

Safety and Diagnostic Accuracy of Dobutamine Stress Echocardiography

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Abstract

Exercise and pharmacologic stress echocardiography has been used routinely in clinical practice for the past twenty to thirty years. Dobutamine stress echocardiography (DSE) is well established as a safe, feasible, and accurate modality for detection of myocardial ischemia and prognostication in patients with known or suspected coronary artery disease, particularly when they have limited exercise capacity. Serious side effects during or shortly after DSE are uncommon, with ventricular fibrillation or myocardial infarction occurring in approximately 1 of 2,000 studies. No deaths have been reported. On the basis of a total number of 2,246 patients, reported in 28 studies, the sensitivity, specificity and accuracy of the test for the detection of coronary artery disease (CAD) were 80%, 84% and 81%, respectively. Mean sensitivities for one, two and three-vessel disease were 74%, 86% and 92%, respectively. The sensitivity of detection of disease in the left circumflex coronary artery (55%) was lower, both compared with that for left anterior descending (72%) and right coronary artery disease (76%). The sensitivity of predicting multivessel disease by multiregional echocardiographic abnormalities varied widely, from 8% to 71%. In direct comparisons, DSE was superior to exercise electrocardiography and dipyridamole echocardiography and comparable to exercise echocardiography and radionuclide imaging. DSE is useful, feasible and safe exercise independent stress modality for assessing the presence, localization and extent of CAD.

Keywords : coronary artery disease; dobutamine stress echocardiography.

INTRODUCTION

Coronary arteriography is widely accepted as a gold standard for the diagnosis of coronary artery disease (CAD) and the evaluation of the extent and severity of vessel stenoses. Non-invasive diagnostic tests detect the consequences of ischemia: impaired cell membrane function, decreased perfusion and impaired myocardial contractility. Exercise and pharmacologic stress echocardiography have been used routinely in clinical practice for the past twenty to thirty years. 1-3 Over this time, stress echocardiography has become an accepted means of evaluation for perfusion-limiting coronary artery or excluding coronary artery disease in patients with chest pain remains a challenge because this disease is still the leading cause of death in the western world. 4 traditionally, exercise electrocardiography is performed as a first-line noninvasive diagnostic stress test. 5 However, large numbers of patients referred for evaluation of chest pain are unable to perform adequate diagnostic exercise testing. Mainly due to deconditioning or neurologic, respiratory, peripheral vascular or orthopedic limitations. 6 In these patients, Dobutamine stress echocardiography (DSE) represents an alternative, exercise-independent stress modality. Dobutamine stress echocardiography (DSE) is well established as a safe, feasible, and accurate modality for detection of myocardial ischemia and prognostication in patients with known or suspected coronary artery disease, particularly when they have limited exercise capacity. 7-12

Dobutamine: pharmacology and mechanism of action.

Dobutamine is a synthetic catecholamine with a relatively short plasma half-life of 2 minutes due to rapid metabolization in the liver to inactive metabolites. 13,14 It has a strong beta1-receptor and mild alpha1- and beta2-receptor agonist activity. When used at low dose (up to 10 µg/kg body weight per min), marked inotropic effects (mediated by both alpha1- and beta1- receptor stimulation) are encountered. When used at high dose (20 to 40 µg/kg per min), heart rate is progressively increased (mediated by beta1-receptor stimulation). Systemic blood pressure increases only minimally due to an combined effect of increase in cardiac output and a decrease in systemic vascular resistance. In patients without a sufficient increase in heart rate, the addition of atropine has been proposed to further increase heart rate by its vagolytic effects. 15 As a result of the hemodynamic changes there is an increase in oxygen demand. However, in myocardial regions supplied by a coronary artery with a critical stenosis, the increase in oxygen demand cannot be met by an adequate increase in blood flow. 15 Hence, regional ischemia develops and causes regional wall motion abnormalities that can be detected by two-dimensional echocardiography. 17-43

Protocol

Protocols for DSE vary from institution to institution, particularly with regard to dobutamine dose (range 20 to 40 µg/kg per min), atropine addition (range 0 to 2 mg) and stage

duration (range 2 to 8 min), 17-45 Centres that use lower peak doses of dobutamine use longer stage durations and stop beta-adrenergic blocking agent treatment more often before the test. The most widely used protocol uses dobutamine up to 40 ig/kg per min, with the addition of atropine up to 1 mg. 15 According to this protocol, a resting electrocardiogram (ECG) and two-dimensional echocardiogram are acquired, intravenous access is secured, and dobutamine is then administered intravenously by an infusion pump, starting at 5 or 10ig/kg per min for 3 min, increasing by 10ig/kg per min every 3 min up to a maximum of 40ig/kg per min. in patients not achieving 85% of their predicted maximal heart rate (220 beats/min minus age for men, beats/min 200 minus age for women) and without symptoms or signs of myocardial ischemia, atropine is administered on top of the maximal dose of dobutamine; starting with 0.25 mg intravenously and repeated up to a maximum of 1.0 mg within 4 min, with continuation of dobutamine infusion. Throughout dobutamine infusion, the ECG (12 leads) is continuously monitored and recorded at 1 minute intervals. Blood pressure is measured and recorded by sphygmomanometry or automatic device every 3 min. the echocardiogram is continuously monitored and recorded on video or quad screen during the final minute of each dobutamine (or atropine) stage and recovery.

Reasons for Termination of the test are:

1. Severe or extensive new wall motion abnormalities.
2. Horizontal or downsloping ST segment depression >0.2 mV at an interval of 80 ms after the j point compared with baseline.
3. ST segment elevation > 0.1 mv in patients without a previous myocardial infarction.
4. Severe angina.
5. A symptomatic reduction in systolic blood pressure \leq 40 mm Hg from baseline.
6. Hypertension (blood pressure \geq 240/120 mm Hg).

Contraindications to DSE include

1. Critical aortic stenosis
2. Hypertrophic cardiomyopathy
3. Uncontrolled hypertension
4. Uncontrolled atrial fibrillation
5. Known severe ventricular arrhythmias and electrolyte abnormalities (mainly hypokalemia). 46,47
6. the addition of atropine is contraindicated in patients with narrow-angle glaucoma. Myasthenia gravis, obstructive uropathy or obstructive gastrointestinal disorders.

Echocardiographic interpretation

The left ventricle is usually divided into the 16 segment model recommended by the American Society of Echocardiography.⁴⁸ Although the quad screen format (with rest, low and high dose and recovery images next to each other in one screen) facilitates wall motion analysis, it is not a prerequisite because videotape analysis seems to be as reliable.⁴⁹

- 1= normal, characterized by a uniform increase in wall excursion and thickening
 2= hypokinesia, denoted by reduced (<5 mm) inward systolic wall motion
 3= akinesia, is marked by an absence of inward motion and

thickening

- 4= dyskinesia, indicated by systolic thinning and outward systolic wall motion

A normal stress echocardiogram is defined by a uniform increase in wall motion and systolic wall thickening, with a reduction in end-systolic cavity area.

A positive test is denoted by development of new wall motion dyssynergy or by worsening of regional dyssynergy in one or more segments.

Other possible dobutamine-induced markers of inchemia

Abnormal left ventricular diastolic filling

Changes in diastolic indexes are known to precede systolic changes and therefore may be a more sensitive indicator of myocardial ischemia. 50

Sinus node deceleration.

Dobutamine stress-induced sinus node deceleration, defined as an initial increase and subsequent decrease in heart rate with progressive dobutamine infusion, occurs more often during dobutamine infusion than during exercise. 51

Mitral regurgitation

The development of new or worsening mitral regurgitation with stress doses of dobutamine. 24,52

Hypotension

It may result from

- 1) An inadequate increase in cardiac output to compensate for an expected decrease in systemic vascular resistance, 53,54
- 2) A disproportionate decrease in systemic vascular resistance in the presence of a normal increase in cardiac output.

ECG changes

Whereas ST segment changes are the hallmark of ischemia in exercise tests. They seem to have less value during dobutamine stress. 5

Feasibility and safety

In 5% of patients, an inadequate acoustic window precludes the performance of successful DSE. 10% of tests are non diagnostic (absence of ischemic markers in submaximal tests) 55,56 because of an insufficient hemodynamic response to dobutamine/atropine administration or limiting side effects.

Adverse effects

Non cardiac side effects (nausea, headache, chills, urgency and anxiety) are usually well tolerated, without the need for test termination.

The most common cardiovascular side effects

1. Angina occurs in 20% of patients 55,57
2. Dobutamine stress-induced hypotension occurs, depending on its definition, in 5% to 37% of patients 54,58-61
3. Arrhythmias are not uncommon 55,57, with frequent premature atrial or ventricular contractions occurring in

- 10% of patients
4. Supraventricular or ventricular tachycardias each occurring in 4% of patients.
5. On the basis of combined diagnostic and safety reports on DSE 17-43, 55-57 it can be roughly estimated that ventricular fibrillation or MI occurs in 1 out of 2,000 studies.
6. Atropine intoxication, although generally requiring a dose of atropine of at least 5 mg, has been reported in a few patients receiving ≥ 1 mg of atropine
7. Fatal events were not reported

Intra observer and inter observer agreement.

Intra observer and inter observer agreement for ischemia within institutes as reported in individual studies 18,19,31,34,36,42 ranged from 95% to 98% and from 92% to 96%, respectively.

Agreement was clearly higher in patients without CAD or with extensive CAD and was lower in patients with limited echocardiographic image quality.

Diagnostic Accuracy

Detection of CAD

As with other testes for detection of CAD, the diagnostic accuracy of DSE is expressed by its sensitivity, specificity and accuracy.

The overall (weighted mean) sensitivity, specificity and accuracy of DSE for a total of 2,246 patients in 28 published studies 17-43 was 80% (95% confidence interval [CI] 78% to 82%), 84% (95% CI 82% to 86%) and 81% (95% CI 79% to 83%), respectively. When only the 17 largest series from single centers were included 19-43 (thus avoiding potential double counting of previously included patients from the same center in an earlier report), these respective numbers were, for a total of 1,454 patients, 81% (95% CI 79% to 84%), 85% (95% CI 82% to 87%) and 82% (95% CI 80% to 85%). The normalcy rate was reported to be 92% 62.

One of the most important avoidable factors influencing test sensitivity is the use of beta blockers. These medications lower peak cardiac work load and inotropic response during DSE and thus have the potential to lower the sensitivity of the test, especially when atropine is not added to dobutamine. 63

Detection of disease in individual coronary arteries

Based on the known anatomic relations between coronary arteries and various myocardial regions, general guidelines have been developed for the assignment of these myocardial regions to specific coronary arteries. It is therefore possible to infer disease of a given coronary artery by noting the location of a wall motion abnormality on echocardiography. The mean reported 24,32,37,42 sensitivities were 72%, 55% and 76%, respectively, and the mean specificities were 88%, 93% and 89%, respectively.

Identification of extensive CAD

An important goal of noninvasive stress testing is the identification of patients with left main or threevessel CAD.

Patients with multi-vessel disease can be differentiated from patients with single-vessel disease by detection of

echocardiographic abnormalities in two or more coronary territories.

Investigators who examined the prediction of multivessel disease by this method 17,19,24,26,29,37 consistently reported a high specificity (range 90% to 100%). However, the sensitivity of DSE for the prediction of multivessel disease varied markedly from 8% to 71%. Several factors contribute to the underestimation of multivessel disease: inadequate stress protocols, the premature cessation of stress because of the development of limiting ischemia in one region, imperfect assignment of myocardial regions to coronary arteries, collateral circulations and anatomically significant but functionally non significant lesions. Recent reports have shown that DSE provides other, unique features to identify multivessel disease, by measuring the ischemic threshold and left ventricular volume changes.

Patients with left bundle branch block or left ventricular hypertrophy.

The ability of noninvasive tests to diagnose or localize CAD in patients with left bundle branch block (LBBB) or left ventricular hypertrophy (LVH) has been disappointing.

Exercise-induced changes on the ECG are non diagnostic in the presence of LBBB 64 and lack specificity in the presence of LVH, even in the absence of baseline ECG abnormalities 65

Reports on the use of DSE in patients with LBBB or LVH are scarce. Small studies including patients without a previous MI and LBBB reported a sensitivity of 80%, a specificity of 87% and an accuracy of 85%. 65,66

These small studies require confirmation from larger series to firmly establish the diagnostic value of DSE in patients with LBBB or LVH.

Comparison with other stress modalities in patients able to exercise adequately

Exercise electrocardiography

Pooled data from eight studies 20,24,31,34-37,41 directly comparing DSE and exercise electrocardiography in the same 560 patients show that the sensitivity (76% vs. 63%, $p < 0.0001$), specificity (88% vs. 64%, $p < 0.0001$) and accuracy (79% vs. 63%, $p < 0.0001$) of DSE was clearly superior. However, since most studies did not specify how many patients were able to exercise adequately, were using digoxin or had abnormal rest ECG result, these results do not indicate that the routine exercise test should be replaced by DSE.

Exercise echocardiography

Pooled data from four studies 34,36,41 directly comparing DSE and exercise echocardiography in the same 334 patients show that the sensitivity (75% vs. 85%, $p < 0.01$) and accuracy (79% vs. 86%, $p < 0.05$) of exercise echocardiography were significantly higher. It should be emphasized that these differences were caused by one particular study in which DSE showed low accuracy. 35 In that study a large number of DSE tests were sub-maximal because a modest decline in systolic blood pressure was used as a, not uncommon, end point, and a substantial number of the study patients were using beta-blockers while atropine was not added to dobutamine.

Comparison with other stress modalities in patients unable to exercise adequately

Dipyridamole echocardiography

In patients unable to perform adequate exercise,

echocardiographic imaging can also be performed with dipyridamole as a pharmacologic stressor. 16 In normal arteries dipyridamole, an indirect coronary vasodilator, causes a three- to fivefold increase in both subendocardial and subepicardial coronary flow. 67 However in stenosed arteries this augmentation is limited (depending on stenosis severity), creating flow heterogeneity. Echocardiographically detected functional evidence of ischemia is not caused by marked changes in blood pressure or heart rate (which change only minimally to moderately) but by coronary steal, either "vertical" (subepicardium from subendocardium) 68 or "horizontal" (nonstenotic from stenotic vessel territory) 69 pooled data from six studies 21,25,31,38,39,41 directly comparing DSE and dipyridamole echocardiography showed that DSE is more sensitive for the detection of CAD (73% vs. 65%, $p < 0.05$), mainly because of a higher sensitivity in patients with single-vessel disease. The specificity (82% vs. 89%) and accuracy (76% vs. 72%) of the respective tests were not significantly different. Recent reports 43,70 have suggested that the addition of atropine to dipyridamole increase the sensitivity of the dipyridamole test for the detection of CAD to a level comparable with dobutamine-atropine stress echocardiography. 71

Radionuclide imaging

During dobutamine stress, coronary blood flow to the vascular bed of a normal artery increases dramatically, whereas perfusion through a stenosed artery may change minimally.

On the basis of this induction in regional flow heterogeneity, the dobutamine stress test can also be performed in conjunction with radionuclide perfusion imaging.

In four studies 72-75 comparing DSE with dobutamine technetium-99m ($Tc-99m$) imaging in 318 patients, sensitivity was 76% versus 81%, specificity 85% versus 71% ($p < 0.01$) and accuracy 80% versus 78%

The finding that DSE is more specific but may be less sensitive (especially in patients with single-vessel disease) is in line with the "ischemic cascade" theory 86, which states that perfusion abnormalities due to limited coronary flow reserve precede echocardiographic and ECG changes.

DSE and radionuclide perfusion imaging seem to have comparable diagnostic accuracy, and the choice of one test over the other can be based on patient characteristics and the competence of the laboratory performing the test 10.

Patients after MI

The major goals of DSE in patients with a previous MI are to assess infarct-related coronary artery patency and to identify patients with multivessel CAD.

Smart et al. 77 reported in a large series of patients, with use of the "biphasic" response, a sensitivity of 82%, a specificity of 80% and a diagnostic accuracy of 82% for the detection of infarct-related coronary artery stenosis.

The presence of multivessel CAD in patients with a previous MI should ideally be based on an ischemic response in two coronary vascular territories. However, an approach in which remote ischemia (ischemia detected outside the infarct-related coronary artery territory) is considered diagnostic for multivessel CAD also seems valid because in most of these patients the infarct-related coronary artery is also significantly narrowed.

Future Developments

At present, the major limitations of DSE are endocardial border definition and subjective interpretation of stress-

induced wall motion abnormalities. Enhancement of border definition (and thus interpretation) in currently under investigation with gray-scale B-mode color encoding, 78 intravenous contrast agents, 79 tissue Doppler interrogation, 80 tissue characterization techniques and backscatter analysis. 61 Eventually, the result of these investigations should lead to improved automatic border detection and objective (computerized), realistic criteria for wall motion abnormalities diagnostic of CAD. 82,83

CONCLUSION

DSE is a feasible, safe and useful exercise-independent stress modality for assessing the presence, localization and extent of CAD. The diagnostic accuracy of DSE seems at least comparable to other, competitive noninvasive stress modalities used in patients with limited exercise capacity. New technical developments are expected to further increase its strengths and should make the interpretation of stress echocardiograms more uniform and less subjective.

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