Dobutamine Stress Echocardiography in the Diagnosis of Coronary Artery Disease in Women with Chest Pain: Comparison with Different Noninvasive Tests

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Summary

Background: Diagnosis of coronary artery disease (CAD) in women remains elusive. The classical diagnostic armamentarium has been found to be very limited. Dobutamine stress echocardiography has emerged as a powerful test in assessing CAD in the general population, but most studies failed to include women.

Hypothesis: The accuracy of dobutamine stress echocardiography in the diagnosis of CAD in women with chest pain is high and superior to dipyridamole echocardiography, exercise electrocardiography, and sestamibi single-photon emission tomography (MIBI-SPECT) scintigraphy.

Methods: We studied 99 consecutive women with chest pain and no previous history of CAD who underwent dobutamine echocardiography and coronary angiography. We also compared these results with those of dipyridamole echocardiography in 63 patients, exercise stress testing in 83 (48 conclusive), and MIBI-SPECT scintigraphy during dobutamine infusion in 54.

Results: Significant CAD was found in 42 women. Sensitivity and specificity of dobutamine stress echocardiography were 69 and 89%, respectively. Dipyridamole echocardiogra-

phy showed similar accuracy (sensitivity 72% and specificity 94%). Finally, sensitivity of exercise test and MIBI-SPECT was similar (76 and 88%, respectively) and specificity was lower (53 and 57%, respectively). After excluding patients known to have a high incidence of false positive results, MIBI-SPECT specificity rose up to 80%.

Conclusion: Dobutamine stress echocardiography and dipyridamole echocardiography bear a high diagnostic accuracy in women with chest pain. MIBI-SPECT is also a useful tool after excluding subgroups with a high incidence of false positive results.

Key words: women, coronary artery disease, diagnosis, dobutamine stress echocardiography

Introduction

Coronary artery disease (CAD) is the leading cause of death in women in Western cultures.¹ Despite considerable progress made in recent years, the diagnosis and management of CAD in women remain a challenge for the clinician. Causes that can account for this include the high frequency of chest pain in the absence of obstructive CAD in women,^{2,3} a lower prevalence of disease^{4,5} in women than in men, as well as a lower prevalence of multivessel CAD.⁶ Therefore, clinical history alone is inadequate to make a correct diagnosis in women and objective tests are required. Moreover, the variable prevalence compromises the accuracy of commonly used noninvasive tests, such as exercise electrocardiography (EX) and myocardial perfusion techniques.

It has been reported that exercise^{7–9} and dipyridamole echocardiography¹⁰ may be better noninvasive tests for diagnosis of CAD in women. Dobutamine stress echocardiography (DOBE) is increasingly used for detection of CAD,^{11,12} but its diagnostic accuracy has not been defined in women.

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The purpose of this study was to assess the role of DOBE for the detection of coronary artery disease in women and to compare this technique with EX, dipyridamole stress echocardiography (DIPE), and sestamibi single-photon emission computed tomography (MIBI-SPECT) scintigraphy with dobutamine (SCINT).

Methods

Study Population (Table I)

The study group was composed of 99 consecutive women (mean age 65 ± 9 years) without previous history of CAD, who had been referred for evaluation of chest pain. All patients entered a prospective protocol in which DOBE and coronary angiography were performed. Many of these patients underwent other noninvasive tests as part of different protocols (63 DIPE, 83 EX, and 54 SCINT).

Patients who had had a previous myocardial infarction, refractory unstable angina, previous revascularization, congestive heart failure, uncontrolled hypertension, or malignant ventricular arrhythmias were excluded. Sixty-seven patients had hypertension, 53 hypercholesterolemia, and 28 diabetes mellitus. Only nine women were smokers. A clinical picture of angina pectoris was present in 67 patients, and the remaining 32 complained of atypical chest pain. There were 65 patients on antianginal treatment: 33 on beta blockers, 49 on calcium antagonists, and 59 on nitrates; 58 of these received combined therapy. Before performing any test, every patient was informed in detail about the technique to be performed.

Exercise Stress Testing

Exercise electrocardiography was performed according to the Bruce protocol. Blood pressure measurement and a 12-lead electrocardiogram (ECG) were taken before exercising and every 3 min during the test. A positive test result was defined as the development of ≥ 1 mm horizontal or downsloping ST-segment depression 80 ms after the J point.

Drug Infusion Protocols

Dobutamine was given intravenously at a dose of $10 \mu\text{g/kg/min}$ with increments of $10 \mu\text{g/kg/min}$ every 3 min up to a total dose of $40 \mu\text{g/kg/min}$, which was maintained for 6 min. At this point, atropine (1 mg) was administered if the test was still negative and if 85% of the maximum predicted heart rate had not been reached. Propranolol (0.5–1 mg) was given intravenously if a positive response appeared. Intravenous glyceryl trinitrate was infused when needed.

A dose of 0.84 mg/kg of dipyridamole was infused over 6 min. The development of myocardial ischemia was reversed by intravenous aminophylline (240 mg over 1–3 min) and glyceryl trinitrate, if necessary.

Technetium-99m methoxy-isobutyl-isonitrile (MIBI; 20 mCi) was injected 1 min before cessation of dobutamine infusion. For rest studies, patients were injected with 20 mCi of MIBI at least 24 h after the stress study.

The infusion was prematurely terminated if any of the following presented: achievement of 85% of the age-predicted maximal heart rate, a new or worsening wall motion abnormality, ST-segment depression > 3 mm or elevation > 2 mm, symptomatic hypotension, systolic blood pressure > 220 mmHg or diastolic blood pressure > 120 mmHg, and significant ventricular arrhythmia.

Echocardiography

Echocardiographic monitoring was performed during drug infusion and up to 10 min after the infusion was stopped. Images were generated by using a commercially available machine with a 2.5 MHz probe. Four standard views (parasternal long- and short-axis and apical 4, 2, and 3 chambers) were recorded on videotape at each stage. Interpretation was based on side-by-side comparison of images and reviewing of the videotape recordings by two experienced echocardiographers who were blinded to the exercise electrocardiographic, scintigraphic, or angiographic reports.

The left ventricle was divided into seven segments: proximal septum, distal septum, apical, anterolateral, posterolateral, posterobasal, and diaphragmatic. This is a simplified classification based on guidelines of the American Society of Echocardiography, in which the coronary anatomy is taken into account.

Segmental wall motion at baseline examination was studied and graded as normal, mild hypokinesia, severe hypokinesia, akinesia, and dyskinesia. Stress echocardiography results were considered positive for CAD when new or worsening regional wall motion abnormalities were induced by drug infusion.

MIBI-SPECT Scintigraphy

The tracer was injected at peak stress during dobutamine infusion and at least 24 h after stress. Scintigraphic data were obtained 60 min after the injection of Tc-99m-SESTAMIBI with a Siemens Orbiter gamma camera (Siemens Medical Solutions, Iselin, N.J., USA) equipped with a high-resolution

TABLE I Risk factors and clinical data of the study population

	N
Age	65 ± 9 years
Hypertension	67
Hypercholesterolemia	53
Diabetes	28
Smoking	10
Effort angina	11
Unstable angina	56
Atypical chest pain	29
Coronary artery disease	42
Single-vessel	27
Multivessel	15

collimator. Thirty-two projections were collected over a 180° arc, from the 45° right anterior oblique to the 45° left posterior position. Images were reconstructed using back projection with a Butterworth filter. For a better comparison of stress echocardiography and scintigraphy, scintigraphic segmentation corresponded to that used for echocardiography. A qualitative comparison of stress and rest perfusion images was made on a segmental basis. Regions were interpreted as having normal perfusion, stress-induced perfusion defect, or fixed-perfusion defect. Both types of defects were considered positive responses for the presence of CAD.

Coronary Arteriography

All patients underwent coronary arteriography by using the Judkins technique. Coronary angiograms were evaluated by hand-held electronic calipers. Significant CAD was defined as a diameter stenosis > 50% in a major epicardial artery.

Statistical Analysis

Quantitative variables are expressed as mean $\pm$ standard deviation (SD) and were compared using the Student's *t*-test. Qualitative variables are expressed as percentages and were compared with the chi-square method. The Fisher test was used when indicated. A *p* value of < 0.05 was considered statistically significant. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were all calculated with standard formulae.

Results (Table II)

Coronary Angiography

Significant CAD was present in 42 women: 27 (64%) had single-vessel disease, 8 (19%) double-vessel disease, 4 (9%) triple-vessel disease, and 3 (7%) had left main CAD.

Dobutamine Stress Echocardiography

Dobutamine stress echocardiography was completed in all patients. Minor side effects such as palpitations or headache appeared in 20 patients, and significant side effects were experienced by 25 patients. The most frequent side effects were hypotension (*n* = 18) and arrhythmias (*n* = 5), but they did not lead to test interruption. Thirty-six patients (36%) required atropine to reach the target heart rate; 35 developed transient asynergy during dobutamine infusion and 29 had CAD. Therefore, the sensitivity of DOBE was 69% (29/42). The test resulted in segmental asynergy detected by echocardiography in 15 patients with single-vessel disease (55%), 7 with double-vessel disease (87%), 4 with triple-vessel disease (100%), and 3 with left main disease (100%). Thirteen patients with CAD had a negative result; 12 of these had single-vessel disease and the remainder double-vessel disease.

Dobutamine stress echocardiography was negative in 51 of the 57 women without CAD (specificity 89%). Of the six patients with a false positive response to dobutamine, wall-motion abnormalities appeared in posterobasal and diaphragmatic segments in five, and one had nonsignificant coronary stenosis in the three major vessel. The positive predictive value of DOBE in detecting CAD was 83%, the negative predictive value 79%, and the accuracy 81%.

Comparison of Dobutamine Stress Echocardiography and Exercise Stress Testing

Basal heart rate was significantly higher before exercise test (78 ± 16 vs. 67 ± 11 ; *p* < 0.05). Heart rate at peak stress was similar during both stress test (117 ± 21 vs. 110 ± 25 ; *p* = NS). Double product achieved with exercise ($18,778 \pm 4,773$) was higher than that obtained with dobutamine infusion ($15,833 \pm 3,816$; *p* < 0.05).

Of 83 women who underwent both DOBE and EX, only 48 (58%) performed a conclusive EX (positive or negative if at least 85% of maximum predicted heart rate was reached). Nonconclusive tests were caused by slow heart rate achieved

TABLE II Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of the different noninvasive techniques in the diagnosis of coronary artery disease in women

	ECHO-DOB	ECHO-DOB	ECHO-DIP	ECHO-DOB	ECG-EXERCISE	ECHO-DOB	MIBI-SPECT
Sensitivity (%)	29/42 (69)	23/29 (79)	21/29 (72)	21/29 (72)	22/29 (76)	21/26 (80)	23/26 (88)
Specificity (%)	51/57 (89)	30/34 (88)	32/34 (94)	17/19 (89)	^a 10/19 (53)	25/28 (89)	^a 16/28 (57)
PPV (%)	29/35 (83)	23/27 (85)	21/23 (91)	21/23 (91)	^a 22/31 (71)	21/24 (87)	^a 23/35 (65)
NPV (%)	51/64 (79)	30/36 (83)	32/40 (80)	17/25 (68)	10/17 (59)	25/30 (83)	16/19 (84)
Accuracy (%)	80/99 (81)	53/63 (84)	53/63 (84)	38/48 (79)	32/48 (66)	46/54 (85)	39/54 (72)
N	99	63		48 ^b		54	

^a *p* ≤ 0.05.

^b Only conclusive exercise stress tests have been included.

Abbreviations: DOB = dobutamine, DIP = dipyridamole, ECG = electrocardiogram, MIBI-SPECT = sestamibi single-photon emission computed tomography, ECHO = echocardiography.

in 29 (35%) and basal electrical abnormalities in 6 women (7%). Angiography demonstrated significant CAD in 29 patients (60%). Echocardiographic monitoring detected transient asynergy in 21 of 29 patients during DOBE (sensitivity 72%), and EX was positive in 22 of 29 (sensitivity 76%; $p = \text{NS}$). Dobutamine stress echocardiography was negative in 17 of the 19 women without significant CAD and EX in 10 (specificity was 89 and 53%, respectively; $p < 0.05$). Positive predictive value was higher for DOBE (91 vs. 71%, respectively; $p = 0.05$). Negative predictive value was similar for both techniques (68 vs. 59%, respectively; $p = \text{NS}$). According to these results, diagnostic accuracy was 79% for DOBE (38 with correct diagnosis in 48 women) and 66% for EX (32 of 48; $p = \text{NS}$).

Comparison of Dobutamine and Dipyridamole Stress Echocardiography

Heart rate, systolic blood pressure, and double product achieved with dobutamine infusion were significantly higher (119 ± 25 , 139 ± 28 , and $16,314 \pm 3,837$, respectively) than those with dipyridamole infusion (89 ± 21 , 106 ± 17 , and $9,650 \pm 3,108$, respectively; $p < 0.05$ in all cases).

Both echocardiographic techniques were performed in 63 women. Dobutamine infusion induced segmental asynergy in 23 of the 29 women with significant CAD and dipyridamole infusion in 21 (sensitivity 79 and 72%, respectively, $p = \text{NS}$). The sensitivity for single-vessel disease was 70% (12 of 17) with DOBE and 65% (11 of 17) with DIPE ($p = \text{NS}$). Dobutamine stress echocardiography was negative in 30 of the 34 women without CAD and DIPE in 32 (specificity 88 and 94%, respectively; $p = \text{NS}$). Positive (85% with DOBE and 91% with DIPE; $p = \text{NS}$) and negative predictive values (83 and 80%, respectively; $p = \text{NS}$) were similar with both pharmacologic stress tests. Diagnostic accuracy was the same (84%) for DOBE and DIPE.

Comparison of Dobutamine Stress Test and MIBI-SPECT Scintigraphy

In all, 54 women underwent both DOBE and SCINT, and 26 had significant CAD (single-vessel disease in 15, multivessel disease in 11). Echocardiography revealed new wall motion abnormalities in 24 patients during dobutamine infusion. Reversible perfusion defects were seen with SCINT in 29 patients and fixed perfusion defects in 6. Sensitivity was 80% (21/26) for DOBE and 88% (23/26; $p = \text{NS}$) for SCINT. On the other hand, DOBE showed higher specificity than SCINT (89 and 57%, respectively; $p < 0.05$). Twelve patients without significant CAD had perfusion defects. Of these 12, 4 had non-significant coronary stenoses, 3 had left bundle-branch block, and 1 had left ventricular hypertrophy. When these eight patients were excluded, the specificity of the SCINT increased to 80% (16/20). Dobutamine stress echocardiography showed a higher positive predictive value than SCINT (87 vs. 65%; $p < 0.05$), but when the aforementioned patients were excluded, the positive predictive value of SCINT was 82%. No dif-

ferences were found in the negative predictive value between both tests (83 vs. 84%; $p = \text{NS}$). Diagnostic accuracy was slightly superior with DOBE than with SCINT (85 and 72%, respectively; $p = \text{NS}$).

Discussion

The diagnosis of CAD in women remains a challenge for clinicians. The high specificity and positive predictive value of stress echocardiography have raised the question whether dobutamine test could solve the gender limitations of noninvasive techniques. It has been demonstrated to be a safe and useful method for detecting CAD.¹¹⁻¹³ However, results were obtained in studies in which patient populations were predominantly men, who have a higher prevalence of CAD than women; in addition, scant information is available in women. Studies have reported on heterogeneous populations since patients with previous myocardial infarction or known CAD had been included.¹⁴⁻¹⁶ To our knowledge, this is the first study in which DOBE has been compared directly with EX, DIPE, and SCINT on an homogeneous consecutive group of women with chest pain and no previous history of CAD.

This study demonstrates that DOBE has a good sensitivity and an excellent specificity for detecting CAD in women. The sensitivity and specificity obtained in this study are comparable with those obtained in previous studies performed on women.¹⁴⁻¹⁶ Recently, the Women's Ischemia Syndrome Evaluation (WISE) group has reported on a striking overall sensitivity of 21% for DOBE in women without baseline wall-motion abnormalities.¹⁷ This is in disagreement with other studies whose cohort is composed predominantly of men^{11, 12} or exclusively women.¹⁴⁻¹⁶ Differences in population and methodology can explain discrepancy in results.

Compared with studies mostly composed of men, we have obtained a somewhat lower sensitivity; the higher incidence of single-vessel disease (64%) in our population contributes to account for it, as has been shown in other studies.¹⁸ Of 10 women with false-negative stress echocardiograms, 9 had single-vessel disease. On the other hand, we had six patients with false-positive results. Five of these developed stress-induced abnormalities located in the posterobasal and inferior regions of the left ventricle. Both are territories in which false positives are found to be frequent, probably in relation to tethering by the fibrous skeleton of the heart.¹⁹

In this study, both pharmacologic stress tests showed optimal and identical accuracy for the diagnosis of CAD in women. There is a trend toward a greater sensitivity of dobutamine (79 vs. 72%) and a slightly higher specificity of dipyridamole (94 vs. 88%). Results obtained in our work are similar to those found by us²⁰ and other investigators^{21, 22} who have compared DOBE and DIPE in a general population. A recently published meta-analysis comparing both tests further supports our findings.²³ Moreover, our clinical findings agree with those of Masini *et al.*¹⁰ who performed DIPE in women.

Regarding EX, we have found that it has two main limitations. First, EX is not of help in a high percentage of women

because either they are not capable of exercising sufficiently or they have basal electrical abnormalities which make the ECG uninterpretable during effort. Second, in women with conclusive tests and an intermediate probability of CAD like in our population, abnormal test results are likely to be false positive.^{24,25} According to these results, EX should be discouraged as a screening test in women suspected of having ischemic chest pain.

Scintigraphy during dobutamine infusion showed an excellent sensitivity for detecting CAD.^{17, 26–28} The lower specificity of SCINT in our investigation is attributable to the false positive results associated with mild coronary stenosis, left bundle-branch block, and left ventricular hypertrophy as has been reflected in previous reports.^{28–30} It has been reported that diagnostic accuracy of SPECT analysis is lower in women than in men and is probably related to a smaller left ventricular chamber size in women.³¹ With these considerations in mind, SCINT can be advocated in the diagnosis of CAD in women after excluding subgroups known to decrease specificity.

We are aware of several limitations of our study. Not all tests were performed on all patients; in addition, 65 of the 99 patients were taking antianginal medication. This may explain, at least in part, the high percentage of nonconclusive EX in our population. Thus, results must be interpreted with caution. Moreover, exercise stress scintigraphy and echocardiography have not been included in the tests assessed. These tests have proven high accuracy in the diagnosis of CAD.

Conclusion

We conclude that stress echocardiography can be used as a first-line diagnostic technique for detecting coronary artery disease in women. MIBI-SPECT scintigraphy is a good alternative to stress echocardiography if the test is performed on selected groups.

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