JACC Vol. 28, No. 2
August 1996:447–54

Prognostic Value of Dobutamine-Atropine Stress Technetium-99m Sestamibi Perfusion Scintigraphy in Patients With Chest Pain

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Objectives. **This study investigated the prognostic value of dobutamine-atropine technetium-99m (Tc-99m) sestamibi single-photon emission computed tomographic (SPECT) myocardial perfusion imaging.**

Background. **Dobutamine-atropine Tc-99m sestamibi SPECT imaging is an accurate method for the detection of coronary disease. However, the prognostic value of this stress modality has not been assessed.**

Methods. **Three hundred ninety-two consecutive patients with chest pain (mean [±SD] age 60 ± 12 years; 220 men, 190 with a previous myocardial infarction) underwent a dobutamine-atropine Tc-99m sestamibi SPECT scintigraphic study. Patients were followed up for 22 ± 13 months to determine the univariate and multivariate variables associated with hard cardiac events (cardiac death, nonfatal myocardial infarction), to define their event-free survival and to determine whether the extent and severity of reversible perfusion defects correlated with events.**

Results. **Forty-four patients (11%) had hard cardiac events. Multivariate models demonstrated that older age (odds ratio [OR] 2.1, 95% confidence interval [CI] 1.0 to 4.4), history of heart failure (OR 2.6, 95% CI 1.3 to 5.2), abnormal sestamibi scan results (OR 10.0, 95% CI 2.3 to 43.0) and reversible perfusion defects (OR 3.2, 95% CI 1.6 to 6.4) had independent predictive value. Patients without perfusion defects, with fixed defects alone, reversible defects alone and fixed plus reversible defects had annual hard cardiac event rates of 0.8%, 6.8%, 8.1% and 11.6%, respectively. Patients with increasing reversible defect scores had increasing annual event rates of 2.1%, 5.0%, 5.5%, 13.0% and 14.6%, respectively.**

Conclusions. **Dobutamine-atropine stress Tc-99m sestamibi SPECT imaging provides excellent prognostic information. The single most important independent predictor for future hard cardiac events is an abnormal pattern, and a reversible defect provides additional, independent prognostic information. Moreover, the extent and severity of reversible defects are major determinants for prognosis.**

(J Am Coll Cardiol 1996;28:447–54)

Exercise testing provides important diagnostic and prognostic information in patients with known or suspected coronary artery disease (1). Addition of technetium-99m (Tc-99m) sestamibi single-photon emission computed tomographic (SPECT) myocardial perfusion imaging has incremental value for the diagnosis of coronary artery disease (2–4), and a recent study also reported incremental prognostic value (5). However, up to 40% of patients with chest pain are not able to exercise adequately (6), which may significantly reduce the detection of coronary disease. In contrast to exercise stress testing, dobutamine–atropine stress Tc-99m sestamibi SPECT imaging is not dependent on the level of exertion achieved. It is increasingly used as an alternative stress technique (in particular, in patients with contraindications for vasodilator stress), and several investigators have reported that it is an accurate method for the detection of coronary artery disease (7–12). However, to date no study has assessed the prognostic value of this stress modality. Therefore, we studied a large, unselected, consecutive group of patients with chest pain, unable to perform an adequate exercise test, with dobutamine-atropine Tc-99m sestamibi SPECT myocardial perfusion scintigraphy. We hypothesized that abnormal sestamibi scan results carry an increased risk of subsequent cardiac events and that this risk is proportional to the extent of the abnormalities and the presence of reversible perfusion defects.

Methods

Patient selection. Over a 4-year period, between November 1990 and October 1994, 418 consecutive patients with chest pain were referred to the nuclear cardiology laboratory at the Thoraxcentre for the evaluation of suspected myocardial ischemia with dobutamine-atropine Tc-99m sestamibi SPECT imaging. All patients were unable to perform an adequate

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Manuscript received September 12, 1995; revised manuscript received March 14, 1996, accepted March 27, 1996.

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exercise test, and none had undergone prior heart transplantation or had significant congenital or valvular heart disease, primary dilated cardiomyopathy, recent (<3 months) angioplasty or unstable angina. Twenty-six patients with early elective coronary revascularization within 60 days after stress testing were excluded from the analysis. None of these 26 patients sustained a major cardiac event before coronary revascularization. The mean age of the remaining 392 patients was 60 ± 12 years (range 23 to 85), 220 were men (56%), 190 (48%) had a previous myocardial infarction, and 43 (11%) were known to have coronary artery disease without myocardial infarction. Ninety-five patients (24%) had typical angina, 196 (50%) had atypical angina, and 101 (26%) had nonanginal chest pain. At the time of the study, 279 patients (71%) were receiving antianginal therapy, including beta-adrenergic blocking agents in 161 patients (41%), administrated either alone in 43 (11%) or in combination with nitrates or calcium channel blocking agents, or both, in 118 patients (30%).

Dobutamine-atropine stress test. After routine preparation, a rest electrocardiogram (ECG) was obtained, intravenous access was secured and dobutamine was administered intravenously by an infusion pump. The infusion rate was 10 μg/kg body weight 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 predicted maximal heart rate for their age and gender and without symptoms or signs of myocardial ischemia, atropine was administered in addition to 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 (3 leads) was continuously monitored and recorded (12 leads) at 1-min intervals. The level of ST segment shift was calculated, after signal averaging, by a computer-assisted system (Cardiovit CSG/12; Schiller, Baar, Switzerland). Blood pressure was measured and recorded by sphygmanometry every 3 min. Reasons for interruption of the test were 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 previous myocardial infarction, severe angina, a symptomatic reduction in systolic blood pressure (>40 mm Hg from baseline), hypertension (blood pressure >240/120 mm Hg), significant cardiac tachyarrhythmias and any serious side effect regarded as being due to dobutamine. Metoprolol was available and used to reverse the effects of dobutamine if they did not revert spontaneously and quickly.

Perfusion imaging. At peak stress, 370 MBq of Tc-99m sestamibi was injected intravenously while dobutamine infusion was continued for at least 1 min. Stress scintigraphic images were acquired on average 1 h after the termination of the dobutamine infusion. For rest studies, patients were reinjected with 370 MBq of Tc-99m sestamibi at least 24 h after the stress study. Image acquisition was done with a Siemens Gammasonics single-head Orbiter camera. For each study six oblique (short-axis) slices were defined from the apex to the base and three sagittal (vertical long-axis) slices from the septum to the lateral wall. To compare the stress and rest studies, each of the six short-axis slices was divided into eight equal segments. The septal part of the two basal slices (four segments) was not evaluated because this region corresponds to the fibrous portion of the interventricular septum and normally exhibits reduced uptake. The apical region was assessed from the three central sagittal cross sections. A total of 47 segments/patient were analyzed. All tomographic views were reviewed in side-by-side pairs (stress and rest) by two experienced observers who were unaware of the patient's clinical history and other stress results. In case of disagreement, a third investigator reviewed the images and a majority decision was made. Subsequently, the 47 segments were grouped into six major segments: anterior, septum anterior, septum posterior, inferoposterior, lateral and apical. The myocardial uptake of radiotracer was evaluated visually (with the assistance of circumferential profiles analysis, including the normal values) for each of the six major segments during both rest and stress with a four-point scoring method (0 = normal; 1 = equivocal or minimally reduced uptake; 2 = moderately reduced uptake; 3 = severely reduced or absent uptake). Scan results were initially characterized as *abnormal* or *normal*. Scan results were considered normal in the absence of any defect or the presence of only equivocal defects. Abnormal scan results were further classified as demonstrating *fixed defects* (rest perfusion defects) or *reversible defects* (perfusion defects during stress that partially or totally resolved at rest). To measure the influence of the extent and severity of the perfusion defect, a fixed defect score was calculated by summing the fixed perfusion defects, according to a 6 (extent) × 4 (severity) point model (range 0 to 18); similarly, a reversible defect score was calculated by summing the reversible perfusion defect scores. Subsequently, this latter score was corrected for stress level by dividing it by the following correction factor: percent target heart rate reached times peak systolic blood pressure divided by 100. Patients with a zero reversible defect score were classified into a low stress level group (correction factor <1.6) and a high stress level group (correction factor >1.6). This cutoff value was chosen to classify patients with zero scores into two equally sized groups.

Follow-up. Follow-up data were obtained over 22 ± 13 months (range 6 to 54) by outpatient clinic assessment, review of case notes and contacting the patient, general practitioner or other hospitals when necessary. Outcome events were cardiac death, nonfatal myocardial infarction and revascularization (coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty). Cardiac death was defined as a death temporally associated with a known or suspected acute myocardial infarction, life-threatening arrhythmia or pulmonary edema. Unexpected death without an identified noncardiac cause and heart transplantation were also considered as cardiac death. Occurrence of an acute myocardial infarction was confirmed using standard clinical and ECG criteria and when total creatine kinase (CK) enzyme levels exceeded twice normal. Hard cardiac events (cardiac death

Table 1. Clinical and Stress Test Data for 392 Study Patients (hard cardiac events)

	No Cardiac Event (n = 348)	Cardiac Event (n = 44)	p Value
Age >70 yr	64 (18%)	12 (27%)	0.0804
Male	187 (54%)	33 (75%)	0.0037
Risk factors			
Diabetes	50 (14%)	9 (20%)	0.1440
Hypercholesterolemia	89 (26%)	9 (20%)	0.7698
Hypertension	146 (42%)	22 (50%)	0.1551
Smoking	96 (28%)	15 (34%)	0.2958
History			
Myocardial infarction	160 (46%)	30 (68%)	0.0028
Congestive heart failure	59 (17%)	17 (39%)	0.0003
Revascularization	105 (30%)	17 (39%)	0.1269
Typical angina	80 (23%)	15 (34%)	0.0529
Stress test			
Angina during stress	86 (25%)	16 (36%)	0.0487
ST-T wave changes	57 (16%)	11 (25%)	0.0776
MIBI scan pattern			
Abnormal	220 (63%)	42 (95%)	0.0000
Fixed defect	169 (49%)	33 (75%)	0.0005
Reversible defect	130 (37%)	30 (68%)	0.0000

Data presented are number (%) of patients. MIBI = technetium-99m sestamibi.

Table 2. Clinical and Stress Test Data for 392 Study Patients (all cardiac events)

	No Cardiac Events (n = 314)	Cardiac Events (n = 78)	p Value
Age >70 yr	61 (19%)	15 (19%)	0.5156
Male	167 (53%)	53 (68%)	0.0094
Risk factors			
Diabetes	46 (15%)	13 (17%)	0.3281
Hypercholesterolemia	80 (25%)	18 (23%)	0.6692
Hypertension	132 (42%)	36 (46%)	0.2557
Smoking	87 (28%)	24 (31%)	0.2958
History			
Myocardial infarction	138 (44%)	52 (67%)	0.0002
Congestive heart failure	53 (17%)	23 (29%)	0.0059
Revascularization	88 (28%)	34 (44%)	0.0040
Typical angina	61 (19%)	34 (44%)	0.0000
Stress test			
Angina during stress	73 (23%)	29 (37%)	0.0061
ST-T wave changes	47 (15%)	21 (27%)	0.0063
MIBI scan pattern			
Abnormal	190 (61%)	72 (92%)	0.0000
Fixed defect	146 (46%)	56 (72%)	0.0000
Reversible defect	108 (34%)	52 (67%)	0.0000

Format as in Table 1.

and nonfatal myocardial infarction) and all cardiac events (hard events or revascularization) were analyzed as end points.

Statistical analysis. Values were expressed as mean value ± SD, when appropriate. Comparison (two-tailed) of patients with and without cardiac events was performed with the Student *t* test for continuous variables and chi-square test for discrete variables. Differences of $p < 0.05$ were considered significant. Multivariate logistic regression using the BMDP package (13) was performed to identify factors that were related to events. A forward and backward stepping algorithm was used with $p < 0.05$ to identify the independent predictors for both hard and all events. Baseline variables tested were the clinical and stress test variables, as displayed in Tables 1 and 2. Odds ratio and 95% confidence intervals were calculated for variables used in the multivariate model. Kaplan-Meier life-table estimates of infarction-free survival (survival without cardiac death or nonfatal myocardial infarction) and event-free survival (survival without cardiac death, nonfatal myocardial infarction or revascularization) were used to summarize the follow-up experience and to clarify presentation.

Results

Dobutamine-atropine stress test. *Hemodynamic results, end points and side effects.* The maximal dobutamine dose used was 10 μg/kg per min in 1 patient, 20 μg/kg per min in 5 patients, 30 μg/kg per min in 56 patients and 40 μg/kg per min in 330 patients. Atropine was added in 169 patients (43%) and was more often used in patients receiving beta-blockers (108 of 161 with vs. 61 of 231 without beta-blockers, $p < 0.0001$). In the overall group, dobutamine-atropine increased heart rate by 65 ± 15 beats/min to a peak heart rate of 135 ± 17 beats/min, systolic blood pressure by 10 ± 27 mm Hg to a peak pressure of 148 ± 31 mm Hg and rate-pressure product by 10,332 ± 3,764 mm Hg × beats/min to a peak rate-pressure product of 20,025 ± 4,848 mm Hg × beats/min.

Target heart rate (85% of maximum for age and gender) was not reached in 77 tests (20%) either after the maximal dobutamine-atropine dose had been given in 28 patients (7%) or when prematurely stopping the test in 49 patients (14%). The test was prematurely stopped in patients because of angina in 33, ST segment changes in 3, hypertension in 3, symptomatic hypotension in 4, nonsustained ventricular tachycardia in 3, anxiety in 2 and headache in 1. Most patients not reaching their target heart rate because of an insufficient dose of dobutamine-atropine were on beta-blockers (22 of 28 with vs. 6 of 28 without beta-blockers, $p < 0.0001$). Nondiagnostic tests (target heart rate not reached in the absence of reversible perfusion defects) were present in 30 patients (8%). Tachyarrhythmias during dobutamine infusion or recovery were not uncommon; 10 patients (3%) had supraventricular tachycardia, and 17 (4%) had (nonsustained) ventricular tachycardia. Apart from angina (induced in 102 patients [26%]), side effects were unusual and minor (side effects occurring in >5% of patients were chills in 5%, headache in 6% and nausea in 5%). Three hundred twenty-two patients (82%) were free of any side effect (not considering angina).

Distribution of imaging patterns. One hundred thirty patients (33%) had normal (or equivocal in 30) scan results, and 262 (67%) had abnormal results. Scan abnormalities

JACC Vol. 28, No. 2
August 1996:447–54

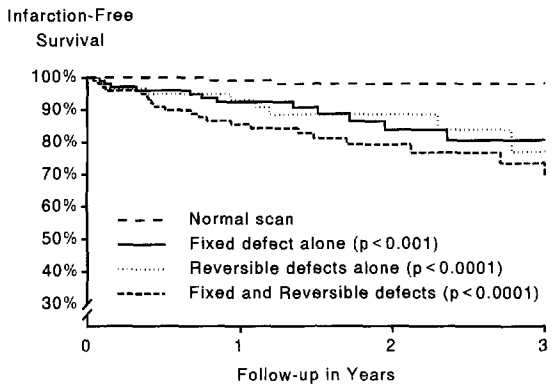


Figure 1. Kaplan-Meier infarction-free survival curves in patients with normal scan results, fixed defects alone, reversible defects alone and mixed defects. Infarction-free survival was significantly lower in patients with fixed defects alone ($p < 0.001$), reversible defects alone ($p < 0.0001$) and mixed defects ($p < 0.0001$) than in those with normal scan results. The number of patients available for follow-up at 0, 1, 2 and 3 years, respectively, was 130, 109, 46 and 28 in the subset with normal scan results; 102, 74, 32 and 17 in the subset with fixed defects alone; 60, 48, 26 and 9 in the subset with reversible defects alone; and 100, 76, 34 and 20 in the subset with mixed defects.

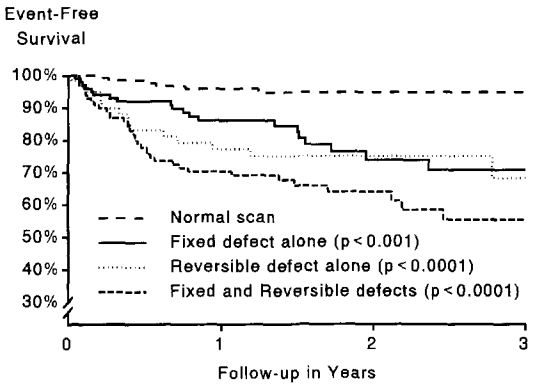


Figure 2. Kaplan-Meier event-free survival curves in patients with normal scan results, fixed defects alone, reversible defects alone and mixed defects. Event-free survival was significantly lower in patients with fixed defects alone ($p < 0.001$), reversible defects alone ($p < 0.0001$) and mixed defects ($p < 0.0001$) than in those with normal scan results. The number of patients available for follow-up at 0, 1, 2 and 3 years, respectively, was 130, 105, 44 and 27 in the subset with normal scan results; 102, 69, 29 and 15 in the subset with fixed defects alone; 60, 39, 23 and 8 in the subset with reversible defects alone; and 100, 62, 25 and 15 in the subset with mixed defects.

included fixed defects alone in 102 patients (26%), reversible perfusion defects alone in 60 (15%) and fixed plus reversible defects (or partially reversible defects) in 100 (26%). In total, 202 patients (52%) had fixed defects, and 160 (41%) had reversible perfusion defects.

Clinical outcome. The mean follow-up period was 22 ± 13 months for patients with and without reversible defects. Eighteen patients (5%) had an "incomplete" follow-up, 13 because of noncardiac death (cancer in 8, pneumonia in 2, acquired immune deficiency syndrome in 1, complicated hip fracture in 1 and myelodysplasia in 1) and 5 because of geographic relocation. Cardiac events occurred in 78 patients, 44 of whom had hard cardiac events (nonfatal myocardial infarction in 17 and cardiac death in 27).

Prediction of events from clinical and stress test results. *Univariate analysis.* In Tables 1 and 2 the clinical and stress test data in patients with and without hard and all cardiac events are summarized. Clinical variables associated with hard cardiac events were male gender, a history of myocardial infarction and a history of congestive heart failure. Clinical variables associated with all cardiac events were male gender and history of myocardial infarction, coronary revascularization, congestive heart failure or typical angina. Apart from peak heart rate in patients with any versus without any event (132 ± 18 vs. 136 ± 17, $p < 0.05$), no hemodynamic variable (rest and peak heart rate, blood pressure and rate-pressure product) was associated with an increased rate of hard or all cardiac events. Of the other stress test variables, stress-induced angina was associated with both hard and all events and ST-T wave changes were only associated with all cardiac events. Sestamibi scan patterns associated with both hard and all cardiac events were the presence of abnormalities on the scan (any perfusion abnormality), fixed perfusion defects and reversible perfusion defects.

The infarction-free and event-free survival curves in patients with normal scan results, fixed defects alone, reversible defects alone and mixed (fixed and reversible) defects are depicted in Figures 1 and 2. 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 defects alone, reversible defects alone and fixed plus reversible 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. Compared with normal scan results, reversible perfusion defects alone increased the risk for future hard events tenfold and for all events sixfold. Compared with fixed defects alone, fixed plus reversible perfusion defects increased the risk for both hard events and all events twofold.

Multivariate analysis, addition of perfusion scintigraphy to clinical data. Tables 3 and 4 summarize the results of univariate and multivariate (stepwise logistic regression) analysis of clinical and stress test data to predict subsequent hard and all cardiac events. Multivariate analysis of clinical variables (Table 3, Clinical Data) revealed male gender (odds ratio [OR] 2.3, 95% confidence interval [CI] 1.1 to 4.7) and a history of congestive heart failure (OR 2.7, 95% CI 1.4 to 5.4) as independent predictors of subsequent hard cardiac events. The addition of scan patterns to this analysis was performed according to two different models. In the first model (Table 3, Model I) the only scan pattern variable entered was the presence of an "abnormal scan" (any abnormality), and in the second model (Table 3, Model II) the presence of a fixed or reversible perfusion defect was separately included. A history of congestive heart failure (OR 2.0, 95% CI 1.0 to 3.9) and

Table 3. Association by Univariate and Multivariate Analysis of Clinical and Stress Test Data With Hard Cardiac Events: Odds Ratios (95% confidence intervals)

		Multivariate Analysis of Clinical and Stress Test Data		
	Univariate Analysis	Clinical Data	Model I	Model II
Clinical data				
Age >70 yr	1.6 (0.8–3.4)*	*	*	2.1 (1.0–4.4)
Male	2.6 (1.3–5.3)	2.3 (1.1–4.7)	*	*
History of infarction	2.5 (1.3–4.9)	*	*	*
History of revascularization	1.5 (0.8–2.8)*	*	*	*
History of heart failure	3.1 (1.6–6.0)	2.7 (1.4–5.4)	2.0 (1.0–3.9)	2.6 (1.3–5.2)
Typical angina	1.7 (0.9–3.4)*	*	*	*
Stress test data				
Angina	1.7 (0.9–3.4)*	—	*	*
ST-T wave changes	1.7 (0.8–3.6)*	—	*	*
Scan abnormalities	12.2 (2.9–51.3)	—	10.0 (2.3–43.0)	—
Fixed defect	3.2 (1.6–6.5)	—	—	*
Reversible defect	3.6 (1.8–7.0)	—	—	3.2 (1.6–6.4)

*p value not significant. In model I, scan variables included scan abnormalities. In model II, pattern variables included fixed defect and reversible defect and excluded scan abnormalities. — = variable excluded.

abnormal scan results (OR 10.0, 95% CI 2.3 to 43.0) in model I were independent predictors of hard cardiac events. In model II, older age (OR 2.1, 95% CI 1.0 to 4.4) and reversible perfusion defects (OR 3.2, 95% CI 1.6 to 6.4) were independent predictors of hard cardiac events.

For all cardiac events (Table 4), the clinical variables history of myocardial infarction (OR 2.9, 95% CI 1.7 to 5.1) and typical angina (OR 3.3, 95% CI 1.9 to 5.7) were independent predictors in the clinical model. In model I, independent predictors were history of typical angina (OR 3.2, 95% CI 1.9 to 5.6) and abnormal scan results (OR 7.9, 95% CI, 3.3 to 18.9). In model II, a history of typical angina (OR 2.9, 95% CI 1.7 to 5.1), fixed perfusion defects (OR 2.5, 95% CI 1.4 to 4.4) and reversible perfusion defects (OR 3.1, 95% CI 1.8 to 5.4) were independent predictors of all cardiac events.

Extent and severity of perfusion defects and prognosis. As described in the legend to Figure 3, 162 patients had a fixed perfusion defect score of zero, 114 had a score of one to three, 70 of four to six, 27 of seven to nine and 19 of ten or higher. At the end of the follow-up period, the annual hard event rate for patients with these fixed perfusion defect scores were 3.3% (mean follow-up 23 months), 5.0% (23 months), 8.1% (21 months), 11.5% (23 months) and 36.4% (12 months), respectively. For all events, these numbers were 5.6%, 13.2%, 13.0%, 17.2% and 36.4%, respectively. As seen in the legend to Figure 4, 100 patients had a stress level corrected reversible perfusion defect zero score with "high stress" (correction factor >1.6), 100 patients had a zero score with "low stress" (correction factor <1.6), 109 had a score of one or two, 62 of three or four and 21 of five or higher. At the end of the follow-up period, the annual hard event rate for the different reversible perfusion defect scores was 2.1% (mean follow-up 21 months), 5.0% (23 months), 5.5% (22 months), 13.0% (22 months) and 14.6% (20 months), respectively. For all events, these numbers were 4.2%, 7.8%, 11.5%, 20.9% and 26.3%, respectively.

Discussion

The present study addressed the prognostic value of dobutamine-atropine stress Tc-99m sestamibi SPECT imaging in patients referred with chest pain and suspected myocardial ischemia. Dobutamine stress is frequently used in conjunction with echocardiography and has been shown to provide important prognostic information (14). However, to our knowledge, no information is available when dobutamine stress is used in conjunction with perfusion imaging. The main finding of this study is that, in patients with chest pain who are unable to perform an adequate exercise test, the test provides useful prognostic information in addition to clinical data.

Stress technique. Dobutamine is a synthetic sympathomimetic amine that stimulates $beta_1$, $beta_2$ and $alpha_1$ receptors. As a result, there is a marked inotropic response (mediated by both $alpha_1$ and $beta_1$ receptors), a modest chronotropic response (mediated by $beta_1$ receptors) and a minor increase in systolic blood pressure (due to $alpha_1$- and $beta_1$-mediated increase in cardiac output and relative stable peripheral vasculature tonus, mediated by $alpha_1$ vasoconstriction and $beta_2$ vasodilation) (15). As a result of this augmentation of myocardial contractility, heart rate, left ventricular pressure and wall stress, more oxygen is required. Normally a dose-related increase in subepicardial and subendocardial blood flow occurs within myocardium supplied by normal coronary arteries (16,17). However, blood flow increases minimally within vascular beds supplied by significantly stenosed arteries, with most of the increase occurring within the subepicardium rather than the subendocardium (16). This heterogeneity in myocardial blood flow between normal and abnormal perfused areas can be visualized by Tc-99m sestamibi myocardial perfusion scintigraphy.

Although direct vasodilators (dipyridamole and adenosine) are believed to be superior in creating blood flow heterogene-

Table 4. Association by Univariate and Multivariate Analysis of Clinical and Stress Test Data With All Cardiac Events: Odds Ratios (95% confidence intervals)

		Multivariate Analysis of Clinical and Stress Test Data		
	Univariate Analysis	Clinical Data	Model I	Model II
Clinical data				
Age >70 yr	1.0 (0.5–1.9)*	*	*	*
Male	1.9 (1.1–3.2)	*	*	*
History of infarction	2.5 (1.5–4.3)	2.7 (1.6–4.5)	*	*
History of revascularization	2.0 (1.2–3.3)	*	*	*
History of heart failure	2.1 (1.2–3.6)	*	*	*
Typical angina	3.2 (1.9–5.4)	3.3 (1.9–5.7)	3.2 (1.9–5.6)	2.9 (1.7–5.1)
Stress test data				
Angina	2.0 (1.2–3.3)	—	*	*
ST-T wave changes	2.1 (1.2–3.8)	—	*	*
Abnormal scan	7.8 (3.3–18.6)	—	7.9 (3.3–18.9)	—
Fixed defect	2.9 (1.7–5.0)	—	—	2.5 (1.4–4.4)
Reversible defect	3.8 (2.3–6.5)	—	—	3.1 (1.8–5.4)

Format as in Table 3.

ity (16), dobutamine Tc-99m sestamibi SPECT imaging has a good accuracy for the detection of coronary artery disease when used in conjunction with perfusion scintigraphic techniques. Pooled data from six published studies in 380 patients (7–12) show a sensitivity of 84% and a specificity of 71% for the detection of coronary artery disease. Moreover, a direct comparison by Marwick et al. (18) between vasodilator and dobutamine for Tc-99m sestamibi myocardial perfusion scintigraphy in 97 patients yielded similar diagnostic accuracies of the two stress agents. Thus, dobutamine can be regarded as an excellent alternative stress agent in patients unable to perform adequate exercise, in particular in those patients with relative contraindications for vasodilator stress (mainly patients with obstructive airway disease) or in patients who have ingested caffeine or aminophylline shortly before undergoing myocardial perfusion stress imaging.

Safety and feasibility. As shown in other (echocardiographic) studies (19–21), dobutamine-atropine stress is a safe and feasible stress method in patients with chest pain. In this study, there were no serious side effects like sustained ventricular tachycardia, ventricular fibrillation, myocardial infarction or death. The feasibility of the test was also high, as only 30 patients (8%) had a nondiagnostic test and 322 patients (82%) were free of any side effect.

Prognostic value. The present study indicates that patients at greater risk for hard or all cardiac events can be identified from a stable chest pain population by virtue of their clinical (older age, male gender and history of myocardial infarction, revascularization procedures, congestive heart failure or typical angina) and scintigraphic (abnormal scan results, fixed or reversible perfusion defects) profile.

The single most important independent predictor of subsequent events was abnormalities on the perfusion study (any abnormality); such an abnormal finding increased the risk for subsequent hard cardiac events tenfold and for all events

Figure 3. Histogram showing the annual event rate for hard events **(open bars)** and all events **(hatched bars)** according to extent and severity score of fixed perfusion defects. The number of patients in each category was 162, 114, 70, 27 and 19, respectively.

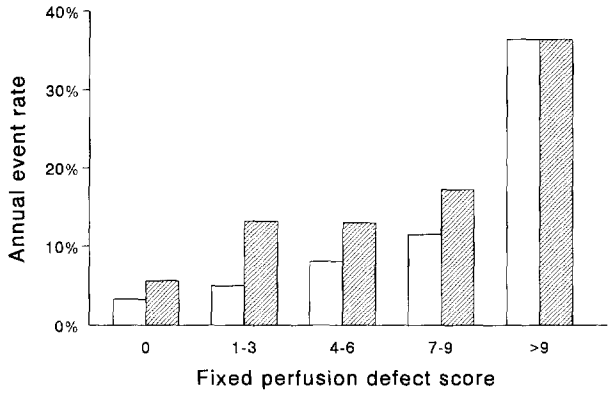
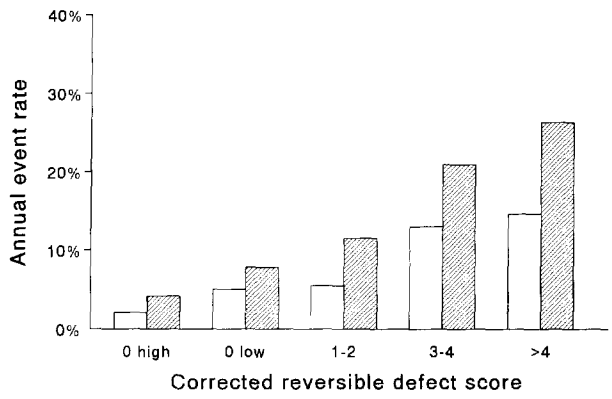


Figure 4. Histogram showing the annual event rate for hard events **(open bars)** and all events **(hatched bars)** according to the (stress level [high/low] corrected) extent and severity score of reversible perfusion defects. The number of patients in each category was 100, 100, 109, 62 and 21, respectively.



eightfold. A normal scan conferred a good prognosis and identified 33% of the subgroup that was at a very low risk for hard events (annual event rate 0.8%) and low risk for all events (annual event rate 2.5%). Furthermore, an ischemic pattern provided additional, independent prognostic value. Compared with patients without ischemia, these patients had a threefold increased risk for both hard and all events.

Prognostic value according to extent and severity of perfusion defects. This study clearly shows a direct relation between the extent and severity of the perfusion defects and prognosis. Several other investigators, using mainly exercise planar or SPECT thallium-201 imaging, have described a relation between the extent of the perfusion defect and subsequent coronary events (22–25). In particular, the degree of hypoperfusion on SPECT imaging, with its ability to provide much finer segmental analysis, avoiding the problem of superimposition that occurs with planar imaging, is directly related to the extent of the myocardium either already destroyed by a previous infarct or ischemic but viable and at risk for necrosis. Although the extent of coronary artery disease is an important prognostic indicator (26), sestamibi SPECT imaging represents the functional significance of the stenoses, a factor which may be superior to angiographic data (27).

Comparison with other sestamibi studies. In comparable patient populations, most published data regarding Tc-99m sestamibi in combination with other stress techniques found striking similar results. Stratmann et al. (5) reported the prognostic value of exercise Tc-99m sestamibi imaging in 521 patients. During multivariate analysis, abnormal scan results (OR 11.9, 95% CI 1.6 to 89.4) and reversible defects (OR 2.9, 95% CI 1.2 to 7.0) were the only independent predictors of hard cardiac events. Patients with normal scan results had an annual event rate of 0.4%. In another study by Stratmann et al. (28), comparable prognostic results were reported for dipyridamole Tc-99m sestamibi imaging in 308 patients. Patients with normal scan results had an annual event (unstable angina, nonfatal myocardial infarction or cardiac death) rate of 1.7%. Several studies focused on the predictive value of normal Tc-99m sestamibi imaging for the prediction of hard cardiac events. Both exercise (29,30) and dipyridamole (31) studies found annual event rates <1%.

Study limitations. Although recurrent angina may be a marker of ischemia, the subjective nature of this symptom, as well as influence by medication usage and other factors, makes this a potential unreliable end point of prognostic testing. Furthermore, the decision to perform coronary arteriography and subsequent coronary artery bypass graft surgery is frequently influenced by individual physicians' biases and may also be affected by the presence of abnormal findings on the stress study. Therefore, we excluded patients with early elective revascularizations and we analyzed the "hard" events (nonfatal myocardial infarction and cardiac-related death) separately. Because there is limited angiographic information available, our study does not permit assessment of the specificity and sensitivity of dobutamine stress sestamibi perfusion scintigraphy for the detection of significant coronary artery disease.

Increased lung radiotracer uptake, a prognostic marker in previous scintigraphic studies (32) was also not available in the current Tc-99m sestamibi tomographic investigation. The interpretation of the SPECT images was semiquantitative. This type of analysis, however, is still the most frequently used in daily clinical practice. Antianginal medications were not routinely withheld before stress testing; we believe this also reflects daily clinical practice.

Conclusions. In patients unable to exercise adequately, with chest pain and suspected or known coronary disease, dobutamine-atropine stress Tc-99m sestamibi SPECT perfusion imaging is a safe and feasible stress technique. The test provides useful prognostic information, probably comparable with exercise or dipyridamole stress Tc-99m sestamibi imaging studies. The single most important independent predictor of both hard (nonfatal myocardial infarction or cardiac death) and all (hard events or revascularization procedures) cardiac events is an abnormal perfusion pattern (any abnormality); the presence of a reversible perfusion defect provides additional, independent prognostic information. Moreover, the extent and severity of the perfusion defects are major determinants for prognosis.

We thank Joyce Postma-Tjoa, nuclear medicine technician, for invaluable help in maintaining the data base.

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Synergistic value of simultaneous stress dobutamine sestamibi single-photon emission computerized tomography and echocardiography in the detection of coronary artery disease. Am Heart J 1994;128:713–8.
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