Diagnostic Value of Myocardial Perfusion SPECT with Dipyridamole in a Female Population

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SUMMARY

Background
Exercise stress scintigraphy is a safe procedure widely used for the diagnosis of ischemic heart disease. Pharmacologic stress testing is an important alternative. The delayed presentation of ischemic heart disease in women, together with a lower diagnostic accuracy of exercise stress testing in this population, has generated interest in the potential benefits provided by myocardial perfusion imaging tests.

Objective
To determine the diagnostic value of myocardial perfusion images with Tc-99m tetrofosmin in a one day protocol after a pharmacologic stress with dipyridamole in a female population, and the relation with the coronary territories using coronary angiography as a reference technique.

Material and Methods
In total, 149 clinical charts of women with suspected ischemic heart disease undergoing myocardial perfusion imaging tests and coronary angiography were retrospectively analyzed.

Results
Sensitivity and specificity were 94% (93.47%-94.53%) and 82% (80.94%-83.06%), respectively. Values of sensitivity and specificity according to coronary territories were 71.62% (70.88%-72.36%) and 76% (75.27%-76.73%) for the left anterior descending (LAD) artery, 69.09% (68.11%-70.07%) and 76.84% (76.26%-77.42%) for the left circumflex (LCx) coronary artery, and 87.23% (86.11%-88.36%) and 74.51% (73.97%-75.05%) for the right coronary artery (RCA), respectively.

Conclusion
Myocardial perfusion scintigraphy with Tc-99m tetrofosmin and dipyridamole using a one day stress-rest protocol has high sensitivity and specificity for the diagnosis of ischemic heart disease in women.

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Key words > Scintigraphy - Technetium - Perfusion - Myocardium - Women - Sensitivity - Specificity

Abbreviations >

LBBB	Left bundle-branch block	**HT**	Hypertension
RCD	Right coronary artery	**AMI**	Acute myocardial infarction
IHD	Ischemic heart disease	**ACEI**	Angiotensin-converting enzyme inhibitors
LCx	Left circumflex	**BMI**	Body mass index
LAD	Left anterior descending	**SPECT**	Single photon emission-computed tomography
DM	Diabetes mellitus	**NPV**	Negative predictive value
CAD	Coronary artery disease	**PPV**	Positive predictive value
ECG	Electrocardiogram		

BACKGROUND

When women have angina, they are more likely than men to experience atypical symptoms. (1) Women with ischemia are more prone to present angina of variable threshold, chest pain under the breast, palpitations or acute and/or sharp chest pain. However, as an isolated symptom, chest pain is very frequent in women and generally is not due to coronary artery disease (CAD). (1, 2) Women with chest pain, angina or after acute myocardial infarction (AMI) are less likely to undergo either non-invasive (exercise stress test and other tests to detect ischemia) or invasive procedures than men. (3)

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Myocardial perfusion scintigraphy is widely used in clinical practice to evaluate regional coronary artery blood flow for the diagnosis of CAD diagnosis and for stratification. (4, 5) The advantage of perfusion images obtained with radionuclides is that they provide information about the coronary territory compromised and the extension of the myocardium at risk. (6)

Exercise stress scintigraphy is a safe procedure widely used for the diagnosis of ischemic heart disease (IHD). (4) Perfusion studies performed under pharmacologic stress are also a valid option. (7) Ischemic heart disease has a delayed presentation in women compared to men; in addition, gender-related limitations associated with exercise stress testing have generated interest in the potential benefits provided by myocardial perfusion imaging tests in women. (8)

Women have lower pretest likelihood and greater morbidity and mortality associated with coronary revascularization procedures. For these reasons, women with IHD, either confirmed or suspected, are referred for non-invasive testing less frequently than men. (9)

The goal of the present study was to determine the diagnostic value of myocardial perfusion imaging with Tc- 99m tetrofosmin in a one day protocol after a pharmacologic stress with dipyridamole as a diagnostic and prognostic test in a female population, and its relation with the coronary territories using coronary angiography as a reference technique.

MATERIAL AND METHODS

A total of 149 clinical charts of women with suspected ischemic heart disease undergoing exercise stress/rest myocardial perfusion imaging with Tc-99m tetrofosmin after a pharmacologic stress with dipyridamole at the Department of Nuclear Medicine, *Hospital Carlos Haya* in Malaga during 2003 to 2006 were retrospectively analyzed. Subsequently, all patients underwent a coronary angiography at the catheterization laboratory of the same hospital.

Source of variables: all female patients with IHD were referred from the Department of Cardiology with the indication of myocardial perfusion imaging test either to confirm the condition or for risk stratification. A questionnaire was designed to obtain the information recorded in the clinical chart: clinical parameters of CAD, presence of other diseases, type of physical activity and medication.

Pharmacologic treatment: the questionnaire included data of medical therapy that might affect the result of the scintigraphy, such as antihypertensive drugs, cardiac glycosides, organic nitrates, calcium channel blockers, beta blockers, diuretics and ACEIs. (10, 11)

Risk factors: age, body mass index (BMI), smoking habits, dyslipemia, hypertension (HT) (upper/lower limit 140/90 mmHg), (12, 13) history of ischemic heart disease [acute myocardial infarction (AMI) or angina], diabetes mellitus (DM) were retrieved from the clinical charts.

Dyslipemia was considered when total cholesterol and triglycerides blood levels were above normal values or when the patient was treated with lipid lowering drugs. The variable *history of IHD (AMI* or *angina)* was classified as *healthy individual* (without personal history), *ischemic heart disease* (AMI or typical angina), *hypertensive heart disease*, *valvular heart disease*, *dilated cardiomyopathy* or *others*.

Biochemical parameters of metabolic control: in all cases the following laboratory tests were ordered at the moment of hospitalization: glycemia (< 110 mg/dl), total cholesterol (< 240 mg/dl)), HDL-cholesterol (35-94 mg/dl) and LDL-cholesterol (80-180 mg/dl) levels, triglycerides (< 200 mg/dl) and uric acid (2,6-7,2 mg/dl). (14)

Basal electrocardiogram (ECG): an ECG was taken in all patients at the emergency room; strips were evaluated by a cardiologist who reported the ECG characteristics: *normal ECG*, *non-sinus rhythm*, *left bundle-branch block (LBBB)*, *T-wave abnormalities* or *abnormal Q-waves*. (15)

Final diagnosis: the final diagnosis was made by the cardiologist at the moment of discharge and was classified in: *typical angina, atypical chest pain, AMI and others*.

Myocardial perfusion scintigraphy: Tc-99m tetrofosmin (Myoview®, Amersham Health) was prepared following the manufacturer's indications, (16) obtained from sodium 99mTc pertechnetate eluted from a 99 Mo/99mTc generator (Drytec, Amersham Health).

Myocardial perfusion imaging test: patients were asked not to eat or drink anything the night before or 12 hours before the test, except for patients with DM who were asked to have a meal and then take the usual dose of insulin before the test. Medications that could interfere with the result of the test - analgesics, stimulants and weight loss drugs, and metilxantines (coffee or tea) were withheld for 12 to 24 hours before the test. Persantine was withheld for at least 24 hours before testing. Beta blockers and calcium channel blockers were withheld for 72 hours and 48 hours, respectively.

All patients underwent a one-day Tc-99m tetrofosmin protocol. (17, 18) Firstly, pharmacologic stress testing was performed after intravenous dipyridamole infusion (0.56 mg/kg over a 4-minute period) under continuous ECG monitoring (Cardiolife TEC-7100-E monitor, Nihon Codeen Corporation, 31-4 Nishiochiai 1-Chome, Shinkuju-ku, Tokio 161, Japan). Two minutes after dipyridamole infusion ended Tc-99m tetrofosmin was injected at a dose of 222 to 296 MBq (6-8 mCi). Immediately after, the patient was asked to eat a fatty meal. Myocardial SPECT imaging was started 60 mm after radiotracer injection. A second dose of 666-888 MBq (18-24 mCi) of Tc-99m tetrofosmin was then injected and image acquisition started after one hour.

Images were acquired using a dual head Picker Axis gamma camera with the detector heads disposed at 102°, equipped with a low-energy high-resolution (LEHR) parallel-hole collimator. In total, 64 images were obtained along a 180° elliptical orbit using step-and-shoot method from right anterior oblique to the left posterior oblique position. Data was acquired with a 20% energy window centered over the 140 KeV photopeak of 99mTc. Image reconstruction was performed using a double spatio-temporal filter, firstly applying a ramp filter followed by a butterwoth filter of order 5, with a cut-off frequency of 0.4 cycles/pixel; in this way 17 segments were obtained. Exercise images were obtained within 15 seconds and rest images were acquired within 10 seconds.

Short-axis, horizontal long-axis and vertical-long axis slices were created with a slice size of 3 pixels and a thickness of 7.1mm. All images were evaluated by a nuclear medicine specialist who was blind to the results of the coronary angiography.

A "*fixed perfusion defect*" was defined as a mild, moderate or severe hypoperfusion on exercise images in at least 2 axes or 3 contiguous slices from the same axis that persisted on images at rest. A perfusion defect on the exercise images that completely or partially resolved at rest was considered a "*reversible defect*" or a "*partial defect*".

The extent and severity of perfusion defects at stress and rest was evaluated using a semi-quantitative analysis and

a score was given based on the percentage of radioisotope uptake normalized for each segment. (19) The distribution of tracer uptake was classified as: normal (86-100%), mildly reduced (85-60%), moderately reduced (59-50%), severely reduced (< 50%) and absent. A perfusion defect during exercise that reverted at rest was considered diagnostic of myocardial *ischemia*. *Necrosis* was considered when a perfusion defect on exercise images persisted at rest. Perfusion defects during exercise that persisted at rest in some segments and partially reverted in others were considered *combined defects*. *Reverse redistribution* corresponds to perfusion defects that are only visualized during rest images.

Coronary angiography: all patients underwent coronary angiography according to clinical criteria. Coronary angiography was considered positive when stenosis > 50% in any of the three main coronary arteries or their branches was present, and negative in the absence of stenosis. The three main coronary arteries were correlated with the coronary territories they perfused according to Hesse et al. (19)

Validity of diagnostic tests: the results of myocardial perfusion scintigraphy images were compared with a reference diagnostic test (coronary angiography). The perfect test should always be positive in the presence of the disease and negative in its absence. (20, 21)

Sensitivity (S) measures the proportion of actual positives which are correctly identified as such. *Specificity* (Sp) measures the proportion of negatives which are correctly identified as healthy people. (22) A 95% confidence interval was calculated in all cases. The *positive predictive value* (PPV) is the proportion of patients with positive test results who are correctly diagnosed (20, 23) while the *negative predictive value* (NPP) is the proportion of patients with negative test results who are correctly diagnosed. (20, 23) The prognostic values were calculated considering a 95% confidence interval.

Descriptive analysis was calculated using SPSS software package. Socio-demographic and clinical characteristics of the population were analyzed using descriptive statistics (distribution and central tendency).

Ethical considerations: the study protocol was approved by the Committee on Ethics of the *Hospital Regional Universitario Carlos Haya* of Malaga. Prior to the test, each patient received a written information sheet describing the possible adverse outcomes and oral information about the procedure was given following the EANM guidelines. Finally, all patients gave their consent to be included in the study. (19)

RESULTS

Mean age was 65.28 ± 8.55 years.

Table 1 shows the population distribution according to symptoms, risk factors, pharmacologic treatment, history of cardiovascular diseases and basal ECG.

Mean systolic blood pressure was 143.67 ± 31.64 mm Hg (n = 149); mean diastolic blood pressure value was 77.38 ± 16.29 mm Hg (n = 149).

Mean values of biochemical parameters are detailed in Table 2.

Table 3 describes the results of the coronary angiography in the population studied.

Table 4 displays the results of myocardial perfusion scintigraphy and the type of defect.

The final diagnosis of the cardiologist was typical angina in 55.7%, atypical chest pain in 20.8%, AMI in 20.1% and "other diagnoses" in 12.1%.

Diagnostic value in the population

Table 5 shows the values of sensitivity, specificity and predictive values.

These parameters were calculated based on the number of vessels affected (single- vessel, two-vessel or multivessel-disease); Figure 1 illustrates the comparison of the sensitivities estimated. Specificity was 79.55% in all cases. The diagnostic values obtained by coronary artery territory are shown in Table 6.

DISCUSSION

We consider that this group of 149 non-revascularized female patients who underwent myocardial perfusion scintigraphy followed by coronary angiography is particularly interesting as it represents a population still in the diagnostic phase. In this population, myocardial perfusion scintigraphy has proved to be a reliable test to perform before coronary angiography. Sensitivity and specificity were 94% and 82%, respectively. The results of this study indicate that the prognostic value of exercise stress/rest myocardial perfusion scintigraphy with Tc-99m tetrofosmin and dipyridamole is optimal for women with suspected ischemic heart disease.

Some authors (24, 25) have declared that coronary angiography does not add any significant prognostic value to the combination of clinical data, myocardial perfusion images and the results of cardiac catheterization. in fact, the extent of the perfusion abnormality is has got the highest predictive value. Our study confirms that affirmation, demonstrated by the high predictive values we obtained (PPV 91.26%; NPV 87.23%).

The guidelines published by the *American College of Cardiology/American Heart Association/American Society for Nuclear Cardiology* (26) for the clinical use of cardiac radionuclide imaging determined that the sensitivities of vasodilator stress perfusion SPECT averaged 73% and 75%, (26) and our data are very similar to or even better than these values.

According to Peix et al. (27) microvascular angina should be taken into account in postmenopausal women as a cause of positive scintigraphy with normal coronary arteries, and thus should not be considered a false positive result of myocardial ischemia. The term *"microvascular angina"* refers to patients with coronary microcirculatory derangements but with normal coronary angiograms and absence of coronary artery spasm. (27) In our series, 92.6% of women were in the postmenopause and 95.51% presented chest pain; both findings are frequent in patients with microvascular angina and may help to explain the specificity obtained in both groups in our study.

Johansen et al. (28) determined the diagnostic accuracy of myocardial perfusion imaging by use of an exercise/rest dual-isotope protocol with Tc-99m sestamibi and adenosine as vasodilator in a population of 357 patients (165 women). The presence of CAD was defined as at least one coronary artery stenosis ≥ 50% in any of the main coronary arteries. The sensitivity

Table 1. Characteristics of the population

	n (149)	%
Symptoms		
Chest pain	146	98
Dyspnea	45	30.2
Palpitations	18	12.1
Dizziness	18	12.1
Syncope	4	2.7
Risk factors		
Diabetes	66	44.3
Dyslipemia	77	51.7
BMI		
Normal	18	12.2
Overweight	49	33.1
Obesity	81	54.7
Previous AMI	20	13.4
Previous angina	59	39.6
Current smoking	32	21.5
HT	110	73.8
Pharmacologic treatment		
Antihypertensive drugs	35	23.5
Cardiotonic glycosides	6	4.0
Organic nitrates	62	41.6
Calcium channel blockers	34	22.8
Beta blockers	64	43
Diuretics	27	18.1
ACEI	54	36.2
History of cardiovascular disease		
Absent	48	32.2
Hypertensive heart disease	41	27.5
Ischemic heart disease	68	45.6
Valvular heart disease	1	0.7
Dilated cardiomyopathy	5	3.4
Others	7 **	4.7
Electrocardiogram		
Normal	23	15.4
Abnormal	126	84.6
Non-sinus rhythm	3	2.1
Left bundle-branch block	17	11.9
T wave abnormalities	103	72.0
Abnormal Q waves	16	11.2

BMI: Body mass index AMI: Acute myocardial infarction. IHD: Ischemic heart disease. HT: Hypertension. ACEI: Angiotensin-converting enzyme inhibitors. **Paroxysmal atrial fibrillation (n = 5); X syndrome (n = 1); hiatal hernia (n = 1).

Table 2. Biochemical parameters

Biochemical parameters	n (149)	x ± SD*
Total cholesterol (mg/dl)	121	188.28 ± 38.42
HDL-C (mg/dl)	115	41.42 ± 15.86
LDL-C (mg/dl)	106	117.15 ± 33.42
Triglycerides (mg/dl)	114	155.97 ± 68.58
Glycemia (ng/dl)	144	132.34 ± 57.01
Uric acid (mg/dl)	95	5.27 ± 1.67

* x ± SD: Mean ± standard deviation.

Table 3. Coronary angiography

	n (149)	%
Coronary angiography		
Normal	44	29.50
Abnormal	105	70.50
Coronary artery disease		
Single-vesssel disease	42	28.20
Two-vessel disease	33	22.10
Multivessel disease	30	20.10

Table 4. Patients' distribution according to the results of myocardial perfusion scintigraphy and type of defect

	n (149)	%
Myocardial perfuion imaging		
Normal	47	31.50
Abnormal	102	68.50
Type of defect		
Ischemia	46	45.10
Necrosis	13	12.70
Combined	42	41.20
Reverse redistribution	1	1.0

Table 5. Diagnostic value of myocardial perfusion scintigraphy

	Value	95% IC
Sensitivity (%)	**94.0**	(93.47-94.53)
Specificity (%)	**82.0**	(80.94-83.06)
PPV (%)	**91.26**	(90.74-91.78)
NPV (%)	**87.23**	(86.11-88.36)

CI: confidence interval. PPV: Positive predictive value. NPV: Negative predictive value. N = 149

and specificity of the test in women were 67% and 82%, respectively. The values obtained in our study were greater (94% and 82%).

The sensitivity of myocardial perfusion imaging reported by these authors was 71%, 69%, and 89% in patients with 1-, 2-, and 3-vessel disease, respectively, for both genders. In our population we found that the sensitivity of the test was 80.95%, 93.94% and 93.33% for 1-, 2-, and multi-vessel disease, respectively. Considering that our study was performed only in women, we estimated that the sensitivity of myocardial perfusion scintigraphy was higher. The prognostic information provided by the test is important and reduces the neces-

Table 6. Diagnostic value of myocardial perfusion scintigraphy by coronary artery territory

	LAD		LCx		RCA	
	Value	95% CI	Value	95% CI	Value	95% CI
S (%)	**71.62**	(70.88-72.36)	**69.09**	(68.11-70.07)	**87.23**	(86,11-88.36)
Sp (%)	**76.0**	(75.27-76.73)	**76.84**	(76.26-77.42)	**74.51**	(73,97-75.05)
PPV (%)	**74.65**	(73.88-75.41)	**63.33**	(62.43-64.24)	**61.19**	(60,38-62.01)
NPV (%)	**73.08**	(72.38-73.78)	**81.11**	(80.51-81.72)	**92.68**	(92,04-93.33)

LAD: Left anterior descending coronary artery. LCx: Left circumflex coronary artery. RCD: Right coronary artery. CI: confidence interval. S: Sensitivity Sp: Specificity. PPV: Positive predictive value. NPV: Negative predictive value. N = 149

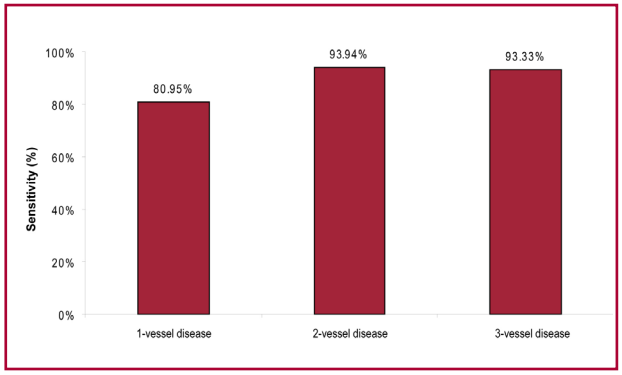

Fig. 1. Sensitivity of scintigraphy according to the number of vessels compromised.

sity of performing a coronary angiography in patients with known CAD.

Elhendy et al. (29) studied the accuracy of stress Tc-99m tetrofosmin myocardial perfusion imaging for the diagnosis and localization of CAD in 88 women: 42 under exercise stress test and 46 under pharmacologic stress with dobutamine-atropine. They reported that overall sensitivity was 83% and specificity was 80%. The sensitivity was 72% in patients with single-vessel disease and 93% in patients with multivessel CAD. Again, we found greater values in our population using dipyridamole; in addition, our sample size was greater.

Our findings (high sensitivity, specificity and predictive values) indicate that myocardial perfusion scintigraphy is a reliable tool for the diagnosis of CAD in women with suspected IHD. Sensitivity and specificity for each coronary artery territory were as follows: left anterior descending (LAD) coronary artery, 71.62% and 76%, respectively; left circumflex (LCx) coronary artery, 69.09% and 76.84%, respectively; right coronary artery (RCA), 87.23% and 74.51%, respectively.

In his study, Elhendy reported that sensitivity and specificity of myocardial perfusion scintigraphy for the diagnosis of CAD in LAD were 82% and 84%, respectively; 74% and 80%, respectively, in the LCx; and 77% and 84%, respectively, in the RCA. Our findings are slightly lower than these values; however, these authors did not consider patients with previous myocardial infarction, coronary artery bypass graft surgery or congestive heart failure. The presence of these factors in our population might have reduced the sensitivity and specificity of the test.

In the study by Rosas et al. (30) 152 consecutive women underwent exercise/rest dual-isotope protocol with Tc-99m sestamibi/201 Tl. The global sensitivity of the test was 95.29%. The sensitivity was 92.10%, 96.2% and 91% in patients with single-vessel, two-vessel and multivessel disease, respectively. Sensitivity for each coronary artery territory was 90.69%, 100% and 85% for LAD, LCx and RCD, respectively. These results are better than ours, yet 91.15% of the patients within this series had abnormal coronary angiography compared to 77.2% in our study.

CONCLUSIONS

Myocardial perfusion scintigraphy with Tc-99m tetrofosmin and dipyridamole using a one day stress-rest protocol has high sensitivity and specificity for the diagnosis of IHD in women. In addition, sensitivity is greater among women with multivessel disease compared to those with single- or two-vessel disease. The diagnostic value of myocardial perfusion scintigraphy is greater in women with suspected IHD undergoing myocardial revascularization after the test and with a stenosis between 50% and 70% in any coronary artery. Finally, the use of dipyridamole as a pharmacologic stressor has improved the diagnostic yield reported by other authors with other stressor agents.

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