Symptoms, Adverse Effects, and Complications Associated With Dobutamine Stress Echocardiography Experience in 1118 Patients

Horst Mertes, MD; Stephen G. Sawada, MD; Thomas Ryan, MD; Douglas S. Segar, MD; Roxanne Kovacs, RN; Judy Foltz, RN; and Harvey Feigenbaum, MD

Background. The use of dobutamine stress echocardiography for the evaluation of coronary artery disease is rapidly expanding. New applications of the technique are being investigated in a wide variety of patients including those with advanced coronary artery disease. Despite its widespread use, the safety of dobutamine stress echocardiography has not been sufficiently documented.

Methods and Results. A consecutive series of 1118 patients undergoing dobutamine stress echocardiography for evaluation of known or suspected coronary artery disease form the basis of this report. Dobutamine stress testing was performed for evaluation of chest pain, risk assessment before noncardiac surgery, after recent myocardial infarction, or as a part of ongoing research protocols. Over the study period, the maximal dose of dobutamine used was increased from 30 to 50 \( \mu \)g/kg per minute, and atropine was used in 420 (37%) patients. There were no occurrences of death, myocardial infarction, or episodes of sustained ventricular tachycardia as a result of dobutamine stress testing. The major reasons for test termination were achievement of target heart rate in 583 patients (52.1%), maximum dose in 255 (22.8%), and angina pectoris in 142 (13%). The test was terminated in 36 (3%) patients because of noncardiac side effects including nausea, anxiety, headache, tremor, and urgency. Angina pectoris occurred in 216 (19.3%) patients. Sublingual nitroglycerin, a short-acting \( \beta \)-blocker, or both types of medication were administered in 80 of these patients for relief of angina pectoris. None required intravenous nitroglycerin. A total of 736 (65%) patients had stable sinus rhythm throughout the test. The most common arrhythmias were frequent premature ventricular complexes (six or more per minute) in 172 patients (15%), and frequent premature atrial complexes in 86 (8%). There were 40 patients with nonsustained ventricular tachycardia. None had symptoms associated with the tachycardia, and only one received specific pharmacological treatment to prevent recurrence of the arrhythmia after the test was terminated. The patients who were evaluated after recent myocardial infarction and those who received atropine did not have a higher frequency of ventricular tachycardia compared with those without recent infarction and those not receiving atropine.

Conclusions. Dobutamine stress echocardiography was safely performed using supplemental atropine and an aggressive dosing protocol. Noncardiac side effects were usually minor. Arrhythmias were well tolerated and rarely required treatment. In this study, serious complications from myocardial ischemia did not occur. Symptomatic ischemia was effectively treated with test termination, sublingual nitroglycerin, or short-acting \( \beta \)-blockers. (Circulation 1993;88:15-19)

Key Words • nonexercise stress testing • catecholamines • side effects

Dobutamine is a synthetic catecholamine with a dextro form that binds to \( \beta_1 \)- and \( \beta_2 \)-receptors and a levo form that stimulates \( \alpha \)-receptors.1,2 The affinity of dobutamine for cardiac muscle \( \beta_1 \)- and \( \alpha \)-receptors results in a positive inotropic, and to a lesser extent, a positive chronotropic effect. These various actions are dose dependent, with increased contractility predominating at lower doses and progressive tachycardia developing at higher doses.

The use of dobutamine as a cardiac stress agent was first reported in 1984.3 The rationale for this application is based on the ability of the drug to augment both heart rate and contractility, resulting in an increase in myocardial oxygen demand. Myocardial ischemia will be induced if coronary flow reserve is inadequate to meet the increase in demand.

In recent years, the use of dobutamine stress testing in ischemic heart disease has dramatically increased.3-9 When combined with two-dimensional echocardiographic imaging, it has been shown to have expanding diagnostic and prognostic applications. Dobutamine stress testing protocols frequently use high doses of the
drug. Additionally, some investigators have supplemented the dobutamine infusion with atropine to further augment the heart rate response.10,11

With expanding applications and increasingly aggressive protocols, concerns about the safety of the test have arisen. To date, there are limited data specifically addressing the safety and side effect profile of dobutamine stress echocardiography. Clinical reports that have mentioned safety as an issue have consistently included small numbers of patients, and one group of investigators has reported a high frequency of ventricular arrhythmias during dobutamine stress testing.13,14,15 The purpose of this investigation was to analyze and review the Indiana University experience with dobutamine stress echocardiography to define the safety, adverse event profile, and complication rate of the test.

Methods

Patient Population

Between June 1988 and May 1992, dobutamine stress echocardiography was performed in 1118 patients at Indiana University Hospitals. There were 488 women and 630 men, with a mean age of 60±12 (range, 20 to 90) years. In patients who had two or more examinations, only the first was included in this series. Reasons for pharmacological rather than exercise stress testing included inability to exercise because of musculoskeletal disorders (n=196), claudication (n=183), advanced age (n=55), or other medical conditions not allowing adequate physical exercise (n=244). Dobutamine stress echocardiography was performed in 440 patients capable of exercise as a part of ongoing research protocols.

Indications for dobutamine stress echocardiography included evaluation of chest pain (n=372), preoperative risk assessment before transplantation of liver (n=85), kidney (n=56), or lung (n=9), vascular (n=201) or orthopedic (n=40) surgery, risk stratification and/or assessment of viable myocardium after recent (less than 6 weeks) myocardial infarction (n=189), and miscellaneous reasons (n=166). A total of 374 patients had a history of myocardial infarction. One hundred fourteen patients had previous coronary artery bypass grafting, and 90 patients had prior coronary angioplasty. Diabetes was present in 317 patients. Medications were not withheld before stress testing. In the study group, 639 patients were receiving antianginal medication including a triple drug combination of β-blockers, long-acting nitrates, and calcium antagonists in 52, β-blockers and nitrates in 62, calcium antagonists and nitrates in 177, or monotherapy with nitrates (n=132), β-blockers (n=69), or calcium antagonists in 147 patients.

Dobutamine Infusion Protocol

Examinations were performed in a fully equipped exercise testing laboratory. Dobutamine infusion was begun at a dose of 2.5 μg/kg per minute and increased to 5, 10, 20, and 30 μg/kg per minute every 3 minutes in the first 188 patients. The protocol was subsequently altered, and 50 μg/kg per minute was used as the peak dose. In 420 patients, atropine (in divided doses of 0.25 to 0.4 mg) was used when there was an inadequate heart rate response to dobutamine as judged by the operator. The infusion was terminated after the maximal dose was reached or for one of the following end points: 1) ≥2 mm ST-segment depression on the ECG, 2) significant side effects or arrhythmias, 3) achievement of 85% of the age-predicted maximal heart rate, 4) a systolic blood pressure >250 mm Hg, or 5) a significant fall in systolic blood pressure as judged by the operator. In a subset of patients evaluated before October 1989, a stress-induced wall motion abnormality involving two or more segments was used as an early end point for the test. Echocardiographic images were recorded as described previously,7,10 and multiple ECG leads were continuously monitored throughout the infusion and for 6 minutes after dobutamine was discontinued.

Data Collection

Pertinent medical history, demographic features, hemodynamic data, and echocardiographic findings were assessed and coded on prepared computer forms for all patients at the time of the study. The adverse effects of dobutamine infusion were classified as cardiac symptoms, arrhythmias, or noncardiac side effects. Complete data sets were obtained in all patients and entered into a data base for analysis.

Statistics

Hemodynamic data are presented as mean±1 SD. Subgroup differences were tested by unpaired t tests. Proportions between groups were compared by Fisher's exact test. Doses between subgroups were compared by the Mann-Whitney U Test. A value of P<.05 was considered statistically significant.

Results

There were no deaths, myocardial infarctions, sustained episodes of ventricular tachycardia, or syncope associated with the dobutamine stress test.

Dosage and Hemodynamic Findings

The mean maximal dose of dobutamine was 36.2±11.2 μg/kg per minute. The maximal heart rate ranged from 44 to 197 beats per minute (mean, 128±21 beats per minute) and was significantly lower in patients receiving β-blockers compared with those not receiving β-blockers (117±25 versus 131±18 beats per minute, respectively, P<.0001). Atropine was administered in a subset of 420 patients. The peak dose achieved in patients with recent myocardial infarction was similar to the rest of the group (35.8±5 versus 36.2±6 μg/kg per minute).

Reasons for Discontinuing Dobutamine Infusion

The reasons for terminating the dobutamine infusion are listed in Table 1. The most common reasons for test termination were achievement of target heart rate (52.1% of cases), maximal dose (22.8% of cases), and angina pectoris (12.7%). In a subset of patients who were evaluated before October 1989, the infusion was stopped in 32 cases because of stress-induced wall motion abnormalities. In 36 patients, the test was terminated because of a systolic blood pressure decline according to the judgment of the physician monitoring the test. The magnitude of blood pressure decrease in this subgroup ranged from 16 to 84 mm Hg. None of these patients had symptoms of lightheadedness or syncope. No study was terminated because of poor echocardiographic image quality.
TABLE 1  Reasons for Test Termination

<table>
<thead>
<tr>
<th>Reason</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attaining target heart rate</td>
<td>583</td>
<td>52.1</td>
</tr>
<tr>
<td>Maximum dose</td>
<td>255</td>
<td>22.8</td>
</tr>
<tr>
<td>Chest pain</td>
<td>142</td>
<td>12.7</td>
</tr>
<tr>
<td>ST-segment depression ≥2 mm</td>
<td>12</td>
<td>1.1</td>
</tr>
<tr>
<td>Increase in systolic blood pressure ≥250 mm Hg</td>
<td>10</td>
<td>0.9</td>
</tr>
<tr>
<td>Noncardiac side effects</td>
<td>36</td>
<td>3.2</td>
</tr>
<tr>
<td>Blood pressure decrease</td>
<td>36</td>
<td>3.2</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>24</td>
<td>2.1</td>
</tr>
<tr>
<td>LVOT obstruction (by Doppler)</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>IV access malfunction</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td>Patient request</td>
<td>1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

LVOT, left ventricular outflow tract.

Noncardiac Side Effects

One or more noncardiac side effects occurred in 296 (26%) patients. The most common side effects were nausea (n=88, 8%), anxiety (n=72, 6%), headache (n=54, 4%), tremor (n=42, 3.7%), and urgency (n=14, 1%). Most noncardiac side effects were well tolerated and required test termination in only 36 studies (3.2%).

Cardiac Symptoms

In 730 patients (65.3%), dobutamine administration did not elicit cardiac symptoms. Ninety-five patients (8.4%) developed atypical chest pain, and 56 (5.0%) had dyspnea. Typical angina pectoris developed in 216 patients (19.3%). Stress-induced wall motion abnormalities or ST-segment depression ≥1 mm below baseline occurred in 101 patients with angina. In addition to termination of the infusion, 80 patients (9.4%) who had angina received specific pharmacological treatment for their symptoms. In 47 patients, an intravenous short-acting β-blocker was administered. Twenty-one others received sublingual nitroglycerin, and 12 patients received both medications for relief of angina. Thirty-six of 65 patients (55.3%) who had angina lasting 6 minutes or more received treatment compared with 44 of 151 patients (29%, P<0.02) who had angina of less than 6 minutes’ duration. No patient required intravenous nitroglycerin or emergency coronary angiography because of persistent angina.

Angina pectoris occurred with comparable frequency in those who received supplemental atropine (16.4%) and in those who received dobutamine alone (21%, P=.1). There were also no significant differences in the frequency of atypical chest pain (8.2% versus 9%, P=.72) and dyspnea between those who did and did not receive atropine (4.5% versus 3%, P=.68).

In patients with recent myocardial infarction (n=189), dobutamine-induced angina was more common (24.8%) than in those patients without a history of recent myocardial infarction (18.1%, P=.01). The occurrence of dyspnea (5.3% versus 4.9%, P=.9) and atypical chest pain (7.4% versus 8.7, P=.6) was similar between the groups. Patients who reported a history of angina pectoris (n=291) were also more likely to develop angina during the test (35.7% versus 13.5%, P<.0001).

TABLE 2  Arrhythmias Induced During Dobutamine Stress Testing

<table>
<thead>
<tr>
<th>Arrhythmias</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus rhythm</td>
<td>726</td>
<td>64.9</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>7</td>
<td>0.6</td>
</tr>
<tr>
<td>Atrial flutter</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>PACs (six or more per minute)</td>
<td>86</td>
<td>7.7</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>38</td>
<td>3.4</td>
</tr>
<tr>
<td>Junctional rhythm</td>
<td>28</td>
<td>2.5</td>
</tr>
<tr>
<td>PVCs (six or more per minute)</td>
<td>172</td>
<td>15.3</td>
</tr>
<tr>
<td>Three consecutive PVCs</td>
<td>8</td>
<td>0.7</td>
</tr>
<tr>
<td>Nonsustained ventricular tachycardia</td>
<td>40</td>
<td>3.5</td>
</tr>
<tr>
<td>Second-degree AV block</td>
<td>7</td>
<td>0.6</td>
</tr>
<tr>
<td>Rate-dependent LBBB or RBBB</td>
<td>5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

PACs, premature atrial complexes; PVCs, premature ventricular complexes; LBBB, left bundle branch block; RBBB, right bundle branch block.

Arrhythmias, General Observations

Arrhythmias occurring during the dobutamine infusion are listed in Table 2. The majority of patients had no arrhythmias (n=736, 65%) and remained in stable sinus rhythm throughout the test. The most common arrhythmia was frequent premature ventricular complexes (PVCs, six or more per minute), which occurred in 172 (15.3%) patients. Frequent premature atrial complexes (PACs, six or more per minute) developed in 7.7% of the patients. The overall incidence of arrhythmias in patients who received atropine was similar compared with those patients who were not given atropine (34% versus 35%, respectively). The overall incidence of arrhythmias was significantly higher in those patients who were evaluated under the high-dose protocol (peak dose, 50 μg/kg per minute) (24% versus 37%, P<.001, respectively). Frequent PACs (3.7% versus 7%, P<.05), supraventricular tachycardia (1.5% versus 3.1%, P<.05), and nonsustained ventricular tachycardia (0% versus 4.2%, P<.05) were more common in those evaluated under the high-dose protocol.

Ventricular Tachycardia

Nonsustained ventricular tachycardia (defined as more than three consecutive premature ventricular complexes) occurred in 40 patients (3.5%). Most episodes were brief, consisting of less than 10 complexes. The longest duration of ventricular tachycardia was 20 seconds. All patients were asymptomatic. In one patient, specific treatment for the arrhythmia (75 mg of intravenous lidocaine) was administered to terminate repetitive short runs of nonsustained ventricular tachycardia associated with a decrease in systolic blood pressure. Sixteen patients (40%) with nonsustained ventricular tachycardia developed evidence of myocardial ischemia during dobutamine infusion. Fourteen had stress-induced wall motion abnormalities or significant ST-segment depression. Six of these 14 patients also had angina. Two additional patients with nonsustained ventricular tachycardia experienced angina in the absence of significant echocardiographic or ECG changes.

Episodes of nonsustained ventricular tachycardia were confined to those patients evaluated with the
high-dose protocol. However, the peak dose of dobutamine administered in patients with and without nonsustained ventricular tachycardia (38.1±7 versus 36.4±8 μg/kg per minute, respectively) were comparable. Fifteen patients who had nonsustained ventricular tachycardia received atropine during stress testing.

Nonsustained ventricular tachycardia developed in 20 patients with and in 20 without previous myocardial infarction. The arrhythmia occurred in only 5 of 189 (2.6%) who were evaluated within 6 weeks after acute myocardial infarction. Nonsustained ventricular tachycardia occurred with a similar frequency in patients with and without a history of angina pectoris (3.8% versus 3.5%, \( P = .98 \)). When global wall motion scores were determined at rest, patients with nonsustained ventricular tachycardia had systolic function comparable to the entire group (1.3±0.36 versus 1.2±0.34, \( P = .22 \)).

Supraventricular Arrhythmias

In seven patients, transient second-degree AV block occurred, one of whom was treated with atropine. In seven patients (0.6%) with sinus rhythm at baseline, atrial fibrillation was induced during the stress test. Of these, five spontaneously reverted to sinus rhythm and two required digitalis administration to restore sinus rhythm.

Discussion

Dobutamine stress echocardiography is being increasingly used for the diagnosis of coronary artery disease in patients who cannot exercise adequately. In addition, new applications of the technique are being investigated in a broad spectrum of patients, including those with advanced coronary artery disease and recent myocardial infarction. The growing acceptance of dobutamine stress as a clinical and investigative tool underscores the need for careful documentation of the safety of this method. In many protocols, dobutamine is administered in higher doses than ordinarily would be used for therapeutic purposes,\(^7,11,13\) potentially increasing the risk of arrhythmic and ischemic complications.

To our knowledge, this is the first large series that has examined the safety of dobutamine stress echocardiography. The study population included patients who are potentially at increased risk of complications, including those with multiple medical problems, advanced coronary artery disease, and recent myocardial infarction. The stress protocol used both aggressive dosing of dobutamine and supplemental atropine. Despite the potential for increased complications, this method of stress testing was safely performed in over 1100 subjects.

In this study, the overall frequency of side effects was higher (26%) than previously reported from our laboratory (18%) in an investigation of patients evaluated with the less aggressive (peak dose, 30 μg/kg per minute) dobutamine infusion protocol.\(^7\) However, severe side effects that warranted termination of dobutamine infusion were unusual (3%). Other investigators have also demonstrated that severe side effects are uncommon and rarely preclude completion of the test.\(^3,4,8,9,11,13\)

Single PACs and PVCs accounted for the majority of arrhythmias that occurred during dobutamine infusion. Life-threatening arrhythmias, sustained ventricular tachycardia, and ventricular fibrillation did not occur. There have been no reports of unstable ventricular arrhythmias leading to cardiac arrest or death in 7 previous studies encompassing over 1000 patients.\(^3,4,7,9,11,13\) In this study, the most serious arrhythmia encountered was nonsustained ventricular tachycardia, which was infrequent, and all patients were asymptomatic. Clinical predictors for the occurrence of nonsustained ventricular tachycardia were not identified. Evaluation early after myocardial infarction, abnormal rest wall motion, and atropine administration were not associated with an increased risk for the development of the arrhythmia. Ventricular tachycardia occurred only in those evaluated with the high-dose protocol, but the peak doses of dobutamine administered in subjects with and without the arrhythmia were comparable.

In this study, 40% of the subjects with nonsustained ventricular tachycardia had evidence of myocardial ischemia that may have contributed to the development of this arrhythmia. Ischemia was absent in the majority of patients who had ventricular tachycardia. In these subjects, the arrhythmia may be attributed to \( \beta \)-receptor stimulation or to a dobutamine-induced reduction in plasma potassium.\(^14,15\) The frequency of ventricular ectopy and the potential for complications resulting from arrhythmias may be modified by the use of concomitant medications. Antianginal medications may limit the occurrence of ischemia and thereby reduce the frequency of ventricular arrhythmias. Atropine, by removal of parasympathetic tone, may increase the risk of serious arrhythmias in patients evaluated after myocardial infarction. The results of this study and those of McNeill et al\(^13\) suggest that the combined administration of dobutamine and atropine does not increase the occurrence of serious arrhythmias.

In this study, no patient had myocardial infarction or death resulting from provocation of myocardial ischemia. In our early experience with dobutamine stress echocardiography, the development of new wall motion abnormalities was used as an end point for termination of the test to avoid complications from extensive or prolonged ischemia. The results of this study suggest that dobutamine stress testing can be safely performed using clinical and ECG markers of ischemia as test end points. Termination of the dobutamine infusion is frequently all that is required for rapid reversal of ischemia because of the short half-life of the drug. In a proportion of patients, sublingual nitroglycerin or an intravenous \( \beta \)-blocker is appropriate treatment for symptomatic ischemia. In this investigation, those who had angina for 6 or more minutes were more likely to receive specific treatment compared with those without prolonged symptoms. Treatment with a \( \beta \)-blocking agent is warranted in the symptomatic patient who exhibits a delay in return of the heart rate to baseline after termination of dobutamine. In addition, we use a \( \beta \)-blocking agent in symptomatic patients who have extensive echocardiographic or ECG signs of ischemia. A history of angina and recent myocardial infarction identified patients who were more likely to develop angina. However, the clinical history does not allow accurate prediction of those who will develop symptomatic or extensive ischemia. For this reason, sublingual nitroglycerin and \( \beta \)-blockers are available for use in every patient evaluated in our laboratory.

The results of this and previous studies using dobutamine stress indicate that this method has a comparable
Safety profile to pharmacological stress testing using dipyramide. The safety of this potent coronary vasodilator was documented in a large multicenter investigation.16 Myocardial infarction and cardiac death occurred in a few subjects, and this has been attributed to "coronary steal" from areas supplied by severely diseased vessels. Ischemic injury from reduction in coronary blood flow may be less likely to occur with dobutamine stress, which results in little or no reduction of flow through stenosed vessels.17

Conclusions
In this investigation, dobutamine stress echocardiography was safely performed even when an aggressive dosing protocol and supplemental atropine were used. Testing was conducted in a wide variety of patients, including those with recent myocardial infarction, without serious complications. Asymptomatic nonsustained ventricular tachycardia occurred in a small percentage of patients, but none had a life-threatening arrhythmia. Symptomatic ischemia was effectively treated by test termination, sublingual nitroglycerin, or an intravenous β-blocker.

Acknowledgments
This study was supported in part by the Herman C. Kranert Fund; grants HL-06308 and HL-07182 from the National Heart, Lung, and Blood Institute of the National Institutes of Health, US Public Health Service; and the American Heart Association, Indiana Affiliate, Inc. We gratefully acknowledge the technical assistance of Patricia Brennerman.

References
Symptoms, adverse effects, and complications associated with dobutamine stress echocardiography. Experience in 1118 patients.
H Mertes, S G Sawada, T Ryan, D S Segar, R Kovaes, J Foltz and H Feigenbaum