Sex-Specific Criteria for Interpretation of Thallium-201 Myocardial Uptake and Washout Studies

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A study was undertaken to determine the effect of gender on criteria for the quantitative analysis of exercise-redistribution ^{201}Tl myocardial scintigraphy. The studies of 26 normal females and 23 normal males were subjected to bilinear interpolative background subtraction and horizontal profile analysis. Significant sexual differences were found in both regional uptake ratios and washout rates. These differences primarily reflected a proportionately decreased anterior and upper septal uptake in females, and faster washout in females. Faster myocardial ^{201}Tl washout rates in females could not be clearly ascribed to either a physiological or artifactual explanation. It is concluded that since important differences exist between males and females in the detected pattern of ^{201}Tl myocardial uptake and washout, sex-specific criteria may enhance the predictive accuracy of exercise-redistribution ^{201}Tl myocardial scintigraphy.

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Exercise-redistribution thallium-201 (^{201}Tl) myocardial scintigraphy is heavily relied upon for the management of patients with suspected or known coronary artery disease (*1*). However, major pitfalls are associated with the interpretation of ^{201}Tl studies. These include subjectivity of visual assessment, artifacts caused by soft-tissue attenuation, and variability of the anatomic location of outflow tracts (*2,3*). Quantitative computer techniques objectify the interpretation of ^{201}Tl myocardial scintigraphy and are reported to improve the accuracy of this test (*4,5*). Interestingly, quantitative criteria published to date have been derived from normal groups consisting of both men and women (*4,5*). Since breast attenuation can affect regional count densities of ^{201}Tl scintigrams, combination of sexes can be expected to blur the normal boundaries of quantitative criteria and result in patient misclassifications. A study was therefore undertaken to determine the effect of gender on criteria for the quantitative analysis of this technique.

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MATERIALS AND METHODS

Study Group

Forty-nine normal subjects underwent exercise-redistribution ^{201}Tl myocardial scintigraphy. The characteristics of the normal study group are given in Table 1. The group consisted of 23 males and 26 females. Eleven patients, five male and six female, had atypical chest pain, negative or uninterpretable exercise electrocardiography and normal cardiac catheterization. The remaining 38 did not undergo cardiac catheterization but were considered normal on the basis of a low disease probability (<2.5%) based on the computer program CADENZA which uses a Bayesian algorithm (*6*).

Each patient underwent maximal treadmill exercise. The 23 males achieved a mean peak heart rate of 184, range 169–195. The 26 females achieved a mean peak heart rate of 174, range 143–205. At peak exercise, 2.2 mCi of ^{201}Tl was injected intravenously through a forearm catheter and flushed with 1/2 normal saline. There-

TABLE 1
Characteristics of Normal Population

		Age			Cath unproven		
						Pre-test likelihood	
	No.	Mean	Range	Cath* proven	Risk factors	Mean (%)	Range (%)
Males	23	39	21–57	5	0	0.5	0.1–1.8
Females	26	43	33–65	6	0	0.4	0.1–2.3

* Catheterization.

after, the patients continued to exercise at peak heart rate for an additional 90–120 sec.

Within 5 min of the cessation of exercise, imaging commenced in the anterior, LAO 45° and LAO 70° views. All images were acquired with a standard-field Anger camera equipped with a high-resolution, parallel hole collimator. Twenty-five and twenty percent windows were centered around the 80 keV and 167 keV photopeaks of ^{201}Tl, respectively. Each poststress view containing 325,000 counts was stored on a minicomputer* for later processing. Each patient was instructed not to exercise and to eat a light snack (juice, jello, clear soup) during the ensuing 4 hr. The 4-hr redistribution images were acquired in the same sequence as poststress and each contained 400,000 counts. The durations of each poststress and redistribution image acquisition were recorded for future computations.

Image processing was carried out according to a modification of the method of Watson et al. (*7*). After bilinear interpolative background subtraction, four horizontal profiles were assigned per view (Fig. 1). The lowest, first profile was positioned by the operator exactly through the middle of the inferior wall (or inferoapical wall in the LAO-45° projection). All profiles were positioned an equal number of pixels from each other, the absolute number depending upon the height of the left ventricle in that view. The uppermost fourth profile was not included in further quantitative analysis because of the anatomic variability in outflow tract location. The peak counts per pixel was determined for eight of the nine remaining horizontal profiles. The only exception to this rule was the lowermost profile in the LAO-45° view, where the nadir was selected in order to preserve low interobserver variability. Also, due to the anatomic variability in outflow tract location, only the anterior peak of profile 2 in the anterior and LAO-70° projections was utilized. From these count values, 12 regional uptake ratios were calculated: ANT.1/INF. and ANT.2/INF. from the anterior view; SEP.1/INFAP., SEP.2/INFAP., PL.1/INFAP., PL.2/INFAP., PL.1/SEP.1, PL.1/SEP.2, PL.2/SEP.1 and PL.2/SEP.2 from the LAO-45° view; ANT.1/INFPOST. and ANT.2/INFPOST from the LAO-70° view.

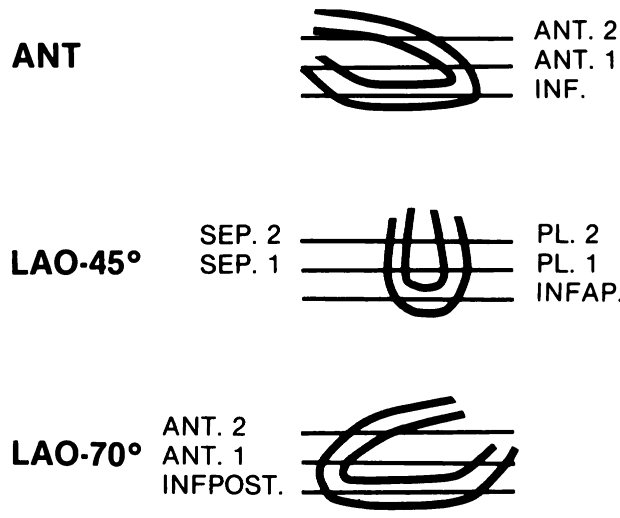

FIGURE 1
Schematic representation of acquired views with assigned horizontal profiles and resultant 12 myocardial regions. ANT = anterior; INF = inferior; INFPOST = inferoposterior; PL = posterolateral; SEP = septal

Eleven regional washout rates were calculated according to the formula:

$$\frac{\text{poststress counts} - (\text{redistribution counts} \times \text{view correction factor})}{\text{poststress counts}},$$

where view correction factor

$$= \frac{\text{duration of poststress view acquisition}}{\text{duration of redistribution view acquisition}}.$$

Finally, a poststress lung to heart ratio was calculated from a 10 pixel × 5 pixel rectangular region of interest positioned over the left lung and a 4 pixel × 4 pixel rectangular region of interest positioned over the hottest myocardial area on the immediate postexercise anterior view.

The interobserver variability of this method for analyzing ^{201}Tl studies was assessed. Ten randomly selected exercise-redistribution ^{201}Tl studies were processed by two independent observers. The mean absolute difference between Observer 1 and Observer 2 for each of the 12 uptake ratios, 11 washout rates and one lung to heart ratio was computed.

Statistical Analysis

Significance testing of differences between males and females for each of the quantitative parameters was performed using the unpaired t statistic. Significance testing of clinical differences between female subgroups with and without fast myocardial ^{201}Tl washout rates was performed using the nonparametric Wilcoxon statistic.

A coefficient of linear correlation (r) between the results of Observer 1 and Observer 2 was calculated for

TABLE 2
Comparison of Regional Uptake Ratios in Males and Females

View	Uptake Ratio	Males		Females		p-Value
		Mean	Range (±2 s.d.)	Mean	Range (±2 s.d.)	
Anterior	ANT.1/INF.	1.04	0.79–1.29	0.93	0.66–1.20	0.01
	ANT.2/INF.	1.06	0.79–1.33	0.93	0.67–1.18	0.001
LAO-45°	SEP.1/INFAP.	1.20	0.89–1.51	1.16	0.79–1.52	0.35
	SEP.2/INFAP.	1.11	0.73–1.48	1.00	0.60–1.40	0.08
	PL.1/INFAP.	1.17	0.84–1.50	1.12	0.82–1.42	0.30
	PL.2/INFAP.	1.06	0.70–1.42	1.03	0.69–1.37	0.61
	PL.1/SEP.1	0.98	0.70–1.26	0.99	0.69–1.28	0.90
	PL.1/SEP.2	1.07	0.79–1.36	1.14	0.77–1.52	0.14
	PL.2/SEP.1	0.88	0.60–1.17	0.90	0.59–1.22	0.65
	PL.2/SEP.2	0.97	0.70–1.23	1.05	0.62–1.48	0.11
LAO-70°	ANT.1/INFPOST.	1.05	0.73–1.35	0.93	0.68–1.12	0.01
	ANT.2/INFPOST.	1.04	0.72–1.37	0.84	0.60–1.09	0.001

each quantitative uptake and washout parameter. A t ratio was computed for each value of r. A p-value of ≤0.05 was considered significant.

RESULTS

Comparison of regional uptake ratios in the male and female subgroups is given in Table 2. In the anterior view, ANT.1/INF. and ANT.2/INF. were significantly lower in females than males. The same was true of ANT.1/INFPOST. and ANT.2/INFPOST. in the LAO-70° projection. While there was a tendency for SEP.2/INFAP. in the LAO-45° view to be lower in females, statistical significance was not reached. The mean post-stress lung to heart ratio was 0.38 in males and 0.35 in females (p = N.S.).

Comparison of regional washout rates in the male and female subgroups is presented in Table 3. Females demonstrated faster washout from each of the 11 regions. Statistical significance was reached for each of the anterior and LAO-45° view regions and for one of the three LAO-70° view regions. The females were subdivided according to whether or not they had three or more regional myocardial washout rates in excess of 0.70. As seen in Table 4, the two subgroups of females did not differ significantly in age, peak exercise heart rate, peak heart rate-blood pressure product or mean brassiere size.

The results of the interobserver variability study are presented in Table 5. The two observers' results were very highly correlated for 23 of 24 quantitative parameters. A discrepancy in profile positioning at the level of an obvious posterolateral defect in one case resulted in a less highly correlated PL.2/SEP.2 uptake ratio.

DISCUSSION

The results of this study reveal important differences between male and female myocardial ^{201}Tl uptake and washout characteristics after maximal exercise stress. The diminished anterior to inferior uptake ratios of females can be directly attributed to breast attenuation. There was also a tendency for females to have reduced upper septal to inferoapical uptake ratios. The reduced

TABLE 3
Comparison of Regional Washout Rates in Males and Females

View	Region	Males		Females		p-Value
		Mean	Lower limit (−2 s.d.)	Mean	Lower limit (−2 s.d.)	
Anterior	INF.	0.58	0.45	0.66	0.52	0.001
	ANT.1	0.58	0.47	0.67	0.51	0.0001
	ANT.2	0.58	0.49	0.64	0.51	0.003
LAO-45°	INFAP.	0.56	0.42	0.68	0.54	0.0001
	SEP1	0.55	0.41	0.64	0.44	0.002
	SEP2	0.55	0.42	0.63	0.48	0.001
	PL1	0.58	0.44	0.68	0.50	0.001
	PL2	0.56	0.40	0.67	0.52	0.0001
LAO-70°	INFPOST.	0.54	0.38	0.61	0.40	0.02
	ANT.1	0.57	0.43	0.62	0.39	0.08
	ANT.2	0.57	0.42	0.62	0.39	0.11

TABLE 4
Comparison of Normal Females with and without Fast Regional Thallium-201 Myocardial Washout Rates

	Fast myocardial washout rates*		
	Present (N = 10)	Absent (N = 10)	p-Value
Age	40 ± 8	37 ± 7	>0.05
Peak HR†	175 ± 14	176 ± 12	>0.05
Peak PRP‡	284 ± 39	281 ± 35	>0.05
Brassiere size	36 ± 2	36 ± 2	>0.05

* Six cases excluded from washout analysis due to incomplete data

† HR = heart rate

‡ PRP = pressure-rate product (HR × systolic arterial pressure/100)

upper septal wall uptake could be a combined effect of breast attenuation and a smaller left ventricular size in females. In our experience, upper septal "defects" which are part of the spectrum of normal ^{201}Tl scans tend to occur in patients with small sized left ventricles.

Both physiological and artifactual causes for the faster regional ^{201}Tl washout rates observed in females were considered. It is highly unlikely that monovalent cation cellular kinetics differ in males and females. If females achieved higher levels of myocardial blood flow with exercise than males, their faster myocardial ^{201}Tl washout rates could be explained. In fact, the mean peak exercise heart rate for males was slightly greater than that for females. Thus, if anything, one would have expected a slightly faster myocardial washout in males on this basis (*8*).

The possibility that breast attenuation accounted for the faster ^{201}Tl washout rates in females was explored. Assuming a linear gamma-camera counting efficiency, breast attenuation should not cause rapid washout, unless of course, there was some shifting of the breast artifact between stress and 4-hr redistribution imaging. Special care was always taken to allow the breast to lie naturally in all studies. Furthermore, breast attenuation as a cause was not supported by the subgroup analysis which showed that females with three or more fast washout segments did not have larger brassiere sizes (Table 4). In fact, "fast" washout rates were observed in several females in this series who had small breasts. Furthermore, ^{201}Tl washout rates from inferior myocardial segments which are much less affected by breast attenuation were also faster in females.

It is unlikely that errors in computer quantitative analysis accounted for the observed differences in ^{201}Tl washout between the sexes. The highly correlated results generated by two independent observers support the reproducibility of the data.

At the moment, faster myocardial ^{201}Tl washout rates in females cannot be clearly ascribed to either a physiological or artifactual explanation. The importance of this observation would remain even if it were due to the method of image acquisition and processing. The techniques employed in the present study do not differ substantially from those employed by most other nuclear cardiology laboratories.

The above male-female differences can be expected to result in patient misclassifications when one set of quantitative criteria are applied to the entire population of patients undergoing ^{201}Tl studies. It is difficult to conclude from the present data what magnitude of patient misclassifications arises from the utilization of total population as opposed to sex-specific quantitative criteria. Our initial experience with sex-specific criteria in a prospective series suggests that they are not required in cases where visual assessment is unequivocally negative or positive. Sex-specific criteria may, however, make a significant contribution in a minority of cases,

TABLE 5
Interobserver Variability of Quantitative Parameters

	Uptake ratios					Washout rates				
View	Ratio	Mean	Mean diff. ± s.d.	r	p	Ratio	Mean	Mean diff. ± s.d.	r	p
Anterior	ANT.1/INF.	1.05	0.04 ± 0.05	0.99	<0.001	INF.	0.48	0.05 ± 0.04	0.95	<0.001
	ANT.2/INF.	1.15	0.07 ± 0.08	0.95	<0.001	ANT.1	0.51	0.02 ± 0.02	0.99	<0.001
						ANT.2	0.51	0.02 ± 0.02	0.97	<0.001
LAO-45°	SEP.1/INFAP.	1.33	0.06 ± 0.09	0.91	<0.001	INFAP.	0.43	0.05 ± 0.03	0.98	<0.001
	SEP.2/INFAP.	1.24	0.09 ± 0.09	0.87	<0.001	SEP.1	0.49	0.04 ± 0.05	0.94	<0.001
	PL1/INFAP.	1.21	0.07 ± 0.07	0.97	<0.001	SEP.2	0.45	0.03 ± 0.02	0.99	<0.001
	PL2/INFAP.	1.17	0.12 ± 0.10	0.95	<0.001	PL.1	0.53	0.03 ± 0.01	0.99	<0.001
	PL1/SEP.1	0.92	0.06 ± 0.06	0.91	<0.001	PL.2	0.52	0.03 ± 0.02	0.99	<0.001
	PL1/SEP.2	0.99	0.06 ± 0.07	0.93	<0.001					
	PL2/SEP.1	0.88	0.06 ± 0.07	0.88	<0.001					
	PL2/SEP.2	0.95	0.05 ± 0.07	0.75	<0.05					
LAO-70°	ANT.1/INFPOST.	1.15	0.09 ± 0.12	0.96	<0.001	INFPOST.	0.47	0.02 ± 0.02	0.99	<0.001
	ANT.2/INFPOST.	1.19	0.12 ± 0.15	0.91	<0.001	ANT.1	0.52	0.02 ± 0.01	0.99	<0.001
						ANT.2	0.51	0.04 ± 0.02	0.92	<0.001
	Lung/Heart	0.42		0.98	<0.001					

where visual interpretation is equivocal. They may also improve the accuracy of individual coronary stenosis detection.

While the use of two sets of quantitative uptake and washout criteria is inherently sensible, the potential shortcoming of this approach in the female patient is recognized. The approach does not take into account the marked variation of breast size and shape within the female population. Thus certain normal females with particularly large breasts will have uptake ratios outside the boundaries established from the 26 normal females in this study. Certain normal females with particularly small breasts will have a pattern of ^{201}Tl uptake approaching more that of the normal male. One solution for this shortcoming would be to study a larger number of normal females for the purpose of developing uptake criteria incorporating some index of breast size. While this approach sounds tedious and lacking somewhat in exactitude, it may be the only way in which ^{201}Tl myocardial scintigraphy can be made a more effective diagnostic tool in the large female population presenting with chest pain. In the final analysis, it may prove to be that no set of quantitative criteria will be entirely acceptable for the female population at large. For the present, it is recommended that poststress ^{201}Tl myocardial images of women be immediately checked for a pattern of uptake suggestive of a breast shadow. In some cases, repetition of a view with the breast taped upward and medially can be helpful in the visual interpretation of the study.

Finally, the confounding effect of gender on the quantitative interpretation of ^{201}Tl scintigrams is not limited to planar imaging. Recently, a report concerning the quantitative analysis of normal ^{201}Tl rotational tomographic studies stressed the need for gender-matched normal data sets (*9*).

CONCLUSION

Gender significantly affects the detected pattern of both ^{201}Tl myocardial uptake and washout. A prospective study to determine whether sex-specific criteria enhance the predictive accuracy of exercise-redistribution ^{201}Tl myocardial scintigraphy for coronary artery disease detection and localization is warranted.

FOOTNOTE

* Medical Data Systems.

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