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Safety of Dobutamine-Atropine Stress Myocardial Perfusion Scintigraphy

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Dobutamine stress testing is increasingly used for the diagnosis and functional evaluation of coronary artery disease. However, the relationship between myocardial perfusion abnormalities and complications of the test has not been studied. **Methods:** We studied the hemodynamic profile, safety and feasibility of dobutamine (up to 40 μg/kg/min)-atropine (up to 1 mg) stress myocardial perfusion SPECT imaging (with ^{201}Tl, ^{99m}Tc-MIBI or tetrofosmin) in a consecutive series of 1076 patients (age = 59 ± 11 yr, 50% with previous myocardial infarction) referred for evaluation of myocardial ischemia. **Results:** No infarction or death occurred during the test. The test was considered feasible (achievement of 85% of the target heart rate or an ischemic endpoint) in 1005 patients (94%). Hypotension (systolic blood pressure drop ≥ 40 mm Hg) occurred in 37 patients (3.4%). Independent predictors were higher baseline systolic blood pressure ($p < 0.0001$), number of ischemic segments ($p < 0.05$) and age ($p < 0.05$). Supraventricular tachyarrhythmias occurred in 48 patients (4.4%). Independent predictors were fixed perfusion defect (infarction) score ($p < 0.005$) and age ($p < 0.05$). Ventricular tachycardia occurred in 41 patients (3.8%). Independent predictors were infarction score ($p < 0.01$) and male gender ($p < 0.05$). All arrhythmias terminated spontaneously or after metoprolol administration. **Conclusion:** Dobutamine-atropine myocardial perfusion scintigraphy is a feasible method for the evaluation of coronary artery disease with a safety profile and feasibility comparable to those reported for dobutamine stress echocardiography. Patients with more severe fixed perfusion abnormalities are at a higher risk of developing tachyarrhythmias during the test.

Key Words: dobutamine; myocardial perfusion; safety; coronary artery disease

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Myocardial perfusion scintigraphy in conjunction with an exercise stress test is an accurate method for the diagnosis, localization and functional evaluation of coronary artery disease (*1*). In patients with limited exercise capacity, pharmacological stress testing is a feasible alternative (*2,3*). Vasodilator agents (adenosine and dipyridamole) are the most commonly used pharmacological agents in conjunction with myocardial perfusion scintigraphy. Dobutamine perfusion scintigraphy is an exercise simulator stress modality used for the diagnosis and prognostic stratification of patients with coronary artery disease, particularly in those who are not candidates for vasodilator stress agents such as patients with obstructive airway disease and patients with sinoatrial or atrioventricular nodal disease (*4–13*). Despite experience in the safety and feasibility of dipyridamole and adenosine myocardial perfusion scintigraphy (*2,3*), only one article described the safety of dobutamine perfusion scintigraphy in a large number of patients (*4*). Tachyarrhythmias and hypotension are not uncommon side effects of the dobutamine stress test (*4,14–19*). Dobutamine stress testing is more frequently performed in conjunction with echocardiography, and the studies are increasing regarding the safety of this modality (*14–19*). The difference in the safety profile between dobutamine stress echocardiography and myocardial perfusion scintigraphy relies on the ability of echocardiography to detect extensive ischemia necessitating termination of the test. The aims of this study were to assess the safety and feasibility of dobutamine myocardial perfusion scintigraphy in a large number of patients referred for evaluation of myocardial ischemia and to assess the relationship between myocardial perfusion abnormalities and complications of the test.

MATERIALS AND METHODS

Patients

The study population comprised 1076 consecutive patients (383 women, 693 men; mean age 59 ± 11 yr) with limited exercise capacity referred to our imaging laboratory for evaluation of myocardial ischemia by dobutamine stress myocardial perfusion scintigraphy between November 1990 and March 1997. Patients were referred primarily for dobutamine stress testing without being evaluated for pharmacologic vasodilators. Contraindications for the test were severe heart failure, significant valvular heart disease, severe hypertension (blood pressure ≥ 180/110), hypotension (blood pressure < 90/60) and unstable chest pain. All patients gave a verbal informed consent

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to undergo the study. The Hospital Ethical Committee approved the use of the dobutamine stress test for evaluation of coronary artery disease.

Clinical Characteristics

A history of previous myocardial infarction was encountered in 534 patients (50%). Eighty-one patients were studied after a recent myocardial infarction (range 7–27 days; mean 10 ± 9 days after acute infarction). The remaining 453 patients with old myocardial infarction were studied 5.1 ± 5.6 yr after infarction. Indications for the test were evaluation of chest pain in 769 patients (71%) of whom 373 had typical anginal pain, exertional dyspnea in 29 patients (3%), assessment of revascularization in 61 patients (6%), assessment of myocardial viability in 82 patients (8%) and routine evaluation of prior myocardial infarction in 135 patients (13%). Medications at the day of the test included beta blockers in 397 patients (37%), calcium channel blockers in 456 patients (42%), nitrates in 410 patients (38%) and angiotensin converting enzyme inhibitors in 331 patients (31%).

Dobutamine Stress Test

Dobutamine was infused through an antecubital vein starting at a dose of 5 μg/kg/min followed by 10 μg/kg/min (3-min stages), increasing by 10 μg/kg/min every 3 min to a maximum of 40 μg/kg/min. Atropine (up to 1 mg) was given to patients not achieving 85% of age-predicted maximal heart rate, and the dobutamine infusion was continued. The echocardiogram was monitored throughout dobutamine infusion and recorded each minute. Cuff blood pressure was measured at rest, every 3 min during stress and at maximal stress. The test was interrupted if severe chest pain, ST-segment depression > 2 mm, significant ventricular or supraventricular arrhythmia, hypertension (blood pressure ≥ 240/120), systolic blood pressure fall > 40 mm Hg or any intolerable side effect regarded as being due to dobutamine occurred during the test. Metoprolol (1–5 mg) was available and used intravenously to reverse the effects of dobutamine if they did not revert quickly. The test was considered feasible if the patient could achieve 85% of the maximal heart rate predicted for age and/or when an ischemic endpoint (angina, ST-segment depression, reversible perfusion abnormalities) was reached.

SPECT Imaging

Approximately 1 min before the termination of the stress test, an intravenous dose of 370 MBq ^{99m}Tc-sestamibi (MIBI; 543 patients) or tetrofosmin (328 patients) or 74 MBq ^{201}Tl (205 patients) was administered. The acquisition of stress SPECT imaging was started immediately after the thallium injection and 1 hr after the technetium injection. In patients who received technetium-labeled agents, resting studies were performed 24 hr after the stress study, 1 hr after injection of 370 MBq MIBI or tetrofosmin. The same isotope administered during stress was used for rest studies. In patients who received ^{201}Tl at stress, resting studies were acquired 4 hr after the test, 30 min after reinjection of 37 MBq ^{201}Tl. Reinjection of the thallium protocol was used because all patients referred to ^{201}Tl SPECT had left ventricular dysfunction. Image acquisition and interpretation were performed according to previously described protocols (*9,20*). For each study 6 oblique (short-axis) slices from the apex to the base and 3 sagittal (vertical long axis) slices from the septum to the lateral wall were defined. Each of the 6 short-axis slices was divided into 8 equal segments. The interpretation of the scan was performed by visual analysis assisted by the circumferential profiles analysis. All tomographic views were reviewed in side-by-side pair (stress and rest) by an experienced observer who was unaware of the patients' clinical data. A reversible perfusion defect was defined as a perfusion defect on stress images that partially or completely resolved at rest images in 2 or more contiguous segments or slices. This was considered diagnostic of ischemia. A fixed perfusion defect was defined as a perfusion defect on stress images in 2 or more contiguous segments or slices that persists on rest images. Six major myocardial segments were detected: anterior, inferior, septal anterior, septal posterior, posterolateral and apical. To assess the severity of perfusion abnormalities, each of the 6 major left ventricular segments was scored using a four-grade scoring method: (a) 0 = normal; (b) 1 = slightly reduced; (c) 2 = moderately reduced; (d) 3 = severely reduced or absent uptake. The perfusion score was derived by the sum of the score of the 6 myocardial segments for rest and stress images. The ischemic score was obtained by subtracting the rest from the stress score. The rest (fixed perfusion defect) score was considered as the infarction score.

Statistical Analysis

Unless specified, data are presented as mean values ± s.d. The chi-square test was used to compare differences between proportions. The Student's t-test was used for analysis of continuous data. Stepwise logistic regression models were used to detect independent predictors of hypotension and arrhythmias. Differences were considered significant if the null hypothesis could be rejected at the 0.05 probability level.

RESULTS

Symptoms and Hemodynamic Response

No death or myocardial infarction occurred during or shortly after the test. Heart rate and systolic blood pressure increased significantly from rest to peak stress 73 ± 15 [range 45–118] versus 135 ± 20 [range 62–210] beats/min, $p < 0.00001$ and 137 ± 22 [range 90–178] versus 149 ± 30 [range 71–280] mmHg, $p < 0.00001$), whereas diastolic blood pressure decreased significantly (80 ± 13 [range 41–118] versus 76 ± 16 [range 35–135] mmHg, $p < 0.00005$). The maximal tolerated dose of dobutamine was 10 μg/kg/min in 9 patients (0.8%), 20 μg/kg/min in 39 patients (4%), 30 μg/kg/min in 231 patients (21%) and 40 μg/kg/min in 797 patients (74%). Atropine was administered in 405 patients (38%, mean dose = 0.61 ± 0.29 mg). Atropine induced a significant increase of the heart rate (from 127 ± 24 to 135 ± 17 beats/min). ST-segment depression occurred in 210 patients (20%) and ST-segment elevation occurred in 114 patients (11%). The prevalence of symptoms and various types of arrhythmias during the test is shown in Table 1. Ventricular and supraventricular tachycardia were terminated in all cases, spontaneously, by stopping dobutamine infusion or by administration of metoprolol. A systolic blood pressure drop of > 20 mm Hg occurred in 155 patients (14%) and a drop of ≥ 40 mm Hg occurred in 37 patients (3.4%) during stress. Reasons for terminating the test are shown in Table 2.

Myocardial Perfusion Scintigraphy

SPECT results were normal in 299 patients (28%). A fixed perfusion defect was detected in 318 patients (30%), whereas 459 patients (43%) had partially or completely reversible perfusion defects. Ischemia at the scan was detected in 70 of the 141 patients (50%) who failed to achieve 85% of the maximal heart rate and had no angina or ST-segment depression. Therefore, the test was considered feasible (achievement of 85% of maximal heart rate and/or an ischemic endpoint) in 1005 patients (94%).

TABLE 1
Symptoms and Arrhythmias During Dobutamine-Atropine Stress Test

Symptoms/arrhythmias	No. of patients (%)
Nausea	7 (0.6%)
Flushing	2 (0.2%)
Dizziness	45 (4%)
Anxiety	23 (2%)
Chills	58 (5%)
Headache	71 (6.5%)
Symptomatic hypotension	9 (0.8%)
Dyspnea	63 (5.8%)
Typical angina	290 (27%)
Atypical chest pain	134 (12%)
Premature atrial contractions	68 (6.3%)
Premature ventricular contractions	332 (31%)
Supraventricular tachycardia	38 (3.5%)
Atrial fibrillation	10 (0.9%)
Ventricular tachycardia < 10 beats	40 (3.7%)
Ventricular tachycardia ≥ 10 beats	1 (0.1%)

Predictors of Hypotension and Arrhythmias

Myocardial perfusion abnormalities in patients with and without arrhythmias and hypotension are shown in Table 3. Independent predictors of hypotension and arrhythmias are shown in Table 4. Multivariate analysis detected baseline systolic blood pressure, older age and number of ischemic segments as independent predictors of hypotension. The trend to a higher number of ischemic segments in patients with, rather than without, hypotension was observed in technetium studies (0.9 ± 1.2 versus 0.5 ± 0.9, $p = 0.15$) as well as in thallium studies (1.7 ± 2.4 versus 1.2 ± 1.9, $p = 0.2$). Independent predictors of supraventricular tachyarrhythmias were infarction score and age. Independent predictors of ventricular tachycardia were infarction score and male gender. Figure 1 demonstrates the infarction score in patients with and without tachyarrhythmias on thallium and technetium studies.

Safety Profile in Patients with Recent Versus Old Myocardial Infarction

There was no significant difference between patients with recent as opposed to patients with old myocardial infarctions with regard to maximal dobutamine dose (36.5 ± 8.4 versus 36.2 ± 8.1 μg/kg/min), peak stress rate pressure product (18416 ± 4940 versus 18864 ± 5219), infarction score (4.5 ± 3.2 versus 4.8 ± 3.4), prevalence of supraventricular tachycardia (4% versus 6%), ventricular tachycardia (3% versus 5%) or hypotension (1% versus 5%, $p = 0.2$). There was a trend to a higher ischemic score in patients with old as opposed to patients with recent infarctions (2.1 ± 2.6 versus 1.5 ± 2.2, $p = 0.07$).

TABLE 2
Reasons for Termination of Dobutamine Stress Test

Reasons for test termination	No. of patients (%)
85% of maximal heart rate	851 (79%)
Maximal dose	75 (7%)
Angina	72 (6.7%)
ST changes	12 (1.1%)
Arrhythmias	15 (1.4%)
Hypertension	1 (0.01%)
Hypotension	28 (2.6%)
Dyspnea	12 (1.1%)
Chills, flushing, anxiety, dizziness	10 (0.09%)

DISCUSSION

Our study demonstrates that dobutamine-atropine stress perfusion scintigraphy is a feasible and safe method for evaluating myocardial ischemia in patients with known or suspected coronary artery disease and limited exercise capacity. No myocardial infarction or death occurred during or shortly after the test. Ventricular and supraventricular tachycardia were terminated in all cases, spontaneously, by stopping dobutamine infusion or by administering metoprolol. Minor side effects including chills, dizziness, headache, nausea and anxiety were frequent, but mostly well tolerated, and were the reason for terminating the test only in 0.09% of patients.

Predictors of Arrhythmias and Hypotension

The severity of fixed perfusion defects independently predicted the occurrence of ventricular and supraventricular tachycardia. The relation between ventricular tachycardia and perfusion abnormalities may be explained by the fact that patients with more severe fixed perfusion abnormalities would have more severe left ventricular dysfunction and, consequently, more substrate for arrhythmias. A similar relationship between dobutamine-induced supraventricular tachyarrhythmias (including atrial fibrillation) and fixed perfusion abnormalities can be explained by the association of left ventricular dysfunction with an increase in left atrial pressure and size, which are known predisposing factors for these arrhythmias. The extent of myocardial ischemia was an independent predictor of hypotension in multivariate analysis. Previous studies on dobutamine stress echocardiography failed to find a relationship between myocardial ischemia and hypotension (*18,19,21*). The discrepancy between echocardiographic studies and this scintigraphic study is hard to explain. It is possible that in the presence of diffuse ischemia, diffuse hypokinesis may be overlooked by visual echocardiographic assessment due to the absence of hyperkinesis in adjacent segments, which makes subtle diffuse changes difficult to interpret. We demonstrated previously that, in patients with coronary artery disease and reversible perfusion defects on dobutamine MIBI SPECT, hypotension was more frequent in patients without as opposed to those with transient wall-motion abnormalities on simultaneous echocardiogram (*22*).

Age was an independent predictor of hypotension in accordance with previous studies (*19,21,23*). This may be explained by the impairment of compensatory mechanisms for hypotension with aging. We also found age to be an independent predictor of supraventricular tachyarrhythmias. This finding may be explained by the tendency of these arrhythmias to increase in frequency with aging both spontaneously (*24*) and with exercise (*25*). Male gender was an independent predictor of ventricular tachycardia. This cannot be explained on the basis of more severe perfusion abnormalities in men as the independent value of gender was demonstrated in addition to the fixed perfusion abnormalities in the multivariate analysis model. We recently showed that in patients who had coronary angiography, the prevalence of ventricular tachycardia was higher in men than in women during dobutamine stress echocardiography (*26*). In that study, men had a higher prevalence and extent of coronary artery disease and more severe left ventricular dysfunction. It is possible that in the current study, other factors that were not available for multivariate analysis as the prevalence of coronary artery stenosis and global left ventricular function contributed to an apparently independent value of gender for the prediction of ventricular tachycardia. Patients with recent myocardial infarction did not have a higher risk of

TABLE 3
Myocardial Perfusion Abnormalities in Patients With and Without Arrhythmias or Hypotension During Dobutamine Stress Test

	SBP drop ≥40 mm Hg			SVT or AF			Ventricular tachycardia		
	Yes n = 37	No n = 1039	p value	Yes n = 48	No n = 1028	p value	Yes n = 41	No n = 1035	p value
Scan diagnosis									
Normal	7 (19)	289 (28)	ns	7 (15)	289 (28)	0.04	8 (20)	288 (28)	ns
Ischemia	4 (11)	128 (12)	ns	5 (10)	127 (12)	ns	3 (7)	129 (12)	ns
Infarction	13 (35)	302 (29)	ns	14 (29)	301 (29)	ns	14 (34)	301 (29)	ns
Infarction + ischemia	13 (35)	320 (31)	ns	22 (46)	311 (30)	0.04	16 (39)	317 (31)	ns
Stress defects*	2.2 ± 1.6	1.7 ± 1.5	0.04	2.4 ± 1.6	1.7 ± 1.7	0.001	2.3 ± 1.6	1.7 ± 1.5	0.017
Rest defects*	1.5 ± 1.4	1.2 ± 1.4	0.2	1.8 ± 1.6	1.2 ± 1.4	0.009	1.9 ± 1.6	1.2 ± 1.4	0.004
Reversible defects*	1.1 ± 1.5	0.7 ± 1.1	0.04	1.1 ± 1.3	0.7 ± 1.1	0.03	0.8 ± 1.1	0.8 ± 1.1	0.7
Stress score	5.9 ± 4.8	4.3 ± 4.3	0.04	6.5 ± 4.7	4.3 ± 4.3	0.0005	6.2 ± 4.9	4.3 ± 4.3	0.008
Infarction score	3.6 ± 3.5	2.8 ± 3.3	0.1	4.4 ± 4.1	2.8 ± 3.5	0.002	4.5 ± 3.8	2.8 ± 3.3	0.001
Ischemic score	2.3 ± 3.0	1.5 ± 2.3	0.06	2.2 ± 2.7	1.5 ± 2.3	0.04	1.7 ± 2.3	1.6 ± 2.3	0.8

*Numbers are based on the six-segment left ventricular model.
SBP = systolic blood pressure; SVT = supraventricular tachycardia; AF = atrial fibrillation; ns = not significant.

arrhythmias compared to patients with old myocardial infarction despite the similar infarction score in both groups.

Comparison with Previous Studies

Dakik et al. (*4*) reported the safety and hemodynamic profile of dobutamine perfusion scintigraphy in 1012 patients. Complications of the test were nonsustained ventricular tachycardia (4.2%), atrial fibrillation (1.1%) and atrial flutter (0.1%). Minor side effects were headache (13.6%), dyspnea (12.2%), flushing (10.3%), palpitations (9.7%), nausea (8%) and tremors (1.1%). However, Dakik et al. did not report the feasibility of the test or the relationship between the safety of the test and perfusion abnormalities. In addition, atropine was not used and, therefore, the safety of the test in conjunction with atropine was not studied. The prevalence of atrial fibrillation (0.9%) and ventricular tachycardia (3.8%) in our study is comparable to their findings. Systolic blood pressure drop > 20 mm Hg was more frequent in our study (14% versus 6%). This may be explained by the higher prevalence of abnormal scans in our study (72% versus 50%) and the association between perfusion abnormalities and hypotension.

TABLE 4
Independent Predictors of Hypotension and Tachyarrhythmias During Dobutamine Stress Test

Predictors	p value	Chi square
Hypotension ≥20 mm Hg		
Resting SBP	<0.0001	34
Age	<0.0001	15.8
Ischemic segments	<0.05	4
Hypotension ≥40 mm Hg		
Resting SBP	<0.0001	23.4
Ischemic segments	<0.05	5.3
Age	<0.05	4.1
SVT		
Infarction score	<0.005	9.8
Age	<0.05	4.8
VT		
Infarction score	<0.05	6.4
Male gender	<0.05	4.4

SBP = systolic blood pressure; SVT = supraventricular tachycardia; VT = ventricular tachycardia.

Studies of Dobutamine Echocardiography

The prevalence of supraventricular tachycardia (including atrial fibrillation) (4.8%) and ventricular tachycardia (3.8%) in our study is consistent with that reported by Meters et al. (*14*) at 4.1% and 4.2%, respectively. Arrhythmias were the reason for terminating the test in 1.4% of patients in our study, which is comparable to the findings of Meters et al. (*14*) at 2.1% and Secknus et al. (*18*) at 1.6%. Feasibility of dobutamine perfusion scintigraphy in this study (94%) is comparable to that reported with dobutamine stress echocardiography by Poldermans et al. (*16*) at 98%, Cornel et al. (*15*) at 97%, Picano et al. (*17*) at 88% and Elhendy et al. (*19*) at 91%.

Study Limitations

The study was performed using different protocols of dobutamine perfusion scintigraphy and different tracers. It has been demonstrated that thallium gives a larger reversible defect size than MIBI (*27*), which may give fallacies when the perfusion scores of these studies are pooled together. However, the difference in the defect size between both tracers was reported only for reversible abnormalities, whereas the extent and severity of fixed perfusion abnormalities were similar (*27*). In our study, separate analysis of thallium and technetium studies showed the same significant difference in the fixed perfusion

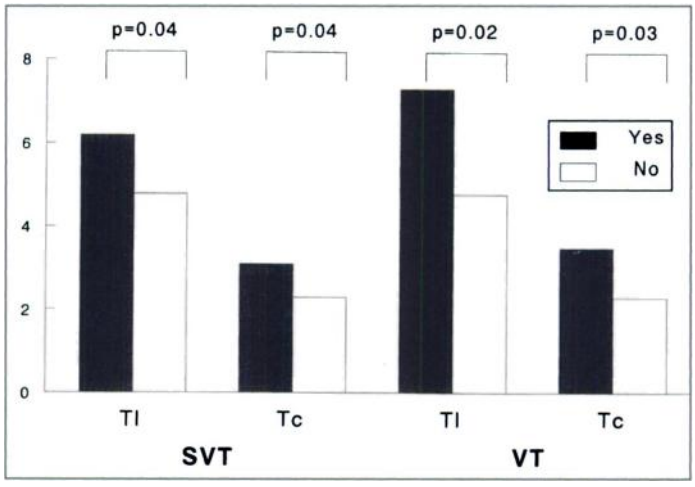

FIGURE 1. Fixed perfusion defect (infarction) score in patients with and without supraventricular tachycardia and in patients with and without ventricular tachycardia presented separately for ^{201}Tl and ^{99m}Tc studies.

defect score between patients with and without tachyarrhythmias and the same trend to a higher number of ischemic segments in patients with, as opposed to without, hypotension. The dose of MIBI and tetrofosmin used in this study is low relative to the doses used in other studies (*28*). However, a dose of 370 MBq provided an adequate imaging quality in this study. We have reported a high accuracy of dobutamine SPECT for the diagnosis and prognostic stratification of coronary artery disease using the same doses of these isotopes (*8–13*).

CONCLUSION

Dobutamine-atropine stress myocardial perfusion scintigraphy is a feasible method for evaluation of myocardial ischemia with a safety profile and feasibility comparable to those reported with dobutamine stress echocardiography. Patients with more severe myocardial perfusion abnormalities are at a higher risk of developing hypotension and tachyarrhythmias during the test.

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