ORIGINAL ARTICLE

Effect of sex on the diagnostic efficacy of dobutamine stress echocardiography with early atropine administration in the detection of coronary artery disease

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KEY WORDS

atropine, coronary artery disease, dobutamine stress echocardiography

ABSTRACT

INTRODUCTION Considering a poorer diagnostic accuracy of exercise stress test in women, echocardiographic stress tests are often recommended for the diagnosis of coronary artery disease (CAD) in this patient group.

OBJECTIVES The aim of the study was to compare the diagnostic value of a modified protocol of dobutamine-atropine stress echocardiography between men and women.

PATIENTS AND METHODS This was a prospective study including 250 patients with symptoms suggesting CAD. Coronary anatomy was examined in 248 subjects, and 1 female patient was excluded owing to coronary anomaly. We analyzed the results of dobutamine stress echocardiography with early atropine administration separately for patients with a history of myocardial infarction (109 women and 138 men; mean age, 62 ±9 years; group A) and patients without such history (72 women and 71 men; mean age, 62 ±9 years; group B). Atropine at a dose of up to 2 mg was administered after dobutamine infusion of 20 μg/kg/min. Coronary luminal stenosis of 50% or more in diameter in the left main coronary artery and of 70% and more in the other arteries was considered significant.

RESULTS In group A, echocardiography had higher specificity and negative predictive value in women compared with men (84.5% vs. 64.4%, $P = 0.001$, and 92.3% vs. 64.4%, $P < 0.0001$, respectively). The accuracy was 85.3% and 76.8% in women and men, respectively ($P = 0.03$). In group B, a higher specificity was observed in women compared with men (82.6% vs. 60%, $P = 0.01$), but the accuracy was similar between the sexes.

CONCLUSIONS Dobutamine stress echocardiography with early atropine administration offers a higher diagnostic value in women, especially with regard to specificity.

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INTRODUCTION Coronary artery disease (CAD) and its complications remain the leading cause of premature mortality in men and women. Diagnosis and treatment of CAD requires use of a wide range of methods and is associated with significant costs.[1-4] Sex differences are observed in diagnosis, prognosis, and treatment of cardiovascular diseases, particularly with regards to the incidence of risk factors, diastolic function, and the outcomes of interventions.[5-11] Lower diagnostic accuracy of the exercise stress test in women with CAD has been well-documented by a meta-analysis including more than 24,000 patients. It showed the sensitivity and specificity of 68% and 77%, respectively, in men, and only 61% and 70% in women.[12] According to the concept of the ischemic cascade, a decrease in perfusion and impaired myocardial contractility precedes both ischemic electrocardiographic (ECG) changes and angina, which is consistent with the advantages

of various protocols for stress echocardiography, especially in less severe CAD.[13-16] A large number of clinical studies corroborated this hypothesis, documenting higher diagnostic accuracy of echocardiographic stress tests including female patients. For example, Kwok et al.[17] reported that the sensitivity and specificity of exercise echocardiography for the detection of CAD in women were 86% and 79%, respectively. However, there is still a paucity of data comparing the diagnostic value of different stress test protocols, especially between men and women. Older studies suggested similar diagnostic values in both sexes, while the recently published data on the rapid pacing stress echocardiography revealed a trend for lower accuracy in women (75% vs. 88% in men, $P = 0.04$).[18] As regards the protocol for dobutamine stress echocardiography, some modifications have been proposed to limit the prevalence of complications. An important alteration is the introduction of early atropine administration to reduce the total dose and the duration of dobutamine infusion.[19] The aim of our study was to compare the diagnostic value of the modified protocol of dobutamine stress echocardiography with early atropine administration in the detection of CAD in men and women.

PATIENTS AND METHODS

Study group and protocol

Our study recruited 250 subjects with anginal symptoms suggesting significant CAD and scheduled for diagnostic workup. All patients provided written informed consent to participate in the study. The protocol was approved by the Ethical Committee of the Medical University of Lodz.

We excluded 1 woman in whom a coronary anomaly had been diagnosed (fistula draining from the circumflex artery to the left ventricle) and 2 more women in whom the coronary arteries had not been examined. In our group, in 11 stress echocardiography tests, the heart rate limit was not achieved, and 2 women from this group did not agree for coronary artery examination. Therefore, we decided to include 9 verified tests into the analysis and classified them as negative because the heart rate ranged from 65% to 96% of the calculated heart limit (mean value, 84% ±10%) and no impairment of contractility was observed. By the end of the protocol of stress echocardiography, the heart limit was not reached in 5 patients.

Since a history of myocardial infarction could affect the diagnostic value of the stress echocardiography test, we performed the analysis twice; first, in a group including patients with a history of myocardial infarction (group A) and then in a group after exclusion of patients with a history of myocardial infarction. Group A consisted of 247 clinically stable patients (109 women, 138 men; mean age, 62 ±9 years; mean left ventricular [LV] ejection fraction, 58% ±10%). In this group, there were 59 men and 13 women after myocardial infarction (31% of the patients). In 41 of those patients (57%; 6 women and 35 men), myocardial infarction was treated with percutaneous coronary intervention and stent implantation. The remaining 31 patients (7 women and 24 men) received medical treatment. Chronic total occlusion was observed in 27 patients.

Group B included only patients without a history of myocardial infarction. Moreover, it included only those patients who underwent invasive coronary angiography (and excluded those who underwent only computed tomography). The group comprised 143 subjects (72 women and 71 men). The study protocol involved a medical history, physical examination, laboratory tests (lipid profile, glucose, creatinine), transthoracic echocardiography, dobutamine stress echocardiography, and coronary angiography. Dobutamine stress echocardiography with early atropine administration was followed by coronary angiography performed no later than 3 months after echocardiography. The anatomy of the coronary artery was evaluated by invasive coronary angiography in 220 patients and by computed tomography in 35 subjects (7 patients had both examinations) (**FIGURE**). Invasive coronary angiography was performed using the standard method with 3 to 5 images recorded for the left coronary artery and 2 to 3 images for the right coronary artery (RCA). The severity of stenosis was evaluated visually by an invasive cardiologist. The cut-off value for significant coronary artery diameter stenosis was defined as ≥50% for the left main coronary artery (LMCA) and ≥70% for other major epicardial arteries (the left anterior descending artery, circumflex artery, and RCA). All patients had a sinus rhythm and no significant valvular disease.

The ECG-gated computed tomography for the assessment of coronary artery anatomy was performed with 64-row multidetector Toshiba or Siemens Somatom Sensation scanners with IV infusion of Iomeron 400 contrast (2 ml/kg; (Bracco, Italy). The acquisitions were done during breath-holding and medications were not discontinued on the day of examination. The stenosis of ≥50% for the LMCA and ≥70% for other epicardial arteries was considered significant.

The exclusion criteria were as follows: acute coronary syndrome during 7 days from its onset, severe heart failure (New York Heart Association class III or IV), left bundle branch block, atrial fibrillation, a pacemaker or a cardiac resynchronization device, valve or outflow tract stenosis, pregnancy, lack of informed consent, and other contraindications for dobutamine and atropine (blood pressure >200/100 mmHg, ventricular tachycardia, glaucoma, and prostate adenoma). The characteristics of the study subjects are summarized in **TABLES 1** and **2**.

Echocardiography

Transthoracic echocardiography was performed with VIVID 7 Dimension (GE Vingmed Ultrasound AS, Horten, Norway) using an M4S probe in a harmonic mode, 2.0/4.3 MHz. During rest echocardiography and

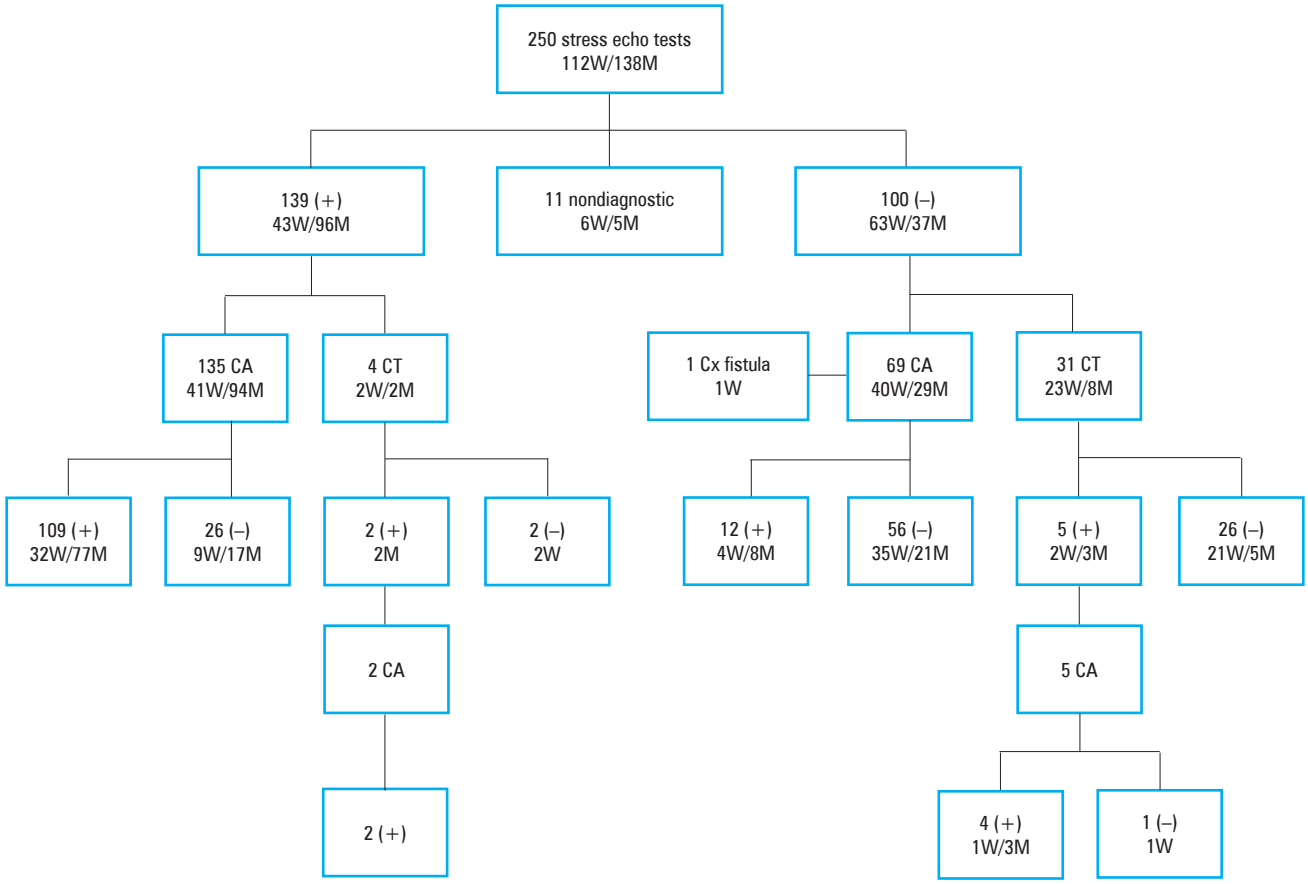

FIGURE Patients flow
Abbreviations: CA – coronary angiography, CT – computed tomography, Cx – circumflex artery, M – men, W – women, (+) – positive result, (–) – negative result

stress echocardiography, the ECG tracing was continuously monitored. The LV mass was calculated using the formula by Devereaux with LV walls and cavity measurements according to to the Penn convention. The wall thickness and chamber dimensions were measured by 2-dimensional imaging in the parasternal long axis view. Echocardiographic measurements were performed following the guidelines of the American Society of Echocardiography/European Association of Echocardiography. The protocol included the assessment of the mitral inflow pattern (from the apical 4-chamber view with the pulse Doppler sample volume at the tips of the open mitral valve leaflets), and pulsed tissue Doppler analysis of the mitral annular motion.

LV contractility was assessed visually by 2 experts in echocardiography and classified for each LV segment as normokinesis, hypokinesis, akinesis, or dyskinesis after the consensus had been reached. We used an 18-segment model of the left ventricle, dividing each of the LV walls visualized from the apical projections into 3 segments: basal, mid, and apical. The semiquantitative assessment of the regional systolic function was done by scoring each segment (1, normokinesis; 2, hypokinesis; 3, akinesis; and 4, dyskinesis) and calculating the wall motion score index (WMSI) as an averaged score for the visualized segments. Contractility deterioration in at least 2 adjacent segments of the left ventricle was considered as a positive result of the dobutamine stress echocardiogram.

Dobutamine stress echocardiography Dobutamine was administered in the continuous intravenous infusion at the doses of 10, 20, 30, and 40 μg/kg/min for 3 min each, and atropine was added after the second stage of the infusion up to the total dose of 2 mg. Atropine was administered as repeated 0.5-mg boluses at 1-minute intervals. The infusion of dobutamine was stopped when one of the following was observed: the heart rate limit, the end of the protocol, a positive stress test result, anginal pain, ventricular or supraventricular tachycardia, atrial fibrillation, numerous extrasystoles, sinus bradycardia, atrioventricular block, hypotension (<90 mmHg), a drop of systolic blood pressure exceeding 30 mmHg, or an increase of blood pressure exceeding 220/120 mmHg. Standard echocardiographic views (3 apical and LV short axis at 3 levels: mitral valve, papillary muscle, and apical) were digitally stored at the baseline and peak stage of the infusion and after 3 min of the recovery for further analysis. Chest pain, blood pressure, and ECG were monitored during dobutamine stress echocardiography.

Statistical analysis A statistical analysis was performed using MedCalc V. 12.1.4. (Frank Schoonjans, Belgium). Continuous variables were expressed as means and standard deviations and the means were compared with the *t* test for unpaired variables. The test for the comparison of proportions was used to compare dichotomous variables. The diagnostic values of dobutamine

TABLE 1 Differences in demographic data, risk factors, and treatment regimens in the whole study group

Variable	Women, n = 109	Men, n = 138	*P* value[a]
age, y	63 ±10	62 ±9	NS
heart rate, bpm	67 ±9	65 ±10	NS
systolic blood pressure, mmHg	132 ±18	126 ±17	0.01
diastolic blood pressure, mmHg	71 ±10	71 ±10	NS
body mass index, kg/m^2	29 ±5	29 ±4	NS
body surface area, m^2	1.8 ±0.2	2.0 ±0.2	<0.0001
hypertension, n (%)	92 (84)	124 (90)	NS
diabetes mellitus, n (%)	30 (28)	39 (28)	NS
smoking, n (%)	48 (44)	91 (66)	0.001
hypercholesterolemia, n (%)	98 (90)	122 (88)	NS
hypertriglyceridemia, n (%)	65 (60)	91 (66)	NS
family history of coronary artery disease, n (%)	23 (21)	22 (16)	NS
history of myocardial infarction, n (%)	14 (13)	62 (45)	<0.0001
acetylsalicylic acid, n (%)	94 (86)	132 (96)	0.01
clopidogrel, n (%)	23 (21)	55 (40)	0.002
β-blockers, n (%)	80 (73)	120 (87)	0.01
angiotensin-converting enzyme inhibitors, n (%)	85 (78)	117 (85)	NS
statins, n (%)	94 (86)	127 (92)	NS
long-acting nitrates, n (%)	43 (39)	83 (60)	0.0016

Data are presented as mean ± standard deviation or number (percentage).

a statistical significance at a *P* value of <0.05

Abbreviations: NS – nonsignificant

TABLE 2 Differences in demographic data, risk factors, and treatment regimens in the group without a history of myocardial infarction

Variable	Women, n = 72	Men, n = 71	*P* value[a]
age, y	63 ±10	61 ±9	NS
heart rate, bpm	66 ±9	66 ±10	NS
systolic blood pressure, mmHg	131 ±19	130 ±16	NS
diastolic blood pressure, mmHg	71 ±11	72 ±10	NS
body mass index, kg/m^2	29 ±5	30 ±5	NS
body surface area, m^2	1.8 ±0.2	2.1 ±0.2	<0.0001
hypertension, n (%)	60 (83)	52 (73)	NS
diabetes mellitus, n (%)	21 (29)	19 (27)	NS
smoking, n (%)	30 (42)	45 (63)	0.02
hypercholesterolemia, n (%)	66 (92)	61 (86)	NS
hypertriglyceridemia, n (%)	41 (57)	43 (61)	NS
family history of coronary artery disease, n (%)	14 (19)	6 (8)	NS
acetylsalicylic acid, n (%)	64 (89)	64 (90)	NS
clopidogrel, n (%)	16 (22)	19 (27)	NS
β-blockers, n (%)	54 (75)	57 (80)	NS
angiotensin-converting enzyme inhibitors, n (%)	56 (78)	56 (79)	NS
statins, n (%)	62 (86)	60 (85)	NS
long-acting nitrates, n (%)	28 (39)	34 (48)	NS

Data are presented as mean ± standard deviation or number (percentage).

a statistical significance at a *P* value of <0.05

Abbreviations: see **TABLE 1**

TABLE 3 Distribution of coronary artery stenosis in the whole study group

Coronary artery	Women, n = 109	Men, n = 138	*P* value
CAD	38 (35)	93 (67)	<0.0001
1-vessel disease	19 (17)	46 (33)	0.01
2-vessel disease	12 (11)	30 (22)	0.04
3-vessel disease	7 (6)	17 (12)	NS
LMCA	5 (5)	7 (5)	NS
LAD	20 (18)	59 (43)	0.0001
Cx	22 (20)	47 (34)	0.02
RCA	19 (17)	49 (36)	0.002
stenosed arteries, n	0.59 ±0.9	1.14 ±1.0	<0.0001

Data are presented as mean ± standard deviation or number (percentage).

Abbreviations: CAD – coronary artery disease, LAD – left anterior descending artery, LMCA – left main coronary artery, RCA – right coronary artery, others – see FIGURE and TABLE 1

TABLE 4 Distribution of coronary artery stenosis in the group without a history of myocardial infarction

Coronary artery	Women, n = 72	Men, n = 71	*P* value
CAD	26 (36)	41 (58)	0.023
1-vessel disease	16 (22)	22 (31)	NS
2-vessel disease	2 (3)	10 (14)	0.02
3-vessel disease	8 (11)	9 (13)	NS
LMCA	4 (6)	5 (7)	NS
LAD	13 (18)	26 (37)	0.02
Cx	13 (18)	16 (23)	NS
RCA	10 (14)	22 (31)	0.02
stenosed arteries, n	0.61 ±1	0.97 ±1	0.03

Data are presented as mean ± standard deviation or number (percentage).

Abbreviations: see FIGURE and TABLES 1 and 3

stress echocardiography for the detection of CAD in men and women were calculated according to standard formulas and were additionally compared using the receiver-operating characteristic (ROC) curve analysis. A *P* value of less than 0.05 was considered significant.

RESULTS Men and women in the study subgroups did not differ in terms of age. In group A, a history of myocardial infarction was more common in men than in women (45% vs. 13%, *P* <0.0001). Moreover, a higher percentage of men were taking antiplatelet drugs, β-blockers, and long-acting nitrates (TABLE 1). In group B, the differences in medical treatment between men and women was no longer observed (TABLE 2).

We observed no serious complications during stress tests. Mild and spontaneously reversible side effects (mild arrhythmia, prolonged chest pain, distinct hypertensive response, or hypotonia) occurred in 10% of dobutamine stress tests. The distribution of significant coronary stenosis in the whole study group and the group without a history of myocardial infarction is shown in TABLES 3 and 4.

The prevalence of chest pain, ischemic ECG changes, and positive dobutamine stress test results in men and women are presented in TABLES 5 and 6. The prevalence of chest pain and ischemic ECG changes (ST depression ≥1 mm) did not differ significantly between men and women in group A despite more advanced CAD in men. In group B, ST depression was more often observed in women, which corresponds to low specificity of ECG changes in women for the detection of CAD.

Interpretation of dobutamine stress test results by 2 experts was the same in 231 subjects (97.1% of the tests) and was different in 7 cases. Weighted κ was 0.939 (95% confidence interval, 0.895–0.984).

In group A, a visual assessment of the dobutamine stress test results showed higher diagnostic efficacy in women than in men. The sensitivity, specificity, and accuracy of the dobutamine stress test for CAD detection reached 86.8%, 84.5%, and 85.3%, respectively, for women, and 82.8%, 64.4%, and 76.8%, respectively, for men. Specificity and negative predictive value of the test were significantly higher in women. A significantly higher diagnostic value of the test in women

TABLE 5 Chest pain, electrocardiographic changes, wall motion score index, and positive dobutamine stress test results in the whole study group

Variable	Women, n = 109	Men, n = 138	*P* value
chest pain	45 (41)	70 (51)	NS
ischemic ECG changes	66 (61)	68 (49)	NS
baseline WMSI	1.05 ±0.13	1.16 ±0.22	<0.0001
peak WMSI	1.10 ±0.15	1.27 ±0.25	<0.0001
delta WMSI	0.05 ±0.08	0.11 ±0.14	0.0001
positive stress test result	45 (41)	94 (68)	<0.0001
peak heart rate, bpm	140 ±15	139 ±14	NS
peak systolic blood pressure, mmHg	143 ±24	142 ±26	NS
peak diastolic blood pressure, mmHg	77 ±13	75 ±11	NS
mean atropine dose, mg	0.95 ±0.56	1.0 ±0.5	NS
contractility impairment in the LAD	8 (7)	29 (21)	0.004
contractility impairment in the Cx	20 (18)	56 (41)	0.0002
contractility impairment in the RCA	27 (25)	53 (38)	0.04

Data are presented as mean ± standard deviation or number (percentage).

Abbreviations: ECG – electrocardiogram, WMSI – wall motion score index, others – see FIGURE and TABLES 1 and 3

TABLE 6 Chest pain, electrocardiographic changes, wall motion score index, and positive dobutamine stress test results in the group without a history of myocardial infarction

Variable	Women, n = 72	Men, n = 71	*P* value
chest pain	34 (47)	39 (55)	NS
ischemic ECG changes	46 (64)	32 (45)	0.04
baseline WMSI	1.02 ±0.06	1.04 ± 0.07	NS
peak WMSI	1.08 ±0.11	1.17 ± 0.13	<0.0001
delta WMSI	0.06 ±0.09	0.13 ± 0.11	0.0001
positive stress test result	30 (42)	48 (68)	0.003
peak heart rate, bpm	141 ±15	141 ±14	NS
peak systolic blood pressure, mmHg	141 ±24	143 ±27	NS
peak diastolic blood pressure, mmHg	76 ±13	76 ±12	NS
mean atropine dose, mg	0.95 ±0.53	1.0 ±0.52	NS
contractility impairment in the LAD	6 (8)	14 (20)	NS
contractility impairment in the Cx	15 (21)	31 (44)	0.006
contractility impairment in the RCA	18 (25)	30 (42)	0.1

Data are presented as mean ± standard deviation or number (percentage).

Abbreviations: see FIGURE and TABLES 1, 3, and 5

was also confirmed by comparing the areas under the ROC curves (0.857 in women and 0.736 in men; $P < 0.05$). In group B, the sensitivity, specificity, and accuracy of the test for CAD detection reached 84.6%, 82.6%, and 83.3%, respectively, for women, and 87.8%, 60.0%, and 76.1%, respectively, for men. In group B, the specificity of the test was still higher in women, while the negative predictive value and accuracy lost their statistical significance (TABLES 7 and 8).

DISCUSSION The results of our study suggest that dobutamine stress echocardiography with early atropine administration has a higher diagnostic accuracy for the detection of significant coronary artery stenosis in women than in men, when evaluated in a group of consecutive subjects examined in echocardiography laboratory. After exclusion of patients with a history of myocardial infarction and inclusion only of those patients who underwent coronary angiography, the dobutamine stress test still showed significantly higher specificity in women.

According to the literature, noninvasive ECG tests used to detect ischemia, such as the most common exercise stress test, provide a number of false-positive results in women.[20] This was confirmed by our study—ischemic ECG changes were common in women on dobutamine stress echocardiography (61% of women) and often recorded in

TABLE 7 Diagnostic value of dobutamine stress echocardiography in men and women including patients with a history of myocardial infarction (n = 247)

Variable	Women, n = 109	Men, n = 138
sensitivity, %	86.8	82.8
specificity[a], %	84.5	64.4
positive predictive value, %	75.0	82.8
negative predictive value[a], %	92.3	64.4
accuracy, %	85.3	76.8
AUC ROC[a]	0.857	0.736

a $P < 0.05$

Abbreviations: AUC – area under the curve, ROC – receiver-operating characteristic

TABLE 8 Diagnostic value of dobutamine stress echocardiography in men and women excluding patients with a history of myocardial infarction and those who did not undergo coronary angiography (n = 143)

Variable	Women, n = 72	Men, n = 71
sensitivity, %	84.6	87.8
specificity[a], %	82.6	60
positive predictive value, %	73.3	75
negative predictive value, %	90.5	78.3
accuracy, %	83.3	76.1
AUC ROC	0.836	0.756

a $P < 0.05$

Abbreviations: see TABLE 7

the absence of significant coronary lesions (the prevalence of CAD in women was 35%). A relatively low specificity of ECG criteria for ischemia encourage the use of nuclear and imaging studies as the first-line noninvasive methods in CAD detection in women.[21] Nevertheless, such diagnostic strategy is still poorly documented with no randomized trials available and a small number of direct comparisons between different diagnostic modalities for the detection of CAD. In the WOMEN trial involving 824 women randomized to the standard exercise stress test or exercise myocardial perfusion imaging (MPI), no prognostic advantage of MPI over the exercise stress test was reported after a 2-year follow-up. Simultaneously, significant cost savings were observed when the exercise stress test was used as the primary examination.[22]

No association between the type of the diagnostic test and prognosis was observed despite a significantly higher percentage of abnormal ECG findings (nearly one-third of women) compared with abnormal MPI scans (only 9%). Data from meta-analyses allow to estimate the sensitivity and specificity in women to be 61% and 70%, respectively, for the exercise stress test, 78% and 64%, respectively for thallium scintigraphy, and 86% and 79%, respectively, for stress echocardiography.[10,12] In our study, the visual assessment of contractility impairment during the dobutamine stress test provided even higher sensitivity, specificity, and accuracy than expected based on the literature, especially in women. High sensitivity of the dobutamine stress test in our study (exceeding 80%) may be related to the cut-off values for significant coronary artery stenosis applied in our study (≥70% diameter reductions), compared with some other studies that used a lower threshold, namely, ≥50%. Moreover, a higher percentage of previous myocardial infarction and subsequent resting contractility impairment might have impeded the visual detection of wall motion abnormalities during the dobutamine stress test; this is why we observed lower test sensitivity in men in group A (82.8%) compared with those in group B (87.8%).

Tsutsui et al.[23] observed differences between men and women in terms of the reactions of heart rate and blood pressure to dobutamine during stress echocardiography in 494 patients who were not treated with β-blockers or calcium-channel blockers. Higher doses of dobutamine and atropine were needed in men to achieve heart limit, but this difference was no longer observed when subjects were taking drugs with negative chronotropic action (326 patients). In our group, in which the majority of patients were taking β-blockers, we did not observe any differences in heart limit and blood pressure between men and women. As far as the effect of the treatment on stress echocardiography test results is concerned, the guidelines accept the results of the test performed in patients on cardiovascular medications although it may be difficult to achieve the heart rate limit in these tests.[24]

In our study, the most notable differences between men and women were observed for specificity. While specificity observed for women was similar to the values reported in the previous studies, the specificity reported for men was lower than that reported in the available literature. Low specificity is related to a high percentage of false-positive results, which poses a substantial problem in stress tests. There is an ongoing debate regarding the significance of false-positive stress test result, which may depend on borderline coronary lesions (e.g., 50% stenoses causing ischemia but not regarded as significant in our analysis), dysfunction of microcirculation, ischemia caused by myocardial hypertrophy, and, finally, on potential underestimation of stenosis in coronary angiography. The presence of a patent coronary artery supplying the region of former myocardial infarction might contribute to an increased rate of false-positive results in the setting of systolic dysfunction, which increases during dobutamine stress echocardiography.

Accordingly, knowing that LV hypertrophy impairs coronary flow reserve, the high percentage of arterial hypertension and LV hypertrophy might have lowered the specificity in both our study groups. However, this effect seems to be limited to male subjects.[25] On the other hand, the assessment of LV hypertrophy in our study was based on wall thickness of the basal segments of the interventricular septum and posterior wall,

which has significant limitations, especially in the setting of regional contractility impairment.

Our methodology does not allow us to investigate more closely the correlations between angiographic coronary artery stenosis and wall motion abnormalities observed in women. Hypothetically, a similar degree of stenosis might decrease the coronary flow to a greater extent in the narrower coronary arteries in women, but the observed sex difference in the diagnostic utility of the widely-used stress echocardiography test requires further research.

Our study has several limitations. First, we assessed only the diameter stenosis of the coronary artery but not its functional significance with the coronary flow reserve test. Second, we did not examine collateral circulation and its effect on contractility impairment. Furthermore, the assessment of coronary stenosis was limited to the qualitative estimation of lesion severity. Yet another limitation was the fact that a history of myocardial infarction and more advanced CAD were more common in male patients; however, this reflects the real-world setting. The higher prevalence of myocardial infarction in history in male subjects was associated with a more frequent use of antianginal medications in this group, which might have affected the sensitivity of the dobutamine stress test. However, this difference lost its significance after the exclusion of patients after myocardial infarction.

Finally, limitations are inherent to the subjective visual assessment of ischemia during dobutamine stress echocardiography. In the future, this should be partially overcome by including diastolic or deformation parameters in the assessment of myocardial perfusion.[26-29]

In conclusion, our data indicate a high diagnostic efficacy of dobutamine stress echocardiography with early administration of atropine for the detection of significant coronary artery stenosis. Moreover, our results suggest that this test has a better diagnostic value in women than in men.

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REFERENCES

1 Wild RA, Wu C, Curb JD, et al. Coronary heart disease events in the Women's Health Initiative hormone trials: effect modification by metabolic syndrome: a nested case-control study within the Women's Health Initiative randomized clinical trials. Menopause. 2013; 20: 254-260.

2 Jaworski R, Jankowska EA, Ponikowski P, et al. Costs of management of patients with coronary artery disease in Poland: the multicenter RECENT study. Pol Arch Med Wewn. 2012; 122: 599-607.

3 Krzych ŁJ, Paraniak-Gieszczyk B, Morawski W, et al. Assessment of left ventricular function with computed tomography and magnetic resonance in patients with low ejection fraction scheduled for coronary artery bypass grafting: a preliminary study. Pol Arch Med Wewn. 2012; 122: 398-405.

4 Warsz-Wianecka A, Mizia-Stec K, Lasek-Bal A, et al. Segmental left ventricular hypokinesis is associated with embolic signals in transcranial Doppler. Pol Arch Med Wewn. 2012; 122: 531-536.

5 Du XJ, Fang L, Kiriazis H. Sex dimorphism in cardiac pathophysiology: experimental findings, hormonal mechanisms and molecular mechanisms. Pharmacol Ther. 2006; 111: 434-475.

6 Mizia-Stec K, Gasior Z, Mizia M, et al. Flow-mediated dilatation and gender in patients with coronary artery disease: arterial size influences gender differences in flow-mediated dilation. Echocardiography. 2007; 24: 1051-1057.

7 Wierzbowska-Drabik K, Krzemińska-Pakuła M, Kurpesa M, et al. Impact of gender on left ventricle function in postmenopausal women and age-matched men: analysis of echocardiographic parameters in healthy participants and patients with coronary artery disease. Menopause. 2010; 17: 560-565.

8 Elhendy A, van Domburg RT, Bax JJ, et al. Optimal criteria for the diagnosis of coronary artery disease by dobutamine stress echocardiography. Am J Cardiol. 1998; 82: 1339-1344.

9 Tadic MV, Ivanovic BA, Petrovic M. Is gender responsible for everything? The relationship between sex and right ventricular remodeling in metabolic syndrome. Echocardiography. 2013; 30: 778-785.

10 Nowakowska-Arendt A, Grąbczewska Z, Koziński M, et al. Gender differences and in-hospital mortality in patients undergoing percutaneous coronary interventions. Kardiol Pol. 2008; 66: 632-639.

11 Jankowska-Polańska B, Uchmanowicz I, Dudek K, et al. Gender differences in depressive symptoms associated with acute coronary syndrome. Polish Journal of Cardiology. 2012; 14: 180-185.

12 Gianrossi R, Detrano R, Mulvihill D, et al. Exercise-induced ST depression in the diagnosis of coronary artery disease. A meta-analysis. Circulation. 1989; 80: 87-98.

13 Heyndrickx CR, Baig H, Nellens P, et al. Depression of regional blood flow and wall thickening after brief coronary occlusion. Am J Physiol. 1978; 234: H653-H659.

14 Wejner-Mik P, Lipiec P, Kasprzak JD. Real-time myocardial perfusion stress echocardiography for the assessment of prognosis in patients with suspected ischemic heart disease. Polish Journal of Cardiology. 2012; 14: 13-17.

15 Falcado SNS, Rochitte CE, Junior WM, et al. Incremental value of perfusion over wall-motion abnormalities with the use of dobutamine – atropine stress myocardial contrast echocardiography and magnetic resonance imaging for detecting coronary artery disease. Echocardiography. 2013; 30: 45-54.

16 Miszalski-Jamka T, Kuntz-Hehner S, Tiemann K, et al. Quantitative myocardial contrast supine bicycle stress echocardiography for detection of coronary artery disease. Echocardiography. 2013; 30: 392-400.

17 Kwok Y, Kim C, Grady D, et al. Meta-analysis of exercise testing to detect coronary artery disease in women. Am J Cardiol. 1999; 83: 660-666.

18 Płońska-Gościniak E, Lancellotti P, Kleinrok A, et al. Influence of gender on diagnostic accuracy of rapid atrial and ventricular pacing stress echocardiography for the detection of coronary artery disease: a multicenter study (Pol-RAPSE final results). J Am Soc Echocardiogr. 2008; 21: 1116-1120.

19 Tsutsui JM, Osório AF, Lario FA, et al. Comparison of safety and efficacy of the early injection of atropine during dobutamine stress echocardiography with the conventional protocol. Am J Cardiol. 2004; 94: 1367-1372.

20 Mieres JH, Shaw LJ, Arai A, et al. Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease. Circulation. 2005; 111: 682-696.

21 Lucas FL, DeLorenzo MA, Siewers AE, et al. Temporal trends in the utilization of diagnostic testing and treatments for cardiovascular disease in the US. Circulation. 2006; 113: 374-379.

22 Shaw LJ, Mieres JH, Hendel RH, et al. Comparative effectiveness of exercise electrocardiography with or without myocardial perfusion single photon emission computed tomography in women with suspected coronary artery disease: results from the what is the optimal method for ischemia evaluation in women (WOMEN) trial. Circulation. 2011; 124: 1239-1249.

23 Tsutsui JM, Falcao SNR, Dourado PMM, et al. Gender differences in chronotropic and hemodynamic responses during dobutamine-atropine stress echocardiography. Echocardiography. 2007; 24: 843-850.

24 Sicari R, Nihoyannopoulos P, Evangelista A, et al. Stress echocardiography expert consensus statement. European Association of Echocardiography (EAE) (a registered branch of the ESC). Eur J Echocardiogr. 2008; 9: 415-437.

25 Galderisi M, Rigo F, Gherardi S, et al. The impact of aging and atherosclerotic risk factors on transthoracic coronary flow reserve in subjects with normal coronary angiography. Cardiovascular Ultrasound. 2012; 10: 20.

26 Picano E, Lattanazi F, Orlandini A, et al. Stress echocardiography and the human factor: the importance of being expert. J Am Coll Cardiol. 1991; 17: 666-669.

27 Senior R, Moreo A, Gaibazzi N, et al. Comparison of sulfur hexafluoride microbubble (SonoVue)-enhanced myocardial echocardiography to gated single photon emission computerized tomography for the detection of significant coronary artery disease: a large European multicentre study. J Am Coll Cardiol. 2013; 62: 1353-1361.

28 Nakajima Y, Kane GC, McCully RB, et al. Left ventricular diastolic filling pressures during dobutamine stress echocardiography: relationship to symptoms and ischemia. J Am Soc Echocardiogr. 2009; 22: 947-953.

29 Ryo K, Tanaka H, Kaneko A, et al. Efficacy of longitudinal speckle tracking strain in conjunction with isometric handgrip stress test for detection of ischemic myocardial segments. Echocardiography. 2012; 29: 411-418.

ARTYKUŁ ORYGINALNY

Wpływ płci na wartość diagnostyczną dobutaminowej echokardiografii obciążeniowej z wczesnym podaniem atropiny w wykrywaniu choroby wieńcowej

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atropina, choroba wieńcowa, dobutaminowa echokardiografia obciążeniowa

STRESZCZENIE

WPROWADZENIE Ze względu na mniejszą dokładność diagnostyczną elektrokardiograficznej próby wysiłkowej u kobiet, w rozpoznawaniu choroby wieńcowej (*coronary artery disease* – CAD) w tej grupie pacjentów rekomenduje się często obciążeniowe badania echokardiograficzne.

CELE Celem badania było porównanie wartości diagnostycznej zmodyfikowanego protokołu echokardiograficznego testu obciążeniowego z dobutaminą i atropiną u kobiet i mężczyzn.

PACJENCI I METODY Prospektywne badanie objęło 250 pacjentów z objawami sugerującymi CAD. Anatomię tętnic wieńcowych zweryfikowano u 248 pacjentów, wykluczono pacjentkę z anomalią tętnicy wieńcowej. Analizowano wyniki dobutaminowej echokardiografii obciążeniowej z wczesnym podaniem atropiny odrębnie w grupie obejmującej pacjentów po przebytym zawale (109 kobiet i 138 mężczyzn, średni wiek 62 ±9 lat, grupa A) oraz w podgrupie po wykluczeniu pacjentów z przebytym zawałem w wywiadzie (72 kobiety i 71 mężczyzn, średni wiek 62 ±9 lat, grupa B). Atropinę do dawki maksymalnej 2 mg podawano po zakończeniu etapu wlewu o szybkości 20 μg/kg/min. Zwężenie pnia lewej tętnicy wieńcowej ≥50% oraz zwężenia ≥70% w pozostałych tętnicach uznawano za istotne.

WYNIKI W grupie A echokardiografia wykazała u kobiet wyższą swoistość i ujemną wartością predykcyjną w porównaniu z mężczyznami (odpowiednio 84,5% *vs* 64,4%, p = 0,001, oraz 92,3% *vs* 64,4%, p <0,0001). Dokładność wynosiła 85,3% *vs* 76,8%, odpowiednio u kobiet i mężczyzn, p = 0,03. W grupie B obserwowano wyższą swoistość u kobiet: 82,6% *vs* 60%, p = 0,01, przy podobnej dokładności.

WNIOSKI Dobutaminowa echokardiografia obciążeniowa z wczesnym podaniem atropiny zapewnia większą wartość diagnostyczną u kobiet, szczególnie w aspekcie swoistości.

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