Safety of Dobutamine Stress 
Real-Time Myocardial Contrast Echocardiography

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OBJECTIVES

The aim of this study was to determine the safety of dobutamine stress myocardial perfusion imaging (MPI) obtained by real-time contrast echocardiography (RTCE) and intravenous ultrasound contrast in a large cohort of patients with suspected coronary artery disease (CAD).

BACKGROUND

Despite the increasing number of studies showing the potential clinical utility of myocardial contrast perfusion imaging with commercially available contrast agents, the safety of this technique in a clinical setting has not been demonstrated.

METHODS

Over a four-year period, 1,486 patients underwent dobutamine stress RTCE with low mechanical index pulse sequence schemes after intravenous injections of commercially available contrast agents (35% Definity, Bristol Myers Squibb Medical Imaging Inc., North Billerica, Massachusetts; 65% Optison, GE-Amersham, Princeton, New Jersey). The hemodynamic and adverse effects of RTCE were compared with 1,012 patients who underwent conventional dobutamine stress echocardiography (DSE) without contrast. The feasibility of image analysis was defined as the ability to analyze MPI in at least two of the three standard segments in each left ventricular wall.

RESULTS

No myocardial infarction or death occurred during dobutamine stress. There was no difference in the incidence of nonsustained ventricular tachycardia, sustained ventricular tachycardia, or supraventricular tachycardia during dobutamine infusion between RTCE and DSE. Myocardial perfusion imaging was considered feasible for analysis in 94% of the walls at baseline and 95% at peak stress. The anterior, lateral, and posterior walls were the most common regions in which MPI was not feasible. Myocardial perfusion imaging with RTCE had a higher accuracy for detecting patients with angiographically significant CAD than the analysis of wall motion (84% vs. 66%, respectively; p < 0.001).

CONCLUSIONS

Dobutamine stress RTCE appears to be a safe and feasible technique for evaluating patients with known or suspected CAD. (J Am Coll Cardiol 2005;45:1235–42) © 2005 by the American College of Cardiology Foundation

Dobutamine stress echocardiography (DSE) is a widely used technique for the assessment of patients with known or suspected coronary artery disease (CAD). Over the last 10 years, several studies have confirmed its safety and effectiveness for the diagnostic and prognostic evaluation of different patient populations (1–4). Myocardial contrast echocardiography has been proven useful for the assessment of myocardial perfusion after intravenous injections or infusions of ultrasound contrast agents (5,6). Real-time contrast echocardiography (RTCE) is a recently developed technique that utilizes a low mechanical index causing minimal microbubble destruction (7–9). Real-time contrast echocardiography is particularly advantageous over intermittent harmonic imaging techniques when the simultaneous evaluation of myocardial perfusion imaging (MPI) and wall motion is necessary, such as during DSE. The analysis of MPI with RTCE has been shown, in studies with relatively small numbers of patients, to improve the sensitivity of DSE in detecting significant CAD (7,10).

However, the Food and Drug Administration (FDA) has not formally approved the use of intravenous ultrasound contrast agents to detect myocardial perfusion, and recent studies have raised concerns regarding unwanted bioeffects related to ultrasound-induced microbubble destruction (11–13). Specifically, during DSE, there may be concerns about potentiation of cardiac arrhythmias. The aims of this study were to determine the safety of dobutamine stress RTCE in a large number of patients with suspected or known CAD and to compare the safety profile of RTCE with the conventional DSE profile.

METHODS

Patients. From January 2000 to January 2004 we studied 2,498 patients with known or suspected CAD referred for a dobutamine stress test. Among them, 1,486 patients underwent RTCE with the analysis of wall motion and MPI after intravenous injections of commercially available contrast agents at rest and during dobutamine stress. The analysis of data from these studies was approved by the Institutional Review Board of the University of Nebraska Medical Center, and all patients gave informed consent to participate. The exclusion criteria observed were: age <18 years, hemodynamic instability, unstable angina, recent myocar-
Abbreviations and Acronyms

CAD = coronary artery disease
DSE = dobutamine stress echocardiography
FDA = Food and Drug Administration
LV = left ventricular
MPI = myocardial perfusion imaging
PVC = premature ventricular complexes
RTCE = real-time contrast echocardiography
WMA = wall motion abnormalities

dial infarction, and contraindications to any drug used in the protocol (14). The incidence of arrhythmias, adverse effects, and hemodynamic data of these 1,486 patients were compared with those of 1,012 patients who underwent conventional DSE without contrast agents in the same time period at our institute. The selection of patients to undergo contrast versus noncontrast DSE studies was based on the preference and experience of the attending physician, and not on a patient’s pre-test probability for CAD or echocardiographic windows. The clinical characteristics of both groups are described in Table 1.

Study protocol. For all stress protocols, patients were generally instructed to discontinue beta-blockers at least 24 h before the stress test. Dobutamine was infused intravenously at a starting dose of 5 \( \mu \)g/kg/min, followed by increasing doses of 10, 20, 30, 40, up to a maximal dose of 50 \( \mu \)g/kg/min, in 3- to 5-min stages (2). Atropine (up to 2.0 mg) was injected in patients without symptoms or signs of myocardial ischemia not achieving 85% of the age-predicted maximal heart rate, calculated as 220 – age in years. The contrast agents used were the commercially available albumin-encapsulated microbubble Optison (GE-Amersham, Princeton, New Jersey) or the lipid-encapsulated microbubble Definity (Bristol-Myers Squibb Medical Imaging Inc., North Billerica, Massachusetts). The doses of contrast used for the assessment of MPI were the same doses recommended for enhancement of the left ventricular (LV) border delineation during stress testing (15). Optison was injected in bolus doses of 0.2 to 0.3 ml and Definity in a bolus of 0.1 ml, followed by a 3 to 5 ml saline flush.

Blood pressure and cardiac rhythm were monitored continuously before and during the dobutamine infusion. Twelve-lead electrocardiograms were obtained at three-min intervals. End-points of the stress test were: achievement of the target heart rate (85% of predicted maximal heart rate), maximal dobutamine/atropine doses, development of severe or extensive wall motion abnormalities (WMA), ST-segment elevation >0.1 mV at an interval of 80 ms after the J point in non-Q-wave leads, sustained arrhythmias, severe chest pain, or intolerable side effects (14). The tests were considered diagnostic if the target heart rate and/or an ischemic end point were achieved (WMA or perfusion defects). The tests were considered nondiagnostic if the patient failed to achieve the target heart rate without inducible ischemia.

Image acquisition. Real-time contrast echocardiography was performed using the commercially available ultrasound scanners HDI 5000 in 868 (58%) patients (Philips Medical Systems, Bothell, Washington), Sonos 5500 in 381 (26%) patients (Philips Medical Systems), or Sequoia 6.0 in 237 (16%) patients (Siemens Acuson, Mountain View, California). Each was equipped with low mechanical index real-time pulse sequence schemes, which deploy pulses of alternating polarity and/or amplitude. Each system was adjusted to achieve optimal nonlinear signal at a mechanical index \( \leq 0.3 \) and frame rate \( \geq 25 \) Hz. Time gain compensation and two-dimensional gain settings were adjusted to suppress any nonlinear signals from tissue before contrast injection. Equipment settings were then kept unchanged throughout the study. Contrast-enhanced images were obtained in the apical four-chamber, two-chamber, and three-chamber views at baseline, at low doses of dobutamine if resting WMA were present, at intermediate stage when 70% of the predicted maximal heart rate was achieved, and at peak stress as previously defined. The RTCE images were digitally acquired after peak myocardial opacification until disappearance of contrast from the myocardium. No high mechanical index frames (mechanical index >0.6) were applied when myocardial contrast was present.

In the conventional DSE without contrast protocol, two-dimensional images were obtained with the same ultrasound machines using second-harmonic imaging at a high mechanical index. The standard echocardiographic views (parasternal long and short axis, apical four-, two-, and three-chamber) were acquired at the same stages as described in RTCE. All images were recorded on videotape and digitized in continuous loop format for side-by-side analysis.

Image analysis. Both the contrast-enhanced wall motion and the myocardial perfusion were evaluated during the dobutamine stress RTCE by an experienced observer. The left ventricle was divided in 17 segments according to the

<p>| Table 1. Patient Demographics in the RTCE and in the Conventional DSE |
|--------------------------|--------------------------|</p>
<table>
<thead>
<tr>
<th>Variables</th>
<th>RTCE (n = 1,486)</th>
<th>DSE (n = 1,012)</th>
</tr>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>62 ± 14</td>
<td>63 ± 13</td>
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<tr>
<td>Male gender</td>
<td>756 (51%)</td>
<td>431 (43%)*</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>87 ± 23</td>
<td>86 ± 23</td>
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<tr>
<td>Diabetes mellitus</td>
<td>508 (34%)</td>
<td>263 (26%)*</td>
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<tr>
<td>Dyslipidemia</td>
<td>669 (45%)</td>
<td>493 (49%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>933 (63%)</td>
<td>702 (69%)*</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>499 (34%)</td>
<td>315 (31%)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>220 (15%)</td>
<td>109 (11%)*</td>
</tr>
<tr>
<td>Previous coronary bypass surgery</td>
<td>162 (11%)</td>
<td>81 (8%)*</td>
</tr>
<tr>
<td>Previous percutaneous coronary intervention</td>
<td>166 (11%)</td>
<td>108 (11%)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>633 (43%)</td>
<td>430 (42%)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>308 (21%)</td>
<td>202 (20%)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>199 (13%)</td>
<td>127 (12%)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>60 ± 11</td>
<td>59 ± 10</td>
</tr>
</tbody>
</table>

Data are mean ± SD and number (%) of patients. *p < 0.05 between groups.

DSE = dobutamine stress echocardiography; RTCE = real-time contrast echocardiography.
recommendations of the American Society of Echocardiography (16). Myocardial perfusion imaging was analyzed during a 15-s period that typically appeared after each contrast injection. Using the wall motion criteria, the test was defined as positive if there were new or worsening of pre-existing WMA in ≥2 contiguous segments (14). The MPI results were considered abnormal if ≥2 contiguous segments failed to exhibit contrast enhancement (subendocardial or transmural) at peak stress when compared with other segments at the same depth in the same view, as well as compared with contrast enhancement in the same segments at baseline using a side-by-side image analysis. Patients with normal wall motion both at baseline and at peak stress were classified as having a negative study for WMA. Patients with normal wall motion at baseline and new WMA at peak stress were classified as having inducible WMA. Patients with WMA at baseline that did not change throughout dobutamine infusion were classified as having fixed WMA. Those studies in which there were resting WMA that did not change but in which new WMA in other segments did occur during dobutamine infusion were characterized as having fixed plus inducible WMA. The classification of normal, inducible, fixed, and fixed plus inducible MPI abnormalities was performed using the same criteria as for WMA. The interobserver agreement for the interpretation of perfusion with RTCE in our laboratory is 84% (Kappa = 0.63) and 91% for wall motion analysis (Kappa = 0.64) (7).

Safety of RTCE. The adverse effects that occurred during dobutamine stress were evaluated in patients who received RTCE with Optison, RTCE with Definity, and the conventional DSE without contrast. The presence of premature ventricular complexes (PVC), premature supraventricular complexes, and any other cardiac arrhythmias was determined by reviewing the 12-lead electrocardiograms of all patients acquired at baseline and during each stage of dobutamine infusion. Hypotension was defined as a fall of systolic blood pressure below 80 mm Hg or a reduction ≥40 mm Hg from baseline. A hypertensive response was defined as blood pressure ≥230/120 mm Hg (1). Minor adverse effects were defined as those that were self-limiting, which responded promptly to dobutamine infusion interruption or metoprolol administration, and did not require hospital admission, whereas major adverse effects were defined as those that led to a new hospital admission as well as death and myocardial infarction (2).

Diagnostic accuracy of RTCE. The diagnostic accuracy of both the wall motion analysis and MPI obtained by RTCE for detecting CAD was determined in 249 patients who underwent coronary angiography within one month of the stress test. Wall motion and MPI were analyzed on a coronary artery territory basis by one independent reviewer who was blinded to the results of the angiogram. Coronary angiography was performed at the discretion of the referring physician. Patients with an intervening cardiac event were excluded from this analysis. Quantitative coronary angiographic analysis was performed by an experienced interventional cardiologist unaware of the results of RTCE. Any visually evident stenosis was measured using a hand-held electronic caliper (Tesa S.A., Renes, Switzerland) operated with custom-developed PC software (17). Measurements were expressed as the percent diameter narrowing using the diameter of the nearest normal-appearing region as the reference. Significant CAD was defined as ≥50% luminal diameter stenosis in ≥1 major coronary artery.

Feasibility of RTCE image interpretation. The feasibility of MPI image interpretation was determined for each LV wall and for each coronary artery territory (left anterior descending, left circumflex, and right coronary artery territories) in 524 randomly chosen patients (35% of the entire population). Feasibility was determined by an experienced observer blinded to the initial test results. Attenuation from contrast or lung interference was defined as present if the endocardial and epicardial borders of a segment could not be visualized and, thus, were not distinguishable from surrounding tissues (7).

Analysis of MPI was deemed feasible in a wall if myocardial contrast enhancement was analyzable in at least two of three segments of each wall (septal, lateral, inferior, anterior, posterior, and anteroseptal walls). For the purpose of coronary artery territory analysis, the LV apex, the anteroseptal, and the anterior walls were attributed to the left anterior descending artery. The lateral and posterior walls were assigned to the left circumflex artery territory. The inferior and basal to mid segments of the septum were assigned to the right coronary artery territory. Myocardial perfusion imaging was considered feasible in the coronary artery territory when at least one of the walls could be analyzed for MPI according to the previously described criteria.

Statistical analysis. Continuous variables were expressed as mean and standard deviation, and categorical variables as proportions. Two-tailed unpaired and paired Student t tests were used for inter- and intragroup comparisons, respectively. Chi-square test was used for comparisons of proportions. Analysis of variance was used to compare hemodynamic data between RTCE with Optison, RTCE with Definity, and DSE. The sensitivity, specificity, predictive values, and accuracy of wall motion and MPI for detecting angiographically significant CAD were calculated according to standard definitions and were presented with their respective 95% confidence intervals. All data analysis was performed with SPSS 11.0 for Windows (SPSS Inc. Chicago, Illinois). A p value <0.05 was considered significant.

RESULTS

Among the 1,486 patients who underwent RTCE, Optison was used in 963 (65%) patients using a mean cumulative dose of 2.8 ± 0.8 ml. Definity was used in the remaining 523 (35%) patients using a mean cumulative dose of 1.0 ± 0.3 ml. The mean peak dose of dobutamine was 32 ±
8 μg/kg/min. Atropine was injected in 1,240 (83%) patients using a mean cumulative dose of 0.8 ± 0.6 mg. Patient weight and body habitus were similar between RTCE and conventional DSE groups (Table 1).

The analysis of both wall motion and MPI by RTCE was completed in 1,351 (91%) patients, whereas it was considered nondiagnostic in 135 patients. This was due to failure to reach the target heart rate in 110 (7%) patients, and failure to achieve myocardial contrast enhancement in 25 (2%) patients.

Among the 1,351 patients with diagnostic dobutamine stress RTCE, 1,046 (77%) patients had no WMA, 159 (12%) had inducible WMA, 85 (6%) had fixed WMA, and 61 (5%) had fixed plus inducible WMA. When analyzing MPI, 861 (64%) patients had no myocardial perfusion defects, 351 (26%) had inducible myocardial perfusion defects, 49 (4%) had fixed myocardial perfusion defects, and 90 (6%) had fixed plus inducible myocardial perfusion defects. Myocardial perfusion imaging was abnormal in a higher number of patients than WMA, as illustrated in Figure 1. Inducible defects within at least one coronary artery territory were identified in 32% of patients by MPI and 17% by WMA (p < 0.01). All patients with WMA during dobutamine stress also exhibited perfusion defects by RTCE.

In the conventional DSE without contrast group, the doses of dobutamine and atropine used were 33 ± 8 μg/kg/min (p = NS vs. RTCE) and 0.6 ± 0.5 mg (p = 0.001 vs. RTCE), respectively. The conventional DSE tests were diagnostic in 922 (91%) patients. There were 90 (9%) patients in which the DSE was nondiagnostic, mainly due to failure to achieve target heart rate. Among the 922 patients with diagnostic DSE without contrast, 769 (83%) had no WMA, 68 (8%) had inducible WMA, 59 (6%) had fixed WMA, and 26 (3%) had fixed plus inducible WMA.

Safety. Table 2 summarizes the hemodynamic profile observed in the patients who underwent RTCE with Optison, RTCE with Definity, and conventional DSE. The groups reached a similar percentage of predicted maximal heart rate at peak stress, and there were no differences in the heart rate, blood pressure, or rate-pressure product between RTCE and DSE at peak stress.

The incidence of arrhythmias and other adverse effects were similar between the groups (Table 3). Only five (0.3%) patients in RTCE and three (0.2%) patients in DSE had ventricular tachycardia that required dobutamine interruption and metoprolol injection. The proportion of patients with sustained arrhythmias, which included sustained ventricular tachycardia, atrial fibrillation/flutter, and supraventricular tachycardia, was similar in RTCE with Optison (4.2%), RTCE with Definity (4.0%), and conventional DSE without contrast (3.6%). The groups had similar incidences of hypotension, hypertension, and dyspnea. Chest pain at peak dobutamine stress occurred with equal frequency in both the abnormal and normal RTCE and conventional DSE studies. No myocardial infarction or death during dobutamine stress occurred in either group.

Diagnostic accuracy of RTCE. As has been described previously (10), MPI improved the sensitivity, negative predictive value, and accuracy for the detection of CAD when compared with WMA. The specificity of MPI was lower than WMA. An abnormal MPI study correctly identified 173 of the 180 patients with CAD by quantitative coronary angiography and failed to identify 7 of them. On the other hand, MPI was negative in 35 patients without angiographically significant CAD and positive in 34 patients. A positive wall motion study correctly identified 115 of the 180 patients with CAD by quantitative coronary angiography and failed to identify 65. Wall motion analysis was negative in 50 patients without CAD and was positive in 19. There were 58 patients (32%) with CAD who had no WMA and a positive MPI. The diagnostic accuracies of WMA and MPI for the detection of angiographically significant CAD are shown in Table 4.
Feasibility of RTCE image interpretation. Among the 524 patients randomly chosen for determining the feasibility of MPI, a total of 3,144 walls were evaluated both at baseline and during dobutamine stress. The analysis of contrast-enhanced wall motion by RTCE was considered feasible in all these LV walls. Myocardial perfusion imaging was deemed feasible in 2,949 (94%) walls and not feasible in 171 (5%) walls. Interpretation of perfusion was not feasible in the lateral wall in 46 patients (9%), the anterior wall in 40 patients (8%), the posterior wall in 36 patients (7%), the inferior wall in 26 patients (5%), the anteroseptal wall in 24 (5%), and the septum in 23 patients (4%). At peak stress, MPI was feasible in 2,973 (95%) walls and not feasible in 171 (5%) walls. Interpretation of perfusion was not feasible in the lateral wall in 39 patients (7%), the anterior wall in 36 patients (7%), the posterior wall in 30 patients (6%), the inferior wall in 24 patients (5%), the anteroseptal wall in 22 (4%), and the septum in 20 patients (4%). The distribution of walls that were not feasible is illustrated in Figure 2. The anterior, lateral, and septum were the most common walls in which MPI was not feasible both at baseline and peak stress.

Among the 1,572 coronary artery territories analyzed, MPI was deemed feasible in 1,484 (94%) and not feasible in 88 territories (6%) at baseline. The left anterior descending coronary artery territory had the highest feasibility of interpretation (96% of patients), whereas the left circumflex territory was feasible in 94% of patients and the right coronary artery territory in 94% of patients. At peak stress, 1,496 (95%) of coronary artery territories were deemed feasible and 76 (5%) territories were not feasible. The feasibility was 96% for the left anterior descending coronary artery, 94% for left circumflex, and 95% for right coronary artery territories. There was no significant difference in the feasibility of MPI interpretation between baseline and stress conditions.

### DISCUSSION

Real-time contrast echocardiography has the potential to image myocardial perfusion and wall motion simultaneously after intravenous injections of ultrasound contrast agents at the same doses approved by the FDA for LV opacification. Recent studies have found that MPI with RTCE is a useful technique for the detection of CAD during both dobutamine and dipyridamole stress testing (7,9,10). Neverthe-
less, contrast agents are not yet approved by the FDA for the evaluation of myocardial perfusion, and data regarding the safety of MPI with dobutamine stress RTCE have been limited. Therefore, in the current study we assessed the safety and feasibility of MPI in a large number of patients who underwent dobutamine stress RTCE. With this low mechanical index imaging technique, we did not observe an increased incidence of adverse complications, and the feasibility for regional evaluation of myocardial perfusion was >90% both at baseline and at peak stress.

**Incidence of adverse effects during dobutamine stress.** We observed that the incidence of arrhythmias and other minor adverse effects with RTCE was similar to that observed in patients examined during the same period with conventional DSE. The lack of increased propensity for arrhythmias using RTCE in conjunction with dobutamine stress might be related to the lower mechanical index used for imaging microbubbles, which is known to reduce the risk for cavitation. The bioeffects of microbubble cavitation by ultrasound scanning have been shown in vitro and in vivo (11,18,19). There is some evidence that the intravenous injection of contrast agents is associated with induction of premature ventricular depolarizations when using a high mechanical index ultrasound scan. One study using intravenous contrast agents has reported an increased number of PVC when applying end-systolic–triggered imaging at a mechanical index of 1.5 (13). The induction of arrhythmias was related to both the dose of contrast agent and the acoustic pressure studied. Although we gave intravenous bolus injections of microbubbles that create transient high concentrations of microbubbles in the LV cavity and imaged throughout the cardiac cycle, the low mechanical index pulse sequence scheme (<=0.3) did not produce a significant increase in PVC. The most likely reason for this was the lower number of microbubbles being destroyed at this mechanical index.

It is possible that one would see a greater incidence of arrhythmias had we used a higher mechanical index impulse during the catecholamine stress in this situation (20). To date, there are no data showing this with dobutamine. However, high mechanical index–triggered ultrasound scanning has been used with vasodilator stress without an increased incidence of arrhythmias. Raisinghani et al. (21) reported no increase in the number of PVC in patients undergoing imaging with triggered ultrasound scanning at a high mechanical index during dipyridamole stress.

The other adverse effects of dobutamine stress are related to the intense sympathomimetic stimulation. These include hypertension, chest pain, and shortness of breath. The incidence of these side effects was also not higher in the presence of intravenous ultrasound contrast agents when compared with the conventional DSE protocol. Although there have been concerns about myocardial necrosis being induced by ultrasound–mediated microbubble destruction, we did not observe any increased incidence of chest pain in the abnormal studies, and there was no incidence of myocardial infarction or death.

**Table 4. Diagnostic Parameters of MPI and WMA by RTCE for Detecting Angiographically Significant Coronary Artery Disease**

<table>
<thead>
<tr>
<th></th>
<th>WMA</th>
<th>MPI</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>115/180; 64% (57%–71%)</td>
<td>173/180; 96% (93%–99%)*</td>
</tr>
<tr>
<td>Specificity</td>
<td>50/69; 72% (62%–83%)</td>
<td>35/69; 51% (39%–63%)*</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>115/134; 86% (80%–92%)</td>
<td>173/207; 84% (79%–89%)*</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>50/115; 43% (60%–72%)</td>
<td>35/42; 83% (78%–88%)*</td>
</tr>
<tr>
<td>Accuracy</td>
<td>165/249; 66% (60%–72%)</td>
<td>208/249; 84% (79%–88%)*</td>
</tr>
</tbody>
</table>

Results are number; percent of patients (corresponding 95% confidence intervals). *p < 0.05 compared to wall motion abnormalities (WMA).

MPI = myocardial perfusion imaging; other abbreviations as in Table 1.

**Figure 2.** Distribution of the left ventricular walls in which the myocardial perfusion imaging was considered not feasible both at baseline and at peak stress. The lateral, anterior, and posterior walls were the most frequently considered as not feasible.
Feasibility of MPI image interpretation. Our results show that RTCE was able to assess myocardial perfusion in 95% of LV walls during dobutamine infusion and 94% under resting conditions. Because of the lateral resolution of the ultrasound beam, the lateral wall was the most common wall in which the analysis of MPI was considered not feasible. Furthermore, the basal segments of LV walls are more susceptible to have contrast attenuation or poor contrast signal. For this reason, when only these segments were not adequately evaluated, we used the contrast enhancement in the mid and apical segments to perform the analysis of MPI in that specific ventricular wall. Using this methodology, feasibility was high, and diagnostic accuracy was excellent.

The use of intravenous contrast agents has been shown to improve the assessment of segmental wall motion and interobserver agreement by enhancing the endocardial border delineation (22,23). Because RTCE permits the analysis of both wall motion and perfusion, the injection of contrast agents during RTCE should also assist in detecting WMA. Hundley et al. (24) have shown that the analysis of lateral wall during stress was possible in 81% of cases without contrast, and this rate increased to 99% after the addition of contrast for endocardial border delineation. We also found that the analysis of wall motion was feasible in all walls in the presence of contrast.

Study limitations. Recently, the combination of intravenous contrast agents and RTCE with application of high mechanical index impulses for microbubble destruction followed by myocardial replenishment has allowed for the quantification of myocardial blood flow (9,25). The effect of these high mechanical index impulses on the incidence of arrhythmias was not addressed in our study.

Because the coronary angiography was performed at the discretion of the referring physician, we do recognize that the diagnostic accuracy of RTCE was evaluated in a biased group of patients. The results of the stress test probably influenced the indication for coronary angiography, resulting in the observed high prevalence of CAD in our study population. Although we have shown that perfusion assessed with RTCE has improved sensitivity in this selected group of patients, larger prospective studies will be required to examine both the diagnostic accuracy and prognostic value of MPI over wall motion analysis during DSE.

CONCLUSIONS

Dobutamine stress RTCE is a safe and feasible test for the evaluation of patients with known or suspected CAD. In a large patient population, we observed no increased incidence of major side effects or arrhythmias when using intravenous ultrasound contrast and low mechanical index real-time perfusion imaging. Myocardial perfusion imaging during RTCE, therefore, may add incremental value in detecting CAD without increasing risk.

REFERENCES