obtained, dobutamine was infused at an initial rate of 5 μg·kg⁻¹·min⁻¹, followed by an incremental regimen of 5 μg·kg⁻¹·min⁻¹ at 2-minute intervals. The time to reach a steady-state condition, which is necessary to obtain a stable heart rhythm for triggering purposes, at peak infusion rate was 14±2 minutes after the infusion was started. Subsequently, peak dobutamine infusion rate was maintained, and cine MRI was performed. Criteria for terminating the dobutamine infusion were (1) significant side effects (chest pain, severe arrhythmias, dyspnea, or other intolerable symptoms); (2) systolic blood pressure >220 mm Hg or a decrease >20 mm Hg; (3) diastolic blood pressure >110 mm Hg; (4) achievement of the target heart rate (85% of the age-predicted maximal heart rate); and (5) maximum infusion rate of 20 μg·kg⁻¹·min⁻¹ reached. Metoprolol (1 mg/ml) was available for intravenous administration to reverse side effects promptly. Blood pressure was recorded by an automatic device at the left arm before the test and every minute during infusion. During the dobutamine stress test, a physician was always present at the upper end of the magnet’s bore to stay in close contact with the patient for evaluation of chest pain. In addition, the patient was continuously observed by video monitoring.
Magnetic Resonance Imaging Analysis

Both at rest and during dobutamine stress, the four short-axis images were displayed in a movie (cine) format to provide a qualitative impression of the contraction pattern throughout the cardiac cycle. End diastole was defined as the image obtained at 8 milliseconds after the onset of the R wave, and end systole was defined as the image with the smallest luminal area. The level showing the worst grade of wall motion abnormality as determined qualitatively during cine display was selected for quantitative wall motion analysis and compared with the equivalent level in the normal volunteers. Wall motion was scored qualitatively on the basis of both inward endocardial wall motion and systolic wall thickening. A normal response to dobutamine infusion was defined as a hyperdynamic motion consisting of an increased inward endocardial motion and enhanced systolic wall thickening.

The endocardial and epicardial borders of the end-diastolic and end-systolic images were manually traced with an optical cursor (Gyroview HR workstation, Philips Medical Systems) and were transferred to a workstation (IPC, SUN Microsystems Inc). Subsequently, a modification of the centerline method was used. The short-axis images were analyzed at 100 equidistant chords constructed perpendicular to a centerline drawn midway between the end-diastolic and end-systolic contours to calculate wall thickness at both time frames (Fig 2). The length of each chord defined the wall thickness at the corresponding point on the left ventricular contour. The papillary muscles, trabeculae, and epicardial fat were carefully excluded from these measurements. Wall thickening was expressed as the percent systolic wall thickening according to the formula: percent systolic wall thickening = [(end-systolic wall thickness − end-diastolic wall thickness)/end-diastolic wall thickness] × 100%. In each image, the internal posterior junction of the right ventricular free wall with the interventricular septum was designated as the starting point, ie, chord 1 as reference marker, followed by clockwise numbering from 1 to 100. The short-axis images were divided according to the vascular distribution of the coronary arteries (Fig 3). At the basal- and high-papillary muscle levels (Fig 3A), the anteroseptal and anterior segments were considered specific for the left anterior descending coronary artery distribution comprising chords 11 through 50 and the lateral region for the left circumflex coronary artery distribution comprising chords 51 through 70, whereas the posterior and posteroseptal areas

![Fig 1. Illustrations of double angulation of the magnetic resonance scout images. Upper left, Coronal spin-echo scout image with line indicating the intersecting short-axis plane. Upper right, Sagittal spin-echo scout image with line indicating the intersecting short-axis plane. Lower left, Final imaging plane achieved after double angulation. Lower right, Resulting short-axis cine MR image. L indicates left; A, anterior; and P, posterior.](http://circ.ahajournals.org/content/141/11/e160)

![Fig 2. Schematic representation of a modification of the centerline method. The short-axis magnetic resonance images were analyzed at 100 equidistant chords constructed perpendicular to a centerline drawn midway between the end-diastolic and end-systolic contours to calculate wall thickness at both time frames.](http://circ.ahajournals.org/content/141/11/e160)
were regarded as being the territory of the right coronary artery, comprising chords 71 through 100 and 1 through 10. In case of dominancy of the left circumflex artery, the posterior and posteroseptal areas were regarded as supplied by the left circumflex coronary artery. At the mid- and low-papillary muscle levels (Fig 3B), the entire septum and anterior segments, comprising chords 1 through 50, represent the left anterior descending artery distribution; the lateral region represents the left circumflex coronary artery distribution comprising chords 51 through 70, whereas the posterior area represents the right coronary artery distribution comprising chords 71 through 100.

At separate chords, the percent systolic wall thickening during dobutamine stress was considered abnormal when the response was below the mean value of the normal subjects minus two times the corresponding SD. However, to minimize the effect of coincidental abnormalities, the response to dobutamine stress was considered positive for coronary artery disease only when a number of adjacent chords were abnormal. The optimal number of adjacent abnormal chords, optimizing both the sensitivity and the specificity, was determined with receiver operator characteristic curve analysis.

Only interobserver variability was assessed. Two authors (F.P.v.R., S.J.S.) separately analyzed all wall motion data, and the interobserver variability was 5.8±2.7%.

Statistical Analysis

Hemodynamic data are presented as mean±SD. The sensitivity, specificity, and predictive accuracy for dobutamine MRI were estimated with the 95% confidence intervals. The hemodynamic alterations during dobutamine stress compared with rest were analyzed by a paired t test. The sensitivities for detecting individual coronary artery lesions were compared by the χ² test. A value of P<.05 was considered statistically significant.

Results

Normal Subjects

All normal subjects tolerated the dobutamine MRI test well. During peak dobutamine stress, the mean maximal heart rate (105±9 versus 63±7 beats per minute, P<.001), the maximal systolic blood pressure (186±14 versus 129±5 mm Hg, P<.001), and maximal rate-pressure product (19 646±2586 versus 8215±1016 mm Hg/min, P<.001) increased significantly compared with rest. The increase in diastolic blood pressure was small but significant (82±9 versus 72±8 mm Hg, P<.02).

Fig 4 shows the percent systolic wall thickening of 100 chords at the four adjacent short-axis levels, both at rest and during peak dobutamine stress, respectively. From all 10 volunteers, the mean percent systolic wall thickening (dashed line) ±2 SD (shaded area) are depicted. Obviously, during dobutamine stress, the curves were shifted upward at all levels, indicating the effect of dobutamine on wall motion dynamics and thickening.

Patient Population

The cine MRI images were of good quality in all patients, permitting accurate manual contour drawing. All patients completed the study protocol without evidence of major adverse effects during dobutamine MRI; no patient demonstrated >10 mm Hg decrease in systolic blood pressure, whereas 1 patient showed accelerated idioventricular rhythm immediately after the MRI procedure, which was registered electrocardiographically outside the magnetic environment and resolved rapidly after termination of dobutamine infusion.

During peak dobutamine stress, the mean maximal heart rate (113±10 versus 71±10 beats per minute, P<.001), the maximal systolic blood pressure (168±18 versus 136±15 mm Hg, P<.001), and maximal rate-pressure product (19 915±2620 versus 9631±1780 mm Hg/min, P<.001) increased significantly compared with control state. Diastolic blood pressure did not change during dobutamine stress (85±11 versus 86±12 mm Hg, P=NS). The hemodynamic data are summarized in Table 1.

All side effects were mild and transient and reversed rapidly after termination of the dobutamine infusion. Chest pain developed in 10 of 39 patients (26%) during dobutamine infusion, but it was not necessary to stop the infusion because no further chest pain was judged mild by all patients. At the end of the imaging procedure, dobutamine-induced chest pain was controlled by reducing the infusion rate, and no patient needed administration of sublingual nitroglycerin or intravenous metoprolol. Mild ventricular arrhythmias, isolated premature systolic beats, occurred in 8 of 39 patients (21%). None of the patients demonstrated
ventricular tachycardia at peak dobutamine infusion. In no case did the arrhythmias require premature termination of the test.

Coronary Arteriographic Findings

The arteriographic data are listed in Table 2. Significant coronary artery disease (≥50% diameter stenosis) was present in 33 of the 39 patients (85%): one-vessel disease was present in 17 patients, two-vessel disease in 11, and three-vessel disease in five, but no patient had left main disease. None of the patients demonstrated resting wall motion abnormalities on the ventriculograms. A total of 54 coronary arteries were identified as having stenosis of ≥50% luminal narrowing.

Dobutamine Magnetic Resonance Imaging: Overall Findings

The sensitivity and the false positive fraction of dobutamine MRI for detecting functionally significant

<table>
<thead>
<tr>
<th>Table 1. Hemodynamic Changes During Peak Dobutamine Stress</th>
</tr>
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<tbody>
<tr>
<td>Normal Subjects</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
</tr>
<tr>
<td>Rate-pressure product, mm Hg/min</td>
</tr>
</tbody>
</table>

bpm indicates beats per minute; BP, blood pressure.
*P<.001, †P<.02, ‡P=NS vs baseline.
coronary artery disease are displayed in Fig 5 for varying numbers of adjacent abnormal chords. In the present study, the optimal number appeared to be four or more adjacent chords.

Dobutamine stress-induced wall motion abnormalities, as determined by four or more adjacent chords exhibiting percent systolic wall thickening < 2 SD below normal mean values, developed in 30 of 33 patients with

<table>
<thead>
<tr>
<th>Patient</th>
<th>Localization of Coronary Artery Stenosis (≥50% Diameter Stenosis)</th>
<th>Level Showing Worst Grade of Wall Motion Abnormality During Cine Display</th>
<th>≥4 Adjacent Chords With %WTh&lt;2 SD</th>
<th>Detected Coronary Artery With Stenosis Supplying Asynergic Chords</th>
</tr>
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<tbody>
<tr>
<td>1-Vessel CAD</td>
<td></td>
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</tr>
<tr>
<td>1</td>
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<td>10-15</td>
<td>LAD</td>
</tr>
<tr>
<td>2</td>
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<td>LP</td>
<td>2-37</td>
<td>LAD</td>
</tr>
<tr>
<td>3</td>
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<td>HP</td>
<td>9-17/30-53</td>
<td>LAD</td>
</tr>
<tr>
<td>4</td>
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<td>B</td>
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<td></td>
</tr>
<tr>
<td>5</td>
<td>LAD ... ... ...</td>
<td>MP</td>
<td>15-50</td>
<td>LAD</td>
</tr>
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<td>MP</td>
<td>1-27</td>
<td>LAD</td>
</tr>
<tr>
<td>7</td>
<td>... LCx ... ...</td>
<td>B</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>... LCx ... ...</td>
<td>HP</td>
<td>51-100</td>
<td>LCx</td>
</tr>
<tr>
<td>9</td>
<td>... LCx ... ...</td>
<td>B</td>
<td>68-98</td>
<td>LCx</td>
</tr>
<tr>
<td>10</td>
<td>... LCx* ... ...</td>
<td>HP</td>
<td>49-100</td>
<td>LCx</td>
</tr>
<tr>
<td>11</td>
<td>... LCx* ... ...</td>
<td>HP</td>
<td>54-84</td>
<td>LCx</td>
</tr>
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<td>54-70</td>
<td>LCx</td>
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<td>13</td>
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<td>MP</td>
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<td>64-92</td>
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</tr>
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<td>HP</td>
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<tr>
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</tr>
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<td>HP</td>
<td>11-19</td>
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</tr>
<tr>
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<td>HP</td>
<td>10-68</td>
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</tr>
<tr>
<td>21</td>
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<td>LAD</td>
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<tr>
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<tr>
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<td>12-27</td>
<td>LAD</td>
</tr>
<tr>
<td>24</td>
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<td>B</td>
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<td>LAD+RCA</td>
</tr>
<tr>
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<td>80-83/87-100</td>
<td>RCA</td>
</tr>
<tr>
<td>26</td>
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<td>B</td>
<td>81-100</td>
<td>RCA</td>
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<td>27</td>
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<td>69-100</td>
<td>RCA</td>
</tr>
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<td>44-100</td>
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<tr>
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<tr>
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<td>23-26/86-100</td>
<td>LAD+RCA</td>
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</tbody>
</table>

MRI indicates magnetic resonance imaging; %WTh, percent systolic wall thickening; CAD, coronary artery disease; LAD, left anterior descending coronary artery; B, basal level; LP, low-papillary muscle level; HP, high-papillary muscle level; MP, mid-papillary muscle level; LCx, left circumflex coronary artery; and RCA, right coronary artery.

*LCx dominancy.
significant coronary artery disease (sensitivity, 91%; 95% confidence interval, 81% to 100%). Two negative studies were observed in patients with one-vessel disease (patients 4 and 7), resulting in a sensitivity of 88% (15 of 17 patients; 95% confidence interval, 72% to 100%) for detection of one-vessel coronary artery disease. One patient with two-vessel disease (patient 18) did not show abnormal systolic wall thickening at peak dobutamine stress, resulting in a sensitivity of 91% (10 of 11 patients; 95% confidence interval, 74% to 100%) for detection of two-vessel coronary artery disease. The 5 patients (100%) with three-vessel disease demonstrated a positive dobutamine MRI test.

The detection rate of multivessel coronary artery disease, ie, regional dysfunction induced in more than one coronary vascular supply region, was 50% (8 of 16 patients; 95% confidence interval, 25% to 75%). The overall detection rate of ischemia in patients with multivessel disease was 94% (15 of 16 patients; 95% confidence interval, 82% to 100%). Abnormal stress-induced wall thickening was absent in 5 of 6 patients (specificity, 80%; 95% confidence interval, 47% to 100%) without significant coronary artery disease. The only false-positive study was observed in a patient with left ventricular hypertrophy, as established by MRI, with angiographically normal coronary arteries.

**Dobutamine Magnetic Resonance Imaging: Individual Coronary Artery Stenoses**

Of 20 stenoses in the left anterior descending coronary artery, 15 (75%; 95% confidence interval, 56% to 94%) were detected by dobutamine MRI, based on stress-induced wall motion abnormalities followed by quantitative wall motion analysis. Five stenoses were not identified; three had 50% to 70% luminal narrowing, and two were located distally in the left anterior descending artery.

Of 19 stenoses identified in the left circumflex coronary artery, 12 (63%; 95% confidence interval, 41% to 85%) were detected by dobutamine MRI. Of the seven lesions that were not detected by the dobutamine MRI test, only one negative test result was found in a patient with one-vessel disease, whereas four negative test results were found in patients with two-vessel disease and two in patients with three-vessel disease.

Of the 15 right coronary artery stenoses, 13 (87%; 95% confidence interval, 70% to 100%) were detected by dobutamine MRI. The two negative test results were observed in patients with multivessel disease. There was no significant difference in the percentage of positive studies detected among the three coronary artery distributions (P>.12). An example of a stress MRI scan in a patient with one-vessel disease is shown in Fig 6.

**Discussion**

Evaluation of left ventricular function is of great importance in the diagnosis and management of patients with known or suspected coronary artery disease. In addition, global systolic left ventricular ejection fraction, in particular left ventricular end-systolic volume, is a major determinant of prognosis in patients with coronary artery disease.20 Since contraction abnormalities have been shown to appear immediately after reduction of coronary blood flow,3,4 analysis of wall motion has become an early and sensitive indicator of myocardial ischemia. Moreover, myocardial ischemia becomes manifest predominantly as a focal disorder, starting with transient and reversible wall motion dysfunction. On the other hand, global left ventricular performance reflects the cumulative functional properties of both ischemic and nonischemic myocardium. In the presence of moderate ischemia, development of hyperfunction in nonischemic areas remote from the ischemic myocardium makes global left ventricular function an insensitive marker of myocardial ischemia.21 Therefore, accurate assessment of the presence, site, and degree of regional left ventricular dysfunction represents an important parameter to identify patients with functionally significant coronary artery disease for determination of the therapeutic strategy as well as to evaluate the effects of therapeutic interventions designed to salvage or preserve left ventricular function.15,16

**Assessment of Regional Left Ventricular Function**

The majority of studies on the assessment of regional left ventricular function have relied on qualitative wall motion analysis. Qualitative evaluation of wall motion is based on visual scoring of contraction patterns in the different regions and is often facilitated by display in a cinematographic format, which has increased its feasibility and clinical usefulness. However, several studies have demonstrated that wall motion abnormalities overestimate ischemic areas and are less accurate than wall thickening data to distinguish ischemic from nonischemic myocardium.6,7,22-23 Wall thickening has been considered an active process that is closely associated with myocardial fiber-shortening dynamics.24 Furthermore, impairment of wall thickening is clearly related to a reduction in subendocardial blood flow.25 The complex myocardial fiber structure of the heart necessitates optimal plane selection for tomographic cardiac imaging, since the left ventricular wall consists primarily of deep constrictor fibers, which cause predominantly transverse shortening.26 As a consequence, tomographic imaging with respect to the intrinsic cardiac short axis may depict contraction abnormalities most appropri-
Fig 6. Facing page. Four short-axis magnetic resonance imaging (MRI) scans and two plots of percent systolic wall thickening (%WTh) at the mid-papillary level, both at rest (left column) and during peak dobutamine stress (right column) at end diastole (top) and end systole (middle) in a patient with one-vessel coronary artery disease located in the left anterior descending coronary artery (patient 5). In the MRI scans, the endocardial and epicardial contours are depicted in green, the centerline in red, and the chords in blue. Chord 1 is located at the inner posterior junction between the right ventricular wall and the interventricular septum (top left, white arrowhead). Note the decreased systolic wall thickening at the anteroseptal wall (middle right, white arrows). The results of %WTh are graphically illustrated in the bottom panels. The shaded area represents normal mean (dotted line) ± 2 SD at rest and during peak dobutamine stress; the continuous black line represents the percent systolic wall thickening of this patient. The normal wall thickening (bottom left) compared with the decreased wall thickening (bottom right) between chords 15 and 50 corresponding with the anteroseptal wall.

Observations in the Present Study

In the present study, we demonstrated the ability of dobutamine MRI to detect and localize myocardial ischemia in a group of patients referred for diagnostic coronary angiography. The present study is the first to report a combined qualitative and quantitative wall motion analysis; it yielded a high sensitivity, 91%, in the overall detection of coronary artery disease. This compares favorably with the sensitivity value of 81% found in our previous study,14 which was largely due to the difference in detection rate in patients with single-vessel disease (75% in the previous study versus 88% in the present study). Dobutamine MRI was not capable of detecting all the individually diseased coronary arteries by provoking and detecting wall motion abnormalities in the myocardial areas supplied by those vessels (sensitivity: left anterior descending coronary artery, 75%; right coronary artery, 87%; and left circumflex artery, 63%). This may be explained by the submaximal imposed level of dobutamine stress. Furthermore, in some patients dobutamine stress may be a less potent stimulus for inducing ischemia than exercise. Increasing the dobutamine infusion rate up to 30 to 40 μg·kg⁻¹·min⁻¹, as reported in dobutamine echocardiographic studies,9,10 may further enhance the diagnostic accuracy of dobutamine MRI. Otherwise, in many patients with either single-vessel or multivessel disease, the coronary obstructions might have been not severe enough to cause stress-induced wall motion dysfunction. Our preliminary results emphasize the relation between coronary arterial stenosis and its functional importance in providing information as to which vessels are likely to be responsible for the patient's symptoms. These observations are of potential clinical value in patients with multivessel disease, since therapeutic intervention should be focused primarily on the ischemia-producing or "culprit" lesion. We purposely did not include patients with prior myocardial infarction in the present study because we preferred to have a rather homogeneous group of patients. Second, we were interested only in the development of new wall motion abnormalities (ie, myocardial ischemia), which are difficult to assess and to interpret in patients after myocardial infarction because of the tethering effect of the infarcted area on the noninfarcted myocardium.27 Third, the clinical question in patients with myocardial infarction is nowadays not only ischemia but also the presence of myocardial viability.28 Since dobutamine may detect both viability (in low doses) and ischemia (in high doses), we decided, in view of our purpose to detect ischemia alone, not to include patients with myocardial infarction.

Effects of Dobutamine

In patients with coronary artery disease, dobutamine is effective in provoking myocardial ischemia, resulting in stress-induced wall motion abnormalities. The predominant β₁-adrenergic effects of dobutamine result in potent inotropic and chronotropic effects. In patients with coronary artery disease and no evidence of heart failure, these effects lead to a substantial increase in myocardial oxygen demand beyond myocardial oxygen supply.29 When the increase in heart rate supervenes during inotropic stimulation with dobutamine, regional myocardial blood flow distal to coronary stenosis falls, and contractile function of the ischemic myocardium deteriorates.30,31 In the present study, the dobutamine infusion protocol was designed to optimize safety, feasibility, and patient tolerance. Since in all patients the β-blocking medication was discontinued at least 48 hours before the test, a maximum dose of 20 μg·kg⁻¹·min⁻¹ proved to be adequate in provoking cardiac stress by inducing substantial increases in heart rate and systolic blood pressure without occurrence of major side effects. In our study, only 10 of 39 patients (26%) experienced mild chest pain, and in no case did the dobutamine stress test have to be terminated prematurely. In our previous study,14 9 of 45 patients (20%) developed mild chest pain. Taking these results together, 19 of 84 patients (22%) developed mild chest pain during dobutamine infusion. Dobutamine infusion has been reported as a valuable alternative stress method for evaluation of patients with coronary artery disease by two-dimensional echocardiography9,10 and MRI.11,14 However, these studies relied on qualitative wall motion analysis followed by a semiquantitative scoring system. McGillem et al12 were the first who modified the original centerline method for purposes of wall thickness measurements using echocardiography after experimental coronary occlusion. They concluded that wall thickness analysis by the criterion "less than normal mean value minus 2 SD" most closely approximated regional myocardial risk area as assessed by microsphere injection. However, their method considered only mid-ventricular echocardiographic tracings, and no information concerning stress-induced wall thickness was obtained.

Centerline Method

The centerline method applied offers several advantages for analyzing regional left ventricular function. Wall thickness is measured along 100 equidistant chords, thereby increasing the sensitivity to detect subtle wall motion abnormalities. Moreover, wall motion is assumed to proceed in a multicentric manner rather than toward a single point. This multicentric movement is potentially advantageous over other reference-depen-
dent methods that assume that ventricular contractile motion proceeds toward a single point or centroid, an assumption that has generally been regarded as invalid.32 The centerline method does not require a centroid to correct for in-plane translational motion and avoids dependence on reference figures or coordinate systems.33 However, the centerline method needs a reference marker to correct for rotational transformation during systole to determine systolic thickening. For that purpose, we used a fixed anatomic landmark (chord 1), the internal posterior junction of the right ventricular wall with the interventricular septum. Because of larger variations in wall thickness in regions after myocardial infarction, the centerline approach can be more problematic in patients with previous myocardial infarction, since border definition may be difficult, particularly in regions with reduced wall thickness.

Limitations of the Study

Several limitations of our study should be mentioned. First, a case-by-case approach was required because of the relatively low number of patients and volunteers. In addition, data were obtained in a selected group of patients with a high pretest likelihood of coronary artery disease. As a result, the population without coronary artery disease was small, which influenced our specificity value (80%). In fact, a 20% false-positive rate may be considered suboptimal in our study group. Future investigations are required to determine whether a similar feasibility and diagnostic accuracy can be achieved in other groups of patients with chest pain syndromes who have an intermediate pretest probability of coronary artery disease. Our study would be strengthened with inclusion of more patients with <5% likelihood of coronary artery disease or with normal coronary arteries for a truer assessment of specificity of the technique. Second, although quantitative coronary arteriographic analysis may be superior to qualitative analysis in assessing the dimensions of coronary artery stenoses, it should be recognized that physiological effects of coronary artery stenoses cannot accurately be determined by conventional visual interpretation34 or by quantitative angiography.35 However, functional evaluation using systolic wall thickening integrates the angiographic data and hemodynamic behavior of a stenosis, thereby offering a clinically useful reference for the physiological consequences of a coronary arterial stenosis. In addition, the use of a preconceived pattern of specific coronary artery myocardial supply can certainly be unreliable, especially in patients with multivessel disease and in the presence of intracoronary collaterals. In the present study, we were not able to use an overlap model,36 because only four short-axis slices were imaged and the required long-axis views for such a procedure were not obtained. Third, a methodological limitation of our analysis is the lack of correction for through-plane motion. Obviously, the MRI short-axis slice was externally fixed in space, whereas it is evident that the heart exhibits through-plane motion. During tomographic imaging, the slices near the base will be affected predominantly by this through-plane motion. Unfortunately, a reliable and comprehensive method for correction is not available. Recent advances in myocardial tagging37 and three-dimensional display38 are promising and may be widely available in the near future. In addition, only one short-axis level per patient was used for quantitative assessment. It would, of course, have been better to include all four levels in the analysis. However, we had two reasons to use only one level. First, accurate quantitative analysis is rather time-consuming, but second, more importantly, we chose the particular level showing the worst grade of wall motion abnormality by visual analysis. In that case, we assume that we did not miss any wall motion abnormality. In this respect, our sensitivity and specificity values were quite similar to the values reported by Hays et al,38 who used dobutamine thallium single photon emission computed tomography; sensitivities of dobutamine 201Tl and of dobutamine MRI were 86% and 91%, and specificities were 90% and 80%, respectively. It should be realized that the authors used short-axis and horizontal and vertical long-axis views for the detection of ischemia. Fourth, the accuracy of the wall thickness measurements may have been affected by the gradient-echo MRI technique used. During stress-induced myocardial ischemia, wall motion dysfunction may cause reduced in-plane blood flow as well as reduced through-plane blood flow. These effects will result in partial saturation and reduced “spin refreshment,” respectively. As a consequence, blood near the endocardium can demonstrate lower signal and may not be optimally visualized because of the decreased blood-endocardium contrast. Particularly when one has to rely on manual tracings of the endocardial and epicardial borders, the end-systolic wall thickness may be overestimated, and actually decreased systolic wall thickening could be misinterpreted as normal or increased. In the present study, only interobserver variability was assessed, which was 5.8±2.7%. This value is quite in line with previously determined values for interobserver and intraobserver variabilities for wall thickness measurements in our institution, which were relatively small, 7.7±2.6% and 5.6±2.3%, respectively.

Finally, accurate estimation of the extent of jeopardized myocardium is difficult, since there may be a zone of normally perfused but dysfunctional myocardium at the lateral margins of ischemic areas because of the so-called tethering phenomenon.25 The region of mechanical dysfunction results in a functional border zone that potentially overestimates the actual size of ischemic myocardium. However, recent studies have shown that this nonischemic but well-perfused myocardium may respond to inotropic stimulation during dobutamine infusion.40 As a result, a significant decrease in the size of the functional border zone was observed, which may favor the use of dobutamine as stress inducer during tomographic imaging.

Clinical Implications

Our study may have important clinical implications. A precise discrimination between ischemic and nonischemic regions is invaluable in the diagnosis and management of patients with chest pain syndromes. Therefore, a major advantage of our approach is that dobutamine MRI permits accurate detection and localization of myocardial areas at risk in patients with suspected coronary artery disease. Whether the dobutamine stress test using the centerline method will provide similar results in patients with myocardial infarction remains to be demonstrated. Further stress MRI studies, providing a complete data set of the myocardial wall thickening at
multiple short-axis planes between base and apex, have the potential to accurately delineate the infarcted area and to quantify the actual myocardium at risk.

Conclusions
In conclusion, dobutamine MRI provides a new non-invasive approach to discern and quantify subtle wall motion abnormalities associated with functionally significant coronary artery disease. The present technique requires further improvement using faster imaging sequences, algorithms for automatic border recognition, and three-dimensional display. In particular, the addition of an automated border recognition program would constitute a considerable advantage in the assessment of global and regional wall motion. Therefore, further clinical application of this technique may be most helpful in the early assessment of the site, extent, and severity of myocardial ischemia in patients with suspected or known coronary artery disease, who might benefit from therapeutic interventions. In the near future, combination with ultrafast MRI and MRI coronary angiography may provide a complete evaluation of the coronary anatomy, myocardial perfusion, and left ventricular function.

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