Prognostic Value of Dobutamine Stress Myocardial Contrast Perfusion Echocardiography

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Background—Myocardial perfusion (MP) imaging with real-time contrast echocardiography (RTCE) improves the sensitivity of dobutamine stress echocardiography for detecting coronary artery disease. Its prognostic value is unknown. We sought to determine the value of MP and wall motion (WM) analysis during dobutamine stress echocardiography in predicting the outcome of patients with known or suspected coronary artery disease.

Methods and Results—We retrospectively studied 788 patients with RTCE during dobutamine stress echocardiography using intravenous commercially available contrast agents. The incremental prognostic value of MP imaging over clinical risk factors and other echocardiographic data was examined through the use of a log-likelihood test (Cox model). During a median follow-up of 20 months, 75 events (9.6%) occurred (58 deaths, 17 nonfatal myocardial infarctions). Abnormal MP had significant incremental value over clinical factors, resting ejection fraction, and WM responses in predicting events ($P<0.001$). By multivariate analysis, the independent predictors of death and nonfatal myocardial infarction were resting left ventricular ejection fraction $<50\%$ (relative risk [RR], 1.9; 95% CI, 1.2 to 3.2; $P=0.01$), hypercholesterolemia (RR, 0.5; 95% CI, 0.3 to 0.9; $P=0.01$), and abnormal MP (RR, 5.2; 95% CI, 3.0 to 9.0; $P<0.0001$). The 3-year event free survival was 95% for patients with normal WM and MP, 82% for normal WM and abnormal MP, and 68% for abnormal WM and MP.

Conclusion—MP imaging during dobutamine stress RTCE provides incremental prognostic information in patients with known or suspected coronary artery disease. Patients with normal MP have a better outcome than patients with normal WM. (Circulation. 2005;112:1444-1450.)

Key Words: coronary artery disease | echocardiography | exercise test | prognosis
for CAD were diabetes mellitus in 387 (49%), systemic hypertension in 535 (68%), hypercholesterolemia in 406 (51%), and cigarette smoking in 253 (32%). One hundred forty-nine patients (19%) had a history of a previous myocardial infarction, 111 (14%) had previous CABG, and 106 (13%) had previous percutaneous interventions. Two hundred sixty-three patients (33%) were taking β-blockers, and 209 (27%) were taking calcium channel blockers. Diabetes mellitus was defined as a fasting glucose level ≥140 mg/dL or the need for insulin or oral hypoglycemic agents. Hypercholesterolemia was defined as total cholesterol ≥200 mg/dL or treatment with lipid-lowering medications. Hypertension was defined as blood pressure ≥140/90 mm Hg or use of antihypertensive medication.

**RTCE Study**

RTCE was performed with the commercially available albumin-encapsulated microbubble Optison (GEAmersham) or the lipid-encapsulated microbubble Definity (Bristol-Myers Squibb Medical Imaging, Inc). The doses of contrast used for the assessment of MP were the same doses recommended for left ventricular opacification during stress testing. Optison was injected in doses of 0.2 to 0.3 mL and Definity in doses of 0.1 mL for each apical window, followed by a 3- to 5-mL saline flush.

RTCE was performed with commercially available ultrasound scanners (HDl 5000 and Sonos 5500, Philips Medical Systems, or Sequoia 6.0, Siemens Acuson). Each is equipped with low-mechanical-index real-time pulse sequence schemes that deploy either interpulse amplitude modulation or interpulse phase and amplitude modulation. The systems were adjusted to achieve optimal nonlinear signals at a mechanical index ≤0.3 and frame rate ≥25 Hz. Time gain compensation and 2D gain settings were adjusted to suppress any nonlinear signals from tissue before contrast administration. Equipment settings were then kept unchanged throughout the study. Perfusion images were obtained in the apical 4-, 2-, and 3-chamber views at baseline and at peak stress. The RTCE images were digitally acquired after peak myocardial opacification until disappearance of contrast from the myocardium. All images were reviewed side-by-side analysis.

**Stress Protocol**

Dobutamine was infused at a starting dose of 5 µg · kg⁻¹ · min⁻¹, followed by increasing doses of 10, 20, 30, and 40 µg · kg⁻¹ · min⁻¹ to a maximal dose of 50 µg · kg⁻¹ · min⁻¹ in 3- to 5-minute stages. Atropine (up to 2 mg) was injected in patients without symptoms or signs of myocardial ischemia to achieve 85% of the age-predicted maximal heart rate, calculated as 220 minus age in years. Blood pressure and cardiac rhythm were monitored before and during the dobutamine infusion. Twelve-lead ECGs were obtained at 3-minute intervals. The stress ECG was considered positive for ischemia in the presence of horizontal or downsloping ST-segment depression >0.1 mV at 0.06 seconds after the J point. End points of the stress test were achievement of target heart rate (85% of age-predicted maximal heart rate), maximal dobutamine/atropine doses, development of severe or extensive WM abnormalities, ST elevation >0.1 mV at an interval of 80 ms after the J point in non-Q-wave leads, sustained arrhythmias, severe chest pain, and intolerable side effects. The dobutamine stress test was considered diagnostic if the target heart rate and/or inducible abnormalities were detected by analysis of WM or MP. The tests were considered nondiagnostic if the patients failed to achieve the target heart rate without inducible WM or MP abnormalities.

**Image Analysis**

Baseline left ventricular ejection fraction was visually estimated after review of contrast enhanced images. Ejection fractions estimated to be <50% were confirmed by the biplane Simpson’s formula using contrast enhanced images to delineate endocardial borders. Patients were considered to have normal left ventricular function when ejection fraction was ≥50% and abnormal left ventricular function when ejection fraction was <50%. The left ventricle was divided in 17 segments according to the recommendations of the American Society of Echocardiography. MP and WM were evaluated by an experienced observer. The interobserver agreement of RTCE in our laboratory is 84% for MP (κ = 0.63) and 91% for WM (κ = 0.64) analysis.

The study was considered abnormal by segmental WM criteria if there was a resting or new WM abnormality in ≥2 segments. Myocardial contrast enhancement was analyzed during the period of myocardial opacification after each injection of contrast, after attenuation from left ventricular cavity contrast had resolved. Resting images were compared side by side with stress images using digitally captured cardiac cycles for each apical view. MP was considered abnormal when ≥2 segments exhibited a perfusion defect, defined as a transmural or subendocardial decrease in contrast enhancement. Patients with normal MP at both baseline and peak stress were classified as having a normal MP study. Patients with normal MP at baseline and a new perfusion defect with stress were classified as having an inducible perfusion defect. Patients with a perfusion defect at baseline associated with WM abnormality without extension observed at peak dobutamine stress were classified as having a fixed perfusion defect, and those with a resting perfusion abnormality who developed a new perfusion defect in other segments were characterized as having fixed plus inducible perfusion defects. Artifacts resulting from contrast or lung interference were considered present if the endocardial and epicardial borders of a segment could not be visualized and thus were not distinguishable from surrounding tissues. Thus, a transmural defect was only considered present when ≥2 segments exhibited a decrease in contrast enhancement but both the endocardial and epicardial borders were still evident. WM response was also described with these same criteria. In addition, patients with a biphasic response of WM in segments with resting abnormalities were considered to have both resting and inducible WM abnormalities.

Patients were classified according to the extent of abnormality. They were considered to have single-vessel abnormality when the perfusion defect or WM abnormality involved only 1 coronary artery territory and multivessel abnormality when the perfusion defect or WM abnormality involved >1 coronary artery territory. The left ventricular apex, anteroseptal, distal septum, and anterior walls were assigned to the left anterior descending coronary artery, the lateral wall to the left circumflex, and the inferior wall and basal septum to the right coronary artery. The posterior wall was considered an overlap zone that could be assigned to either right coronary or left circumflex artery. The results of both MP and WM analyses were made available to the referring physicians.

**Follow-Up**

Follow-up was obtained by review of the patient’s hospital chart, electronic records, and telephone interview with the patient. The study end points were death from any cause and nonfatal myocardial infarction.

Cardiac death was defined as death associated with known or suspected myocardial infarction, life-threatening arrhythmia, or pulmonary edema. Sudden unexpected death occurring without another explanation was included as cardiac death. Nonfatal myocardial infarction was defined by means of a serial increase in cardiac specific enzymes and/or development of new ECG changes. Patients who underwent revascularization within 3 months after RTCE were excluded. Patients who underwent CABG and percutaneous coronary intervention >3 months after RTCE were censored at the time of revascularization.

**Statistical Analysis**

Continuous variables are expressed as mean and SD; categorical variables are expressed as proportions. The concordance of WM and MP analyses during dobutamine stress RTCE was calculated as the percentage of agreement and κ statistics. Kaplan-Meier curves were used to estimate the distribution of time to death or nonfatal myocardial infarction. The Cox model was used to estimate the relative risk (RR) of events for each variable. Differences between time-to-event curves were compared with the log-rank test. Age and
left ventricular ejection fraction were analyzed as qualitative variables because of their varying clinical significance at different cutoff values. Additional clinical variables considered for both univariate and multivariate analyses were defined according to the Framingham risk score assessment. They included diabetes, hypercholesterolemia, and hypertension. Additional clinical variables included a history of prior myocardial infarction. Echocardiographic parameters were ejection fraction and WM and MP responses to dobutamine. Multivariate predictors of events were determined by the Cox proportional-hazards model. The incremental value of stress echocardiographic information over clinical data was assessed in 4 modeling steps. The first step consisted of fitting a multivariate model of only clinical data. Baseline left ventricular ejection fraction was then added to this model, followed by WM (normal versus abnormal) and then MP data (normal or abnormal). The significance of adding additional variables to previous modeling steps was based on the change in model-based likelihood statistics, with degrees of freedom equal to the number of additional variables. A value of P<0.05 was considered significant.

Results

The mean maximal dose of dobutamine was 32±9 μg·kg⁻¹·min⁻¹. Atropine was injected in 83% of patients with a mean cumulative dose of 0.7±0.6 mg. Heart rate increased from 75±13 bpm at baseline to 145±13 bpm at peak stress (P<0.001), and the rate-pressure product increased from 11 065±2950 mm Hg/min at baseline to 20 762±5770 mm Hg/min at peak stress (P<0.0001). The mean percentage maximal predicted heart rate achieved at peak stress was 91±11%. Target heart rate was achieved in 701 patients (89%). The contrast agent Optison was used in 575 patients (73%). The mean cumulative dose was 2.8±0.9 mL. Definity was used in 213 patients (27%). The mean cumulative dose was 1.1±0.4 mL.

The mean left ventricular ejection fraction was 58±12%. There were 131 patients (17%) with baseline left ventricular ejection fraction <50%; among them, 41 had ejection fraction <30%. Seventy-seven patients had either percutaneous revascularization (n=51) or bypass surgery (n=26) within 3 months of the DSE. Two of these patients had normal WM and MP responses to DSE, 21 had normal WM and abnormal MP, and 54 had both abnormal WM and MP responses during DSE.

In the remaining patients, the stress echocardiogram was interpreted as normal for WM in 587 patients (74%) and abnormal in 201 patients (26%). MP was interpreted as normal in 462 patients (59%) and abnormal in 326 (41%). WM and MP analyses were concordant in 663 patients (84%; κ=0.65). Both tests were normal in 462 and abnormal in 201 patients. There were 125 patients (16%) with normal WM but abnormal MP. All patients with abnormal WM also had abnormal MP. The distributions of the results of WM and MP analysis are presented in Table 1.

Myocardial revascularization was performed in 84 patients (29 CABG, 55 percutaneous coronary interventions) >3 months after the stress test. Of these patients, 10 had normal WM and MP (2% of all normal WM and MP studies), 29 had normal WM but abnormal MP (23% of all normal WM but abnormal MP studies), and 45 had both abnormal WM and abnormal MP (22% of all abnormal WM and MP studies). These patients were censored at the time of revascularization.

Predictors of Death or Nonfatal Myocardial Infarction

The median follow-up for patients who did not experience an event was 19.9 months. A total of 75 (9.6%) patients had events during the follow-up. Events occurred at a median of 12 months (range, 1 day to 46 months) after the dobutamine stress test and included death in 58 patients (cardiac in 30 patients) and nonfatal myocardial infarction in 17 patients. The clinical characteristics of patients with and without subsequent events are presented in Table 2. No differences in hemodynamic or ECG responses to dobutamine stress were observed between patients with or without events (Table 3).

Outcome According to Extent and Type of Perfusion Defect

The outcome of patients according to the type of perfusion defect is depicted in Figure 1. The 3-year event-free survival was 95% in patients with normal MP, 86% in patients with fixed perfusion defects, 84% in patients with inducible perfusion defects (both P<0.001 versus normal perfusion), and 41% in patients with both fixed plus inducible perfusion defects (P<0.001 versus other groups).

**TABLE 1.** Distribution of WM and MP Results in the Study Population

<table>
<thead>
<tr>
<th>Results</th>
<th>WM, n (%)</th>
<th>MP, n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>587 (74)</td>
<td>462 (59)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Abnormal</td>
<td>201 (26)</td>
<td>326 (41)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of abnormalities</th>
<th>WM, n (%)</th>
<th>MP, n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inducible</td>
<td>82 (11)</td>
<td>215 (27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fixed</td>
<td>63 (8)</td>
<td>41 (5)</td>
<td></td>
</tr>
<tr>
<td>Fixed plus inducible</td>
<td>56 (7)</td>
<td>70 (9)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Extent of abnormalities</th>
<th>WM, n (%)</th>
<th>MP, n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single vessel</td>
<td>126 (16)</td>
<td>196 (25)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multivessel</td>
<td>75 (10)</td>
<td>130 (16)</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 2.** Clinical Features of Patients With and Without Subsequent Events

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients Without Events, n (%)</th>
<th>Patients With Events, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=713)</td>
<td>(n=75)</td>
</tr>
<tr>
<td>Male gender</td>
<td>345 (48)</td>
<td>42 (56)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>490 (69)</td>
<td>45 (60)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>228 (32)</td>
<td>25 (33)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>372 (52)</td>
<td>34 (45)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>238 (33)</td>
<td>26 (35)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>123 (17)</td>
<td>26 (35)*</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>91 (13)</td>
<td>20 (27)*</td>
</tr>
<tr>
<td>Previous percutaneous coronary intervention</td>
<td>91 (13)</td>
<td>15 (20)</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>322 (45)</td>
<td>41 (54)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>194 (27)</td>
<td>15 (20)</td>
</tr>
</tbody>
</table>

Data are mean±SD.

*P<0.05 by log-rank test (see Table 5 for details).
The territorial extent of perfusion defect was an additional determinant of prognosis (Figure 2). The 3-year event-free survival was 85% in patients with a single-vessel perfusion defect and 56% in patients with multivessel perfusion defects ($P<0.001$). The cumulative event rate for each pattern of abnormality is demonstrated in Table 4. The Kaplan-Meier curves of event-free survival according to the results of WM and MP are illustrated in Figure 3. The 3-year event-free survival was 95% in patients with normal WM and MP, 82% in patients with normal WM but abnormal MP, and 68% in those patients with abnormal WM and MP. This difference in event-free survival was significant between each of the 3 groups. The 3-year cumulative event rate in all patients who had normal WM was estimated to be 7.3%. For the 78% of these patients who also had normal MP, the 3-year cumulative event rate was 4.5%. Therefore, this group had nearly a 3% lower event rate over the three year period when compared with the total population of patients with normal WM studies.

### Incremental Value of WM and MP for Predicting Death and Nonfatal Infarction

Table 5 presents the univariate and multivariate predictors of follow-up events. By univariate analysis, the predictors of events were previous CABG, previous myocardial infarction, resting left ventricular ejection fraction <50%, abnormal WM, and abnormal MP. By multivariate analysis, the only independent predictors of events were hypercholesterolemia (RR, 0.5; 95% CI, 0.3 to 0.9), left ventricular ejection fraction <50% (RR, 1.9; 95% CI, 1.2 to 3.2), and an abnormal MP (RR, 5.2; 95% CI, 3.0 to 9.0). After adjustment for MP, the analysis of WM no longer had predictive value. Although hypercholesterolemia was not a significant univariate predictor, it had a protective effect in the multivariate analysis. One reason was a higher prevalence of hypercholesterolemia in patients with abnormal MP (60%) than in those with normal MP (40%). Assessment of the predictive value of clinical and echocardiographic variables to predict exclusively cardiac events (cardiac death or nonfatal myocardial infarction) showed that the only independent predictor of these events was abnormal MP (RR, 9.0; 95% CI, 3.1 to 26.3; $P<0.0001$). The sensitivity and specificity of MP for the prediction of death or nonfatal MI at 2 years were 72% and 63%, respectively, compared with 54% and 73% for WM analysis.

### Sequential Cox Regression Models

Sequential Cox regression models were fit to test the incremental value of MP analysis over clinical and echocardiographic variables (Figure 4). The presence of left ventric-
ular ejection fraction <50% increased the likelihood of death or nonfatal infarction over the analysis of clinical variables ($\chi^2=8.9; P<0.005$). Abnormal WM at dobutamine stress RTCE increased the $\chi^2$ of 16.3 compared with left ventricular ejection fraction <50% and clinical data ($P<0.001$). However, the addition of abnormal MP to all of these variables added significant incremental value in predicting outcome ($\chi^2=42.7; P<0.001$).

**Discussion**

In this study, we compared the ability of 2 different imaging techniques during dobutamine stress to predict outcome and demonstrated an incremental value of MP imaging over WM analysis in predicting outcome in patients with known or suspected CAD. MP abnormalities were independently predictive of death and nonfatal myocardial infarction. A normal MP response during DSE identified a low-risk patient group with a better outcome than patients with normal WM.

Several studies have demonstrated the prognostic value of WM analysis during DSE.\textsuperscript{3,4,23–29} Our 3-year event-free survival of 7.3% after a negative WM response is similar to what was observed in these studies, in which normal WM responses to dobutamine were associated with annualized mortality rates up to 8% and cardiac event rates up to 3.6%.\textsuperscript{3,4,23–29} Annualized rates of death or nonfatal myocardial infarction after a negative dobutamine sestamibi SPECT have ranged from 0.7% to 1.5%,\textsuperscript{30–32} with higher event rates when outcomes other than death or infarction are included.\textsuperscript{27} In all these studies, disease prevalence varied significantly, which played a major role in positive or negative predictive value of the test. In only 1 study was there a direct comparison of an MP imaging technique (radionuclide SPECT) and WM by echocardiography in the same patients.\textsuperscript{27} In this study, there were no differences in cardiac death (0.6% to 0.7%) or cardiac event rates (3.3% to 3.6%) in patients with normal SPECT versus normal WM responses. However, an abnormal study (WM or MP) was seen in >60% of the patients compared with 41% with normal perfusion and 26% with abnormal WM responses in our study. Thus, at higher disease prevalence rates, the additive predictive value of perfusion over WM in predicting outcome may not be as great as observed in our study.

**Role of MP and WM Imaging With RTCE in Predicting Events**

The present study is the first to evaluate the role of RTCE as a prognostic tool in patients with known or suspected CAD.

![Figure 3](image-url)  
**Figure 3.** Kaplan-Meier curves based on the combination of WM and MP data. Differences between curves are statistically significant ($P<0.001$).

![Figure 4](image-url)  
**Figure 4.** Incremental values (expressed on $y$ axis as $\chi^2$ values with incremental degrees of freedom) of left ventricular ejection fraction (EF), abnormal WM, and abnormal MP over the clinical variables using a Cox model.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate RR (95% CI)</th>
<th>P</th>
<th>Multivariate RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age $&gt;70$ y</td>
<td>1.6 (1.0–2.5)</td>
<td>0.05</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>0.8 (0.5–1.2)</td>
<td>0.27</td>
<td>0.5 (0.3–0.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.7 (0.4–1.1)</td>
<td>0.15</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.1 (0.7–1.7)</td>
<td>0.81</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Previous CABG</td>
<td>2.5 (1.5–4.2)</td>
<td>0.0003</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>2.2 (1.4–3.6)</td>
<td>0.0008</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction &lt;50%</td>
<td>1.9 (0.9–4.2)</td>
<td>&lt;0.0001</td>
<td>1.9 (1.2–3.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Abnormal WM</td>
<td>4.1 (2.6–6.5)</td>
<td>&lt;0.0001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Abnormal MP</td>
<td>5.3 (3.1–9.1)</td>
<td>&lt;0.0001</td>
<td>5.2 (3.0–9.0)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
RTCE has advantages over myocardial scintigraphy, including no irradiation, higher resolution, shorter test duration, immediate availability of results, the ability to perform stress and rest images in the same setting, and the ability to have real-time imaging of both MP and WM.

Studies comparing dobutamine stress RTCE with quantitative angiography have demonstrated a significant improvement in test sensitivity with MP imaging over WM analysis and greater accuracy in identifying multivessel CAD.9,10,33 Therefore, MP imaging during dobutamine stress RTCE appears better than WM analysis at identifying the amount of myocardium at risk, a marker that consistently outperforms other variables in predicting hard event rates.34,35 This was affirmed in our study in that patients with a multivessel pattern of perfusion abnormalities had the lowest event-free survival of all patients in the study.

Despite the incremental value of MP imaging during RTCE, our study indicates that assessing both WM and MP during dobutamine stress is helpful in determining risk. First, the Cox sequential regression model indicated that both WM and MP analyses added significant value to the prediction of outcome. Second, patients with both WM and MP abnormalities had the worst prognosis, indicating improved specificity for the prediction of events when results of both techniques are abnormal.

Using RTCE to evaluate WM and MP is a recently developed technique; interpretation of results requires some degree of expertise. MP was based on the analysis of myocardial contrast enhancement after bolus injection of contrast agents, which reflects the myocardial blood volume. Although the analysis of microbubble kinetics using destruction-replenishment sequences during a continuous infusion of contrast permits the analysis of myocardial blood flow changes,11,36 we have previously demonstrated that the analysis of myocardial blood volume with RTCE during dobutamine stress is highly feasible and accurate for detecting angiographically significant CAD.9,10 Because WM during RTCE is analyzed at frame rates of 25 to 30 Hz, more subtle WM abnormalities like tardoekinesis may not have been identified at these frame rates.37

However, the contrast-enhanced WM analysis performed in our study has the advantage of permitting a better delineation of endocardial borders and detection of WM abnormalities. Contrast-enhanced WM scoring has been demonstrated to be superior to non–contrast-enhanced WM compared with MRI.18,19 We have recently compared the ability of WM analysis with high-mechanical-index harmonic imaging at frame rates >60 Hz without contrast against low-mechanical-index RTCE with intravenous ultrasound contrast during DSE to detect >50% diameter stenoses.38 In this study, the sensitivity of the 2 WM analysis methods were not significantly different (33% without contrast, 40% with contrast). The sensitivities of both WM techniques in this pilot study were 30% lower than MP imaging.

Study Limitations
We censored patients who underwent revascularization after the stress testing. Although we may have eliminated patients who were more likely to have events, most of these patients had abnormal MP and were evenly distributed between those with normal WM and those with abnormal WM. Therefore, the error incurred by not including these patients would have to underestimate the predictive value of assessing MP during dobutamine stress RTCE.

Although abnormal MP during dobutamine stress echocardiography was the most significant independent predictor of events, hypercholesterolemia and reduced ejection fraction were significant predictors as well. The prognostic importance of ejection fraction is well known. The reason for the association of hypercholesterolemia with reduced risk of events is unclear. Although hyperlipidemia was not a significant univariate predictor, it had a protective effect in the multivariate analysis. This phenomenon appears to have occurred because there was a higher prevalence of hypercholesterolemia in patients with normal MP (60%) than in those with normal MP (40%), resulting in a confounding of the univariate comparison. Also, because we defined hypercholesterolemia to include patients who were on lipid-lowering agents, the protective benefits of these agents in patients with abnormal MP may have resulted in a proportionately better outcome in the patients with abnormal MP studies.

Finally, our results are based on the analysis of studies in a single center. Larger multicenter studies are necessary to address the feasibility and reproducibility of this technique.

Conclusions
MP analysis during dobutamine stress RTCE provides independent information for predicting mortality and nonfatal myocardial infarction in patients with known or suspected CAD after adjustment for clinical data, ejection fraction, and WM analysis. The extent of perfusion defects predicts outcome. Patients with abnormal WM and MP are at higher risk for hard events. A normal MP study is associated with better survival than a normal WM study.

Disclosure
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