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Article

Myocardial perfusion stress test in women

Isidora Grozdic Milojevic[1,2,*], Katja Petrovic[1], Olga Radivojevic[1], Lenka Grujicic[1], Milica Kotur[1], Dragana Sobic Saranovic[1,2]

[1] Department of Nuclear medicine and PET, University Clinical Center of Serbia, 11000 Belgrade, Serbia
[2] Medicine Faculty, Belgrade University, 11000 Belgrade, Serbia
*** Corresponding author:** Isidora Grozdic Milojevic, drisidora.grozdic@yahoo.com

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Abstract: Aim: The utility of the ^{99m}Tc-sestamibi myocardial perfusion stress imaging (MPI) over stress echo test (SEHO) in women with intermediate pre-test probability scores. **Methodology:** Our study included 98 women with suspected ischemic heart disease and intermediate pre-test probability scores who underwent MPI and SEHO. They were followed for 26 ± 6 months. The data about MACE and possible coronary angiography were collected. **Results:** The SEHO test was pathological in 31% of the study population. Almost half of those patients had atypical chest pain. MPI was positive in 32% of the examined group. In the follow-up period, MACE was present in 36 patients: PCI (20), CABG (8), acute coronary syndrome (8). The results of the MPI had a high statistically significant correlation with the coronary angiography findings in the follow-up period ($p < 0.001$, $\mu = 0.878$). Additionally, the SEHO test and coronary angiography results correlated well ($p < 0.05$, $\mu = 0.582$). However, MPI test result and SEHO result were not significantly associated with MACE based on Cox proportional hazard analyses ($p > 0.05$). **Conclusion:** MPI may be the complementary procedure for the evaluation of heart conditions in women with intermediatepre-test probability scores, since it correlates well with coronary angiography findings.

Keywords: MPI; SEHO coronary angiography; MACE

1. Introduction

Coronary artery disease is a leading cause of death in the world. Nowadays, we encounter the fact that more and more young people are suffering from this disease and that the age limit of the patients is decreasing. Women are mostly protected from serious cardiovascular events during their reproductive period due to the protective effects of estrogen. However, around 6% of women over the age of 20 in the USA are suffering from coronary heart disease or coronary artery disease. It is important to underline that the annual mortality rate of cardiovascular disease in women is higher than the mortality of all forms of cancer combined [1].

Fortunately, there are many diagnostic procedures that can be used for evaluating coronary heart disease. Nevertheless, the presence of breasts, atypical cardiac pain, and the minimization of symptoms make the evaluation of cardiac diseases in women more complicated. ECG and exercise stress tests are the first-line examinations. Afterwards, patients are referred to additional evaluation—stress echo test (SEHO) or myocardial perfusion imaging stress test (MPI). The presence of ECG disorders, obesity, and large breasts aggravates the stress echo test results. Following the indications from clinical recommendations and guidelines, some patients meet the criteria for MPI. This refers especially to patients with intermediate

pre-test probability scores [2]. MPI enables a sensitive evaluation of myocardial perfusion and left ventricular function at both rest and stress. Stress can be induced in the form of dynamic exercise (usually done on a treadmill) or by the administration of pharmacologic substances (adenosine, regadenoson, etc.). Either way, it requires an intravenous administration of a radioisotope, usually iso-nitrile (^{99m}Tc-sestaMIBI or ^{99m}Tc-tetrofosmin) [3]. However, nuclear medicine tests still raise some concerns regarding radiation effective dose, availability, etc [4–6].

The aim of this research was to evaluate the utility of MPI in women and to correlate its findings with SEHO and coronary angiography results.

2. Materials and methods

2.1. Study population

The investigation included 400 consecutive patients with intermediate pre-test likelihood of coronary artery disease, who were sent to MPI to evaluate ischemic heart disease.

Patients with irregular heart rhythm, low ejection fraction, significant valvular disease, previous coronary artery bypass grafting, male patients, and those aged below 18 were excluded from this study.

After applying these criteria, the study population was composed of 98 women. All patients underwent SEHO and were followed for 26 ± 6 months afterwards. The data about new major cardiac events (MACE) were collected. MACE was defined as the composite of total cardiac death, stroke, myocardial infarction, hospitalization for unstable angina, or revascularization procedures (percutaneous coronary intervention (PCI) or CABG). Written informed consent was obtained from all patients.

The Ethics Committee at the University of Belgrade—Faculty of Medicine approved the study protocol (IRB 668/6; 19/4/2018).

2.2. Data acquisition

MPI was performed as a two-day MPI protocol. Stress MPI was performed on the first day on an ergo bicycle (Bruce protocol), and at the end of the stress test, 444 MBq of ^{99m} Tc-MIBI was administered i.v. Single-photon emission tomography data were acquired 45 min after the injection of radiopharmaceutical. On the next day, the SPECT data were acquired during rest, also 45 min after the i.v. injection of 444 MBq of ^{99m} Tc-MIBI.

The patients were imaged in the supine position using a single-head SPECT camera (e.cam; Siemens) with high resolution, a low-energy and a parallel-hole collimator. Acquisition was done in 180 degrees by using an anterior noncircular orbit in 64 projections, step-and-shoot mode with zoom 1.45, and a matrix size of 64 × 64 × 16. Gating was done 8 frames per cardiac cycle, with T 50% R-R window and energy window 140 T 10% KeV.

2.3. Data reconstruction and image analysis

E.soft and 4D-MSPECT software enabled visual and quantitative assessment.

The reconstructed data were projected as tomographic slices on the short,

vertically long, and horizontally long axes. For assessing the MIBI uptake, we used a 17-segment model of the left ventricle with a 5-point scoring system [7]. Perfusion quantification parameters were determined (summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS)). The regional wall motion was assessed both visually and quantitatively. End-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction (EF) were assessed by using 4D-MSPECT software.

2.4. Statistical analysis

The correlation between the MPI, the SEHO, and the coronary angiography was done using the Spearman correlation coefficient. Cox proportional hazard regression analyses were used to determine which variables were significant predictors of MACE. The results were presented as mean *T* standard deviation (SD), and *P* value of less than 0.05 was considered significant.

3. Results

The study included 98 women (56 ± 8 years) with suspected ischemic heart disease and intermediate pre-test likelihood of CAD. The most women had dyslipidemia (86%), hypertension (95%), smoking habits (69%), and positive family history for CAD (71%).

Firstly, patients performed the SEHO test, which was positive in 31% of them. During the exercise stress test, patients usually reached a load of 4 METs (**Table 1**).

Table 1. Exercise testing variables.

Heart rate		**Blood pressure**				**Maximal workload (METs ± SD)**
Resting (bpm ± SD)	Peak (bpm ± SD)	Resting systolic (bpm ± SD)	Resting diastolic (bpm ± SD)	Peak systolic (bpm ± SD)	Peak diastolic (bpm ± SD)	4.44 ± 2.21
63.56 ± 10.55	121.56 ± 10.55	128.63 ± 17.27	80.25 ± 10.31	160.27 ± 23.07	90.20 ± 14.84	

The majority of the patients had typical chest pain, while 43% of them had atypical chest pain. There were 14% of patients who had no symptoms during the exercise stress test. After the SEHO test, the MPI stress test was done (**Figures 1** and **2**). It was positive in 35% of the patients (**Table 2**).

Table 2. Myocardial perfusion stress test variables.

Ejection fraction		**End diastolic volume**		**End systolic volume**		**Summed rest score (SRS)**	**Summed stress score (SSS)**	**Summed difference score(SDS)**
Rest (%)	After stress test (%)	Rest(mL)	After stress test (mL)	Rest (mL)	After stress test (mL)	0.81 ± 1.33	2.06 ± 3.43	1.56 ± 2.73
68.56 ± 7.58	71.94 ± 9.32	79.38 ± 22.93	73.50 ± 25.19	23.20 ± 8.31	23.69 ± 16.11			

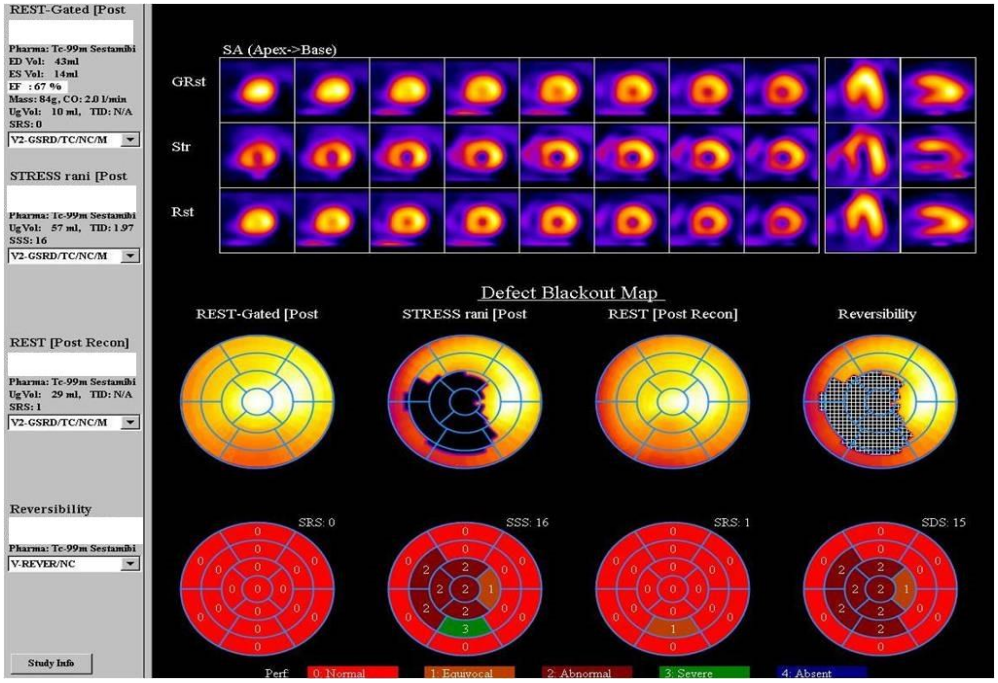

Figure 1. Myocardial ischemia of the anterior wall, septum, apex and inferior wall based on MPI.

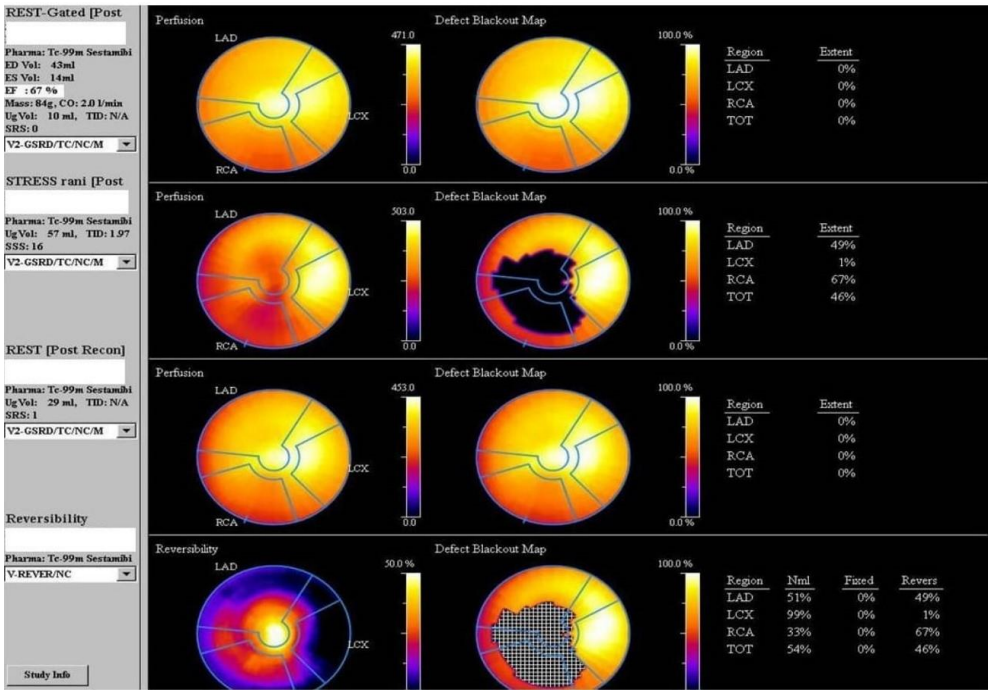

Figure 2. Calculation of ischemia magnitude and origin, done with MPI.

During the follow-up we unfortunately lost contact with 10 patients. However, there was no statistically significant difference between these patients and others who came to the follow-up examination in: age, SEHO test result, MPI test result, type of chest pain, presence of family history for CAD, presence of dyslipidemia, and hypertension (based on T test for continuous variables and X^2 test for dichotomous variables, $p > 0.05$). Thus, there was no selection bias caused by follow-up examination.

After the follow-up, MACE occurred in 36 patients. They had usually: PCI

(20pts), CABG (8 pts), or acute coronary syndrome (12 pts). There were no cardiac deaths during the follow-up period.

During the follow-up, we collected data about possible coronary angiography. The results of the MPI had a high statistically significant correlation with the coronary angiography findings in the follow-up ($p < 0.001$, $\mu = 0.878$). Moreover, SEHO and coronary angiography correlated well ($p < 0.05$, $\mu = 0.582$).

Based on Cox proportional hazard analyses, there were no variables that could be predictors of MACE ($p > 0.05$) (**Table 3**).

Table3. Cox regression models predicting MACE in patients with suspected/known ischemic heart disease and intermediate pre-test likelihood of CAD.

	Univariate analysis			**Multivariate analysis**		
	HR	95%CI	*P*	HR	95%CI	*P*
Age	0.99	0.81–1.21	0.95	0.87	0.54–1.42	0.58
SSS	1.05	0.79–1.34	0.73	5.15	0.20–2.30	0.94
SDS	0.44	0.85–3.57	0.44	0.15	0.70–5.21	0.89
SPECT result (pathological vs. normal)	1.5	0.45–55.14	0.05	2.06	0.70–18.00	0.59
SEHO result (pathological vs.normal)	0.41	0.04–4.24	0.45	0.01	0.12–9.44	0.42

4. Discussion

Coronary artery disease is one of the main causes of mortality and morbidity in both genders [8]. The historical underrepresentation of women in studies led to the common misconception that CAD is a men's disease [9,10].

Although active smoking, congestive heart failure, and left ventricular systolic dysfunction are less often present in women, the prevalence of diabetes mellitus, hyperlipidemia, and family history of premature CAD is usually similar between the genders [11]. In our study sample, women had a very high presence of dyslipidemia, hypertension, smoking habits, and positive family history of CAD. This can be explained by the culturological background of late visits to the doctor and inadequate preventive examinations.

Twenty years ago, data suggested different diagnostic accuracy and frequency of cardiac procedures in women [10,12,13]. Lower pre-test and post-test estimates of CAD led to fewer cardiac angiographies in women. However, women with previous myocardial infarction (within one year after hospitalization) have a higher chance of death than men (38% to 25%, respectively) [1]. Thus, the use of sensitive diagnostic tests is crucial to improve outcomes and reduce mortality and morbidity [10].

The exercise stress test is the most used test for the evaluation of CAD. Unfortunately, it is troublesome in women, since it has a high rate of false-positive results, lower diagnostic accuracy, and average sensitivity and specificity [14]. Hormonal dysbalance, lower electrocardiographic voltage, and frequent ST-T wave changes in hypertensive women can affect test accuracy [15,16]. Furthermore, older women have poor exercise capacity and an inability to attain maximal stress. Thus, exercise stress tests are recommended as a first-line test only in the female population with normal baseline ECG who are able to reach maximal stress [17].

Stress echo tests and MPI are more sensitive procedures, usually indicated in

symptomatic patients with intermediate pre-test probability scores for CAD. Appropriate use criteria for MPI were published over a decade ago; however, there are always doubts about using this procedure [2,11,18]. As our results show, both procedures correlate well with coronary angiography findings (MPI and coronary angiography $p < 0.001$, $\mu = 0.878$; SEHO test and coronary angiography $p < 0.05$, $\mu = 0.582$). Yet, stress echo is slightly less objective since it depends directly on the person performing it. On the other hand, semi-quantification objectifies the MPI finding.

Women with intermediate pre-test probability of CAD benefit from the MPI; however, based on our results, it did not have prognostic value [6,10].

Other studies report that MPI has a negative predictive value, even in patients with a high pre-test probability of CAD. A very low frequency of MACE was observed after a normal MPI result [19]. On the other hand, Miereas and Amanullah state that an abnormal MPI result is an independent predictor, exceeding any other clinical or stress echo parameter [10,20]. The odds ratio for MACE with abnormal MPI was higher in the female population [19]. Future multicentric, randomized studies are advised in the future in order to get more results about this topic. Pharmacologic stress testing MPI is also useful since women presenting with a CAD are usually older with decreased exercise capacity. It is reported that almost half of women who are referred to MPI can benefit from pharmacologic tests [10].

In spite of the recommendations, 14% of MPIs are considered inappropriate, especially in women. This can be explained by the fact that women who present with angina often have nonobstructive CAD due to the presence of microvascular disease. On the contrary, there is a more understandable relation between angina and epicardial disease in men [11].

Younger women are less likely to undergo appropriate tests, especially if they have atypical CAD symptoms [11,21]. Moreover, routine follow-up MPI in asymptomatic patients with previously normal stress test results within two years was a common cause of inappropriate MPI.

The diagnostic accuracy of MPI depends on several parameters, especially in women. It is affected by breast attenuation, small ventricular size, and high frequency of single-vessel CAD [10]. Attenuation artifacts due to breasts, diaphragm, abdomen, lateral chest, and obesity may interfere with final results. On the other hand, attenuation correction is required since it improves the diagnostic accuracy of SPECT MPI. Additionally, semi-quantification depends on the highest signal detected in the left ventricle. The fact that women have smaller left ventricles than men can easily underestimate the extent and severity of ischemia in high-risk CAD patients [8,22,23].

PET/CT is superior to conventional SPECT MPI for risk stratification of CAD, considering that the attenuation correction is done through the CT component of the device. In addition, the measurement of myocardial blood flow (MBF) and flow reserve (MFR) allows identification of previously underestimated groups of patients. Those groups of patients are suffering from diffuse and balanced ischemia, and they are often reclassified after PET/CT examination as high-risk patients for CAD [8,24,25].

Nuclear medical procedures carry a moderate radiation risk equivalent to

coronary angiography. Using the MPI stress-only protocol, or the stress-first protocol, reduces the amount of radiation by half. PET/CT reduces radiation exposure significantly by 80%. Unluckily, it is an expensive, insufficiently available procedure, considering the use of short-lived positron emitters that mainly require a cyclotron.

Recently, cadmium-zinc-telluride gamma cameras allow higher image resolution, shorter acquisition, dose reduction, and a high number of counts. It is also able to reduce attenuation artifacts and to measure MBF and MFR. Limited studies reported higher sensitivity and specificity of the diagnostic performance of cadmium-zinc-telluride gamma cameras in comparison with coronary angiography. It is now recommended for routine practice, especially in overweight, obese, and female patients [8].

This study has some limitations. The main limitation is a relatively small sample size and loss of follow-up for some patients. Considering that a larger number of patients from distant cities were referred to this institution, unfortunately, some of them did not respond to the follow-up examination. Also, with respect to the incidence of CAD, the sample size could be bigger. However, we evaluated only women with suspected ischemic heart disease and intermediate pre-test likelihood of CAD, and after exclusion criteria (irregular heart rhythm, low ejection fraction, significant valvular disease, previous coronary artery bypass grafting, male patients, and those younger than 18 years), the study population was 98/400, given the smaller incidence of CAD in women compared to men. Future studies should be multicentric, done in the larger sample in order to assess this entity objectively.

Also, MACE was considered as defined as the composite of total cardiac death, stroke, myocardial infarction, hospitalization for unstable angina, or revascularization procedures (percutaneous coronary intervention (PCI) or CABG). Nowadays, it seems that there are different definitions of MACE in the literature. General composites could be carefully constructed and defined. For example, MACE should come into the three-point (death, MI, and stroke), four-point (unstable angina in addition), or five-point (heart failure in addition). This illustrates a desire for standardized definitions. The consistency and transparency of their use enable us to compare findings of clinical trials, which in turn influence guidelines and practice [26].

5. Conclusion

SPECT MPI may be a useful procedure for evaluating cardiac blood flow in women with an intermediate pre-test probability score, since it correlates well with coronary angiography findings. It is informative and objective since it uses semi-quantification.

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the published version of the manuscript.

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