# Functional Imaging of Peripheral Vascular Disease: A Comparison Between Exercise Whole-Body Thallium Perfusion Imaging and Contrast Arteriography

George M. Segall, Elvira V. Lang, Shelly E. Lennon, and C. Drew Stevick

*Nuclear Medicine, Radiology, and Surgery Services, Veterans Administration Medical Center, Palo Alto, California and the Department of Radiology, Stanford University School of Medicine, Stanford, California*

Whole-body thallium scintigraphy was used to study leg muscle perfusion in 12 healthy individuals and 31 patients with peripheral vascular disease. Subjects were scanned immediately after exercise and 4 hr later. Buttock, thigh and calf perfusion were measured in terms of fractional uptake relative to whole-body activity, percent change in fractional uptake over 4 hr and interextremity symmetry ratios. The results were compared to contrast arteriography on a region by region basis. The overall sensitivity and specificity of thallium scintigraphy were 80% and 73%, respectively. The results suggest that thallium scintigraphy may provide useful information about the hemodynamic significance of noncritical anatomic lesions.

**J Nucl Med 1992; 33:1797–1800**

Contrast angiography is the gold standard in the diagnosis and evaluation of peripheral vascular disease. Although it provides anatomical information about large vessels, information about the hemodynamic significance of borderline lesions, small vessel disease or the adequacy of collateral flow is difficult to obtain.

Radionuclide scintigraphy using $^{201}$Tl has been used for many years to noninvasively evaluate blood flow. Following intravenous administration, thallium distributes throughout the large muscle groups of the body in proportion to blood flow (*1*). Thallium remains in constant flux when injected after exercise and redistributes over several hours in a pattern approximating resting blood flow. Although thallium can be injected at rest, resting blood flow is not significantly reduced unless vessels are critically stenosed. Furthermore, fractional cardiac output and thallium delivery to the legs is very low during rest which makes imaging difficult. For these reasons, thallium is usually injected during exercise with images obtained immediately after exercise as well as 4 hr later. There have been several studies which have looked at the pattern of thallium distribution following exercise in normal individuals and patients with peripheral vascular disease (*2–10*). Hypoperfused regions initially show diminished activity which tends to normalize with time. These studies analyzed thallium distribution using right-left regional symmetry as one criterion of normalcy. The problem with this method alone is that it is insensitive to bilateral disease. Another method was to compare thallium activity to an adjacent area in the same leg and to express the result as thigh/calf, thigh/knee, and calf/ankle ratios. This approach is limited by the frequent occurrence of disease at multiple levels as well as poor counting statistics when using low count areas such as the knee and ankle for comparison. Others have suggested using regional leg to skull activity ratios to avoid false-negative results due to multilevel disease, but this approach is limited still by statistical noise because of inadequate reference counts (*7, 10*). Nevertheless, all of these studies showed that the technique was a sensitive method for detecting peripheral vascular disease. With the introduction of large field of view cameras, it became possible to perform whole-body imaging and quantitate thallium activity in the terms of fractional cardiac output which largely avoided the problems associated with multifocal disease.

We have previously reported normal values for fractional thallium activity in the legs adjusted for age and sex and found that these values where good discriminators between healthy individuals and patients with peripheral vascular disease (*11*). However, there have not been any studies comparing the technique to contrast angiography, which remains the gold standard. Validation of this technique as an accurate noninvasive test for peripheral vascular disease is important. Thallium scintigraphy has a significant advantage over other noninvasive measures since it provides a direct measure of gluteal, thigh and calf

Received Mar. 3, 1992; revision accepted May 28, 1992.

For reprints contact: George M. Segall, MD, Nuclear Medicine Service (115), Veterans Administration Medical Center, 3801 Miranda Ave., Palo Alto, CA 94304.

perfusion which is reproducible and easy to quantify. Furthermore, thallium scintigraphy quantitatively measures regional perfusion during exercise, so it also provides information about the hemodynamic significance of borderline angiographic lesions during routine activity. The purpose of this study was to correlate thallium findings with contrast angiography on a regional basis to determine the diagnostic utility of the test.

## METHODS

### Patients

The study group consisted of 31 men with typical intermittent claudication who were referred to the vascular surgery clinic. All patients had decreased pedal pulses and abnormal resting pedal Doppler blood pressure measurements. Arteriography was performed in all patients. The average age was 64 ± 9 yr.

The control group consisted of 12 men who did not have a history of intermittent claudication or signs of peripheral vascular disease. Angiography was not performed in this group, but all control subjects had normal pedal pulses and normal resting pedal Doppler blood pressure measurements. The average age was 62 ± 9 yr.

The study protocol was approved by the Stanford University Administrative Panel on Human Subjects in Research. Written informed consent was obtained from study participants.

### Exercise Protocol

All subjects performed symptom-limited treadmill exercise according to the Bruce protocol or a low-level modification. Electrocardiograms, blood pressure and pulse were continuously monitored. The test endpoint was leg pain in the patient group. Severity of the leg pain was subjectively rated by the patient on a scale of one to ten for each region. The test endpoint in the control group was fatigue. None of the control subjects had chest pain or leg pain. Exercise duration, hemodynamic changes, and occurrence of symptoms for both groups of subjects are shown in Table 1.

### Scintigraphy

Two millicuries of $^{201}$Tl-chloride were injected intravenously at peak exercise. Exercise was then continued for an additional minute. Posterior whole-body images were acquired approximately 10 min after exercise as well as 4 hr later. Activity was not restricted between the early and late images. Images were acquired in a single pass with a large field of view gamma camera using a general all-purpose collimator. The scan speed was 40 cm/min. Image acquisition time was 6 min. The total count was typically 150,000–250,000.

### Image Analysis

Images were displayed in a 512 × 512 matrix. Symmetric rectangular regions of interest were drawn around the whole body, as well as the gluteal, thigh and calf regions. The same regions were used for the early and late images. Figure 1 shows an example of a normal scan. The fractional cardiac output to each region was calculated by dividing the total count for that region by the whole-body counts. The percent change over 4 hr was also calculated. Symmetry was analyzed by comparing the counts from the right side and left side for each level. This was done only for the early scan. Figure 2 shows an example of an abnormal study.

**TABLE 1**
Comparison Data for Control and Patient Groups (Values Expressed as Mean ± One Standard Deviation)

| | Control group | Patient group |
|---|---|---|
| Age (yr) | 62 ± 9 | 64 ± 9 |
| Exercise duration (min) | 8.5 ± 1.4 | 4.5 ± 1.9* |
| Maximum heart rate (beats per minute) | 132 ± 16 | 119 ± 21 |
| Maximum systolic blood pressure (mmHg) | 158 ± 29 | 165 ± 28 |
| Frequency of leg pain (percent total) | 0 | 100 |

* $p$ value < 0.05.

### Angiography

Angiography with the evaluation of distal runoff was performed in all patients. Percent diameter stenosis was measured with calipers by a single experienced radiologist who was unaware of the thallium findings. Stenoses ≥70% were considered significant. In the case of vessels with multiple lesions, only the most severely diseased segment was recorded. The common iliac and internal iliac arteries were considered to supply the buttock. The common iliac, external iliac, common femoral and deep femoral arteries were considered to supply the thigh. Finally, the common iliac, external iliac, common femoral, superficial femoral, popliteal, peroneal, anterior tibial and posterior tibial arteries were considered to supply the calf. Disease in any one artery supplying a region was considered sufficient for an abnormality to be seen in the corresponding region on the thallium scan.

### Statistical Analysis

Differences between the means of continuous variables among different groups were tested by an unpaired two-tailed t-test. A p value < 0.05 was considered significant.

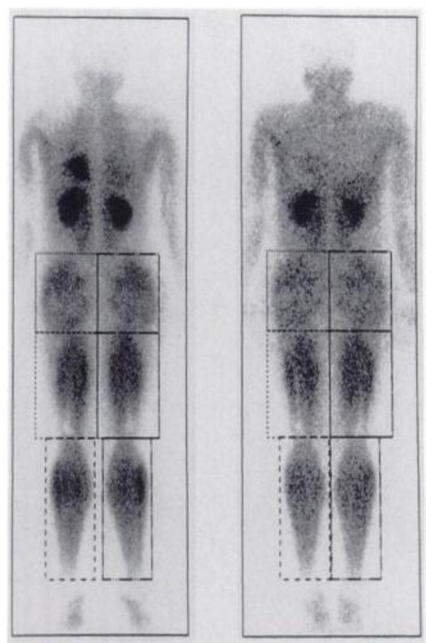

**FIGURE 1.** Posterior whole-body images obtained immediately after exercise (left) and 4 hr later (right) show a normal distribution of thallium activity in an individual without peripheral vascular disease. Each image is scaled to its own maximum count. Symmetric regions of interest are drawn around the buttocks, thighs, and calves as well as the whole body for calculation of regional fractional uptake, percent change over 4 hr and interextremity symmetry ratios.

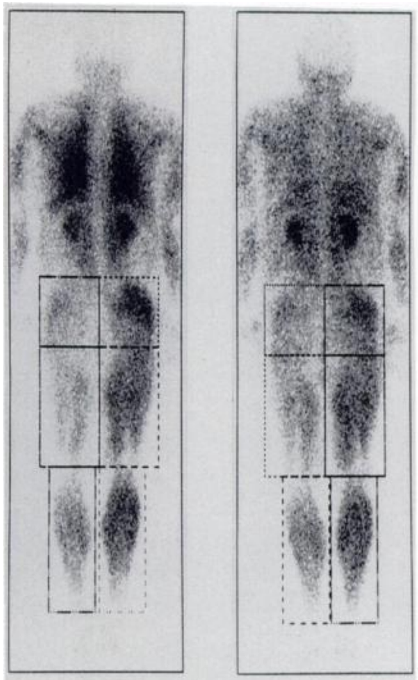

**FIGURE 2.** Posterior whole-body images obtained immediately after exercise (left) and 4 hr later (right) in a patient with an occluded left common iliac artery and an 80% stenosis in the right peroneal artery. Each image is scaled to its own maximum count. The study shows a marked decrease in thallium activity throughout the left leg immediately after exercise with significant improvement after four hours. The right leg is normal. The patient walked 4 min on the treadmill and experienced only left buttock pain.

## RESULTS

Normal values for fractional thallium uptake and percent change over four hours for each region were derived from the measurements in the 12 control subjects. The values are shown in Table 2. These values are similar to the ones we previously reported in a different control group. Values two standard deviations below the mean were considered abnormal. Regional symmetry ratios were greater than 90% in all control subjects in agreement with published studies and our own previous experience (*3,5,6,11*). Values below 90% were considered abnormal. A region was considered abnormal on the thallium scan if it was abnormal using any one of the above three criteria.

**TABLE 2**
Normal Scintigraphic Values in 12 Control Subjects (Values Expressed as Mean ± One Standard Deviation)

| | Buttock | Thigh | Calf |
|---|---|---|---|
| Fractional thallium activity immediately after exercise (percent of whole body activity) | 9.6 ± 0.9 | 9.7 ± 1.4 | 8.9 ± 1.1 |
| Percent change in fractional thallium activity over 4 hours | −4.5 ± 5.7 | −0.3 ± 3.7 | −9.0 ± 4.5 |
| Interextremity symmetry ratio immediately after exercise (percent of leg with highest value) | 96.2 ± 2.8 | 95.6 ± 3.2 | 95.2 ± 2.9 |

All but one of the 31 patients had at least one region which was abnormal on thallium scan. The results of the regional analysis are shown in Figure 3. Sensitivity for significant stenoses in arteries supplying the buttock, thigh and calf was 66%, 73% and 91%, respectively. Specificity for significant stenoses in arteries supplying these regions was 82%, 76% and 33%, respectively. The analysis of specificity for stenoses in arteries supplying the calf (common iliac to popliteal trifurcation) was hindered by the small number of limbs (nine) without significant arterial disease.

The effect of duration of exercise on thallium uptake in the legs of patients with peripheral vascular disease was also investigated. Only the leg with the most normal uptake was noted in order to minimize the effect of arterial disease on thallium delivery. There was no significant correlation between fractional thallium activity and exercise duration in the 28 of 31 patients who could walk at least two minutes on the treadmill.

## DISCUSSION

Exercise whole-body thallium scintigraphy appears to be a useful method to evaluate regional blood flow in patients with suspected peripheral vascular disease. In comparison to contrast angiography, the test has an overall sensitivity of 80% and a specificity of 73%. Our results are consistent with other studies which have shown that measurements of percent diameter stenosis do not accurately predict blood flow (*12*). The physiologic severity of a lesion depends on many factors, including absolute diameter, eccentricity, multiplicity, length and the presence of collateral flow. One of the potential advantages of scintigraphy is that it provides information about the hemodynamic significance of anatomic lesions.

The thallium scan was more sensitive and less specific in detecting blood flow abnormalities in the calves when compared to the thighs or buttocks. This finding has been noted by others and is probably due to the effect of serial lesions on distal flow. Serial lesions are more likely to cause a decrease in flow even though individual lesions might not be hemodynamically significant. Most of our patients had disease at multiple levels.

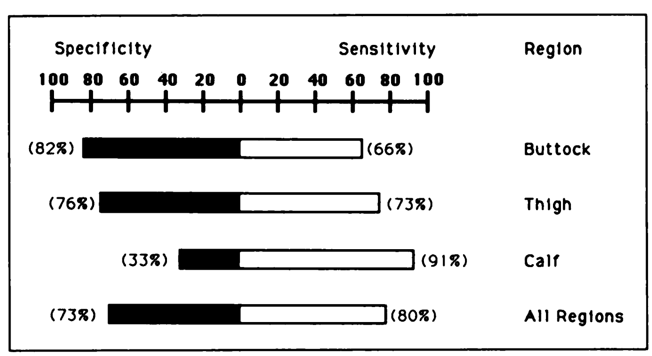


**FIGURE 3.** Sensitivity and specificity of the thallium scan compared to contrast arteriography when significant disease is defined as luminal diameter stenosis ≥70%.

There has only been one other study which has looked at fractional thallium activity in the legs of normal volunteers and patients with peripheral vascular disease (*8*). The normal values after exercise in this study were 12.3% ± 1.9% for the thigh and 6.6% ± 0.6% for the calf. Gluteal values were not reported. The thigh value in that report is higher than our own although the calf value is lower. Differences may be due to the effect of gender and age which we have previously determined to be important (*11*). Differences in technique may also play a role. The authors do not report whether they calculated the fractional thallium uptake from posterior whole-body measurements or used the geometric mean value from anterior and posterior measurements. We have found significant attenuation of muscle activity by the long bones on the anterior images. Their study also found that patients with peripheral vascular disease have a significantly lower value after exercise than normal controls but did not present any data on the regional sensitivity and specificity.

Some studies have measured thallium distribution during post-occlusive reactive hyperemia rather than exercise because the amount of stress (duration of occlusion) can be standardized (*5,14*). It has been shown that walking distance varies more than 20% in 18% of patients with claudication who have serial exercise tests (*16*). A potential problem with using exercise is that fractional cardiac output to the legs depends on oxygen demand which is determined by the amount of exercise. Individuals without peripheral vascular disease might show low thallium activity in the legs because their exercise is limited by musculoskeletal, cardiopulmonary, or other disease. We did not find this to be a problem in the 28 out of 31 patients who were able to walk at least two minutes on the treadmill. One explanation may be that maximal peripheral vasodilation occurs much sooner in patients with arterial disease because of early development of ischemia. We therefore prefer to use exercise rather than post occlusive reactive hyperemia because it provides information about functional capacity. An ability to perform even minimal exercise is a limitation of this technique, which occurred in 10% of our patients.

Another potential limitation is the presence of neuromuscular disease which can lead to atrophy and decreased thallium activity due to decreased muscle mass despite normal blood flow. This problem was not encountered in our population.

We rescanned patients 4 hr after exercise in order to determine the percent change in fractional thallium activity with time. Other investigators have noted that delayed images show a trend toward normalization although this amount has not been quantitated before (*5,6*). Redistribution of activity is not an important indicator of disease since it was the sole abnormality in only 3% of regions. However, the presence of redistribution increases the specificity of the test when accompanied by other scan abnormalities. We did not limit the activity of our patients between scans because it was difficult in an outpatient setting. It is possible that limitation of activity during this 4-hr interval or scanning patients the following day without limitation of activity might have improved the sensitivity of the test.

We have shown that exercise whole-body thallium scintigraphy may be used to evaluate peripheral vascular disease. The ability of scintigraphy to provide information about the hemodynamic significance of arteriographic lesions may make it a useful test in patients who have equivocal physical findings and noncritical arteriographic lesions.

## ACKNOWLEDGMENT

This project was supported in part by the Biomedical Research Support grant RR05353 awarded by the Biomedical Research Support Grant Program, Division of Research Resources, National Institutes of Health.

## REFERENCES

1. Strauss HW, Harrison K, Pitt B. Thallium-201: non-invasive determination of the regional distribution of cardiac output. *J Nucl Med* 1977;18:1167–1170.
2. Christenson J, Larsson I, Svensson S-E, Westling H. Distribution of intravenously injected $^{201}$Tl in the legs during walking. *Eur J Nucl Med* 1977;2:85–88.
3. Siegel ME, Siemsen JK. A new noninvasive approach to peripheral vascular disease: thallium-201 leg scans. *AJR* 1978;131:827–830.
4. Glass EC, DeNardo G. Abnormal peripheral distribution of thallium-201 due to arteriosclerosis. *AJR* 1978;131:718–720.
5. Siegel ME, Stewart CA. Thallium-201 peripheral perfusion scans: feasibility of single-dose, single-day, rest and stress study. *AJR* 1981;136:1179–1183.
6. Seder JS, Botvinick EH, Rahimtoola SH, Goldstone J, Price DC. Detecting and localizing peripheral arterial disease: assessment of $^{201}$Tl scintigraphy. *AJR* 1981;137:373–380.
7. Robert J, Thouvenot P, Schmidt C, Escanye J-M, Schmitt J. Leg arteritis exploration by quantitative muscle scintigraphy with $^{201}$Tl. *Microcirculation Endothelium and Lympatics* 1984;1:525–546.
8. Hamanaka D, Odori T, Maeda H, Ishii Y, Hayakawa K, Torizuka K. A quantitative assessment of scintigraphy of the legs using $^{201}$Tl. *Eur J Nucl Med* 1984;9:12–16.
9. Burt RW, Mullinex FM, Schauwecker DS, Richmond BD. Leg perfusion evaluated by delayed administration of thallium-201. *Radiology* 1984;151:219–224.
10. Chevreaud C, Thouvenot P, Lapeyre G, Laurens M-H, Renard C. Thallium-201 muscle scintigraphy: application to the management of patients with arterial occlusive disease. *Angiology* 1987;38:309–314.
11. Segall GM, Lennon SE, Stevick CA. Exercise whole-body thallium scintigraphy in the diagnosis and evaluation of occlusive arterial disease in the legs. *J Nucl Med* 1990;31:1443–1449.
12. Marcus ML. Physiologic effects of a coronary stenosis. In: Marcus ML. ed. *The coronary circulation in health and disease*, 1st edition. New York: McGraw-Hill; 1983:242–269.
13. Criqui MH, Fronek A, Barrett-Connor E, Klauber MR, Gabriel S, Goodman D. The prevalence of peripheral arterial disease in a defined population. *Circulation* 1985;71:510–515.
14. Criqui MH, Fronek A, Klauber MR, Barrett-Connor E, Gabriel S. The sensitivity, specificity, and predictive value of traditional clinical evaluation of peripheral arterial disease: results from noninvasive testing in a defined population. *Circulation* 1985;71:516–522.
15. Oshima M, Akanabe H, Sakuma S, Yano T, Nishikimi N, Shionoya S. Quantification of leg muscle perfusion using thallium-201 single photon emission computed tomography. *J Nucl Med* 1989;30:458–465.
16. Wilkinson S, Parkin A, Wowden P, Robinson PJ, Kester RC. The application of a new method of limb blood flow measurement using a radioactive isotope and a gamma camera. *J Cardiovasc Surg* 1989;30:618–623.