Stress Echocardiography in the Detection of Myocardial Ischemia
Head-to-Head Comparison of Exercise, Dobutamine, and Dipyridamole Tests

Branko D. Beleslin, MD; Miodrag Ostojić, MD, PhD; Jelena Stepanovic, MD; Ana Djordjevic-Dikic, MD; Sinisa Stojkovic, MD; Milan Nedeljkinov, MD; Goran Stankovic, MD; Zorica Petrasinovic, MD; Ljiljana Gojkovic, MD; Zorana Vasiljevic-Pokrajcic, MD, PhD; Srečko Nedeljkinovic, MD, PhD

Background Exercise and pharmacological stress echocardiography have emerged as convenient alternatives to myocardial scintigraphy. The objective of this study was to compare in the same patients the diagnostic values of exercise, dobutamine, and dipyridamole stress echocardiography tests for detection of myocardial ischemia.

Methods and Results We performed exercise (maximal treadmill Bruce protocol), dobutamine (up to 40 μg/kg per minute) and dipyridamole (up to 0.84 mg/kg over 10 minutes) stress echocardiography tests, in random sequence and on separate days, in 136 consecutive patients. All patients underwent coronary angiography. Significant coronary artery disease was defined by quantitative coronary angiography as a lesion with a diameter stenosis ≥50%. A stress echocardiogram was considered positive when new or worsening of preexisting wall motion abnormality was observed. Most of the patients (94%) were receiving the same antianginal medication for each stress test; 59 patients were receiving concurrent β-blocker therapy. The prevalence of coronary artery disease was 87.5%, with 108 patients having one-vessel coronary artery disease. Peak heart rate and systolic blood pressure were higher with exercise than with dobutamine or dipyridamole (P<.01). Sensitivity of exercise, dobutamine, and dipyridamole stress echocardiography was 88%, 82%, and 74% (dipyridamole versus exercise, P<.01), respectively. Specificity was 82%, 77%, and 94%, respectively. The overall accuracy was 87%, 82%, and 77% (dipyridamole versus exercise, P<.01), respectively. The accuracy of dipyridamole was higher (P=.02) in the group of patients not receiving β-blockers (84%) than in the patients receiving β-blocker therapy (66%), whereas the accuracy of exercise and dobutamine were only slightly higher in the patients not receiving β-blockers. Significant side effects occurred in 3%, 11%, and 1% of patients during exercise, dobutamine, and dipyridamole tests, respectively.

Conclusions Despite the different hemodynamic effects, exercise, dobutamine, and dipyridamole echocardiography have high overall diagnostic values. In this group of patients with a predominance of one-vessel coronary artery disease, the overall diagnostic accuracy of stress echocardiography tests was higher for exercise than for dobutamine or dipyridamole. Concomitant β-blocker therapy significantly decreased the accuracy of the dipyridamole stress echocardiography test. Pharmacological stress testing (dipyridamole without β-blockers) can therefore be used as an efficient option for detection of myocardial ischemia in patients who are unable or poorly motivated to exercise adequately. (Circulation. 1994;90:1168-1176.)

Key Words • exercise • testing • echocardiography • dobutamine • dipyridamole

Over the past decade, stress echocardiography has emerged as a sophisticated and sensitive noninvasive method for the detection of coronary artery disease and a cost-effective alternative to myocardial scintigraphy.1 Individually, both physical and pharmacological stress echocardiography have shown high diagnostic accuracy for the diagnosis of coronary artery disease.2-11 Furthermore, both dobutamine and dipyridamole stress echocardiography have been proposed as alternatives to exercise testing in patients who are unable to exercise. To further define the role of pharmacological stress testing in comparison to exercise, head-to-head comparative studies are required. To date, few studies have been performed comparing different pharmacological agents12-16 or exercise with dipyridamole stress echocardiography.17 The purpose of the present study was to compare in the same group of patients the diagnostic values of exercise, dipyridamole, and dobutamine stress echocardiography tests for the detection of myocardial ischemia using quantitative coronary angiography as the standard for comparison.

Methods

Study Population

Between August 1991 and April 1993, 136 consecutive patients (116 men and 20 women; mean age, 50±9 years) scheduled for coronary angiography were enrolled in the study. None of them had congestive heart failure, unstable angina, severe congenital or valvular heart disease, or documented cardiomyopathy. Patients with severe hypertension (systolic pressure ≥200 mm Hg and diastolic pressure ≥120 mm Hg), recent malignant ventricular arrhythmias, or severe

Received January 13, 1994; revision accepted May 23, 1994. From the Institute for Cardiovascular Diseases, Department of Diagnostic and Catheterization Laboratories, University Clinical Center, Belgrade, Serbia. Correspondence to Miodrag Ostojić, MD, Institute for Cardiovascular Diseases, Department of Diagnostic and Catheterization Laboratories, University Clinical Center, 8 Koste Todorovica, 11000 Belgrade, Serbia. © 1994 American Heart Association, Inc.
asthmatic or chronic obstructive pulmonary disease were excluded, since these conditions represent a contraindication to dobutamine and dipyridamole stress testing. The study was approved by our institution’s human use committee, and informed consent was obtained from all patients.

This was a prospective study in which each patient performed exercise, dobutamine, and dipyridamole stress testing in random sequence within a 2-day period. Of the 136 patients, 36 had a previous non-Q-wave myocardial infarction, 41 had a Q-wave myocardial infarction, 49 had angina pectoris, and 10 patients complained of atypical chest pain. Stress echocardiography tests were performed at least 14 days after myocardial infarction. The diagnosis of acute myocardial infarction was based on the presence of two of three criteria: typical symptoms including severe chest pain lasting >30 minutes, unequivocal ECG findings of infarction, and characteristic rise and fall in plasma creatine kinase activity. Forty-five percent of patients (35 of 77 with myocardial infarction) received thrombolytic therapy (streptokinase) during the early stages (<6 hours from the beginning of the chest pain) of myocardial infarction.

In 94% of patients, the clinically prescribed antianginal medications (single or combined) were continued and were the same during each stress modality. These consisted of nitrates in 113 patients, calcium antagonists in 59 patients, and β-blockers in 59 patients. Theophylline, caffeine-containing products, and dipyridamole preparations were not allowed for at least 12 hours before the tests.

**Stress Protocols**

Exercise testing was performed according to the maximal Bruce treadmill protocol. Criteria for interrupting the test were severe chest pain, development of marked ST-segment depression, age-predicted maximal target heart rate, systolic hypotension (decrease in systolic blood pressure >20 mm Hg) or hypertension (increase in systolic blood pressure >220 mm Hg and diastolic blood pressure >120 mm Hg), appearance of frequent or complex ventricular arrhythmias, and exercise-limiting dyspnea, fatigue, claudication, or other non-cardiac symptoms necessitating cessation of exercise.

Dobutamine was infused intravenously using a mechanical pump, starting at the dose of 5 µg/kg per minute for 3 minutes, increasing by 5 µg/kg per minute at 3-minute intervals to a maximal rate of 40 µg/kg per minute administered over 5 minutes. Dipyridamole was infused intravenously at the dose of 0.56 mg/kg over 4 minutes, followed by 4 minutes of no infusion, and then, if the test was still negative, 0.28 mg/kg over 2 minutes. The cumulative dose therefore was 0.84 mg/kg over 10 minutes. The infusions were stopped before reaching maximal dose for any of the following reasons: obvious echocardiographic positivity, progressive and severe angina accompanied by marked ST-segment changes, symptomatic hypotension (decrease in systolic blood pressure ≥20 mm Hg accompanied by nausea, sweating, dizziness, etc) or hypertension (same criteria as during exercise), severe ECG rhythm or conduction abnormalities, or intolerable symptoms. Intravenous aminophylline (250 mg) and intravenous propranolol (0.5 mg) were available after dipyridamole and dobutamine infusions, respectively.

**Monitoring**

A 12-lead ECG and blood pressure recordings were performed at baseline and thereafter at the end of each stress protocol stage or before the premature cessation of the test. ECG tracing was considered diagnostic for myocardial ischemia in the presence of ST-segment horizontal or downsloping depression of at least 0.1 mV, 0.08 second after J-point compared with baseline. Double product was calculated by multiplying systolic blood pressure and heart rate. Patients were asked to describe the symptoms they experienced.

ECG results were reviewed without knowledge of clinical data or of echocardiographic or angiographic findings.

**Echocardiographic Analyses**

Two-dimensional echocardiography was performed with the patient in the left lateral decubitus position before and immediately after exercise test and continuously before, during, and after dobutamine and dipyridamole infusion. At the end of each stage and when new or worsening of preexisting wall motion abnormalities developed, all views obtained at baseline were imaged. After cessation of the tests, echocardiographic imaging was continued until the return of hemodynamic parameters and/or left ventricular wall motion to the basal state. Interpretable echocardiograms were obtained in all patients, and none of the patients were excluded because of a poor-quality echocardiogram. In each patient, the apical approach (two-chamber, four-chamber, and five-chamber views) was used, making the segmentation model for the purpose of analyses based on this approach. Whenever possible, parasternal long-axis and short-axis views were obtained, depending on the patient’s acoustic window. All echocardiograms were performed using a commercially available imaging system (Toshiba SSH60A, Diasonics). A stress echocardiography test was interpreted from the off-line digitalized videotapes (ImageView, ATL), with these images, at rest and peak stress test, displayed in quad-screen cine-loop mode. The videotapes were analyzed by two observers, who were unaware of patient clinical data, angiography findings, or other echocardiographic test results. For the analyses, left ventricular walls were divided into an 11-segment model15,16: apex, proximal, and distal anterior septum; proximal and distal inferior septum; proximal and distal anterior wall; proximal and distal lateral wall; and proximal and distal inferior wall (Fig 1). Segmental wall motion was evaluated and scored using the method by the American Society of Echocardiography19 as normal (score of 1), hypokinetic (score of 2), akinetic (score of 3), or dyskinetic (score of 4). A wall motion score index was derived by summation of individual segment scores divided by the number of interpreted segments. Inadequately visualized segments were not scored. A final wall motion score index was derived for rest and peak stress echocardiograms by the consensus between the two observers. If a consensus in reading stress echocardiography study could not be reached, the judgment of a third observer was obtained. A stress echocardiography test was considered positive when new or worsening of preexisting wall motion abnormality was observed. Only echocardiographic criteria (a new or worsened wall motion abnormality) were considered as positive tests. Neither the presence of a resting wall motion abnormality nor the presence of stress-induced angina or ischemic ECG changes was considered as positive test results. The absence of hyperkinesia in normal myocardial segments in response to exercise and dobutamine was not considered as a criterion for a positive test result.

To explore the interobserver and intraobserver variability in reading stress echocardiography images, in 40 randomly selected patients all three stress echocardiography studies (exercise, dobutamine, dipyridamole) were separately analyzed by two independent observers.

**Coronary Angiography and Angiographic Analyses**

All patients underwent selective coronary angiography using the Judkins and Sones technique within 10 days of the stress echocardiography tests. Multiple views of each coronary artery were obtained. After visual inspection of the coronary artery in all views, the frame of optimal clarity was selected, showing lesion at maximal narrowing and arterial silhouette in sharpest focus, independent of cardiac cycle timing. The images were digitized and analyzed with the quantitative coronary angiography imaging system (MEDIS CMS) by an observer unaware of the patient clinical data and echocardiographic results. Significant coronary artery stenosis was considered present...
when ≥50% diameter stenosis of at least one major coronary artery was observed.

Statistical Analysis

The data are expressed as mean±SD. Continuous variables were compared using ANOVAs and the Newman-Keuls procedure; t test for two independent groups was used where appropriate. Dichotomous variables were compared using a χ² (McNemar’s test for paired proportions). A coefficient of correlation (r) was used to compare systolic wall motion index changes between the tests. Calculations of sensitivity, specificity, and accuracy were done according to the standard definitions. Where appropriate, 95% confidence intervals (CIs) were given. A value of P<.05 was considered statistically significant.

Results

Significant coronary artery stenoses were present in 119 of the 136 patients and absent in 17. Of the 17 patients without significant coronary artery stenosis, 5 had previous myocardial infarction that was treated with thrombolysis, 3 had effort angina pectoris, and 9 complained of atypical chest pain. One-vessel coronary artery disease was present in 108 patients, two-vessel disease in 6 patients, and three-vessel disease in 5 patients. Distribution of affected vessels was: left anterior descending coronary artery in 80, circumflex branch of left coronary artery in 23, and right coronary artery in 32 patients.

Hemodynamics

The heart rate, systolic and diastolic blood pressures, double product at peak exercise stage, and dobutamine and dipyridamole doses are presented in Fig 2. The mean heart rate, systolic and diastolic blood pressures, and double product were similar before each stress test, except for systolic and diastolic blood pressures, which were higher before exercise echocardiography (144±17 and 92±9 mm Hg, respectively) than before infusion of dobutamine (136±16 mm Hg, P<.05, and 85±10 mm Hg, P<.05, respectively) and dipyridamole (138±15 mm Hg, P<.05, and 87±10 mm Hg; exercise versus dipyridamole, P<.05, respectively). Exercise and dobutamine significantly (P<.01) increased heart rate, systolic and diastolic blood pressures, and double product. Heart rate and double product increased significantly (P<.01) during dipyridamole infusion; systolic blood pressure was similar (P=NS); but diastolic blood pressure decreased slightly but significantly compared with basal value (87±10 versus 84±12 mm Hg, P=.04). Heart rate, blood pressure, and double product reached significantly (P<.01) higher levels during exercise than during dobutamine and dipyridamole infusion. Likewise, these parameters were also significantly (P<.01) higher at the peak of dobutamine infusion than during dipyridamole infusion.
Echocardiography

The diagnostic value of stress echocardiography using a new or worsening of preexisting systolic wall motion abnormality is shown on Fig 3. The sensitivity of exercise echocardiography (88%; 95% CI, 82% to 94%) was higher than that of dipyridamole echocardiography (74%; 95% CI, 66% to 82%, P = .002). The specificity of dobutamine echocardiography (82%; 95% CI, 75% to 89%) was in between that of the exercise and dipyridamole echocardiography and did not differ significantly from either of them. The specificity of dipyridamole echocardiography (94%; 95% CI, 83% to 100%) appeared higher than that of the exercise (82%; 95% CI, 64% to 100%) and dobutamine echocardiography (77%; 95% CI, 56% to 97%), but the differences did not reach statistical significance. The accuracy of stress echocardiography tests was as follows: exercise, 87% (95% CI, 82% to 93%); dobutamine, 82% (95% CI, 75% to 88%); and dipyridamole, 77% (95% CI, 69% to 84%) (P = .001 versus exercise). Differences between exercise and dobutamine and between dobutamine and dipyridamole echocardiography in regard to their accuracy were not statistically significant.

The sensitivity of exercise echocardiography for detection of one-vessel coronary artery disease (95 of 108, 88%) was higher than that of dobutamine (89 of 108, 82%) and dipyridamole (78 of 108, 72%; P = .002 versus exercise) echocardiography. The wall motion abnormalities seen in these patients corresponded always to the territory of the affected coronary vessel. The sensitivity for detection of multivessel coronary artery disease, which was present in a small number of patients, was similar for all three stress tests (exercise, 10 of 11, 91%; dobutamine, 9 of 11, 82%; dipyridamole, 10 of 11, 91%).

When only 59 patients without myocardial infarction were considered (coronary artery disease was present in 47, and absent in 12 patients; 44% of patients were receiving β-blockers), the diagnostic value of stress tests disclosed a similar trend but did not reach statistical significance (P = NS), as was observed in the overall population. Sensitivity was 83%, 77%, and 74%, for exercise, dobutamine, and dipyridamole stress tests, respectively. Specificity was 92% for exercise and dipyridamole stress tests and 83% for dobutamine stress tests. Diagnostic accuracy was 85% for exercise echocardiography and 78% for dobutamine and dipyridamole echocardiography.

Baseline left ventricular wall motion abnormalities were observed in 37 patients (with previous Q-wave myocardial infarction) with significant coronary artery stenosis. Worsening of the resting wall motion abnormality occurred with exercise in 34 of the 37 patients (92%), with dobutamine in 33 of 37 patients (89%), and with dipyridamole in 27 of 37 patients (73%). Thus, if resting wall motion abnormalities were to be combined with the stress-induced abnormalities, the overall sensitivity of exercise, dobutamine, and dipyridamole echocardiography to detect not just myocardial ischemia but also the presence of coronary artery disease would increase to 91%, 86%, and 82%, respectively. In patients with significant coronary artery disease, the wall motion score index increased significantly from the rest (1.07±0.11) to peak stress for all three tests, and the values during stress were similar (exercise, 1.32±0.17; dobutamine, 1.28±0.18; dipyridamole, 1.28±0.19). A significant (P < .001) correlation of wall motion score index was observed between each stress test: exercise versus dobutamine, r = .77; exercise versus dipyridamole, r = .73; and dobutamine versus dipyridamole, r = .72.

Two observers independently reviewed echocardiographic stress tests, with an overall interobserver agreement of 93%. By subgroup analyses, the interobserver agreement was the highest with dipyridamole (95%) and then dobutamine (93%) and then exercise (90%) echocardiography testing. One observer reviewed the same 120 studies twice within 14 days, with an overall intraobserver agreement of 96%: 95% for exercise, 95% for dobutamine, and 98% for dipyridamole.

Relation of Echocardiography Results to ECG Changes and Angina Pectoris

In patients with coronary artery disease (n = 119), diagnostic ST-segment depression was found in 63 after exercise (53%), 41 after dobutamine (34%; P < .001 versus exercise), and 48 after dipyridamole (40%; P = .025 versus exercise; P = NS versus dobutamine). Angina pectoris was present in 74 patients during exercise (62%), 64 patients during dobutamine (54%; P = NS versus exercise), and 71 patients during dipyridamole (60%; P = NS versus exercise and versus dobutamine). In patients without significant coronary artery disease (n = 17), angina pectoris developed during exercise, dobutamine, and dipyridamole tests in 4, 7, and 5 patients, respectively (specificity: exercise, 77%; dobutamine, 59%; dipyridamole, 71%; P = NS). Also, in patients without significant coronary artery disease, significant ST-segment changes occurred in 2, 4, and 2 patients during exercise, dobutamine, and dipyridamole stress tests, respectively (specificity: exercise, 88%; dobutamine, 77%; dipyridamole, 88%; P = NS).

The diagnostic accuracy of exercise (87%), dobutamine (82%), and dipyridamole (77%) echocardiography was superior to and statistically significantly (P < .05) higher than that of ECG (57%, 40%, and 46%, respectively) or angina pectoris (64%, 54%, and 61%, respectively) (Fig 4).
Effect of β-Blocker Therapy on Echocardiography Results

Of 136 patients, 59 stress echocardiography tests were performed in patients receiving β-blockers (Fig 5). The clinical, angiographic, and rest echocardiographic characteristics of patients on and off β-blocker therapy are presented in Table 1.

The peak heart rate, blood pressure, and double product of patients receiving and not receiving β-blockers are presented in Table 2. The peak heart rate and double product of patients receiving β-blockers were lower than in the patients not receiving them (P<.05 for all three stress tests). The accuracy of exercise, dobutamine, and dipyridamole echocardiography in the group of patients receiving β-blockers was 87%, 80%, and 66% (dipyridamole versus exercise, P=0.003, respectively, and 88%, 84%, and 84% (P=NS), respectively, in the group of patients not receiving β-blockers.

The accuracy of dipyridamole echocardiography was significantly higher (P=.02) in patients not receiving β-blockers than in patients on β-blocker therapy. The accuracy of dobutamine echocardiography was also higher, but statistically nonsignificant, in patients not receiving β-blockers, whereas the accuracy of exercise echocardiography was almost the same in both groups.

Table 1. Clinical, Angiographic, and Rest Echocardiographic Data of Patients With and Without β-Blocker Therapy

<table>
<thead>
<tr>
<th>Patients</th>
<th>With β-Blockers (n=59)</th>
<th>Without β-Blockers (n=77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>51±10</td>
<td>50±10</td>
</tr>
<tr>
<td>Male gender</td>
<td>48 (81)</td>
<td>68 (88)</td>
</tr>
<tr>
<td>Q-wave myocardial infarction</td>
<td>15 (25)</td>
<td>26 (34)</td>
</tr>
<tr>
<td>Non-Q-wave myocardial infarction</td>
<td>18 (31)</td>
<td>18 (23)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>25 (39)</td>
<td>26 (34)</td>
</tr>
<tr>
<td>Atypical chest pain</td>
<td>3 (5)</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Coronary artery stenosis &lt;50%</td>
<td>5 (8)</td>
<td>12 (16)</td>
</tr>
<tr>
<td>One-vessel coronary artery disease</td>
<td>51 (86)</td>
<td>57 (74)</td>
</tr>
<tr>
<td>Multivessel coronary artery disease</td>
<td>3 (5)</td>
<td>8 (10)</td>
</tr>
<tr>
<td>Rest wall motion score index</td>
<td>1.06±0.12</td>
<td>1.07±0.10</td>
</tr>
<tr>
<td>Concomitant calcium antagonist therapy</td>
<td>22 (37)</td>
<td>37 (48)</td>
</tr>
<tr>
<td>Concomitant nitrate therapy</td>
<td>48 (81)</td>
<td>65 (84)</td>
</tr>
</tbody>
</table>

Values refer to number of patients in each group, with percentage in parentheses. P=NS for all intergroup differences.

Safety

The incidence of side effects during each stress test is shown on Table 3. The rate of side effects was highest during dobutamine (P<.01) due to a high number of patients who experienced the sensation of chilling and shivering (52%) and single premature ventricular contractions (32%). The common side effects for pharmacological stress tests occurred in fewer than 20% of the patients and included flushing, headache, and dyspnea. All of these symptoms were well tolerated and graded as mild.

The rate of significant side effects for all stress tests was minor and most frequently (P<.01) observed during dobutamine infusion, mostly including symptomatic hypotension and/or bradycardia (8 patients) and nonsustained ventricular tachycardia (3 patients). They did not cause any consequences and were well controlled by immediate cessation of the test and intravenous administration of aminophylline after dipyridamole. Furthermore, in 1 patient with significant right coronary artery stenosis, intermittent atioventricular block grade II (Mobitz II) developed at the peak dobutamine dose and resolved after the termination of the test. All the symptoms and ECG disturbances resolved almost immediately on termination of dobutamine infusion, and none of the patients required additional therapy.
TABLE 2. Peak Hemodynamic Data During Exercise, Dobutamine, and Dipyridamole Stress Echocardiography Tests In Patients With and Without β-Blocker Therapy

<table>
<thead>
<tr>
<th></th>
<th>Exercise</th>
<th>Dobutamine</th>
<th>Dipyridamole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With β-Blockers</td>
<td>Without β-Blockers</td>
<td>With β-Blockers</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>130±20</td>
<td>142±21*</td>
<td>100±30</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>189±21</td>
<td>195±22</td>
<td>176±27</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>110±11</td>
<td>110±13</td>
<td>92±14</td>
</tr>
<tr>
<td>Double product, mm Hg · bpm/100</td>
<td>244±47</td>
<td>277±63*</td>
<td>176±62</td>
</tr>
</tbody>
</table>

Values are given as mean±SD. *P<.05.

Discussion

In this study we performed a direct comparison, ie, in the same patients, between exercise, dobutamine, and dipyridamole stress echocardiography for the assessment of coronary artery disease. In this group of patients with a predominance of one-vessel coronary artery disease patients, the overall diagnostic accuracy favored exercise echocardiography over pharmacological echocardiography stress testing. Our data show that dobutamine and dipyridamole stress echocardiography are feasible and well tolerated, with comparable diagnostic accuracy for detection of coronary artery disease. Dobutamine echocardiography shows an insignificant higher sensitivity but lower specificity than dipyridamole echocardiography.

During all three stress tests, the same regions of myocardium became dysynchronous, and a high correlation of the degree and extent of provoked ischemia was observed, emphasizing the spatial comparability of pharmacological and exercise echocardiography. The lower sensitivity of pharmacological, particularly dipyridamole stress echocardiography, may be due to the predominance of patients with one-vessel coronary artery disease in our population and the presence of antianginal medication at the time of stress testing. As previously reported, the ability of dipyridamole to detect multivessel coronary artery disease was higher than the ability to detect one-vessel coronary artery disease and similar to that of exercise echocardiography.

The relation of echocardiography results to ECG changes and angina pectoris may be methodologically and conceptually under discussion, because of the different clinical end points during upright exercise and “comfortable” pharmacological testing with continuous echocardiographic imaging. This may be the reason for higher sensitivity of exercise over pharmacologically induced ECG changes and angina pectoris. Nevertheless, this relation emphasizes superiority of echocardiography in detection of myocardial ischemia.

Effects of β-Blockers on Stress Echocardiography Results

β-Blockers are known to protect from exercise-induced ischemia and from dipyridamole-induced ischemia, whereas conflicting findings have been reported on the protective effects of this class of medications on ischemia induced by dobutamine, a drug of which they are partial antagonists. Experimental studies on the model of the exercising dog have shown that β-blockers protect myocardium from stress-induced myocardial dysfunction by improving the regional flow-function relation: for a given transmural flow, there is a rise of subendocardial and a fall in subepicardial flow. This might be a general mechanism of the protection exerted by β-blockers on stress echocardiography positivity, since it is known that regional function is linearly linked to subendocardial—not subepicardial—flow. In our population, the impact of β-blockers was more striking on dipyridamole stress results, despite the fact that this stress was the least affected in its hemodynamic profile by β-blocker administration. On the average, β-blockers reduced the heart rate by only 6 beats per minute with dipyridamole, by 17 beats per minute with dobutamine, and by 12 beats per minute with exercise. Also, peak double product was reduced by about 5000 with exercise, by about 2000 with dobutamine, and by only 1000 with dipyridamole. This dissociation between a hemodynamic and antischemic effect might appear surprising if we think of stress-induced ischemia within the familiar framework of “supply-demand” mismatch in which every fall in peak demand should parallel the reduction of ischemia.

TABLE 3. Rate of Side Effects During Exercise, Dobutamine, and Dipyridamole Stress Echocardiography

<table>
<thead>
<tr>
<th></th>
<th>Exercise, n (%)</th>
<th>Dobutamine, n (%)</th>
<th>Dipyridamole, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any symptom</td>
<td>62 (46)</td>
<td>107 (79)</td>
<td>50 (37)</td>
</tr>
<tr>
<td>Shivering, chilling</td>
<td>0 (0)</td>
<td>71 (52)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Flushing</td>
<td>0 (0)</td>
<td>11 (8)</td>
<td>19 (14)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>19 (14)</td>
<td>10 (7)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (10)</td>
<td>5 (4)</td>
<td>21 (15)</td>
</tr>
<tr>
<td>PVCs</td>
<td>18 (13)</td>
<td>44 (32)</td>
<td>14 (10)</td>
</tr>
<tr>
<td>Serious symptom</td>
<td>4 (3)</td>
<td>15 (11)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Symptomatic hypotension</td>
<td>1 (1)</td>
<td>3 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Bradycardia + hypotension</td>
<td>0 (0)</td>
<td>5 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>SVT</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>AF</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>VT</td>
<td>1 (1)</td>
<td>3 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>ABV</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

PVCs indicates premature ventricular contractions; SVT, supraventricular tachycardia; AF, atrial fibrillation; VT, ventricular tachycardia; and ABV, atrioventricular block.
However, in the presence of a maximal arteriolar vasodilation—as with dipyridamole—the true mechanism of ischemia is an absolute reduction in absolute subendocardial flow supply, which under conditions of maximal vasodilation is critically affected by minimal heart rate changes, as shown by the increased sensitivity of dipyridamole stress induced by atropine coadministration. The greater sensitivity gap in the population receiving β-blockers that we found for dipyridamole and, to a lesser extent, for dobutamine might have been explained by the fact that for the pharmacological stress we did not use atropine coadministration, which is now proposed for the state-of-the-art protocols and critically increases the test sensitivity, especially in patients with one-vessel disease who are receiving β-blockers.

**Comparison With Previous Studies: Dipyridamole and Dobutamine Stress Accuracy**

Several studies have addressed the issue of the direct comparison between dobutamine and dipyridamole stress echocardiography, in both the experimental and clinical setting.

In animal experiments, a higher frequency of transient dissynergy with dobutamine than with dipyridamole (100% versus 56%) was reported by Fung et al. However, submaximal doses of both dipyridamole (0.56 mg/kg) and dobutamine (15 μg/kg per minute) were used in that study. When appropriately high doses of dobutamine (40 μg/kg per minute) and dipyridamole (0.7 mg/kg) were used, a similar effect on regional left ventricular function was observed. In the clinical setting, there are four published reports on the direct comparison between the two pharmacological tests, all describing a similar diagnostic accuracy. When the results are pooled, there is a trend toward a marginal superior sensitivity of dobutamine (70% versus 59%, P=NS) and a marginal superior specificity of dipyridamole (88% versus 80%, P=NS). Furthermore, Marwick et al found that high-dose adenosine had a similar specificity to dobutamine echocardiography, with a lower sensitivity in patients with one-vessel coronary artery disease. However, in that study, the sensitivity gap between adenosine and dobutamine echocardiography may be considered in light of the ≤25% of the patients who did not tolerate the maximal adenosine dose. Our results, on a population with a large prevalence of one-vessel coronary artery disease, are in agreement with these experimental and clinical data: the diagnostic accuracy was similar for both tests, although dipyridamole tended to have a slightly higher specificity and slightly lower sensitivity.

Regarding the comparison with exercise, it is interesting that in the animal study exercise is capable of inducing a slightly greater degree of dissynergy than high-dose dipyridamole and dobutamine. Clinical evidence also emphasizes a comparable accuracy of pharmacological and exercise echocardiography. Picano et al in the comparative study of exercise and dipyridamole stress echocardiography in the diagnosis of coronary artery disease found a sensitivity of 72% for dipyridamole and 76% for exercise echocardiography. In comparison to our study, the smaller sensitivity gap in favor of exercise may be due to a higher number of patients with multivessel coronary artery disease and, most important, to the fact that all patients were studied off therapy.

**Echocardiographic Analyses: Reproducibility**

We did not address the problem of reproducibility of the stress echocardiography tests in terms of doing repetitive studies. The excellent short-term reproducibility of pharmacological stress tests is well documented in the literature. The overall success rate was very high in expert hands for all evaluated stresses: however, there is no doubt that the acquisition and interpretation of stress studies are most technically demanding with exercise due to hyperventilation, excessive chest wall motion, and tachycardia; substantially less demanding for dobutamine, which induced a markedly lower tachycardia, in the absence of hyperventilation and with the patient comfortable lying in the position more suitable for ultrasonic imaging; and easiest with dipyridamole, during which—as an additional technical advantage over dobutamine—the peak heart rate remains at <100 beats per minute, even in patients studied off β-blockers. Our separate analyses of interobserver and intraobserver variability of these three different stress echocardiography methods also confirm that general stress echocardiographers’ opinion. From the technical viewpoint, dipyridamole represents the “primary school,” dobutamine the “secondary school,” and exercise the “university” in the stress echo cursus studiorum.

**Mechanisms of Ischemia**

Exercise and dobutamine cause myocardial ischemia through a marked increase in myocardial oxygen demand, resulting from an increase in heart rate, systolic blood pressure, and contractility. When blood supply is limited, as in the presence of significant coronary stenosis, the increase in myocardial oxygen demand may exceed supply, resulting in subendocardial ischemia necessary to induce regional dissynergy. When the hemodynamic changes during exercise and dobutamine were compared, the double product was 50% higher during exercise, suggesting that exercise imposes a higher myocardial oxygen demand and consequent greater supply-demand mismatch in the presence of significant coronary artery stenosis. This may be the reason for the highest sensitivity of exercise observed in this study.

Dipyridamole-induced ischemia is mainly due to blood flow maldistribution, with a reduction in subendocardial flow in the regions of myocardium supplied by a stenotic coronary artery. The slight increase in myocardial oxygen demand (slight increase of double product due to increase of heart rate) is considered to be of trivial importance for induction of ischemia. Thus, in the presence of significant coronary stenosis, dipyridamole decreases myocardial oxygen supply, thus predominantly affecting the supply part of the supply-demand ratio. However, in the presence of moderate reduction in coronary reserve, the flow maldistribution provoked by dipyridamole may not occur or may not be severe enough to induce subendocardial ischemia, thus explaining the lower sensitivity of dipyridamole in comparison to exercise and dobutamine.
Safety

Our experience concerning the safety of stress tests, particularly pharmacological, is similar to previous reports showing that dobutamine and, in particular, dipyridamole are safe stress testing agents. The overall rate of symptoms was highest with dobutamine, provoking in a high number of patients single premature ventricular beats and a sensation of shivering and chilling. Furthermore, significant side effects occurred in just a few patients and did not cause any consequences.

Study Limitations

Our patients were studied on a consecutive basis, but it should be pointed out that Belgrade University Institute for Cardiovascular Diseases is a tertiary care referral center for coronary angioplasty. The study protocol was complex, based on the strict respect of informed consent obtained from all patients to perform all three stress tests along with angiography and with correct consideration of contraindication to pharmacological testing, as well as motivation to perform adequate exercise testing according to maximal Bruce treadmill protocol. This may explain the unusually high percentage of patients in the study with one-vessel coronary artery disease.

Concerning the diagnostic value of pharmacological stress testing and its relation to exercise, another limitation is that we have used conventional high-dose regimens for dipyridamole (up to 0.84 mg/kg) and dobutamine (up to 40 μg/kg per minute). For both tests, this infusion protocol cannot be considered truly state of the art because recently it was shown that atropine (up to 1 mg over 4 minutes) further rises the test sensitivity without decreasing specificity for both dobutamine and dipyridamole.28 Also, it has been shown that the immediate addition of dobutamine to dipyridamole negative tests increases the sensitivity of dipyridamole echocardiography without affecting specificity.40

Furthermore, all of our patients could perform adequate exercise, a majority were men, many had a previous myocardial infarction and consequently presumed coronary artery disease, and most of them were receiving antianginal medication at the time of stress testing. Therefore, this group of patients may not be quite representative for those patients who will undergo physical or pharmacological stress echocardiography testing.

Clinical Implications

We performed a direct comparison of exercise, dobutamine, and dipyridamole stress echocardiography for the detection of myocardial ischemia. The vast majority of patients with coronary artery disease had rather severe one-vessel coronary artery disease (91%); most were referred afterward to receive a coronary angioplasty procedure. In this group of patients with a predominance of one-vessel coronary artery disease, the overall diagnostic accuracy of stress echocardiography tests was higher for exercise than for dobutamine and dipyridamole. Concomitant β-blocker therapy significantly decreased the accuracy of dipyridamole stress echocardiography test. Thus, to achieve more adequate pharmacological stress (dipyridamole specifically), the β-blockers should be withdrawn before testing. Exercise stress testing remains the most popular, valuable, and performed method for provoking myocardial ischemia. However, performance of exercise is strongly dependent on patient motivation and the ability to perform adequate exercise. As presented in this study, dobutamine and dipyridamole stress echocardiography testing provides the opportunity to induce and detect myocardial ischemia and may be used as an alternative to exercise in patients who are unable or poorly motivated to exercise adequately. The choice of the agent for pharmacological stress testing may be governed by the clinical situation and physician preference and experience.

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