

## Prevalence of Ischemia on Myocardial Perfusion Scintigraphy of Pre-and Postmenopausal Women

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### Abstract

**Background:** In postmenopausal women, the presence of risk factors for coronary artery disease (CAD) increases. However, the difference in prevalence of ischemia between pre- and postmenopausal women with multiple risk factors for CAD has not been well established.

**Objectives:** To compare the prevalence of ischemia on Tc<sup>99m</sup>-sestamibi myocardial perfusion scintigraphy (MPS) in pre-and postmenopausal women, and to evaluate whether menopause can be considered an independent risk predictor of ischemia in women with multiple risk factors for CAD.

**Methods:** This study retrospectively assessed 500 MPS of pre- and postmenopausal women with multiple risk factors for CAD. Statistical analysis was performed by using Fisher exact test and univariate and multivariate analysis, a p value  $\leq 0.05$  being considered significant.

**Results:** Postmenopausal women represented 55.9% of the sample; 83.3% were hypertensive; 28.9%, diabetic; 32.1%, smokers; 25%, obese; 61.2% had high cholesterol levels; and 34.3% had known CAD. Postmenopausal women were more often hypertensive, diabetic and dyslipidemic, and had lower functional capacity on exercise testing ( $p < 0.005$ ). The presence of ischemia on MPS did not significantly differ between the pre- and postmenopausal groups ( $p = 0.395$ ). The only variable associated with ischemia on MPS was known CAD ( $p = 0.004$ ).

**Conclusion:** The results suggest that, in women with multiple risk factors for CAD, menopause was not an independent predictor of ischemia on MPS. Those data support the idea that the investigation of ischemia via MPS in women with multiple risk factors for CAD should begin prior to menopause. (Arq Bras Cardiol. 2013; 101(6):487-494)

**Keywords:** Myocardial Ischemia/radionuclide imaging; Women; Premenopause; Postmenopause; Risk factors.

### Introduction

It was only recently that the major studies on coronary artery disease (CAD) began to include women<sup>1-3</sup>.

Women are usually more obese and smoke more than men; 25% of women have sedentary lifestyles, 52% of those over the age of 45 years have arterial hypertension and 40% of those over the age of 55 years have hypercholesterolemia<sup>1,2</sup>. Diabetic women are at an extremely high cardiovascular risk, comparable to that of women who already had myocardial infarction, with more adverse outcomes<sup>4,5</sup>.

The clinical manifestations of CAD appear approximately 10 to 15 years later in women, a fact possibly related to estrogen protection. With the increase in life expectancy, the postmenopausal period began to represent one third of a woman's life, drawing more attention to that specific population<sup>1,2,6,7</sup>.

Some of the traditional diagnostic tests for CAD investigation do not function so properly in the female sex, and evidence has suggested that they have a greater prognostic rather than diagnostic value for women<sup>8,9</sup>.

Exercise testing provides important information, but its mean sensitivity and specificity are lower than in the male sex, around 61% and 69%, respectively<sup>10</sup>. In addition, unspecific baseline electrocardiographic alterations of the ST segment, due to estrogenic hormone action, might generate tests whose results "falsely" suggest ischemia<sup>10</sup>.

Myocardial perfusion scintigraphy (MPS) has become a highly important tool for diagnostic investigation in the female sex, particularly in women with unspecific alterations on baseline electrocardiogram and with low functional capacity or difficulty to achieve the proper heart rate, which is very common in the group of diabetic women and those with peripheral vascular disease<sup>11,12</sup>. In addition, the reduction in breast attenuation artifacts and the acquisition of images guided by electrocardiography (gated-SPECT) increase the accuracy of the test, helping to differentiate real defects and artifacts<sup>13</sup>.

Previous studies<sup>7,14</sup> have reported that estrogenic protection is associated with a reduction in cardiovascular risk; however, there is scarce literature about the role of non-invasive diagnostic methods, especially Tc<sup>99m</sup>-sestamibi MPS in pre/postmenopausal women, mainly in those with multiple risk factors for CAD.

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Manuscript received February 26, 2013; revised manuscript June 27, 2013; accepted June 28, 2013

DOI: 10.5935/abc.20130221

## Objectives

The present study aimed at comparing the presence of ischemia on Tc<sup>99m</sup>-sestamibi MPS in pre/postmenopausal women at high risk for CAD, and at assessing whether menopause is an independent predictive factor of ischemia in that group of patients.

## Methods

This is an observational, retrospective study carried out at the nuclear medicine sector of the Instituto Dante Pazzanese de Cardiologia, based on the review of medical records, analyzing consecutive 500 MPS of women performed in 2011 and 2012. This study was approved by the committee of ethics and research (02020312.7.0000.5462). All patients provided written informed consent before undergoing MPS.

Exercise and pharmacological (dipyridamole and dobutamine) stress test and acquisition and processing of nuclear medicine images were performed by using standard techniques, according to the guidelines of the Brazilian Society of Cardiology/Department of Ergometry, Exercise, Nuclear Cardiology and Cardiovascular Rehabilitation<sup>15,16</sup>.

Myocardial perfusion scintigraphy was performed by use of the gated-SPECT technique, one-day protocol, the baseline phase being followed by the stress phase. A GE Ventri dedicated cardiac gamma camera was used for image acquisition. To assess myocardial perfusion, the myocardium was divided into 17 segments. Normal perfusion was considered the absence of reduced uptake of the radiotracer in both phases (baseline and stress); perfusion suggestive of ischemia and fibrosis was considered the presence of reversible and fixed reduced uptake of the radiotracer after the stress phase as compared to the baseline phase, at least in 3 of the 17 myocardial segments analyzed<sup>15</sup>.

The qualitative visual analysis of the presence or absence of perfusion alterations was performed by two observers specialized in cardiology and nuclear medicine, and, in case of disagreement, a third observer also specialized in cardiology and nuclear medicine was consulted.

This study considered the presence of myocardial ischemia on scintigraphy. Of all patients assessed, 69 had

perfusion alterations suggestive of myocardial fibrosis, 41 of whom were postmenopausal women and 28, premenopausal ( $p = 0.069$ ).

The patients were classified as pre/postmenopausal according to data in medical records.

The classical cardiovascular risk factors assessed were arterial hypertension, diabetes mellitus, dyslipidemia, smoking and obesity, defined according to the Brazilian Society of Cardiology guidelines<sup>17</sup>.

Patients with known CAD were those with previous diagnosis of myocardial infarction, unstable/stable angina and percutaneous or surgical myocardial revascularization. In addition, patients with the following characteristics were considered to be at equivalent high cardiovascular risk: stroke; carotid and peripheral artery disease; abdominal aorta aneurysm; and chronic renal failure<sup>17</sup>.

Patients with non-ischemic heart diseases and those with no information regarding menopause in their medical records were excluded.

Statistical analysis was performed with Fisher exact test and univariate and multivariate analyses, and the significance level adopted was  $p \leq 0.05$ .

## Results

Table 1 shows the clinical and epidemiological characteristics of the patients assessed according to their menopausal status.

The physicians of the outpatient clinics where the patients were followed up requested the MPS according to clinical indications. Such indications were divided into symptomatic and asymptomatic patients (Tables 2 and 3). Table 4 shows the results of the MPS in asymptomatic patients.

Tables 5 to 7 show the number of exercise stress tests and dipyridamole and dobutamine stress tests performed according to the menopausal status of the patients, as well as patients' clinical and electrocardiographic characteristics, and physical fitness and functional capacity.

The degree of physical fitness, known as functional capacity, measured in metabolic equivalents (MET) on the exercise test was significantly lower in postmenopausal women. Of all patients, 91 reached 10 MET or less, 56 were postmenopausal

**Table 1 - Clinical and epidemiological characteristics of the pre- and postmenopausal groups**

	Total (%)	Premenopausal N = 221	Postmenopausal N = 279	p value
Mean age $\pm$ SD	500 (100)	45.4 $\pm$ 4.16	65.7 $\pm$ 8.67	< 0.001
Hypertension	414 (83.3)	164 (74)	250 (89)	< 0.001
Diabetes	144 (28.9)	36 (16)	108 (38)	< 0.001
Dyslipidemia	305 (61.2)	100 (45)	205 (74)	< 0.001
Smoker/ex-smoker	160 (32.1)	70 (32)	90 (32)	0.92
Obesity	125 (25)	49 (22)	76 (28)	0.213
CAD	171 (34.3)	69 (31)	102 (37)	0.218

CAD: previous coronary artery disease.

**Table 2 - Indications for MPS in symptomatic patients**

Functional test	Total	Premenopausal	Postmenopausal
MPS	396	179	231
<b>Indications</b>			
Atypical chest pain	169	87	82
Typical chest pain	103	47	52
Functional class worsening	92	33	59
Palpitations	20	8	12
Vertigo	4	0	4
Syncope	8	4	4

MPS: myocardial perfusion scintigraphy.

**Table 3 - Indications for MPS in asymptomatic patients**

Functional test	Total	Premenopausal	Postmenopausal
MPS	104	42	62
<b>Indications</b>			
Preoperative assessment	5	3	2
After PTCA/stent or CABG	33	9	24
To assess the etiology of dilated cardiomyopathy	10	4	6
To assess the etiology of arrhythmia	15	6	9
To assess the etiology of LBBB	2	0	2
Other altered functional test	14	10	4
Cardiovascular risk stratification or other non-specified reasons	25	10	15

MPS: myocardial perfusion scintigraphy; PTCA: percutaneous transluminal coronary angioplasty; CABG: coronary artery bypass graft surgery; LBBB: left bundle-branch block.

**Table 4 - Subanalysis of asymptomatic patients**

Asymptomatic patients = 104	altered MPS = 60 patients	Premenopausal patients = 23 Postmenopausal patients = 37
	normal MPS = 44 patients	Premenopausal patients = 19 Postmenopausal patients = 25

MPS: myocardial perfusion scintigraphy.

and 35, premenopausal ( $p < 0.005$ ). The only variable predictive of ischemia on MPS was the presence of previous CAD ( $p < 0.05$ ).

Of the 500 patients assessed with MPS, ischemia was identified in 102 (58.5%) postmenopausal patients and in 72 (41.5%) premenopausal patients, with no statistical significance ( $p = 0.395$ ).

Figure 1: Findings suggesting ischemia on the dipyridamole MPS of a 46-year-old female patient with diabetes, hypertension, obesity, dyslipidemia, sedentary lifestyle, and known CAD (stent in the anterior descending artery for three years): ECG showing ST-segment depression during

the infusion of dipyridamole; and myocardial perfusion showing transient reduction in radiotracer uptake in the anterior, anteroseptal and apical walls.

## Discussion

Diagnosing CAD in the female sex is a great challenge. Because its symptoms are less typical in women, non-invasive tests have an unquestionable value for its effective investigation in women before submitting them to invasive, sometimes unnecessary, tests. In the Coronary Artery Surgery Study (CASS), half of the women submitted to coronary angiography showed no significant lesions<sup>17</sup>.

**Table 5 - Clinical and electrocardiographic characteristics and functional capacity on exercise stress testing**

	Total	Premenopausal	Postmenopausal
Total	200	112	88
<b>Total of normal tests</b>	93	55	38
Normal tests reaching > 10 MET	61	39	22
<b>Total of altered tests</b>	107	57	50
ECG alteration	40	23	17
Alteration due to chest pain	41	24	17
ECG alteration + chest pain	24	9	15
Complex ventricular arrhythmia during the test	2	1	1
Altered tests reaching < 10 MET	91	44	47
<b>Other symptoms during the test</b>	37	22	15
Unspecific chest pain	24	14	10
Dyspnea	13	8	5
Headache	0	0	0

ECG: electrocardiography.

**Table 6 - Clinical and electrocardiographic characteristics on dipyridamole stress testing**

	Total	Premenopausal	Postmenopausal
Total	279	105	174
<b>Total of normal tests</b>	130	46	84
<b>Total of altered tests</b>	149	59	90
ECG alteration	31	9	22
Alteration due to chest pain	69	31	38
ECG alteration + chest pain	48	19	29
Complex ventricular arrhythmia during the test	1	0	1
<b>Other symptoms during the test</b>	50	15	35
Unspecific chest pain	23	7	16
Dyspnea	5	2	3
Headache	22	6	16

ECG: electrocardiography.

**Table 7 - Clinical and electrocardiographic characteristics on dobutamine stress testing**

	Total	Premenopausal	Postmenopausal
Total	21	4	17
<b>Total of normal tests</b>	9	0	9
<b>Total of altered tests</b>	12	4	8
ECG alteration	5	2	3
Alteration due to chest pain	6	2	4
ECG alteration + chest pain	1	0	1
<b>Other symptoms during the test</b>	5	0	5
Unspecific chest pain	2	0	2
Dyspnea	0	0	0
Headache	3	0	3

ECG: electrocardiography.

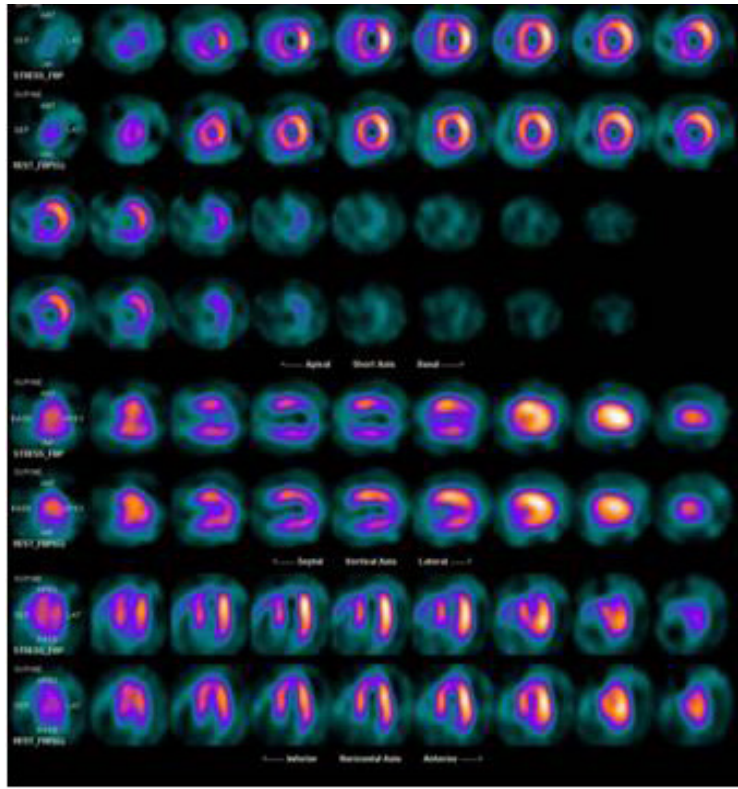


Figure 1 - Ischemia on myocardial perfusion scintigraphy of a premenopausal woman.



As our institution is a tertiary cardiological hospital, women followed up there usually have multiple risk factors for CAD, and most of them already had a previous myocardial infarction and/or myocardial revascularization procedure (as reported in this study, 34% with previous known CAD). Thus, we decided to carry out a study reflecting the reality of women referred for MPS, and those with previous CAD were not excluded.

The objective of this study was to assess whether menopause was an independent predictor of ischemia in women at our institution, with and without known CAD.

It is worth emphasizing that, in our study, many women had previous electrocardiographic alterations on baseline ECG and low functional capacity, which motivated their referral for MPS, aimed at diagnostic investigation and cardiovascular risk stratification.

As already observed, the choice and interpretation of non-invasive procedures are not easy tasks. Exercise testing is known to have lower sensitivity and specificity in the female sex than in the male sex<sup>18</sup>. The sensitivity and specificity of the pharmacological or exercise stress tests can be improved by imaging methods that increase diagnostic accuracy<sup>10,11,18</sup>. With the refinement of the technique, a reduction in attenuation artifacts (breast, for example) was observed, leading to greater specificity<sup>13</sup>.

In the present study, MPS proved to be an important tool to investigate ischemia, which was observed in 35% of the women assessed. Such data are in accordance with those of the literature. Smanio et al<sup>11</sup>, studying the MPS of 104 asymptomatic diabetic women, have reported myocardial ischemia in 34 (32.7%).

Myocardial scintigraphy plays a role in CAD diagnosis and cardiovascular risk stratification in both sexes, considering that it provides information on myocardial perfusion, left ventricular function and, if necessary, myocardial viability. Its combination with exercise testing, particularly in the female sex, significantly increases diagnostic accuracy<sup>7,19</sup>.

Mieres et al<sup>20</sup> have assessed 46 postmenopausal women with exercise test and MPS, and the sensitivity and specificity values found were, respectively, 67% and 69% for the exercise test, and 88% and 87.5%, for MPS ( $p < 0.0001$ ).

The prognostic importance of scintigraphy in the female sex is well known<sup>9,21</sup>. There is a large body of evidence on the association of myocardial scintigraphy and stress testing, showing that it effectively stratifies the risk in women suspected of having CAD. Women with a normal myocardial perfusion study have an annual event rate much lower (0.6% per year) than those with abnormal myocardial perfusion study (5% per year)<sup>22</sup>.

The lower cardiovascular risk in the premenopausal phase is attributed to the protection provided by plasma estrogen levels<sup>23,24</sup>. Such levels promote arterial

vasodilation by increasing the nitric oxide synthesis by endothelial cells, increase HDL-cholesterol particles and decrease LDL-cholesterol particles, and reduce the serum levels of fibrinogen, antithrombin and protein S<sup>24</sup>.

The decreased estrogen levels of the postmenopausal phase lead to microvascular endothelial dysfunction and consequent progression of the atherosclerotic plaque<sup>23,24</sup>. Differently from the endogenous estrogen effects, exogenous hormone therapy has shown to increase the cardiovascular disease risks<sup>23-26</sup>.

In 2002, the Women's Health Initiative (WHI) study showed that the benefits of hormone replacement therapy (HRT) were restricted to a small group of women in the so-called "window of opportunity", at the beginning of menopause (between 50 and 59 years), in the presence of no cardiovascular risk factors. Recent studies have confirmed that information<sup>27</sup>. However, a recent publication of the American Heart Association (AHA) contra-indicates the use of HRT as primary and secondary prevention of cardiovascular diseases<sup>28</sup>.

Leuzzi et al<sup>29</sup>, in an interesting editorial, have reported that, despite the higher prevalence of CAD after menopause, further studies are required to clarify whether menopause is a cardiovascular risk factor.

The association between menopause and presence of CAD might be observed in low-risk women, but for those with multiple risk factors, such as diabetes, hypertension, dyslipidemia, obesity, sedentary lifestyle, as seen in our study, menopause might not be a predictive factor of ischemia. These same findings have been observed by Sood et al<sup>14</sup> when assessing 2,194 pre- and postmenopausal women at an intermediate risk for CAD according to Duke score on exercise testing and according to MPS. In that study, menopause has not proved to predict cardiovascular events, and MPS provided risk stratification beyond the Duke score. A study with a larger number of patients should be performed to confirm that statement.

## Conclusion

The results obtained suggest that, in women with multiple risk factors for CAD, menopause was not an independent predictor of ischemia on Tc<sup>99m</sup>-sestamibi MPS. The only proven predictor in that group was the presence of known CAD. Those data support the idea that the investigation of ischemia via MPS in women with multiple risk factors for CAD should begin prior to menopause.

## Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Statistical analysis, Writing of the manuscript, Critical revision of the manuscript for intellectual content: Santos DAM, Sierralta WY, Alexandre LM, Smanio PEP, Cestari PF.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### Sources of Funding

There were no external funding sources for this study.

### Study Association

This article is part of the thesis of specialization in Cardiology submitted by Daniel Augusto Massage dos Santos e Wendy Yasdin Sierraalta by Institute Dante Pazzanese.

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