JACC Vol. 28, No. 5
November 1, 1996:1214–9

Lower Diagnostic Accuracy of Thallium-201 SPECT Myocardial Perfusion Imaging in Women: An Effect of Smaller Chamber Size

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Objectives. **We attempted to formally compare the diagnostic accuracy of thallium-201 single-photon emission computed tomographic (SPECT) myocardial perfusion imaging in men and women and the effect of chamber size on accuracy.**

Background. **The diagnostic accuracy of conventional exercise testing has been shown to be lower in women. Less is known about the relative accuracy of perfusion imaging. Because of smaller body size, women have a smaller heart size than men, a factor that may reduce accuracy.**

Methods. **We identified 323 patients undergoing thallium-201 SPECT myocardial perfusion imaging who either had <5% probability of coronary artery disease (CAD) by Bayesian analysis or who underwent cardiac catheterization within 60 days of stress testing. Patients with documented history of infarction, coronary artery bypass grafting, pathologic Q waves on the electrocardiogram, left bundle branch block or nonischemic cardiomyopathy were not included. We performed strict quantitative analysis, and receiver operating characteristic (ROC) curves were generated and the area under the curve was calculated for men and women. A size index was generated from the number of short-axis slices and average radius of each slice, and the group was classified as having a large or a small chamber size. The ROC areas of men and women with a large and a small chamber size were then compared.**

Results. **Diagnostic accuracy was lower in women than in men (ROC area 0.82 vs. 0.93, $p < 0.05$) despite similar values for peak heart rate and rate-pressure product and similar severity of CAD. There was a greater difference in accuracy between patients with a large versus a small chamber size (ROC area 0.94 vs. 0.73, $p < 0.01$) despite similar levels of exercise and severity of CAD. When we compared men and women in groups stratified by chamber size, we could not detect a significant difference between ROC area values of men and women (large: 0.94 men, 0.93 women, $p = 0.77$, power to detect difference in area of 0.15 = 91%; small: 0.79 men, 0.72 women, $p = 0.58$, power to detect difference in area of 0.15 = 35%).**

Conclusions. **The diagnostic accuracy of thallium SPECT myocardial perfusion imaging is lower in women than in men. Most of the difference appears to be due to smaller left ventricular chamber size in women, although a small residual gender effect in smaller heart sizes cannot be entirely excluded. It is proposed that the most likely cause for this difference is the relatively greater effect of imaging blurring on smaller hearts.**

(J Am Coll Cardiol 1996;28:1214–9)

Cardiovascular diseases are the leading cause of death in women in the United States; the total mortality rate is slightly higher than in men (1). Therefore, clinicians need to be aware of the relative strengths and weaknesses of the available noninvasive tests for the diagnosis of coronary artery disease (CAD) in women. The lower accuracy of conventional stress testing in women has been appreciated for some time (2,3). The relative accuracy of perfusion imaging in women is less certain. Women have a smaller body surface area than do men and thus have a smaller average heart size, which may affect accuracy. The purpose of this study was to formally compare the diagnostic accuracy of myocardial perfusion imaging in men and women and to assess the effects differences in chamber size have on accuracy.

Receiver operating characteristic (ROC) curve analysis has been borrowed from information theory and applied to medical decision making (4–6). Each point on the ROC curve represents the sensitivity and specificity (or, as it is usually plotted, the false positive rate which is 1 − specificity) for a given decision threshold. The decision threshold is made more and more lenient by moving to the right, which increases sensitivity and decreases specificity. An ROC curve thus demonstrates the tradeoff between sensitivity and specificity over the entire range of decision thresholds and provides more information about test accuracy than are provided by isolated values for sensitivity and specificity. The most commonly used variable from ROC analysis is the area under the ROC curve. An intuitive interpretation of this variable is that it is equal to the probability that a diagnostic test can correctly differentiate randomly paired normal and abnormal cases (6).

From the Section of Cardiology, Temple University Hospital, Philadelphia, Pennsylvania. Preliminary results of this study were presented at the 44th Annual Scientific Session of the American College of Cardiology, New Orleans, Louisiana, March 1995.

Manuscript received March 19, 1996; revised manuscript received May 30, 1996, accepted June 17, 1996.

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0735-1097/96/$15.00
PII S0735-1097(96)00304-X

Abbreviations and Acronyms

CAD = coronary artery disease
ECG = electrocardiogram
METs = metabolic equivalents
ROC = receiver operating characteristic
SPECT = single-photon emission computed tomography

Methods

Patients studied. We identified 323 patients undergoing maximal stress testing with thallium-201 SPECT myocardial perfusion imaging who fit into one of two groups. The first group consisted of patients with <5% probability of CAD by Bayesian analysis (7); these patients were classified as normal subjects. The second group consisted of consecutive patients who had no documented history of myocardial infarction, pathologic Q waves on electrocardiogram (ECG), history of coronary artery bypass grafting, left bundle branch block or evidence of nonischemic cardiomyopathy and who underwent cardiac catheterization within 60 days of exercise testing; these were classified as patients. The patients exercised with use of either a Bruce or a modified Bruce protocol. End points of exercise were limiting fatigue, worsening chest pain, >3-mm horizontal or downsloping ST segment depression and arrhythmia. The patients received 3 to 3.5 mCi of thallium-201 and were imaged on a single-head General Electric Starcam camera using a low energy all purpose collimator. Thirty-two images were acquired for 40 s each over a standard 180° orbit. The coronary angiograms were read by two experienced observers; stenosis ≥50% was considered significant. Patients with <50% stenosis of any coronary artery were reclassified as normal subjects.

Twenty men and 20 women from the normal group were used to create gender-based normal data bases. The remaining 283 patients and normal subjects underwent quantitative analysis. The analysis software for this study was written in C and has been previously described (8,9). The images were reconstructed by using filtered back-projection and a Ramp-Hanning filter with a cutoff of 100% of the Nyquist frequency.

ROC analysis. The area under the ROC curve and its SE were calculated for men and women by using a modification of the Dorfman maximal likelihood technique (4). To assess a range of threshold criteria, the fraction of the left ventricle falling below 1, 2, 2.5, 3 and 4 SD from the mean of the gender-based normal data base was calculated for each of the studies. A study was considered abnormal if, at the given number of SD, >5% of the left ventricular mass fell below the threshold. A size index, which incorporated pixel size, was then generated from the number of short-axis slices and the average radius of each slice. A size index <75 was empirically chosen as representing a small chamber. ROC analysis was performed on large and small chamber sizes and again for large and small chamber sizes grouped by gender.

Exercise capacity was estimated by the duration of exercise and reported in metabolic equivalents (METs). The maximal amount of horizontal and downsloping ST segment depression was recorded. The Gensini score was calculated from the location and severity of the coronary lesions (10). Because the Bayesian process for selecting low probability patients biases toward younger patients who have achieved higher exercise levels on testing, demographic and exercise variables for the normal subjects were not reported, except as noted.

Statistical methods. Variables were compared by a two-tailed Student *t* test. The significance in the difference between the areas of two ROC curves was calculated by the critical ratio (4,6). A p value < 0.05 was considered significant.

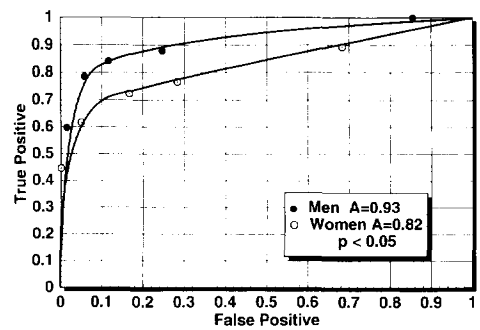

Figure 1. The receiver operating characteristic (ROC) curves are plotted for men and women. Each point represents the true positive and false positive rate using quantitative analysis and successively more stringent criteria. Differences in the area under the ROC curves (A) show that the diagnostic accuracy of perfusion imaging is significantly lower in women than in men.

Results

There were 129 normal subjects (60 women, 69 men) and 154 patients with CAD (47 women, 107 men). Left ventricular size (normal subjects and patients) was significantly larger in men than in women (99 ± 30 vs. 74 ± 23, $p < 0.001$). Sixty-seven percent of the women had a chamber identified as small versus only 20% of the men. Heart size was significantly larger in patients (men and women) than in normal subjects (100 ± 34 vs. 77 ± 16, $p < 0.001$).

Diagnostic accuracy by patient gender. The diagnostic accuracy of quantitative SPECT thallium, as determined by area under the ROC curve, was significantly higher in men than in women (0.93 vs. 0.82, $p < 0.05$, Fig. 1). This difference could not be explained by differences in exercise-induced changes in coronary blood flow or in severity of underlying disease. Although men exercised to a higher level of maximal oxygen consumption, the variables reflecting coronary blood flow—peak heart rate, percent maximal predicted heart rate and peak rate-pressure product—showed no significant difference (Table 1). Also, there was no significant difference in severity of CAD between men and women as judged by either the average number of diseased vessels (1.9 in men vs. 1.8 in women, $p = 0.30$) or the Gensini score. However, men with CAD had more ST segment depression than did women.

Table 1. Clinical, Exercise and Catheterization Variables for All Patients (154 men and women with coronary artery disease undergoing catheterization)

Variable	Women (n = 47)	Men (n = 107)	p Value
Clinical			
Age (yr)	61 ± 9	60 ± 11	0.77
BSA (m^2)	1.78 ± 0.20	1.99 ± 0.19	< 0.001
Exercise			
Peak heart rate (beats/min)	133 ± 21	134 ± 20	0.92
%MPHR	82 ± 12	78 ± 11	0.12
RPP/1,000	22.7 ± 5.7	22.4 ± 4.8	0.8
Mvo_2 (METs)	4.5 ± 2.3	6.8 ± 3.0	< 0.001
ST↓ (mm)	0.7 ± 0.8	1.1 ± 1.0	0.004
Catheterization			
Stenosed vessels (no.)	1.8 ± 0.8	1.9 ± 0.8	0.30
Gensini score	32 ± 32	32 ± 28	0.99

Data are presented as mean value ± SD. Men and women had similar exercise-induced increases in coronary blood flow and similar severity of disease. BSA = body surface area; Mvo_2 = estimated maximal oxygen consumption in metabolic equivalents (METs); %MPHR = percent of maximal predicted heart rate achieved; RPP = rate-pressure product at peak exercise; ST↓ = ST segment depression.

Table 2. Clinical, Exercise and Catheterization Variables for All 154 Patients, Classified According to Large Versus Small Chamber Size

	Chamber Size		
Variable	Large (n = 116)	Small (n = 38)	p Value
Clinical			
Age (yr)	60 ± 11	63 ± 9	0.10
BSA (m^2)	1.97 ± 0.20	1.79 ± 0.20	< 0.001
Exercise			
Peak heart rate (beats/min)	134 ± 21	134 ± 19	0.99
%MPHR	78 ± 12	81 ± 11	0.26
RPP/1,000	22.5 ± 5.2	22.6 ± 4.8	0.91
Mvo_2 (METs)	6.2 ± 3.1	5.9 ± 2.8	0.54
ST↓ (mm)	1.1 ± 1.0	0.8 ± 0.9	0.10
Catheterization			
Stenosed vessels (no.)	1.9 ± 0.8	1.8 ± 0.8	0.27
Gensini score	32 ± 29	31 ± 30	0.84

Data are presented as mean value ± SD. There were similar exercise-induced increases in coronary blood flow and similar severity of disease. Abbreviations as in Table 1.

Diagnostic accuracy by chamber size. There was a greater and much more significant difference between the area under the ROC curve for all patients (men and women) with a large chamber versus all patients with a small chamber (0.94 vs. 0.73, $p < 0.01$, Fig. 2). This marked difference in diagnostic accuracy could not be explained by differences in coronary blood flow with exercise or by the severity of the underlying CAD. Patients with large and small chamber sizes had comparable peak heart rates, percent of maximal predicted peak heart rates, rate-pressure products, average number of stenosed vessels and Gensini scores (Table 2). There was a trend toward more ST segment depression with large chambers.

When we compared men and women after correcting for chamber size, there was no longer any significant difference between them. The ROC curve areas for men and women with a large chamber were virtually identical (0.94 vs. 0.93, $p = 0.77$, Fig. 3). There were no significant differences in the exercise or catheterization variables between men and women with a large chamber (Table 3). When men and women with a small chamber were compared, there was also no significant gender difference (0.79 vs. 0.72, $p = 0.58$, Fig. 4). The power to detect a difference in ROC area of 0.15 was 91% in the large hearts but only 35% in the small hearts. Although there were more stenosed vessels in the men than in the women with a small chamber, the difference in Gensini score was not significantly different (Table 4).

Discussion

The results of this study show that by using strict quantitative criteria, the diagnostic accuracy of SPECT myocardial perfusion imaging is greater in men than in women and that this difference appears to be primarily due to differences in chamber size. Smaller chamber size has a major detrimental impact on diagnostic accuracy; women are more likely to have

Figure 2. Format as in Figure 1. ROC analysis performed on large versus small chambers demonstrates that chamber size results in a greater difference in diagnostic accuracy than does gender.

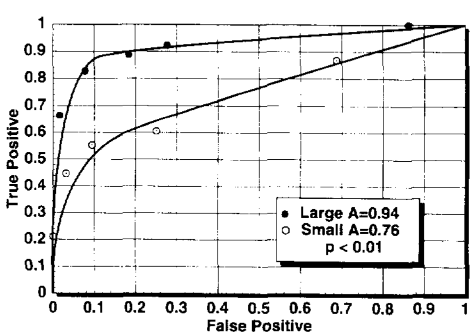

Figure 3. Format as in Figure 1. When men and women with a large chamber size are compared, there is no longer a gender-based difference in diagnostic accuracy.

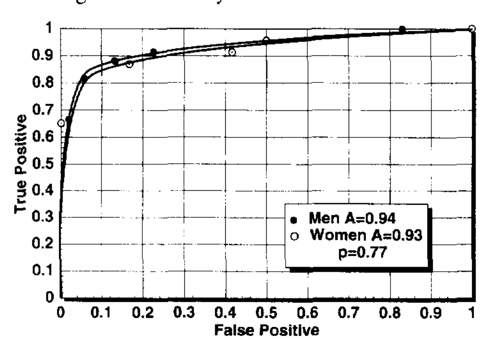

Table 3. Clinical, Exercise and Catheterization Variables for 116 Men and Women With a Large Chamber Size

Variable	Women (n = 23)	Men (n = 93)	p Value
Clinical			
Age (yr)	60 ± 10	60 ± 11	0.89
BSA (m^2)	1.84 ± 0.21	2.00 ± 0.18	0.001
Exercise			
Peak heart rate (beats/min)	134 ± 23	133 ± 20	0.95
%MPHR	82 ± 12	78 ± 12	0.19
RPP/1,000	23.2 ± 6.1	22.3 ± 5.0	0.49
MVo_2 (METs)	3.8 ± 1.5	6.8 ± 3.1	< 0.001
ST↓ (mm)	0.7 ± 0.8	1.2 ± 1.0	0.02
Catheterization			
Stenosed vessels (no.)	2.1 ± 0.8	1.9 ± 0.8	0.18
Gensini score	37 ± 33	31 ± 28	0.38

Data are presented as mean value ± SD. Abbreviations as in Table 1.

Table 4. Clinical, Exercise and Catheterization Variables for 38 Men and Women With a Small Chamber Size

Variable	Women (n = 24)	Men (n = 14)	p Value
Clinical			
Age (yr)	62 ± 8	64 ± 10	0.36
BSA (m^2)	1.73 ± 0.17	1.91 ± 0.22	0.01
Exercise			
Peak heart rate (beats/min)	133 ± 21	135 ± 17	0.76
%MPHR	82 ± 13	80 ± 9	0.70
RPP/1,000	22.2 ± 5.3	23.2 ± 3.8	0.48
MVo_2 (METs)	5.2 ± 2.8	7.1 ± 2.4	0.03
ST↓ (mm)	0.7 ± 0.9	1.0 ± 0.9	0.31
Catheterization			
Stenosed vessels (no.)	1.5 ± 0.7	2.3 ± 0.8	0.002
Gensini score	27 ± 31	38 ± 28	0.27

Data are presented as mean value ± SD. Although there is a slightly higher average number of stenosed vessels in men, there is no significant difference in Gensini score. Abbreviations as in Table 1.

a smaller chamber size because of their smaller body surface area.

We could find no significant difference in the ROC areas between men and women when they were further classified by size, although the power of the study to exclude a small difference in the subgroup with small hearts was lower. In this group, the ROC area was slightly higher in men. They had slightly more stenosed vessels and a slightly higher Genisini score, though only the difference in the number of stenosed vessels was significant (Table 4). However, because the power was lower in the group with smaller hearts, a small residual gender effect cannot be excluded with certainty in this group.

Because chamber size tends to enlarge after infarction, it could be argued that selecting patients by chamber size biases toward more severe CAD. We corrected for this by excluding patients with documented infarction or pathologic Q waves on their ECG. Although patients had a larger heart size than did normal subjects, there was no significant difference in severity of disease between patients with a large versus a small heart (Table 2). Our choice of the cutoff point between large and small heart size was somewhat arbitrary and dictated by the sample we had. Moving this point up or down by small amounts did not change our results. Moving it further resulted in inadequate sample sizes for analysis. The cutoff point we chose is close to the mean value of the chamber size in women.

Figure 4. Format as in Figure 1. When men and women with a small chamber size are compared, there is no significant gender difference between the areas of the two curves.

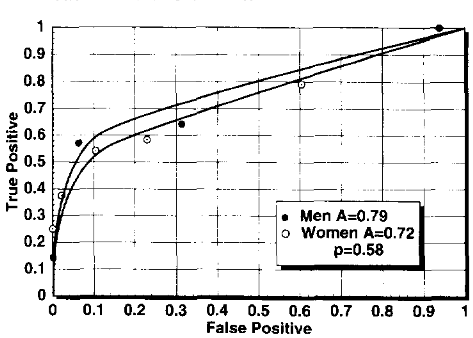

Image blurring and possible solutions. In a preliminary report of these data (11), we proposed that the difference in diagnostic accuracy between large and small chamber sizes was due to the combined blurring effects of imaging the isotope and filtered back-projection. The spatial resolution of thallium-201 at depth is ~1.5 to 2 cm. Motion, occurring from the contraction of the heart and respiration, increases blurring. The mathematic process of filtered back-projection causes additional blurring of the reconstructed image. A coronary lesion in a small chamber is more likely to produce a defect that is too small to be identified by the imaging system than is a proportional lesion in a patient with a larger chamber size.

Several procedures to compensate or correct for this blurring may be useful in increasing the accuracy of perfusion imaging in patients with a small chamber size. All-purpose collimators were used in this study; high resolution collimators could conceivably increase accuracy. The creation of normal limits based on chamber size or on both size and gender could be considered. The mathematic description of the blurring process involves what is known as the line spread function. There is a class of filters, which includes the Metz and Wiener filters, that employ the inverse of the line spread function to correct for blurring (12,13). Although they have been used in other forms of imaging, their utility in myocardial perfusion imaging has not been fully explored. In our experience, the ability to use deconvolving filters with thallium-201 SPECT images is limited by the relatively low count rates obtained with this isotope.

It is possible that technetium-based myocardial perfusion agents would not have the same loss in diagnostic accuracy in small hearts. They employ a higher energy isotope and thus have less intrinsic scatter and blurring than thallium-201.

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Clinical studies to date have shown no significant difference in diagnostic accuracy between technetium perfusion agents and thallium (14–16), though none of these studies has addressed the specific problem of small chamber size. Technetium-based perfusion agents have higher count rates than thallium because their photons have a higher energy level, and the shorter half-life of technetium-99m allows administration of higher doses. The higher count rate of the technetium-based agents may make them more amenable to deconvolving filters. Also, a higher count rate makes image gating more practical, a factor that could reduce the blurring introduced by cardiac motion.

Other possible areas for improvement would be the use of image matrixes with a higher resolution, such as 128×128 or even greater. The standard 64×64 matrix size was established >10 years ago, when the cost of memory and slow computation speeds made higher resolution images impractical. Camera designs that are specific for cardiac applications may permit higher amounts of hardware or software zooming without causing truncation artifacts.

Previous investigations. Not much research has been done comparing the accuracy of thallium perfusion imaging in men and women. Two small early studies suggested that the diagnostic accuracy of planar thallium perfusion imaging was similar (17,18). Hung et al. (19) showed that thallium-201 scintigraphy improved the diagnostic accuracy of stress testing in women but did not directly compare results between women and men. Kong et al. (20) reported comparable sensitivity and specificity between men and women for dipyridamole thallium-201 imaging. Morise and associates (21), using logistic analysis and ROC curves, reported equal incremental increases in diagnostic accuracy for men and women but did not specifically compare the accuracy of thallium between them. Chae et al. (22), in a report that evaluated the ability of SPECT thallium imaging to identify high risk subgroups of women, referred to unpublished data from their group that showed decreased accuracy of thallium perfusion imaging in women.

We found that men with CAD had more ST segment depression than did women. These results agree with data from other investigators (2,3), who reported lower diagnostic accuracy of ST changes in women. Our results are not definite, but they suggest that the difference in ST segment depression between men and women cannot be explained solely by chamber size.

Effects of blurring versus attenuation. It has long been assumed that breast attenuation is the major limiting factor of the accuracy of thallium-201 perfusion imaging in women. Readers of perfusion images are frequently challenged by defects that appear to be due to breast artifact; most readers learn how to "read around" these defects (18,23). The results of this study showed no significant difference in accuracy between men and women after correcting for chamber size, which suggests that breast attenuation artifact was not a major problem in our study. In our experience, most breast artifact tends to create defects that are mild, and mild defects should have only a modest effect on the area under the ROC curve. Diaphragmatic attenuation is more severe in men (24). It is possible that the utilization of gender-based normal data bases corrected for this difference so that the effect on accuracy of breast attenuation in women was equal to the effect of diaphragmatic attenuation in men. If, as the results of this study suggest, blurring has a greater effect on accuracy than on attenuation, the hoped for increase in diagnostic accuracy from the recent introduction of attenuation-correction algorithms might not be realized (25,26).

Conclusions. The diagnostic accuracy of quantitative SPECT analysis is lower in women than in men; this difference cannot be explained by differences in severity of CAD or the amount of exercise achieved. The results of this study suggest that most of the difference is due to differences in the size of the left ventricle; there may be a small residual gender effect in patients with small chamber size. Attempts at improving diagnostic accuracy of SPECT thallium in women should focus on improving image resolution.

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