Exercise Whole-Body Thallium Scintigraphy in the Diagnosis and Evaluation of Occlusive Arterial Disease in the Legs

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Whole-body thallium scintigraphy can be used to diagnose and evaluate occlusive arterial disease in patients with leg claudication. We performed exercise and redistribution scans in 36 healthy individuals and 17 patients with claudication. Regions of interest were drawn around the whole body, as well as each buttock, thigh, and calf. Counts in each region were expressed as a percentage of whole-body activity, as well as an interextremity activity ratio for each level. Significant differences due to gender and age were found. The sensitivity and specificity of the test in men was 94% and 71%, respectively, using the criterion of percentage regional uptake and 81% and 90%, respectively, using interextremity comparison. We conclude that exercise whole-body thallium imaging is a simple and accurate test for the evaluation of suspected occlusive arterial disease in the legs.

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The gold standard for the diagnosis of occlusive arterial disease in the legs is the arteriogram. An inference regarding function (or dysfunction) is made from the anatomy revealed by the arteriogram. However, the correlation between structure and function is not perfect. The arteriogram studies large vessels but does not provide information about flow, which is also dependent upon such factors as level of exercise, collateral circulation, and the presence of small vessel disease. Furthermore, the test is invasive, sometimes requires hospitalization, and carries a small risk of complication.

Radionuclide assessment of arterial disease provides physiologic information, is simple to perform, relatively noninvasive, quantifiable, and may be used for serial evaluation. Many different techniques have been employed. Early attempts in the 1960s used the clearance rate of xenon-133 following intramuscular injection (*1–3*). A significant disadvantage of the technique was the requirement of multiple injections if more than one vascular territory was being investigated. Particulate tracer methods using radiolabeled albumin microspheres were described in the 1970s. Although relative regional perfusion can be acurately measured with this technique, its major disadvantage is the requirement of arterial injection (*4–6*). The full potential of nuclear medicine in evaluating vascular disease was not realized until thallium became available. After i.v. injection, the fractional organ distribution of thallium approximates fractional cardiac output. It was first suggested that thallium could be used to quantify blood flow to the lower extremities in 1977 (*7*). Since that time, several reports have been published regarding the use of thallium in this setting (*8–16*). However, most reports were limited by the technology available at the time. Assessment was done by probe counting or regional imaging with comparison of intra- or inter-regional activity ratios. This made it difficult to detect disease when it was present at multiple levels or in both legs for lack of an absolute reference standard. With a whole-body scanner, it is possible to measure thallium activity in the legs relative to whole-body activity, which would avoid the limitations of regional imaging. There has been only one report using whole-body thallium scintigraphy to establish normal values for lower extremity arterial flow during exercise (*14*). However, this report did not investigate the effect of gender and age. Furthermore, normal values for gluteal activity were not reported. An assessment of gluteal activity is especially important since ischemia in the distribution of the internal iliac artery can mimic arthritis and is not detectable by other noninvasive tests of arterial disease. Finally, there have been no reports of the utility of whole-body imaging of thallium redistribution 4 hr after its injection.

We conducted a prospective study of thallium whole-body scintigraphy in order to standardize the method-

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ology, create a data base of normal values in patients of differing age and sex, and then to use this data to examine the sensitivity and specificity of the test in paients with arterial disease.

MATERIALS AND METHODS

Subjects

Fifty-three individuals had whole-body thallium scans. Individuals who could exercise without development of leg fatigue, pain, or cramps; who did not have a history of trauma or surgery involving the legs; and who had an ankle-brachial index (see below) ≥ 1.0 at rest, were used as normal controls. Group 1A was comprised of 14 healthy men with an average age of 37.8 ± 8.3 yr who were recruited for the study. Group 1B included 10 men with an average age of 61.8 ± 7.5 yr and suspected coronary artery disease who were referred to nuclear medicine for a thallium treadmill test and who agreed to undergo whole-body scintigraphy in addition to cardiac evaluation. Group 1C was composed of 12 healthy women with an average age of 34.8 ± 9.6 yr who were also recruited specifically for this study.

Group 2 consisted of 17 patients, 16 men and 1 woman, with occlusive arterial disease in the legs. The diagnosis was made only if all of the following criteria were met: 1) presence of typical intermittent claudication; 2) diminished or absent pulse at the femoral, popliteal, or pedal levels; and 3) a resting ankle-brachial index <1.0. Nine patients had arteriographically documented large vessel disease. Three patients had diabetes and six had multiple lesions. The average age of this group was 66.3 ± 5.4 yr.

Ankle-Brachial Index

Doppler-assisted measurements of systolic blood pressure at rest were obtained in all individuals before exercise. Measurements were taken with the patients supine. The ankle-brachial index was derived by dividing the pressure measured at the ankle by the pressure measured in the antecubital fossa. Measurements at the ankle were taken over the posterior tibial or dorsalis pedis artery. The finding of an ankle-brachial index <1.0 is highly suggestive of functional arterial obstruction (*11*).

Exercise Protocol

All patients performed symptom-limited treadmill exercise with cardiac monitoring. Patients exercised according to the Bruce protocol, or a low-level modification of the protocol. The test endpoint for individuals in Group 1 (controls) was fatigue whereas all patients in Group 2 stopped exercising because of intermittent claudication. Duration of exercise, as well as peak blood pressure and heart rate for both groups is shown in Table 1.

Scintigraphy

Two to 3 mCi of thallium-201-chloride (^{201}Tl-chloride) were injected at peak exercise, and patients were asked to walk for an additional minute. Five minutes later they were placed supine on the imaging table and whole-body scintigraphy was performed in the posterior projection. A few early patients also had anterior whole-body scintigrams. Scans were performed in a single-pass using a rectagular large field of view gamma camera. A high-sensitivity low-energy collimator was used most often in order to maximize counts, although a high-resolution low-energy collimator was occasionally used for convenience with equally good results. A 70–90 keV window was used for acquisition. The scan speed was 40 cm/min and all scans were completed in 5 min. The total count was typically, 150,000–250,000. Patients returned 4 hr after thallium injection for redistribution imaging. No limitations were placed on diet or activity during the interim period.

Analysis

Images were acquired on computer in a 512 × 512 pixel matrix. Only the posterior view was used for quantitative analysis. Rectangular regions of interest of equal size were drawn around the whole body, buttocks, thighs, and calves (Fig. 1). No correction was made for background activity, which was negligible. Total counts in each region were determined by computer and expressed as a percentage of whole-body activity. Symmetry of activity was measured by dividing the average pixel value of any given region by the average pixel value of the contralateral region at the same level. These ratios were determined for legs as well as buttocks, thighs, and calves. The ratio was always derived by dividing the smaller number by the larger number so that all values were less than or equal to 1.0.

Statistical Analysis

Values are expressed as mean ± 1 s.d. Student's unpaired t-test was used for inter-group comparison. Probability (p) values <0.05 were considered significant.

RESULTS

Anterior and posterior whole-body images obtained 5 min after exercise in an individual with a normal scan

TABLE 1
Exercise Data According to Group (Values Expressed as mean ± 1 s.d.)

Group	Age	Exercise duration (min)	Peak hemodynamic parameters heart rate	sys bp	dia bp
1A	37.8 ± 8.3	14.8 ± 1.6	180 ± 11	165 ± 20	73 ± 10
1B	61.8 ± 7.5****	8.2 ± 1.7****	118 ± 18****	166 ± 35	81 ± 16
1C	34.8 ± 9.6	11.5 ± 3.1**	178 ± 11	142 ± 24*	76 ± 11
2	66.3 ± 5.4****	5.0 ± 3.0****	105 ± 20****	163 ± 40	87 ± 14**

Group 1A = healthy men; Group 1B = men with suspected CAD; Group 1C = healthy women; and Group 2 = men with claudication. Asterisks indicate p value for Groups 1B, 1C, or 2 versus Group 1A: * p < 0.05; ** p < 0.01; *** p < 0.001; and **** p < 0.0001.

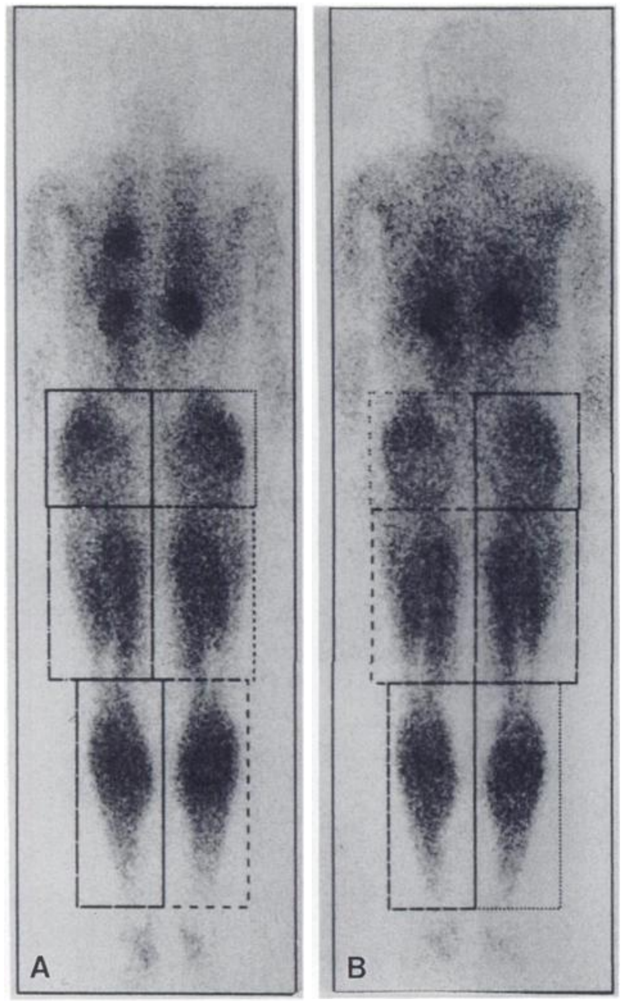

FIGURE 1
Early (A) and 4-hr (B) post-exercise posterior whole-body images of a healthy man without peripheral vascular disease showing the rectangular ROIs around the whole body, gluteal regions, thighs, and calves used for quantitative analysis. Regions at the same level are equal in size.

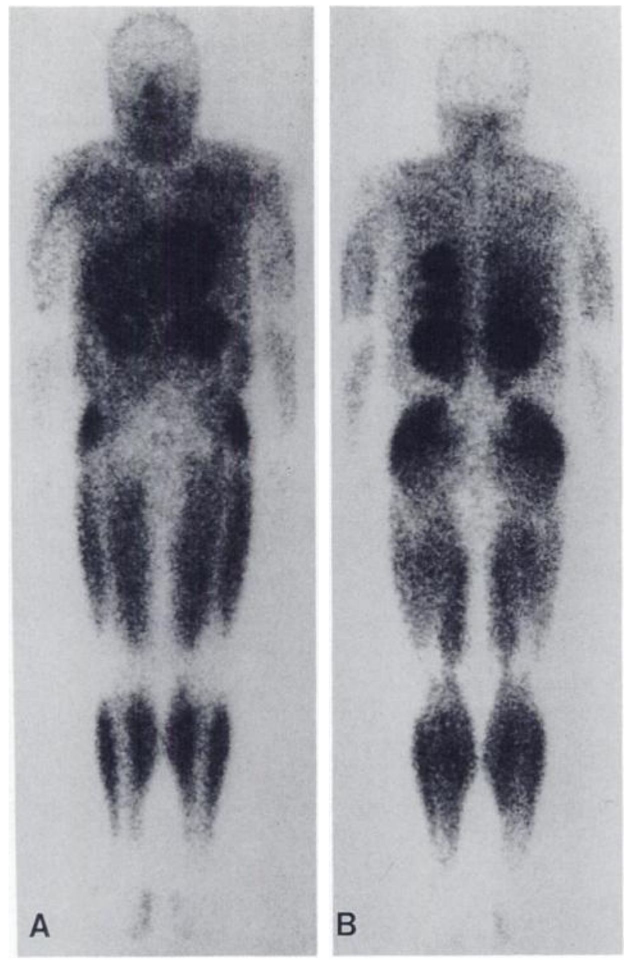

FIGURE 2
Early post-exercise anterior (A) and posterior (B) whole-body images of a man with a normal study. The gluteal muscles are not well seen on the anterior view and activity in the thigh and calf muscles is significantly attenuated by the long bones. In contrast, muscle groups are clearly defined in the posterior view.

are shown in Figure 2. The gluteal region is not seen on the anterior view and the long bones cause a marked attenuation defect in the thigh and calf. In contrast, the gluteal, thigh, and calf regions are well demarcated on the posterior view. Since the anterior view only provided limited information, it was abandoned after the first several individuals so that only the posterior view was acquired and used for analysis.

Regional thallium activity for all the individuals studied is shown in Table 2. Approximately one-quarter of the injected dose is distributed in the muscles of the lower extremities. Healthy women show significantly less activity in the gluteal and thigh regions than healthy men, but have comparable calf values. This is true for both early scans and scans done at 4 hr. Healthy women also show differences in regional wash-out when compared to healthy men, although the percent decrease in total leg activity is not significantly different. The results show that different normal values must be established for men and women.

Age is also an important factor. Men in Group 1B were on average 24 yr older than men in Group 1A. Older men had slightly less thallium activity in the whole leg than younger men, as well as lower overall thallium wash-out. There were also significant regional differences between the two groups.

Men with claudication had markedly lower values for thallium activity in the leg and calf when compared to either healthy younger or older men. These differences were highly significant. Furthermore, men with claudication showed net gains in thallium activity in all regions of the leg in contradistinction to both control groups, which showed net decreases. These differences were also highly significant. Figure 3 shows an example of a typical scan in a man with claudication and signs of occlusive arterial disease.

TABLE 2
Regional Thallium Activity Expressed as a Percentage of Whole-Body Activity (mean ± 1 s.d.)

Group	Early scan	4-hr scan	% change
Gluteal			
1A	9.2 ± 0.9	8.7 ± 0.8	−4.9 ± 5.0
1B	9.8 ± 0.9*	9.5 ± 0.7**	−3.4 ± 6.0
1C	8.4 ± 0.7****	8.2 ± 0.7*	−1.8 ± 6.2*
2	##8.8 ± 1.3	9.0 ± 1.1	##2.9 ± 8.6
Thigh			
1A	11.4 ± 0.8	10.7 ± 0.7	−5.8 ± 4.4
1B	9.6 ± 1.5****	9.5 ± 1.3***	−0.4 ± 5.9***
1C	10.0 ± 1.1****	9.2 ± 0.9****	−7.7 ± 4.5
2	8.8 ± 1.5****	9.2 ± 1.4****	##5.3 ± 7.0****
Calf			
1A	9.0 ± 0.6	7.9 ± 0.4	−11.5 ± 4.8
1B	8.6 ± 1.1	7.8 ± 0.8	−8.9 ± 5.3
1C	9.0 ± 1.3	7.7 ± 0.8	−14.2 ± 4.4*
2	####6.1 ± 1.5****	####6.3 ± 1.2****	####6.8 ± 10.1****
Leg			
1A	29.5 ± 1.5	27.3 ± 1.2	−7.3 ± 3.4
1B	28.1 ± 2.5*	26.8 ± 1.9	−4.4 ± 4.6*
1C	27.4 ± 1.4****	25.2 ± 1.1****	−8.1 ± 3.9
2	####23.7 ± 2.4****	###24.5 ± 1.9****	####4.0 ± 4.3****

Group 1A = healthy men, Group 1B = men with suspected CAD; Group 1C = healthy women; and Group 2 = men with claudication.

Asterisks indicate p-value for Group 1B, 1C, or 2 versus Group 1A. Pound signs indicate p value for Group 2 versus Group 1B.

* or # $p < 0.05$; ** or ## $p < 0.01$; *** or ### $p < 0.001$, **** or #### $p < 0.0001$.

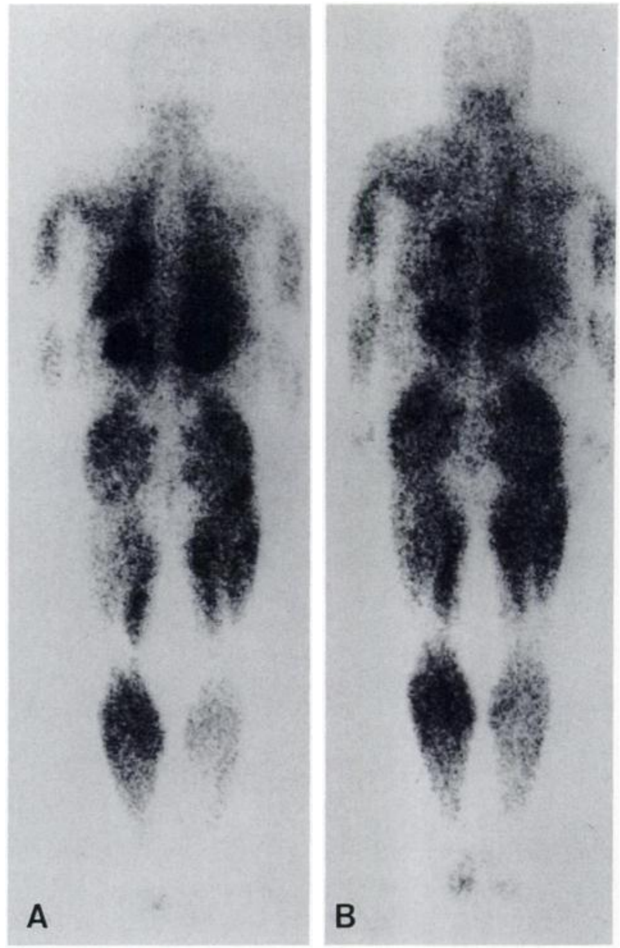

FIGURE 3
Early (A) and 4-hr (B) post-exercise posterior whole-body images of a man with bilateral intermittent claudication of the buttocks and calves and signs of occlusive arterial disease. Decreased activity on the early scan is very apparent in the right calf, and to a lesser extent, in the left thigh. Quantitative analysis also reveals decreased activity in the left gluteal region on the early scan. The 4-hr image shows some redistribution of activity to the left thigh and, questionably, the right calf. However, quantitative analysis indicates higher than normal redistribution to both thighs and both calves.

Figure 4 compares the frequency of abnormal findings on exercise whole-body scintigraphy using different "normal" values of thallium activity. The graph depicts the percentage of patients with claudication whose fractional whole-leg thallium uptake is <2 s.d.s below the mean for either healthy young men or older men with suspected coronary artery disease. Generally speaking, the test is more sensitive if young healthy men are used to define normal values. Figure 5 depicts the specificity of the exam by comparing the two control groups against one another. The specificity of the test is high in healthy young men when they are compared to older men with suspected coronary artery disease. The specificity of the test in older men is lower when they are compared to healthy young men. Possible explanations for this difference include subclinical disease in older men as well as higher thallium delivery to the legs in healthy young men who are able to exercise longer.

The same observations about the accuracy of the test are true if one looks at individual regions as opposed to the whole leg. If healthy young men are used as controls, then 16/16 men with claudication have at least one abnormal region on the early or 4-hr scan, or show at least one region with abnormal distribution. However, 9/10 older men with suspected coronary artery disease also have one or more abnormalities (overall sensitivity and specificity of 100% and 10%, respectively). If older men are used as controls, then at least one regional abnormality is detected in 15/16 patients with claudication and 10/14 healthy young men (overall sensitivity and specificity of 97% and 71%, respectively).

Table 3 lists the frequency of normal results when regional side-to-side thallium symmetry ratios are examined in the four groups of patients studied. Using an empirically defined normal of 90% or greater, specificity is very high for healthy young men and women as well as for older men without claudication. This finding has also been observed by others (*9,12*). The sensitivity of this method of analysis ranges from a low of 31% in the thigh to a high of 62% in the calf. The corresponding

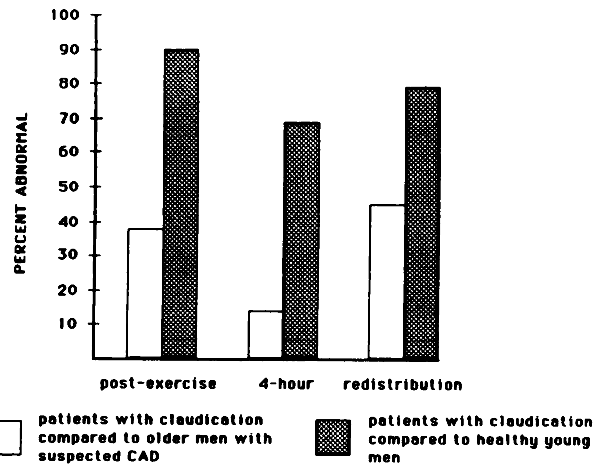

FIGURE 4
Frequency of abnormal fractional whole-leg thallium activity in patients with claudication, using either healthy young men or older men with suspected coronary artery disease (CAD) for comparison. Sensitivity is highest when healthy young men are used to define normal.

values are all lower for the 4-hr scans owing to redistribution of thallium activity. Overall, 13/16 patients with claudication (81%) have at least one region with interextremity asymmetry, whereas 0/10 healthy young men (0%), 2/12 healthy young women (17%), and 2/10 older men with suspected coronary artery disease (20%) have one abnormality.

DISCUSSION

Previous studies of thallium scintigraphy for diagnosis of occlusive arterial disease have compared images obtained at rest to those obtained after exercise (*9,10,* *14*). Images obtained after rest and exercise in normal individuals are qualitatively similar, although muscle activity is much higher after exercise. In patients with peripheral vascular disease, however, the images are dissimilar. Hamanaka et al. found that resting images in patients with peripheral vascular disease were not significantly different from normal controls whereas post-exercise images showed significantly less fractional leg activity (*14*). This situation is analogous to myocardial perfusion imaging where it is well known that exercise is necessary to identify subcritical hemodynamically significant lesions.

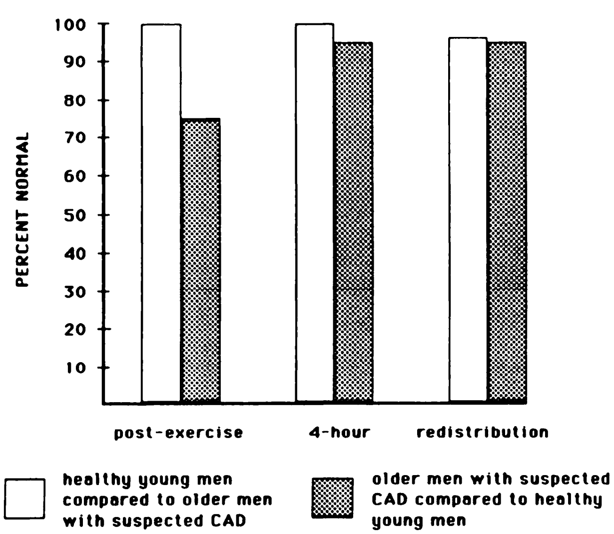

FIGURE 5
Frequency of normal fractional whole-leg thallium activity in two control groups when compared to one another. Specificity is highest when older men with suspected coronary artery disease are used to define normal.

TABLE 3
Percentage of Individuals with Normal (≥90%) Regional Thallium Symmetry Ratios

Group	Early scan (%)	4-hr scan (%)
Gluteal		
1A	100	100
1B	100	100
1C	92	92
2	56	69
Thigh		
1A	100	100
1B	90	90
1C	100	100
2	69	75
Calf		
1A	100	100
1B	90	90
1C	92	100
2	38	59

Group 1A = healthy men; Group 1B = men with suspected CAD; Group 1C = healthy women; and Group 2 = men with claudication.

The earliest studies of thallium scintigraphy employed intraextremity (gluteal-to-thigh, thigh-to-knee, thigh-to-calf, calf-to-ankle) and interextremity (thigh-to-thigh, calf-to-calf) ratios to evaluate limbs in healthy individuals and patients with occlusive arterial disease (*9,11,12*). In the report of Seder et al., the diagnostic accuracy for disease in the gluteal region and thigh was 82% whereas the accuracy for calf disease was 95% (*12*). The lower accuracy for proximal disease was due to low sensitivity (75%), which the authors thought could be explained by a balanced reduction in gluteal and thigh activity in some patients. None of the previous reports using this kind of analysis stated whether intraextremity or interextremity ratios could be used separately or which was more accurate.

The interpretation of exercise thallium whole-body scintigraphy using the criterion of interextremity symmetry is very appealing because the concept is intuitive and it is easy to appreciate when reading a scan. Eighty-one percent (13/16) of patients with claudication and signs of occlusive arterial disease in this study had at least one region which showed asymmetric thallium activity. Furthermore, among the 26 healthy young men and women studied (Groups 1A and 1C) only two women would have been misclassified as abnormal. The degree of asymmetry in these two women was minimal. The side-to-side thallium activity ratio was 88% in the calf region in one, and 89% in the gluteal region in the other.

The problem of evaluating symmetry is the possible presence of bilateral disease causing a commensurate degree of diminished thallium uptake. Others have also commented on the problems posed by bilateral disease with this kind of analysis (*8*). This is not a great problem if scintigraphy is merely used to screen for the presence or absence of disease anywhere in the legs to establish that symptoms are indeed due to claudication which is vascular in origin. In this situation, less than 20% of patients will be mistakenly classified as normal. However, the evaluation of symmetry will only detect the most severely diseased limb when both limbs are affected. To overcome this limitation, it is necessary to have some measure of absolute thallium activity to increase the sensitivity of the test. Regional fractional uptake relative to whole-body thallium activity can be used for this purpose and is easy to measure.

There has only been one previous study which has reported on the results of post-exercise whole-body thallium scintigraphy for the diagnosis and evaluation of occlusive arterial disease (*14*). In that study, the control group was comprised of ten subjects without signs or symptoms of atherosclerosis or peripheral vascular disease whose average age was 39 yr. The number of men and women was not specified. The reported average regional fractional uptake post-exercise was 12.26% ± 1.91% for the thigh and 6.58% ± 0.99% for the calf. This compares to 9.6%–11.4% for the thigh and 8.6%–9.0% for the calf, depending on control group, observed by us. The differences between the two studies are probably due to patient selection as well as technical factors. Hamanaka et al. did not report whether rectangular or irregular regions of interest were used, whether the analysis was based on anterior and/or posterior whole-body images, or whether any background subtraction was employed (*14*). In any case, it underscores the need for normative data to be developed in each laboratory.

It is interesting that healthy young men have higher fractional thallium uptake in the thigh, but lower fractional uptake in the gluteal region than older men without peripheral vascular disease. At first, we thought this may be an artifact due to the occasional difficulty encountered in separating gluteal from thigh muscle, but careful redrawing of the regions of interest gave the same results. It seems more likely that this difference is due to an actual redistribution of muscle mass with age.

The definition of normal is a problem. It is probably better to use age-matched rather than healthy young controls. However, using patients with suspected coronary artery disease as controls is not ideal since these patients may have subclinical peripheral vascular disease which is not evident because heart disease limits their exercise. This problem can be minimized by only using individuals with normal cardiac thallium evaluations whose exercise endpoint is generalized fatigue rather than angina.

In summary, we believe that exercise thallium whole-body scintigraphy is a promising technique in evaluating patients with suspected occlusive arterial disease in the legs. Laboratories interested in performing this test may quickly and easily generate a normal data base by scanning patients referred for cardiac evaluation who have no signs of heart disease. Only the posterior view is required for analysis. Regional fractional thallium uptake should be determined for early and 4-hr scans. Late imaging is helpful because significant redistribution is sometimes the only abnormal finding. Evaluation of symmetry is less sensitive, but significant asymmetry is highly specific.

Finally it should be pointed out that our values for sensitivity and specificity based on regional thallium analysis are for presence or absence of disease in a limb, without regards to actual location. All nine patients in this study who had claudication and arteriographically documented disease also had an abnormal thallium scan. At this point, we can only conclude that exercise thallium whole-body scintigraphy may be a useful screening test in identifying patients with occlusive arterial disease. Demonstration that the test can be used in conjunction with arteriography to evaluate the functional significance of anatomic disease and help select patients for revascularization requires further study.

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Erratum

Due to a production error, Equations 3–4 in "Left Ventricular Volume Calculation Using a Count-Based Ratio Method Applied to Multigated Radionuclide Angiography" by Massardo et al. in the April issue of the *Journal* were printed incorrectly. The correct equations are as follows:

The constant of proportionality is eliminated by taking the ratio $R = C_t/N_m$, which from Equations 1 and 2 is as follows:

$$R = \frac{C_t}{N_m} = \frac{KV_t}{KV_{ref}} = \frac{V_t}{V_{ref}} = \frac{\left(\frac{\pi}{6}\right)D^3}{M^2D} = \frac{\left(\frac{\pi}{6}\right)D^2}{M^2} \qquad (3)$$

It is clear that R is a dimensionless quantity that is equal to the number of reference volumes contained in the entire spherical volume.

Equation 3 may be solved for D as follows:

$$D = \sqrt{\frac{6M^2R}{\pi}} \qquad (4)$$

The volume of the sphere is:

$$V_t = \frac{\pi}{6} D^3,$$

hence from Equation 4,

$$V_t = \frac{\pi}{6}\left[\sqrt{\frac{6M^2R}{\pi}}\right]^3$$