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Comparison of Dobutamine and Treadmill Exercise Echocardiography in Inducing Ischemia in Patients With Coronary Artery Disease

LOUKIANOS RALLIDIS, MD, PHILIP COKKINOS, MD, DIMITRIS TOUSOULIS, MD, PHD, FACC, PETROS NIHOYANNOPOULOS, MD, FACC, FESC

London, England, United Kingdom

Objectives. **We sought to compare the magnitude of ischemia precipitated by both treadmill exercise and dobutamine stress echocardiography.**

Background. **Although it is alleged that dobutamine stress produces ischemia similar in degree and extent to that produced during treadmill exercise, a direct comparison with treadmill exercise, the most common form of exercise, has not been performed.**

Methods. **Eighty-five consecutive patients with known coronary artery disease underwent both stress tests on the same day, in random order.**

Results. **Sixty-two patients (73%) had positive results on exercise echocardiography compared with 53 (62%) who had positive results on dobutamine stress (p = NS). Of the 53 patients with positive dobutamine test results, wall motion abnormalities appeared after the addition of atropine in 35 patients (66%). During dobutamine infusion, 22 patients (26%) had a hypotensive response that was reversed in 16 by prompt administration of atropine. At peak dobutamine–atropine stress, heart rate was higher than that at peak exercise (p < 0.001), whereas systolic blood pressure and rate–pressure product were higher at peak exercise than at peak dobutamine–atropine stress (p = 0.0001). In the 53 patients with positive results on both tests, peak wall motion score index was greater with treadmill exercise than with dobutamine–atropine infusion ([mean ± SD] 1.73 ± 0.45 vs. 1.57 ± 0.44, p < 0.001).**

Conclusions. **Echocardiography immediately after treadmill exercise induces a greater ischemic burden than dobutamine–atropine infusion. In the clinical setting, exercise echocardiography should therefore be chosen over dobutamine echocardiography for diagnosing ischemia, when possible. When dobutamine echocardiography is used as an alternative modality, maximal heart rate should always be achieved by the addition of atropine.**

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The value of two-dimensional echocardiography for the noninvasive diagnosis of coronary artery disease during exercise (1–4) and dobutamine infusion (5–9) has been widely investigated in a variety of stress modalities. Transient left ventricular regional myocardial dysfunction seen on echocardiography represents an earlier and more sensitive marker for myocardial ischemia than electrocardiographic (ECG) changes or chest pain alone (10). Dobutamine and treadmill exercise are the two most popular forms of stress coupled with echocardiographic imaging (11).

Although treadmill exercise is the most popular form of exercise and provides the best workload (2), dobutamine has become the most widely used pharmacologic stressor. Both forms of stress can be used in conjunction with cross-sectional echocardiography in an attempt to increase the predictive accuracy of the stress test for detection of myocardial ischemia. Both have their advantages and disadvantages when used in daily clinical practice. Dobutamine stress is easier to perform, can be applied in patients unable to exercise and allows imaging throughout the study. It also provides invaluable information on myocardial viability when required. However, dobutamine stress requires the positioning of an intravenous cannula and therefore becomes a semi-invasive test that is frequently complicated by unpleasant side effects (12) and uninterpretable ECG results. Conversely, treadmill exercise is the best available physiologic stressor; it is truly noninvasive; patients and physicians are familiar with it; and it provides additional important hemodynamic and ECG information, as well as assessing the patient's symptoms and functional capacity. However, exercise treadmill echocardiography is technically more demanding, requires a digital line loop system to overcome the effects of hyperventilation, cannot precisely identify the time of onset of ischemia and carries the theoretic risk of losing information if the reversible mechanical dysfunction resolves quickly into recovery before echocardiographic imaging can be performed (13). Although there are studies comparing dobutamine stress with bicycle echocardiography (14,15), there are no data directly comparing dobutamine with echocardiography immediately after treadmill exercise.

In the present study, we hypothesized that, immediately echocardiography after treadmill exercise, because of its superior hemodynamic effects, would induce myocardial ischemia

From the Department of Medicine, Cardiology Unit, Hammersmith Hospital, London, England, United Kingdom.

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Address for correspondence: Dr. Petros Nihoyannopoulos, Department of Medicine, Clinical Cardiology, Hammersmith Hospital, Imperial College School of Medicine, Du Cane Road, London W12 ONN, England, United Kingdom. E-mail: petros@rpms.ac.uk.

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Table 1. Clinical Characteristics of 85 Study Patients

Age (yr)	57 ± 11
Men/women	72/13
BMI (kg/m^2)	26.9 ± 4.2
Effort angina (%)	60 (71%)
1 VD	45 (53%)
2 VD	22 (26%)
3 VD	18 (21%)
Akinesia at rest (%)	42 (49%)
Beta-blockers*	47 (55%)

*Stopped in 19 patients for 48 h. Data presented are mean value ± SD or number (%) of patients. BMI = body mass index; VD = vessel disease.

of greater magnitude than dobutamine in the same patient cohort with chronic stable coronary artery disease.

Methods

Study patients (Table 1). Eighty-five consecutive patients with a mean [±SD] age of 57 ± 11 years (range 35 to 75) and known coronary artery disease were enrolled in the study. All patients were referred for evaluation of the extent and severity of ischemia. Patients with heart failure, unstable angina, recent myocardial infarction (within the preceding 6 months), previous cardiac surgery or coronary angioplasty, congenital or valvular heart disease, uncontrolled hypertension or documented serious arrhythmia were excluded, as were patients unable to exercise. The coronary anatomy had been delineated during cardiac catheterization performed within 6 months before the day of the test in all patients (mean 2.8 ± 1.4). Significant coronary artery disease was defined as >70% reduction in lumen diameter of any of the three coronary arteries or their primary branches or >50% narrowing of the lumen diameter of the left main coronary artery. All patients had significant coronary artery disease (one-vessel disease in 45, two- or three-vessel disease in 40 [left main disease in 2]). Two of the remaining patients without rest akinesia had left bundle branch block.

Patient scheduling. Each patient underwent dobutamine and exercise treadmill echocardiography on the same day, in random order. The second test was not performed until all ECG, echocardiographic and hemodynamic characteristics of the patient had returned to baseline status and remained stable for an additional 10 min.

Exercise echocardiography. A symptom-limited maximal treadmill exercise stress test was performed according to the modified Bruce protocol. End points also included a systolic blood pressure >220 mmHg or a diastolic blood pressure >120 mmHg or serious arrhythmia, alone or in combination.

Chest leads were positioned for best access to echocardiographic imaging. Twelve-lead ECG monitoring and symptom notation were performed throughout the study, and blood pressure was determined at rest and every 3 min.

Echocardiographic images were acquired before and immediately after treadmill exercise using a commercially available cardiac ultrasound system (Toshiba SSH 160A, Manor Court, Crawley, West Sussex, UK). These were recorded simultaneously on 0.75-in. videotape and, from a separate black-and-white output, in digital format (Image View III, DCR, Nova MicroSonics) using parasternal long- and short-axis (best mid-papillary muscle level) as well as apical four- and two-chamber projections. Particular attention was given to imaging the entire endocardial surface. Immediately after exercise, patients returned to the same position, and echocardiographic images were again acquired in similar manner. Before commencing exercise, patients practiced their return to the original lateral decubitus position to minimize the time between end of exercise and echocardiographic image acquisition.

Dobutamine stress echocardiography. Graded dobutamine infusion was administered through a peripheral arm vein in 3-min stages at infusion rates of 5, 10, 20, 30 and 40 μg/kg body weight per min. In patients not achieving 85% of their maximal predicted heart rate, 0.6 mg of atropine was given intravenously and repeated up to a maximum of 1.8 mg while the dobutamine infusion was continued. Continuous echocardiographic recording was performed, and a 12-lead ECG was recorded every 3 min. Blood pressure was also measured by an automatic cuff sphygmomanometer every 1 min.

End points for termination of the stress test were similar to exercise stress, with two exceptions: the maximal dose of dobutamine (±atropine) replaced exercise-induced exhaustion and the presence of a hypotensive response (blood pressure drop >20 mm Hg from baseline accompanied by dizziness and bradycardia). In the event of hypotension accompanied by a drop in heart rate, atropine (0.6 mg) was first administered while the infusion was continued, in an attempt to reverse the hypotensive response and complete the test (11). However, if the symptoms persisted, the test was stopped.

Two-dimensional echocardiography from parasternal long- and short-axis and apical four- and two-chamber views was continuous throughout the study and during recovery until resolution of new wall motion abnormalities that might have occurred during stress. Images were digitized on-line at 1) baseline; 2) low dose (10 μg/kg per min); 3) high dose (40 μg/kg per min); and 4) peak stress (±atropine), after completion of the 3 min but while the dobutamine infusion was continued.

Analysis of echocardiograms. Baseline echocardiographic images were evaluated from videotape playback as well as by side by side comparison of digitized images, according to routine practice in our laboratory. On-line digital images in quad screen format were used to evaluate the presence, extent and location of ischemia throughout the tests. During dobutamine stress, wall motion assessment was performed at each of the aforementioned four stages. To assess wall motion abnormalities, the left ventricle was divided into 16 segments according to the recommendations of the American Society of Echocardiography (16). Six segments (basal and midanteroseptal, basal and midanterior free wall and two anteroapical) were assigned to the left anterior descending coronary artery perfusion bed; three segments (basal, midlateral and midposterior)

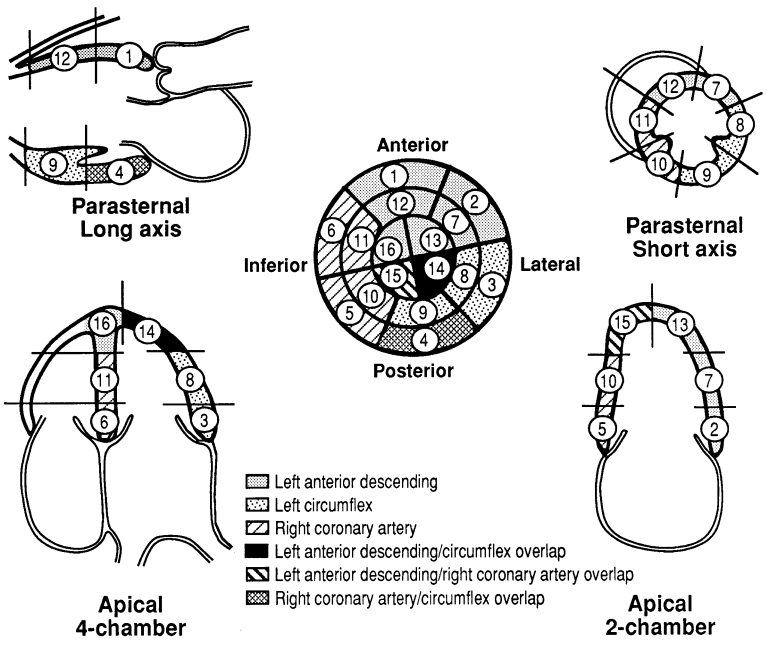

Figure 1. Parasternal and apical views of two-dimensional echocardiographic images with the corresponding vascular regions. In the center, a bull's eye view representing the various vascular beds is shown. Ant. = anterior, IVS = interventricular septum; Post = posterior.

Wall motion abnormalities detection												
Segment	Rest						Peak-stress					
	Basal		Middle		Apex		Basal		Middle		Apex	
Anterior IVS	1		12		13		1		12		13	
Ant. Free Wall	2		7		14		2		7		14	
Lateral	3		8				3		8			
Posterior Wall	4		9		15		4		9		15	
Inferior	5		10				5		10			
Post IVS	6		11		16		6		11		16	
Score : Normokinetic = 1; Hypokinetic = 2; Akinetic = 3; Dyskinetic = 4												

were assigned to the left circumflex coronary artery territory; and four segments (basal and midinferior, basal and midposterior septal) were assigned to the right coronary artery territory. An additional three segments were assigned to overlapping regions: left anterior descending/circumflex vascular bed (apicolateral), left anterior descending/right coronary (inferoapical) and right coronary/circumflex (posterobasal) (9) (Fig. 1).

Positive results on exercise or dobutamine echocardiography were defined as the development of a new or worsening regional wall motion abnormality not present at baseline. *Regional myocardial contractile function* was graded from 1 to 4 as normal, hypokinetic, akinetic or dyskinetic, respectively, in each myocardial segment, with reference to systolic wall thickening rather than endocardial motion. The *total wall motion score* was derived by adding the score of all segments and the wall motion index obtained by dividing the total score by the number of segments. In the presence of rest wall motion abnormalities, stress-induced new or worsening wall motion abnormalities were considered *homozonal* if they were supplied by the infarct-related vessel. *Remote asynergy* was defined as wall motion abnormalities that developed in territories corresponding to the different coronary arteries and having normal wall motion at rest. Echocardiograms were independently reviewed by two experienced observers (L.R., P.N.) who were unaware of the results of cardiac catheterization. In case of disagreement, a consensus was reached.

The *wall motion score difference* between peak stress and rest was introduced as a measure of the magnitude of reversible ischemia during the stress test. The greater the difference between peak and rest scores, the greater the ischemic burden.

ECG analysis. *An ischemic response* was defined as the development of ≥0.1-mV horizontal or downsloping ST segment depression 80 ms after the J point in a lead with a normal baseline ST segment.

Statistical analysis. Results are expressed as mean value ± SD. Frequency data were compared using chi-square analysis and continuous variables using a Student *t* test for paired or unpaired data with the Yates correction when appropriate. To test the hypothesis of whether the first test had any influence on the second test, we performed analysis of variance using Genstat 5, Release 3.1 statistical software. A value <0.05 was considered significant.

Results

Exercise versus dobutamine. The average time between the two stress tests was 62.1 ± 16.1 min. Sixty-two patients

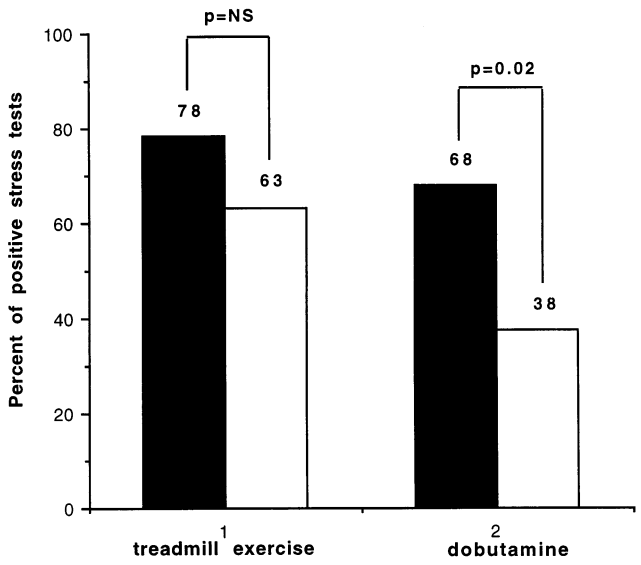

Figure 2. Comparison of the total number of positive stress test results obtained with exercise and dobutamine stress echocardiography during maximal **(solid bars)** and submaximal stress **(open bars)**. Note that submaximal stress produced consistently fewer positive stress test results.

(73%) had positive results on exercise echocardiography compared with 53 (62%) who had positive results on dobutamine (p = NS). There were no patients with positive dobutamine stress and a negative exercise. In four patients (5%), the treadmill test was stopped prematurely and was considered to have failed because of poor patient compliance in one and leg pains in the remaining three. In six patients (7%), dobutamine stress was stopped prematurely and was considered to have failed because of a symptomatic hypotensive response. When all failed tests were excluded, the percent of patients with positive stress test results increased to 77% for exercise and to 67% for dobutamine echocardiography (p = NS). There was a trend for a greater number of patients with one- and two-vessel disease to have positive results on exercise echocardiography than on dobutamine stress (64 and 77 vs. 49 and 68, respectively); for three-vessel disease, the number of patients with positive test results was the same (89 patients). On both stress modalities, the incidence of positive test results was greater in patients with multivessel than in those with one-vessel disease, but this was only significant with dobutamine echocardiography, which also had a lower incidence of positive test results in patients with one-vessel disease (49 vs. 89, $p < 0.01$).

When submaximal stress results (>70% to <85% of age-predicted maximal heart rate) were excluded, the incidence of positive results on exercise echocardiography and dobutamine further increased to 78% (43 of 55) and 68% (47 of 69), respectively. There was a lower incidence of positive submaximal test results for both exercise (19 [63%] of 30) and dobutamine echocardiography (6 [38%] of 16, p = 0.02) when the stress test results were submaximal (Fig. 2).

Duration of stress and patient preference. Overall, dobutamine–atropine echocardiography lasted longer than exercise echocardiography (18.5 ± 2.1 vs. 12.8 ± 3.4 min, $p < 0.001$). When patients were asked for their preference, 69 (81%) preferred treadmill exercise, 9 (11%) preferred dobutamine–atropine infusion, and 7 (8%) had no preference.

Table 2. Hemodynamic Responses Before and After Addition of Atropine During Dobutamine Stress in 73 Patients

	Before Atropine	After Atropine	p Value
Duration of infusion (min)*	17.4 ± 1.95	18.7 ± 2.1	0.06
HR (beats/min)	120.5 ± 20.2	153.3 ± 16.3	0.0001
SBP (mm Hg)	127.6 ± 21.8	126.6 ± 22.3	0.3
DBP (mm Hg)	70.4 ± 12	70.6 ± 14.6	0.5
Mean BP (mm Hg)	88.5 ± 17	88.9 ± 16	0.5
% max HR	73.3 ± 13.1	93.1 ± 9.5	0.0001
RPP	15,427 ± 3,867	19,527 ± 4,036	0.0001
Wall motion score	21.2 ± 7.2	24 ± 7.5	0.0001
Wall motion index	1.33 ± 0.45	1.5 ± 0.47	0.0001

*Comparison based on 79 patients only, after exclusion of 6 with premature discontinuation of dobutamine infusion due to hypotensive response. Data presented are mean value ± SD. BP = blood pressure; DSP = diastolic blood pressure; HR = heart rate; max = maximal; RPP = rate–pressure product; SBP = systolic blood pressure.

Role of atropine. In an attempt to reach maximal heart rate, atropine was added half-way through the 40-μg/kg per min infusion stage in 73 patients (86%) at an average dose of 0.74 ± 0.32 mg (range 0.6 to 1.8). Forty-two (95%) of 44 patients taking beta-adrenergic blocking agents received atropine. In the remaining 41 patients, atropine was needed in 31 (76%) ($p < 0.01$). The duration of the dobutamine infusion was similar between the 69 patients who received atropine and the 10 who did not (Table 2) when the 6 patients with a failed test (premature discontinuation due to hypotensive response) were excluded.

Of 53 patients with positive dobutamine test results, wall motion abnormalities developed before the addition of atropine in 18 (34%) at 40 μg/kg per min. In the remaining 35 (66%) patients, wall motion abnormalities occurred after the addition of atropine ($p < 0.0001$). Consequently, there was an incremental value to the addition of atropine in developing new wall motion abnormalities during dobutamine stress (Fig. 3).

Table 2 shows the hemodynamic responses before and after the addition of atropine. Systolic, diastolic and mean blood pressure remained unchanged, whereas heart rate and rate–pressure product increased significantly after the addition of atropine.

Rest and peak physiologic variables at exercise and dobutamine stress (Table 3). Rest heart rate and systolic, diastolic and mean blood pressures were similar in both stress tests. However, at peak stress heart rate was higher during dobutamine (±atropine) ($p < 0.001$), whereas blood pressure and rate–pressure product were higher at peak exercise ($p < 0.0001$). Systolic blood pressure increased during exercise but remained unchanged during dobutamine. Diastolic and mean blood pressures increased during exercise but decreased during dobutamine infusion.

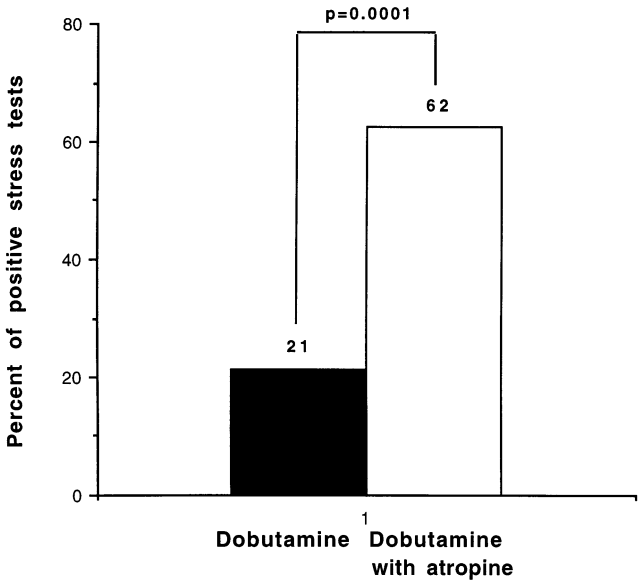

Figure 3. Comparison of dobutamine and dobutamine–atropine stress in 53 patients with positive results on both exercise and dobutamine stress testing. The addition of atropine consistently produced more positive stress test results.

Hypotensive response. During treadmill exercise, a systolic blood pressure decrease necessitated discontinuation of the test in one patient. This patient had 60% left mainstem stenosis. During dobutamine infusion, 22 patients (26%) developed hypotension ($p < 0.01$). Six patients were severely symptomatic, but hypotension was not associated with ischemia and was not reversible with atropine, necessitating premature discontinuation of the test. The remaining 16 patients were asymptomatic or mildly symptomatic, and hypotension was reversible after administration of 0.6 mg of atropine. In 9 patients, the blood pressure drop was gradual, occurring over two or more stages; in 13 patients, it was more precipitous, occurring within one stage; in 16 patients, the systolic drop started at the 20- to 30-μg/kg per min stage and in 6 at the 40-μg/kg per min stage.

Table 3. Rest and Peak Stress Characteristics Between Exercise Immediately After Treadmill Exercise and Peak Dobutamine–Atropine Infusion in 85 Patients

	Exercise	Dobutamine	p Value
At rest			
HR (beats/min)	72 ± 12	73 ± 12.7	0.4
SBP (mm Hg)	128.6 ± 16	127.6 ± 16.7	0.2
DBP (mm Hg)	80.8 ± 11	80.2 ± 11	0.4
Mean BP (mm Hg)	97 ± 12	95.2 ± 12	0.1
Wall motion score	21.2 ± 7	21.2 ± 7	NS
Wall motion index	1.32 ± 0.4	1.32 ± 0.4	NS
Peak stress			
Positive test results	62 (73%)	53 (62%)*	0.2
Failed stress tests	4 (5%)	6 (7%)	0.7
HR (beats/min)	142.6 ± 20*	153 ± 16	<0.001
SBP (mm Hg)	171.2 ± 25.4*	127.2 ± 22.8	<0.001
DBP (mm Hg)	89.6 ± 9.5	70.2 ± 14.6	<0.0001
Mean BP (mm Hg)	117.2 ± 14*	88.6 ± 16.1	<0.0001
% max HR	87.1 ± 12.8	94.2 ± 13	<0.001
RPP	24,577 ± 5,680	19,399 ± 3,923	<0.0001
Image acquisition			
Started (s)	18.4 ± 4.4	Continuous	—
Completed (s)	61.2 ± 9.4	Continuous	—
Wall motion score	25.5 ± 7.7*	23.7 ± 7.4*	<0.0001
Wall motion index	1.6 ± 0.4*	1.5 ± 0.4*	<0.0001
Stress − rest	4.6 ± 5	2.7 ± 3.5	<0.0001

*$p < 0.01$, rest versus peak stress. Data presented are mean value ± SD or number (%) of patients. Abbreviations as in Table 2.

Table 4. Echocardiographic Findings and Clinical Characteristics in Patients According to the Development of Hypotensive Response

	Hypotension (n = 22)	No Hypotension (n = 63)	p Value
Fractional shortening	35 ± 7	30.2 ± 9.2	0.03
IVS (mm)	10 ± 0.97	10 ± 1.2	0.5
LVED (mm)	44 ± 5.3	48 ± 7.5	0.02
LVES (mm)	28.8 ± 5.5	33.9 ± 9.7	0.02
Rest wall motion index	1.1 ± 0.3	1.4 ± 0.5	0.02
Peak wall motion index	1.3 ± 0.3*	1.6 ± 0.5	0.001
(peak − rest) score	1.8 ± 2*	3.1 ± 3.8	0.06
Rest akinesia	22.7%	49.2%	0.03
1 VD	72.7%	46%	0.03
3 VD	27.3%	54%	0.03
BMI (kg/m^2)	27.8 ± 3.6	26.7 ± 4.4	0.2

*Dobutamine infusion was completed despite hypotension in 16 patients. Data presented are mean value ± SD or percent of patients. IVS = interventricular septum; LVED = left ventricular end-diastolic diameter; LVES = left ventricular end-systolic diameter; other abbreviations as in Table 1.

Table 4 shows the clinical and echocardiographic characteristics of patients with or without a hypotensive response. Patients prone to a hypotensive response had smaller ventricles, better ventricular function and less ischemia (lower wall motion index at peak) than patients who were not prone to a hypertensive response.

Magnitude of ischemia. Sixty-two patients (73%) had positive results on exercise echocardiography, of whom 53 (85%) also had positive results on dobutamine stress. Of the nine patients with negative results on dobutamine stress, seven had one- and two had two-vessel disease. No patient had negative results on exercise and positive results on dobutamine echocardiography.

Overall, the magnitude of myocardial ischemia was greater immediately after exercise than at peak dobutamine infusion (Fig. 4). Fifty-three patients (62%) had positive results on both stress tests. Of those 53 patients, the wall motion score was greater after exercise in 33 (62%) and similar in 18 (34%); only in 2 patients (4%) was the score higher during dobutamine stress. Of the 33 patients with a higher wall motion score during exercise, a total of 51 segments became ischemic in areas where no abnormality had been detected during dobutamine infusion. In particular, additional wall motion abnormalities were detected immediately after exercise in the left

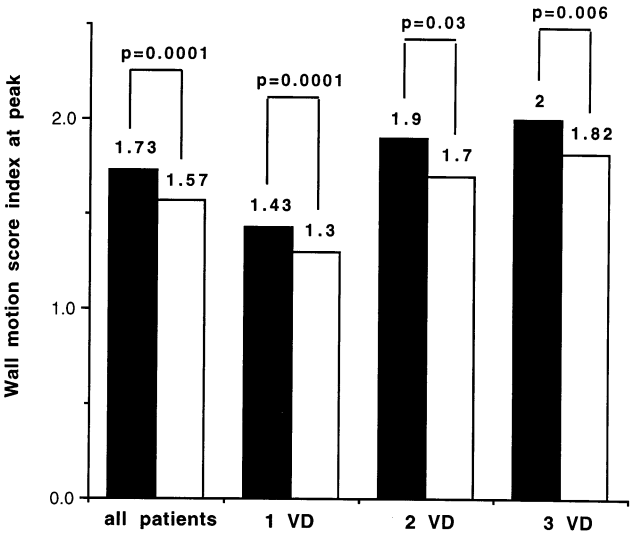

Figure 4. Comparison between exercise **(solid bars)** and dobutamine stress **(open bars)** in patients with one-, two- and three-vessel disease (VD).

anterior descending coronary artery perfusion bed in three patients, in the left circumflex coronary artery territory in four and in the right coronary artery in five. All these patients had multivessel disease (two with two-vessel, and nine with three-vessel disease). In the remaining 21 patients, the additional ischemic regions detected after exercise echocardiography had either a greater number of ischemic segments in the same vascular bed or worsening ischemia. The majority of these patients had one-vessel disease (one-vessel disease in 12, multivessel disease in 9). In two patients with extensive anteroapical akinesia, the apex became dyskinetic after exercise but was akinetic during dobutamine.

To exclude any possible interaction between the testing order of the first stress test and the second with regard to the magnitude of ischemia, an analysis of variance was performed using the maximal rate–pressure product, the wall motion score and score index at peak stress as well as the difference between wall motion score at rest and peak stress. Although it was again demonstrated that each of these variables was greater immediately after exercise than during dobutamine stress ($p < 0.001$), each was independent of the order of the test, with no interaction between tests and the order of the tests (i.e., no significant carryover effects from one sequence to the next).

ECG during exercise and dobutamine stress. Forty-one patients (48%) developed ischemic ST changes during treadmill exercise and 15 (18%) during dobutamine infusion ($p < 0.001$). The incidence of ischemic ECG changes in patients with one-, two- and three-vessel disease was 44% (20 of 45), 64% (14 of 22) and 83% (15 of 18) during exercise ECG and 13% (6 of 45), 14% (3 of 22) and 33% (6 of 18) during dobutamine ECG, respectively ($p < 0.001$). Of the 62 patients with myocardial dysfunction after exercise, 1 had left bundle branch block, and 14 had rest ST changes; of the 53 patients with positive dobutamine test results, 1 had left bundle branch block (same patient), and 13 had rest ST changes. Of the remaining 47 patients with positive results on exercise echocardiography and an interpretable ECG, 40 (85%) also developed ischemic ST changes; of the remaining 39 patients with positive dobutamine test results, only 15 (38%) had concordant ischemic ST changes.

Interobserver agreement. Of the 1,360 myocardial regions analyzed in the 85 patients, a concordant analysis of wall motion between observers was made in 1,285 (94%) at peak dobutamine and in 1,298 regions (95%) after treadmill exercise. There was a 100% concordance with regard to the presence or absence of ischemia. The average wall motion score index was 1.63 ± 0.44 for Observer 1 (L.R.) and 1.65 ± 0.45 for Observer 2 (P.N.) ($p = NS$).

Discussion

Detection of ischemia. To our knowledge, this is the first crossover study to directly compare the effects of echocardiography immediately after treadmill exercise with dobutamine echocardiography in the same patients and on the same day in patients with known coronary artery disease. We showed that the incidence and magnitude of myocardial ischemia were greater on echocardiography immediately after exercise than with dobutamine, after both maximal as well as submaximal stress. Importantly, this difference was greater on echocardiography immediately after treadmill exercise when maximal stress was not achieved during dobutamine stress. In patients with multivessel coronary artery disease, the incidence of positive stress test results was similar for both modalities; however, the fewer diseased vessels, the greater the incidence of ischemia with exercise echocardiography than with dobutamine.

Advantages of exercise echocardiography. The high predictive value of stress echocardiography for the detection of coronary artery disease has been reported by several investigators (1–9). Although dobutamine stress has shown similar predictive values with exercise, most direct comparisons have been made with supine exercise, which may produce an inferior workload than upright treadmill exercise (17). In our study, we performed echocardiography immediately after treadmill exercise using a computer-based system to allow for quick capture and side by side comparison with the rest images.

Although exercise echocardiography provides excellent hemodynamic and humoral response to exercise, it may be that obtaining images after exercise, albeit captured quickly, may be too late to detect early and rapidly resolving regional ventricular dysfunction. In a study by Presti et al. (13) that compared echocardiography performed immediately after upright bicycle exercise with echocardiography at peak upright bicycle exercise, it was found that wall motion abnormalities in as many as 29% of their patients would have been missed had imaging been performed after exercise alone. However, in that study Presti et al. do not mention the precise time of image acquisition after exercise, and the time factor is of essence in

this postexercise period. In our study, image acquisition started just 18.4 ± 4.4 s after exercise was stopped and was completed in 61.2 ± 9.4 s. In no patient did ECG changes resolve before the start of image acquisition in patients with positive ECG results. Thus, it is unlikely that any significant wall motion abnormality was missed, particularly as regional myocardial dysfunction typically precede the onset of ECG changes and persist after their resolution (18).

Dobutamine stress. Dobutamine stress has emerged as the best alternative to exercise, with very similar diagnostic accuracy (5–9). Because of its versatility in providing information on myocardial viability as well as ischemia, together with its ease of performance, dobutamine stress has become the prevailing stress modality used with echocardiography.

Dobutamine is a catecholamine with selective $beta_1$-adrenoreceptor agonist activity and relatively weak action on alpha- and $beta_2$-adrenoreceptors (19). It increases myocardial contractility, with a resulting increase in stroke volume and cardiac output. Dobutamine also decreases central venous, pulmonary artery and capillary wedge pressures, resulting in a decrease in left ventricular filling pressures and volume. Reduction of ventricular size is particularly important for decreasing wall stress. At the usual doses of 5 to 40 μg/kg/per min, dobutamine increases myocardial oxygen demand through an increase in heart rate and contractility but a decrease in blood pressure. In our study, systolic blood pressure did not increase at peak infusion. This is expected because $alpha_1$-mediated vasoconstriction is balanced by $beta_2$-mediated vasodilation. However, some studies (14,20,21) have reported an increase in systolic blood pressure.

The main disadvantage of dobutamine stress testing is the occurrence of "paradoxic" hypotension. Systemic hypotension may occur in ~20% of patients undergoing dobutamine stress (12,22). Although systemic hypotension during exercise usually indicates severe coronary artery disease (23), hypotension during dobutamine stress is often associated with bradycardia and is not an indicator of ischemia (22). Although the precise mechanism of paradoxic hypotension remains unclear, it is most likely due to a cardiovascular vasodepressor reflex. Neurally mediated hypotension and bradycardia is a frequent cause of syncope as a result of cardiac vagal afferents that innervate mechanoreceptors in the inferoposterior wall of the left ventricle. Vigorous myocardial contraction around a small chamber, as happens during dobutamine stress, may trigger sympathoinhibition and increased parasympathetic discharge, leading to bradycardia and hypotension. In a recent study (24), patients with a higher rest left ventricular ejection fraction were more likely to develop hypotension during dobutamine infusion. This effect was also seen in our study, where patients with small and well contracting ventricles showed a higher propensity to hypotension than those with larger ventricles and extensive hypokinesia. Whether beta-blockade or atropine coadministration prevents dobutamine-induced hypotension is at present unclear. In our study we were able to abort the occurrence of hypotension in 16 (73%) of 22 patients with a hypotensive response with the prompt administration of 0.6 mg. of atropine. When reflex hypotension occurs, it is now our common practice to administer atropine as soon as heart rate decreases, which we believe interrupts the parasympathetic discharge and allows completion of the stress test.

Exercise versus dobutamine. During treadmill exercise, there is an increase in heart rate that is mainly due to sympathetic stimulation and, to a lesser degree, to parasympathetic withdrawal. Systemic vascular resistance slightly decreases, whereas stroke volume increases, as a result of the Frank-Starling effect, predominantly due to increased venous return mediated by sympathetic vasoconstriction of the large-capacitance veins as well by the pumping effect of muscular contraction (17). Despite the decrease in peripheral resistance, the much greater increase in cardiac output results in an increase in systolic blood pressure. In our study, systolic, diastolic and mean blood pressures as well as heart rate all increased at higher levels than those obtained with peak dobutamine stress. Although the addition of atropine during dobutamine infusion resulted in a greater increase in heart rate than during exercise, the greater increase in systolic blood pressure observed with exercise led to a much higher rate–pressure product with treadmill exercise, indicative of a higher workload than with dobutamine.

Myocardial oxygen consumption depends on heart rate, myocardial contractility, systolic blood pressure, left ventricular end-diastolic volume and wall thickness (17). Although it is difficult to assess the contribution of all these variables separately in the clinical setting, the difference in hemodynamic responses between the two tests allows the assumption that the increased systolic blood pressure during exercise imposed a higher oxygen demand on the heart by increasing left ventricular stress, possibly explaining the greater ischemic burden observed with exercise.

Anatomic considerations. Although stress echocardiography is commonly used for the detection of coronary artery disease, failure to detect ischemia with echocardiography does not necessarily imply its absence. It usually requires 50% to 70% of coronary lumen narrowing to produce a 50% reduction in hyperemic flow (17). Although minimal lumen diameter is a better anatomic marker for assessing the severity of coronary stenosis than is a visual estimate (9), the location of the stenosis, complexity of the lesions (25) and number of stenoses along a single vessel are all important variables that can affect the physiologic significance of the stenosis. Therefore, failure to detect ischemia by virtue of a contraction abnormality in a patient with coronary artery stenosis may not necessarily represent a false negative test. Conversely, it is possible that an apparently insignificant lesion (<50%) may produce a regional wall motion abnormality that may be misinterpreted as false positive. Future studies that involve regional flow measurement coupled with myocardial contraction and a precise description of the anatomic lesion may be necessary to better describe the anatomic/functional correlation in patients with myocardial ischemia.

Single- versus multivessel disease. Patients with single-vessel disease often have less severe ischemia, depending on

the precise location of the stenosis along the vessel. Previous studies have demonstrated a lower sensitivity for one-vessel disease, ranging from 63% to 75% for exercise echocardiography (2,14,25) and 40% to 70% for dobutamine stress (14,15,20,21). In our study, of the 53% of patients with single-vessel disease, none had a proximal stenosis. This high proportion of patients with one-vessel disease may therefore account for the relatively high number of negative test results and could explain the relatively low overall sensitivity for both tests, especially that of dobutamine echocardiography, compared with other studies (8,20,21). However, the failure of both tests to identify patients with one-vessel disease does not represent a great limitation from a clinical standpoint because these patients have a better prognosis (26,27).

In patients with multivessel disease, one reason for underestimating the extent of ischemia is the premature interruption of the stress test when the first ischemic territory becomes apparent (4,27). It is therefore now routine to continue with every stress test until patients are severely limited by symptoms, so that the full extent of ventricular dysfunction can be ascertained.

Impact of submaximal stress. In patients with stable coronary artery disease, failure to achieve 85% of age-predicted maximal heart rate compromises the sensitivity of exercise echocardiography. Marwick et al. (4), achieved an overall sensitivity of 90% when patients with a submaximal heart rate were excluded. In our study a maximal treadmill exercise showed greater reliability for detecting ischemia than a submaximal test. Similarly, heart rate was a significant determinant in inducing ischemia during dobutamine infusion. These findings justify our policy of pursuing maximal heart rate by adding atropine at the end of the 40-μg/kg per min stage. Atropine was given to most of our patients and significantly improved the ability of dobutamine stress to detect ischemia (28).

Although it has been postulated (14) that during dobutamine infusion an increase incontractility is the most important contributor in myocardial oxygen consumption, our data suggest that the increased heart rate and blood pressure are both very important for unmasking ischemia.

Comparison of magnitude of ischemia. Although both exercise and dobutamine were comparable for detecting ischemia in patients with single-vessel disease, the magnitude of ischemia was greater after exercise and is due to the ability of exercise to induce more extensive ventricular dysfunction than dobutamine in the same vascular area. This more extensive ischemia is due either to recruitment of more ischemic segments or to conversion of hypokinetic or akinetic segments to akinetic or dyskinetic segments, respectively. Conversely, in patients with multivessel disease, exercise was superior to dobutamine in inducing ischemia in a greater number of regions.

Myocardial stunning/preconditioning. The first stress test may have an advantageous effect on the second stress test by preconditioning the myocardium; alternatively, it may have an adverse effect by inducing myocardial stunning. Kloner et al. (29) reported that positive exercise treadmill test results can be followed by myocardial stunning, persisting for ~30 min after exercise. In a recent study (30), we demonstrated that wall motion abnormalities may persist for up to 20 min after exercise and may represent a form of stunning. In all our patients in the current study the second test was not performed until echocardiographic, hemodynamic and ECG variables had all returned to baseline levels (average time 62 min). Whether an ischemic response to the exercise or dobutamine test could have preconditioned the heart, thus providing some protection against the second ischemic insult can only be speculated (31). However, such preconditioning was effectively ruled out in our study, by randomizing the order of testing. Nevertheless, because the two tests might not be identical in their provocation of ischemia, and thus one test could still precondition the heart for subsequent ischemia, analysis of variance was performed to test this hypothesis. It was convincingly demonstrated that despite the greater magnitude of ischemia that exercise had induced, there was no interaction between stress type and sequence of testing.

Clinical implications. Because of its superior hemodynamic effects, exercise echocardiography should be chosen over dobutamine for diagnosing ischemia, when possible. Dobutamine should be used in patients who are unable to exercise or for the detection of viable myocardium. Treadmill exercise echocardiography is a better stressor, able to induce a greater magnitude of ischemia than dobutamine. In addition, exercise treadmill echocardiography provides useful information with regard to symptoms, functional capacity and prognosis; takes less time to complete, and has fewer side effects. In the present study we used the modified Bruce protocol; therefore, our results may not be extrapolable to other exercise protocols because cardiac effects may differ.

The development of digital technology has enhanced the diagnostic efficacy and ease of performance of echocardiography immediately after exercise. Importantly, it is also overwhelmingly preferred by patients over dobutamine. When dobutamine echocardiography is used as an alternative test, a maximal heart rate should always be sought by the addition of atropine to enhance its diagnostic accuracy, particularly in patients with single-vessel coronary artery disease.

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