Normal SPECT Thallium-201 Bull’s-eye Display: Gender Differences


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The bull’s-eye technique synthesizes three-dimensional information from single photon emission computed tomographic 201Tl images into two dimensions so that a patient’s data can be compared quantitatively against a normal file. To characterize the normal database and to clarify differences between males and females, clinical data and exercise electrocardiography were used to identify 50 males and 50 females with < 5% probability of coronary artery disease. Results show inhomogeneity of the 201Tl distributions at stress and delay: septal to lateral wall count ratios are < 1.0 in both females and males; anterior to inferior wall count ratios are > 1.0 in males but are approximately equal to 1.0 in females. Washout rate is faster in females than males at the same peak exercise heart rate and systolic blood pressure, despite lower exercise time. These important differences suggest that quantitative analysis of single photon emission computed tomographic 201Tl images requires gender-matched normal files.


A major advance in analysis of single photon emission computed tomographic (SPECT) thallium-201 (201Tl) myocardial perfusion scans is the quantitation of stress, delay, and washout data (1–4). To carry out this analysis, it is necessary to define quantitatively the normal range of 201Tl distribution within the heart. The purpose of the present study is to answer the following questions:

1. What is the variability in myocardial 201Tl distribution among normal individuals?
2. Are there systematic differences in the 201Tl distribution to different regions of the normal heart?
3. Does the myocardial 201Tl distribution differ between females and males?
4. Does the 201Tl washout rate between stress and 3-hr delay images vary among different regions of the normal heart?
5. Does it vary between females and males?

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Detailed answers to these questions are required to use effectively a normal reference file for the quantitative comparison of each new patient being tested against the expected range of normals. The data are analyzed and displayed using the bull’s-eye format (4).

METHODS

Study Population

We studied 130 females and 180 males who were referred for exercise ECG and SPECT myocardial 201Tl imaging by their attending physicians. When the patient came to the exercise laboratory after an overnight fast, she or he was interviewed by a cardiologist who characterized the presence or absence of the following risk factors for coronary artery disease (CAD): smoking, hypertension, diabetes, elevated cholesterol, and abnormal resting ECG. Next, each patient was interviewed concerning a history of chest discomfort. The discomfort was characterized according to the following three features: (1) location in the chest, whether central or lateral; (2) duration, whether it was 2–20 min, briefer, or more prolonged; and finally (3) whether it was induced by exercise and relieved by rest. The pain was characterized as “typical angina pectoris” if it showed all three features, i.e., was located in the center of the chest, lasted 2–20 min, and was precipi-
tated by exercise and relieved by rest. If the pain showed only
two of these three characteristics it was considered “atypical
chest pain,” and if the pain showed only one of the three
characteristics, then it was called “nonanginal chest pain.”

Exercise Testing

After this interview, the cardiologist supervised a symptom-
limited exercise treadmill test according to the Bruce protocol
while a 12-lead ECG was recorded as described previously (3).
The resting ECG was analyzed for baseline ST-T wave abnor-
mality, evidence of prior myocardial infarction (Q waves >
0.03 sec that were at least ¼ the depth of the R wave) and left
ventricular hypertrophy. No patient selected for this study had
prior myocardial infarction. The criterion for a positive ECG
response to exercise was 0.1 mV flat or downsloping ST
segment depression 0.08 sec after the J point in at least three
consecutive heart beats with a normal baseline ST-T wave
segment. If the baseline ECG was abnormal or if the patient
was taking digitalis, then the test was called equivocal if there
was at least 0.1 mV flat or downsloping ST segment depres-
sion. No patient selected for analysis of normal 201TI distri-
bution was taking digitalis or had a positive exercise ECG. In
addition, the patient was required to reach 85% of age-pre-
dicted maximum heart rate to be included in this analysis of
normal 201TI distribution. The patients were exercised to a
symptomatic end-point of chest discomfort, dyspnea, fatigue,
or leg discomfort. Patients were not stopped simply because
of achieving a target heart rate, but would have been stopped
for cardiac arrhythmias or ST segment depression if it ex-
ceeded 0.2–0.3 mV. Patients had an i.v. catheter placed before
the exercise test and were asked to tell the physician when
they felt that they could only exercise for 60 sec more, at
which time 3.5 mCi 201TI was injected.

Definition of “Normal” Subject

Without knowledge of 201TI results, we selected 73 females
and 77 males from the 310 subjects analyzed as “normal”
subjects based on their having < 5% probability of CAD, from
a nomogram (6) that summarized Framingham Study data
for age, sex and risk factors (7) and the summary of chest
pain histories by Diamond and Forrester (8). Exercise ECG
results (chest pain or ST depression) were included in the
nomogram for sequential Bayesian analysis of clinical and test
data (6). Briefly, no patient had more than three risk factors;
no woman had typical angina although some had atypical
chest pain; no man had atypical chest pain although some had
nonanginal chest pain; and no woman or man had a positive
exercise ECG-ST response or chest pain on the treadmill
although some had equivocal tests. All subjects had to achieve
at least 85% age-predicted maximum heart rate for this analy-
sis. The final probability of CAD based on age, sex, risk factors,
chest pain history, and exercise ECG results was < 5%. Most
subjects had much less than 5% probability of CAD, but we
included a few older subjects with negative screening tests to
achieve broad age representation.

All subjects selected had been referred by their private
physicians for clinical reasons, and none were volunteers. All
patients were identified as normal (< 5% probability of CAD)
without knowledge of their 201TI data. We identified 73 fe-
males and 77 males as normal. From these, 50 females and
50 males were selected randomly for the present study. Ages
ranged from 29 to 79 for women (average = 45 ± 11 yr) and
27 to 68 for men (average = 45 ± 10 yr).

Tomographic Image Acquisition and Processing

Immediately after exercise, the patient was seated for a
recovery period of 2–3 min and then walked to a SPECT
imaging system (General Electric 400 ACT/STAR). The
gamma camera was started in approximately the 45° right
anterior oblique (RAO) view and rotated through an anterior
180° arc. Thirty-two planar views were obtained (40 sec/view).
Data for each view were acquired into a 64 × 64 digital matrix
with each picture element (pixel) in the array having a linear
dimension of 6.2 mm. A 30-million count cobalt-57 (57Co)
flood acquisition was used to obtain uniformity correction
factors for each pixel in the image. After the initial period of
imaging, which required about 22 min, the patient was asked
to return 3 hr after beginning the first image acquisition for
delay images.

Before SPECT reconstruction, the images were analyzed
for patient motion during acquisition by a program recently
developed in this laboratory (9). This program was used to
correct vertical motion of the subject if it exceeded 0.5 pixels
(≤ 3 mm). If there was horizontal motion, this was quantitated
but could not be corrected. No subject in the present study
had horizontal motion over 0.5 pixels.

Ball’s-eye Processing and Quantitative Analysis

The signal to noise ratio in each of the acquired views was
improved by convolving with a nine-point smoothing func-
tion. From the smoothed view data, one-pixel thick transaxial
slices were reconstructed using a conventional ramp-filtered
backprojection algorithm without any attenuation correction
(General Electric 400 ACT/STAR). An oblique angle slice
reconstruction procedure (General Electric 400 ACT/STAR)
allowed reorientation of the transaxial planes so that slices
corresponding to the three mutually perpendicular planes in
a coordinate system fixed to the heart could be obtained (i.e.,
horizontal and vertical long axis and short axis).

Quantitative analysis (Digital Design Crystal V) was per-
formed on each of the short axis slices. The procedure is
shown in Figure 1. From apex to base, each short axis slice
was subjected to a maximal count circumferential profile
analysis similar to that performed in quantitative analyses of
planar thallium view data (10). For all slices, except for the
first two apical slices, the maximum count was determined
along 40 radial vectors (i.e., nine-degree angular increments),
which emanated from an operator-defined center of the left
ventricle. For the first two slices, which generally do not have
the doughnut-shaped appearance of the other short axis slices,
the maximum count in the slice was obtained. After short axis
slice selection and the placement of a cursor at the center of
the left ventricle, the only other operator interaction involved
in the analysis was the drawing of a circular region of interest
about the left ventricular myocardial wall on the summed
short axis slices. The circle established the boundary for the
radial search procedure. The number of circumferential profile
curves corresponded to the number of short axis slices. As
shown in Figure 1, the extracted profile curve provides infor-
mation on the distribution of 201TI in the walls of the myocar-
dium. In our analysis program, as shown in Figures 1 and 2,
the anterior wall, septal wall, inferior wall, and lateral wall are
described by the radial vector segments 1–10 (0°–90°, 11–20
(90°–180°), 21–30 (180°–270°) and 31–40 (270°–360°), respectively. In contrast to other approaches (1,2) no slice to slice normalization procedure was forced on the data so that relative count variations from slice to slice can be appreciated in the quantitative images. All the profiles were first displayed in a two-dimensional rectangular array (Fig. 1), where the horizontal axis corresponds to radial vector number (i.e., 1–40 or 0°–360°), and the vertical axis corresponds to slice number with the apex on top and the basal region on the bottom. The color in the image is associated with the count value in the profile curve. As shown in Figure 1, high count regions appear as white and low count regions appear as blue. A horizontal profile through a given portion of the rectangular array gives the maximal count profile curve appropriate to the short axis slice.

To simplify the analysis program we have fixed the patient rectangular array to consist of 15 slices. Patient data having more than 15 slices are automatically minified, and those with < 15 slices are magnified to conform to this convention. The magnification or minification is accomplished through an interpolation algorithm.

A more convenient display of the 201Tl tomographic data is obtained by transforming the rectangular data array to polar coordinates, which effectively ties the 0° and 360° ends of the array together. This bull’s-eye image, shown in Figures 1 and 2, has the counts corresponding to the apical region in the center while the counts in the basal region are shown in the outer portions.

The normal bull’s-eye images reflect the average distribution of 201Tl from the normal female and male populations. These images were obtained by averaging the counts from each of the 50 normal females and 50 normal males in each of the 600 (40 radial vectors multiplied by 15 slices) pixels in the rectangular array. The actual magnitude of 201Tl uptake in each subject was not important to the present work, so each subject’s array was scaled before averaging. This scaling was accomplished by multiplying the actual counts by the ratio of a subject-independent constant to the subject-dependent (total) counts in the midventricular region of the array (slices 4–12). This normalization is preferable to that which includes the apical and basal regions because these regions show more variability and depend more on the actual choice of slices as determined by the operator doing the analysis. As shown in Figure 2, each bull’s-eye image was divided into 13 segments for quantitative analysis. Along with the normal (mean bull’s-eye image, the standard deviation bull’s-eye image was also calculated. The value of each pixel in this image reflects the variation of the normal subjects.

Analysis of Washout Data

We selected all patients for whom stress and delay image acquisitions were begun 170–190 min apart (180 ± 10 min) to minimize variability due to different delay times (37 females and 30 males). The absolute washout images were constructed using the actual counts in the stress and delay rectangular arrays. Relative washout used normalized arrays at stress and delay. In both cases, washout (%/100) = (stress − delay)/ (stress).

Statistical Analysis

The mean and standard deviations of relative counts in each of the 13 regions were calculated. Comparisons were performed by Student’s t-test for unpaired data, and differences were considered significant when p < 0.05. The male and female stress distributions were compared to those expected from a normal distribution.
RESULTS

Exercise Test Results

The results of the exercise tests are shown in Table 1 for the subjects whose data were included in washout analysis. Their exercise data were virtually identical to the larger groups of 50 females and 50 males. The exercise time on the Bruce protocol was greater in men than in women \( (p < 0.01) \), although the peak heart rates were nearly identical. Peak systolic blood pressures were not significantly higher in males than females.

Comparison Against Normal Distribution

Figure 3 shows the frequency distribution of the patient population (solid curve) of the average counts in the anterior, septal, inferior, and lateral walls in the midventricular region of the stress bull’s-eye image for males and females. The mean and standard deviation \( (\bar{x} \pm \text{s.d.}) \) determined from these curves was used to generate the normal distributions \( (\bar{x}'' - \text{points}) \) in Figure 3, which correspond well with the patient curves.

Comparison of Male and Female Bull’s-eye Images

Figure 4 shows the male and female bull’s-eye images at stress and delay. The corresponding 13 segment
numerical displays in Figures 5 and 6 show the relative ratios with respect to the region with the highest counts (region 4 in the lateral wall) at stress and delay, respectively. The bull's-eye images show significant differences between males and females at stress and delay (stress: 9/13 regions, \( p < 0.05 \); delay: 10/13 regions, \( p < 0.05 \)). The relative percent differences between males and females at stress and delay are shown in Figure 7.

For males at stress and delay:
1. Each septal wall segment from apex to base showed decreased counts compared to the corresponding lateral wall segment.
2. Each inferior wall segment from apex to base showed decreased counts compared to the corresponding anterior wall segment.
3. The apical region showed decreased counts compared to adjacent septal, anterior, and lateral wall segments, but approximately the same counts as the adjacent inferior wall segment.

For females at stress and delay:
1. As for males, each septal wall segment from apex to base showed decreased counts compared to the corresponding lateral wall segment.
2. In contrast to males, each inferior wall segment
from apex to base showed similar counts compared to the corresponding anterior wall segment.

3. As for males, the apical region showed decreased counts compared to adjacent septal, anterior, and lateral wall segments; however, in contrast to males the apical region also showed decreased counts compared to the adjacent inferior wall segment.

4. In general, the female bull’s-eye image shows less segmental variation than the male bull’s-eye image.

**Thallium-201 Washout Differences**

Comparisons of stress versus delay bull’s-eye images showed significant differences for both males (9/13 regions, p < 0.05) and females (10/13 regions, p < 0.05). Larger percent changes are seen in the female distributions (see Fig. 8 for relative washout).

The absolute values of washout (Fig. 9) showed slower washout in males than in females for all regions of the bull’s-eye (p < 0.05 for 10/13 regions). For the whole bull’s-eye, the washout rate was (40 ± 6)% in males and (45 ± 8)% in females (p < 0.01, males versus females). In Figure 10 and Figure 11, the washout bull’s-eyes for each gender are shown for those subjects with ages less than or greater than 45 yr old, respectively. The differences between the genders in washout rate occur mainly in the younger group (11/13 regions with p < 0.05 in the younger group versus 1/13 regions with p < 0.05 in the older group). We find no strong relationship between the washout rates and peak exercise heart rate, percent age-predicted maximum heart rate, body surface area, or peak systolic blood pressure.

**DISCUSSION**

The results of the present study are important because they define the expected range of normals in SPECT $^{201}$TI stress, delay, and washout distributions with a larger database than previously reported. This information is crucial to quantify differences in $^{201}$TI distributions for the diagnosis of CAD. Differences in body habitus and resulting attenuation, as well as differences in size, shape, and position of the heart may all alter the relative count density in the reconstructed SPECT.
images independent of myocardial perfusion (11). Since programs which can correct for variable attenuation are not currently available, the best way to deal with this variability is to define a normal file and to compare any one individual with this file quantitatively. The variability in $^{201}$Tl uptake is normally distributed among individuals with a low probability of CAD in the present study (Fig. 3). This observation validates the use of parametric statistics such as the mean and standard deviation to describe the variability. Thus, the likelihood of CAD in any one individual can be estimated by determining the number of standard deviations that an area on his or her bull's-eye falls below the mean of the normal file (12,13).

The major findings of the study emphasize differences between females and males in the stress, delay, and washout distributions of SPECT $^{201}$Tl myocardial perfusion scans. The females showed 4.8%-9.2% fewer counts in the anterior wall at stress than did the males. On the other hand, the males showed 7.1%-13.2% fewer counts in the inferior wall than did the females. Other features of the images in females and males deserve mention. The region with the most $^{201}$Tl activity is the lateral wall near the apex. In general, beyond the center of the bull's-eye (the apex), the apical midventricular regions had more $^{201}$Tl activity than did the more basal regions. From a physiologic standpoint, we would expect a more homogeneous distribution of $^{201}$Tl in the myocardium than is observed in the SPECT images. There is evidence from animal studies to indicate that there are only minor systematic differences in blood flow to different regions of the left ventricle as measured by radiolabeled plastic microspheres during treadmill exercise or rest (14,15). Presumably, the relative decrease in $^{201}$Tl activity in the anterior wall in females is due to breast tissue attenuation (12); the relative decrease in $^{201}$Tl activity in the inferior wall in males may be due to diaphragmatic attenuation. In our limited experience with $^{201}$Tl images in females after mastectomies, the pattern resembles the male normal file. Further, in a small number of males with gynecomastia, we have observed mild decreases in $^{201}$Tl counts in the anterior wall. The location of maximum counts in the lateral wall has been predicted by previous work from this laboratory using a simulated cardiac model with variable attenuation and resolution (11). The greater

**FIGURE 8**
The 13 segment display showing relative differences between stress and delay for males and females.

**FIGURE 9**
The 13 segment absolute washout display showing significant differences between males and females.
The 13 segment absolute washout display showing significant differences between males and females < 45 yr old.

$^{201}$TI activity in the apical-midventricular region than in the basal region may be related to the thinning of the base of the left ventricle as it nears the mitral valve plane (15) or to the effects of variable attenuation and resolution (17). The papillary muscles may also contribute to midventricular $^{201}$TI activity.

The faster washout in women versus men was significant only for persons < 45 yr of age, not for persons > 45 yr of age. The faster washout in females cannot be explained with certainty but is not likely to be due to differences in attenuation between females and males, since attenuation due to chest wall anatomy should remain constant between stress and delay images. Also, faster washout in women occurs in the inferior, inferoseptal, and inferolateral segments which should not be influenced by breast tissue attenuation. It is possible that the females had higher peak coronary blood flow during exercise than did the males, even though their peak heart rates and blood pressures were similar. However, they had reduced exercise times on the treadmill. In upright bicycle exercise, females show less increase in ejection fraction but a greater increase in left ventricular end-diastolic volume, compared to males (16). These changes might increase myocardial oxygen demand and coronary blood flow and $^{201}$TI washout rate in females more than in males because the increased ventricular volume would increase preload and afterload. On the other hand, the higher left ventricular ejection fraction in males would suggest that myocardial contractility would be increased more in men than in women, which should increase myocardial oxygen demand and coronary blood flow (17) and $^{201}$TI washout rate more in males than in females. This issue cannot really be resolved without direct measurements of coronary blood flow. The higher washout rate in females may also be related to differences in body composition of females and males, which could cause different distributions of $^{201}$TI during stress and delay conditions. It should be noted, however, that washout rate did not correlate with body surface area in women. The washout rate difference between females and males has also been noted on planar exercise $^{201}$TI imaging.

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(18). Whatever the cause, it is obviously important to account for this difference in diagnostic applications of exercise 201TI.

Critique of Methods

Our subjects were classified as normal by their clinical and exercise ECG data. All subjects had been referred by their personal physicians for exercise 201TI imaging to rule out coronary disease, so that none were healthy volunteers. All were defined as normal without knowledge of the 201TI image data, and none had cardiac catheterization. Defining normal subjects without cardiac catheterization avoided potential selection basis (19) since subjects are often referred for cardiac catheterization based on positive noninvasive test results or histories of more severe chest pain (5,19). Despite having <50% coronary arterial narrowing on angiograms, many of these ("cath normal") patients may have some other form of heart disease. The most obvious potential error due to our method of selecting a normal file would be to include a few subjects with some large vessel coronary disease, but this should affect <5% of our subjects, based on our selection criteria.

In conclusion, these results define quantitatively the normal range of the SPECT 201TI myocardial images. There are important differences between females and males, which require the use of separate normal reference files for quantitative analysis.

REFERENCES