Echocardiographic Detection of Coronary Artery Disease During Dobutamine Infusion

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Background. Two-dimensional echocardiography performed during dobutamine infusion has been proposed as a potentially useful method for detecting coronary artery disease. However, the safety and diagnostic value of dobutamine stress echocardiography has not been established.

Methods and Results. In this study, echocardiograms were recorded during step-wise infusion of dobutamine to a maximum dose of 30 µg/kg/min in 103 patients who also underwent quantitative coronary angiography. The echocardiograms were digitally stored and displayed in a format that allowed simultaneous analysis of rest and stress images. Development of a new abnormality in regional function was used as an early end point for the dobutamine infusion. No patient had a symptomatic arrhythmia or complications from stress-induced ischemia. Significant coronary artery disease (≥50% diameter stenosis) was present in 35 of 55 patients who had normal echocardiograms at rest. The sensitivity and specificity of dobutamine-induced wall motion abnormalities for coronary artery disease was 89% (31 of 35) and 85% (17 of 20), respectively. The sensitivity was 81% (17 of 21) in those with one-vessel disease and 100% (14 of 14) in those with multivessel or left main disease. Forty-one of 48 patients with abnormal echocardiograms at baseline had localized rest wall motion abnormalities. Fifteen had coronary artery disease confined to regions that had abnormal rest wall motion, and 26 had disease remote from these regions. Thirteen of 15 patients (87%) without remote disease did not develop remote stress-induced abnormalities, and 20 of 26 (81%) who had remote disease developed corresponding abnormalities.

Conclusions. Echocardiography combined with dobutamine infusion is a safe and accurate method for detecting coronary artery disease and for predicting the extent of disease in those who have localized rest wall motion abnormalities. (Circulation 1991;83:1605–1614)

Dobutamine infusion has been proposed as an alternative to exercise for producing cardiovascular stress in patients with known or suspected coronary artery disease. Early clinical studies have shown that echocardiography may be used to detect regional wall motion abnormalities resulting from myocardial ischemia produced by dobutamine infusion.1,2 However, recent clinical and experimental studies suggested that dobutamine stress echocardiography may have limited sensitivity for detecting coronary artery disease.3,4 Abnormalities in regional function, produced by moderate doses of dobutamine, may be limited in extent or severity except in patients with severe or extensive coronary artery disease.3–5 Detection of subtle abnormalities may be difficult using videotape analysis.3

Newer computer-based techniques for acquisition and display of echocardiograms have facilitated the performance of exercise echocardiography, and they allow direct comparison of rest and stress images.6,7 These techniques have contributed to the clinical applicability and accuracy of exercise echocardiography.6,7 Dobutamine stress echocardiography permits evaluation of patients who cannot adequately exercise, and optimal quality images can be obtained without the respiratory artifact that accompanies exercise. These potential advantages encouraged our investigation of this technique with computer-based techniques and high-dose dobutamine infusion (30 µg/kg/min) to maximize cardiac stress.

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Supported in part by the Herman C. Krannert Fund, Indianapolis; grants HL-06308 and HL-07182 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md.; American Heart Association, Indiana Affiliate, Indianapolis; and Eli Lilly and Company, Indianapolis.

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Received January 23, 1990; revision accepted January 3, 1991.
In this study, echocardiograms were recorded during step-wise infusion of dobutamine to determine the safety and clinical usefulness of this technique for evaluating patients with known or suspected coronary artery disease.

Methods

Patient Selection

Between June 1988 and August 1989, 202 patients underwent dobutamine stress echocardiography at Indiana University Hospitals. The study group comprised 103 patients who also underwent coronary angiography. The mean age was 58.9 years (range, 28–85 years), and 64 were men. Eighty-seven patients (85%) underwent dobutamine stress echocardiography because of claudication, severe arthritis, prior stroke, or other medical conditions that precluded adequate leg exercise. Thirty patients were referred for the diagnosis of chest pain or other cardiac symptoms. Thirty-five patients with a history of coronary artery disease were referred for the assessment of the functional significance of their disease. Thirty-eight patients underwent evaluation for risk stratification before noncardiac surgery. Ten patients had previous coronary artery bypass grafting.

Clinical Features

Fifty-four of 103 patients (52%) had a history of one or more cardiac symptoms (angina, 20 patients; atypical chest pain, 16; dyspnea or fatigue, 18). The remaining 49 (48%) were asymptomatic.

Seventy patients (68%) were receiving medical therapy. Seven patients were receiving a β-adrenergic receptor blocking agent alone, and 42 were receiving one or more coronary vasodilators. An additional 21 patients were receiving β-blockers and one or more coronary vasodilators. Ten patients were receiving digitalis. The baseline echocardiogram was normal in 28 patients, and 39 had only nonspecific ST segment or T wave changes. Thirty-five patients had pathological Q waves (≥40 msec in duration), and one had marked intraventricular conduction delay.

Dobutamine Infusion Protocol

Dobutamine was administered intravenously beginning at a dose of 2.5 μg/kg/min. After 3 minutes, the dose was increased to 5.0 μg/kg/min. Thereafter, the dose was increased by 5.0-μg/kg/min increments every 3 minutes. The electrocardiogram was continuously monitored, and blood pressure was recorded at the beginning of each stage.

The dobutamine infusion was terminated with the development of ischemia manifested by a new abnormality in regional wall motion or thickening that involved two or more wall segments, 2 mm or more of ST segment depression, or angina. Development of an abnormality in regional function frequently precedes development of significant ST segment depression or angina during stress-induced ischemia. A new abnormality in regional function was used as an early end point for the infusion to allow a margin of safety where the infusion could be discontinued before development of severe or extensive ischemia. The infusion was also terminated when the patient developed more than a 15-mm decline in systolic blood pressure from baseline, significant side effects, or arrhythmia. If none of the above end points were achieved, the infusion was discontinued at 85% of the patient’s age-predicted maximal heart rate or at a maximal dose of 30 μg/kg/min. In the event of demonstrable ischemia, sublingual nitroglycerin or a short-acting intravenous β-blocker was administered at the discretion of the investigator. The electrocardiogram was recorded during the last stage of dobutamine infusion, and the patient was monitored for 6 minutes after termination of the infusion.

Stress Electrocardiography

Three bipolar electrocardiographic leads (CCS, CM₃, and modified lead II) were recorded in 74 patients, and 12-lead electrocardiograms were recorded in 29. The stress electrocardiographic response was graded as normal, ischemic, or nondiagnostic by an investigator who had no knowledge of the clinical data and stress echocardiographic or angiographic results. An ischemic response was defined as 1 mm or more of horizontal to downsloping ST segment depression developing in a lead with a normal ST segment at baseline. In patients who had ST segment depression at baseline, development of an additional 1 mm of ST segment depression was considered an ischemic response. The electrocardiographic response was defined as nondiagnostic if less than 1 mm of additional ST segment depression developed in a lead with ST segment depression at baseline or if ST segment depression developed in patients who had left bundle branch block or in those receiving digitalis.

Coronary Angiography

Coronary cineangiograms were obtained using the Judkins’ technique. Quantitative angiographic measurements of percent diameter stenosis were obtained by an investigator who had no knowledge of the clinical data and stress electrocardiographic or echocardiographic results. The frames demonstrating each stenosis at its greatest severity were selected for analysis. Each frame was digitized in a 512×512×8-bit pixel matrix using a digital radiographic computer system (ADAC DPS 400c, Milpitas, Calif.). Measurements were performed with an edge detection program as described by Popma et al.

Significant coronary artery disease was defined as 50% or more diameter stenosis of a major epicardial coronary artery or major branch vessel. In patients who had previous coronary artery bypass grafting, significant coronary artery disease was also defined as 50% or more diameter stenosis of a bypass graft supplying a coronary artery with significant stenosis. This criterion for significant graft stenosis was used in only two patients who had previous bypass grafting.
The remaining eight had either widely patent or occluded grafts. Visual estimation of percent diameter stenosis was performed for six coronary stenoses that could not be measured because of technical factors.

**Echocardiography**

With the patient in the left lateral decubitus position, two-dimensional echocardiograms were obtained with commercially available equipment (Ultramark 4, Advanced Technology Laboratories, Seattle, Wash.) with a 3.0-MHz mechanical sector scanner. Echocardiograms were monitored during each stage by an investigator. In addition to videotape recordings, an on-line analysis system (Nova Microsonics Pre-Vue, Indianapolis, Ind.) was used for acquisition and digital storage of parasternal long- and short-axis and apical four- and two-chamber echocardiograms. With an electrocardiogram R wave–triggered mechanism, eight sequential images of each echocardiographic view were captured at 50-msec intervals at rest, at a dose of 5 μg/kg/min (low dose), at peak dose of dobutamine infusion, and at 5 minutes after terminating the infusion. The echocardiograms were arranged in a quad screen display so that rest, low-dose, peak-dose, and postinfusion images of each echocardiographic view could be directly compared during playback in a continuous loop format. The completed study was transferred to 5.25-in. floppy disks for permanent storage and analysis.

**Echocardiogram Analysis**

The digitized studies were independently interpreted by two investigators who had no knowledge of the patients’ clinical history, results of stress electrocardiography, or results of coronary angiography. Videotape recordings were not routinely used for analysis but were made available to the interpreters when additional information was required. A third investigator in a blind fashion reviewed the echocardiograms when the first two investigators were not in agreement. Left ventricular contractility progressively increases with increasing doses of dobutamine in the absence of coronary artery disease. Therefore, a normal response to dobutamine infusion was defined as a progressive increase in myocardial thickening and wall motion from rest to low dose to peak dose of dobutamine. An abnormal stress response was defined as a reduction in wall thickening or wall motion at any stage of the dobutamine infusion compared with the previous stage.

The left ventricle was divided into 16 segments. The location of segmental wall motion abnormalities was correlated with the location of diseased coronary arteries according to a three-region scheme of coronary perfusion depicted in Figure 1. For the purposes of analysis of the echocardiographic results, patients were divided into two groups: those who had normal wall motion at rest and those who had rest wall motion abnormalities. The sensitivity and specificity of dobutamine stress echocardiography for the detection of coronary artery disease was determined in the group with normal wall motion at rest by using quantitative coronary angiography as the reference standard. In subjects with localized rest wall motion abnormalities, a stress-induced wall motion abnormality remote from the location of the rest abnormality was correlated with the presence of a significantly diseased vessel supplying the region that demonstrated the stress-induced abnormality.

A wall motion score index was derived for rest, low-dose, and peak-dose echocardiograms in each patient. Segmental wall motion was graded as 1) normal: normal motion at rest and progressive increases in wall motion (hyperkinesis) with increasing doses of dobutamine; 2) hypokinetic: less than 5 mm of endocardial excursion at rest and reduction in motion from lower to higher doses of dobutamine; 3) akinetic: near absence of inward motion; 4) dyskinetic: paradoxical wall motion away from the center of the left ventricle in systole. The wall motion score was derived by summation of individual segment scores divided by the number of interpreted segments. Inadequately visualized segments were not scored. An individual study was defined as technically difficult when more than two segments could not be adequately visualized during any one stage.

**Statistical Analysis**

Values for heart rate, blood pressure, and the peak heart rate–systolic blood pressure product (double
product) were compared between patients receiving β-blockers and those not receiving β-blockers by use of unpaired t tests. Fisher’s exact test was used to compare proportions between patient groups. Wall motion scores and low- to peak-dose and rest- to peak-dose changes in wall motion scores were compared between patient groups by use of unpaired t tests. The peak doses of dobutamine infused in patients with one-vessel and multivessel disease were compared with the Mann-Whitney U test. The test was also used to compare the peak doses of dobutamine administered in patients receiving or not receiving β-blocker therapy.

Results

Dobutamine Infusion

Mean values for rest and stress heart rate, blood pressure, and the double product are recorded in Table 1. The mean values for heart rate at rest, heart rate at peak stress, and the double product were significantly decreased in patients receiving β-blockers compared with these values in patients not receiving β-blockers.

Quantitative coronary angiography demonstrated significant coronary artery disease in 81 patients and no significant disease in 22. A stress-induced wall motion abnormality was an end point for dobutamine infusion in 32% of all patients who had coronary artery disease and in 43% (26 of 61) of patients with disease who developed ischemia (Table 2). Five patients experienced side effects judged severe enough to terminate dobutamine infusion; however, four of these achieved other end points in addition to limiting side effects. Overall, 19 of 103 patients (18%) experienced side effects during dobutamine infusion that included nausea in five patients, apprehension or anxiety in five, headache or lightheadedness in three, tremors in three, palpitations in two, and chills in one. Fourteen had mild or moderate side effects that were tolerated during the infusion.

The incidence of arrhythmias was determined both in the study group and in those who did not undergo angiography to provide the largest population for evaluation of the safety of dobutamine infusion. Arrhythmias occurred in 30 of 202 patients (15%), including 12 of 103 (12%) in the study group. No patient had ventricular tachycardia (more than three consecutive premature ventricular contractions) or hypotension or symptoms due to an arrhythmia. Sixteen patients (53%) who had arrhythmias were receiving one or more antianginal medications. The most common end points in patients with arrhythmias were target heart rate in 10 patients, maximum dose in 10, and ischemia in nine.

Nine patients had frequent (>6/min) premature atrial contractions, and five others had accelerated junctional rhythms that occurred transiently during dobutamine infusion. A sustained supraventricular arrhythmia occurred in a single patient who developed asymptomatic atrial fibrillation that resolved 3 hours after termination of dobutamine infusion.

Twelve patients had frequent (>6/min) premature ventricular contractions, and three other patients had runs of up to three consecutive premature ventricular contractions. Ten of 15 patients (67%) who developed ventricular ectopy manifested one or more symptoms or signs of ischemia, including two of the patients with three consecutive premature ventricular contractions. Eight patients (53%) who had ventricular ectopy were receiving drug therapy for ischemia.

In the study group, six patients received sublingual nitroglycerin for angina. Three who developed angina and extensive wall motion abnormalities received intravenous esmolol that resulted in resolution of ischemia within 5 minutes of drug administration.

Feasibility Analysis

The value of dobutamine stress echocardiography is potentially reduced in patients who have poor quality images or in those who develop severe side effects or arrhythmias before they achieve end points for ischemia, target heart rate, or maximum dose. In the study group, 24 of 103 patients (23%) had echocardiograms of reduced quality or had devel-

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**Table 1. Rest and Dobutamine Stress Hemodynamic Data**

<table>
<thead>
<tr>
<th></th>
<th>No β-blocker</th>
<th>β-blocker</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest HR</td>
<td>76.7±14.2</td>
<td>65.0±11.5</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Rest SBP</td>
<td>126.3±23.0</td>
<td>123.7±16.7</td>
<td>0.526</td>
</tr>
<tr>
<td>Peak HR</td>
<td>119.0±16.4</td>
<td>100.5±28.6</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Peak SBP</td>
<td>140.5±30.4</td>
<td>140.7±20.8</td>
<td>0.974</td>
</tr>
<tr>
<td>HR×BP</td>
<td>16,501±4,176</td>
<td>13,961±3,924</td>
<td>0.006*</td>
</tr>
</tbody>
</table>

Values are means±SEM. HR, heart rate; SBP, systolic blood pressure; HR×BP, peak heart rate–systolic blood pressure product.

*Statistically significant values.

**Table 2. End Points for Dobutamine Infusion**

<table>
<thead>
<tr>
<th></th>
<th>No significant CAD</th>
<th>Significant CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Maximum dose</td>
<td>15</td>
<td>68.2</td>
</tr>
<tr>
<td>Target HR</td>
<td>5</td>
<td>22.8</td>
</tr>
<tr>
<td>Stress WMA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1</td>
<td>4.5</td>
</tr>
<tr>
<td>≥2 mm ST depression</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt;15 mm fall in SBP</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Side effects</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>4.5</td>
</tr>
</tbody>
</table>

n=22 patients without significant CAD; n=81 patients with significant CAD.

CAD, coronary artery disease; HR, heart rate; WMA, wall motion abnormality; SBP, systolic blood pressure. Other: unable to lie supine in one patient, dyspnea in one, no heart rate response to dobutamine in one, extensive rest wall motion abnormalities precluding useful interpretation in two.

*Three other patients achieved end points of stress WMA and side effects.
†Four of five patients achieved other end points; stress WMA in three, target HR in one.
opposed arrhythmias or severe side effects. Although 10 studies were defined as technically difficult, all were judged to be of adequate quality for interpretation. No patient was excluded from analysis because of an inadequate stress echocardiogram. Only two patients, both of whom had three consecutive premature ventricular contractions occurring in the setting of stress-induced wall motion abnormalities, were judged to have arrhythmias that would have warranted termination of dobutamine infusion in the absence of inducible wall motion abnormalities. Of the five patients who experienced side effects that were judged severe enough to discontinue dobutamine infusion, three also achieved ischemic end points, and one achieved target heart rate, or maximum dose.

Subjects With Normal Rest Wall Motion
Fifty-five patients had normal wall motion at baseline. Quantitative coronary angiography demonstrated significant coronary artery disease in 35 and no significant disease in 20. One-vessel disease was present in 21 patients, two-vessel disease in seven, three-vessel disease in six, and left main coronary artery involvement in one.

The dobutamine stress electrocardiogram was normal in 26 patients, nondiagnostic in 20, and ischemic in nine. The sensitivity of an ischemic electrocardiogram for coronary artery disease was 23% (eight of 35), and the specificity was 95% (19 of 20). Fourteen patients developed angina during dobutamine infusion. The sensitivity of angina for coronary artery disease was 37% (13 of 35), and the specificity was 95% (19 of 20). The sensitivity of angina or of an ischemic electrocardiogram or both was 46% (16 of 35). The specificity (absence of both angina and an ischemic electrocardiogram) was 90% (18 of 20).

Stress-induced wall motion abnormalities developed in 31 of 35 patients (89%) who had significant coronary artery disease. An abnormal dobutamine stress echocardiogram is illustrated in Figure 2. All four false-negative studies occurred in patients who had one-vessel disease, resulting in a sensitivity of 81% (17 of 21) for those with one-vessel disease and a sensitivity of 100% (14 of 14) for those with multivessel and left main disease. Patients who had false-negative echocardiograms also lacked symptoms and ischemic electrocardiographic changes during dobutamine administration. Three patients had stenoses less than 70%, and one patient had 80% stenosis of a diagonal vessel. None was receiving β-blockers.

FIGURE 2. Low-dose and peak-dose dobutamine stress echocardiograms obtained in a patient with significant right coronary artery disease. At low dose, the inferior wall myocardium thickens normally from diastole (DIAS) to systole (SYS). At peak dose, there is no systolic thickening (arrowheads), and basal inferior and midinferior segments are hypokinetic.
TABLE 3. Wall Motion Scores in Patients With Coronary Disease and Normal Rest Wall Motion

<table>
<thead>
<tr>
<th></th>
<th>One-vessel disease (n=21)</th>
<th>Multivessel and left main disease (n=14)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose (5 µg/kg/min)</td>
<td>1.01±0.02</td>
<td>1.03±0.07</td>
<td>0.219</td>
</tr>
<tr>
<td>Peak dose</td>
<td>1.21±0.16</td>
<td>1.34±0.21</td>
<td>0.052</td>
</tr>
<tr>
<td>Rest to peak dose</td>
<td>0.21±0.16</td>
<td>0.34±0.21</td>
<td>0.052</td>
</tr>
<tr>
<td>Low to peak dose</td>
<td>0.21±0.16</td>
<td>0.31±0.21</td>
<td>0.104</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

Stress-induced wall motion abnormalities were absent in 17 of 20 patients (85%) who had no significant coronary artery disease. Mild one-vessel stenosis was present in two patients who had false-positive studies, including one with 47% stenosis of the left circumflex and one with 49% stenosis of the right coronary artery. The remaining false-positive study occurred in a 58-year-old woman with diabetes mellitus, hypertension, and left ventricular hypertrophy who developed angina and extensive wall motion abnormalities during dobutamine infusion. The stress electrocardiogram was nondiagnostic, and the coronary angiogram was normal.

The location of stress-induced wall motion abnormalities correlated with the distribution of the angiographically diseased vessel in 16 of 17 patients (94%) who had echocardiographic abnormalities and one-vessel disease. In four patients who had one-vessel disease, wall motion abnormalities extended beyond the territory of the diseased vessel. In three of these patients, a mild stenosis (range, 25–48% diameter stenosis) was observed in a second vessel. The location of stress-induced abnormalities correlated with the distribution of at least one significantly diseased vessel in 13 of 14 patients (93%) who had multivessel or left main disease. Stress echocardiography correctly predicted the presence of multivessel disease in 10 of 14 patients (71%) based on multiregion wall motion abnormalities.

There were no significant differences in the wall motion scores between patients who had one-vessel disease and those who had multivessel or left main disease (Table 3). There was also no significant difference in the doses of dobutamine achieved in those who had one-vessel disease compared with doses achieved in those who had multivessel disease. Five patients developed wall motion abnormalities at a dose of 5 µg/kg/min, all of whom had more than 70% stenosis of the vessel supplying the ischemic region.

Subjects With Rest Wall Motion Abnormalities

Forty-eight patients had abnormal wall motion at rest, including seven who had diffuse abnormalities involving all three regions of coronary perfusion. These patients were excluded from further analysis because of the absence of regions with normal wall motion at rest.

The 41 patients that were analyzed had localized rest wall motion abnormalities. Fifteen patients had either no significant coronary artery disease or disease that was confined to regions that had abnormal rest wall motion. In these patients, all regions with normal wall motion at baseline were supplied by vessels without significant disease. Two patients had no significant coronary artery disease, 12 had one-vessel disease, and one had two-vessel disease. The remaining 26 patients had one or more regions with normal wall motion at rest that were supplied by diseased vessels (remote disease). Two patients each had disease of a single vessel that supplied a region with normal wall motion at rest and had a previously infarcted region supplied by a vessel without significant disease. The remaining 24 patients had multivessel disease (two vessel in 16, three vessel in eight).

In patients who had localized rest wall motion abnormalities, the dobutamine stress electrocardiogram was normal in 10 patients, nondiagnostic in 22, and ischemic in nine. The sensitivity of an ischemic electrocardiogram for detection of remote disease was 23% (six of 26), and the specificity was 80% (12 of 15). Ten of 26 patients (38%) with remote disease developed angina and 13 of 15 patients (87%) without remote disease had no angina. Twelve of 26 patients (46%) with remote disease had either an ischemic electrocardiogram, angina, or both findings. An ischemic electrocardiogram and angina were both absent in 10 of 15 (67%) without remote disease.

Remote, stress-induced wall motion abnormalities were absent in 13 of 15 patients (87%) without remote disease. The stress echocardiogram was abnormal in the right coronary distribution in one patient who had 40% stenosis of the right coronary artery and an ischemic electrocardiogram. Three patients who had rest wall motion abnormalities involving a limited number of segments within a region developed additional stress-induced abnormalities in the same region.

Twenty-one of 26 patients (81%) with remote disease developed stress-induced wall motion abnormalities in regions that corresponded to the location of remotely diseased vessels. Four of five patients who had false-negative echocardiograms for remote disease developed new wall motion abnormalities within a region that had segments with both normal and abnormal rest wall motion. The severity of the stenosis of the remotely diseased vessel ranged from 51% to 64% in these four patients. In three of these patients, the remotely diseased vessels had less-severe stenoses compared with the vessels supplying the regions that exhibited rest and stress-induced abnormalities. Two of these patients developed additional evidence of ischemia (angina in one, electrocardiographic evidence of ischemia in one). Two patients who had undetected remote disease were receiving β-blockers.

The mean wall motion score at peak dose and the changes in mean wall motion score with dobutamine infusion were significantly greater in patients with
TABLE 4. Wall Motion Scores in Patients With Localized Rest Wall Motion Abnormality

<table>
<thead>
<tr>
<th></th>
<th>No remote disease (n=15)</th>
<th>Remote disease (n=26)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>1.49±0.22</td>
<td>1.44±0.27</td>
<td>0.582</td>
</tr>
<tr>
<td>Low dose (5 μg/kg/min)</td>
<td>1.34±0.26</td>
<td>1.44±0.29</td>
<td>0.395</td>
</tr>
<tr>
<td>Peak dose</td>
<td>1.44±0.24</td>
<td>1.68±0.33</td>
<td>0.019*</td>
</tr>
<tr>
<td>Rest to peak dose</td>
<td>−0.06±0.19</td>
<td>0.24±0.22</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Low to peak dose</td>
<td>0.11±0.17</td>
<td>0.25±0.18</td>
<td>0.029*</td>
</tr>
</tbody>
</table>

*Statistically significant values.

remote disease than in those without remote disease (Table 4). Although 23 of 26 patients (88%) with remote disease had an increase in wall motion score from rest to peak dose, six of 15 (40%) with no remote disease also demonstrated an absolute increase in wall motion score.

**B-Blocker Effect on Echocardiogram Sensitivity**

Seventeen patients who had remote disease or coronary artery disease with normal baseline echocardiograms were receiving β-blockers. Fifteen of these 17 patients (88%) had stress-induced wall motion abnormalities, and in 13 of the 15 patients (87%), these abnormalities developed in regions supplied by vessels with more than 60% diameter stenosis. Of the two remaining patients, one had multiple stenoses of a remotely diseased vessel and another achieved the target heart rate. The doses of dobutamine administered to patients receiving β-blockers were not significantly increased above the doses given to those who were not receiving β-blockers.

**Echocardiogram Analysis**

Rest and stress echocardiograms were of adequate quality for interpretation in all 103 patients. In 10 patients (10%) who had technically difficult studies, the angiographic and echocardiographic results correlated in nine. Only two investigators were required for interpretation of the rest and stress echocardiograms in 92 of 103 studies (89%). In nine studies, two investigators disagreed on the presence or absence of a stress-induced abnormality. In two studies, there was disagreement on the extent of rest wall motion abnormalities. Sixty-seven studies were analyzed by the same two investigators (D.S. and T.R.), with agreement in 59 (89%). In three studies, the videotape was reviewed in addition to the digitized images.

**Discussion**

Dobutamine stress echocardiography has several potential advantages over currently used noninvasive stress testing techniques. It is inexpensive compared with competing technologies and provides an alternative in the patient who cannot perform leg or arm exercise. The equipment required is highly portable, and thus, studies can be performed in the intensive and coronary care units. High-quality images from dobutamine stress echocardiography may be obtained more easily than those from exercise stress echocardiography because of the absence of patient motion and limited respiratory interference. The level of stress achieved can be controlled, and potentially, the suppression of heart rate by β-blockers may be overcome.

Dobutamine stress echocardiography has shown promise as a clinically useful technique in several studies. Palace et al.2 reported an 84% sensitivity and an 86% specificity for dobutamine stress echocardiography in 25 patients with coronary artery disease and in 14 normal subjects. Berthe et al.1 reported an accuracy of 87% for the technique in differentiating one-vessel from multivessel disease in 30 patients after myocardial infarction. However, in a more recent study by Mannering et al.,13 echocardiographic imaging during dobutamine infusion was successful in only 82% of patients, and stress-induced abnormalities were limited to patients with extensive disease. In support of the clinical findings of Mannering et al.,13 experimental studies have indicated that moderate doses of dobutamine or isoproterenol may only produce abnormalities in regional function in the setting of severe coronary stenoses with minimal or absent coronary flow reserve.4,12,13

The methods used for dobutamine infusion and echocardiography were designed to minimize the limitations of the technique. We used high-dose (30 μg/kg/min) dobutamine infusion to produce significant increases in heart rate based on evidence suggesting that heart rate is the most important determinant of myocardial oxygen consumption during dobutamine infusion.14 Serial echocardiographic imaging was performed to facilitate detection of relatively small reductions in contractility that occurred with increasing doses of dobutamine in those patients with less-severe coronary disease. Last, on-line digital storage permitted acquisition of serial images along nearly identical planes and allowed direct comparison of these images during analysis.

In this study, rest and stress echocardiograms were of adequate quality for interpretation in all patients. This rate of successful imaging generally exceeds that reported for exercise echocardiography.15 The availability of multiple echocardiographic windows for imaging during stress contributed to the high success rate. Ten percent of studies were of reduced quality due in part to excessive cardiac motion at peak stress that rendered some segments uninterpretable. However, the accuracy of the technique was maintained in patients with technically difficult studies.

In patients with normal rest wall motion, the sensitivity (89%) and specificity (85%) of dobutamine stress echocardiography for the detection of coronary artery disease was comparable to the values reported for other stress testing techniques.16-18 As with other techniques, the sensitivity for detecting multivessel disease exceeded that for one-vessel disease. Seven patients had discordant echocardiographic and angiographic results. All four patients with false-negative stress echocardiograms had one-
vessel disease, including three of whom had vessels with less than 70\% diameter reduction. In two of three patients who had false-positive stress echocardiograms, quantitative angiography demonstrated one-vessel disease with 40\% to less than 50\% diameter reduction. Thus, most patients with discordant angiographic and echocardiographic results had mild-to-moderate one-vessel stenosis.

The extent of angiographic disease correlated with the extent of stress-induced wall motion abnormalities. Wall motion abnormalities were confined to a single region in 76\% of those who had one-vessel disease and stress-induced abnormalities. Multiregion wall motion abnormalities developed in 71\% of patients who had multivessel or left main disease. Underestimation of disease occurred in four patients, all of whom achieved at least one ischemic end point for the dobutamine infusion but only one of whom received the maximum dose of dobutamine. The design of the infusion protocol may have reduced the ability of the technique to predict the presence of multivessel disease.

In patients who had localized rest wall motion abnormalities, dobutamine stress echocardiography predicted the presence or absence of a remotely diseased vessel with an accuracy of 83\% (34 of 41). As in patients with normal wall motion at rest, underestimation of the extent of disease resulted partly from using a stress-induced abnormality as an end point for the dobutamine infusion. Four of five who had remotely diseased vessels that were not detected by echocardiography developed new wall motion abnormalities adjacent to segments with abnormal rest wall motion. These patients had prior myocardial infarction and were presumed to have inducible perinfarction ischemia.

In this study, the reported sensitivity and specificity of dobutamine stress echocardiography was based almost exclusively on analysis of digitally stored, continuous loop images. The sensitivity of the technique may also depend on performance of serial echocardiographic imaging. Detection of coronary artery disease was facilitated by comparison of low- and peak-dose images in addition to comparison of rest and peak-dose echocardiograms. In patients who had coronary artery disease, the increase in wall motion noted at low doses of dobutamine was diminished at higher doses that produced significant increases in heart rate. The observation is consistent with the differential in inotropic and chronotropic potency of low doses of dobutamine.19

The progressive infusion of dobutamine used in this study was generally well tolerated. Five percent of patients in the study group had limiting side effects, and 15\% of all patients had arrhythmias. None had hypotension or symptoms due to an arrhythmia. Most patients who developed ventricular ectopy had ischemia, which is similar to the findings of Marieb et al20 with exercise testing. The sensitivity of dobutamine stress echocardiography is potentially limited in those who develop serious arrhythmias or side effects requiring termination of infusion before development of ischemia. However, in this study, nearly all patients who had arrhythmias or serious side effects achieved end points for ischemia, target heart rate, or maximum dose.

Development of a new wall motion abnormality involving at least two segments was used as an early end point for dobutamine infusion, which potentially limited complications from severe ischemia. This end point was used in one third of all patients who had coronary artery disease and in almost one half of those who developed ischemia. In a manner similar to exercise, dobutamine administration primarily produces ischemia by elevating myocardial oxygen demand out of proportion to supply without severely reducing coronary perfusion.21 Interventions that profoundly reduce coronary perfusion produce a more severe and extensive impairment of myocardial function than interventions that produce ischemia by increasing myocardial oxygen demand.13 Thus, ischemic complications from dobutamine infusion may be unusual even in those who have severe coronary artery disease. However, rapid reversal of the effects of dobutamine with a short-acting \( \beta \)-blocker is desired in the setting of wall motion abnormalities or angina that persist after termination of the infusion.

The electrocardiogram and assessment of symptoms during dobutamine infusion had low sensitivity but high specificity for significant coronary artery disease in patients who had normal rest wall motion and for remote disease in those who had abnormal wall motion at rest. Previous studies1,14,22–24 have reported the sensitivity of catecholamine stress electrocardiography to be 50–87\%. The reduced sensitivity in this study may be due to the use of a wall motion abnormality as an end point, use of a three-lead system in most patients, and the high frequency of antianginal medication and baseline electrocardiogram abnormalities.

**Study Limitations**

In this study, the sensitivity of the stress echocardiogram was not affected by \( \beta \)-blocker therapy. This unexpected finding may be due in part to the severity of coronary artery disease in those patients who were treated with \( \beta \)-blockers. Although these patients had reduced peak heart rates compared with those not receiving \( \beta \)-blockers, both groups had similar increases in heart rate from baseline. In addition, decreased coronary blood flow, due to unopposed \( \alpha \)-adrenergic receptor-mediated vasoconstriction, might have contributed to induction of ischemia in those receiving \( \beta \)-blockers.25,26 Regardless of the above considerations, one would expect reduced sensitivity of the stress echocardiogram in patients with mild-to-moderate coronary artery disease who have significantly attenuated heart rate responses.

The study population was referral based, and a large proportion of these patients had medical conditions that precluded exercise testing. In addition, one half of the patients were asymptomatic, including
many of those referred for risk assessment before undergoing noncardiac surgery. Thus, the results of this study may not be directly applicable to patients who are able to exercise or to those who are evaluated in a primary-care setting for cardiac symptoms.

An investigator, skilled in echocardiographic interpretation, monitored each study. The necessity of using an echocardiographer and echocardiographic end points for patient safety is unknown. Results in a previous study suggest that high dose (40 μg/kg/min) dobutamine infusion can be safely used without echocardiographic end points. Use of an echocardiographic end point might have limited the ability of the stress echocardiogram to specifically identify those who had multivessel disease. Whether a more aggressive infusion protocol would enhance the diagnostic value of the technique without imposing additional patient risk is the subject of ongoing investigation.

Use of higher doses of dobutamine may be limited by increasing side effects or by the α-adrenergic receptor properties of the drug that, like dopamine, may result in reflex suppression of the increase in heart rate. Two-dimensional echocardiography performed during isoproterenol or epinephrine infusion has been reported to have modest sensitivity for detection of coronary artery disease. However, the safety and efficacy of these β-adrenergic receptor agonists for stress testing have not been fully investigated.

Quantitative analysis of regional or global function was not performed in this study. However, qualitative analysis proved to be accurate and reproducible. Global parameters of left ventricular function evaluated during catecholamine stress were previously shown to have limited sensitivity. Visual estimation of wall thickening was incorporated in our analysis in recognition of the fact that it is not influenced by cardiac translation or rotation. The high quality of most studies may permit quantification of wall thickening in future investigations.

Conclusion

In this study, the presence and extent of coronary artery disease was accurately determined by digitally stored continuous loop echocardiograms recorded during high-dose infusion of dobutamine. The high quality of echocardiographic images permitted accurate localization of disease. The procedure was safe and well tolerated. For patients who cannot adequately exercise, dobutamine stress echocardiography provides a low cost, clinically useful alternative.

Acknowledgments

We are indebted to Barbara Wolfe for secretarial assistance and to Norman Howard, Deborah Hess, Cris Davis, Julie Kern, Susan Swanson, and Cindy Wyse for technical assistance.

References


**Key Words** • echocardiography • β-adrenergic receptor agonists • dobutamine • coronary artery disease
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Circulation. 1991;83:1605-1614
doi: 10.1161/01.CIR.83.5.1605

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/83/5/1605

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