Diagnostic Techniques

Dobutamine Stress Echocardiography in Clinical Practice

with a Review of the Recent Literature

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Stress echocardiography has been developed in recent years as an effective noninvasive test for the detection and assessment of coronary artery disease. This method combines exercise with 2-dimensional echocardiography, which can assess regional and global left ventricular function during stress. Dobutamine infusion, a pharmacologic means of producing cardiovascular stress, appears to be an excellent alternative to exercise in echocardiographic studies. Currently, it is reserved for patients who cannot exercise at a meaningful level because of advanced age, physical deconditioning, or other factors. This review evaluates the current clinical application of dobutamine stress echocardiography and compares its efficacy with that of exercise echocardiography and nuclear perfusion imaging. ***(Texas Heart Institute Journal 1994;21:202-10)***

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Continuous improvements in ultrasound technology and imaging acquisition have led to the development of a new noninvasive test known as stress echocardiography. This method, which combines exercise with cross-sectional echocardiography, was 1st described in 1979 by Wann and colleagues.[1] It is based on a principle proposed by Gallagher's group[2] and by Ross,[3] which states that during stress-induced ischemia, the decrement in contractile function is directly related to the decrease in regional subendocardial blood flow. Because it can assess regional, as well as global, left ventricular function during stress, 2-dimensional echocardiography is an excellent tool when combined with any stress-producing modality.

For technical, pathophysiologic, and economic reasons, pharmacologic stress may be preferable to exercise as a partner for echocardiography.[4] In this setting, stress may be produced by positive inotropic drugs such as dobutamine, which increase myocardial oxygen demand, or by arterial vasodilators such as dipyridamole or adenosine, which induce flow maldistribution and unmask myocardial ischemia.

This review discusses the use of dobutamine stress echocardiography (DSE) for detection and assessment of coronary artery disease (CAD) and myocardial viability. It also compares DSE to exercise echocardiography and nuclear perfusion imaging.

Dobutamine: Pharmacology and Mode of Action

Dobutamine is a synthetic catecholamine that binds to β_1 and β_2 adrenoreceptors (in its dextro form) and, to a lesser extent, stimulates α_1 postsynaptic adrenoreceptors (in its levo form).[5,6] The drug has a half-life of approximately 2 minutes, and a steady state is achieved after 10 minutes of continuous intravenous infusion.[7] It is metabolized extensively by the liver.

Dobutamine increases perfusion 6 times as much in normal coronary arteries as it does in diseased arteries.[8] Some experimental results indicate that in the presence of severe coronary disease, the drug can induce inhomogeneous perfusion and subsequent myocardial ischemia.[8,9] At a dosage of 8 μg/kg/min, dobutamine has strong inotropic and lusitropic effects, increasing the 1st derivative of left ventricular pressure (LV dP/dt) by 128%, cardiac output by 52%, mean arterial

pressure by 25%, heart rate by 10%, and relaxation velocity by 41%.[10,11] Moreover, patients who experience myocardial ischemia during DSE have a decrease in stroke volume without a concomitant increase in left ventricular end-diastolic pressure. This finding, which contrasts with the hemodynamic response to ischemia induced by exercise and atrial pacing stress tests, is explained by the absence of increased venous return during dobutamine administration.[12]

Assessment of CAD in the Echocardiography Laboratory

Protocol

Most echocardiography laboratories use the following protocol for evaluating CAD. After the patient has signed an informed consent and has undergone a 3-hour fast, then baseline blood pressure, heart rate, 12-lead electrocardiography, and 2-dimensional Doppler echocardiography are performed. Dobutamine is infused with a mechanical pump, starting at 5 μg/kg/min. At 3-minute intervals, the dose is increased incrementally by 5 or 10 μg/kg/min until a maximal dose of 40 μg/kg/min is reached or one of the end-points is achieved. If the target heart rate is not attained, intravenous atropine is given (0.25 mg/min; maximal dose, 1 mg). For myocardial viability assessment, the maximal dose is 10 μg/kg/min, with each test stage lasting 5 minutes. After the infusion is terminated, the patient is monitored continuously until baseline conditions return. Two-dimensional echocardiography is performed using the standard views; results are recorded on videotape at the end of each stage and again 6 minutes after drug infusion is stopped. Baseline, low-dose (10 μg/kg/min), peak-dose, and recovery images are digitized in a continuous loop and are displayed in a quad screen format.[13-15]

Regional wall motion may be assessed semiquantitatively by means of visual inspection or quantitatively with the aid of a computerized digitizing system.[16] The left ventricle is divided into 16 segments, as suggested by the American Society of Echocardiography.[17] Wall motion is reported according to an arbitrary numerical classification in which Normal (1) is characterized by a uniform increase in endocardial excursion and thickening; Hypokinesia (2) is denoted by reduced (<5 mm) inward systolic wall motion and delayed contraction; Akinesia (3) is marked by an absence of inward motion and thickening; and Dyskinesia (4) is indicated by systolic thinning and outward systolic endocardial motion. A wall motion score index (WMSI) is computed by dividing the sum of the segment scores by the number of interpreted segments. A WMSI of 1 is normal (when all 16 segments are visualized), and any increase in the score reflects worsening wall motion.

Doppler interrogation of mitral inflow or left ventricular outflow has been examined by a few investigators.[14,15] Pulsed Doppler interrogation of left ventricular ejection dynamics was studied by Mazeika and associates[18] in a group of 24 patients. A blunted Doppler response was found in patients with extensive asynergy, which reflected severe myocardial ischemia. Pulsed-wave Doppler interrogation of mitral inflow for assessment of diastolic function has not proved useful because of a fusion of early (E) and late filling (A) waves secondary to tachycardia. In another study by Mazeika's group,[19] color Doppler interrogation of left ventricular inflow disclosed an 11% incidence of minimal or mild mitral regurgitation in patients with ischemia and no regurgitation in those without ischemia.

The end-points of DSE are 1) significant chest pain or dyspnea, 2) 85% of the target heart rate, 3) systolic blood pressure >220 mmHg and/or diastolic blood pressure >120 mmHg, 4) symptomatic hypotension and/or bradycardia, 5) diagnostic ST-segment shift, and 6) severe arrhythmias or 7) development of new wall-motion asynergy involving at least 2 contiguous segments. If necessary, the effects of dobutamine can be rapidly reversed with intravenous β-blockers.

A positive test result is denoted by worsening of regional asynergy or by development of new wall-motion asynergy in at least 2 contiguous segments. Conversely, a negative result is characterized by uniform wall motion and thickening of all myocardial segments (or the absence of wall-motion asynergy other than that encountered during the baseline study). The dichotomous interpretation of the test results is progressively changed, however, by a more pathophysiologic interpretation in which the relationship between wall-motion asynergy and dobutamine dosage is taken into consideration.

Safety of DSE

The most common side effects encountered during DSE are listed in Table I.[13-15,20-23] There have been isolated cases of ventricular tachycardia[24] and ventricular fibrillation with successful resuscitation[25] in patients undergoing DSE. Several investigators[26-28] have also noted hypotension and bradycardia during dobutamine infusion. In 21% of their patients, Pellikka and colleagues[26] observed dynamic intraventricular obstruction characterized by a late-peaking systolic velocity profile that exceeded basal velocity by at least 1 m/sec; systolic anterior motion of the mitral valve did not develop in all of these cases. Furthermore, vigorous myocardial contraction in a small left ventricular cavity may trigger sympathetic inhibition and may increase the parasympa-

TABLE I. Side Effects Associated with Dobutamine Stress Echocardiography*

Side Effect	Incidence (%)
Typical coronary chest pain	17-23
Arrhythmias	11-35
Atypical chest pain	8
Severe side effects	3-5
Dyspnea	2-5
Hypotension	0-27
Nausea	0-10
Total incidence of side effects	26-35

* These data were derived from several studies.[13-15,20-23]

thetic discharge, resulting in severe hypotension-bradycardia.[27] Mid-ventricular obstruction may be more likely to occur in patients with higher resting left ventricular ejection fractions and those who exhibit a greater increase in heart rate upon dobutamine infusion. In patients in whom hyperdynamic function develops during dobutamine infusion, administration of a bolus of 250 to 500 mL of normal saline has been advocated.[26]

To some extent, the side-effect profile of DSE is a function of the patient population and the study protocol. In analyzing more than 1,000 DSE studies, Mertes and coworkers[15] found that patients with a recent acute myocardial infarction had more dobutamine-induced angina than those without a recent infarction, but there was no significant difference in the incidence of arrhythmias between the 2 groups. In a study of 103 patients in which the maximal dose of dobutamine was 30 μg/kg/min, the incidence of arrhythmias was half of that reported by Mertes and colleagues.[13,15] Nevertheless, when dobutamine was administered at a maximal dosage of 20 μg/kg/min but in 8-minute stages, the overall frequency of side effects was 41%.[19] As Baudhuin and associates[14] have shown, age has no effect on the incidence of such side effects.

With respect to the influence of β-blockers and calcium channel blockers on the results of DSE, some investigators have found no difference in the sensitivity of CAD detection.[29,30] Nevertheless, Mertes and colleagues[15] observed that at a peak dobutamine dose, the maximal heart rate dose is significantly lower in patients on chronic β-blocker therapy. Therefore, in patients taking β-blockers or calcium channel blockers, atropine is used to reach the target heart rate.

Applications of DSE

Dobutamine stress echocardiography in clinical practice should be reserved for patients who cannot exercise at a meaningful level because of certain illnesses (severe chronic obstructive pulmonary disease; obesity; or neuromuscular, neurologic, or orthopedic problems), advanced age, significant physical deconditioning, or lack of motivation to exercise.

Dobutamine stress echocardiography testing is indicated for the following determinations. 1) Detection and localization of CAD: typical clinical situations include chest pain or dyspnea on exertion during investigation and preoperative evaluation for noncardiac surgery. 2) Assessment of severity, extent, and functional significance of CAD (detection of inducible ischemia): clinical situations include risk stratification after acute myocardial infarction, as well as pre- and postcoronary revascularization. 3) Evaluation of myocardial viability: clinical situations include post-thrombolytic therapy for acute myocardial infarction, preoperative assessment before myocardial revascularization for severe angina, and medically refractory congestive heart failure.

Detection and Localization of CAD

Palac's group[31] was among the 1st to use dobutamine in combination with 2-dimensional echocardiography for the evaluation of CAD. Most investigators have compared the results of DSE with those of coronary angiography. This comparison is not completely valid, however, because these 2 modes of investigation are very different in nature (functional vs anatomic, respectively).

Nine DSE studies using comparable protocols are summarized in Table II.[13,14,20-23,32-34] Together, these studies involved approximately 1,000 patients, with a minimum enrollment of 50 patients per study. The lower specificity of DSE (66%) reported by Marcovitz and Armstrong[21] has been explained by pre- and post-test selection biases. Pretest selection bias occurs as a consequence of including patients with a high probability of disease or those with nonischemic cardiac disease who have resting wall-motion asynergy and, therefore, a greater number of false-positive results. Post-test selection bias occurs when only the patients with a positive DSE are catheterized, resulting in decreased specificity.

Table III shows the sensitivity of DSE in detecting the extent of CAD, as reported by different investigators.[13,14,19,23,24,33] Detection of the number and location of coronary arteries with significant stenosis has very practical implications. Overall, as in other stress tests, the larger the number of critically stenosed arteries, the higher the sensitivity for detection of the diseased arteries.

TABLE II. Sensitivity and Specificity of Dobutamine Stress Echocardiography for Detection of Coronary Artery Disease

Author	No. of Patients	Peak Diastolic Pressure (mmHg)	Stenosis (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)
Sawada[13]	103	30	>50	89	85	83
Segar[20]	85	30	>50	95	82	92
Marcovitz and Armstrong[21]	141	30	>50	96	66	89
Hoffmann[32]	66	40	>70	79	81	80
Marwick[33]	217	40	>50	72	83	-
Previtali[22]	80	40	>50	79	83	80
Forster[34]	105	40	>50	75	89	-
Cohen[23]	52	40	>70	86	87	87
Baudhuin[14]	136	40	>50	80	81	-

In patients without wall-motion asynergy at rest, Segar and coworkers[20] found that an ischemic response to dobutamine at a heart rate of ≤125 beats/min is more frequently associated with multivessel disease.

The literature concerning the detection of individual coronary artery stenoses is controversial. Some investigators[19,35] have obtained more false-positive results in the posterior segments than in the anterior segments, particularly in patients with resting wall-motion asynergy.[19] The reason for this finding is unclear, but it may involve an overlap in perfusion areas between the right and left circumflex arteries,[20] observer error because of suboptimal visualization, or wall-motion asynergy associated with unidentified nonischemic mechanisms.[35] This finding has also been observed with exercise echocardiography.[36,37] Nevertheless, in evaluating the test's ability to detect coronary artery lesions in all 3 vascular territories, Segar's group[20] found no statistically significant differences.

TABLE III. Sensitivity of Dobutamine Stress Echocardiography for Detecting the Extent of Coronary Artery Disease

Author	Maximum Dose (μg/kg/min)	Sensitivity (%)		
		1 vessel	2 vessel	3 vessel
Sawada[13]	30	81	-	100
Marwick[33]	40	68	-	77
Marwick[24]	40	84	-	86
Cohen[23]	40	75	90	100
Baudhuin[14]	40	76	-	95
Mazeika[19]*	20	50	60	86

* In the protocol used by Mazeika,[19] each test stage of dobutamine stress echocardiography lasted 8 minutes.

Preoperative Evaluation of Noncardiac Surgical Patients. Dobutamine stress echocardiography has been shown to have a sensitivity of 100%, a specificity 69%, and positive and negative predictive values of 19% and 100%, respectively, for perioperative myocardial ischemic events.[38] It has been useful in evaluating patients before vascular, intraabdominal, major orthopedic, and other noncardiac operations. Patients with peripheral vascular disease have a high incidence (60%) of significant CAD.[39] In 1 study, an ischemic response to dobutamine identified a group that had a 21% risk of cardiac events.[40] In the experience reported by Poldermans and associates,[25] the most powerful independent predictors of perioperative events were 1) new wall-motion asynergy during dobutamine infusion and 2) age greater than 70 years. Davila-Roman and coworkers[41] found a positive vs negative DSE result to be a significant predictor of perioperative events (20% vs 0%; p=0.003). Thus, a negative DSE result predicts freedom from perioperative cardiac complications with a high level of confidence.

Assessment of Severity, Extent, and Functional Significance of CAD

Risk Stratification after Acute Myocardial Infarction. No large studies are available regarding the role of DSE in patients who have had an acute myocardial infarction. Berthe and colleagues[42] found that DSE had a sensitivity of 85%, a specificity of 88%, and an accuracy of 87% in detecting multivessel CAD in patients with wall-motion asynergy at rest. After acute myocardial infarction, the detection of remote wall-motion asynergy suggested the presence of multivessel CAD, a finding which has been confirmed by other studies.[30,43]

In evaluating a group of patients with acute myocardial infarction who had received thrombolytic therapy, Smart and co-authors[44] reported a 76% positive predictive value and a 74% negative predictive value of DSE for the presence of multivessel disease.

Assessment of Percutaneous Transluminal Coronary Angioplasty Results. Dobutamine stress echocardiography may be a valuable alternative for early evaluation after percutaneous transluminal coronary angioplasty. Exercise electrocardiography has a low sensitivity for assessing single-vessel coronary disease, and exercise thallium scintigraphy frequently reveals persistent reversible defects in myocardial areas nourished by the dilated coronary artery.[45,46] McNeill and associates[47] found that the preangioplasty sensitivity of dobutamine/atropine stress echocardiography was 71% in patients who were taking medication and had primarily single-vessel disease. A successful angioplasty demonstrated reversal of dobutamine-stress-induced ischemia early (mean, 1.3 days) after the procedure. Akosah and coworkers[48] demonstrated an immediate improvement in regional myocardial function after successful angioplasty in their patients. The accuracy of the results was not affected by concomitant chronic β-blocker therapy.

Evaluation of Myocardial Viability

Dobutamine stress echocardiography is useful in the detection of myocardial tissue viability after pharmacological or mechanical coronary artery recanalization in patients with an acute myocardial infarction. The technique is also used before myocardial revascularization in patients with severe left ventricular dysfunction, significant angina, or both.

Preliminary studies done in the catheterization laboratory to assess myocardial viability using intravenous nitrates, inotropic stimulation, or extrasystolic stimulation have been replaced by more accurate evaluation techniques such as nuclear perfusion scintigraphy, positron emission tomography (PET), and dobutamine echocardiography. Of these methods, PET scanning is currently considered the "gold standard" for detecting myocardial viability.[49]

Myocardial stunning, hibernation, and the more-recently described functional border zone[50,51] may be accompanied by a decreased level or an absence of myocardial contraction, detected by rest echocardiography. Management of these events is substantially influenced by the results of viability studies.[52] The ability of low-dose dobutamine echocardiography (5 to 10 μg/kg/min) to identify viable myocardial tissue by improvement in wall thickening has been demonstrated in experimental[53] and clinical studies.[54-57] Low-dose dobutamine echocardiography has been compared to perfusion scintigraphy,[58] PET,[54] and to histopathological evidence of viability.[59] Ultimately, the gold standard to which each of the enumerated methods must be compared is the functional recovery after revascularization of those myocardial segments found viable by one or another technique.

Signs of myocardial viability during dobutamine infusion include one or both of the following: 1) regional contractility in at least 2 ventricular segments with sufficient improvement to decrease the WMSI by 2 points or more; 2) normal contractility under basal conditions in at least 2 segments of the area at risk. A segment remaining akinetic or dyskinetic under the influence of dobutamine is considered necrotic.[54] Resting wall-motion asynergy that worsens during dobutamine infusion also suggests viability.[60]

Due to the existence of a functional border zone,[61] improvement in contraction in the border zone of the ischemic area that includes <30° of the circumference or <1 cm of the left ventricular length may not reflect improvement in the ischemic region. In addition, improvement in systolic wall thickening and not just in wall motion is mandatory for diagnosis of a viable wall.

In a study of 21 patients after an acute anterior wall myocardial infarction, Barilla and co-authors[57] reported that dobutamine-responsive wall motion predicted functional recovery after revascularization with 77% accuracy. In another study in which patients were treated with thrombolytic therapy after an acute myocardial infarction,[56] dobutamine echocardiography had a high specificity (93%) and sensitivity (86%) for detection of reversible dysfunction.

In a study of 49 patients with multivessel coronary disease and depressed left ventricular function, Cigarroa and associates[49] reported that dobutamine echocardiography correctly identified the functional recovery of the segments that showed contractile reserve.

When DSE was compared with thallium and sestamibi for the detection of viable myocardium,[58] all 3 tests had similar sensitivities and specificities. Pierard's group[54] found a concordance of 79% between dobutamine echo and ^{18}F-deoxyglucose PET for assessment of viability.

Lau and colleagues[59] compared DSE and PET with histopathological evidence of viability in 5 explanted human hearts, and found a similar sensitivity in dobutamine and PET.

Because of its high sensitivity and specificity for the detection of myocardial viability, DSE may be used successfully in this capacity in medical institutions that do not have access to PET. Taking into consideration its high accuracy in the detection of ischemia and, importantly, its lower cost, DSE may be an attractive alternative test for identifying potentially functional recoverable myocardium, even in medical centers where PET is available.

Contraindications to DSE

Contraindications to DSE include the following: critical aortic stenosis; hypertrophic cardiomyopathy; uncontrolled conditions such as arrhythmias, arterial hypertension, myocardial ischemia, and congestive heart failure; hemodynamic instability; electrolyte abnormalities; and inadequate echo windows. Most of the conditions that preclude application of DSE are similar to those that preclude exercise testing. Electrolyte abnormalities, particularly hypokalemia (as in patients with a recent acute myocardial infarction), must be corrected because of the known stimulatory effect of catecholamines on β_2 adrenoreceptors, with subsequent shifting of potassium ions from extracellular to intracellular space.[62] When stimulated by dobutamine, malignant arrhythmias may develop in an irritable myocardium that has sustained a recent acute ischemic insult.

DSE Compared with Other Methods of Evaluation

Comparison of DSE, Exercise Electrocardiography, and Thallium-201 Scintigraphy in the Evaluation of CAD. During upright isotonic exercise, the hemodynamic response of the cardiovascular system resembles that recorded during dobutamine infusion.[63] The main differences observed during exercise are greater heart rate and blood pressure.

In comparing DSE with exercise electrocardiography for detection of CAD, various investigators have reported a sensitivity of 79% vs 63%; specificity of 79% vs 72%; and accuracy of 77% vs 63%, respectively.[18,25,26,28,43,64,65]

Researchers have also compared the ability of DSE to diagnose CAD with that same ability in stress thallium and technetium-99m isobutyl nitrile (MIBI) scintigraphy. Both DSE and thallium-201 perfusion scintigraphy have a high sensitivity (about 90%) and specificity (about 80%) for detecting CAD.[60,66]

Marwick and colleagues[33] used technetium-99m MIBI and DSE in 217 patients without previous Q wave myocardial infarction, and found a sensitivity of 76% (compared with 72% for DSE) and specificity of 67% (83% for DSE). The results obtained from patients with left ventricular hypertrophy accounted for most of the variation in specificity between echocardiography and scintigraphy (94% vs 59%). It appears that perfusion scintigraphy is more sensitive in patients with milder degrees of ischemia (due to single-vessel CAD or submaximal stress) and that echocardiography is more specific in patients with left ventricular hypertrophy or left bundle-branch block. In another study by Marwick's group,[24] similar levels of sensitivity, specificity, and accuracy were noted between DSE and dobutamine MIBI.

Forster and associates,[34] using DSE and MIBI SPECT (single-photon emission computed tomography) to study 105 patients with either proven or suspected CAD, reported that both techniques detected ischemia at a rate of 74%. In patients without a previous myocardial infarction, the 2 techniques were equivalent at 84%.

Comparison of DSE with Adenosine and Dipyridamole Echocardiography. In a study of 40 patients undergoing coronary angiography within 6 weeks of stress echocardiography, Martin and coworkers[65] found the sensitivity of DSE (76%) to be significantly higher than that of adenosine echocardiography (40%) or of high-dose (0.84 mg/kg) dipyridamole echocardiography (56%). The specificity of the adenosine test (93%) was significantly higher than that of dobutamine (60%) and dipyridamole (67%) echocardiography. Two other studies have reported similar sensitivity and specificity of DSE and dipyridamole echo.[67,68]

Limitations of DSE

In contrast to exercise stress tests, which evaluate the *actual* functional capacity, DSE assesses *simulated* functional capacity. The wall-motion analysis during DSE is a subjective, semiquantitative analysis, and it is therefore dependent on the observer's expertise. However, it is performed in most clinical laboratories with a high level of accuracy. Currently, there is no consensus regarding which quantitative technique to use.[32] In addition, about 10% of the patients studied do not have acceptable acoustic windows and therefore are not well suited to this test. The side effects of dobutamine administration and the length of time necessary for test performance and interpretation (about 1 hour) must also be considered when DSE is ordered.

Conclusions

In contemporary cardiology, dobutamine stress echocardiography is already an established test for

detection and assessment of coronary artery disease and myocardial viability in patients who cannot exercise. It has been shown to be safe, versatile, cost-effective, and highly reliable. Its sensitivity, specificity, and accuracy are comparable and, in some instances, are similar to those of nuclear perfusion scintigraphy studies. It is the method of choice for evaluation of patients with left ventricular hypertrophy or left bundle-branch block. Initial studies comparing the diagnostic accuracy of dobutamine stress echocardiography with that of PET have demonstrated a strong correlation between these 2 techniques for the detection of viable myocardium. Dobutamine stress echocardiography does not replace any of the noninvasive methods used today for the assessment of patients with coronary artery disease, but complements them to achieve the highest possible diagnostic and prognostic accuracy.

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