METHODS

Dobutamine Thallium Myocardial Perfusion Tomography

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Dobutamine has favorable properties for the pharmacologic manipulation of myocardial oxygen demand in the provocation of ischemia during the investigation of coronary artery disease. The value of dobutamine infusion for thallium myocardial perfusion tomography was assessed in 50 patients with exertional chest pain undergoing coronary arteriography. Dobutamine was infused in 5-min stages at incremental rates from 5 to 20 μg/kg per min or until limited by symptoms. The myocardium was divided into nine segments for analysis of perfusion.

Thirty-nine of 40 patients with coronary artery disease had a reversible perfusion defect demonstrated by dobutamine thallium tomography (sensitivity 97%) and 8 of 10 patients with normal coronary arteries had normal myocardial perfusion (specificity 80%). These values were significantly better than the sensitivity and specificity of exercise electrocardiography (78% and 44%, respectively; p < 0.01). There was a significant relation between the mean number of segments with abnormal perfusion and the number of diseased coronary vessels (0.6, 2.6, 4.4 and 6 segments in zero-, one-, two- and three-vessel disease, respectively; p < 0.001). There was also a significant relation between the maximal tolerated dose of dobutamine and the treadmill exercise time (r = 0.56, p < 0.001), but a wide range of exercise times was achieved in the 15- and 20-μg/kg per min groups, principally because of exercise limitation by noncardiac symptoms. Dobutamine infusion was well tolerated in all patients, including six with asthma. There were no significant arrhythmias or limiting symptoms other than chest pain.

Dobutamine thallium myocardial perfusion tomography is a useful technique for the detection, localization and assessment of myocardial ischemia, particularly when exercise potential is limited. Both the safety of dobutamine in asthmatic patients and the relation between achieved dose and exercise time represent advantages over the use of adenosine or dipyridamole.

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0735-1097/91/$3.50
Methods

Study patients. Fifty patients who were scheduled to undergo coronary angiography because of known or suspected coronary artery disease were studied. Forty-two were male and the mean age was 54 years (range 36 to 75). All patients had a history of exertional chest pain, 15 (30%) had had a previous myocardial infarction and 36 (72%) had ST segment depression on the exercise ECG. Excluded from the study were patients with chest pain at rest, adverse reaction during conventional exercise testing, systolic blood pressure >200 mm Hg or diastolic blood pressure >100 mm Hg, known ventricular arrhythmias, second or third degree atrioventricular heart block, implanted pacemaker, hypertrophic cardiomyopathy, valvular heart disease or heart failure of New York Heart Association class III or IV. Normal medication was continued except for beta-adrenergic blockers, which were discontinued 48 h before the study. The study was approved by the local Ethical Committee and informed consent was obtained from each patient. The estimated radiation exposure to the patient from 80 MBq of thallium is 25 mSv (17).

Dobutamine stress test. The patients were supine and dobutamine was infused by an IVAC 711 syringe pump (IVAC Corp.) into a peripheral vein, starting at a rate of 5 μg/kg per min and increasing by 5 μg/kg per min each 5 min to a maximum of 20 μg/kg per min or until the occurrence of significant symptoms or signs. These were defined as chest pain of a severity that would normally require the use of sublingual nitroglycerin, any other intolerable symptom, sustained arrhythmia or hypertension (systolic pressure >220 mm Hg, diastolic pressure >110 mm Hg). Lead CM5 of the ECG was monitored and blood pressure was measured at each stage of the infusion. At the peak dobutamine infusion rate, 80 MBq of thallium was injected through a second intravenous cannula and the dobutamine was continued for a further minute.

Imaging technique. Emission tomographic imaging was begun within 5 min of stopping the dobutamine infusion and redistribution imaging was performed 4 h later in an identical manner. A General Electric 400AZS gamma camera and a Star computer system were used. Thirty-two planar images (64 x 64 pixel matrix, 400-mm field of view, 30 s/image) were acquired over a 180° arc from the right anterior oblique to left posterior oblique position. The planar images were reconstructed into transaxial tomograms of 1-pixel depth using back projection and a Ramp-Hanning filter with a 0.75-pixel⁻¹ cutoff frequency. From these, oblique tomograms were reoriented in the vertical long-axis, horizontal long-axis and short-axis planes.

Data analysis. The thallium tomograms were assessed by two experienced operators without knowledge of the coronary anatomy. The heart was divided into nine segments corresponding to the basal and apical portions, respectively, of the anterior, inferior and lateral walls and septum, with a single segment at the apex (Fig. 1). Thallium uptake was classified in each segment as normal, mildly, moderately or severely reduced or absent. A reversible defect was one that improved by at least one category after redistribution and a fixed defect was one that was unchanged in both images. Differences in interpretation were resolved by consensus. Coronary angiograms in multiple projections were interpreted visually by the clinician in charge of the patient’s care without knowledge of the thallium images. Significant disease was defined as a reduction of normal luminal diameter by ≥50% in a major vessel or its principal branches. An exercise ECG was performed with use of the Bruce protocol and an abnormal ST segment response was defined as >1-mm planar or downsloping ST segment depression 80 ms after the J point.

Statistical analysis. McNemar’s test for comparison of two proportions was used to analyze the difference between thallium tomography and the exercise ECG in the detection of coronary artery disease. One-way analysis of variance with repeated measures was used to compare the hemodynamic data for the groups. Linear regression analysis was

<p>| Table 1. Mean Hemodynamic Effects of Dobutamine at Each Stage of the Infusion |</p>
<table>
<thead>
<tr>
<th>Rate of Dobutamine Infusion (μg/kg per min)</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>135.5</td>
<td>152.1</td>
<td>157.8</td>
<td>158.4</td>
<td>162.4</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>77.1</td>
<td>75.9</td>
<td>75.8</td>
<td>75.8</td>
<td>77</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>71.7</td>
<td>84.2</td>
<td>96.6</td>
<td>112.3</td>
<td>120.5</td>
</tr>
<tr>
<td>Rate-pressure product (mm Hg/min × 10⁵)</td>
<td>9.7</td>
<td>12.8</td>
<td>15.2</td>
<td>17.8</td>
<td>19.6</td>
</tr>
</tbody>
</table>

All variables except diastolic blood pressure show a significant increase with dobutamine (p < 0.001).
Table 2. Overall Sensitivity and Specificity of Dobutamine Thallium-201 Tomography in the Detection of Coronary Artery Disease

<table>
<thead>
<tr>
<th>Coronary Artery Disease</th>
<th>Dobutamine Thallium-201 Myocardial Perfusion Tomography</th>
<th>Dobutamine Thallium-201 Tomography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present (n = 40)</td>
<td>Abnormal 39, Normal 1, Sensitivity 97%</td>
<td>Abnormal 25, Specificity 100%</td>
</tr>
<tr>
<td>Absent (n = 10)</td>
<td>2, 8,  —, 80%</td>
<td>2, 25, 40, 92%</td>
</tr>
</tbody>
</table>

Thallium-201 tomography was significantly superior to exercise electrocardiography in the detection of coronary artery disease (p < 0.01).

Results

Hemodynamic effects of dobutamine (Table 1). Each increment in dobutamine infusion rate was associated with an increase in systolic blood pressure, heart rate and double (rate-pressure) product (all p < 0.001), but diastolic blood pressure did not change significantly. At the maximal infusion rate of 20 μg/kg per min, the rate-pressure product approximately doubled.

Sensitivity of dobutamine thallium tomography (Tables 2 to 5). Significant coronary artery disease was present in 40 patients (80%) with one-, two- and three-vessel involvement in 14, 16 and 10 patients, respectively. The left main stem was involved in two patients. The stress thallium tomograms showed reversible ischemia in 39 of these patients (Table 2, Fig. 2), yielding an overall sensitivity of 97% for the detection of coronary artery disease. The one patient with coronary artery disease who had a normal dobutamine thallium tomogram had relatively minor disease with an occluded nondominant left circumflex artery and a lesion of the diagonal branch of the left anterior descending artery. There was a significant relation between the number of diseased coronary arteries and the mean number of abnormal myocardial segments (Spearman rank correlation coefficient \([r_s]\) = 0.76, p < 0.001), but the large range of number of ischemic segments in each group reflected the difference between the anatomic and functional assessment of the severity of the coronary artery disease (Table 3). Both patients with left main stem stenosis had reversible ischemia of the anterior and lateral walls. Twenty-five (92%) of 27 patients with disease of the left anterior descending coronary artery had reversible ischemia of the anterior wall, septum or apex. Twenty-one (87%) of 24 patients with right coronary artery disease had reversible ischemia of the inferior wall, but only 10 (40%) of 25 patients with disease of the left circumflex coronary artery had a lateral wall defect (Table 4).

Because a majority (n = 21) of the 25 patients with left circumflex artery lesions had reversible inferior wall ischemia but only a minority (n = 10) had reversible lateral wall ischemia, we separately analyzed the patients with isolated disease of either the left circumflex (n = 12) or the right (n = 11) coronary artery (Table 5). Inferior wall ischemia (50%) was more common than lateral wall ischemia (25%) in patients with isolated left circumflex artery lesions, but lateral wall ischemia was unusual (9%) in patients with an isolated right coronary artery lesion. If either the inferior or lateral wall is considered to be the territory of the left circumflex artery, then sensitivity for the detection of left circumflex artery disease in these patients was 83%.

Fifteen patients had had a previous myocardial infarction, 12 with and 4 without Q waves (1 patient had a Q wave and a non-Q wave infarction in different territories). In 12 patients with a Q wave infarction, 11 had a fixed defect of

Table 5. Site of Perfusion Defect in 23 Patients With Either a Left Circumflex or a Right Coronary Artery Lesion but Not Both

<table>
<thead>
<tr>
<th>Site of Isolated Vessel Stenosis</th>
<th>No. of Stenoses</th>
<th>Inferior</th>
<th>Lateral</th>
<th>Apex</th>
<th>Inferior and Lateral</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCx</td>
<td>12</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>RCA</td>
<td>11</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 4.
Figure 2. Thallium myocardial perfusion tomography using dobutamine stress in a patient with three-vessel coronary artery disease. A, B and C, Stress images. D, E and F, Redistribution images. A and D, Vertical long-axis plane. B and E, Horizontal long-axis plane. C and F, Short-axis plane. There is reversible ischemia of the distal anterior wall, septum and apex and lateral wall. There is a fixed perfusion defect of the inferior wall. The patient had inferior Q waves on the electrocardiogram, with a blocked proximal right coronary artery and proximal stenoses of the left circumflex and left anterior descending coronary arteries.
exercise electrocardiography. Thirty-one of the patients without significant stenosis of either the right or left circumflex coronary artery had an abnormal tomogram suggesting reversible ischemia in the anterior wall (specificity 80%) (Table 2). Both patients with an abnormal thallium tomogram were subsequently classified by the supervising clinician as having syndrome X. One was a 58-year-old woman who was limited by chest pain and dyspnea with 2-mm ST depression in the lateral ECG leads after only 3 min of a standard Bruce protocol exercise test. Dobutamine thallium tomography showed anteroseptal reversible ischemia (Fig. 3). The other patient, a 42-year-old man, had an exercise time of 7 min that was limited by chest pain and dyspnea with 3 mm of inferolateral ST depression. Dobutamine thallium tomography showed reversible anteroseptal ischemia.

Five of 23 patients without significant stenosis of the left anterior descending coronary artery had an abnormal tomogram suggesting reversible ischemia in the anterior wall, septum or apex (specificity for left anterior descending artery disease 78%) (Table 6). Two of the five had a stenosis that was judged to be 40%, one had a left anterior descending artery myocardial bridge and two had a diagnosis of syndrome X. Because of the difficulty in assigning an exclusive territory to the left circumflex artery, this artery was considered together with the right coronary artery. Three of 13 patients without significant stenosis of either the right or left circumflex coronary artery had an abnormal tomogram suggesting reversible ischemia of either the inferior or the lateral wall (specificity for both right and left circumflex artery disease 76%) (Table 6). Two of these patients had severe ectasia of the right coronary artery; the third patient had an occluded large left anterior descending artery that supplied the inferior wall.

Comparison of dobutamine thallium tomography and exercise electrocardiography. Thirty-one of the 40 patients with coronary artery disease had an abnormal ST segment response during dynamic exercise suggestive of myocardial ischemia (sensitivity 78%). In the remaining nine patients exercise was mainly limited by noncardiac symptoms: fatigue in four and arthritis, claudication, dyspnea, chest pain and left bundle branch block in one patient each.

Five of the 10 patients without coronary artery disease had an abnormal ST segment response to exercise and I had left bundle branch block (specificity 44%). Three of the four patients with a normal exercise ECG developed chest pain and one was limited by claudication. Dobutamine thallium myocardial perfusion tomography was significantly superior overall to the exercise ECG in the detection of coronary artery disease (p < 0.01).

Figure 4 shows the relation between the treadmill exercise time and the maximal dose of dobutamine that was tolerated. All patients are shown, but those who terminated exercise for reasons other than angina are distinguished from those who were limited by angina. A better correlation between dobutamine dose and exercise time would be expected in the latter group of patients and this was observed (all patients r = 0.32, p < 0.05; patients achieving maximal exercise r = 0.56, p < 0.001). Although the number of patients who tolerated only low doses of dobutamine is small, the relation to exercise time suggests that the dobutamine dose could be used in the same way as exercise time to classify the severity of angina.

Side effects of dobutamine. A dose of 5, 10, 15 and 20 μg/kg per min of dobutamine was tolerated by 50, 49, 44 and 33 patients, respectively. The symptoms reported and signs observed during infusion are shown in Figure 5. Chest pain was the limiting symptom in 39 patients (78%), but 11 (22%) achieved the maximal dose without pain. In one patient, dyspnea without chest pain was the limiting symptom. Eight patients reported no chest pain or other side effects during the infusion. Some form of arrhythmia occurred in 19 patients (38%); in 16 of these, ventricular premature beats were seen but were infrequent and not associated with hemodynamic disturbance. Atrial premature beats were seen in six patients, and sinus pauses, accelerated nodal rhythm and left bundle branch block occurred in one patient each. The most common noncardiac side effects were skin tingling and flushing. Overall, the dobutamine infusion was well tolerated and many patients preferred it to dynamic exercise.

Discussion
Dobutamine has been used previously for the detection of coronary artery disease in combination with electrocardiography (5), echocardiography (18) and radionuclide ventriculography (19). It has also been performed in combination with thallium myocardial perfusion imaging with use of a planar technique (20). Improvements in imaging hardware and software have led to a greater sensitivity and specificity for the detection of ischemia with tomographic imaging (21) and this is the first study to our knowledge to combine dobutamine stress with thallium myocardial perfusion tomography.
Figure 3. Thallium myocardial perfusion tomograms of a patient with syndrome X (normal epicardial coronary arteries) displayed in the same format as that in Figure 2. There is reversible ischemia of the anterior wall, septum and apex.
Specificity and sensitivity. We demonstrated an overall sensitivity of 97% and a specificity of 80% for the detection of coronary artery disease with dobutamine thallium myocardial perfusion tomography. This level of sensitivity is high, but such results might be expected in a group of patients who had extensive coronary artery disease and who were sufficiently symptomatic to be admitted for coronary arteriography. It is likely that the two patients with normal coronary arteries but abnormal scans who were diagnosed in retrospect to have syndrome X had true perfusion abnormalities and that the tests were not falsely positive. Thallium defects are known to occur in this syndrome in the absence of epicardial coronary artery disease (22-24). For this reason, we do not believe that sensitivity and specificity are good methods of assessing the accuracy of a functional technique such as thallium imaging because anatomic and functional data do not always agree. Nevertheless, the results do illustrate that dobutamine infusion is an excellent alternative to dynamic exercise in this group of patients.

Comparison with exercise electrocardiography. The sensitivity and specificity of exercise electrocardiography (78% and 44%, respectively) were not as high. The lower sensitivity agrees with the results of many previous studies (25,26) comparing the exercise ECG and exercise thallium images and does not necessarily result from the different stress techniques used in this study. The low specificity is peculiar to the group of patients that we studied and is not representative of the exercise ECG in the general population of patients with stable angina. Because an abnormal or difficult exercise ECG may lead to referral for coronary arteriography, there is a strong pretest bias toward patients with a false positive ECG and hence a low specificity.

Patients with disparity between thallium tomographic and coronary angiographic data. It is relevant to consider the five other patients in whom there was disparity between the results of thallium tomography and coronary angiography. Two patients had a reversible anterior perfusion defect with a left anterior descending lesion that was judged to be <50% diameter stenosis. In light of the variability of visual assessment of coronary arteriograms, it is likely that the lesions in these patients were indeed hemodynamically significant. In one patient, a myocardial bridge constricted the left anterior descending artery in systole but not in diastole and the patient was therefore classified as not having significant disease. In fact, the association of myocardial bridging with a corresponding thallium defect has been reported previously (27,28). Two patients with an inferior wall defect in the absence of significant right coronary or left circumflex artery stenosis had a severely ectatic right coronary artery that may have limited coronary flow. These cases again emphasize the problems of comparing functional and anatomic tests.

Relation between dobutamine dose and exercise time. In this study we demonstrated for the first time a relation between the maximal tolerated dobutamine dose and treadmill exercise performance in patients being assessed for coronary artery disease, although a relation was previously reported (29) between the maximal cardiac output achieved with dobutamine and dynamic exercise in patients with heart failure. The relation was fairly coarse because the patients who tolerated the two highest doses of dobutamine achieved a large range of exercise times. The patients might have been further stratified by use of higher doses, but we decided to limit our initial experience to more conventional doses. In addition, it was clear that it was possible to increase the
dobutamine dose to a maximum in patients whose exercise time had been limited by noncardiac problems or by technician intervention for significant ST segment changes without clinical symptoms.

The relation between dobutamine dose and exercise time is clinically important because exercise time is often used as a measure of the severity of symptoms and is also an indicator of prognosis. Other agents such as dipyridamole and adenosine produce inequalities of perfusion and myocardial ischemia by a mechanism different from that which occurs during dynamic exercise and a relation between dose and severity of symptoms has not been demonstrated. Although we do not have sufficient experience to suggest that dobutamine should be used instead of dynamic exercise in all patients, the relation strengthens the case that it could be used in this way.

Choice of beta-adrenergic agonist. The beta-sympathetic agonists increase myocardial oxygen demand by virtue of their inotropic and chronotropic actions. Epinephrine, nor-epinephrine, isoproterenol, dopamine and dobutamine are the most commonly used agents, but they differ in a number of ways, including hemodynamic effect, arrhythmogenicity and route of administration. Epinephrine-induced myocardial ischemia has been detected by echocardiography (30), but the drug is unsuitable for routine stress testing because its alpha-adrenergic agonism leads to venoconstriction and makes it unsuitable for administration into a peripheral vein. The same is true of norepinephrine and dopamine, although the latter produces less intense venoconstriction. Isoproterenol has pure beta-sympathetic effects, but it is maintained in a solution of pH 2 and is highly irritant. Only dobutamine can be given safely into small peripheral veins. Isoproterenol has been used successfully for the echocardiographic imaging of ischemia (31), but it increases heart rate with no action on blood pressure and therefore has less effect on the rate-pressure product than does dobutamine. Dobutamine is less arrhythmogenic than the other beta-agonists in the ischemic heart (32–34) and is more effective than dopamine in causing wall motion abnormalities (35). It is therefore the beta-agonist of choice for the pharmacologic manipulation of myocardial oxygen demand.

Dobutamine effects. The plasma half-life of dobutamine is 120 s, giving it a rapid onset and cessation of action that allow easy control of blood levels during imaging. The main action of dobutamine is to increase myocardial oxygen demand and, in the setting of acute ischemia, it has been shown to increase oxygen demand above availability (36). In addition, dobutamine has other effects that may provoke myocardial ischemia in patients with coronary artery disease. It dilates the distal coronary vessels, which leads to an increase in coronary flow (37,38) and a decrease in perfusion pressure distal to a coronary stenosis. Flow therefore becomes heterogeneous (39) and may be redirected to the subepicardium (40). In this respect, it is similar to adenosine and dipyridamole. It may also increase flow resistance at the site of a stenosis (40).

The most important limitation of dobutamine is that its action is competitively inhibited by beta-adrenergic blockers. Atenolol was the most commonly prescribed beta-blocker in our group of patients and this has a long plasma half-life of 6 to 9 h. Because of the confounding effects of beta-blockers, our patients discontinued treatment 48 h before the scan (approximately 5 half-lives). No clinical complications resulted, but a worsening of angina or rest pain is a theoretic possibility. One patient inadvertently continued beta-blocker therapy despite instructions. At 20 μg/kg per min of dobutamine, very little change in heart rate or blood pressure had occurred and thallium tomography revealed no evidence of myocardial ischemia. After consenting to a repeat study in the absence of beta-blocker therapy, there was the expected change in rate-pressure product with stress, and reversible ischemia was detected. It is possible that higher doses of dobutamine would compete with beta-blockade, but the safety of such a maneuver has not been established.

Clinical role of dobutamine. We demonstrated the value of dobutamine during thallium myocardial perfusion tomography, but its role in relation to that of dipyridamole or adenosine (6,7) remains to be established. Dobutamine was well tolerated by six patients with asthma in this study and thus would certainly be the agent of first choice in patients with a history of bronchoconstriction, in whom dipyridamole and adenosine are contraindicated. It is also likely to be superior when combined with imaging techniques such as echocardiography, radionuclide ventriculography and nuclear magnetic resonance imaging (41) that require significant myocardial ischemia to produce an abnormality of regional ventricular function. This advantage occurs because the main action of dipyridamole and adenosine is to increase coronary flow rather than oxygen demand so that thallium defects may occur as a result of flow heterogeneity alone without accompanying ischemia (7,42). In addition, dobutamine causes hyperkinesia of normal areas, an effect that accentuates the contrast with the hypokinesia or akinesia of abnormal areas (43), making it particularly suitable for wall motion studies. An advantage shared by dobutamine and adenosine is the short plasma half-life of each, which allows plasma levels to be maintained by constant infusion for operator-defined duration of stress. This ability is essential for radionuclide ventriculography and nuclear magnetic resonance imaging, although it may be less important for echocardiography.

We are grateful to Victor Aber, Royal Brompton Hospital, for statistical advice and Dr. Gordon Coutes of Eli Lilly. We also thank the staff of the Institute of Nuclear Medicine for their contributions.

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