Fewer Women Than Men Have Positive SPECT and PET Cardiac Findings Among Patients with No History of Heart Disease

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A lower detection rate of coronary artery disease (CAD) has been reported for SPECT imaging in women, despite the fact that similar numbers of women and men die each year of heart disease. Ruling out instrumentation as a possible source of this low detection rate for CAD in women could be important in determining the root cause of this difference. **Methods:** Patients were referred by cardiologists and randomized to PET or SPECT by the imaging center. A total of 210 patients (106 women, 104 men) were enrolled in this study, with 105 imaged by dual-isotope SPECT and 105 imaged by ^{82}Rb PET. Rest/stress scanning was performed using dipyridamole. The effects of sex, prior history of CAD, and instrumentation on the detection of positive scans were determined using multiple logistic regression analysis with positive scans as the endpoint. **Results:** For the total study population, sex and prior history of CAD are significantly associated with positive scans, whereas imaging modality and age are not. There was no significant interaction between sex and prior history of CAD. Men have 4.1-fold greater odds of having a positive nuclear scan than women, and patients with prior history of CAD have 5.2-fold greater odds of a positive scan after controlling for the confounding effects of age and imaging modality. In the subgroup of patients with no prior history of heart disease, men have 3.9-fold greater odds of a positive scan than women, and the odds ratio of a positive scan is 2.5-fold greater for PET than for SPECT. There was no statistical difference in the number of positive scans by SPECT or PET, or positive scans by sex in patients with documented history of CAD. **Conclusion:** Fewer women than men have positive nuclear cardiology scans by both PET and SPECT, despite similar symptoms. Instrumentation characteristics alone do not account for this sex-based difference and suggest the possibility that early CAD may present differently in women than in men.

Key Words: PET; SPECT; sex; coronary artery disease; heart disease; nuclear cardiology; ^{82}Rb; ^{201}Tl; ^{99m}Tc-sestamibi

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PET with ^{82}Rb (*1–4*) and SPECT with ^{201}Tl and ^{99m}Tc-sestamibi (*5–8*) are used for the detection of coronary artery disease (CAD) and have been validated against coronary angiography. PET and SPECT have been validated for detection of CAD in the same patient population against coronary angiography by Go et al. (*9*) and Stewart et al. (*10*). These 2 studies have reported typical accuracy numbers of 80%–95% for the detection of CAD for a patient population with a high prevalence of disease. The detection accuracy of PET was slightly better than SPECT for this population, probably as a result of the better physical characteristics of PET for attenuation correction and its higher spatial resolution (*9,10*).

Differences by sex in the detection of CAD is an important clinical and economic issue. Hansen et al. (*11*) reported that SPECT detects CAD in fewer women than in men, and they found a significant statistical correlation of their results to the smaller heart sizes in women and the limited resolution of SPECT. A review of SPECT imaging for detecting heart disease shows that there may be a difference in the detection accuracy in women and men (*12,13*) and that the age of onset of heart disease may be different in men and women (*14*).

A recent publication compared the diagnostic accuracy of SPECT in CAD in men and women and showed that fewer women than men had positive scans among patients without coronary angiography studies (*15*). However, when these numbers were adjusted by the pretest probability of disease, based on angiographic determination of CAD, the detection accuracy for CAD was similar for women and men (*15*).

There is a growing consensus that CAD in men is different from that in women. The American Heart Association (*14*) reports that 239,701 women died of coronary heart disease (CHD) in 1993 compared with 250,362 men. Almost the same number of men and women die each year of CHD, but women seem to have heart disease later in life and there is a higher percentage of mortality from first heart attack in women (*14*). Women have more incidence of chest pain but have more "normal" coronary arteries when studied by coronary angiography (*12,13*). Is the sex difference in positive scans caused by differences in the symptoms and presentation of CAD in men and women? Or is the sex

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difference in positive scans observed with SPECT caused by instrumentation limitations, such as attenuation artifacts, poor resolution, or breast artifacts?

To address the issue of whether instrumentation can explain the sex difference in the detection of CAD by nuclear cardiology, we performed a study in which we compared SPECT with PET in the detection of CAD in the same population. Our assumption is that selecting patients from the same population reduces the referral bias caused by differences in coronary risk factors and allows us to compare one imaging modality to another.

Patients were randomly referred for assessment by either PET or SPECT. Only those patients being considered for dipyridamole stress were enrolled in this study, because exercise stress is not possible with ^{82}Rb PET. The data were analyzed for differences in the number of positive scans by method (PET and SPECT) and sex. A follow-up telephone call was made to the patients 6–12 mo (average, 9 mo) after their scans to assess early outcome.

The goals of this study were to determine whether there is a difference in positive scans by PET and SPECT in the same population and whether a sex difference exists in the number of positive scans by PET and SPECT.

METHODS

Location of Study

This study was performed at the Kennestone/Promina Hospital in Marietta, GA, a 600-bed, suburban, midsized hospital with 12 practicing cardiologists. Two SPECT cameras are located in the hospital for nuclear cardiology and 1 ^{82}Rb PET camera is located off campus for use in detection of CAD. None of the cardiologists had his or her own SPECT or PET cameras and, therefore, there was no economic referral bias in the study. Several nuclear cardiologists trained in SPECT and PET imaging read the images. Validation of the accuracy of this PET facility for CAD detection against coronary angiography has been published previously (*2*).

Patient Selection and Randomization Procedure

The 12 cardiologists who refer to this hospital for nuclear cardiology scans agreed to the randomization procedure and the study protocol before implementing the program. Inclusion criteria for this study were prior history of heart disease documented by coronary angiography and symptoms of CAD, such as shortness of breath, chest pain, and electrocardiogram (EKG) changes. Before randomization, the physician clinically evaluated patients. For patients with no previous history of heart disease, the clinical evaluation combined with symptoms of chest pain, shortness of breath, or resting EKG changes were required before recommending a nuclear cardiology scan for the detection of CHD. Patients with medical reasons that would preclude their being randomized to 1 modality or the other were excluded from this study. Once it was decided that a patient could be randomized, he or she was scheduled for a PET or SPECT scan. The physician was unaware of imaging technique selected and hospital staff were unaware of patient history before the assignment of the test modality. However, physicians could not be blinded to the imaging modality during image interpretation, because of the obvious differences in image quality and presentation format for PET and SPECT systems. Appropriate approvals were obtained from Kennestone Hospital Institutional Review Board for this study before the start of this project.

SPECT Imaging Protocol

The SPECT imaging protocol was performed with a dual-isotope technique, using dipyridamole for stress (*5*). With the exception of 6 patients who underwent dobutamine stress, all of the patients underwent the following procedure. A rest scan with 74–111 MBq ^{201}Tl-chloride was carried with a 180°-arc data collection. Dipyridamole was then infused at the rate of 0.56 mg/kg for 4 min, and, 4 min postinfusion, an injection of 740 MBq ^{99m}Tc-labeled sestamibi was made at peak exercise. After 30 min of wait time, a 180°-arc data acquisition was performed for the stress scan. Three-dimensional images were then constructed and quantitative analyses of images were performed, using the standard rest–stress-uptake images. SPECT results were recorded in a database along with patient information.

PET Imaging Protocol

The PET imaging protocol included a 20-min attenuation scan to correct for radiation absorption in the body, before a rest scan obtained with an infusion of approximately 1480 MBq ^{82}Rb-chloride (*2*). Stress was induced with a standard dose of 0.56 mg/kg dipyridamole for 4 min, after which a stress scan was obtained with another infusion of 1480 MBq ^{82}Rb-chloride. The data acquisition times for both rest and stress scans were 6 min. Visual and quantitative analyses of images were carried for rest–stress images, and PET results were recorded in the database.

Patient Database

Information about age, sex, history of CAD, prior catheterizations, coronary artery bypass grafts (CABG), and percutaneous transluminal coronary angioplasty (PTCA) was recorded in a database. SPECT and PET results were also recorded in the database, and results from catheterizations, CABG, or PTCA performed after scanning were entered. Patients were surveyed by telephone, and information on continuing problems, undiagnosed symptoms, other cardiac procedures, and deaths was obtained. The mean time of the telephone survey was approximately 9 mo after the nuclear scan (range, 6–12 mo).

Data Analysis

Multiple logistic regression analysis was performed using all patients with positive scans as the endpoint and age, sex, modality, and prior history of CAD as covariates. The patient population was further broken down into 2 subgroups, 1 with and 1 without previous history of CAD. These subgroups were analyzed using the multiple regression analysis with positive scans as the endpoint. Results of the telephone survey and the detection rates for each modality were analyzed. Fisher's exact method or χ^2 methods were used to examine whether there were significant differences in the number of positive scans between PET and SPECT. Student t tests were used to determine whether there was a significant difference in age between the 2 groups.

RESULTS

Population, Age, and Sex

There were 210 patients recruited for this study, with an average age of 64 ± 12 y (Table 1). There were 104 men with an average age of 62 ± 11 y and 106 women with an average age of 66 ± 11 y. The age difference between the men and women was statistically significant ($P = 0.004$).

TABLE 1
Population and Age Breakdown of PET and SPECT Patients

Variable	PET (n = 105)	SPECT (n = 105)	*P*
Average age (y)	63 ± 12	65 ± 11	0.277
Women	43 (41%)	63 (60%)	
Men	62 (59%)	42 (40%)	0.006
Patients with history of CAD	31 (30%)	32 (30%)	0.880

There were 63 patients (30%) with prior history of CAD documented by coronary angiography or myocardial infarction. The average age of these patients with prior history of CAD was 65 ± 10 y. The average age of the remaining 147 patients (70%) with no prior history of CAD was 64 ± 11 y. There was no statistical difference in the ages of these 2 subgroups of patients ($P = 0.630$).

A total of 105 patients was imaged with PET and 105 with SPECT. The average age of the patients in the PET group was 63 ± 12 y, whereas the average age of the patients in the SPECT group was 65 ± 11 y. There was no statistical difference in average age between the PET and SPECT groups ($P = 0.277$). The number of patients with history of CAD was 31 for the PET group and 32 for the SPECT group ($P = 0.880$). For the combined PET and SPECT population, the number of women and men was similar. The distribution of men and women between the 2 methods was significantly different ($P = 0.006$) but was considered in the logistic regression analysis. We believe that this distribution is caused by the statistical nature of the data, because we did not stratify by sex in this study.

Patient History, Symptoms, and Risk Factors by Sex

Table 2 shows some of the parameters that describe the history of heart disease, symptoms, and risk factors by gender for the total population. Most of the parameters are very similar for the 2 groups, except women have a higher incidence of chest pain, shortness of breath, and atypical angina compared with men. The average age of the women is higher at 66 ± 12 y than for men at 62 ± 11 y. For the most part, the male and female groups have very similar symptoms, as would be expected from randomization. However, because of the small number of patients in most of the categories, a detailed statistical comparison was not made by different risk factors.

TABLE 2
Breakdown of Patient History, Symptoms, and Risk Factors by Sex

Variable	Women	Men
Average age (y)	66 ± 12	62 ± 11
Shortness of breath	20	13
Chest pain	47	31
Angina		
Exertional	8	6
Stress	3	3
Rest	11	8
Atypical	20	12
High blood pressure	55	47
High cholesterol (>240)	17	11
Family history of CAD	21	19
Myocardial infarction	13	10
Coronary angiography	12	15
Irregular heart beat	11	9
Congestive heart disease	4	3

Values are number of patients in each group.

Positive Scans by PET and SPECT for All Patients

Multiple logistic regression analysis was performed, using all patients, with positive scans as the endpoint. Sex, prior history of heart disease, age, and imaging modality were the covariates (Table 3). Positive scans were significantly associated with sex ($P = 0.001$). The odds of a positive scan in men are 4.1-fold greater than in women. Prior history of CAD was also significantly associated with positive scans ($P = 0.002$). Patients with a prior history of CAD have 5.2-fold greater odds of having a positive scan than those with no prior history of CAD. There was no significant correlation with imaging modality and positive scans ($P = 0.43$) or age and positive scans ($P = 0.85$). Neither the age–sex interaction ($P = 0.192$) nor the age–modality interaction ($P = 0.963$) was significantly associated with positive scans.

Positive Scans as Function of Prior History of CAD

The patient population was then subgrouped into those with and those without previous history of CAD. The number of positive scans detected by PET and SPECT, as a function of prior history of CAD, are shown in Table 4. A χ^2 analysis of the data showed a significant difference in the number of positive scans by SPECT and PET ($P = 0.008$) in the subgroup of patients with no prior history of CAD but not in the group with documented history of CAD.

We performed multiple logistic regression analysis for positive PET and SPECT scans from patients in the subgroup of no prior history of CAD (Table 5). The endpoint for

TABLE 3
Multiple Logistic Regression Analysis of Positive Scans for All PET and SPECT Patients

Variable	Parameter estimate	Standard error	*P*	Odds ratio	95% confidence interval
Age	−0.003	0.014	0.850	0.997	(0.970, 1.025)
Sex*	1.398	0.427	0.001	4.045	(1.751, 9.342)
Prior CAD†	1.653	0.555	0.002	5.224	(1.866, 14.626)
Modality‡	0.260	0.326	0.426	1.296	(0.685, 2.455)
Sex/CAD§	−0.712	0.674	0.291	0.491	(0.131, 1.839)

*Sex = 0 if female, 1 if male.
†Prior CAD = 1 if true.
‡Modality = 0 if SPECT, 1 if PET.
§Sex/CAD = interaction between sex and prior CAD.

TABLE 4
Positive PET and SPECT Scans by History of CAD

No. of positive scans	PET (%)	SPECT (%)	*P*
Total	40/105 (38)	30/105 (29)	0.143
Total in patients with history of CAD	15/31 (49)	19/32 (59)	0.382
Total in patients with no history of CAD	25/74 (34)	11/73 (15)	0.008

this analysis was positive scans, and the covariates were age, sex, and imaging modality. Sex and imaging modality were significantly associated with positive scans for the patients with no prior history of CAD. Men have a 3.9-fold greater chance of having positive scans ($P = 0.002$), and PET has a 2.5-fold greater probability of producing a positive scan than SPECT after controlling for the confounding effect of sex and age in patients with no history of CAD.

There was no significant difference in the number of positive scans by PET and SPECT in the subgroup of patients with documented history of CAD (Table 6). Multiple regression analysis of this subgroup of patients showed no significant association of positive scans with age, sex, or modality of imaging.

Nine Months' Outcome Results

A total of 182 patients of the 210 in the study (87%) were contacted by telephone to assess the outcome of the scans. The survey was conducted from 6 to 12 mo after the scan (mean time, 9 mo). A total of 7 cardiac-related deaths included 4 men and 3 women. There were 3 deaths in the PET group versus 4 in the SPECT group (Table 7). The number of deaths recorded is small, and no statistical difference is attained between the 2 modalities or by sex. It is important to note that 2 of the deaths occurred in patients with prior history of CAD, whereas 5 deaths occurred in patients with no prior history of CAD.

DISCUSSION

Our results can be summarized in 3 major points.

1. Both PET and SPECT yield significantly fewer positive cardiac scans in women than in men in the total population studied. There was no statistical difference in the number of positive scans by PET and SPECT for the total population.

2. In the subgroup of patients with no prior history of CAD, PET yields more positive scans than SPECT, and both PET and SPECT produce fewer positive scans in women than in men. The probability of CAD and the likelihood of disease severity are also low in this subgroup; therefore, the greater number of positive scans by PET may be the result of better resolution and quantification capabilities of PET (*16*).

3. In the subgroup of patients with documented prior history of CAD, there is no significant difference in the number of positive scans by sex or by imaging modality (PET or SPECT). These patients have a high probability of CAD, and there is no sex difference in the number of positive scans by PET and SPECT in patients who are known to have focal CAD.

We have shown that fewer women have positive nuclear cardiac scans than men, independent of the imaging modality (PET or SPECT). Attenuation errors and breast attenuation artifacts, which have been associated with lower detection of CAD in women with SPECT (*17*), are not an issue with PET. Therefore, the previously published sex difference in positive scans in patients with no history of CAD (*15*) is not the result of instrumentation characteristics

TABLE 5
Multiple Logistic Regression Analysis of Positive Scans for Patients with No Prior History of CAD

Variable	Parameter estimate	Standard error	*P*	Odds ratio	95% confidence interval
Age	0.065	0.017	0.702	1.006	(0.974, 1.040)
Sex*	1.365	0.436	0.002	3.918	(1.668, 9.202)
Modality†	0.8969	0.427	0.036	2.452	(1.062, 5.663)

*Sex = 0 if female, 1 if male.
†Modality = 0 if SPECT, 1 if PET.

TABLE 6
Multiple Logistic Regression Analysis of Positive Scans for Patients with Prior CAD

Variable	Parameter estimate	Standard error	*P*	Odds ratio	95% confidence interval
Age	−0.023	0.028	0.407	0.977	(0.925, 1.032)
Sex*	0.832	0.588	0.157	2.298	(0.725, 7.278)
Modality†	−0.796	0.559	0.155	0.451	(0.151, 1.351)

*Sex = 0 if female, 1 if male.
†Modality = 0 if SPECT, 1 if PET.

TABLE 7
Analysis of CAD-Related Deaths After PET or SPECT

Deaths	Sex	Age (y)	History of CAD	Scan results	Comments
PET group					
1	M	72	Yes	Negative	Cath 4 mo postscan
2	M	71	No	Positive	CABG postscan
3	F	73	No	Positive	Cath
SPECT group					
1	F	67	Yes	Positive	Old MI
2	M	69	No	Positive	Atrial fibrillation
3	F	73	No	Negative	
4	M	69	No	Negative	Equivocal scan

Cath = catheterization; MI = myocardial infarction.

of SPECT but is more likely the result of inherent differences in heart disease in men and women.

We have also shown that in the subgroup of patients with documented CAD (>50% diameter stenosis), there is no difference in number of positive scans by sex or imaging modality; therefore, both PET and SPECT detect the perfusion defects resulting from these focal lesions equally well.

The exact reason for the sex difference in positive scans in women is not known. We can speculate on 3 possible explanations for the lower detection rate for CAD in women.

1. Women do not have heart disease until much later in age and, therefore, are not diagnosed by nuclear cardiology at an early age. This is the most quoted reason why women suspected to have CAD have "normal" coronary angiograms. It is based on the angiographic data, which shows that the presence of CAD defined as narrowing of the coronary artery by at least 50% in diameter is lower in women than in men.

2. The chest pain that mimics CAD in women, and which is responsible for referral to nuclear cardiology tests, is caused by other factors, such as syndrome-X (*18*), instead of focal CAD. Women have a higher incidence of chest pain than men (*14*), but the reason for this difference is unknown.

3. Women have a higher incidence of diffuse disease or endothelial dysfunction, instead of focal stenosis disease that is usually associated with CAD. Endothelial dysfunction can cause coronary artery spasm and result in chest pain. This explanation is important, because the chest pain would suggest CAD, but the endothelial dysfunction would not be detected by coronary angiography and the patient would be classified as normal.

Coronary angiography studies have reported that women have fewer focal lesions and smaller coronary artery lumens than men (*19–21*). PET, SPECT, and coronary angiography have been optimized to detect focal lesions that cause abrupt perfusion defects, which are easy to detect (*22*). Patients with diffuse disease or endothelial dysfunction would be missed by current nuclear cardiology methods, because diffuse disease would cause a gradual decrease in perfusion along the artery instead of an abrupt perfusion deficit observed with focal lesions. Nuclear medicine methods are not optimized for detecting small and gradual decreases in perfusion associated with diffuse disease; we may need to develop new methods for detecting mild diffuse disease by nuclear cardiology.

CONCLUSION

We have shown that fewer positive scans result from standard nuclear cardiology methods in women compared with men, among patients who have no prior history of heart disease. However, there is no sex difference in positive scans in patients with documented focal CAD by angiography. Therefore, there is a high probability that early heart disease may be different in women than in men and that women may have a low incidence of focal stenosis disease during the early stages. Detection of mild or early heart disease in women will require measurement of subtle changes in myocardial perfusion during rest and stress. Quantitative measurement of coronary flow reserve will be necessary to detect early diffuse disease in patients.

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