Combined Rest Thallium-201/Stress Technetium-99m-Tetrofosmin SPECT: Feasibility and Diagnostic Accuracy of a 90-Minute Protocol

S. Mahmood, M. Gunning, J.B. Bomanji, N.K. Gupta, D.C. Costa, P.H. Jarritt, H. Swanton and P.J. Ell

Institute of Nuclear Medicine and the Department of Cardiology, University College London Medical School, London, United Kingdom

Technetium-99m tetrofosmin is a recently developed compound that clears from background organs rapidly. Tetrofosmin has a good correlation with ^{201}Tl. This study assesses the feasibility and diagnostic accuracy of a combined protocol involving rest ^{201}Tl SPECT and stress imaging with ^{99m}Tc-tetrofosmin. **Methods:** Twenty-five patients (23 men, 2 women; aged 36–73 yr) with known coronary artery disease underwent the combined protocol. Twenty minutes after the resting injection of ^{201}Tl, resting SPECT data were acquired using low-energy, high-resolution collimators. A stress test using adenosine infusion combined with low-level dynamic exercise was performed. The stress data were collected 20 min later. The reconstructed vertical long-axis, horizontal long-axis and short-axis slices were analyzed qualitatively. Analysis was carried out using nine segments of the left ventricle. The segments were reported either as fixed or reversible. The results were compared to coronary angiography results. **Results:** The sensitivity and specificity for the detection of diseased coronary vessels were 85% and 70% for the left anterior descending territory, respectively, 78% and 71% for the right coronary artery, and 69% and 70% for the left circumflex. Overall, the sensitivity was 80% and the specificity 70%. **Conclusion:** Combined rest ^{201}Tl/stress ^{99m}Tc-tetrofosmin SPECT provides a protocol of short duration which displays similar diagnostic accuracy to a protocol using tetrofosmin as a single agent.

Key Words: thallium-201; technetium-99m-tetrofosmin; coronary artery disease; single-photon emission computed tomography

J Nucl Med 1995; 36:932–935

Thallium-201 myocardial perfusion scintigraphy is a well established method of assessing myocardial perfusion, (*1,2*) despite well known disadvantages. These include a low energy emission that results in significant soft-tissue attenuation in tissue and a rather long half-life, which restricts the amount of dose that can be given safely. Efforts have therefore been directed over the past 5 years toward the development of a suitable ^{99m}Tc-based radiopharmaceutical that would have ideal imaging characteristics for myocardial perfusion scintigraphy. MIBI and teboroxime have been studied, but there are limitations with these agents as well. For example, there is high hepatic and gastrointestinal uptake with MIBI (*3,4*); there is rapid washout with teboroxime (*5,6*).

Technetium-99m-tetrofosmin is a recently developed cationic diphosphine compound and has shown promising imaging characteristics, displaying rapid accumulation in and slow clearance from the myocardium with rapid clearance from background organs (*7–10*). For tetrofosmin's efficacy in the detection of coronary artery disease (CAD), Phase I, II and III studies have been performed which show a good comparison to ^{201}Tl imaging (*10–12*). Technetium-99m-tetrofosmin does not display the redistribution characteristics (*13*) of ^{201}Tl because it is a retention-type agent. Therefore, clinical studies conducted thus far have used separate stress and rest injections, either 4 hr apart or on separate days (*7,14,15*).

This study compares ^{201}Tl rest images and ^{99m}Tc-tetrofosmin poststress images in a 90-min protocol to assess tetrofosmin role in the detection of CAD.

MATERIALS AND METHODS

Patients

Twenty-five patients (23 men, 2 women; aged 36–73 yr) underwent a combined protocol involving rest imaging with ^{201}Tl followed by stress imaging with ^{99m}Tc-tetrofosmin. Patients with obstructive airway disease, unstable angina or second- or third-degree heart block were excluded from the study. Thirteen had a history of previous myocardial infarction, 3 complained of atypical chest pain, 22 complained of an anginal pattern of chest pain, and 4 patients complained of dyspnea as an additional symptom.

Patient Preparation

Patients were advised to abstain from caffeine-containing beverages for at least 10 hr prior to stress testing. Patients on beta-

Received Jun. 27, 1994; revision accepted Jan. 3, 1995.

For correspondence or reprints contact: Prof. P.J. Ell, Institute of Nuclear Medicine, University College London Medical School, Mortimer St., London W1N 8AA, United Kingdom.

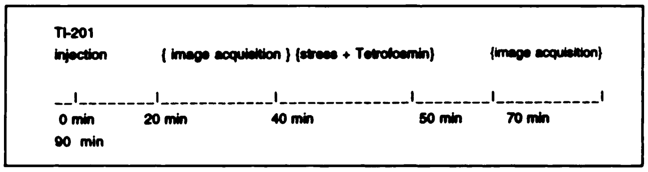

FIGURE 1. Time scale of combined tetrofosmin/thallium protocol.

blockers were asked to withhold the drug for 48 hr prior to the test, and those on dipyridamole were asked to withhold the drug for 72 hr prior to the test. An intravenous cannula was inserted in the right arm, and a three-way stopcock was attached and flushed with normal saline.

Thallium-201 Administration and Rest Image Acquisition

Thallium-201 (74 MBq) was injected as a bolus and flushed with normal saline. Imaging was performed 20 min postinjection and images were acquired on an IGE dual-detector cardiac dedicated camera (International General Electric, Milwaukee, WI) equipped with a low-energy, high-resolution collimator and interfaced with an IGE Star 4000i computer. Data were acquired in a 64 × 64 matrix involving 64 step-and-shoot projections over 180° beginning 45° in the right anterior oblique projection. The acquisition time was 25 sec per projection. Energy peaks of 72 and 169 keV were used with 20% windows and no offset.

Stress Testing and Technetium-99m-Tetrofosmin Administration

The combined adenosine/exercise stress protocol was conducted after the first data acquisition. Adenosine in normal saline was infused at a rate of 140 μg/kg/min through a volumetric pump in a 1 mg/ml concentration for 6 min. Concurrently, the patients cycled at a fixed workload of 25 watts on a bicycle ergometer for 6 min. At 4 min of exercise, 370 MBq of ^{99m}Tc-tetrofosmin were injected as a bolus. Pulse and blood pressure were recorded at rest and then every 2 min until the stress test was completed. Patient symptoms and a three-lead electrocardiogram were monitored throughout the test. Immediately following the completion of the stress test, the patients were given chocolate and milk to facilitate rapid clearance from the gallbladder.

Images were acquired 20 min after stress testing. Data were acquired in a 64 × 64 matrix with 64 projections over 180°. An acquisition time of 20 sec per projection was used. The 140 keV energy peak was used with a 20% energy window and no offset.

Protocol Duration

The imaging protocol required 90 min, including the designated intervals between injection and image acquisition, which allowed for image optimization (Fig. 1).

Data Processing

The data from both acquisitions were reconstructed on a Star 4000i computer (General Electric, Milwaukee, WI) utilizing a Hanning prefilter with a cutoff frequency of 0.8 cycles/cm. A ramp filter was applied during backprojection. The reconstructed transaxial slices were then reoriented into vertical long, horizontal long, and short axes.

Data Analysis

The images were studied by three physicians. Any disagreements were resolved by consensus. Qualitative nine-segment analysis was used. The segments were designated as apical and basal segments of each lateral, anterior and inferior wall and septum; and a single segment for the apex. The segments were scored as normal or abnormal (for abnormal segments, the decreased count was scored as fixed or reversible). In the event of disparity, a consensus was reached between the participating observers.

When the image results were analyzed with respect to coronary artery anatomy, the segments were assigned anatomic regions as follows: left anterior descending artery: basal and apical anterior wall, basal apical septum, apex; left circumflex artery: basal and apical lateral wall; right coronary artery: basal and apical inferior wall.

RESULTS

Hemodynamics

While undergoing adenosine plus exercise stress protocol, the mean heart rate of the subjects rose from 63.6 ± 9.8 to 90.3 ± 20.4 bpm. The mean diastolic blood pressure did not change significantly, from 82.6 ± 10.1 at rest to 83.7 ± 10.1 mmHg at peak stress. The change in mean systolic readings was from 133.1 ± 17.4 to 144.1 ± 17.8 mmHg. The mean double product rose from 8527 ± 2126 to 13,197 ± 4126 mmHg/min.

Cardiac Catheterization

Coronary angiographic results were analyzed. A vessel displaying greater than 50% stenosis on the angiogram was considered diseased. In 4 patients, all three coronary vessels were diseased; 8 patients had two-vessel disease, 10 patients had single-vessel disease and 3 patients had normal coronary arteries. Affected vascular territories comprised 12 lesions of the left anterior descending artery (LAD) territory, 10 lesions of the left circumflex (LCx) territory and 16 lesions of the right coronary artery (RCA) territory.

SPECT Images

Segments were scored in terms of the images obtained (i.e., fixed, reversible or normal) and compared with cardiac catheterization results in the designated vascular territories as described previously. For the LAD territory, the protocol showed a sensitivity of 85% (34/40 segments) for the detection of a diseased vessel; the specificity was 70% (59/84). For the RCA, the results were 78% (28/36) and 71% (10/14), respectively; for the LCx, they were 69% (9/13) and 70% (26/37), respectively.

The territories of the LCx and RCA were then analyzed in combination. These images showed a specificity of 76% and sensitivity of 70%. Overall sensitivity was 80% and specificity was 70% (Table 1).

DISCUSSION

Nuclear medicine physicians have reservations about using two different imaging agents to evaluate CAD in a single subject. In designing this protocol, we attempted to address some of the concerns that might arise.

The rationale for performing stress ^{99m}Tc-tetrofosmin imaging after rest ^{201}Tl imaging, and not in the reverse order, was to prevent Compton scatter of ^{99m}Tc activity into the ^{201}Tl photopeak, which would affect the thallium

TABLE 1
Sensitivity and Specificity of Combined Thallium-201/ Technetium-99m-Tetrofosmin Protocol to Detect Coronary Artery Disease

Site	Sensitivity	Specificity
LAD	85% (34/40)	70% (59/85)
RCA	78% (28/36)	71% (10/14)
LCx	69% (9/13)	70% (26/37)
Combined LCx + RCA	76% (37/49)	71% (36/51)
Overall	80% (71/89)	70% (95/136)

Numbers in parentheses represent the number of segments. LAD = left anterior descending artery; RCA = right coronary artery; LCx = left circumflex artery.

images, creating the potential for overestimation of reversible ischemia. Additionally, the protocol was designed with emphasis on decreasing patient time in the nuclear medicine department. Had the stress study been conducted first, one would have to allow sufficient time for the myocardium to return completely to the resting state before undertaking the rest study, thereby lengthening the patient's stay in the department.

Accepting that the physical properties of the two agents differ, data acquisition was adapted to suit the characteristics of each radionuclide. A high-resolution collimator was used, and the acquisition time for ^{201}Tl rest images was increased to 25 sec per projection compared with 20 sec for ^{99m}Tc-tetrofosmin. Appropriate energy windows of 72 and 169 keV for ^{201}Tl and 140 keV for tetrofosmin were used.

Investigators studying the characteristics of ^{99m}Tc-tetrofosmin have concluded that imaging may be performed 5–30 min postinjection (*7,9,15*). We have found that the optimum time is 20–40 min postinjection. Higley et al. (*9*) showed high gallbladder activity of 3.2% ± 1.9% of total injected activity 5 min after stress injection, which had fallen to 1.0 ± 0.5% by 60 min. To expedite gallbladder clearance in this study, we asked patients to ingest 200 ml of milk and 50 g of chocolate immediately after exercise. Good quality images were obtained 20 min after stress testing, with low activity recorded in the region of the gallbladder.

Because tetrofosmin does not have redistribution characteristics (*13*), it is necessary for patients to receive two separate injections of the radionuclide to assess defect reversibility. Therefore, the one-day protocol involved injection at maximal stress followed by image acquisition 5–30 min later and reinjection 4 hr later, with imaging after 30 min. A two-day protocol involves conducting these two studies more than 24 hr apart. In a study of 23 patients, Sridhara et al. (*11*) found no significant difference in the detection of CAD between these two methods. In the same study, a favorable comparison emerged in the identification of CAD: ^{201}Tl correctly identifying 83% of abnormal segments, whereas ^{99m}Tc-tetrofosmin identified 80% and 83% of diseased segments on the early and late images, respectively. In a study of 26 patients, Nakajima et al. (*15*) showed concordance of 83% between images obtained with ^{201}Tl in a rest/redistribution protocol and with ^{99m}Tc-tetrofosmin in a one-day protocol in the same patients; however, tetrofosmin's sensitivity in detecting coronary disease was lower: 60% compared with 72% for ^{201}Tl.

Thus, the overall sensitivity and specificity (80% and 70%, respectively) in this study of a combined protocol of tetrofosmin and thallium are similar to those reported for the use of tetrofosmin alone but are somewhat lower than values obtained with thallium imaging alone, ranging from 72% to 92% for sensitivity and 84% to 100% for specificity (*15–19*). Figure 2 demonstrates an example of the good quality of the images.

To evaluate the usefulness of this protocol in detecting viable myocardium, further studies need to be performed to assess tetrofosmin's potential. Thallium has been established as a useful agent, but in a stress/redistribution protocol alone, thallium tends to underestimate the presence of ischemic, but viable myocardium (*19*). Better results

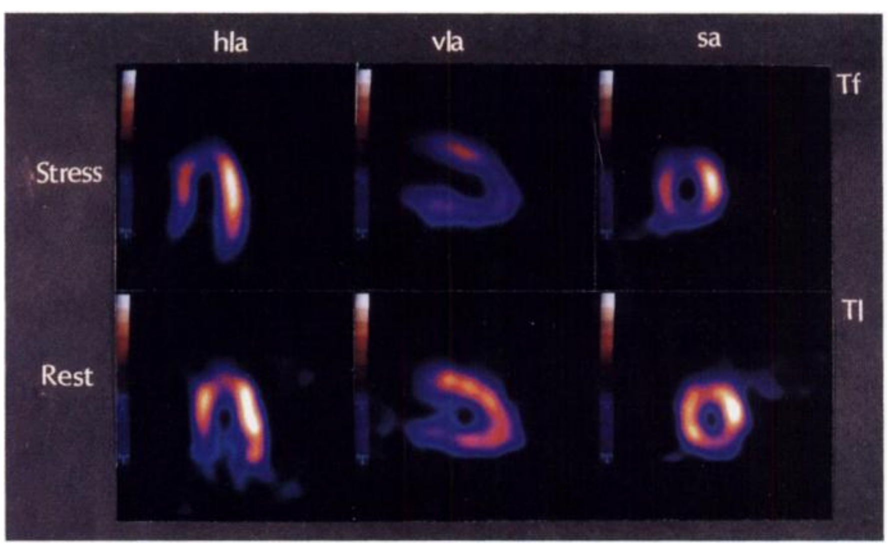

FIGURE 2. Stress/^{99m}Tc-tetrofosmin (upper row) and rest/^{201}Tl (lower row) study. Horizontal long-axis (hla), vertical long-axis (vla) and short-axis (sa) slices are displayed, demonstrating reversible ischemia in the anterior and inferior walls. Coronary angiography confirmed disease of the LAD and RCA.

have been obtained by reinjection of thallium following the standard stress/redistribution imaging, identifying viable or nonviable segments in the same regions as PET with ^{18}F-fluorodeoxyglucose (*20*). The current protocol combining tetrofosmin and thallium would benefit from delaying thallium imaging by 3–4 hr or longer after the rest thallium injection to assess rest-redistribution, both of which would further contribute to accuracy in myocardial viability assessment.

Adenosine infusion coupled with 25 W of ergometer pedaling for 6 min was employed as the stress procedure in this study in keeping with routine clinical practice in this institute. In a previous study comparing the use of adenosine alone with this combination in dynamic exercise, we found little difference in overall sensitivity and specificity in the detection of coronary artery disease between the two groups, but a lesser degree of noncardiac side effects was recorded in the exercise group (*21*).

Limitations. This study compared the results of segmental analysis of combined thallium/tetrofosmin protocol images with coronary angiographic data to obtain sensitivity and specificity values for the detection of diseased segments. Coronary angiography has not been proven to be the gold standard in the assignation of definite regions with respect to myocardial perfusion, and results must be interpreted with an awareness of its limitation as a frame of reference.

Further studies of this combined protocol could be performed comparing the results with those of thallium imaging alone or tetrofosmin alone conducted sequentially in the same subjects. This would assess both comparative accuracy in identifying defects consistent with coronary stenoses as well as the protocol's ability to identify these defects as fixed or reversible in the same regions as the single agent protocol. This, however, raises ethical considerations of performing the stress test twice, as well as an increased radiation dose per subject.

CONCLUSION

A combined myocardial imaging protocol involving ^{201}Tl scintigraphy at rest, followed by ^{99m}Tc-tetrofosmin imaging after stress, is a useful method to investigate the presence of CAD. A multidetector gamma camera has proven useful for establishing this rapid protocol, which results in high resolution images. The decreased duration of 90 min compared to more than 4 hr confers an advantage of this protocol over the use of thallium or tetrofosmin as single agents. The sensitivity and specificity in the detection of coronary artery stenosis, as shown on coronary angiography, are similar to that of tetrofosmin as a single agent, but they are less than thallium alone.

REFERENCES

1. Strauss HW, Pitt B. Thallium-201 as a myocardial imaging agent. *Semin Nucl Med* 1977;7:49–58.
2. Kaul S. A look at 15 years of planar thallium-201 imaging. *Am Heart J* 1989;118:581–601.
3. Okada RD, Glover D, Gaffeny T, Williams S. Myocardial kinetics of technetium-99m-hexakis-2-methoxypropylisonitrile. *Circulation* 1988;77:491–498.
4. Wackers FJ Th, Berman DS, Maddahi J, et al. Technetium-99m hexakis 2-methoxyisobutyl isonitrile: human biodistribution, dosimetry, safety and preliminary comparison to thallium-201 for myocardial perfusion imaging. *J Nucl Med* 1989;30:301–311.
5. Iskandrian A, Heo J, Nguyen T, Mercuro J. Myocardial imaging with Tc-99m teboroxime: technique and initial results. *Am Heart J* 1991;121:889–894.
6. Beller GA, Watson DD. Physiological basis of myocardial perfusion imaging with the technetium-99m agents. *Semin Nucl Med* 1991;21:173–181.
7. Sridhara BS, Braat S, Rigo P, Itti R, Cload P, Lahiri A. Comparison of myocardial perfusion imaging with technetium-99m tetrofosmin versus thallium-201 in coronary artery disease. *Am J Cardiol* 1993;72:1015–1019.
8. Kelly JD, Forster AM, Higley B, et al. Technetium-99m-tetrofosmin as a new radiopharmaceutical for myocardial perfusion imaging. *J Nucl Med* 1993;34:222–227.
9. Higley B, Smith FW, Smith T, et al. Technetium-99m-bis[bis(2-ethoxyethyl) phosphino]ethane: human biodistribution, dosimetry and safety of a new myocardial perfusion imaging agent. *J Nucl Med* 1993;34:30–38.
10. Smith FW, Smith T, Gemmell H, et al. Phase I study of Tc-99m diphosphine(P53) for myocardial imaging [Abstract]. *J Nucl Med* 1991;32:967.
11. Sridhara BS, Braat S, Itti R, Rigo P, Cload P, Lahiri A. Early and late myocardial imaging with a new technetium-99m diphosphine(PPN1011) in coronary artery disease [Abstract]. *J Am Coll Cardiol* 1992;19:202A.
12. The Tetrofosmin Study Group. Comparative myocardial perfusion imaging with Tc-99m-tetrofosmin and thallium-201: results of phase-III international trial [Abstract]. *Circulation* 1992;86(suppl I):I-506.
13. Jain D, Wackers FJ Th, McMahon M, et al. Is there any redistribution with Tc-99m-tetrofosmin imaging: a quantitative study using serial planar imaging [Abstract]. *Circulation* 1992;86(suppl I):I–46.
14. Jain D, Wackers FJ Th, Mattera J, McMahon M, Sinusas AJ, Zaret BL. Biokinetics of technetium-99m-tetrofosmin: myocardial perfusion agent: implications for a one-day imaging protocol. *J Nucl Med* 1993;34:1254–1259.
15. Nakajima K, Taki J, Shuke N, Bunko H, Takata S, Hisada K. Myocardial perfusion imaging and dynamic analysis with technetium-99m-tetrofosmin. *J Nucl Med* 1993;34:1478–1484.
16. Nguyen T, Heo J, Ogilby JD, Iskandrian AS. Single photon emission computed tomography with thallium-201 during adenosine-induced coronary induced hyperemia: correlation with coronary arteriography, exercise thallium imaging and two-dimension echocardiography. *J Am Coll Cardiol* 1990;16:1375–1383.
17. Francisco DA, Collins SM, Go RT, Ehrhardt JC, Kirk OC, Marcus ML. Tomographic thallium-201 myocardial perfusion scintigrams after maximal coronary artery vasodilation with intravenous dipyridamole: comparison of qualitative and quantitative approaches. *Circulation* 1982;66:370–379.
18. Verani MS, Mahmarian JJ, Hixson JB, Boyce TM, Standacher RA. Diagnosis of coronary artery disease by controlled coronary vasodilation with adenosine and thallium-201 scintigraphy in patients unable to exercise. *Circulation* 1990;82:80–87.
19. Nishimura S, Mahmarian JJ, Boyce TM, Verani MS. Equivalence between adenosine and exercise thallium-201 myocardial tomography: a multicenter, prospective crossover trial. *J Am Coll Cardiol* 1992;20:265–275.
20. Bonow RO, Dilsizian V, Cuocolo A, Bacharach SL. Identification of viable myocardium in patients with chronic coronary artery disease and left ventricular dysfunction. Comparison of thallium scintigraphy with reinjection and PET imaging with F-18 fluorodeoxyglucose. *Circulation* 1991;83:26–37.
21. Mahmood S, Gupta NK, Gunning M, Bomanji JB, Jarrit PH, Ell PJ. 201-Tl myocardial perfusion SPET: adenosine alone or combined with dynamic exercise. *Nucl Med Commun* 1994;15:586–592.