Risk Stratification With Electrocardiographic-Gated Dobutamine Stress Technetium-99m Sestamibi Single-Photon Emission Tomographic Imaging

Value of Heart Rate Response and Assessment of Left Ventricular Function

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OBJECTIVES The purpose of this research was to evaluate the significance of heart rate response to dobutamine and the assessment of left ventricular (LV) function during risk stratification of patients undergoing dobutamine stress myocardial perfusion imaging (DSMPI).

BACKGROUND Dobutamine stress myocardial perfusion imaging has been shown to effectively risk stratify highly selected patients. However, based on perfusion alone, patients with normal and abnormal tests have twice the risk as comparable patients with exercise testing. The added value of assessment of LV function and the heart rate response to dobutamine in risk stratification of these patients is unknown.

METHODS Follow-up information (cardiac death or non-fatal myocardial infarction) was obtained on 1,367 consecutive patients who underwent DSMPI due to inability to perform adequate exercise and contraindications to vasodilators. Perfusion images were interpreted using a 17-segment model. Abnormal perfusion and function were defined as: summed stress score ≥4 and ejection fraction <50%, respectively.

RESULTS Annualized event rates (AERs) were related to the extent/severity of perfusion defects and worsening LV function. A three-risk category model was constructed from combined assessment of perfusion and function, with AERs of 2.4% (both normal), 5.8% (discordant), and 11.3% (both abnormal); p < 0.001. Stress electrocardiogram (ECG) data added incremental value to myocardial perfusion alone but not to combined assessment of perfusion and function. Importantly, inability to achieve 85% of mean predicted heart rate was associated with worse outcomes and was an independent predictor of cardiac events. For patients in whom perfusion, function, and stress ECG response were normal, inability to achieve target heart rate was associated with significantly higher AER (1.5% vs. 3.4%, respectively, p = 0.021).

CONCLUSIONS In highly selected patients undergoing DSMPI, assessment of perfusion and function is effective in risk stratification. The stress ECG and heart rate response to dobutamine have prognostic value and should be incorporated into image interpretation so as to maximize risk stratification. (J Am Coll Cardiol 2006;47:781–8) © 2006 by the American College of Cardiology Foundation

Pharmacologic stress myocardial perfusion imaging (MPI) is an excellent alternative for the evaluation of patients with known or suspected coronary artery disease (CAD) who are unable to perform adequate exercise. In general, vasodilator stress is the first choice while dobutamine is reserved for patients with contraindications. While the diagnostic accur-
Outcome (9,10). Efforts to maximize risk stratification with stress MPI have been directed towards incorporation of functional data from electrocardiogram (ECG)-gated single-photon emission computed tomography (SPECT) (11,12) as well as ECG response (8,13). Moreover, identification of the presence and extent of CAD with DSMPI may require, at least in part, an adequate heart rate response (14). To our knowledge, there are no data examining either the importance of heart rate response with DSMPI or incorporation of functional data from ECG-gated SPECT in risk stratification. Therefore, the purpose of this study was to examine the prognostic value of heart rate and ECG response to dobutamine and the utility of combined assessment of perfusion and function by ECG-gated SPECT imaging for risk stratification of a highly selected population.

METHODS

Patient selection. A total of 1,429 consecutive patients underwent dobutamine Tc-99m sestamibi SPECT imaging between October 1995 to November 2002, at Hartford Hospital, Hartford, Connecticut, or Rhode Island Hospital, Providence, Rhode Island, for clinical indications. The main indications were symptoms in patients with suspected CAD (76%), symptoms in patients with known CAD (11%), pre-operative evaluation (5%), and miscellaneous (congestive heart failure [CHF], abnormal ECG, and so on) in 8%. At both institutions, DSMPI was reserved for patients unable to perform adequate exercise and with contraindications to vasodilators. Of those patients, 62 underwent coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting) within 90 days of DSMPI and were excluded from analysis. The remaining 1,367 patients formed the study group (mean age, 67.9 ± 12.4 years). The study protocol was approved by the institutional review board committees of both institutions.

Dobutamine stress test. All patients underwent either a one- or two-day rest and stress Tc-99m sestamibi SPECT imaging protocol. Dobutamine was administered in incremental doses, beginning with 5 μg/kg/min and increased every 3 min through stages at 10, 20, 30, and 40 μg/kg/min. Intravenous atropine and/or arm exercise was added if the target heart rate (THR) (85% of the maximum predicted heart rate [MPHR]) was not achieved at the peak dose. A positive ECG response was defined as ST-segment elevation or ST-segment depression >0.1 mV at 80 ms after the J point. For patients undergoing a two-day stress/rest protocol, 25 to 40 mCi of Tc-99m sestamibi was used for each SPECT study, while for patients undergoing a one-day protocol, 10 to 15 mCi of Tc-99m sestamibi was injected for rest and 30 to 45 mCi for stress imaging; SPECT acquisition was begun 30 to 60 min after stress injection.

Image acquisition. All images were acquired using dual- or single-headed SPECT gamma cameras (Phillips Medical Systems, Milpitas, California). Sixty-four projections (25 s/projection at rest; 20 s/projection at stress) with Tc-99m sestamibi were obtained in a 180° semicircular arc extending from the 45° right anterior oblique to the 45° left posterior oblique plane. All projection images were stored in a 64 × 64 × 16 matrix. Images were processed using a low-pass Butterworth filter with a frequency cutoff of 0.66 cycles/pixel and an order of 5 for reconstruction of the transaxial slices to a thickness of 6.6 mm. Azimuthal definition (from apex to base or anterior to posterior) was obtained from the mid-transverse and sagittal slices for reconstruction of the short-axis and vertical long-axis slices. No preprocessing filtration or attenuation correction was used.

Image interpretation. All SPECT images were interpreted by a consensus of three experienced nuclear cardiologists without knowledge of patient identity or clinical history. For assessment of myocardial perfusion, the left ventricle (LV) was divided according to the American Society of Nuclear Cardiology/American College of Cardiology/American Heart Association recommended 17-segment model (15). All segments were scored for regional perfusion using a 5-point scale (0 = normal photon activity, 1 = mild, 2 = moderate, 3 = severe reduction in photon activity, 4 = absent photon activity). A summed stress score (SSS) and summed rest score (SRS) were obtained by adding the scores of all segments at stress and rest, respectively. A summed difference score (SDS) was calculated as the difference between the SSS and SRS. Based on the SSS, perfusion images were classified as normal (score 0 to 3) or abnormal (score ≥4). Abnormal images were further classified based on SDS: either with a predominantly fixed defect for a score of ≤2 or with a reversible defect for a score of >2. In addition patients were also stratified as low- (SSS 0 to 3), intermediate- (SSS 4 to 8), or high-risk (SSS >8) for subsequent cardiac events. Left ventricular ejection fraction (LVEF) was obtained automatically from the QGS software as described by Germano et al. (16) and confirmed visually for accuracy. Left ventricular function was considered preserved for ejection fraction ≥50% or impaired for LVEF <50%. Impaired LV...
function was further classified as mild to moderately impaired (LVEF 30% to 49%), or severely impaired (<30%).

Follow-up. Individuals blinded to the patient’s test results performed patient follow-up using scripted telephone interviews and mailed questionnaires. Events were defined as cardiac death or non-fatal myocardial infarction and were confirmed by reviews of death certificates, hospital charts, physician records, and appropriate laboratory test results.

Statistical analysis. Patient demographics were expressed as mean ± SD or as proportions. Intergroup comparisons were made using a two-tailed unpaired Student t test for continuous variables and the chi-square test for discrete variables. All p values <0.05 were considered significant. Univariate analyses of hard cardiac event-free (cardiac death or non-fatal myocardial infarction) survival curves were performed using the Kaplan-Meier procedure and compared by means of the log-rank test. Significant variables evaluated in the univariate analysis were entered into a Cox proportional hazards regression model. A backward stepwise selection procedure, with variable removal based on the Wald statistic probability, was performed, with variables entered into the model with a p ≤ 0.10 and removal with a p ≥ 0.05.

RESULTS

Dobutamine stress data. The THR (≥85% of maximum predicted for age) was not reached in 445 (32.5%) patients. The reasons for termination of stress tests in these patients were end of protocol (i.e., after maximum doses of dobutamine and atropine were given) in 75%, worsening symptoms in 16%, hypotension in 4%, worsening ECG changes in 3%, and arrhythmias in 2%. The prior use of beta-blockers was significantly related to the inability to reach the THR (42% of patients not reaching THR received a beta-blocker drug vs. 23% of patients who reached THR, p < 0.01). Dobutamine stress MPI was considered non-diagnostic for patients who did not achieve THR (in absence of symptoms or ECG changes), but had normal perfusion images.

Follow-up. The mean follow-up period was 25 ± 15.2 months and was complete in 97.8% of the 1,367 patients. There were 78 cardiac deaths and 47 non-fatal myocardial infarctions in the follow-up period. Patients who had cardiac events were older, more likely to be women, and more likely to have diabetes, prior history of myocardial infarction, CHF, and prior revascularization as compared to those who did not have events (Table 1). Otherwise, the two groups were comparable for coronary risk factors and use of cardiovascular medications.

Risk stratification according to perfusion imaging results. Images were interpreted as normal in 852 patients (62.3%) and abnormal in 515 patients (37.7%) (Table 2). The annualized hard cardiac event (cardiac death or non-fatal myocardial infarction) rate for patients with normal perfusion images was significantly lower (2.5%) than for those with abnormal images (7.6%, p < 0.01, odds ratio = 3.3 [95% confidence interval, 2.2 to 4.9]). The annual rates for both cardiac death and myocardial infarction increased in relation to the severity of the perfusion abnormality (Fig. 1). When considered in relation to severity of ischemia (SDS), the annualized rates of cardiac death were 2.6%, 2.4%, and 5.7% (p < 0.05; 5.7% vs. 2.6% and 2.4%) and those of myocardial infarction were 1.8%, 3.4%, and 3.7% (p < 0.05; 1.8% vs. 3.4% and 3.7%) in patients with SDS scores of 0 to 2, 3 to 6, and >6, respectively. Thus, the presence of any ischemia was associated with an increased risk of myocardial infarction, while only severe ischemia was associated with an increased risk of cardiac death.

Prognostic value of LV functional assessment by ECGgated SPECT. Electrocardiogram-gated SPECT imaging was performed in 1,205 patients (88%). Left ventricular

Table 1. Patient Demographics and Stress Variables

<table>
<thead>
<tr>
<th>Cardiac Events</th>
<th>No Cardiac Events</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>125</td>
<td>1,242</td>
</tr>
<tr>
<td>Age</td>
<td>73.25 ± 10.99</td>
<td>67.60 ± 12.16</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>60 (48%)</td>
<td>704 (56.7%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>80 (64%)</td>
<td>717 (57.7%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>55 (44%)</td>
<td>401 (32.3%)</td>
</tr>
<tr>
<td>History of MI</td>
<td>51 (40.8%)</td>
<td>203 (16.3%)</td>
</tr>
<tr>
<td>History of CHF</td>
<td>30 (24%)</td>
<td>86 (7.0%)</td>
</tr>
<tr>
<td>Prior CABG/PCI</td>
<td>47 (37.6%)</td>
<td>190 (15.3%)</td>
</tr>
<tr>
<td>Hypercholesterol</td>
<td>61 (48.8%)</td>
<td>463 (37.3%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>56 (44.8%)</td>
<td>513 (41.3%)</td>
</tr>
<tr>
<td>Family history</td>
<td>37 (30.1%)</td>
<td>341 (27.5%)</td>
</tr>
</tbody>
</table>

Medications

- Beta-blockers: 43 (34.4%) vs. 322 (26.0%) NS
- ACE: 31 (24.8%) vs. 309 (25.0%) NS
- Lipid lowering: 42 (33.6%) vs. 300 (24.1%) NS
- ASA: 41 (32.8%) vs. 407 (32.8%) NS

Dobutamine stress variables

- 85% of MPHR: 78 (62.4%) vs. 844 (68.0%) 0.013
- Positive ECG: 82 (65.6%) vs. 544 (44.0%) 0.000

ACE = angiotensin-converting enzyme; ASA = acetylsalicylic acid; CABG = coronary artery bypass grafting; CHF = congestive heart failure; ECG = electrocardiogram; MI = myocardial infarction; MPHR = maximum predicted heart rate; PCI = percutaneous coronary intervention.

Table 2. SPECT Data

<table>
<thead>
<tr>
<th>SPECT (clinical)</th>
<th>Cardiac Events</th>
<th>No Cardiac Events</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>125</td>
<td>1,242</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>39 (31.2%)</td>
<td>813 (65.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reversible defects</td>
<td>43 (34.4%)</td>
<td>210 (17.0%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Fixed defects</td>
<td>43 (34.4%)</td>
<td>219 (17.6%)</td>
<td>0.062</td>
</tr>
<tr>
<td>Global scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSS</td>
<td>7.7 ± 7.7</td>
<td>3.8 ± 6.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SDS</td>
<td>2.0 ± 3.5</td>
<td>1.2 ± 2.7</td>
<td>0.002</td>
</tr>
<tr>
<td>Gated SPECT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF (mean)</td>
<td>24.3 ± 16.5</td>
<td>56 ± 13.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EF &lt;50% (%)</td>
<td>50%</td>
<td>22%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

EF = ejection fraction; SDS = summed difference score; SPECT = single-photon emission computed tomography; SSS = summed stress score.
function was inversely related to annual cardiac event rates, with highest rates observed in those with lowest ejection fractions (annualized rates of 3.0%, 8.3%, and 13.5% for patients with normal LV function \( n = 905 \), mild to moderately impaired LV function \( n = 223 \), and severely impaired LV function \( n = 77 \), respectively). Rates of both cardiac death and myocardial infarction increased with worsening systolic dysfunction; however, there was a disproportionately greater risk of cardiac death over myocardial infarction in patients with severely depressed LV function (ejection fraction <30%) (Fig. 2).

Combining perfusion and functional data categorized patients into three risk categories: patients with normal perfusion and normal function \( n = 702 \) had the best prognosis; those with abnormal perfusion and abnormal function \( n = 203 \) had significantly lower cardiac event-free survival; while those with discordant perfusion and function \( n = 300 \) had an intermediate prognosis (Fig. 3). Annualized hard event rates for the three risk categories were 2.4%, 11.3%, and 5.8%, respectively.

**Value of dobutamine-induced ECG changes.** Information regarding the ST-segment ECG response to dobutamine stress was available in 1,228 (89.8%) of the patients, regardless of the level of heart rate achieved. Of these, 744 (60%) patients had normal stress ECG, 406 (33%) patients had a positive ECG response, and 78 (7%) patients had an abnormal stress ECG. Patients with normal perfusion and function had the best prognosis; those with abnormal perfusion and abnormal function \( n = 203 \) had significantly lower cardiac event-free survival; while those with discordant perfusion and function \( n = 300 \) had an intermediate prognosis (Fig. 3). Annualized hard event rates for the three risk categories were 2.4%, 11.3%, and 5.8%, respectively.

**Figure 1.** Rates of cardiac death (CD) (open bars) and non-fatal myocardial infarction (MI) (solid bars) in relation to the severity of perfusion abnormality. The number of patients in each category is given in parentheses; the numbers above the bars represent the event rates, and the numbers within the bars denote the actual number of events. The data demonstrate increasing annualized CD and MI rates with increasing summed stress score (SSS).

**Figure 2.** Rates of cardiac death (CD) (open bars) and myocardial infarction (MI) (solid bars) plotted according to left ventricular (LV) systolic function as measured by ejection fraction (EF) by gated single-photon emission computed tomography. Cardiac events increased with worsening LV function with a sharp increase in CD with severely depressed LV function.
inconclusive response. When used in combination with perfusion data, patients with a normal ECG response and normal perfusion (n = 482) had the most favorable prognosis, while those with an abnormal ECG response and abnormal perfusion (n = 101) had the least favorable prognosis (Fig. 4). Patients with discordant ECG and perfusion (n = 645) results had an intermediate prognosis, significantly different from the other two categories (p < 0.01).

Thus, stress ECG data had incremental value over perfusion alone. However, stress ECG data did not provide any additional risk stratification when added to the combined assessment of perfusion and function by gated-SPECT. In patients with both normal perfusion and function, the ECG response did not further differentiate the risk (cardiac event rates 3.5% with positive ECG vs. 2.2% with negative ECG, p = NS) nor did it add to the evaluation of patients with abnormal perfusion and function (cardiac event rates 11.9% with positive ECG vs. 11.2% with negative ECG, p = NS).

Importance of heart rate response with dobutamine stress. An important diagnostic issue with DSMPI is the achievement of THR, such that failure to achieve this landmark may underestimate the severity of CAD (14). To evaluate its importance on risk stratification, patients were subclassified according to whether THR was reached. Patients who did not reach the THR had higher event rates than patients who achieved the THR (Fig. 5). Importantly, in the low-risk group (patients with normal perfusion, normal LV function, and negative ECG response), it had incremental value for risk stratification (annualized event rates

Figure 3. Kaplan-Meier analysis demonstrating cardiac event-free survival according to combined assessment of perfusion and function. The number of patients at each time interval is given in parenthesis.

Figure 4. Kaplan-Meier analysis showing incremental prognostic value of electrocardiogram response to dobutamine over perfusion for risk stratification. The number of patients at each time interval is given in parenthesis.
rates 1.5% for those achieving THR [n = 338] vs. 3.4% for patients not reaching THR [n = 144], p = 0.021).

**Variables associated with cardiac events. UNIVARIATE ANALYSIS.** The clinical univariate predictors associated with cardiac events were age; female gender; diabetes; and a history of myocardial infarction, CHF, or revascularization (either coronary artery bypass grafting or percutaneous coronary intervention). Of the stress variables, inability to reach 85% of MPHR and an abnormal ECG response to dobutamine stress were related to increased rate of cardiac events (Table 1). With respect to nuclear variables, the presence of reversible perfusion defects and an ejection fraction <50% were associated with a significantly increased cardiac event rate (Table 2).

**MULTIVARIABLE ANALYSIS: COX PROPORTIONAL HAZARDS.** Clinical variables significantly related to cardiac events were entered into a model for multivariable analysis by Cox proportional hazards method (Table 3). Advanced age, history of CHF, inability to achieve 85% of MPHR, and the presence of either fixed or reversible defects were all independent predictors of cardiac events. When analyzed separately, a reversible defect was a significant predictor of myocardial infarction but not cardiac death, whereas a fixed defect predicted both myocardial infarction and cardiac death. Conversely, an impaired LV function was a significant predictor of cardiac death.

**DISCUSSION**

In the U.S., DSMPI is generally reserved for patients unable to exercise adequately and who have contraindications to vasodilator stress. Few studies are available to describe its value in risk stratification of this patient population; particularly lacking are the data incorporating both myocardial perfusion and function. Our study demonstrates that DSMPI can successfully provide risk stratification alone and in combination with functional data, based upon perfusion scores and the severity of LV dysfunction. While the ECG response to dobutamine is useful, it does not add to the risk stratification provided by combined assessment of perfusion and function. However, achieving the THR is of importance in risk stratification of these patients. As with previous studies of DSMPI, cardiac event rates were higher than those reported in studies of exercise stress MPI, and it is not possible to define an absolute low-risk category (annualized cardiac event rate of <1%), even using a combination of stress testing and ECG-gated SPECT variables.

**Risk stratification with DSMPI.** Dobutamine stress MPI has been used as an alternative pharmacologic stress agent for several years with a high diagnostic accuracy. In an unselected population, risk stratification with DSMPI is comparable to that with exercise MPI (5,6); however, in a highly selected population (as is the current practice in the U.S.), there are important differences as compared to...
exercise MPI. Calnon et al. (8) evaluated the prognostic role of DSMPI in a representative, highly selected population and showed a higher level of risk. In that study, annualized cardiac event rates in patients who underwent DSMPI were approximately two-fold higher than in those referred for exercise MPI at the same institution. Using a similar patient population, we also observed relatively high annual cardiac event rates in patients with normal (2.5%) or abnormal (7.6%) perfusion, which are comparable to those reported by Calnon et al. (8). Furthermore, for DSMPI, similar to exercise and vasodilator stress MPI, we were able to demonstrate the added prognostic value of LV function beyond perfusion data alone. Our study also examined cardiac death and myocardial infarction as separate end points and demonstrated a relationship between both outcomes and the extent/severity of dobutamine-stress-induced perfusion abnormalities and the incremental prognostic value of assessment of LV function by gated SPECT. In addition, we identified the importance of achieving the THR while performing risk stratification with DSMPI. Thus, effective risk stratification is possible with DSMPI for either cardiac death or myocardial infarction, and our study supports the use of this stress modality for decision making, similar to that described with exercise MPI (17).

Risk stratification with combined assessment of myocardial perfusion and function. Previous studies have shown that LVEF as measured by radionuclide angiography is a powerful predictor of cardiac death, particularly after acute myocardial infarction (18). Sharir et al. (11) extended those observations using post-stress LVEF as measured by ECG-gated SPECT. Those investigators found that LVEF after exercise or adenosine stress has incremental value over pre-scan and perfusion variables in the prediction of cardiac death. To our knowledge, no previous study has evaluated the prognostic value of LVEF obtained from gated SPECT in patients referred for DSMPI. We found that, in patients undergoing DSMPI, future cardiac events, cardiac deaths in particular, were directly related to the severity of LV dysfunction. In addition, patients with both normal perfusion and function had a better prognosis than those with both abnormal perfusion and function who had a very poor prognosis. Conversely, patients with either abnormal perfusion or function had an intermediate prognosis. These findings support the use of combined assessment of perfusion and function in risk stratification of patients undergoing DSMPI.

Prognostic value of ECG response to dobutamine. Electrocardiographic changes indicative of myocardial ischemia are more common with dobutamine than vasodilator stress (overall incidence 50%). Although dobutamine-stress–induced ECG changes are more sensitive (58%) for the detection of CAD in comparison with vasodilator-stress–induced ECG changes, they are less specific (60%) (4). Calnon et al. (8) were the first group to demonstrate that the ECG response to dobutamine stress has an important role in risk stratification beyond perfusion. Data from our study confirm the findings of Calnon et al. (8), pointing out that studies with normal perfusion but an abnormal ECG response carry a higher level of risk and should not be reported as “normal.” This is particularly important when assessment of ventricular function is not available.

Prognostic value of achieving THR. In our study, inability to achieve THR was an independent predictor of cardiac death and the combined end point of cardiac death and myocardial infarction. The inability to achieve THR has been shown to impair diagnostic accuracy with both exercise stress MPI (19) and DSMPI (14). To our knowledge, this is the first study to show the prognostic value of this important stress variable. We found that the concomitant use of beta-blockers was associated with an inability to achieve THR during dobutamine stress. Notably, patients in whom perfusion, function, and stress ECG were all normal, but who did not achieve THR with DSMPI, had a significantly higher event rate than those who achieved THR. Similarly, patients in whom perfusion, function, and stress ECG were all abnormal, and who failed to achieve THR, had an extremely poor prognosis. Thus, heart rate response with DSMPI must be considered in risk stratification in addition to the ECG response, myocardial perfusion, and functional information, as those who fail to achieve THR are at greater risk of a cardiac event, probably due to underestimation of the presence and extent/severity of CAD. Discontinuation of beta-blocker therapy before DSMPI may be a consideration, but should be approached with caution by clinicians, particularly in patients with known CAD.

Higher risk of the DSMPI population. In both studies that evaluated the role of DSMPI in a highly selected population, the current study and that of Calnon et al. (8), the annual cardiac event rates with normal perfusion alone were >2% per year, implying an intermediate level of risk rather than low risk. While this has been attributed to the higher intrinsic cardiac risk of the population studied, it was anticipated that the addition of functional data would enable the identification of the low-risk subgroup. However, in our study, even patients with normal perfusion and function had a cardiac event rate of 2.4% per year, an intermediate level of risk. Even the addition of ECG data only lowered the event rate in patients with normal ECG response, normal perfusion, and normal function to 2.2%. In our study, the population with the lowest risk was patients who achieved their THR (85% of mean predicted heart rate) and had a normal ECG response, normal perfusion, and normal LV function (an annualized cardiac event rate of 1.5%). Yet this is still higher than the well-accepted criteria of <1% annual cardiac event rate for classifying patients into the absolute low-risk category.

For several reasons, it is our impression that the inability to identify a truly low-risk subgroup in highly selected patients undergoing DSMPI is not a failure of the dobutamine test to provide effective risk stratification. First, similar findings have recently been reported for pharma-
logic stress imaging in general (20). In a meta-analysis of stress MPI, patients who underwent pharmacologic stress were found to have higher event rates than those who had undergone exercise, in the presence of either normal or abnormal perfusion. The higher event rates seen with pharmacologic stress MPI appeared to be related to the higher intrinsic cardiac risk of the patient population, rather than differences in stressors. Second, when DSMPI has been used in unselected patients, either as an alternative to exercise stress or vasodilator stress (5–7), normal perfusion was associated with excellent outcomes (annualized cardiac event rate of <1%). Thus, the higher event rate with DSMPI is most likely related to the overall population risk rather than issues with the stressor itself.

Study limitations. Data from this study were acquired before the widespread use of attenuation correction technology at our centers. Though attenuation correction improves the diagnostic accuracy of perfusion imaging, it is not clear if its use would improve risk stratification. Its use would not have reduced the cardiac event rates in patients with normal images. The higher event rate on follow-up could be a result of progression of coronary disease. However, our study was not structured to evaluate the progression of coronary disease in this population. Thus, the causality of the higher event rates remains speculative.

Conclusions. In highly selected patients referred for dobutamine stress MPI, effective risk stratification is possible using a combination of perfusion and function data obtained from ECG-gated SPECT as well as the stress ECG response. Of importance, patients who fail to achieve THR with dobutamine stress are at greater risk for future cardiac events. Hence, incorporation of each of these stress-testing variables with image interpretation is critical, so as to maximize the risk stratification potential of this non-invasive procedure.

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REFERENCES