



Influence of gender on the diagnostic and prognostic significance of the dobutamine stress echocardiography for ischemia

Uticaj pola na dijagnostički i prognostički značaj dobutaminskog stres-ehokardiografskog testa na ishemiju

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Abstract

Background/Aim. Cardiovascular diseases are the most common cause of mortality and morbidity worldwide, with the highest incidence in low-middle-income countries. Dobutamine stress echocardiography (DSE) plays a significant role in diagnosing coronary artery disease. The aim of the study was to examine the influence of gender on the accuracy of DSE and on the prognostic significance of the left ventricular wall motion score index (WMSI) as a parameter of DSE for adverse cardiovascular events (ACEs). **Methods.** The prospective, observational study conducted at the Clinic for Cardiovascular Diseases of the University Clinical Center of the Republic of Srpska, Bosnia and Herzegovina, included 143 patients who, due to suspicion of coronary disease, underwent a DSE from January 1, 2021, until February 1, 2022. ACEs that we observed one year after DSE were: unstable angina, acute myocardial infarction, percutaneous coronary intervention, in-stent restenosis, aortocor-

onary bypass, heart failure, and death. **Results.** A positive DSE was more common in men (45%) compared to women (25%), which was statistically significant ($p < 0.05$). The sensitivity of the test in men was 96.0%, and the specificity was 93.9%. In women, the sensitivity was 86.7%, and specificity was also 86.7%. ACEs were more frequent in men (43%) than in women (19%), which was statistically significant ($p < 0.01$). In men, WMSI had a sensitivity of 96.0% and a specificity of 82.4%. In women, WMSI had a sensitivity of 93.3% and a specificity of 90.6% in predicting ACEs. **Conclusion.** Our results confirmed the influence of gender on the accuracy of DSE in diagnosing coronary artery disease. WMSI as a parameter of DSE was identified as a significant prognostic factor for ACEs in both sexes, with the sensitivity being higher in men and specificity in women.

Key words:

coronary disease; diagnosis; echocardiography, stress; sensitivity and specificity; sex factors.

Apstrakt

Uvod/Cilj. Kardiovaskularne bolesti su najčešći uzrok mortaliteta i morbiditeta u celom svetu, sa najvećom incidencijom u zemljama sa niskim i srednjim dohotkom. Dobutaminski stres-ehokardiografski (DSE) test ima značajnu ulogu u dijagnostici koronarne arterijske bolesti. Cilj rada bio je da se ispita uticaj pola na tačnost DSE, kao i na prognostički značaj skora indeksa pokretljivosti zidova (*wall motion score index* – WMSI) leve komore, kao parametra DSE za neželjene kardiovaskularne događaje (NKD). **Metode.** Prospektivnom, opservacionom studijom koja je rađena na Klinici za kardiovaskularne bolesti Univerzitetskog kliničkog centra Republike Srpske, Bosna i Hercegovina, obuhvaćena su 143

bolesnika koji su zbog sumnje na koronarnu bolest bili podvrgnuti DSE u periodu od 1. januara 2021. do 1. februara 2022. godine. Godinu dana od urađenog DSE testa, uočeni su sledeći NKD: nestabilna angina pektoris, akutni infarkt miokarda, perkutana koronarna intervencija, restenoza u stentu (*in-stent restenosis*), aortokoronarni *bypass*, srčana insuficijencija i smrt. **Rezultati.** Pozitivan DSE test bio je češći kod muškaraca (45%) u odnosu na žene (25%), što je bilo statistički značajno ($p < 0,05$). Senzitivnost testa kod muškaraca iznosila je 96,0%, a specifičnost 93,9%. Kod žena su i senzitivnost i specifičnost iznosile 86,7%. NKD su bili češći kod muškaraca (43%) nego kod žena (19%) i ta razlika je bila statistički značajna ($p < 0,01$). Indeks WMSI je kod muškaraca imao senzitivnost 96,0%, a

specifičnost 82,4%. Kod žena je WMSI za predviđanje NKD imao senzitivnost 93,3% i specifičnost 90,6%. **Zaključak.** Naši rezultati su potvrdili uticaj pola na tačnost DSE testa u dijagnostici koronarne arterijske bolesti. Indeks WMSI, kao parametar DSE, identifikovan je kao značajan prognostički faktor za NKD kod oba

pola, s tim što je senzitivnost bila viša kod muškaraca, a specifičnost kod žena.

Ključne reči:
koronarna bolest; dijagnoza; ehokardiografija, stres; senzitivnost i specifičnost; pol, faktor.

Introduction

Cardiovascular diseases are the most common cause of mortality and morbidity worldwide, with the highest incidence in low and middle-income countries^{1,2}. Ischemic heart disease accounts for about 38% of all cardiovascular causes of death in women and 44% in men. The decline in mortality from cardiovascular diseases in men was dramatic. The observed decrease in mortality is significantly less for women than for men^{3,4}. Compared with men, women consistently receive less intensive care, including fewer anti-anginal drugs, less frequent coronary angiography or revascularization, and fewer treatments that modify lifestyle or risk factors⁵⁻⁸.

Stress echocardiography plays a significant role in diagnosing coronary artery disease (CAD). The two most popular pharmacological stress echocardiography tests used are dobutamine and dipyridamole. Dobutamine is the prototype of pharmacological adrenergic or inotropic stress. The high accuracy of the dobutamine stress echocardiography (DSE) in detecting angiographically assessed CAD, with sensitivity and specificity of 81% and 84%, respectively, is reported in a meta-analysis of 102 studies with more than 7,900 patients⁹.

Several studies examined the role of DSE as a predictor of patient outcomes¹⁰⁻¹⁵. Controversy exists regarding the presence of a sex-based difference in the accuracy of DSE in detecting CAD^{16,17}. Compared to men, the noninvasive assessment of CAD in women is more challenging for several reasons: a lower incidence of single-vessel disease and less predictability and atypical symptoms for CAD. In the study by Elhendy et al.¹⁶, sensitivity, specificity, and accuracy of DSE for ischemia in women were 76% [confidence interval (CI) 67-84], 94% (CI 89-99), and 82% (CI 75-90), respectively, and in men, 73% (CI 67-79), 77% (CI 71-83), 74% (CI 68-80), respectively. It was observed that the majority of false-positive DSE occur in women^{18,19}.

The aim of the study was to examine differences in the diagnostic and prognostic significance of the ischemia test according to the gender of the patient. Based on that, we assessed the significance of the left ventricle (LV) wall motion score index (WMSI).

Methods

The prospective, observational study was conducted at the Cardiovascular Clinic of the University Clinical Center of the Republic of Srpska (UCCRS), Bosnia and Herzegovina. The research was conducted according to the permission of the Ethics Committee of UCCRS (No. 01-19-239-2/23, from June 28, 2023). All patients undergoing the test

signed informed consent to protect privacy in the publication process.

The study included 143 patients who, due to suspicion of coronary disease, underwent a DSE from January 1, 2021, to February 1, 2022. The follow-up period was one year. The study inclusion criteria were the following: patients with suspected coronary heart disease, patients with typical anginal pain, patients with atypical anginal pain, patients with risk factors for cardiovascular diseases, patients with left bundle branch block and chest pain, patients with a previous coronary event and recurrent chest pain, and patients with inconclusive ergometric test. Exclusion criteria for the study were valvular or congenital heart disease, significant comorbidities with an expected survival of less than one year, and a poor acoustic window. Before the test, beta blockers and anti-aging drugs were excluded. The test was performed according to the protocol in which the dose of dobutamine was increased every three minutes, starting from 5 mcg/kg/min up to 40 mcg/kg/min. Study endpoints included electrocardiograms, echocardiographic evidence of ischemia, significant symptoms or arrhythmia, target heart rate of 85% of submaximal frequency predicted for age ($220 - \text{age} \times 0.85$), symptomatic hypotension, or protocol completion. If the patient failed to achieve the submaximal frequency of age-predicted heart rate, atropine was added up to a maximum dose of 2 mg intravenously (i.v.). Metoprolol was used (1 to 5 mg i.v.) to reverse the effects of the dobutamine or dobutamine-atropine combination if these did not revert spontaneously. Subjects who underwent DSE had a high percentage of angiotensin-converting enzyme inhibitors (78%), beta-blockers (90%), aspirin (97%), clopidogrel (60%), and statins (68%) in their therapy. Calcium channel blockers (48%) and nitrates (43%) were used in a smaller percentage. Examinations were performed using the Vivid 7 echocardiography device (General Electrics). LV was recorded in apical four-chamber, two-chamber, and three-chamber sections as well as the parasternal two-chamber circular section at rest at the end of the fifth minute in the peak (submaximal age-predicted heart rate) and in the recovery period. The test was considered positive if contractility worsened in two or more segments in the form of hypokinesia and akinesia, new regional wall motion abnormality, and biphasic responses. We used a 17-segment model of LV to calculate the WMSI. WMSI was calculated by dividing the sum of all individual segmental values by the number of myocardial segments. A normal value of the WMSI is 1, greater than 2.5, indicating a poor prognosis. Visual evaluation of the contractility of each LV segment included a four-step scale: 1-normokinetic, 2-

hypokinetic, 4-akinetic, and 5-dyskinetic. The test was negative if there was no abnormality of segmental contractility of LV. The data from the UCCRS information system regarding four monthly control cardiology examinations and echocardiography were recorded. Observed cardiovascular events were: unstable angina (UA), acute myocardial infarction (MI), in-stent restenosis (ISR), percutaneous coronary intervention (PCI), aortocoronary bypass (ACB), heart failure (HF), and death. Patients who had UA, acute MI, and suspected ISR underwent coronary angiography and treatment according to the recommendations of the European Association of Cardiologists (EAC). All patients who had a positive test underwent coronary angiography. Patients with more severe forms of HF were also hospitalized and treated according to the recommendations of EAC.

Statistical analysis

We used Chi-Square tests to determine the difference between the sexes, the probability of CAD, and adverse cardiovascular events (ACEs). We used the independent samples test (*t*-test) to determine differences between the sexes in echocardiographic parameters during DSE. The values of $p < 0.05$ were considered statistically significant.

The optimal cut-off value for WMSI to predict poor outcomes was determined by receiver operating characteristics (ROC) curve analysis. The optimal cut-off value was defined as the one that provides maximum accuracy in distinguishing between patients with and without CAD and ACEs. The value of $p = 0.05$ was considered significant.

Statistical data analysis was performed using IBM SPSS Statistics 22 (SPSS Inc. Chicago, IL, USA).

Results

The study included 143 patients with suspected CAD who underwent a DSE. The study comprised 43% of men and 57% of women. The average age of men was 66.02 years, and of women, 65.99 years, which was not statistically significant ($p = 0.985$).

The baseline characteristics of examined patients are presented in Table 1. Male patients had a higher percentage of risk factors for CAD, such as diabetes mellitus ($p < 0.05$) and elevated blood lipid levels ($p < 0.01$). The family history of MI ($p < 0.01$), as well as revascularization in the form of PCI ($p < 0.01$) and ACB ($p = 0.018$), was more common in men (Table 1).

Parameters of DSE according to gender are presented in Table 2. In the observed echocardiographic characteristics using the *t*-test, a statistically significant difference was found in the LV ejection fraction (LVEF) between men and women ($p < 0.01$). During the test, women had a higher value of the LVEF. Men had a higher value of WMSI at the submaximal frequency at the peak of the test ($p < 0.05$).

The differences in ACEs between men and women are presented in Table 3. A positive DSE test was more common in men (45%) than in women (25%); it was statistically significant. The Chi-Square test showed that ACEs were more frequent in men (43%) than in women (19%). The difference was statistically significant ($p < 0.01$). UA ($p < 0.05$) and PCI ($p < 0.01$) were significantly more common in men than in women.

The sensitivity of the DSE in men was 96.0%, and the specificity was 93.9%. In women, the sensitivity was 86.7%, and specificity was also 86.7%.

Log-Rank tests indicated no statistically significant difference in survival between male and female patients, while

Table 1

Characteristics of patients

Parameter	Men	Women	<i>p</i> -value
Age, years	66.02 ± 9.70	65.99 ± 8.97	0.985
Arterial hypertension	51 (86)	71 (90)	0.533
Diabetes mellitus	22 (38)	15 (18)	< 0.05
Hyperlipoproteinemia	41 (71)	34 (43)	< 0.01
Positive family history	19 (32)	19 (24)	0.289
Previous myocardial infarction	25 (42)	12 (15)	< 0.01
Previous PCI	25 (42)	12 (15)	< 0.01
Previous bypass	3 (5)	1 (1)	0.018

PCI – percutaneous coronary intervention.

All values are given as numbers (percentages) or mean ± standard deviation.

Table 2

Parameters of dobutamine stress echocardiography according to gender

Parameter	Men	Women	<i>p</i> -value
WMSI before test	1.07 ± 0.19	1.03 ± 0.12	0.141 ^a
WMSI in test peak	1.24 ± 0.31	1.12 ± 0.25	< 0.05 ^a
Heart frequency	130.78 ± 9.52	132.03 ± 8.21	0.412
Ejection fraction	55.05 ± 6.35	58.50 ± 5.47	< 0.01 ^a

WMSI – wall motion score index. All values are given as mean ± standard deviation. ^aIndependent samples test (*t*-test).

older patients, as expected, had a lower survival rate in the observed time (Figure 1).

During the follow-up, three patients died – two men and a woman.

By analyzing the ROC curve, we determined that the sensitivity of WMSI in the peak of the DSE in men for the discrimination of ACEs was 96.0% and specificity was

82.4% for the value of WMSI > 1. The area under the curve (AUC) was 90.6% (95% CI 80.2–96.7) ($p < 0.001$). The value of $p \leq 0.001$ confirms the statistical significance of these results (Figure 2).

The sensitivity of the WMSI in women by peak DSE test for the discrimination of ACEs was 93.3%, and the specificity was 90.6%. The optimal WMSI threshold value was >

Table 3

Frequency of adverse cardiovascular events (ACEs) according to gender

Test results	Men	Women	<i>p</i> -value
Positive DSE	27 (45)	20 (25)	< 0.05
Unstable angina	14 (24)	8 (10)	< 0.05
Acute myocardial infarction	3 (5)	1 (1)	0.186
PCI	26 (44)	15 (19)	< 0.01
In-stent restenosis	1 (2)	1 (1)	0.842
CABG	5 (8)	3 (4)	0.246
Heart failure	4 (7)	2 (3)	0.226
Death	3 (5)	2 (2)	0.415
ACE	25 (43)	15(19)	0.01

DSE – dobutamine stress echocardiography; PCI – percutaneous coronary intervention; CABG – coronary artery bypass grafting.

All values are given as numbers (percentages).

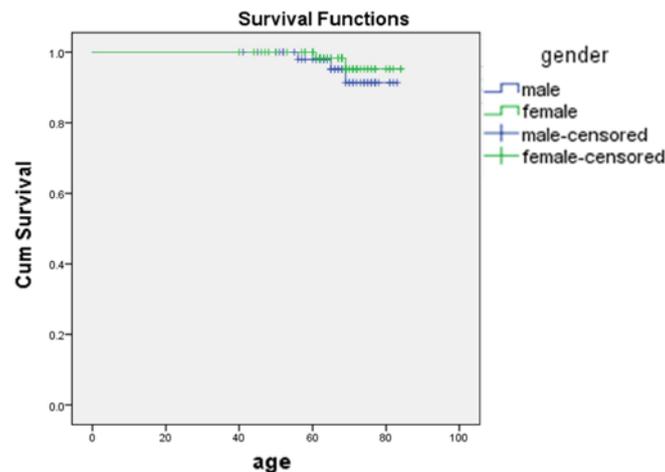


Fig. 1 – Gender differences in survival: Kaplan-Meier curve. cum – cumulative.

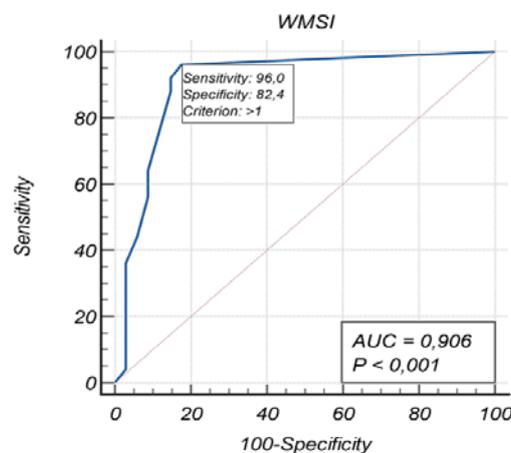


Fig. 2 – Prognostic value of wall motion score index in men: sensitivity 96.0%, specificity 82.4%, optimal threshold value > 1. Area under the curve (AUC) is 90.6% [95% confidence interval (CI) 80.2–96.7] ($p < 0.001$).

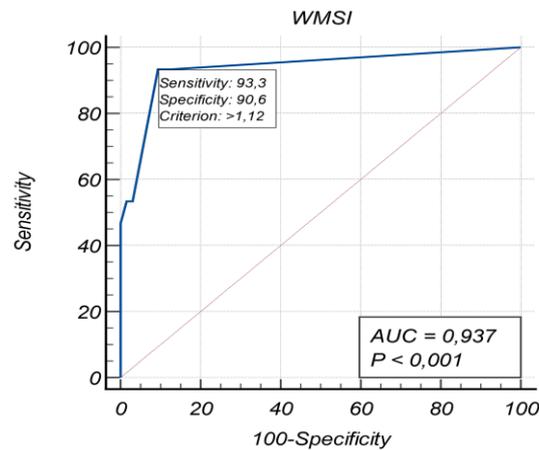


Fig. 3 – Prognostic value of wall motion score index (WMSI) in women: sensitivity 93.3%, specificity 90.6%; optimal threshold value is > 1.12. AUC is 93.7% (95% CI 85.9–97.9) ($p < 0.001$). For abbreviations, see Figure 2.

Table 4

Prognostic impact of wall motion score index on adverse cardiovascular events (ACEs)

ACEs	B	SE	Wald	df	<i>p</i> -value
Unstable angina	4.02	1.05	14.68	1	0.000
AMI	6.09	2.07	8.68	1	0.003
PCI	9.49	1.61	34.89	1	0.000
In-stent restenosis	2.18	2.64	0.67	1	0.410
CABG	5.22	1.48	12.46	1	0.000
Heart failure	2.84	1.54	3.38	1	0.066
Death	8.57	2.52	11.57	1	0.001

B – coefficient for the constant; SE – standard error; df – degrees of freedom; AMI – acute myocardial infarction; PCI – percutaneous coronary intervention; CABG – coronary artery bypass grafting.

1.12. AUC was 93.7% (95% CI 85.9–97.9) ($p < 0.001$). These results indicate a high degree of accuracy of WMSI in identifying ACEs in women (Figure 3).

We examined the difference in WMSI values before the test and at the peak of the test and proved the prognostic significance of this variable. Using binary logistic regression, we proved that an increase in the WMSI value for each unit increased the possibility of the occurrence of ACEs except in ISR and HF (Table 4).

Discussion

The results of our study showed the great importance and usefulness of the application of the DSE in everyday work in diagnosing CAD. In our environment, the DSE is one of the most accessible and economical diagnostic methods.

A significantly higher number of positive tests were in men with clinical suspicion of coronary disease (46% compared to 25% in women). This finding is in line with expectations, considering that men have a significantly higher presence of risk factors for coronary disease. Clinical assessment of CAD has traditionally been more challenging in women compared to men due to lower disease prevalence,

higher incidence of referral bias, and intrinsic performance of different stress testing modalities. DSE has been reported as an effective tool in the diagnosis and prognosis of CAD in women^{20,21}. In our work, false positive tests were registered in a very small number of female patients, as shown by Bach et al.¹⁹. After a positive DSE, coronary angiography findings in these patients were normal. In our study, men had a more frequent occurrence of ACEs compared to women in the observed period. They had UA, MI, ISR, ACB, death, and heart failure more often.

Our results indicate a higher sensitivity and specificity of DSE in men than in women. The sensitivity of DSE in men was 96%, the specificity was 93.4%, while in women, the sensitivity of DSE was 86.7%, and the specificity was 88.9%. The accuracy was 94% and 88.9% in men and women, respectively. The Echocardiography: Value and Accuracy at Rest and Stress (EVAREST) study demonstrated a sensitivity and specificity of the DSE for predicting cardiac outcomes of 95.4% and 96.0%, respectively, with an accuracy of 95.9%, which is consistent with our results. This study provides insight into the current use and accuracy of stress echocardiography in real-world practice in 31 UK-based hospitals. The results of this recent multicenter study provide confidence that stress echocardiography can be safely used

as a first-line test in the treatment of patients with stable chest pain²².

There was no difference in survival between men and women in our study. The survival rate decreases with age. Sedlak et al.²³ proved a worse short-term prognosis for women with non-obstructive disease compared to men. The intermediate and long-term prognosis in subjects with obstructive coronary disease did not differ between genders.

In addition to the analysis of the diagnostic and prognostic significance of DSE, we analyzed and evaluated the prognostic value of WMSI in relation to gender. WMSI in DSE in our research showed high specificity and sensitivity in predicting ACEs. The sensitivity of WMSI in men was 96% and 93.3% in women, while the specificity was lower in men (82.4%) compared to women (90.6%). This analysis indicates that WMSI is effective in predicting unfavorable cardiovascular events in men. Savage et al.²⁴ proved that WMSI is a superior predictor of 12-month mortality over LVEF in ST-elevation MI patients treated with primary PCI. The discriminatory ability of WMSI (AUC: 0.77; 95% CI: 0.68–0.84) was significantly better than LVEF (AUC: 0.71; 95% CI: 0.61–0.79; $p = 0.034$).

Some more recent studies have investigated WMSI compared to other echocardiographic measurements, including global longitudinal strain (GLS), and have shown a good correlation with LVEF, with both WMSI and GLS scores showing superiority over LVEF in predicting ACEs and patient mortality with acute MI²⁵. Wierzbowska-Drabik et al.²⁶ showed that in patients with coronary disease at the peak of DSE, WMSI was a better predictor of coronary SYNTAX and Gensini scores and severity of coronary disease than GLS or LVEF. However, in patients after MI, the

correlation of GLS with the coronary score improved and approached the visual assessment.

Our results show that an increase in WMSI for each unit increases the possibility of unwanted cardiovascular events, which correlates with other studies. Playford et al.²⁷ confirmed the prognostic significance of the increase in WMSI values. In men, there was an increase in all-cause mortality from 38.9% to 49.8%, with an increase in WMSI values from > 1 to > 3 . According to calculated WMSI, all-cause mortality rose in women from 38.5%, with a score > 1.0 , to 49.5%, with a score ≥ 3.0 . The follow-up period in this study was five years. Chuah et al.²⁸ pointed to the predictive significance of WMSI, abnormal LV end-systolic volume response, and percentage fixed wall motion abnormalities. In this examination difference between WMSI at rest and peak DSE was 0.14 ± 0.31 in patients with ACEs. In patients without ACEs, the difference was 0.05 ± 0.23 .

Conclusion

The positive DSE was more common in men. The sensitivity of the DSE in men was 96%, and the specificity was 93.9%. In women, the sensitivity was 86.7%, and the specificity was 86.7%. ACEs were statistically significantly more frequent in men than women. Our study identified WMSI as a predictor of ACEs. In men, WMSI had a higher sensitivity in predicting ACEs, while in women, it showed a higher specificity.

Conflict of interest

The authors declare no conflict of interest associated with the publication of this article.

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Received on December 21, 2023

Revised on March 10, 2024

Revised on April 16, 2024

Accepted on April 23, 2024

Online First June 2024