Selection of the Optimal Nonexercise Stress for the Evaluation of Ischemic Regional Myocardial Dysfunction and Malperfusion

Comparison of Dobutamine and Adenosine Using Echocardiography and $^{99m}$Tc-MIBI Single Photon Emission Computed Tomography

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Background. The mechanisms of action of exercise-simulating and vasodilator stressors support their combination with imaging techniques that evaluate left ventricular function and perfusion, respectively. However, reported accuracies of either pharmacological stress together with two-dimensional echocardiography (2DE) or single photon emission computed tomography (SPECT) of myocardial perfusion are similar. The purpose of this study was to establish the optimal stress for each imaging technique by comparing the results of digitized 2DE and $^{99m}$Tc-methoxyisobutyl isonitrile (MIBI) SPECT using both dobutamine and adenosine stresses in the same patients and conditions.

Methods and Results. Ninety-seven consecutive patients without evidence of previous infarction undergoing coronary angiography for clinical indications were studied prospectively. Dobutamine was infused during clinical, ECG, and echocardiographic monitoring in dose increments from 5 to 40 $\mu$g · kg$^{-1}$ · min$^{-1}$. Adenosine was infused under the same conditions in doses of 0.10, 0.14, and 0.18 mg · kg$^{-1}$ · min$^{-1}$. For each protocol, the end points were achievement of peak dose, development of severe ischemia, or intolerable side effects. At peak stress, 20 mCi of MIBI was injected, and SPECT imaging was performed 2 hours later; abnormal poststress images were compared with resting SPECT. Digitized 2DE images were compared qualitatively before, during, and after stress in a cine-loop display. Significant coronary disease ($n=59$ patients) was defined by the quantification of $>50\%$ stenosis in a major epicardial vessel. The sensitivity of adenosine 2DE was 58%, less than those of adenosine MIBI (86%, $p=0.001$), dobutamine 2DE (85%, $p=0.001$), and dobutamine MIBI (80%, $p=0.01$). Their respective specificities were 77%, 71%, 82%, and 74% ($p=NS$). The accuracy of adenosine 2DE was 69%, compared with 80% for adenosine MIBI ($p<0.001$), 84% for dobutamine 2DE ($p=0.001$), and 77% for dobutamine MIBI ($p=0.005$); the latter three did not differ significantly in either sensitivity or accuracy.

Conclusions. This prospective, direct comparison of alternative pharmacological stresses in patients without myocardial infarction shows vasodilator stress scintigraphy and dobutamine stress echocardiography and scintigraphy to share equivalent levels of sensitivity. All three are significantly more sensitive than adenosine stress echocardiography. Dobutamine stress may be used for wall motion or perfusion imaging, but adenosine stress is best combined with perfusion scintigraphy. (Circulation 1993;87:345–354)

KEY WORDS • adenosine • dobutamine • stress tests • echocardiography • perfusion scintigraphy

The sensitivity of both exercise two-dimensional echocardiography (2DE) and single photon emission computed tomography (SPECT) of myocardial perfusion may be compromised in patients who are unable to exercise maximally. In such individuals, the use of pharmacological stress testing has become an alternative approach with either exercise-simulating agents such as dobutamine or coronary vasodilators such as adenosine.

On the basis of the underlying principles of the tests, the necessity of ischemia for the development of abnormal wall motion would suggest that dobutamine would be more effective than a vasodilator for stress 2DE. Indeed, a comparison performed in an animal model suggested that dobutamine was the most appropriate stress for demonstrating abnormal wall motion due to ischemia, whereas dipyridamole caused the most flow heterogeneity. However, the circumstances of that study differ from those met clinically: the doses of dobutamine (15 $\mu$g · kg$^{-1}$ · min$^{-1}$) and dipyridamole (0.14 mg · kg$^{-1}$ · min$^{-1}$)
were lower than those usually used for stress 2DE, the model was of severe single-vessel stenosis, epicardial 2DE was used, and blood-flow measurements were performed with microspheres. Moreover, studies performed in separate patient groups show a high sensitivity and specificity for each of these techniques. The purpose of the study was to compare dobutamine and adenosine stress in the same patients by use of both digitized 2DE and myocardial perfusion imaging by \textsuperscript{99m}Tc-methoxyisobutyl isonitrite (MIBI) SPECT at each stress.

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Methods

Patient Selection

Patients were eligible for entry into the study if they underwent diagnostic coronary arteriography at our institution during a 7-month period from April to November 1991. Patients with past myocardial infarction were excluded so as to concentrate the study on the diagnosis of ischemia rather than the identification of coronary disease. Those in whom stress testing was contraindicated because of safety considerations, including those with malignant ventricular arrhythmias, sinoatrial and atrioventricular blocks (without a pacemaker), severe valvular disease, cardiomyopathy, asthma, and severe hypertension (systolic pressure >200 mm Hg and diastolic pressure >120 mm Hg at rest) were also excluded. This left a potential study population of 261 patients, 126 of whom declined to participate or could not be scheduled because either personnel or equipment were not available at the time of admission. All of these exclusions were made before any of the imaging protocols were initiated to avoid referral bias. Of the remaining 135 patients enrolled, the protocol was commenced but not completed in 38 patients, either at the patient’s request (n=4); for safety reasons, i.e., diagnosis of severe left main disease at angiography (n=2) and occurrence of a myocardial infarction during angiography (n=1); or because angioplasty at the time of the diagnostic catheterization precluded completion of the protocol.

After these exclusions, the study group consisted of 97 patients. Their mean age was 56±10 years, and 28 (29%) were women. Eighty-three patients had been taking some form of antianginal therapy, including 50 treated with β-adrenergic receptor blocking drugs, 47 with nitrates, and 32 with calcium antagonists. Patients were instructed to stop medications at least one day before admission, but 16 presented on treatment (three on β-blockers alone, nine on calcium antagonists alone, and four on both). These patients (10 with and six without coronary disease) were enrolled in the study to mimic this common clinical situation.

Study Protocol

Dobutamine and adenosine stresses and the resting MIBI SPECT examination were scheduled over 3 successive days at the time of coronary angiography. The sequence varied in accordance with the clinical commitments of the patients but normally involved dobutamine stress on the day before catheterization, resting MIBI SPECT on the day of arteriography, and adenosine stress testing before hospital discharge. Each of the stress tests was performed with both echocardiographic and scintigraphic imaging; the former images were acquired throughout the test, and images at peak stress were acquired simultaneously with MIBI injection.

Coronary Arteriography

Coronary arteriography was performed in multiple projections in all patients with the Judkins technique. All films were read by an experienced observer using a technique previously validated with computer-assisted quantitative angiography. Coronary stenoses were quantified by manually tracing the stenosed vessels in as many planes as possible and then measuring the stenosed and nonstenosed vessels to obtain the percent diameter stenosis (the greatest degree of stenosis in any view being accepted as the stenosis severity). Significant coronary disease was identified by >50% diameter stenosis in a major epicardial artery; results were also analyzed with a cutoff of 70% stenosis.

Dobutamine Stress

After routine preparation for stress testing and insertion of an intravenous line, resting ECG and 2DE were performed. Dobutamine was infused with a mechanical pump, starting at a dose of 5 μg·kg\textsuperscript{-1}·min\textsuperscript{-1}, with the dose increasing in 3-minute intervals to 10, 20, 30, and 40 μg·kg\textsuperscript{-1}·min\textsuperscript{-1}. At the start of the study, the end of each stage, and the conclusion of the stress, clinical signs were recorded, and 2DE images were recorded and digitized. End points of the test were the achievement of the peak dose, development of severe ischemia (manifest as severe angina or extensive wall motion abnormality), or the occurrence of severe side effects (tests terminated prematurely because of side effects were called “submaximal”). The latter included hypertension (systolic pressure >220 mm Hg, diastolic pressure >120 mm Hg), hypotension (>20 mm Hg fall of systolic pressure), dyspnea, or ventricular arrhythmias. One minute before the conclusion of the infusion, MIBI (20 mCi i.v.) was injected; in the presence of severe side effects necessitating the termination of the test, the dose was decreased to the previous level to permit continued stress for 1 minute after MIBI injection unless this was considered to be unsafe.

Adenosine Stress

Adenosine (Sigma Chemical Co.) was administered on a separate day from the dobutamine stress, with patients abstaining from caffeine and other methyloxanthines for at least 12 hours. The agent was infused intravenously under the same conditions as the dobutamine stress, starting at 0.10 mg·kg\textsuperscript{-1}·min\textsuperscript{-1} for 1 minute, progressing to 0.14 mg·kg\textsuperscript{-1}·min\textsuperscript{-1} for 3 minutes, with a final 3-minute stage at 0.18 mg·kg\textsuperscript{-1}·min\textsuperscript{-1} designed to parallel the high-dose phase of vasodilator stress echocardiography with dipyridamole. As with the dobutamine stress protocol, clinical, ECG, and 2DE results were recorded at the conclusion of each stage, and MIBI was injected 1 minute before the conclusion of the study. Equivalent end points were used, but with this protocol, severe side effects leading to termination at a submaximal dose included hypotension (fall in systolic pressure >20 mm Hg), development of sinoatrial or third-degree atrioventricular block, and other
intolerable symptoms including severe dyspnea, abdominal discomfort, or flushing.

**Stress ECG**

ECG monitoring was performed during both stress protocols using the Frank ECG leads X, Y, and Z. These were digitized, and the presence of significant change was defined by ≥0.1 mV of horizontal or downsloping ST segment depression at an interval of 0.06 second after the J-point. Thus, the presence, severity, and time of onset of ST segment depression were recorded. Similarly, the presence and nature of chest pain were recorded, as were side effects of the stress agent. Finally, a subjective score of patient preference was made for each form of stress on an analog scale from 0 (very unfavorable) to 10 (very favorable).

**Two-dimensional Echocardiography**

Echocardiographic images were obtained with standard commercially available equipment in parasternal long- and short-axis and apical four- and two-chamber views. Images were digitized on-line with an R wave trigger to form a continuous-loop, quad-screen display and were stored on VHS videotape as well as on 5¼-in. floppy disks. All stages of the adenosine study (rest and 0.10, 0.14, and 0.18 mg·kg⁻¹·min⁻¹) were digitized, but because of the number of dobutamine stages, only rest, 10 µg, 30 µg, and 40 µg·kg⁻¹·min⁻¹ were recorded digitally, although all were recorded on videotape.

Echocardiographic images were interpreted qualitatively by experienced independent observers guided by previously described criteria. A normal response was characterized by homogeneous contraction at rest and with stress. Regions showing hypokinesis at rest with improvement during stress were also interpreted as normal to deal with the heterogeneity of contraction in the normal heart. Ischemia was identified by stress-induced wall motion abnormalities ranging in severity from dyskinesis and akinesis to grades of hypokinesis. The latter is more difficult to assess and was therefore subclassified into “absolute” hypokinesis (a deterioration of wall motion or thickening compared with rest) and “relative” hypokinesis (failure to improve these parameters with stress to the same degree as other segments). Infarction was defined by akinesis and dyskinesis at rest. Wall motion was categorized in 16 myocardial segments (at basal, mid, and apical levels in the septum, lateral, anterior, and inferior walls, and basal and midventricular levels in the anteroseptal and posterior walls). Left ventricular hypertrophy was defined by left ventricular wall thickness >12 mm in the anteroseptal or posterior walls in the long-axis parasternal view.

**MIBI SPECT Imaging**

As described above, 20 mCi (740 MBq) of MIBI was injected intravenously 1 minute before the conclusion of each pharmacological stress. A resting MIBI scan was performed on another day. In those (n=5 patients) in whom the test had to be performed on the same day because of scheduling considerations, the resting study was performed first, using 5 mCi (185 MBq) of MIBI, with the stress study 6 hours later.

Scintigraphic data were acquired 1–2 hours after MIBI injection with a large-field, single-crystal camera equipped with a high-resolution collimator (General Electric 400 AC/T) and interfaced with a Sun 3 computer (Bartec, UK). The acquisition was performed over 180° (from 45° left posterior to 45° right anterior oblique) in 6° intervals at 40 seconds per stop. Images were obtained by backprojection with a Shepp-Logan filter. The transaxial slices were reoriented into eight short-axis slices, four vertical long-axis slices (showing anterior and inferior walls), and four horizontal long-axis slices (showing septal and lateral walls). These images were read by experienced observers blinded to the clinical, 2DE, and angiographic characteristics of the patient. A qualitative comparison was made of perfusion between stress and rest images on a segmental basis whereby short-axis slices at basal and midventricular levels were used to assess anteroseptal, anterior, lateral, inferolateral, inferior, and septal segments, and long-axis images were combined to assess apical segments. This segmentation corresponded to that used for echocardiography. Regions were then interpreted as showing normal perfusion, a stress-induced perfusion defect, or a fixed perfusion defect.

**Statistical Analysis**

The sensitivity, specificity, and positive and negative predictive accuracy of dobutamine 2DE, dobutamine MIBI SPECT, adenosine 2DE, and adenosine MIBI SPECT were obtained in the usual fashion. The ability of the tests to predict the involvement of individual coronary vessels was assessed by ascribing the septum and anteroseptal and anterior walls to the left anterior descending coronary artery, the lateral wall to the circumflex artery, and the inferior wall to the right coronary artery. Because of the varying vascular supply of the apex, this was allocated to any other involved territory; if the apex alone was involved, the left anterior descending coronary artery was imputed. Likewise, the posterior wall was ascribed to either the right or circumflex territory if either was involved; if the posterior wall alone was implicated, it was ascribed to the circumflex.

The results for each different test were compared by the McNemar test for paired data. Continuous variables were expressed as mean±SD and compared by a paired t test; unpaired data were compared with a χ² or Fisher’s exact test, depending on the sample size.

**Results**

**Hemodynamics**

The hemodynamic responses to dobutamine and adenosine infusions are summarized in Table 1. Although heart rate increased significantly after each stress, the increment in heart rate was greater with dobutamine (reflecting a higher peak heart rate). Similarly, the peak rate–pressure product was greater after dobutamine stress. During dobutamine infusion, 20 patients (21%) achieved 85% of age-predicted maximum heart rate, but none reached this level with adenosine stress (p<0.001).

**ECG Responses**

Among the 59 patients with coronary disease, 57 had ECGs interpretable for ischemic changes. Significant (≥0.1-mV) ST segment depression or elevation oc-
TABLE 1. Hemodynamic Responses to Dobutamine and Adenosine Stress

<table>
<thead>
<tr>
<th></th>
<th>Dobutamine</th>
<th>Adenosine</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting heart rate (bpm)</td>
<td>68±12</td>
<td>70±12</td>
<td>NS</td>
</tr>
<tr>
<td>Peak heart rate (bpm)</td>
<td>111±24</td>
<td>92±15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart rate increment (bpm)</td>
<td>42±21</td>
<td>22±11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Resting systolic blood pressure (mm Hg)</td>
<td>149±19</td>
<td>148±21</td>
<td>NS</td>
</tr>
<tr>
<td>Peak systolic blood pressure (mm Hg)</td>
<td>179±23</td>
<td>157±22</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Resting rate–pressure product (×10⁵)</td>
<td>10.2±2.4</td>
<td>10.2±2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Peak rate–pressure product (×10⁵)</td>
<td>19.8±5.0</td>
<td>14.4±2.9</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

bpm, Beats per minute.

curred in 13 (23%) during dobutamine and in 13 during adenosine stress. In the 33 patients without coronary disease and with interpretable ECGs, these ECG changes were absent in 31 patients (91%) with dobutamine and absent in 30 (90%) with adenosine. Thus, ECG criteria were specific but not sensitive for ischemia. In contrast, the occurrence of chest pain typical of myocardial ischemia was more sensitive but less specific; of the 59 patients with significant coronary disease, chest pain occurred in 33 dobutamine tests (56%) and 23 adenosine tests (39%, p=NS). In those without coronary disease, the tests were completed without pain in 26 dobutamine (68%) and 29 adenosine studies (76%, p=NS). Combining these data such that a positive test was defined by either pain or significant ST segment changes, the sensitivity increased to 38 of 59 (64%) for dobutamine and 29 of 59 (49%, p=NS) for adenosine, whereas specificity decreased to 24 of 38 for dobutamine (63%) and 27 of 38 (71%, p=NS) for adenosine.

Accuracy of 2DE and Scintigraphy

All studies performed in the 97 patients completing the protocol were interpreted and compared. The respective abilities of 2DE and MIBI SPECT with dobutamine or adenosine stress to identify the presence (n=59) or absence (n=38) of ≥50% stenosis are illustrated in Figure 1. Adenosine 2DE had a sensitivity of 58%, a specificity of 87%, and an accuracy of 69%. Adenosine MIBI SPECT had a sensitivity of 86%, a specificity of 71%, and an accuracy of 80%. For dobutamine 2DE, the sensitivity was 85%, specificity 82%, and accuracy 84%. Finally, dobutamine MIBI SPECT had a sensitivity of 80%, a specificity of 74%, and an accuracy of 77%. Thus, in the group of patients with significant disease, the sensitivity of adenosine 2DE was significantly lower than adenosine MIBI SPECT (58% versus 86%, p=0.001), dobutamine 2DE (58% versus 85%, p=0.001), and dobutamine MIBI SPECT (58% versus 80%, p=0.01), but the latter three tests did not differ significantly from each other. These results were not significantly influenced by the 10 patients with coronary disease who took calcium antagonists or β-blockers on the day of the test; in this group, stress sensitivities were 70% for adenosine 2DE, 100% for adenosine MIBI SPECT, and 90% for both dobutamine tests.

Because the group was constituted of patients without previous myocardial infarction, most of the positive 2DE and MIBI SPECT findings reflected stress-induced wall motion or perfusion defects; abnormal results were due to resting akinesia alone in two patients and to abnormal perfusion at rest alone in five patients. Seventy-four patients had neither akinesia nor hypokinesia on the resting 2DE. In this group, the sensitivity and specificity of adenosine 2DE were 50% and 91%, compared with 88% and 68% for adenosine MIBI SPECT, 88% and 82% for dobutamine 2DE, and 78% and 71% for dobutamine MIBI SPECT. Patients with normal resting function, therefore, had results concordant with the population as a whole.

Wall motion was abnormal after dobutamine stress in 57 patients; of the 50 with true positive results, 36 demonstrated akinesia or dyskinesia, six had "absolute" hypokinesia (a deterioration from rest), and eight showed hypokinesia relative to other regions at peak stress. The seven patients with false-positive results comprised four with apparent akinesia and three with hypokinesia (one of which was relative to the stress response of other regions). Thirty-nine patients showed abnormal function after adenosine stress; of 34 true-positive results, 22 showed akinesia and 12 hypokinesia (two relative to other areas at stress), and of five false-positive findings, one was due to akinesia and four to hypokinesia.

In the 38 patients without significant coronary disease, the overall specificities of both 2DE tests were somewhat greater than those recorded with MIBI SPECT, but these differences were not statistically significant. Relevant clinical and angiographic findings for patients having a false-positive result by any technique are summarized in Table 2, which shows that patients with left ventricular hypertrophy or left bundle
branch block were excessively represented among the patients with false-positive MIBI SPECT results, although neither attained statistical significance when considered alone. However, taken together, patients with either left ventricular hypertrophy or left bundle branch block showed higher than true-negative results by both dobutamine (seven of 10 versus seven of 28, \( p=0.02 \)) and adenosine stress MIBI SPECT (seven of 11 versus seven of 27, \( p=0.04 \)). Indeed, in the 14 patients with left ventricular hypertrophy or left bundle branch block and without significant coronary disease, the specificity of MIBI SPECT using either stress technique was 50%, whereas in the remainder, it was 88% by dobutamine \( (p=0.02) \) and 83% by adenosine stress \( (p=0.04) \). Only one patient in the sensitivity group had left bundle branch block (and was correctly identified by all tests); the 22 patients with both coronary artery disease and left ventricular hypertrophy showed no difference in the sensitivity of any test from the remaining coronary disease patients without hypertrophy.

The low sensitivity of adenosine 2DE contributed to a significantly lower accuracy than was found with adenosine MIBI SPECT (69% versus 80%, \( p<0.0005 \)) dobutamine 2DE (69% versus 84%, \( p=0.001 \)), and dobutamine MIBI SPECT (69% versus 77%, \( p=0.005 \)). The three latter tests did not differ in accuracy from each other. The predictive value of the 39 positive adenosine 2DE results was 87%, not significantly different from 82% for the 62 positive adenosine MIBI SPECT results, 88% for 57 positive findings by dobutamine 2DE, and 82% for 57 positive dobutamine MIBI SPECT results. In contrast, the predictive value of a negative adenosine 2DE was 57%, compared with 77%, 78%, and 70% for adenosine MIBI SPECT and dobutamine 2DE and scintigraphy, respectively.

When >70% diameter stenosis was used as the definition of significant disease, the results were altered little, because only four patients had a stenosis severity of 50–70% without the presence of other disease as well. Using this criterion, adenosine 2DE had a sensitivity of 59%, compared with 89% for adenosine MIBI SPECT, 84% for dobutamine 2DE, and 82% for dobutamine MIBI SPECT. Their respective specificities were 78%, 68%, 76%, and 70%.

### Table 2. Relation of False-positive Results to Clinical, Scintigraphic, and Echocardiographic Variables

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Left ventricle</th>
<th>Angiogram</th>
<th>DbEcho</th>
<th>AdEcho</th>
<th>DbMIBI</th>
<th>AdMIBI</th>
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<tbody>
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<td>Normal</td>
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<td>AX isc; PL inf</td>
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<td>Normal</td>
<td>AS inf</td>
<td>S inf</td>
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<td>I sec; AX inf</td>
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<td>No CAD</td>
<td>PL sec</td>
<td>PL sec</td>
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</tbody>
</table>

Db, dobutamine; Echo, echocardiogram; Ad, adenosine; MIBI, methoxyisobutylisonitrile; LVH, left ventricular hypertrophy; LBBB, left bundle branch block; CAD, coronary artery disease; RCA, right coronary artery; LAD, left anterior descending; DI, diagonal branch; L, lateral; sec, ischemia; S, septal; PL, posteriorateral; AS, anteroapical; P, posterior; AX, apical; I, inferior; inf, infarction.

**Influence of the Extent of Coronary Disease**

Coronary disease restricted to a single vessel was present in 31 patients. The sensitivity of adenosine 2DE (52%) was significantly less than those of adenosine MIBI SPECT (81%, \( p=0.03 \)) and dobutamine 2DE (84%, \( p=0.01 \)). In patients with single-vessel disease, the sensitivity of dobutamine MIBI SPECT (71%) was less than the latter two tests \( (p=NS) \) and did not differ significantly from that of adenosine 2DE (Figure 2).

Stenoses in two or more coronary arteries were present in 28 patients. The sensitivity of adenosine 2DE (64%) for the detection of coronary disease in these patients was lower than that of adenosine MIBI SPECT (93%, \( p=0.03 \)), dobutamine 2DE (86%), and dobutamine MIBI SPECT (89%), although the latter two were not significantly different from either adenosine study (Figure 2). The sensitivity of each stress-imaging combination in patients with multivessel disease exceeded its performance in single-vessel disease, although these differences did not reach statistical significance.

A separate aspect relates to the ability of each test to predict the presence of multivessel disease as such (by the presence of wall motion or perfusion defects in
more than one coronary territory). In this respect, the adenosine and dobutamine 2DE tests were less sensitive, predicting 11% and 22% of patients with multivessel disease, respectively, compared with 43% predicted by each MIBI technique. However, the 2DE tests were more specific (100% and 90%, respectively) for this diagnosis, compared with 71% specificity for adenosine MIBI and 74% for dobutamine MIBI. Thus, the accuracies of each test for the prediction of multivessel disease in patients with coronary disease were equivalent.

Side Effects

The end points of each form of stress are summarized in Table 3. Test completion was limited by side effects in 35 dobutamine studies (36%); 29 were terminated at the beginning of the final dose or at 30 μg·kg⁻¹·min⁻¹, three at 20 μg·kg⁻¹·min⁻¹, and three at 10 μg·kg⁻¹·min⁻¹. Side effects limited 27 adenosine studies (28%, p=NS), 21 at the start of the peak dose or at 0.14 mg·kg⁻¹·min⁻¹ and six at 0.10 mg·kg⁻¹·min⁻¹. In the case of dobutamine, the test was more commonly terminated by the physician while the patient was asymptomatic (for example, with hypotension). In contrast, termination of the adenosine protocol because of side effects was more frequent because they were intolerable to the patient (for example, dyspnea), whereas the clinical status was otherwise stable. According to the subjective score for patient preference, there was little difference between dobutamine (7.6±2.1) and adenosine (7.0±2.4, p=NS).

The influence of maximal and submaximal stress on the results of each test are summarized in Table 4. Because the development of ischemia was not an end point (unless chest pain was intolerable or ECG changes severe), many patients whose tests were terminated early because of side effects nonetheless had positive tests; hence, the sensitivity was not significantly compromised by submaximal tests. The proportion of patients with nondiagnostic tests (negative results with a submaximal stress) ranged from 12% to 18%, reflecting a “feasibility” of 82–88%.

Discussion

In this consecutive series of patients without previous infarction, the sensitivity of adenosine MIBI SPECT did not differ significantly from values for dobutamine 2DE and dobutamine MIBI SPECT. Adenosine 2DE had a significantly lower sensitivity. In patients without significant coronary stenoses, 2DE showed a trend toward higher specificity than SPECT, irrespective of the form of stress. Although no serious complications arose in any patient, and a similar proportion of tests were concluded for nonmaximal end points with each stress, safety considerations (blood pressure and rhythm changes) more readily led to termination of the dobutamine studies. Uncomfortable side effects more frequently prompted premature termination of adenosine stress, a factor reflected in a somewhat lower patient preference score with this agent.

Technical Considerations

A comparison of pharmacological stresses for scintigraphy and 2DE brings choices with respect to the selection of vasodilators and radionuclides. Although dobutamine is accepted in preference to the other sympathomimetic agents as a safe and effective exercise-simulating stress, two vasodilator stressors (adenosine and diprydamole) may be selected. Adenosine was chosen for this study because of its shorter half-life (patients are less likely to experience prolonged ischemia after stress with this agent than with dipyridamole) and because of its more rapid action, which permits imaging early after each dose increment. To increase the possibility of steal phenomena, a high cumulative

Table 3. Reasons for Termination of Dobutamine and Adenosine Stress Protocols

<table>
<thead>
<tr>
<th></th>
<th>Dobutamine</th>
<th>Adenosine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak dose</td>
<td>46 47</td>
<td>62 64</td>
</tr>
<tr>
<td>Ischemia</td>
<td>16 16</td>
<td>9 9</td>
</tr>
<tr>
<td>Side effects (&quot;submaximal&quot;)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension (&gt;20 mm Hg fall of SBP)</td>
<td>15 15</td>
<td>7 7</td>
</tr>
<tr>
<td>Hypertension (SBP &gt;220 mm Hg)</td>
<td>3 3</td>
<td>...</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>5 5</td>
<td>13 13</td>
</tr>
<tr>
<td>Rhythm disturbances</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VT</td>
<td>1 1</td>
<td>...</td>
</tr>
<tr>
<td>SVT</td>
<td>3 3</td>
<td>...</td>
</tr>
<tr>
<td>VPCs</td>
<td>4 4</td>
<td>...</td>
</tr>
<tr>
<td>Conduction disturbances</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVB</td>
<td>... 4</td>
<td>4</td>
</tr>
<tr>
<td>SAB</td>
<td>... 1</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cough, headache, anxiety)</td>
<td>4 4</td>
<td>2 2</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; VT, ventricular tachycardia; SVT, supraventricular tachycardia; VPCs, ventricular premature contractions; AVB, atrioventricular block; SAB, sinoatrial block.
TABLE 4. Influence of Maximal and Submaximal Adenosine and Dobutamine Stress on the Sensitivity and Specificity of 2DE and MIBI SPECT

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Nondiagnostic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximal</td>
<td>Submaximal</td>
<td>Maximal</td>
</tr>
<tr>
<td>Ad 2DE</td>
<td>59% of 46</td>
<td>54% of 13</td>
<td>92% of 24</td>
</tr>
<tr>
<td>Ad MIBI-SPECT</td>
<td>87% of 46</td>
<td>85% of 13</td>
<td>63% of 24</td>
</tr>
<tr>
<td>Db 2DE</td>
<td>86% of 36</td>
<td>83% of 23</td>
<td>88% of 26</td>
</tr>
<tr>
<td>Db MIBI-SPECT</td>
<td>81% of 36</td>
<td>78% of 23</td>
<td>69% of 26</td>
</tr>
</tbody>
</table>

2DE, two-dimensional echocardiography; MIBI, methoxyisobutyl isonitrile; SPECT, single photon emission computed tomography; nondiagnostic, negative test at submaximal dose; Ad, adenosine; Db, dobutamine.

dose of adenosine (1.09 mg/kg) was selected, analogous to high-dose (0.84 mg/kg) dipyridamole.\textsuperscript{13}

Perfusion imaging by SPECT may be performed with either \textsuperscript{201}TI or \textsuperscript{99m}Tc MIBI; we selected the latter in this study for three reasons. First, its shorter half-life permitted the performance of scans on successive days (which would have been precluded by the long half-life of \textsuperscript{201}TI). Second, the ability to perform imaging 2 hours after MIBI injection allowed a pure assessment of perfusion rather than of the combination of perfusion and wall motion reflected in imaging during or shortly after ischemia (as is required with \textsuperscript{201}TI), in which partial volume considerations caused by hypokinesis may augment scintigraphic defect size or severity.\textsuperscript{16} Finally, MIBI appears to have benefits over \textsuperscript{201}TI with respect to image quality.\textsuperscript{17}

Both resting wall motion abnormalities and resting perfusion defects are readily identified by 2DE and perfusion scintigraphy, respectively.\textsuperscript{18,19} Thus, the inclusion of postinfarction patients tends to augment the sensitivity of both imaging tests because the techniques are used in an inappropriate population (since the presence of coronary artery disease has generally already been established in patients with prior myocardial infarction). For these reasons, all patients with previous Q wave myocardial infarction were excluded from this study. Unfortunately, this design meant that some pertinent issues in the comparison of stress 2DE and scintigraphy could not be examined. These include the ability of the tests to identify peri-infarct ischemia and their relative abilities to identify ischemia within areas having abnormal resting perfusion and function. Preliminary data suggest that the latter, in particular, may be a specific strength of the scintigraphic techniques.\textsuperscript{20}

In addition to a history of myocardial infarction, other factors (for example, the prevalence of multivessel disease) pertaining to patient selection may influence the accuracy of both imaging approaches.\textsuperscript{18,19} Thus, to ensure that the results represented the performance of the tests in routine practice, we prospectively studied a consecutive population with no exclusions based on image quality. The only patient exclusions were predicated by safety considerations, and none of the exclusion criteria were derived from any of the imaging tests.

Underlying Mechanisms of the Stresses

The exercise-simulating and vasodilator approaches to pharmacological stress were represented by dobutamine and adenosine, respectively. Dobutamine increases both the heart rate and the force of contraction, causing oxygen demand to outstrip coronary supply, leading to ischemia and hence to abnormal regional function. Increased myocardial work also enhances coronary flow so that myocardium supplied by a normal vessel becomes hyperemic, whereas this effect is blunted in regions supplied by vessels with significant stenoses, with the consequent development of perfusion defects. This secondary coronary vasodilator effect might be expected to be less potent than the direct effect of adenosine, analogous to the relative effects of vasodilators and exercise.\textsuperscript{21} The latter considerations are supported by the microsphere measurements of flow by Fung et al\textsuperscript{11} and by a somewhat lower sensitivity of dobutamine than adenosine MIBI SPECT in this study, although this reduction was not statistically significant.

The effect of adenosine is to induce coronary vasodilation; regions subtended by stenosed coronary vessels therefore show less hyperemia than regions supplied by normal vessels and appear to be a perfusion defect. However, such sites are not necessarily ischemic in the sense of oxygen demand exceeding supply, which is a condition necessary for the development of abnormal wall motion. Thus, although ischemia does occur with higher doses of coronary vasodilators,\textsuperscript{13} the experimental data of Fung et al\textsuperscript{11} and the results of this study indicate that the sensitivity of this stress approach for 2DE is significantly less than for perfusion imaging.

Previous Studies of 2DE and Scintigraphy With Pharmacological Stress

Previous studies have examined the sensitivity and specificity of adenosine and dobutamine 2DE, although these have concentrated chiefly on individual evaluation, and few data are available on pharmacological stress testing using MIBI SPECT. Existing series are characterized by varying compositions of the study groups with respect to the numbers with multivessel disease, disease severity, and the proportion of patients with infarction, so that comparisons between these results are difficult. No previous study has compared each of the combinations in a large, consecutive series reflecting routine clinical practice.

Dobutamine stress echocardiography, previously used for the detection of residual ischemia in postinfarction patients, has more recently been applied as a diagnostic test for coronary disease. In 108 patients, Sawada et al\textsuperscript{3} reported a sensitivity of 89% for the detection of >50% stenoses in patients without prior myocardial infarction, with a specificity of 85%. The same protocol was used by Cohen et al\textsuperscript{4} in a study of 70 patients, but in that series, submaximal tests were excluded from the analysis, whereas patients with myocardial infarction were included; the sensitivity for the detection of >70% coronary stenosis was 86% and the specificity 95%. The
results of our study (sensitivity 85%, specificity 82%) conform to these data.

No previous comparisons between dobutamine stress 2DE and MIBI scintigraphy have been published, although some data are available in relation to the combination of dobutamine stress with $^{99m}$Tc imaging. These studies used a more conservative protocol than used with 2DE, attaining a peak dose of 20 $\mu$g·kg$^{-1}$·min$^{-1}$. Using planar $^{99m}$Tc imaging, Mason et al$^5$ reported a sensitivity of 94% in 24 patients without previous infarction but with a substantial prevalence (81%) of multivessel disease. The specificity was 87% among eight patients with normal coronary arteries. Another report$^6$ using a similar protocol with SPECT has confirmed the high sensitivity of dobutamine stress thallium imaging. However, problems may appear with the specificity of this methodology because of SPECT-related artifacts$^7$ as well as partial volume phenomena influencing thallium imaging.

Adenosine stress scintigraphy has been more extensively evaluated. To date, studies have used a peak dose of 0.14 mg·kg$^{-1}$·min$^{-1}$ and have been performed with thallium imaging. The sensitivity of adenosine SPECT thallium imaging in 53 patients with significant coronary artery disease was reported to be 92% by Nguyen et al$^9$, although this value was enhanced by a 37% prevalence of previous myocardial infarction and a 55% prevalence of multivessel disease. The specificity was reported to be 100%, but this group comprised only seven patients. In a series reported by Nishimura et al$^8$, the sensitivity was 82% in 57 patients without previous infarction, and the specificity was 90% in 31 patients with <50% stenoses (15 of whom had normal coronary arteries). Finally, Coyne et al$^{10}$ reported an 83% sensitivity in 47 patients without baseline akinesis, with a specificity of 75% in 53 patients without coronary disease or with low disease probability.

Few data are available on the use of adenosine with 2DE; those reported to date have involved the dose (0.14 mg·kg$^{-1}$·min$^{-1}$) used for scintigraphy. Using a stenosis diameter of 75% to denote the presence of significant disease, Zoghbi et al$^7$ demonstrated an 85% sensitivity and 92% specificity of adenosine 2DE in 73 patients, 27 of whom had abnormal wall motion at rest. Exclusion of those with an abnormal resting ECG left 35 patients with significant disease, in whom the sensitivity was 60%. Similarly, Nguyen et al$^9$, who included patients with abnormal wall motion at rest, reported a 40% sensitivity for the detection of >50% stenoses in 25 patients, this result being significantly inferior to that of simultaneous adenosine thallium scintigraphy. Although the sensitivity of adenosine 2DE in these studies may reflect the use of a low-dose protocol, dosage considerations are unlikely to explain the 58% sensitivity observed in the current study, which used a high-dose protocol.

In the field of vasodilator stress 2DE, many more data are available with dipyridamole than adenosine stress. Unfortunately, extrapolation between the results of dipyridamole and adenosine stress is difficult, because although the compounds share a final common pathway (increased extracellular adenosine causing vasodilation), their speed of onset, duration of action, and the levels of adenosine achieved vary. Nonetheless, previous reports on the sensitivity of high-dose (0.84-mg/kg) dipyridamole 2DE range from 74% to 90%,$^{13,23,24}$ levels higher than those associated with adenosine stress in this and other studies. This may represent the benefit of a longer period of ischemia with dipyridamole than adenosine (the effects of which are limited to the duration of the infusion). However, this apparent advantage more likely pertains to differences between the study groups; in previous high-dose dipyridamole studies,$^{13,23,24}$ 18–48% of patients had past myocardial infarction (versus none in our study), and 67–78% of those with coronary stenoses had multivessel disease (compared with 47% in our study). Thus, the sensitivity of dipyridamole 2DE recorded in the literature may exceed that available in a clinical population referred for the diagnosis of coronary disease; recent data have shown positive dipyridamole 2DE studies to correlate with the presence of multivessel disease or severe stenoses.$^{25}$ In conclusion, although our study does not compare dobutamine and dipyridamole stress echocardiography, previous data suggest that the results of dipyridamole in an equivalent group are more likely to correspond to those of adenosine than dobutamine. Indeed, both published direct comparisons of dobutamine and dipyridamole 2DE show the former to have a higher sensitivity.$^{26,27}$

Detection of Multivessel Coronary Disease

The sensitivity of all of the techniques for the recognition of multivessel disease as such was lower than that reported in other series.$^{1,19}$ In part, this reflects the use of “floating” apical and posterior segments, which reduce the estimation of multivessel disease. It also reflects the use of on-line 2DE during pharmacological stress, which enables cessation of the test once extensive ischemia becomes apparent and before it may be recognized in more than one territory. This is not a consideration during exercise stress, in which imaging is usually performed after conclusion of the test for other end points.

Frequency and Relevance of Side Effects

Side effects (usually minor) are almost universal with adenosine stress.$^7$ However, the frequency of dose-limiting side effects in this study (28%) exceeds that reported previously and to a large extent is a result of the high dose administered. Similarly, the incidence of dose-limiting side effects with dobutamine was higher than previously reported, although this was relatively accentuated by the fact that tests were not terminated because of the development of echocardiographic evidence of ischemia. As a consequence of the latter consideration, the frequency of submaximal tests should not be used as an index of feasibility. A better index of the latter is the frequency of submaximal tests with a negative study; this is 12% for dobutamine and 18% for adenosine stress 2DE (Table 4).

False-positive Studies

No clear correlates of false-positive 2DE were discernable. The major sources of false-positive MIBI SPECT results in our study were patients with left ventricular hypertrophy and left bundle branch block, which have proved to be potential problems with perfusion scintigraphy.$^{28,29}$ Exclusion of such individuals left MIBI SPECT specificities of 88% for dobutamine.
and 83% for adenosine, equivalent to the specificities of stress 2DE (which appear not to be compromised by these abnormalities).

**Pharmacological Stress ECG**

The diagnosis of myocardial ischemia based on ECG changes was associated with an unacceptably low sensitivity (23%), although specificity was ≥90% with either test. The occurrence of chest pain was also insensitive and had lower specificity. Definition of a positive test by either pain or significant ST segment changes increased the sensitivity to 64% for dobutamine and 49% for adenosine, with respective specificities of 63% and 71%. These values are lower than those usually recorded with exercise stress testing and probably reflect a lower work load on the heart than may be achieved with exercise. The accuracies of pharmacological stress ECG were lower than those achievable with imaging; the use of pharmacological stress testing without imaging cannot be recommended.

**Clinical Relevance**

The selection of a noninvasive imaging modality is influenced by issues other than those addressed in this study. Local expertise is an important consideration in relation to stress 2DE, the results of which are clearly operator dependent. Conversely, cost and licensing considerations favor 2DE over the alternative nuclear techniques. The question being addressed in each patient is of critical importance. This study considers the diagnostic application of the tests; their relative prognostic strengths may be different.

Assuming the availability of both methods and ignoring extrinsic considerations such as those of cost, the following cautious suggestions may be made. Both adenosine MIBI SPECT and dobutamine 2DE are sensitive methods for the detection of coronary disease in patients at moderate risk. Patients with asthma or cardiac conduction defects should undergo the dobutamine test, and those with hypertension or arrhythmias should undergo adenosine stress. Because of problems with false-positive MIBI SPECT, our initial impression is that patients with left bundle branch block or left ventricular hypertrophy may be better studied with dobutamine 2DE, although this needs further study. Finally, although both pharmacological stressors are safe and easily administered, neither is feasible in all patients, and their use instead of exercise in those who are able to exercise maximally remains open to question.

**Conclusions**

This prospective, direct comparison of four stress-imaging combinations for the diagnosis of myocardial ischemia confirms their sensitivities to reflect the physiological mechanisms of each stress. If functional evidence of regional ischemia is being examined, dobutamine is the optimal stress. Coronary steal phenomena provoking ischemic wall motion abnormalities are relatively rare during adenosine infusion, so adenosine 2DE is the least sensitive stress-imaging combination. The ability of dobutamine to augment coronary flow by increasing cardiac work may be slightly inferior to the coronary vasodilator effect of adenosine, but this did not lead to a significant difference between the sensitivities of dobutamine and adenosine MIBI SPECT.

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