

## REVIEW ARTICLES

# Dobutamine Stress Myocardial Perfusion Imaging

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In patients with limited exercise capacity and (relative) contraindications to direct vasodilators such as dipyridamole or adenosine, dobutamine stress nuclear myocardial perfusion imaging (DSMPI) represents an alternative, exercise-independent stress modality for the detection of coronary artery disease (CAD). Nondiagnostic test results (absence of reversible perfusion defects with submaximal stress) do occur in approximately 10% of patients. Serious side effects during DSMPI are rare, with no death, myocardial infarction or ventricular fibrillation reported in three DSMPI safety reports for a total of 2,574 patients. On the basis of a total number of 1,014 patients reported in 20 studies, the sensitivity, specificity and accuracy of the test for the detection of CAD were 88%, 74% and 84%, respectively. Mean sensitivities for one-, two- and three-vessel disease were 84%, 95% and 100%, respectively. The sensitivity for detection of left circumflex CAD (50%) was lower, compared with that for left anterior descending CAD (68%) and right CAD (88%). The sensitivity of predicting multivessel disease by multiregion perfusion abnormalities varied widely, from 44% to 89%, although specificity was excellent in all studies (89% to 94%). In direct diagnostic comparisons, DSMPI was more sensitive, but less specific, than dobutamine stress echocardiography and comparable with direct vasodilator myocardial perfusion imaging. In the largest prognostic study, patients with a normal DSMPI study had an annual hard event rate less than 1%. An ischemic scan pattern provided independent prognostic value, with a direct relationship between the extent and severity of the perfusion defects and prognosis. In conclusion, DSMPI seems a safe and useful nonexercise-dependent stress modality to detect CAD and assess prognosis. (J Am Coll Cardiol 2000;36:2017-27) © 2000 by the American College of Cardiology

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 stress testing 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 exercise testing, mainly because of deconditioning or neurologic, respiratory, peripheral vascular or orthopedic limitations (3). In these patients, pharmacological stress nuclear myocardial perfusion imaging (MPI) represents an alternative, exercise-independent stress modality. Usually, dipyridamole or adenosine is used as a stressor because of their superiority in creating blood flow heterogeneity (4) and the extensive experience with these stress modalities. For patients with (relative) contraindications to these direct vasodilators, such as severe obstructive airway disease (particularly patients with active wheezing or recent hospitalization for an exacerbation), high-grade atrioventricular block, arterial hypotension, ingestion of caffeine-containing beverages <12 h before testing or the use of dipyridamole or theophylline-containing compounds or medications <24 h before testing, dobutamine stress myocardial perfusion imaging (DSMPI) represents an alternative stress modality. Since its clinical

introduction in 1984, DSMPI is increasingly used for detecting CAD and assessing prognosis (5-32). This review article deals with the: 1) methodology, 2) feasibility and safety, 3) diagnostic value for the detection of CAD and 4) prognostic value of DSMPI.

## METHODS AND STATISTICAL ANALYSIS

A Medline search on DSMPI (search terms dobutamine and thallium or technetium) studies published in the major English language journals until the end of 1998 was performed. Studies were only included for diagnostic analysis if these studies included patients with and without angiographically defined CAD and if it was stated how many patients with and without CAD had negative and positive DSMPI results. Reports indicating that the patients included were subsets of larger published studies were excluded. Also excluded from the primary diagnostic analysis were studies describing special issues, such as the value of DSMPI in patients with left bundle branch block (LBBB) or left ventricular hypertrophy (LVH) and studies involving only patients with prior myocardial infarction (MI). These subgroups were discussed separately. When DSMPI 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 angio-

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#### Abbreviations and Acronyms

CAD	=	coronary artery disease
CI	=	confidence interval
DSE	=	dobutamine stress echocardiography
DSMPI	=	dobutamine stress myocardial perfusion imaging
ECG	=	electrocardiogram or electrocardiographic
LBBB	=	left bundle branch block
LVH	=	left ventricular hypertrophy
MI	=	myocardial infarction
MPI	=	myocardial perfusion imaging

graphically 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. 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  $p < 0.05$ .

#### TEST METHODOLOGY

##### Dobutamine: pharmacology and mechanism of action.

Dobutamine is a synthetic catecholamine with a relatively short plasma half-life of approximately 2 min due to rapid metabolization in the liver to inactive metabolites (33,34). It has strong  $\beta_1$ -receptor and mild  $\alpha_1$ - and  $\beta_2$ -receptor agonist activity. When used at low dose (up to 10  $\mu\text{g}/\text{kg}$  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 and the identification of dysfunctional, but viable, cardiac muscle. When used at high-dose (up to 40  $\mu\text{g}/\text{kg}/\text{min}$ ), heart rate is progressively increased (mediated by  $\beta_1$ -receptor stimulation). Despite a clear increase in cardiac output, systemic blood pressure increases only minimally due to 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 (25,35). As a result of the hemodynamic changes, there is an increase in oxygen demand resulting in a secondary dilation of the coronary arteries and, thus, an increase in blood flow. Additionally, dobutamine may also have a (minor) direct vasodilative effect on coronary vessels. For high-dose dobutamine infusion, this increase in blood flow in normal coronary arteries has been reported as three times baseline (36). 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 (37).

For successful MPI, dobutamine should not only create an adequate flow disparity between myocardial regions supplied by normal and stenotic arteries, but the radionuclide tracer (thallium-201 or technetium-99m) must be distributed in the myocardium in proportion to blood flow over the range of flows induced by dobutamine also. Several studies (4,38) have shown that dobutamine-induced cardiac thallium-201 uptake expressed as a percentage of whole body uptake is intermediate between exercise and direct vasodilator stress and that heart-to-background ratios of thallium-201 uptake are similar to direct vasodilator stress (but less than exercise stress). Recently published studies on dogs, however, reported that myocardial technetium-99m uptake underestimated the relative blood flow deficit induced by dobutamine, and it was suggested that dobutamine adversely affects myocardial technetium-99m binding (39,40).

**Protocol.** Protocols for DSMPI vary from institution to institution, particularly with regard to dobutamine dose (range 20 to 50  $\mu\text{g}/\text{kg}/\text{min}$ ), atropine addition (range 0 to 2 mg) and stage duration (range 3 to 5 min) (Table 1). Usually, centers that use lower peak doses of dobutamine (used mainly in the early reports) use longer infusion stage durations and stop beta-adrenergic blocking agent treatment more often before the test (Table 1). To date, the most widely used protocol uses dobutamine up to 40  $\mu\text{g}/\text{kg}/\text{min}$ , with the addition of atropine up to 1 mg.

According to this protocol, a rest electrocardiogram (ECG) is acquired; intravenous access is secured, and dobutamine is then administered intravenously by an infusion pump, starting at 10  $\mu\text{g}/\text{kg}/\text{min}$  for 3 min, increasing by 10  $\mu\text{g}/\text{kg}/\text{min}$  every 3 min up to a maximum of 40  $\mu\text{g}/\text{kg}/\text{min}$ . For patients not achieving 85% of their theoretical maximal heart rate ( $220 - \text{age}$ ) 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. The radionuclide tracer should be injected at peak heart rate, and dobutamine infusion should be continued for at least 1 min. Throughout dobutamine infusion, the ECG (3 leads) is continuously monitored and recorded (12 leads) at 1-min intervals. Blood pressure is measured and recorded by sphygmomanometry or automatic device every 3 min. Reasons for interruption of the test are: 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  $\geq 40$  mm Hg from baseline, hypertension (blood pressure  $\geq 240/120$  mm Hg); significant tachyarrhythmias and any serious side effect was regarded as due to dobutamine. A beta-adrenergic blocking agent that can be injected intravenously must be available to reverse the effects of dobutamine if they do not revert spontaneously and quickly. For patients with obstructive airway disease (and in

**Table 1.** Diagnostic Accuracy of Dobutamine Stress Myocardial Perfusion Imaging As Reported in 20 Studies

Year	Author	Protocol	Tracer	Analysis	Patients	Mean Age	Men	MI	Beta Blocker	CAG	Defect	Sensitivity	Specificity	Accuracy
1984	Mason (8)	20 - 5 min	Tl-201	Planar	24	59	NA	0%	48 h stop	>50, V	Rev	94%	88%	92%
1991	Pennell (9)	20 - 5 min	Tl-201	Planar	50	54	84%	30%	48 h stop	>50, V	Rev	98%	80%	94%
1993	Elliott (10)	20+A - 5 min	Tl-201	Planar	27	66	72%	33%	NA	>50, V	Rev	96%	67%	93%
	Günalp (11)	30 - 5 min	Tc-99	SPECT	27	47	85%	0%	48 h stop	>50, V	Rev	94%	89%	93%
	Forster (12)	40+A - 3 min	Tc-99	SPECT	21	62	55%	0%	52%	>50, V	Rev	83%	89%	86%
	Marwick (13)	40 - 3 min	Tc-99	SPECT	217	58	72%	0%	19%	>50, Q	Any	76%	67%	73%
1994	Pennell (14)	40 - 3 min	Tl-201	Planar	20	63	60%	0%	0%	>50, V	Rev	91%	78%	85%
	Hays (15)	40 - 3 min	Tl-201	SPECT	67	65	50%	29%	10%	>50, Q	Any	86%	90%	87%
	Warner (16)	50 - 3 min	Tl-201	SPECT	16	61	44%	56%	24 h stop	>50, Q	Any	93%	100%	94%
	Senior (17)	40 - 3 min	Tc-99	SPECT	61	63	72%	21%	72 h stop	>50, V	Any	95%	71%	89%
1995	Herman (18)	30 - 5 min	Tc-99	SPECT	20	57	92%	29%	42%	>50, V	Any	100%	100%	100%
	Thorley (19)	40+A - 4 min	Tc-99	SPECT	23	57	69%	48%	48 h stop	>50, V	Any	95%	100%	96%
1996	Henzlova (20)	40 - 3 min	Tl-201	SPECT	15	48	65%	0%	NA	>50, V	Rev	100%	36%	53%
	Di Bello (21)	40+A - 3 min	Tc-99	SPECT	45	53	73%	0%	Stopped	>50, V	Rev	87%	86%	87%
	Kisacik (22)	40+A - 3 min	Tc-99	SPECT	69	51	84%	30%	48 h stop	>50, V	Rev	96%	64%	86%
1997	Ifrikhkar (23)	40 - 3 min	Tc-99	SPECT	38	55	57%	33%	9%	>50, V	Any	79%	90%	82%
	Huang (24)	40+A - 3 min	Tl-201	SPECT	93	61	77%	39%	58%	>50, Q	Rev	90%	81%	87%
1998	Caner (25)	40+A - 3 min	Both	SPECT	29	NA	52%	38%	48 h stop	>50, V	Rev	84%	70%	79%
	Santoro (26)	40+A - 3 min	Tc-99	SPECT	60	NA	NA	0%	NA	>70, Q	Any	91%	81%	87%
	San Roman (27)	40+A - 3 min	Tc-99	SPECT	92	64	49%	0%	9%	>50, Q	Any	87%	70%	82%

A = atropine; CAG = coronary angiography; MI = myocardial infarction; NA = not available; Rev = reversible defect; SPECT = single-photon emission computed tomography; Q = (semi) quantitative; V = visual.

particular those with active wheezing), nitrates should be preferred because the safety of even short-acting selective beta-blockers was never demonstrated in these patients. Contraindications to (high-dose) DSMPI include: critical aortic stenosis, hypertrophic cardiomyopathy, uncontrolled hypertension, uncontrolled atrial fibrillation, known severe ventricular arrhythmias and disorders in potassium homeostasis (41,42). The addition of atropine is contraindicated for patients with narrow-angle glaucoma, myasthenia gravis, obstructive uropathy or obstructive gastrointestinal disorders.

**Scintigraphic interpretation.** Stress scintigraphic imaging should take place immediately after the stress test with thallium-201 and approximately 1 h after the stress test with technetium-99m to optimize the scintigraphic images and to prevent redistribution in the case of imaging with thallium-201. To facilitate the interpretation and comparison of cardiac tomographic images, a standardized nomenclature and display of the images is recommended by the Society of Nuclear Medicine (43). A positive test is denoted by a completely or partially reversible perfusion defect, but, sometimes, fixed perfusion defects are also used as a criterion for CAD.

**Other possible dobutamine stress-induced markers of myocardial ischemia.** 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 of patients with severe coronary lesions, dobutamine stress-induced ST segment depression was described as a highly sensitive and specific diagnostic test (44). However, subsequent reports of patients with less severe coronary lesions (8,11,18,22,45) could never confirm the sensitivity of dobutamine stress-induced ST segment depression for the detection of CAD. Whether this is due to less stress (lower rate-pressure product compared with exercise tests) or other factors, such as inclusion of patients with abnormal baseline ECGs still needs to be established. The specificity (and, thus, positive predictive value) of dobutamine stress-induced ST segment depression, however, seems excellent, ranging from 88% to 93% (8,22,45). Also, as in exercise testing (46), dobutamine stress-induced ST segment elevation in patients without a previous MI was consistently reported to be associated with (severe) CAD (44,45,47).

**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 (48-51). In a small DSMPI study (49), it was reported to be a specific marker of reversible inferior wall perfusion defects. Larger, dobutamine stress echocardiography (DSE) studies (50,51), however, found no clear relationship between dobutamine stress-induced sinus node deceleration and inferior wall motion abnormalities or right CAD. It was postulated that

cardiac slowing, in particular in combination with hypotension (see later), may also result from a neurally mediated cardiovascular vasodepressor reflex (52,53). After exclusion of ischemia (angina or ECG changes), it is our policy to administer atropine to reverse sinus node deceleration.

**HYPOTENSION.** Generally, dobutamine stress causes an increase in cardiac output and a reduction in systemic vascular resistance (54,55) 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 or 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 (56), especially in patients with dehydration. Later studies could not confirm this mechanism (57), and the proposed bolus of saline before dobutamine infusion (56,58) did not prevent cavity obliteration in a canine model (59). 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 (53). In contrast with exercise stress-induced hypotension (60), all presently available data indicate that there is no relation between dobutamine stress-induced hypotension and reversible perfusion defects (61), ischemic left ventricular systolic dysfunction (55,57,62,63) or angiographically detected CAD (61,62). After discontinuation of dobutamine infusion and putting the patient in a Trendelenburg position, active treatment (apart as described earlier) with infusion of fluids is rarely required.

### FEASIBILITY AND SAFETY

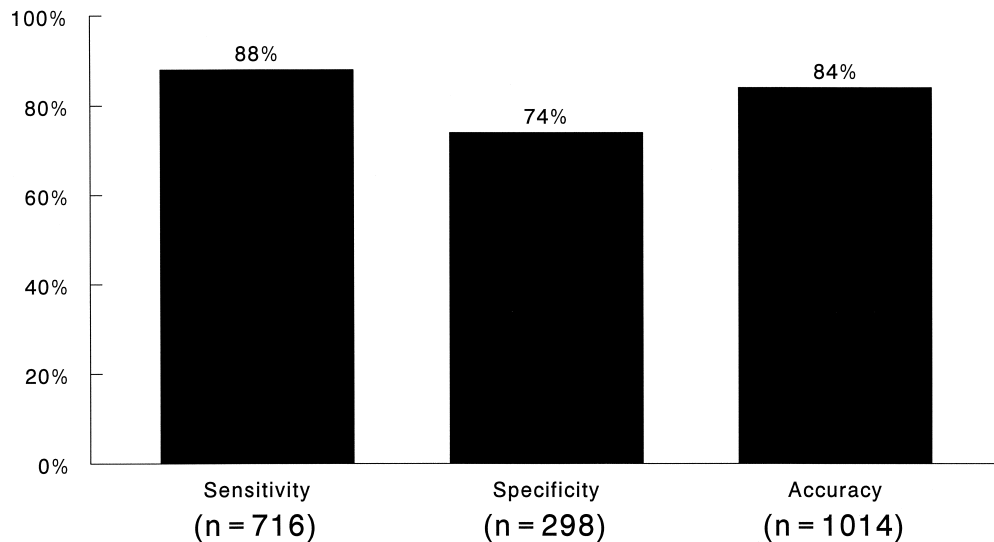
Approximately 10% of DSMPI tests are nondiagnostic (defined as absence of reversible perfusion defects in submaximal tests) because of an insufficient hemodynamic response to dobutamine-atropine or limiting side effects (7,29). Noncardiac side effects (nausea, headache, chills, urgency and anxiety) are not uncommon but 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 approximately 25% of patients (7), severe angina as a test end point without accompanying reversible perfusion defects is rare.

**Table 2.** Safety Reports on Dobutamine Stress Myocardial Perfusion Imaging

	Dakik (5)	Hanson (6)	Elhendy (7)
Dobutamine dose ( $\mu\text{g}/\text{kg}/\text{min}$ )	40	40	40 + atropine
Number of patients	1,012	486	1,076
Complications			
Death/MI/VF	0%	0%	0%
Ventricular tachycardia			
sustained	0%	0%	0.1%
nonsustained	4.2%	6.0%	3.7%
Supraventricular tachycardia			
atrial tachycardia	NA	4.7%	3.5%
atrial fibrillation of flutter	1.2%	1.2%	0.9%

MI = myocardial infarction; NA = not available; VF = ventricular fibrillation.

Dobutamine stress-induced hypotension (defined as a  $\geq 20$  mm Hg decrease in systolic blood pressure) occurs in approximately 15% of patients (5,7,61). Severe, symptomatic hypotension necessitating test termination, however, occurs only rarely. Minor cardiac arrhythmias, such as premature atrial or ventricular contractions, often occur, and supraventricular and ventricular tachycardias occur each in approximately 4% of patients (5-7) (Table 2). Supraventricular tachycardias may be controlled with the injection of a beta-blocker or (in patients with obstructive airway disease) verapamil. Of note, digoxin (although often used) is, in our opinion, not indicated for the acute management of atrial fibrillation because of a delayed onset of action. Ventricular tachycardias are usually nonsustained and have been attributed to  $\beta_1$ -receptor stimulation and dobutamine-induced reduction in plasma potassium concentrations (42). These arrhythmias are more frequently seen in patients with a history of previous ventricular arrhythmias (6,64) or markers for left ventricular dysfunction such as (extensive) fixed perfusion defects (7) or baseline wall motion abnormalities (64). No study has reported an association between ventricular tachycardias and the addition of atropine (64) or reversible perfusion defects (7). Sustained ventricular tachycardias may be managed with an injection of a beta-blocker or lidocaine. In the case of hemodynamic instability, electrical cardioversion is indicated. In three major DSMPI safety reports (5-7) for a total of 2,574 patients, no patient suffered death, MI or ventricular fibrillation, although, in a DSE review on safety, sporadic cases of MI or ventricular fibrillation were described (65). It should be recognized that these severe complications can occur up to 20 min after dobutamine withdrawal (66), and it has been suggested that, in these patients,  $\alpha_1$ -mediated coronary and systemic vasoconstriction might be paradoxically exacerbated, not reversed, by beta-blocker administration. Atropine intoxication (a central anticholinergic syndrome causing confusion or sedation, treated by physostigmine 0.5 to 2.0 mg intravenously), although generally requiring a dose of atropine of at least 5 mg (67), has been reported during DSE in a few patients receiving  $\leq 1$  mg of atropine (66).



**Figure 1.** Sensitivity, specificity and accuracy of dobutamine stress myocardial perfusion imaging for the detection of CAD.

### DIAGNOSTIC VALUE

**Detection of CAD.** As with other tests for detection of CAD, the diagnostic accuracy of DSMPI is expressed by its sensitivity and specificity. These indexes depend on the presence of referral bias (coronary arteriography may be guided by stress test results) and several technical factors such as the stress protocol, the radiotracer (thallium-201 or technetium-99m), the imaging technique (planar or single-photon emission computed tomography), 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 use of beta-blockers, the number of male patients, the presence of collaterals, the type of lesion and the severity (percentage stenosis) and extent (number of diseased vessels) of CAD.

The reported sensitivity, specificity and accuracy for each of the 20 diagnostic studies identified by Medline search (8–27) are shown in Table 1. The overall (weighted mean) sensitivity, specificity and accuracy of DSMPI for a total of 1,014 patients was 88% (95% confidence interval [CI] 86 to 90), 74% (95% CI 71 to 77) and 84% (95% CI 81 to 86), respectively (Fig. 1).

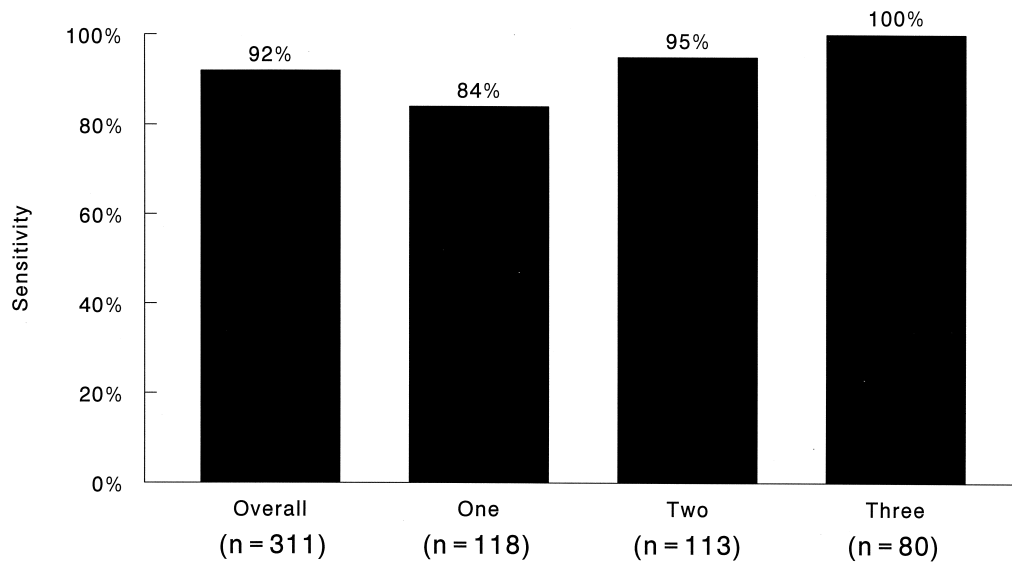
Different reports from center to center are most likely due to the aforementioned factors, in particular the stress protocol and the use of beta-blockers. In the eight studies (12,19,21,22,24–27) that used 40  $\mu$ g dobutamine with atropine, sensitivity for the detection of CAD was higher compared with the six studies (13–15,17,20,23) that used 40  $\mu$ g dobutamine without atropine (90% vs. 82%,  $p < 0.02$ ), without a loss in specificity. This finding was also confirmed in the only study directly comparing the diagnostic accuracy of DSMPI with, versus without, atropine in the same patients (25). The use of atropine is especially recommended for patients using beta-blockers. These latter medications lower the chronotropic and inotropic response

(and, thus, peak cardiac workload) during dobutamine stress (18,68,69) and, thus, have the potential to lower the sensitivity of the test (70,71).

The effect of the number of diseased coronary arteries was assessed in nine studies (9,11,15–17,20,22,24,25) for a total of 311 patients. Mean sensitivity increased significantly from 84% for single-vessel disease to 95% for double-vessel disease and to 100% for triple-vessel disease (Fig. 2).

**Bayesian analysis.** Although values for sensitivity and specificity have a useful role, the use of DSMPI 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 (72). In one report (73) 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 DSMPI, and the ability of DSMPI to reclassify 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, DSMPI defined 97 patients (43%) 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 DSMPI was excellent (91%).

**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 relationship 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

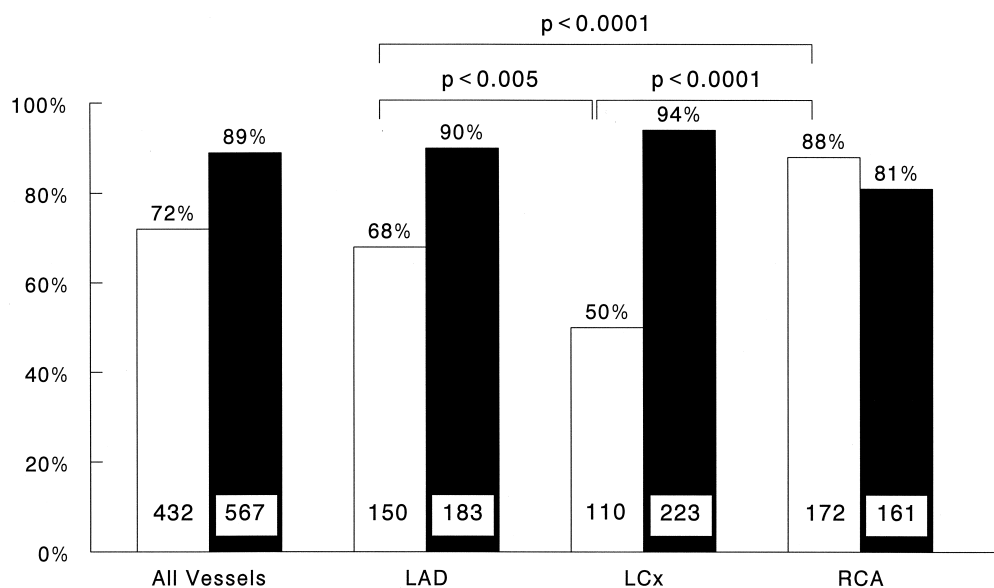


**Figure 2.** Sensitivity of dobutamine stress myocardial perfusion imaging for detection of CAD by number of diseased vessels.

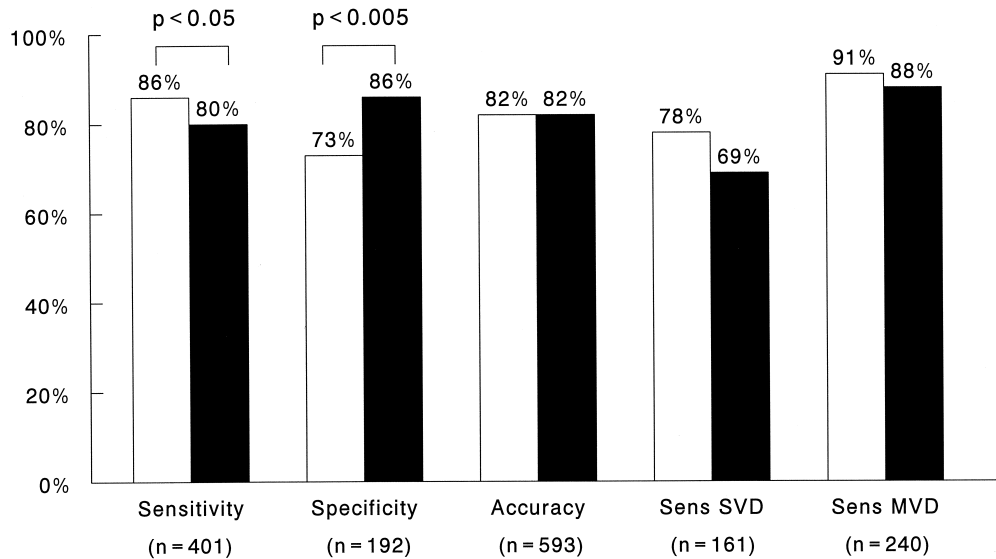
a given coronary artery by noting the location of the perfusion abnormalities. Figure 3 summarizes the sensitivity and specificity for the identification of disease in the left anterior descending, left circumflex and right coronary arteries. The mean reported sensitivities, as assessed in seven studies (11,15-17,19,24,25) for a total of 333 patients, were 68%, 50% and 88%, respectively, and the mean specificities were 90%, 94% and 81%, respectively. Specificity for detection of right CAD was lower than that for left anterior descending CAD ( $p < 0.02$ ) and left circumflex CAD ( $p < 0.0001$ ). Sensitivity for detection of left circumflex CAD was lower than that for left anterior descending CAD ( $p < 0.005$ ) and right CAD ( $p < 0.0001$ ). The lower sensitivity for detection of disease in the left circumflex artery may be

related to variation in coronary anatomy with a small circumflex territory in some patients.

**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 (74). Patients with multivessel CAD can be differentiated from patients with single-vessel CAD by detection of perfusion abnormalities in two or more coronary territories. Investigators who examined the prediction of multivessel CAD by this method (11,17,25,26) consistently reported a high specificity (range 89% to 94%). However, the sensitivity of DSMPI for the prediction of multivessel CAD varied markedly from 44% to 89%. Several factors may contribute



**Figure 3.** Sensitivity (open bars) and specificity (solid bars) of dobutamine stress myocardial perfusion imaging 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 disease. CAD = coronary artery disease; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery. Only the p values for sensitivity are displayed.



**Figure 4.** Sensitivity, specificity and accuracy of dobutamine stress myocardial perfusion imaging (open bars) versus DSE (solid bars) for detection of CAD.

to the underestimation of multivessel CAD: inadequate stress protocols, the premature cessation of stress because of the development of limiting angina, imperfect assignment of myocardial perfusion regions to coronary arteries, collateral circulations and anatomically significant, but functionally nonsignificant, lesions.

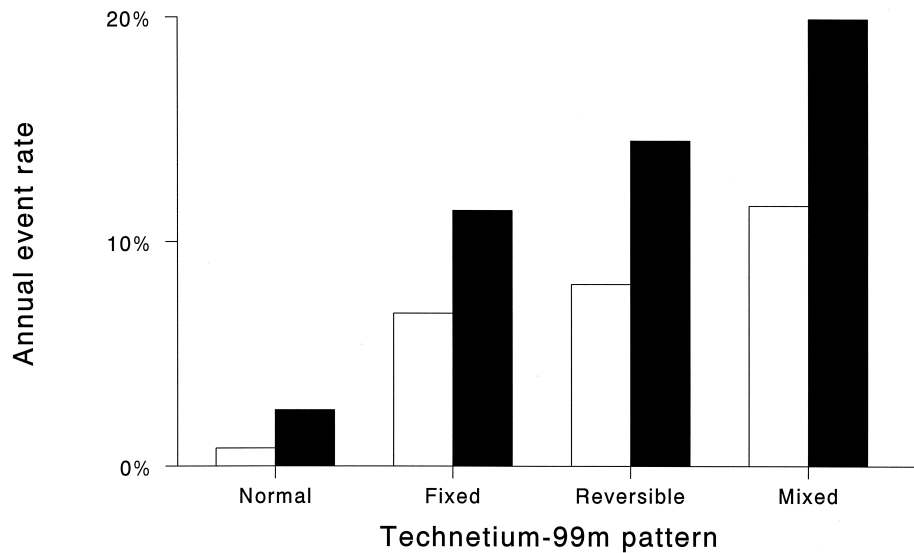
**Comparison with other stress modalities in patients with limited exercise capacity.** DSE. In myocardial regions supplied by a coronary artery with a significant stenosis, dobutamine stress-induced increase in oxygen demand may result in regional ischemia resulting in wall motion abnormalities that can be detected by two-dimensional echocardiography (65). In eight studies (11-13,17,21,22,24,26) comparing DSMPI with DSE in the same 593 patients, sensitivity was 86% versus 80% ( $p < 0.05$ ); specificity was 73% versus 86% ( $p < 0.005$ ), and accuracy was 82% versus 82% (Fig. 4). The finding that DSMPI is more sensitive (especially in patients with single-vessel CAD) is in line with the “ischemic cascade” theory (75), which states that perfusion abnormalities due to limited coronary flow reserve precede wall motion abnormalities.

**VASODILATOR PERFUSION SCINTIGRAPHY.** Direct vasodilators (adenosine or dipyridamole) are considered to be the most effective drugs to create coronary blood flow heterogeneity (4,37,38). Indeed, one study (76) reported that dipyridamole MPI correlated better than DSMPI with a “coronary extent score.” However, these results were based on a small group of patients, and the dobutamine dose used was extremely low. Only two studies (26,77) reported the diagnostic accuracy of DSMPI versus direct vasodilator MPI for the detection of CAD in the same patients. In these two studies in 157 patients, sensitivity was 84% versus 90%; specificity was 77% versus 78%, and accuracy was 81% versus 85%. Although there is no clear evidence for a superiority of direct vasodilator MPI over DSMPI, the use of the former as the drug of choice for MPI in patients with

limited exercise capacity seems reasonable on the basis of theoretical grounds, diagnostic accuracy and extensive experience. However, it should be recognized that in the U.S. (unlike Europe) direct vasodilators (and in particular adenosine) are very expensive in comparison with dobutamine. Whether DSMPI is a more cost-effective test is yet unproven. This requires further, stronger exploration of the relative diagnostic accuracies of both tests, and it should be realized that, despite marked differences in stressor costs, these costs constitute only a small portion of total perfusion scintigraphy costs.

**Special subgroups. PATIENTS WITH LBBB.** The ability of noninvasive tests to diagnose or localize CAD in patients with LBBB has been disappointing. Exercise-induced changes in the ECG are nondiagnostic in the presence of LBBB (78). Moreover, several scintigraphic studies (especially when exercise stress is used) have reported false-positive results for detecting CAD in the left anterior descending coronary artery in the presence of LBBB (79). Reports on the use of DSMPI for patients with LBBB are scarce. Two small studies in respectively 24 and 27 patients (80,81) reported excellent specificities of 80% and 92% for detection of disease in the left anterior descending coronary artery. In another very small study in 19 patients (82), specificity was dramatically low. It should be noted that in this latter study, for unclear reasons, exceptionally high heart rates were achieved, one of the conditions believed to be related with false positive perfusion defects (79).

**PATIENTS WITH LVH.** The specificity of exercise electrocardiography and scintigraphy to diagnose CAD in patients with LVH has also been disappointing, even in the absence of baseline ECG abnormalities (83,84). In one study (13) specificity for the detection of CAD by DSMPI was indeed disappointing (59%). In another study (85), however, specificity was good (85%) and comparable to DSE. Clearly,



**Figure 5.** Histogram showing the annual event rate for hard events (open bars) and all events (solid bars) according to the MIBI imaging pattern. The number of patients in each category was 130, 102, 60 and 100, respectively. Reproduced with permission (29).

further, larger studies are necessary to establish the role of DSMPI for patients with LBBB and/or LVH.

**PATIENTS AFTER MI.** The major goals of DSMPI in patients with a previous MI are (apart from viability issues) to assess infarct-related coronary artery patency and to identify patients with multivessel CAD. Only a few studies have been specifically addressed to these topics. Infarct-related coronary artery patency was assessed in two studies (86,87). In one thallium-201 study (86), sensitivity was 71%, and specificity was 83%; in a technetium-99m study (87), sensitivity was 44%, and specificity was 82%. The presence of multivessel CAD for patients with a previous MI should ideally be based on reversible perfusion defects in two coronary vascular territories. In three studies (86–88) sensitivity ranged from 14% to 64%, and specificity ranged from 80% to 100%. An approach in which remote (outside the infarct-related coronary artery territory) perfusion defects are considered diagnostic for multivessel CAD was assessed in one study (88); sensitivity was 18% and specificity was 100%.

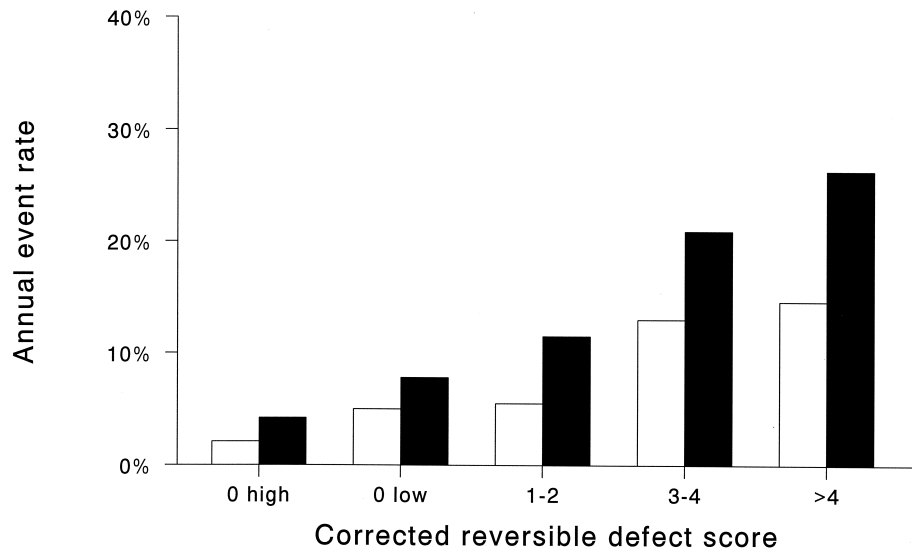
**PROGNOSTIC VALUE**

The prognostic value of DSMPI was assessed in three studies (from the same institution) in patients with stable chest pain (28–30), in one study in patients with known coronary anatomy (31) and in two studies in patients undergoing vascular surgery (10,32). The largest published study of patients with stable chest pain involved 392 patients (mean age 60 ± 12 years, 220 men, 190 with a previous MI) who underwent high-dose dobutamine-atropine technetium-99m sestamibi single-photon emission computed tomography imaging (29). During a mean follow-up period of 22 ± 13 months, 44 patients (11%) suffered a hard cardiac event (cardiac death or nonfatal MI), and 78 patients (20%) suffered any event (hard event or a late revasculariza-

tion procedure). Normal scan results were associated with a favorable prognosis over the follow-up period with an annual event rate of 0.8% for hard events and 2.5% for all events. In contrast, patients with fixed perfusion defects alone, reversible perfusion defects alone and fixed plus reversible perfusion defects had a significantly increased cardiac event rate of 6.8%, 8.1% and 11.6%, respectively, for hard events and 11.4%, 14.5% and 19.9%, respectively for all events (Fig. 5). In a multivariate analysis only age, history of heart failure or typical angina and abnormal scan patterns were independent predictors of cardiac events. Moreover, the (for stress level corrected) extent and severity of reversible perfusion defects was an important predictor of events (Fig. 6). In a study involving 220 of the above described patients (30), all patients underwent both DSMPI and DSE. No differences in prognostic value could be detected between the two imaging modalities. In another very small study (31) of patients with known coronary anatomy, an annual event rate of 3% for patients with a normal scan and 44% for patients with reversible perfusion defects was found. At multivariate analysis the only predictors of events were a history of previous MI and the extent of reversible perfusion defects. Unfortunately, the authors did not analyze whether the extent of reversible perfusion defects had a better predictive value than coronary anatomy. Two studies (10,32) described the value of DSMPI for assessing cardiac risk associated with vascular surgery. Both studies, in respectively 126 and 142 patients, found a significantly increased risk for perioperative major cardiac events in patients with reversible perfusion defects (50% versus 5% and 19% versus 3%, respectively).

**CONCLUSIONS**

Despite some theoretical limitations, DSMPI is a safe and useful nonexercise-dependent stress modality to assess the



**Figure 6.** Histogram showing the annual event rate for hard events (open bars) and all events (solid bars) according to the (for stress level corrected) extent and severity score of reversible MIBI perfusion defects. The number of patients in each category was 100, 100, 109, 62 and 21, respectively. Reproduced with permission (29).

presence, localization and extent of CAD and to assess prognosis. In particular, this stress modality may be of great value for patients with limited exercise capacity and (relative) contraindications to dipyridamole or adenosine stress.

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