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REVIEW ARTICLES

Methodology, Feasibility, Safety and Diagnostic Accuracy of Dobutamine Stress Echocardiography

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Large numbers of patients referred for evaluation of chest pain are unable to perform adequate, diagnostic exercise testing. In these patients, dobutamine stress echocardiography (DSE) represents an alternative, exercise-independent stress modality. Apart from the ~5% of patients with an inadequate acoustic window, 10% of patients referred for this test have nondiagnostic (submaximal negative) test results. Serious side effects during or shortly after DSE are uncommon, with ventricular fibrillation or myocardial infarction occurring in ~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 for 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 multiregion 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 a useful, feasible and safe exercise-independent stress modality for assessing the presence, localization and extent of CAD.

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Confirming or excluding coronary artery disease (CAD) in patients with chest pain remains a challenge because this disease is still the leading cause of death in the Western world (1). Traditionally, exercise electrocardiography is performed as a first-line noninvasive diagnostic stress test (2). However, large numbers of patients referred for evaluation of chest pain are unable to perform adequate diagnostic exercise testing, mainly because of deconditioning or neurologic, respiratory, peripheral vascular or orthopedic limitations (3). In these patients, dobutamine stress echocardiography (DSE) represents an alternative, exercise-independent stress modality. Since its clinical introduction a decade ago (4), DSE has become an established method for the diagnosis of CAD (5–32). This review article deals with (1) methodologic aspects, and (2) clinical applications of DSE to assess the presence, localization and extent of CAD.

Methods and Statistical Analysis

We reviewed all DSE studies published in the major English language journals up to August 1996 that met defined criteria with respect to diagnostic accuracy for the detection of CAD. These criteria were 1) inclusion of patients both with and without angiographically defined CAD; and 2) statement of how many patients with and without CAD had negative and positive DSE results. Reports indicating that the patients included were subsets of larger published studies were excluded. Also excluded from the primary diagnostic analysis were studies solely involving patients with a myocardial infarction (MI) because the diagnosis of CAD is already established in these patients. When DSE was compared with other stress modalities, only those studies making direct comparisons in the same patients were included.

Sensitivity was defined as the number of true positive tests divided by the total number of patients with angiographically significant CAD. *Specificity* was defined as the number of true negative tests divided by the total number of patients without angiographically significant CAD. *Accuracy* was defined by the total number of true positive and true negative tests divided by the total number of patients. *Normalcy rate*, a referral bias independent estimate of specificity (33), was defined as the proportion of patients with a low pretest likelihood of CAD (<10%) who had negative test results. Mean values for sensitivity, specificity and accuracy were calculated by combining the results of individual patient data from multiple studies. Comparisons of sensitivity, specificity and accuracy were performed using the standardized normal distribution test. Statistical significance was defined at $p < 0.05$.

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Abbreviations and Acronyms

CAD = coronary artery disease
CI = confidence interval
DSE = dobutamine stress echocardiography (echocardiographic)
ECG = electrocardiogram, electrocardiographic
LBBB = left bundle branch block
LVH = left ventricular hypertrophy
MI = myocardial infarction
Tc = technetium

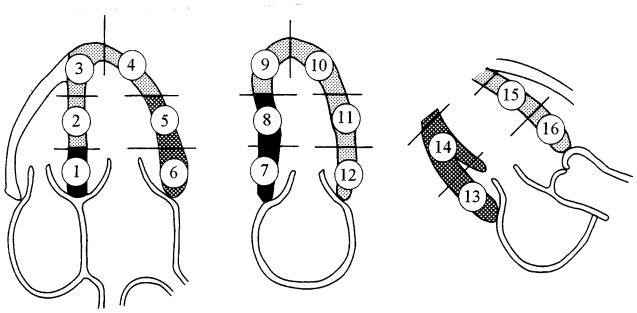

Figure 1. Diagrams showing the 16 regional wall segments and distribution of coronary perfusion. **Left**, Apical four-chamber view; **middle**, apical two-chamber view; **right**, long-axis view. **Dotted areas** = left anterior descending coronary artery; **crosshatched areas** = left circumflex coronary artery; **solid areas** = right coronary artery.

Test Methodology

Dobutamine: pharmacology and mechanism of action. Dobutamine is a synthetic catecholamine with a relatively short plasma half-life of ~2 min due to rapid metabolization in the liver to inactive metabolites (34,35). It has strong $beta_1$-receptor and mild $alpha_1$- and $beta_2$-receptor agonist activity. When used at low dose (up to 10 μg/kg body weight per min), marked inotropic effects (mediated by both $alpha_1$- and $beta_1$-receptor stimulation) are encountered. These effects are extensively used for treatment of heart failure. When used at high dose (20 to 40 μg/kg per min), heart rate is progressively increased (mediated by $beta_1$-receptor stimulation). Systemic blood pressure increases only minimally because of an increase in cardiac output and a decrease in systemic vascular resistance because of peripheral vasoconstrictive effects (mediated by $alpha_1$-receptor stimulation) overwhelmed by vasodilative effects (mediated by $beta_2$-receptor stimulation). 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 (14). 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 (36). Hence, regional ischemia develops and causes regional wall motion abnormalities that can be detected by two-dimensional echocardiography (5–32).

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) (5–32,37). Usually, centers that use lower peak doses of dobutamine use longer stage durations and stop beta-adrenergic blocking agent treatment more often before the test. To date, the most widely used protocol uses dobutamine up to 40 μg/kg per min, with the addition of atropine up to 1 mg (14).

According to this protocol, a rest 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 10 μg/kg per min for 3 min, increasing by 10 μg/kg per min every 3 min up to a maximum of 40 μg/kg per min. In patients not achieving 85% of their theoretic 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 (three leads) is continuously monitored and recorded (12 leads) at 1-min intervals. Blood pressure is measured and recorded by sphygmanometry 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 interruption of the test are severe or extensive new wall motion abnormalities; horizontal or downsloping ST segment depression >0.2 mV at an interval of 80 ms after the J point compared with baseline; ST segment elevation >0.1 mV in patients without a previous MI; severe angina; a symptomatic reduction in systolic blood pressure ≥40 mm Hg from baseline; hypertension (blood pressure ≥240/120 mm Hg); significant tachyarrhythmias; and any serious side effect regarded as due to dobutamine. A beta-blocker that can be injected intravenously must be available to reverse the effects of dobutamine if they do not revert spontaneously and quickly. Contraindications to DSE include critical aortic stenosis, hypertrophic cardiomyopathy, uncontrolled hypertension, uncontrolled atrial fibrillation, known severe ventricular arrhythmias and electrolyte abnormalities (mainly hypokalemia) (38,39). The addition of atropine is contraindicated in patients with narrow-angle glaucoma, myasthenia gravis, obstructive uropathy or obstructive gastrointestinal disorders.

Echocardiographic interpretation. For purposes of analysis, the left ventricle is usually divided into the 16-segment model recommended by the American Society of Echocardiography (Fig. 1) (40). 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 (41). *Wall motion or thickening* is reported according to an arbitrary numerical classification: 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. Hypokinetic segments can be further classified as *mild* (2A) or *severe* (2B) hypokinetic segments to refine the analysis. 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. In patients with rest wall motion abnormalities, use of the "biphasic" response (i.e., initial improvement of dyssynergy at low dose followed by worsening of dyssynergy at high dose) has improved detection of CAD (42). More subtle criteria for positive test are tardokinesia (delayed excursions) and relative failure to augment wall thickening. These more subtle criteria should be used with caution by unexperienced interpreters because too strict application could lead to substantial loss in specificity (43). Moreover, isolated mild wall motion deterioration in mid- or basal inferoposterior segments needs to be interpreted with caution because these segments are known to be less specific for CAD (43,44). Several investigators have reported (8,12,13,25) that the inclusion of rest wall motion abnormalities in addition to new or worsening wall motion abnormalities as a criteria for positive test results in a gain in sensitivity without a loss in specificity for the detection of CAD. However, the inclusion of rest wall motion abnormalities as a criterion for CAD is appropriate only in patients without a previous MI because in patients with a previous MI, this diagnosis is nearly certain and does not require further testing for this purpose.

Other possible dobutamine-induced markers of ischemia. *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 (45). Despite the finding (46) that left ventricular filling is predominantly mediated by a complex interaction of active myocardial relaxation, passive filling properties and left atrial pressure, one study clearly demonstrated (47) that during dobutamine stress testing, an abnormal response of Doppler indexes of left ventricular early filling (E velocity) is a more sensitive marker for the detection of significant single-vessel disease than are wall motion abnormalities. Other, confirmative publications are needed to firmly establish the clinical utility of left ventricular filling indexes.

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 (48). In a small group of patients, it was reported (49) to be a specific marker of inferior wall ischemia, as assessed by dobutamine perfusion scintigraphy. Currently, there are no stress echocardiographic data reporting the pathophysiology of isolated sinus node deceleration. Cardiac slowing, in particular in combination with hypotension (see later), may also result from a neurally mediated cardiovascular vasodepressor reflex (50).

Mitral regurgitation. Low dose dobutamine is known to have a beneficial effect on chronic mitral regurgitation, especially in patients with left ventricular dysfunction (51,52). Although the mechanism of this beneficial effect remains unclear, it may be related to a decrease in afterload or mitral orifice size that results from the vasodilatory and inotropic effects of dobutamine (53). It has been suggested (12) that the development of new or worsening mitral regurgitation with stress doses of dobutamine is related to ischemia and improves the sensitivity of DSE for the detection of CAD. However, a study specifically addressed to this subject reported (51) that in fact very few patients developed new or worsening mitral regurgitation during high dose dobutamine infusion, and there was no association with stress-induced wall motion abnormalities.

Hypotension. Generally, dobutamine stress causes an increase in cardiac output and a small reduction in systemic vascular resistance (53,54), with a small increase in systolic blood pressure as a net result (5–32). Although the pathophysiology of dobutamine stress-induced hypotension has not been completely defined, theoretically, it may result from 1) an inadequate increase in cardiac output to compensate for an expected decrease in systemic vascular resistance; and 2) a disproportionate decrease in systemic vascular resistance in the presence of a normal increase in cardiac output. An inadequate increase in cardiac output may be due to inadequate contractile reserve, severe ischemic left ventricular dysfunction or left-sided obstructive heart disease. Dynamic left ventricular cavity obliteration due to strong inotropic stimulation was proposed as an important cause for reduced cardiac output and hypotension (55), especially in patients with dehydration. Later studies could not confirm this mechanism (56), and the proposed bolus of saline before dobutamine (55,57) did not prevent cavity obliteration in a canine model (58). The second mechanism, a disproportionate decrease in systemic vascular resistance, may be due to excessive sensitivity of the peripheral circulation to $beta_2$-receptor stimulation, increased $beta_2$-receptor density (deconditioned patients) or a neurally mediated mechanism in which vigorous myocardial contraction stimulates the intramyocardial mechanoreceptors, resulting in sympathetic withdrawal and enhanced parasympathetic activity (the Bezold-Jarisch reflex) (59). In contrast to exercise stress-induced hypotension (60), all presently available data indicate that there is no relation between ischemic left ventricular systolic dysfunction (54,56,61,62) or angiographically detected CAD (61) and dobutamine stress-induced hypotension.

ECG changes. Whereas ST segment changes are the hallmark of ischemia in exercise tests (2), they seem to have less value during dobutamine stress. In an early study in patients with mainly unstable angina and severe coronary lesions, dobutamine stress-induced ST segment depression was described as a highly accurate diagnostic test (63). However, subsequent reports in stable patients with less severe lesions could never confirm these data (7,12,29,64). Whether this is due to misplacement of electrodes (because of the apical

acoustic window), less stress (lower rate–pressure product than for exercise tests) or other factors still needs to be established. In contrast, as in exercise testing (65), dobutamine stress-induced ST segment elevation in patients without a previous MI was consistently reported to be associated with (severe) coronary artery disease (63,64,66,67).

Feasibility and safety. In ~5% of patients, an inadequate acoustic window precludes the performance of successful DSE (37,68), although this proportion may underestimate the actual number of patients with an inadequate acoustic window in an unselected population. Furthermore, 10% of tests are nondiagnostic (absence of ischemic markers in submaximal tests) (68,69) because of an insufficient hemodynamic response to dobutamine–atropine administration or limiting side effects. Noncardiac side effects (nausea, headache, chills, urgency and anxiety) are usually well tolerated, without the need for test termination. The most common cardiovascular side effects are angina, hypotension and cardiac arrhythmias. Although angina occurs in ~20% of patients (68,70), severe angina as a test end point without accompanying new or worsening wall motion abnormalities is rare. Dobutamine stress-induced hypotension occurs, depending on its definition, in 5% to 37% of patients (54,56,61,62,68,71): A ≥20-mm Hg decrease in systolic blood pressure occurs in ~20% (54,61,71); severe, symptomatic hypotension necessitating test termination occurs only rarely (71). Arrhythmias are not uncommon (68,70), with frequent premature atrial or ventricular contractions occurring in ~10% of patients and supraventricular or ventricular tachycardias each occurring in ~4% of patients. Ventricular tachycardias are usually nonsustained and have been attributed to $beta_1$-receptor stimulation and dobutamine-induced reduction in plasma potassium concentrations (39). These arrhythmias are more frequently encountered in patients with a history of previous ventricular arrhythmias or baseline wall motion abnormalities (68). No study has reported an association between the addition of atropine or new wall motion abnormalities and ventricular tachycardias (68,70). On the basis of combined diagnostic and safety reports on DSE (5–32,68–70), it can be roughly estimated that ventricular fibrillation or MI occurs in 1 of 2,000 studies. These severe complications can occur up to 20 min after dobutamine withdrawal (69), and it has been suggested (69) that in these patients, $alpha_1$-mediated coronary and systemic vasoconstriction might be paradoxically exacerbated, not reversed, by beta-blocker administration. Atropine intoxication, although generally requiring a dose of atropine of at least 5 mg (72), has been reported in a few patients receiving ≤1 mg of atropine (69). Fatal events were not reported (5–32,68–70).

Intraobserver and interobserver agreement. Intraobserver and interobserver agreement for ischemia within institutes as reported in individual studies (6,7,20,23,25,31) ranged from 95% to 98% and from 92% to 96%, respectively. However, a study specifically addressing interinstitutional agreement in DSE between five centers (73) reported that abnormal or normal results of DSE were agreed on by four or five of the five centers in only 73% of patients. Agreement on the left anterior descending territory (78%) was similar to that for the combined right coronary and left circumflex territories (74%). For specific segments, agreement ranged from 84% to 97% and was highest for the basal anterior segment and lowest for the basal inferior segment. 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 tests for detection of CAD, the diagnostic accuracy of DSE is expressed by its sensitivity, specificity and accuracy. These indexes depend on several technical factors, such as the definition of a positive test and the threshold for defining significant CAD. In addition, several characteristics of the patients studied may affect these indexes, such as the presence or absence of MI, the number of male patients, referral bias, the level of stress and the severity (percent stenosis) and extent (number of diseased vessels) of CAD in the referred cohort.

The reported sensitivity, specificity and accuracy for each of 28 published studies (5–32) are shown in Table 1. The overall (weighted mean) sensitivity, specificity and accuracy of DSE for a total of 2,246 patients was 80% (95% confidence interval [CI] 78% to 82%), 84% (95% CI 82% to 86%) and 81% (95% CI 79% to 83%), respectively (Fig. 2). When only the 17 largest series from single centers were included (7,9–12,14,16,18–21,26–28,30–32) (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% (74).

From the results of the individual studies in Table 1 it cannot be concluded that the addition of atropine improves the diagnostic accuracy of DSE. However, in those studies in which atropine was used, relatively many patients were taking a beta-blocker and had mild CAD. Indeed, all studies directly comparing DSE with versus without atropine (14,32) showed an increase in sensitivity without a loss in specificity. These results were recently confirmed by a study from the Mayo Clinic (75) showing that the addition of atropine significantly increased sensitivity, especially in patients taking a beta-blocker and with milder forms of CAD.

The effect of the number of diseased coronary arteries was assessed in 15 studies (5–8,12,16,20–23,25,26,28,31,32), for a total of 897 patients. Mean sensitivity increased significantly from 74% for single-vessel disease to 86% for double-vessel disease and to 92% for triple-vessel disease (Fig. 3).

Different reports from center to center are most likely due to the aforementioned factors. 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 (5,76) and thus have the potential to lower the sensitivity of the test, especially when atropine is not added to dobutamine (77). Investigators who

Table 1. Diagnostic Accuracy of Dobutamine Stress Echocardiography As Reported in 28 Studies

Year and First Author (ref no.)	Protocol		No. of Pts	Men (%)	MI (%)	No CAD (%)	MVD (%)	Beta-Blocker	Cor Angio		WMA	Sens (%)	Spec (%)	Accuracy (%)
	Dobutamine (μg/kg per min)	Stage Duration (min)							% Diam Stenosis	Anal				
1991														
Sawada (5)	30	3	55	62	0	36	26	+	≥ 50	Q	New	89	85	87
Previtali (6)	40	5	35	86	3	20	34	−	≥ 70	V	New	68	100	74
Cohen (7)	40	3	70	100	27	27	50	−	≥ 70	V	New	86	95	89
1992														
Salustri (8)	40*	3	52	73	27	29	33	+	≥ 50	Q	New	54	80	62
Martin (9)	40	3	40	95	35	38	NA	+	≥ 50	V	New	76	60	70
Segar (10)	30	3	85	61	NA	26	NA	NA	≥ 50	Q	New	95	82	92
Marcovitz (11)	30	3	141	60	29	23	33	+	≥ 50	Q	Any	96	66	89
Mazeika (12)	20	8	50	88	26	28	48	−	≥ 70	V	New	64	93	72
Salustri (13)	40	3	46	70	33	39	39	+	≥ 50	Q	New	57	78	65
McNeill (14)	40*	3	80	74	35	41	NA	+	≥ 50	V	New	70	88	78
1993														
Marwick (15)	40	3	97	71	0	39	29	−	≥ 50	Q	Any	85	82	84
Günalp (16)	30	5	27	85	0	33	33	−	≥ 50	V	New	83	89	85
Forster (17)	40*	3	21	55	0	43	38	+	≥ 50	V	New	75	89	81
Marwick (18)	40	3	217	72	0	35	34	+	≥ 50	Q	Any	72	83	76
Hoffmann (19)	40*	2	60	77	0	20	35	−	≥ 70	Q	New	79	83	80
Previtali (20)	40	5	80	78	19	29	41	−	≥ 50	V	New	79	83	80
Takeuchi (21)	30	5	120	74	52	38	31	+	≥ 50	Q	Any	85	93	88
Baudhuin (22)	40	3	136	61	0	30	29	−	≥ 50	Q	Any	79	83	80
Cohen (23)	40	3	52	98	25	29	40	−	≥ 70	V	New	86	87	87
1994														
Marwick (24)	40	3	86	70	0	35	40	+	≥ 50	Q	Any	54	83	64
Beleslin (25)	40	3	136	85	57	13	8	+	≥ 50	Q	New	82	76	82
Senior (26)	40	3	61	72	21	28	49	−	≥ 50	V	Any	93	94	93
Sochowski (27)	40	3	46	67	0	46	28	+	≥ 50	V	New	68	81	74
Ostojic (28)	40	3	150	83	51	13	11	+	≥ 50	Q	New	75	79	75
1995														
Daoud (29)	30	3	76	58	37	15	55	+	≥ 50	V	Any	92	73	89
Dagianti (30)	40	5	60	79	0	58	25	−	≥ 70	Q	New	72	97	87
Ho (31)	40	3	54	85	41	21	67	NA	≥ 50	V	New	93	73	89
1996														
Pingitore (32)	40*	3	110	83	27	16	46	+	≥ 50	Q	New	84	89	85

*Atropine addition. Anal = analysis; CAD = coronary artery disease; Cor Angio = coronary angiography; Diam = diameter; MI = myocardial infarction; MVD = multivessel disease; NA = not available; Pts = patients; Q = (semi)quantitative; ref = reference; Sens = sensitivity; Spec = specificity; V = visual; WMA = wall motion abnormality.

compared study patients with versus without beta-blocker therapy (13,18,25) consistently found that sensitivity was lower in patients with beta-blocker therapy despite the finding that patients taking beta-blockers generally have a higher prevalence of (extensive) CAD (13).

Bayesian analysis. Although values for sensitivity and specificity have a useful role, the use of DSE in diagnostic practice is to assist in the clinical recognition of CAD. In this sense, tests are used to reclassify the initial clinical impression of the probability of CAD into high, low and intermediate risk subgroups. According to the Bayes theorem, the likelihood of a positive test result is determined by the probability of CAD in the patient studied, as well as the accuracy of the test (78). In one report (79) that included 223 patients without a previous MI, the study cohort was grouped into those with a high (>80%), intermediate (10% to 80%) and low probability (<10%) of CAD before and after DSE, and the ability of DSE to restratify patients was analyzed. According to the pretest likelihood of CAD, 68 patients (30%) were regarded as having a "diagnostic" low or high probability of CAD. By application of the Bayes theorem, DSE defined 121 patients (54%) as being in the high or low posttest probability groups. Importantly, the accuracy of predicting CAD in the high probability group and the absence of CAD in the low probability group after DSE was excellent (87%).

Detection of disease in individual coronary arteries. The coronary arteries and their branches supply different regions of the left ventricular myocardium. Based on the known anatomic relations between coronary arteries and various myocardial regions, general guidelines have been developed for the assign-

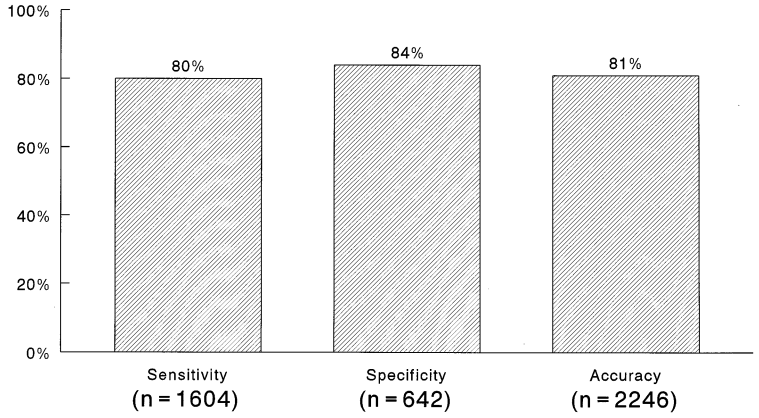

Figure 2. Sensitivity, specificity and accuracy of DSE for detection of CAD.

ment of these myocardial regions to specific coronary arteries (Fig. 1). It is therefore possible to infer disease of a given coronary artery by noting the location of a wall motion abnormality on echocardiography. Figure 4 summarizes the sensitivity and specificity for the identification of disease in the left anterior descending, left circumflex and right coronary arteries. The mean reported (12,21,26,31) sensitivities were 72%, 55% and 76%, respectively, and the mean specificities were 88%, 93% and 89%, respectively. The sensitivity for detection of left circumflex disease was lower than that for left anterior descending ($p < 0.02$) and right coronary disease ($p < 0.005$). The lower sensitivity for detection of disease in the left circumflex artery can be explained by the variation in coronary anatomy (with a small circumflex territory in some patients) and problems with resolution of the lateral wall endocardium because of the parallel orientation of the wall and the ultrasound beam. To compensate for the variation in blood supply of the posterior wall (by either the left circumflex or right coronary artery, depending on their relative size) others (6,11,12) divided the blood supply of the heart into two systems: an anterior (left anterior descending coronary artery) system and a posterior (left circumflex and right coronary arteries) system. For these circulations, the mean reported sensitivities were 75% and 73%, respectively, and the mean specificities were 86% and 80%, respectively.

Identification of extensive CAD. An important goal of noninvasive stress testing is the identification of patients with left main or three-vessel CAD. Such patients could benefit from revascularization from a prognostic point of view (80). Patients with multivessel 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 (5,7,12,15,18,26) 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 nonsignificant lesions. Recent reports have shown that DSE provides other, unique features to identify multivessel disease, by measuring the ischemic threshold (10,81) and left ventricular volume changes (82). Eventually, an algorithm based on patient clinical characteristics, combined with the aforementioned indicators of multivessel disease may lead to improved identification of multivessel disease.

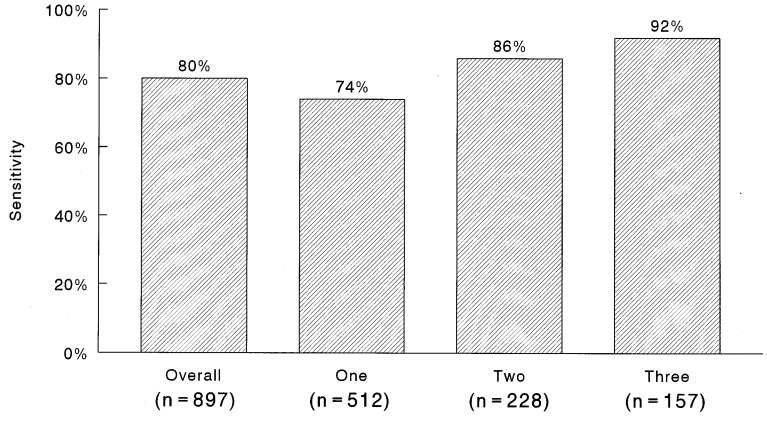

Figure 3. Sensitivity of DSE for detection of CAD by number of diseased vessels.

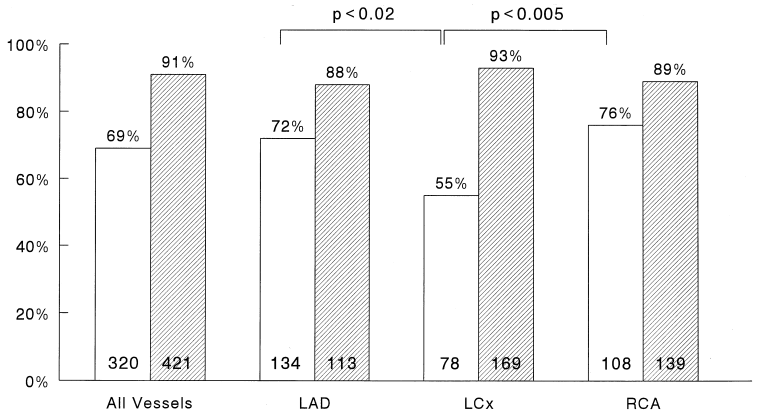

Figure 4. Sensitivity **(open bars)** and specificity **(hatched bars)** of DSE for detection of CAD in individual coronary arteries. **Numbers within bars** indicate number of vessels. Included in the analysis were patients with single-vessel and multivessel CAD. LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

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 nondiagnostic in the presence of LBBB (83) and lack specificity in the presence of LVH, even in the absence of baseline ECG abnormalities (84). Moreover, several scintigraphic studies (85,86) have reported false positive results for detecting CAD in the presence of LBBB (especially when exercise stress is used) and LVH, resulting in a low specificity. Reports on the use of DSE in patients with LBBB or LVH are scarce. One study (87) in 13 patients without a previous MI and LBBB reported a sensitivity of 80%, a specificity of 87% and an accuracy of 85%. A study (84) in 28 patients with a history of hypertension and (echocardiographically defined) LVH reported a sensitivity of 89%, a specificity of 100% and an accuracy of 93%. The latter study reported that DSE was more specific (100% vs. 22%, $p < 0.0001$) and accurate (93% vs. 54%, $p < 0.0001$) compared with exercise electrocardiography. Although both DSE studies reported excellent accuracies for the detection of CAD, 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.* Apart from the special issues, discussed in the previous section of this review, several studies directly compared DSE with exercise electrocardiography in more heterogeneous patient groups. As seen in Figure 5, pooled data from eight studies (8,12,20,23–26,30) 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 results, these results do not indicate that the routine exercise test should be replaced by DSE. Especially in patients with a low pretest likelihood of CAD and in men with normal results on the rest ECG it can be anticipated that DSE will provide little incremental diagnostic information in a cost-effective manner.

Exercise echocardiography. The diagnostic accuracy of DSE has led to enthusiasm for its general use rather than its particular use in patients unable to exercise adequately. However, exercise echocardiography can be performed as well in these patients. As seen in Figure 6, pooled data from four studies (23–25,30) directly comparing DSE and exercise echo-

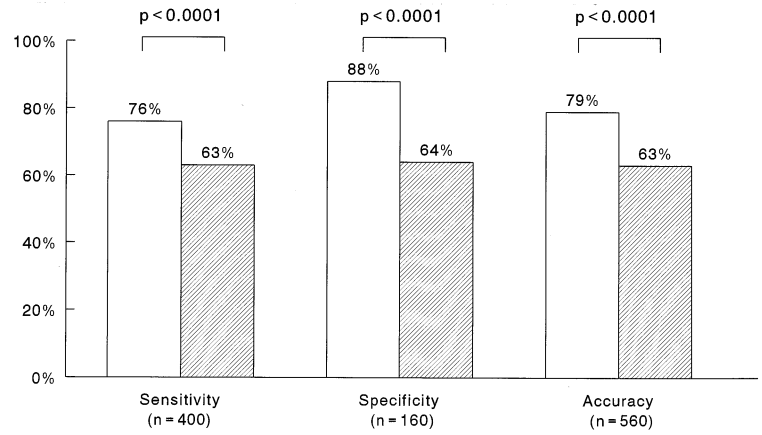

Figure 5. Sensitivity, specificity and accuracy of DSE **(open bars)** versus exercise electrocardiography **(hatched bars)** for detection of CAD.

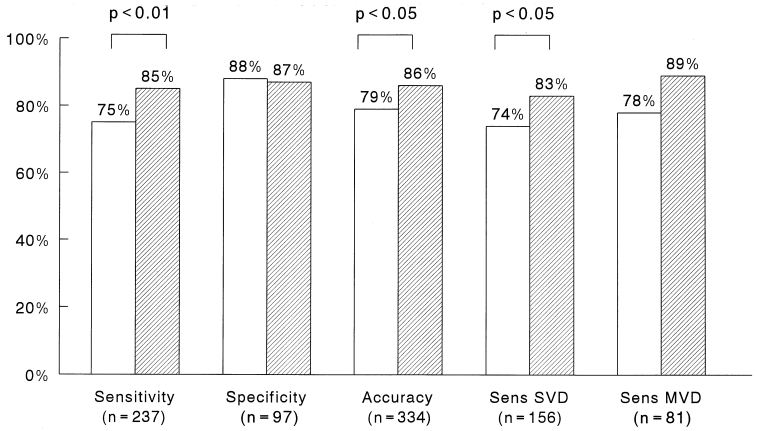

Figure 6. Sensitivity (Sens), specificity and accuracy of DSE (**open bars**) versus exercise echocardiography (**hatched bars**) for detection of CAD. MVD = multivessel disease; SVD = single-vessel disease.

cardiography 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 (24). In that study a large number of DSE tests were submaximal 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. It seems likely that in this patient cohort, the previously described dobutamine–atropine protocol would have resulted in better diagnostic accuracy, probably comparable to exercise echocardiography. However, the choice for the latter in patients who are expected to exercise adequately can be justified by better patient acceptance, fewer unpleasant side effects and the complementary functional information provided by exercise, such as duration of exercise, increase in heart rate, blood pressure response and reproduction of symptoms.

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 (36). In normal arteries dipyridamole, an indirect coronary vasodilator (88), causes a three- to fivefold increase in both subendocardial and subepicardial coronary flow (89). 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) (90) or "horizontal" (nonstenotic from stenotic vessel territory) (91). As seen in Figure 7, pooled data from six studies (9,13,20,27,28,30) directly comparing DSE and dipyridamole echocardiography in the same 422 patients show 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. These results are not surprising because dipyridamole creates primarily blood flow heterogeneity (not detected by echocardiography) and "true" ischemia only in a limited number of patients. Moreover, the detection of ischemia with dobutamine stress is facilitated by the improved thickening of normal segments as opposed to decreased thickening of ischemic segments, whereas dipyridamole has a lesser effect on normal segments. However, recent reports (32,92) have suggested that the addition of atropine to dipyridamole increases the sensitivity of the dipyridamole test for the

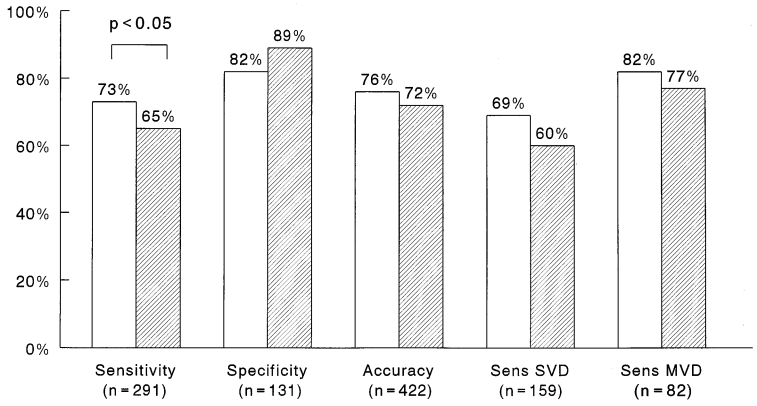

Figure 7. Sensitivity, specificity and accuracy of DSE (**open bars**) versus dipyridamole echocardiography (**hatched bars**) for detection of CAD. Abbreviations as in Figure 6.

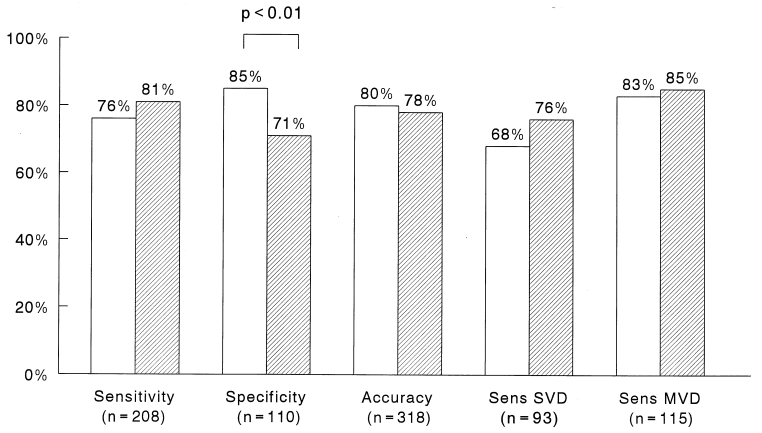

Figure 8. Sensitivity, specificity and accuracy of DSE versus dobutamine technetium-99m perfusion imaging **(hatched bars)** for detection of CAD. Abbreviations as in Figure 6.

detection of CAD to a level comparable with dobutamine–atropine stress echocardiography.

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 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% (Fig. 8). 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 (93), which states that perfusion abnormalities due to limited coronary flow reserve precede echocardiographic and ECG changes. Only two studies (with available angiographic data) reported the diagnostic accuracy of DSE versus vasodilator perfusion imaging. In one study (15) comparing DSE with adenosine Tc-99m imaging in 97 patients, sensitivity was 85% versus 86%, specificity 82% versus 71% and accuracy 84% versus 80%. In another study (31) comparing DSE with dipyridamole thallium-201 imaging in 54 patients, sensitivity was 93% versus 98%, specificity 73% versus 73% and accuracy 89% versus 93%. Therefore, 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.

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. Although the first report on DSE was in patients after MI (4), few studies have been specifically addressed to such patients. Infarct-related coronary artery stenosis was assessed in four studies (94–97) without use of the "biphasic" response (42,98). Sensitivities, specificities and accuracies in these studies ranged between 56% and 93%, 82% and 91% and 63% and 93%, respectively (Table 2). The higher sensitivity found in the study of Takeuchi et al. (94) might be explained by their definition of a positive (ischemic) test. DSE was defined as positive if peak wall motion score index was equal to or higher than that at the rest study. In the other studies, DSE was defined as positive if new or worsening wall motion abnormalities occurred. The detection of significant coronary artery stenosis in patients with rest wall motion abnormalities should be based on new or worsening wall motion abnormalities occurring at any stage, with use of the "biphasic" response (42,98). Thus, Takeuchi et al. probably overestimated, and the other studies probably underestimated, true sensitivity. Smart et al. (99) recently reported in a large series of patients, with use of the "biphasic" response, a sensitivity of 82%, a specificity of 80% and a diagnositc accuracy of 82% for the detection of infarct-related coronary artery stenosis. The presence of multivessel CAD in

Table 2. Diagnostic Dobutamine Stress Echocardiographic Studies in Patients With Myocardial Infarction

Year	First Author (ref no.)	No. of Pts	IRA		Prediction of MVD			
					Remote Ischemia		≥2 Coronary Territories	
			Sens	Spec	Sens	Spec	Sens	Spec
1986	Berthe (4)	30	NA	NA	85%	88%	NA	NA
1994	Takeuchi (94)	40	93%	91%	NA	NA	NA	NA
1995	Bigi (95)	121	70%	NA	84%	93%	NA	NA
1996	Elhendy (96)	132	76%	85%	73%	88%	47%	89%
1997	Elhendy (97)	72	56%	82%	68%	93%	40%	96%
1997	Smart (99)	206	82%	80%	68%	97%	NA	NA

IRA = infarct-related artery; other abbreviations as in Table 1.

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. Several studies (4,95–97, 99) assessed the value of DSE for the identification of multivessel CAD by this latter criterion. Sensitivities, specificities and accuracies in these studies ranged between 68% and 85%, 88% and 97% and 81% and 87%, respectively (Table 2). Importantly, in two of the cited studies (94,97) a direct comparison was made between DSE and radionuclide imaging. In both studies DSE was found to be as accurate as radionuclide imaging and even showed a trend toward greater sensitivity.

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) is currently under investigation with gray-scale B-mode color encoding (100), intravenous contrast agents (101), tissue Doppler interrogation (102), tissue characterization techniques and backscatter analysis (103). Eventually, the results of these investigations should lead to improved automatic border detection and objective (computerized), realistic criteria for wall motion abnormalities diagnostic of CAD (43).

Conclusions

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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