Gender Differences in the Accuracy of *Dobutamine* Stress Echocardiography for the Diagnosis of Coronary Artery Disease

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The accuracy of dobutamine stress echocardiography (DSE) for the diagnosis of coronary artery disease (CAD) has not been yet evaluated in women. We studied the effect of gender on the accuracy of DSE for the diagnosis of CAD in 306 consecutive patients (210 men and 96 women) with limited exercise capacity and suspected myocardial ischemia who underwent coronary angiography within 3 months of DSE. There were no serious complications during DSE. Men had a higher prevalence of nonsustained ventricular tachycardia (7% vs 0.03%, p <0.05) and supraventricular tachycardia (9% vs 0.03%, p <0.05) during the test compared with women. Peak stress rate–pressure product was not different in men and women (18,140 ± 4,187 vs 18,543 ± 4,223). Significant CAD (≥50% luminal diameter stenosis) was present in 171 men (81%) and in 62 women (65%, p <0.005). The sensitivity, specificity, and accuracy of ischemic pattern at DSE for the diagnosis of significant CAD were 76% (confidence interval [CI] 67 to 84), 94% (CI 89 to 99), and 82% (CI 75 to 90) in women and 73% (CI 67 to 79), 77% (CI 71 to 83), and 74% (CI 68 to 80) in men, respectively. Overall specificity was higher in women than in men (p <0.05). Regional accuracy of DSE was significantly higher in women than in men in the 3 arterial regions (84% [CI 79 to 88] vs 75% [CI 72 to 79], p <0.005). It is concluded that DSE is a safe and feasible method for the diagnosis of CAD in women. The overall specificity and the regional accuracy of DSE are higher in women than in men. Further studies are required to evaluate the functional significance of these findings and their reproducibility in different patient populations. ©1997 by Excerpta Medica, Inc.

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Exercise echocardiography has been reported as an accurate and cost-effective method for the diagnosis of coronary artery disease (CAD) in women.[1–5] In patients with limited exercise capacity, dobutamine stress echocardiography (DSE) is a feasible alternative.[6,7] The induction of myocardial ischemia at high-dose dobutamine is due to an increase in myocardial oxygen demand, and therefore the test is considered to be a stress modality that simulates exercise.[8,9] It may be speculated that the high accuracy of exercise echocardiography in women also applies to DSE. However, there are no data to prove this theory. In contrast, it was reported that most of the false–positive DSE tests occur in women.[10] The aim of this study is to determine if there is a gender difference in the accuracy of DSE for the diagnosis of CAD in patients with limited exercise capacity undergoing DSE for evaluation of myocardial ischemia.

METHODS

Patient population: The study population comprised 306 consecutive patients with limited exercise capac-

ity who underwent DSE for evaluation of myocardial ischemia and coronary angiography within 3 months from DSE. Mean age was 58 ± 12 years. There were 210 men and 96 women; 214 patients (70%) had had a previous myocardial infarction. Clinical characteristics and reasons for stress testing in men and women are shown in Table I. Among the 92 patients without previous myocardial infarction, 5 women (11%) and 2 men (4%) had a low-pretest probability of CAD (<10%), 25 women (56%) and 28 men (60%) had an intermediate probability (10% to 80%), and 15 women (33%) and 17 men (36%) had a high probability (>80%) using specific calculations based on age, sex, and chest pain characteristics reported by Diamond and Forrester.[11]

Dobutamine stress test: Dobutamine was infused through an antecubital vein starting at a dose of 5 μg/kg/min followed by 10 μg/kg/min (3-minute stages) and increasing by 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/min. Atropine (up to 1 mg) was given to patients not achieving 85% of age- and gender-predicted maximum heart rate at peak dobutamine dose.[12] The test was interrupted if severe chest pain, ST-segment depression >2 mm, significant ventricular or supraventricular arrhythmia, hypertension, a systolic blood pressure decrease >40 mm Hg, or any intolerable side effect occurred during the test. Ischemia during the electrocardiogram was defined as ≥0.1 mV horizontal or downsloping ST-segment depression 80 ms from the J point compared

TABLE I Clinical Features of Men and Women Undergoing Dobutamine–Atropine Stress Echocardiography

Clinical Features	Men (n = 210)	Women (n = 96)	p Value
Age (yrs)	58 ± 9	58 ± 13	NS
Previous MI	163 (78)	51 (53)	<0.0001
Body weight (kg)	80 ± 14	68 ± 11	<0.00001
Indications for stress testing			
Typical chest pain	98 (47)	34 (35)	0.07
Atypical chest pain	51 (24)	37 (39)	<0.05
Routine post-MI assessment	36 (17)	13 (14)	NS
To assess revascularization	25 (12)	12 (13)	NS
Medications			
β blockers	76 (36)	43 (45)	NS
Calcium channel blockers	99 (47)	48 (50)	NS
Nitrates	116 (55)	46 (48)	NS
ACE inhibitors	98 (47)	27 (28)	<0.005

Data are expressed as mean ± SD or number of patients (%).
ACE = angiotensin-converting enzyme; MI = myocardial infarction.

with baseline level or ≥ 0.1 mV ST-segment elevation in electrocardiographic leads corresponding to segments without wall motion abnormalities at rest.[13]

Stress echocardiography: Echocardiographic images were acquired from standard views at rest and during stress and recovery. The left ventricular wall was divided into 16 segments and scored using a 4-point scale, where 1 = normal, 2 = hypokinesia, 3 = akinesia, and 4 = dyskinesia. Wall motion score index was derived by dividing the sum of the score of the 16 segments by 16. Ischemia was defined as new or worsened wall motion abnormalities. Ischemia was not considered if akinetic segments at rest became dyskinetic during stress.[14] The echocardiograms were recorded on videotapes and digitized on optical disk (Vingmed, CFM 800, Vingmed Sound A/S, Horten, Norway). Images were compared side by side in quad-screen format by 2 independent observers without the knowledge of the patients' gender, clinical, or angiographic data. In case of disagreement, a majority decision was achieved by a third investigator. The inter- and intraobserver agreement for dobutamine stress echocardiographic assessment in our laboratory were 91% and 92%, respectively.[15]

Coronary angiography: Coronary angiography was performed within 3 months of DSE. Significant CAD was defined as a diameter stenosis $\geq 50\%$ in ≥ 1 major epicardial arteries by the quantitative method described previously.[16] Coronary arteries were assigned to myocardial segments as previously described.[17] Because of the frequent vascular overlap in the posterior and inferior walls, these 2 regions were assigned to both the left circumflex and the right coronary arteries.[18]

Statistical analysis: Unless specified, data are presented as mean values ± SD. The chi-square test was used to compare differences between proportions. The Student's t test was used for analysis of continuous data. A p value <0.05 was considered statistically significant. Sensitivity, specificity, and accuracy were derived according to the standard definitions and were represented with 95% confidence intervals (95% CI).

RESULTS

The clinical characteristics of the subjects are shown in Table I. Hemodynamic data are demonstrated in Table II. Dobutamine–atropine induced a significant increase in heart rate (p <0.00001), systolic blood pressure (p <0.0001), and rate–pressure product (p <0.00001) in men and women. Heart rate, systolic blood pressure, and rate–pressure products were not different between men and women at rest or at peak stress. Women received a lower maximum dose of dobutamine and received atropine less frequently than men. Reasons for termination of the test are listed in Table III. The target heart rate was reached more frequently in women. The test was terminated before reaching the maximum dose more frequently in men because of the higher prevalence of angina, ST-segment depression, and arrhythmias necessitating termination of the test in men. Side effects and arrhythmias during the test are shown in Table IV. Supraventricular and ventricular tachycardia occurred more frequently in men. The incidence of hypotension and other side effects was similar in men and women.

Coronary angiography: Significant CAD was detected in 233 patients (76%). Ninety-one patients (30%) had single-vessel CAD, 73 (24%) had 2-vessel CAD, and 69 (23%) had 3-vessel CAD. Normal coronary arteries or <50% lesions were present in 73 patients (24%). Left anterior descending (LAD) coronary artery stenosis was present in 164 patients (54%), left circumflex (LCX) stenosis in 133 patients (43%), and right coronary artery (RCA) stenosis in 147 patients (48%). Men had a higher prevalence of CAD (81% vs 65%, p <0.005) and multivessel CAD (55% vs 27%, p <0.00005).

Stress echocardiography: Wall motion score index was higher in men than in women at rest (1.59 ± 0.46 vs 1.40 ± 0.46, p <0.005) and at peak stress (1.76 ± 0.53 vs 1.49 ± 0.52, p <0.0005). In patients without previous myocardial infarction, the sensitivity, specificity, and accuracy of DSE in men were 72% (CI 59 to 85), 67% (CI 53 to 80), and 70% (CI 57 to 83). The sensitivity, specificity, and accuracy in women were 74% (CI 61 to 87), 95% (CI 89 to 102, p <0.05), and 84% (CI 74 to 95), respectively. In patients with previous myocardial infarction, the sensitivity, specificity, and accuracy of DSE for the diagnosis of infarct-related artery stenosis in men were 64% (CI 56 to 71), 87% (CI 81 to 92), and 68% (CI 61 to 75); in women these were 66% (CI 53 to 79), 94% (CI 87 to 101), and 75% (CI 63 to 86), respectively. Sensitivity, specificity, and accuracy of DSE for the diagnosis of remote coronary artery stenosis in men were 72% (CI 56 to 79), 80% (CI 74 to 86), and 75% (CI 68 to 82); for women it was 75% (CI 63 to 87), 89% (CI 80 to 97), and 84% (CI 74 to 94), respectively. The sensitivity, specificity, and accuracy of DSE for the overall and regional diagnosis of CAD in all patients are shown in Table V. Overall specificity of DSE was higher in women (p = 0.04). Regional accuracy was higher in women than men in the LCX and RCA regions (p <0.05 in both) but not in the LAD region. Regional accuracy of DSE in the 3 arterial regions

TABLE II Hemodynamic Data of Men and Women Undergoing Dobutamine–Atropine Stress Echocardiography

Hemodynamic and Stress Test Variables	Men (n = 210)	Women (n = 96)	p Value
Heart rate at rest (beats/min)	70 ± 13	71 ± 14	NS
Heart rate at peak stress (beats/min)	135 ± 18	134 ± 15	NS
Systolic blood pressure at rest (mm Hg)	128 ± 20	131 ± 24	NS
Systolic blood pressure at peak stress (mm Hg)	135 ± 27	138 ± 27	NS
Rate–pressure product at rest	9,021 ± 2,394	9,406 ± 2,991	NS
Rate–pressure product at peak stress	18,140 ± 4,187	18,543 ± 4,223	NS
Maximum dobutamine dose (μg/kg/min)	38.4 ± 74	36.9 ± 7	0.03
Atropine given	113 (54)	39 (41)	0.03
ST-segment depression	63 (30)	22 (23)	0.2

Data are expressed as mean ± SD or number of patients (%).

TABLE III Reasons for Termination of Dobutamine Stress Testing in Men and Women

Reasons for Test Termination	Men (n = 210)	Women (n = 96)	p Value
85% of maximum heart rate	137 (65)	81 (84)	<0.001
Maximum dose	21 (10)	3 (3)	0.03
Angina	29 (14)	7 (7)	0.1
ST changes	7 (3)	0	0.1
Arrhythmias	6 (3)	0	0.1
Hypotension	8 (4)	4 (4)	NS
Chills, flushing, anxiety, dizziness	2 (0.09)	1 (1.1)	NS

Data are expressed as mean ± SD or number of patients (%).

TABLE IV Symptoms and Complications of Dobutamine–Atropine Stress Test in Men and Women

Symptoms	Men (n = 210)	Women (n = 96)
Nausea	4 (2)	5 (5)
Flushing	1 (0.5)	0
Dizziness	2 (1)	2 (2)
Anxiety	1 (0.5)	1 (1)
Chills	11 (5)	4 (4)
Headache	10 (5)	5 (5)
Symptomatic hypotension	1 (0.5)	1 (1)
Typical angina	92 (44)	36 (38)
SVT	18 (9)	2 (2)*
AF	1 (0.5)	0
VT <10 beats	14 (7)	1 (1)*
VT >10 beats	1 (0.5)	0

*p <0.05.
AF = atrial fibrillation; SVT = supraventricular tachycardia; VT = ventricular tachycardia.

pooled together was higher in women than in men (p <0.005).

Comparison of echocardiography and electrocardiography: Among 177 men with an interpretable electrocardiogram, ischemic electrocardiographic changes occurred in 58 of 144 patients with and in 5 of 33 patients without CAD (sensitivity = 40% [CI 33 to 48], specificity = 85% [CI 79 to 90], and accuracy = 49% [CI 41 to 56]). Echocardiography was more sensitive and accurate than electrocardiography (p <0.00001 for both sensitivity and accuracy). Among 88 women with an interpretable electrocardiogram, ischemic electrocardiographic changes occurred in 16 of 57 patients with and in 6 of 31 patients without significant CAD (sensitivity = 28% [CI 19 to 37], specificity = 81% [CI 72 to 89], and accuracy = 47% [CI 36 to 57], p = NS vs men). Echocardiography was more sensitive and accurate than electrocardiography (p <0.00001 for both sensitivity and accuracy).

DISCUSSION

This is the first study that evaluates the safety, feasibility, hemodynamic profile, and accuracy of DSE for the diagnosis of CAD in women. Our study shows that DSE is a feasible, safe, and accurate method for the diagnosis of CAD in women with limited exercise capacity and suspected myocardial ischemia. There were no serious side effects during the dobutamine stress test and the prevalence of hypotension and minor side effects in women (dizziness, nausea, flushing, and headache) was similar with those in men. Arrhythmias were not the reason for termination of the test in any of the 96 women included in this study. Additionally, the prevalence of supraventricular and ventricular tachycardia was significantly lower in women. This may be explained in part by the lower prevalence of CAD and the better baseline left ventricular function in women than in men.

Gender differences in the accuracy of dobutamine stress echocardiography: The higher overall specificity and regional accuracy of DSE in women than in men in our study is difficult to explain. A possible explanation is the gender difference in the prevalence of CAD.[19] However, the lower prevalence of CAD in women was not associated with reduced sensitivity. Women have smaller left ventricular mass and wall thickness than men.[20] Myocardial regions adjacent to the fibrous skeleton of the heart (the basal regions of the posterior septum and the inferoposterior wall) may demonstrate a heterogeneity of thickening at high-dose dobutamine compared with adjacent caudal segments, giving a false–positive result in the absence of significant coronary artery stenosis.[10] Because men have a thicker myocardium, this heterogeneity of thickening may contribute to more false–positive tests in men than in women in whom myocardial thickness is less and heterogeneity of contraction between these regions during stress may be less evident. Another explanation is the less thick chest wall in women, which may improve imaging compared with men. It has been demonstrated that imaging quality influences the agreement on interpretation of dobutamine stress echocardiographic images[21] and thereby may have an effect on the accuracy of the test. Women reached the

TABLE V Accuracy of Dobutamine Stress Echocardiography for the Diagnosis of Significant Coronary Artery Stenosis in Men and Women

Diagnostic Parameters	Men	Women
Overall diagnosis		
Sensitivity	73 (67–79)	76 (67–84)
Specificity	77 (71–83)	94 (89–99)*
Positive predictive value	93 (90–97)	94 (89–99)
Negative predictive value	39 (33–46)	68 (59–77)†
Accuracy	74 (68–80)	82 (75–90)
Sensitivity in 1-vessel disease	56 (46–66)	64 (53–75)
Sensitivity in 2-vessel disease	78 (70–86)	86 (76–96)
Sensitivity in 3-vessel disease	84 (77–92)	100 (100–100)
Multivessel ischemic pattern		
Sensitivity	53 (47–60)	46 (36–56)
Specificity	90 (86–94)	97 (84–101)
Accuracy	70 (64–76)	83 (76–91)*
LAD stenosis		
Sensitivity	66 (59–72)	68 (59–77)
Specificity	86 (81–91)	88 (81–94)
Accuracy	75 (69–81)	78 (70–86)
LCX stenosis		
Sensitivity	69 (63–76)	82 (74–90)
Specificity	88 (83–92)	91 (84–97)
Accuracy	78 (72–84)	89 (82–95)*
RCA stenosis		
Sensitivity	60 (54–67)	68 (58–77)
Specificity	89 (85–94)	92 (87–98)
Accuracy	73 (67–80)	84 (77–92)*
All arteries		
Sensitivity	65 (61–69)	71 (65–77)
Specificity	88 (85–91)	90 (87–94)
Accuracy	75 (72–79)	84 (79–88)†

*p <0.05; †p <0.005.
Values are presented as percentage (95% confidence interval).
LAD = left anterior descending.

81%. Roger et al[23] compared the diagnostic accuracy of exercise echocardiography in men and women with suspected CAD. They concluded that in clinical practice, test verification bias in angiographic referrals results in a lower observed specificity and a higher sensitivity of exercise echocardiography. The positive predictive value and adjusted sensitivity were lower in women compared with men and the authors concluded that the difference may represent an intrinsic gender difference rather than being related to gender difference in the prevalence of the diseases.

Study limitations: Most of the study patients had a previous myocardial infarction and the prevalence of CAD was high. Therefore, these patients represent the usual patients selected for coronary angiography rather than the overall population subjected to noninvasive testing as has been demonstrated in studies of exercise echocardiography.[23] It is important to conduct a similar study in a large group of patients with suspected CAD, particularly in those with the intermediated probability of CAD. Nevertheless, the trend to better specificity and accuracy of DSE in women than in men was also demonstrated in patients without previous myocardial infarction in our study. Men and women were not matched with regard to the prevalence of CAD and left ventricular function at rest. Referral bias in performing coronary angiography may have contributed to differences in diagnostic accuracy.[23] However, the higher specificity of DSE in women was coupled with a high-positive predictive value despite a lower prevalence of CAD in women, which suggests an intrinsic gender difference in the response to dobutamine rather than a difference in the clinical characteristic or referral bias as the underlying reason for gender difference in specificity and regional accuracy.

target heart rate more often than men. This may explain the higher regional accuracy of DSE in women than in men. Finally, an intrinsic gender difference in myocardial response to dobutamine infusion may exist. Women may have a better response to the same dose of dobutamine than men due to a difference in the volume of distribution. In this study, women could reach the target heart rate more frequently and required atropine administration less frequently than men despite the relatively higher prevalence of therapy with β blockers and the smaller peak dobutamine dose in women.

Comparison with previous studies: Bach et al[10] reported that most of the false–positive DSE studies occurred in women. However, these authors did not report the prevalence of CAD in their study. Therefore, gender difference in the specificity of DSE could not be studied due to the lack of information regarding the true negative tests. The results of our study are aligned with previous reports, which inferred the usefulness of stress echocardiography for the diagnosis of CAD in women.[1–3,22] Massini et al[22] studied the accuracy of high-dose dipyridamole echocardiography in 83 women with a 47% prevalence of CAD. Echocardiography had a sensitivity of 79% and a specificity of 93%. Marwick et al[3] reported that in 161 women with a 63% prevalence of CAD, exercise echocardiography had a sensitivity of 80% and specificity of

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