Diagnostic Accuracy of Technetium-99m-MIBI Myocardial SPECT in Women and Men

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Noninvasive diagnosis of coronary artery disease in women has some limitations due to a higher percentage of false-positive results. In addition, a lower prevalence of disease can be observed in this population. In this study, we evaluated the diagnostic accuracy of ^{99m}Tc-methoxy-isobutyl-isonitrile (MIBI) SPECT in women and men, in a group of patients with proven coronary artery disease by coronary angiography (select minority) and in all patients where a noninvasive test (silent majority) was performed. **Methods:** Seven hundred and two consecutive patients without previous myocardial infarction were studied with ^{99m}Tc-MIBI myocardial SPECT. One hundred sixty-three patients had coronary angiography (select minority) and 539 did not (silent majority). All patients underwent exercise stress testing, and simultaneous dipyridamole was administered in 32% of patients who did not achieve maximum predicted heart rates. Diagnostic accuracy of the test was calculated for the select minority. Then, sensitivity and specificity of the silent majority were recalculated according to the Diamond criteria. **Results:** Prevalence of coronary artery disease (32% versus 80%, $p = 0.0001$) and peak O_2 consumption achieved in exercise tests (watts, exercise duration) were lower in women. The probability of positive results of ^{99m}Tc-MIBI SPECT also was lower in women (34% versus 65%). The sensitivity of ^{99m}Tc-MIBI SPECT in women of the select minority was lower (85% versus 93%, $p = 0.01$), whereas there was no significant difference for specificity (91% versus 89%). After correcting the results for the silent majority, there were no significant differences in sensitivity (87% versus 88%) and specificity (91% versus 96%) between women and men. These results were not different for patients who achieved maximum predicted heart rates during stress testing (without dipyridamole administration). **Conclusion:** The sensitivity of ^{99m}Tc-MIBI myocardial SPECT in women was lower than in men when only the select minority was considered. When the silent majority was considered (correction of selection bias) sensitivity and specificity results did not differ significantly between the sexes.

Key Words: coronary artery disease; technetium-99m-sestamibi; SPECT; exercise stress test; women

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The diagnosis of coronary artery disease in women has some limitations, mostly related to the underestimation of the pretest probability in the Bayesian analysis of coronary disease and, probably, to the low specificity of the conventional exercise stress test (*1–3*).

Likewise, several authors have mentioned the different treatment of coronary disease between men and women, claiming that female patients benefit less from higher complexity noninvasive studies, coronary angiography, surgery or coronary angioplasty (*4–8*). All the patients studied by noninvasive tests could influence these results (*9–11*).

On the other hand, in ^{201}Tl planar perfusion scintigraphy studies, some difficulties may appear in the interpretation of the images due to the interposition of breast tissue (*12,13*). It is reasonable to suppose that these limitations could be partly overcome by using ^{99m}Tc compounds (*14–16*), with better energetic characteristics that can provide a higher quality tomographical image.

This study aimed to compare the diagnostic accuracy of ^{99m}Tc-methoxy-isobutyl-isonitrile (MIBI) myocardial SPECT between both sexes and assess the influence of analyzing only the patients with coronary angiography (select minority) instead of all of the patients who are submitted to study (silent majority) (*9*).

MATERIALS AND METHODS

Patients

Seven hundred and two consecutive patients (44% women; age range 58 ± 10 yr) without previous myocardial infarction in whom ^{99m}Tc-MIBI SPECT had been performed between January 1992 and March 1995 were selected for this study. Five hundred and thirty-nine of these patients did not have coronary angiography (silent majority) and the other 163 underwent a coronary angiography less than 3 mo before the SPECT images (select minority).

In the group of 163 patients, 63 of them were women (mean age 60 ± 10 yr) and 100 were men (mean age 58 ± 8 yr). No patient had previous infarction, and all of them had symptom-limited exercise stress test ^{99m}Tc-MIBI SPECT. Coronary angiography was performed in all the patients and, under the criterion of the attending clinical cardiologist, less than 3 mo before the isotopical study. In 44% of the patients, the purpose of the study was diagnostic (chest pain suggesting angina and/or nonconclusive exercise ECG) and in 56% it was performed to assess the functional severity of the coronary artery disease in patients with previous angiography. Seventy-two percent of these patients had stable angina and in the other 26% SPECT was ordered during their hospitalization within three or more days after the stabilization of an unstable angina. No patient had left bundle branch block or presented with valvular heart disease or cardiomyopathy.

Exercise Test

All patients underwent a symptom-limited exercise test on a bicycle ergometer, with an initial 50-W load and 25-W consecutive increments every 3 min until exhaustion, symptoms or > 2 mm ST-segment depression appeared. By the time of the test performance, 73 patients were receiving beta-blockers (46%), 76 calcium channel blockers (48%) and 82 nitrates (52%).

Intravenous dipyridamole (0.14 mg/kg/min) was administered simultaneously with the test performance to 72 (35% women) of the 163 select minority patients and 167 (32% women) of the 539 silent majority patients who performed an insufficient exercise stress test (< 5 METs, peak heart rate < 80%, without angina or ST-segment depression > 1 mm) (*17*).

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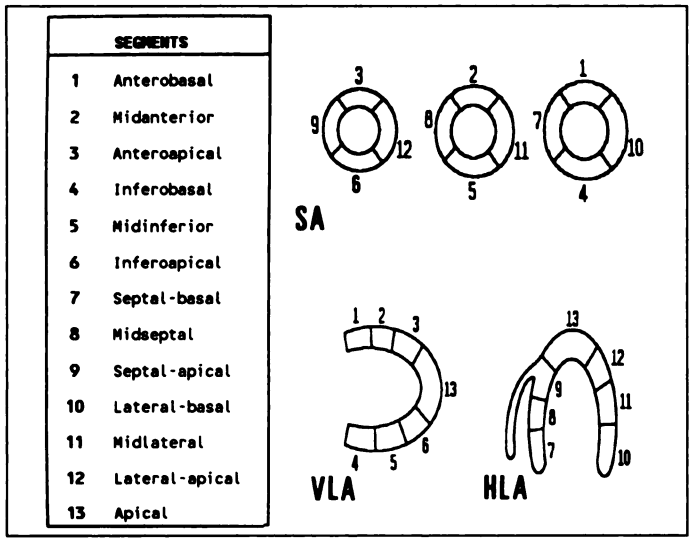

FIGURE 1. Scheme of the 13 segments in which the left ventricle was divided in the sections of the short axis (SA), vertical long axis (VLA) and horizontal long axis (HLA).

Technetium-99m-MIBI SPECT

All patients received an intravenous dose of ^{99m}Tc-MIBI (15 mCi) between 30 and 60 sec before ending the exercise test. For the rest study, which was performed at least 24 hr after imaging the exercise stress test, the same dose was administered. In both studies, acquisition was performed 1 hr after tracer injection. Images were acquired with an Elscint SP4 (Haifa, Israel) scintillation camera equipped with a high-resolution collimator and 180° semicircular orbit, starting at 30° right anterior oblique and detections every 3°. Images were reconstructed (order 5 Butterworth filter, section frequency 0.4) and short-axis, horizontal long-axis and vertical long-axis sections were obtained according to the current recommendations (*18*).

Myocardial uptake was assessed by consensus of three expert observers who were unaware of coronary angiography results. Thirteen segments for each patient were evaluated: anterobasal, midanterior, anteroapical, septal-basal, midseptal, septal-apical, inferobasal, midinferior, inferoapical, lateral-basal, midlateral, lateral-apical and apical (Fig. 1). Each of these segments was assessed during the stress and rest studies in accordance with the following scale: normal, equivocal or minimal defect, mild defect, moderate defect and severe defect (similar to the background uptake). The SPECT image was considered positive whenever there was a mild, moderate or severe defect in at least two of three axes or three consecutive tomographic sections of the same axis, with reversibility at rest (*19*). Since this population did not have a previous infarct, nonreversible defects were attributed to artifacts.

Cardiac Catheterization

The 163 select minority patients underwent cardiac catheterization. The procedure included ventriculography and coronary angiography, using standard Seldinger's technique, within less than 3 mo after the SPECT study. At least four projections were performed (ortogonal 2 × 2) for the left coronary artery and two projections (ortogonal) for the right coronary artery. Two expert observers, without any knowledge of the scintigraphic results, made a visual assessment of the coronary stenoses severity. Stenoses > 50% were considered significant lesions.

Statistical Analysis

Mean ± 1 s.d. for quantitative data and absolute and relative frequencies for categorical data were used for data description. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy for SPECT were calculated globally and by gender. Chi-square testing was used to compare the results between these groups.

TABLE 1
Clinical Characteristics and Results of Exercise Testing and Coronary Angiography in Women and Men

	Women (n = 63)		Men (n = 100)
Treatment			
Beta-blockers	21 (33%)		42 (42%)
Calcium channel blockers	25 (40%)		50 (50%)
Nitrates	28 (44%)		59 (59%)
Exercise test			
Peak heart rate	117 ± 29		114 ± 26
Watts	53 ± 29	p=0.04	77 ± 25
Duration (min)	6.8 ± 2	p=0.004	7.8 ± 3
Heart rate × SBP	19220 ± 62		19920 ± 68
% Heart rate	73 ± 16		70 ± 15
SBP	162 ± 24		171± 28
METs	4.5 ± 1.5		5.5 ± 1.7
↓ ST > 1 mm	12 (19%)	p=0.04	39 (39%)
↓ ST > 0.5 < 1 mm	8 (13%)		10 (10%)
↓ ST (mm)	0.3 ± 0.7		0.5 ± 0.7
Angina	18 (29%)		39 (39%)
Dipyridamole	25 (40%)		47 (47%)
Cardiac catheterization			
Ejection fraction (%)	66 ± 10		63 ± 9.9
Normal coronary arteries	43 (68%)	p=0.0001	20 (20%)
One-vessel disease	4 (6%)		19 (19%)
Two-vessel disease	10 (16%)		27 (27%)
Three-vessel disease	6 (10%)	p=0.004	34 (34%)

SBP = systolic blood pressure.

The corrections proposed by Diamond (*9*) were used for sensitivity and specificity correction, taking into account the probability of positive results in the silent majority as follows:

$$\text{Sensitivity} = \text{PRP} \times \text{PPV}/(\text{PRP} \times \text{PPV}) + [\text{Co NPV} \times (1 - \text{PRP})]$$

$$1 - \text{Specificity} = \text{PRP} \times \text{Co PPV} \,/\, (\text{PRP} \times \text{Co PPV}) + [\text{NPV} \times (1 - \text{PRP})]$$

$$\text{PPV} = \text{TP} \,/\, \text{TP} + \text{FP}$$

$$\text{Co PPV} = \text{FP} \,/\, \text{FP} + \text{TP}$$

$$\text{NPV} = \text{TN} \,/\, \text{TN} + \text{FN}$$

$$\text{Co NPV} = \text{FN} \,/\, \text{FN} + \text{TN}$$

$$\text{PRP} = \text{positive results} \,/\, \text{total population}$$

$$\text{Accuracy} = \text{TP} + \text{TN} \,/\, \text{total population}, \qquad \text{Eq. 1}$$

where PRP = positive result probability; PPV = positive predictive value; NPV = negative predictive value; Co PPV = complementary positive predictive value; Co NPV = complementary negative predictive value; TP = true-positives; TN = true-negatives; FP = false-positives; and FN = false-negatives.

RESULTS

Table 1 shows the treatment as well as the ergometric and catheterization parameters from the select minority group composed of 63 women and 100 men. The duration of the test and the maximal load achieved were lower in the group of women in relation to that of men (6.8 ± 2 versus 7.8 ± 3 min, p =

TABLE 2
Diagnostic Accuracy of Exercise Test in Select Minority

	Sensitivity	Specificity	PPV	NPV	Accuracy
Global	67% (58–76)	71% (58–82)	79% (69–87)	57% (45–68)	69% (62–76)
Women	60% (36–81)	67% (51–81)	46% (27–67)	78% (62–90)	65% (52–77)
Men	69% (58–79)*	79% (54–94)†	93% (84–98)‡	38% (23–54)§	71% (61–80)

*p = 0.02.
†p = 0.03.
‡p = 0.003.
§p = 0.009 vs. women.
Data are expressed as mean value with 95% confidence interval in parentheses. PPV = positive predictive value; NPV = negative predictive value.

0.004, and 53 ± 29 versus 77 ± 35 W, p = 0.04 respectively). Furthermore, the percentage of patients with ST-segment depression > 1 mm was lower in the group of women with regard to the group of men (19% versus 39%, p = 0.04). This would be in relation to the lower prevalence of coronary artery disease in the group of women as compared with that of men (32% versus 80%, p = 0.0001).

Eighty-six patients (53%) had > 50% stenosis in the anterior descending artery, 71 (44%) in the right coronary artery and 61 (37%) in the circumflex. A lower percentage of women with three-vessel disease was observed (10% versus 34%, p = 0.004).

Table 2 shows the diagnostic accuracy of the conventional exercise stress test in all the patients who had coronary angiography (select minority) and in men and women. In the exercise test, the results of sensitivity (p = 0.02), specificity (p = 0.03) and PPV (p = 0.003) were significantly better in men. The NPV was significantly higher in women than in men (p = 0.009).

Moderate or severe nonreversible perfusion defects were not found in any patients from the series. Table 3 shows the positive and negative results of SPECT in both the silent majority and select minority. More men than women were studied (56% versus 44%, p = 0.006), and the percentage of positive tomographic studies was significantly higher in men, both in the silent majority (65% versus 34%, p < 0.0001) and in the select minority (77% versus 33%, p = 0.005).

Sensitivity (93% versus 85%, p = 0.01) and positive predictive value (97% versus 81%, p = 0.005) of SPECT images were significantly better in men when only select minority was considered (Table 4). The NPV was higher, however, in women (93% versus 74%, p = 0.003).

Since these results may be influenced by the higher prevalence of coronary disease in men compared to women, and the different percentage of positive tests in patients of both sexes who were not catheterized, the correction for the silent majority proposed by Diamond (*9*) was used on the SPECT images.

SPECT images in women: TP= 17; TN = 39; FP = 4; and FN = 3.

$$SEN = 0.34 \times 0.80 \;/\; ((0.34 \times 0.80) + (0.07 \times (1 - 0.34)) = 87\% \quad \text{Eq. 2}$$

$$SPE = 0.34 \times 0.19 \;/\; ((0.34 \times 0.19) + (0.92 \times (1 - 0.34)) = 91\%,$$

SPECT images in men: TP = 75; TN = 17; FP = 2; and FN = 6.

$$SEN = 0.65 \times 0.97 \;/\; ((0.65 \times 0.97) + (0.26 \times (1 - 0.65)) = 88\% \quad \text{Eq. 3}$$

$$SPE = 0.65 \times 0.02 \;/\; ((0.65 \times 0.02) + (0.74 \times (1 - 0.65)) = 96\%$$

where SEN = sensitivity; SPE = specificity; TP = true-positives; TN = true-negatives; FP = false-positives; NF = false-negatives.

Figure 2 shows the sensitivity and specificity results with and without correction according to the these criteria. It can be observed that once the Diamond (*9*) correction for the silent majority had been applied, no significant differences were noticed between men and women.

Similar results were found when patients who had needed dipyridamole injection were excluded. In these patients, sensitivities of 83% for women and 94% for men from the select minority changed to 93% and 90%, respectively, after Diamond correction (*9*). Specificities changed from 95% in women and 92% in men to 95% and 96%, respectively.

TABLE 3
Positive and Negative Results of Technetium-99m-MIBI SPECT in Silent Majority and Select Minority

	Silent majority		Select minority		
	+	−	+	−	Total
Global	274 (51%)	265 (49%)	98 (60%)	65 (40%)	702 (100%)
Women	83 (34%)	161 (66%)	21 (33%)	42 (67%)	307 (44%)
Men	191 (65%)*	104 (35%)†	77 (77%)‡	23 (23%)§	395 (56%)¶

*p < 0.0001.
†p = 0.0001.
‡p = 0.005.
§p = 0.001.
¶p = 0.006 vs. women.

TABLE 4
Diagnostic Accuracy of Technetium-99m-MIBI SPECT in Select Minority

	Sensitivity	Specificity	PPV	NPV	Accuracy
Global	91% (84–96)	90% (80–96)	94% (87–98)	86% (75–93)	91% (85–95)
Women	85% (62–97)	91% (78–97)	81% (58–94)	93% (80–98)	89% (81–97)
Men	93% (87–98)*	89% (67–99)	97% (91–99)†	74% (56–92)‡	92% (87–97)

*p = 0.01.
†p = 0.005.
‡p = 0.003 vs. women.
Data are expressed as mean value with 95% confidence interval in parentheses. PPV = positive predictive value; NPV = negative predictive value.

DISCUSSION

Different studies (*1–3*) have shown that the conventional exercise test can be less efficient in the diagnosis of coronary disease in women than in men. More false-positive results have been reported in women, therefore, the specificity of the conventional exercise test can be lower (*20–21*). Iskandrian et al. (*15*) observed that the PPV of the ST-segment depression was lower in women (47% versus 77%, $p < 0.05$). In our series, we have observed that specificity, sensitivity and PPV of the conventional exercise test are significantly lower in women (Table 2), while the NPV is higher.

On the other hand, lower specificity of perfusion planar scintigraphy also has been described in women due to the false-positive results in the anterior region that are attributable to attenuations by mammary interposition (*1,3,12,15,22*). Even quantitative tomography with ^{201}Tl has demonstrated lower uptake in the anterior region in women (*23,24*).

For these reasons, we intended to assess the diagnostic accuracy of myocardial ^{99m}Tc-MIBI SPECT in women and men using our current methodology and interpretation criteria for patient care. On the other hand, taking into account the bias introduced when selecting more men than women for the catheterization study, we evaluated not only those patients who underwent coronary angiography (select minority) but also the population studied with myocardial SPECT during the same period of time, even though they did not have coronary angiography (silent majority).

Diagnostic Accuracy of SPECT in Select Minority

Sensitivity and specificity results obtained with ^{201}Tl (*25,26*) or ^{99m}Tc SPECT (*27,28*) are clearly higher than those of the planar scintigraphy. In our series, using ^{99m}Tc-MIBI SPECT, there were no significant differences in the specificity between men and women in those patients who had undergone angiography (Table 4). In our series, the rate of women who had normal coronary arteries in angiography was high (68%). This may be explained because angiography had been indicated for chest pain suggesting angina and/or nonconclusive exercise ECG irrespective of the scintigraphic results. With the methodology and criteria used (equivocal or minimal nonreversible defects were considered negative), the number of true-negative results was high and we did not observe a higher number of false-positive results in the anterior region in women. This finding is probably related to the higher energy and penetration of ^{99m}Tc compared with ^{201}Tl, and is in agreement with Taillefer et al. (*29*).

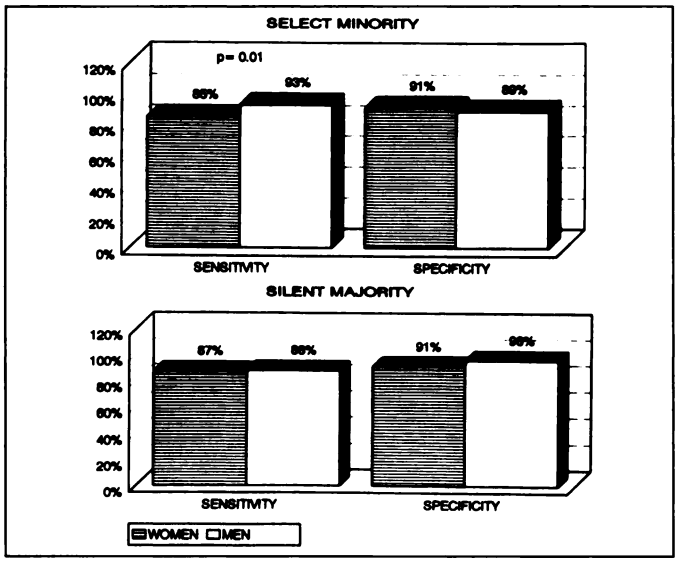

FIGURE 2. Sensitivity and specificity results of ^{99m}Tc-MIBI SPECT by gender in the select minority and the silent majority.

However, the sensitivity of SPECT in women (85%) in our series was lower than that of men (93%) (Table 4). This fact could be explained by the lower prevalence of three-vessel disease in women and by lower peak O_2 consumption achieved by them during the exercise, even in women who achieved a sufficient exercise level (*30*).

The percentage of women with angiography in the global group was clearly lower than that of men (9% versus 14%). On the other hand, the presence of positive scintigraphic studies was higher in men than in women, both in the silent majority (65% versus 34%) and the select minority (77% versus 33%) (Table 3).

Diagnostic Accuracy of SPECT in Silent Majority

The lower percentage of positive results in women, due to the lower prevalence of disease, and the lower number of women in whom angiography was performed is a common feature of different reports (*31,32*). Thus, Shaw et al. (*33*) in a series of 840 patients (47% women) with suspected coronary artery disease in whom the less complex initial studies (exercise test and ^{201}Tl planar scintigraphy) were performed similarly in men and women (22% versus 19%), coronary angiography was indicated with a higher frequency in men (62% versus 38%, $p < 0.01$). Lauer et al. (*34*), in a series of 2351 men and 1318 women studied with ^{201}Tl perfusion scintigraphy, also found that fewer coronary angiography studies were performed in women than in men (6% versus 14%) and that the severity of coronary disease and the prevalence of positive studies was higher in men (29% versus 8%).

The correction methodology for the silent majority described by Diamond (*9*) is based on the application of Bayes's theorem to the sensitivity and specificity values. It is habitually accepted that both values are fixed and that the observed variations in the PPV and NPV are due to the use of the test in populations with different disease prevalences. Thus, the Bayesian approach is used to obtain the corrected values for the PPV and NPV according to prevalence (*35*). Nevertheless, it is also known that the variability of sensitivity and specificity are not only due to

the technical characteristics or the use of several assessment criteria of a diagnostic test, but also to the probability of a test positive result in a certain population sample (*11*). The approach by Diamond (*9*) of the Bayesian analysis to calculate sensitivity and specificity uses the known diagnostic efficiency of a test in the select minority, which has been checked with a gold standard, to the silent majority, which is assessed with the test and where real disease prevalence is unknown. In this broad group of patients it is possible to estimate the PRP which, ideally, will be very similar to the prevalence. From the comparison of the PRP between the select minority and the silent majority, we can obtain a first approach to the test capacity for selecting patients who will be evaluated against the gold standard.

Through the formulation propounded by Diamond (*9*), and despite its possible limitations (*36*), the sensitivity and specificity calculation weighted by the PRP of the global population to whom the test is applied probably allows better estimation of its real diagnostic efficiency. For ^{99m}Tc-MIBI SPECT, this kind of analysis shows that its efficiency may be similar in men and women when the whole population is considered, not only the patients who undergo angiography. The higher PRP, linked to the higher prevalence of coronary disease in men, conditions a post-test selection bias that leads to a higher proportion of men who undergo coronary angiography studies. Finally, it seems that the speculations about the technical limitations of SPECT in women have little effect, if at all, on its diagnostic efficiency, at least in our population, and only statistical aspects related to the population selection cause the moderate difference in the observed sensitivity value.

CONCLUSION

Our results suggest, on the basis of Diamond (*9*) correction, that the diagnostic accuracy of ^{99m}Tc-MIBI SPECT is globally satisfactory and that the lower sensitivity observed in women, whenever only the population undergoing angiography is considered, ranks equally with that of men, when the majority who do not undergo coronary angiography are considered.

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