Assessing Coronary Artery Disease with Dipyridamole Technetium-99m-Tetrofosmin SPECT: A Multicenter Trial

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Exercise ^{99m}Tc-tetrofosmin myocardial scintigraphy is as accurate as exercise ^{201}Tl imaging. Thus far, no data are available on tetrofosmin imaging during pharmacologic stress. We evaluated the feasibility of using ^{99m}Tc-tetrofosmin myocardial SPECT during vasodilation with dipyridamole for detecting coronary artery disease. **Methods:** Sixty-four patients, enrolled in three centers in the U.S., underwent one-day dipyridamole/rest tetrofosmin SPECT. Coronary angiography, performed in 59 patients within 2 mo of the SPECT study, revealed normal coronary arteries or insignificant coronary stenosis in 11 patients and significant (≥50% luminal diameter stenosis) coronary stenoses in 48 patients. **Results:** Sensitivity and specificity of tetrofosmin SPECT for detecting coronary artery disease were 85% and 55%, respectively, in the overall population and 81% and 55% in patients without prior coronary artery bypass surgery. The overall sensitivity and specificity of tetrofosmin tomographic imaging for detection of individual coronary stenoses were 53% and 72%, respectively, in the overall population and 54% and 80% in the patients without prior coronary artery bypass surgery. **Conclusion:** One-day dipyridamole/rest ^{99m}Tc-tetrofosmin myocardial perfusion imaging is feasible and has a high sensitivity for detection of coronary artery disease.

Key Words: technetium-99m-tetrofosmin; coronary artery disease; SPECT; dipyridamole

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It has been well documented that myocardial perfusion imaging is an accurate technique for noninvasive detection of coronary artery disease (*1*). The most widely used agent for myocardial perfusion imaging has been ^{201}Tl (*2*). Technetium-99m has several advantages over ^{201}Tl, such as a more suitable photon energy, a shorter half-life and greater availability. During the last decade, several ^{99m}Tc-labeled compounds have been developed. Among them, sestamibi and teboroxime have been approved for clinical use in the U.S. and abroad (*3*).

Technetium-99m-tetrofosmin is another new myocardial perfusion agent (*4–7*). Experimental studies have shown that its distribution in the myocardium is proportional to the regional myocardial blood flow (*6*). In humans, this radioactive tracer clears rapidly from the blood and extracardiac structures after an intravenous injection (*7–9*) and undergoes only minimal redistribution in the myocardium (*7*). In a recent phase III multicenter clinical trial, ^{99m}Tc-tetrofosmin myocardial imaging during exercise compared well with ^{201}Tl imaging in patients with coronary artery disease (*10*).

Although myocardial imaging using ^{201}Tl and ^{99m}Tc-sestamibi in conjunction with either dipyridamole or adenosine is comparable to exercise imaging (*11–20*), no data are available on tetrofosmin imaging in conjunction with dipyridamole. Therefore, the purpose of the present study was to evaluate the value of ^{99m}Tc-tetrofosmin myocardial imaging during coronary vasodilation with dipyridamole for detecting coronary artery disease.

MATERIALS AND METHODS

Protocol

The protocol involved an open-label, multicenter study (Baylor College of Medicine and The Methodist Hospital; Philadelphia Heart Institute; Creighton University Medical Center) designed to determine the sensitivity, specificity and predictive accuracy of ^{99m}Tc-tetrofosmin SPECT in conjunction with dipyridamole to detect coronary artery disease. A secondary goal was to determine the ability of this technique to predict the location of coronary artery stenoses. The study protocol consisted of two injections of ^{99m}Tc-tetrofosmin on the same day, the first (185–296 MBq, 5–8 mCi) 4 min after the infusion of dipyridamole (0.56 mg/Kg over 4 min) and the second (555–888 MBq, 15–24 mCi) at rest, 4 hr later (Fig. 1). Written informed consent was obtained from each patient and the protocol was approved by the Institutional Review Board of Medical Investigations in each participating institution.

Study Population

Patients older than 30 yr of age referred for the evaluation of known or suspected coronary artery disease were eligible for inclusion into the study. The patients were required to have coronary angiography within 2 mo of the nuclear myocardial imaging.

Patients with the following conditions were excluded from the study: historical or clinical evidence of bronchospasm; recent myocardial infarction (within 1 wk of the scans); persistent unstable angina within 3 days of study entry; decompensated congestive heart failure; primary valvular disease; left bundle branch block; congenital heart defect; cardiomyopathy; uncontrolled arrhythmias; second- or third-degree heart block; a significant vascular event or coronary intervention during the interval between the invasive and noninvasive studies; use of caffeine- or theophylline-containing products within 12 hr before the test; and unwillingness or inability to comply with the protocol.

Radiopharmaceutical Preparation

Each tetrofosmin vial was reconstituted with 4–8 ml of a sterile sodium pertechnetate solution containing less than 1110 MBq/ml (30 mCi/ml) of ^{99m}Tc. The vial was then shaken gently to ensure complete dissolution of the lyophilized powder and allowed to stand at room temperature (15°–25°C) for 15 min. Determination of radiochemical purity was performed before use. The injectate was stored at room temperature (15°–25°C) and used within 8 hr of reconstitution.

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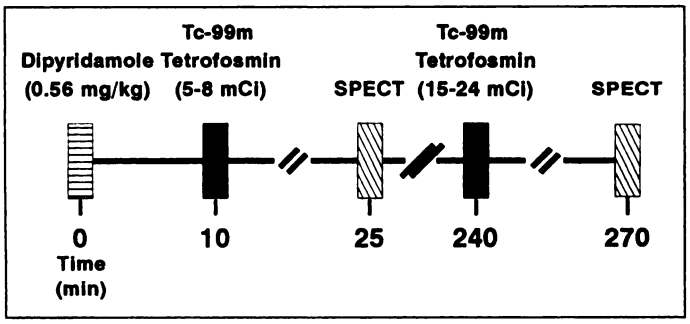

FIGURE 1. Dipyridamole/rest ^{99m}Tc-tetrofosmin SPECT protocol.

Acquisition and Reconstruction of SPECT Imaging

Image acquisition began 15 to 30 min after administration of ^{99m}Tc-tetrofosmin. The rest injection was performed 3 to 4 hr after completion of the stress acquisition. The SPECT study was performed on a single-head gamma camera equipped with a high-resolution collimator, with the energy discriminator set at a peak energy of 140 keV and a 20% window. Projections (n = 32) were obtained over a 180° arc using a 64 × 64 matrix and word mode with an acquisition time of 40 sec/step for the stress study and 25 sec/step for the rest study. All raw data were placed on floppy disks and submitted to the core laboratory for standardized processing.

Reconstruction of SPECT imaging was performed at the core laboratory (Philadelphia Heart Institute). Myocardial tomograms were reconstructed with a filtered backprojection algorithm using a Butterworth filter (cutoff frequency of 0.50 and order of 10). Transaxial slices were then reoriented into the short, horizontal long and vertical long axes.

Interpretation

The data processed in the core laboratory were used for the blinded interpretation, which was obtained by consensus of three experienced investigators. The images during stress and rest were displayed side-by-side. Left ventricular myocardium was divided into 13 segments (Fig. 2). A graded score was applied to the stress and rest images expressing the tracer activity: a score of 0 corresponded to normal activity and a score of 4 to absent activity, with scores of 1, 2 and 3 corresponding to progressively less activity. A score of 2 or more was considered abnormal. Liver and bowel were visually evaluated as mild, moderate or large in comparison with myocardial activity (less, equal or more than myocardial activity, respectively). Image quality was scored on a scale of 1 to 10 (1 = poor, 10 = excellent).

Coronary Angiography

All angiographic data were sent to the core laboratory (Philadelphia Heart Institute) and interpreted by a blinded experienced angiographer. Quantitative analysis was used to determine the severity of coronary stenoses. Angiographically significant coronary artery disease was defined as 50% or more luminal diameter stenosis of epicardial coronary arteries or their major branch. Fifty percent or more luminal diameter stenosis in the grafts, in the bypassed vessel distal to the graft insertion or in an unbypassed artery was considered significant when patients had had prior coronary artery bypass surgery.

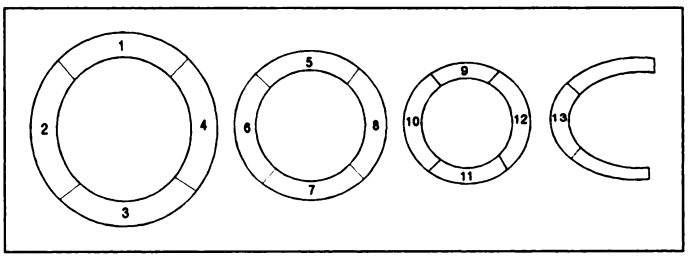

FIGURE 2. Diagram of the left ventricular segmentation scheme used for interpretation of ^{99m}Tc-tetrofosmin SPECT imaging. Segments 1, 5, 9: anterior wall; segments 2, 6, 10: septum; segments 4, 8, 12: lateral wall; segments 3, 7, 11: inferior wall; segment 13: apex.

TABLE 1
Demographic Data

	Number (%)
Mean age	57 yr (range 36–82 yr)
Men	41 (64%)
Previous myocardial infarction	33 (52%)
Prior bypass grafts	11 (18%)
Prior angioplasty	11 (18%)

SPECT image data were related to specific coronary territories in a standard manner used in our laboratory (*21*): anterior or septal defects were assigned to the left anterior descending artery; inferior defects to the right coronary artery; and lateral defects to the circumflex coronary artery. Apical defects were assigned to the artery corresponding to defects contiguous with the apex.

Statistical Analysis

Data were expressed as mean ± s.d. To assess the level of agreement between tetrofosmin imaging and coronary arteriography, kappa statistics were calculated. This statistic is a measure of agreement in excess of that attributable to chance and ranges from −1 to 1. Values above 0 indicate better than chance agreement, whereas 1 indicates perfect agreement and −1 total disagreement.

RESULTS

Demographic Data

Sixty-four patients were recruited into the study. Their demographic data are summarized in Table 1. Two patients who had angiography more than 2 mo before tetrofosmin imaging, and three patients who did not undergo coronary angiography were not included in the accuracy analysis.

Electrocardiographic Changes and Symptoms During Dipyridamole Administration

During dipyridamole infusion, eight patients (13%) had abnormal ST-segment depression (≥1 mm depression measured at 80 msec after the J point), and 55 patients (87%) had no ST-segment depression. Overall, 43 patients (67%) experienced side effects considered to be related to dipyridamole. Forty-three patients (67%) received aminophylline to treat their side effects.

Imaging Evaluation

The number of patients achieving quality evaluation scores of 7 or greater (good or excellent) was 50 (78%), whereas the numbers of patients with fair or poor quality images were 13 (20%) and 1 (2%), respectively.

After dipyridamole, 39 patients (61%) exhibited mild liver activity, with 14 (22%) and 11 (17%) patients exhibiting moderate and large liver activity, respectively. The corresponding figures for the rest images were 46 (72%), 10 (16%) and 8 (13%). At stress, 53 patients (83%) had mild bowel activity, with 9 (14%) and 2 (3%) patients exhibiting moderate and severe bowel activity, respectively. The corresponding figures for rest were 56 (88%), 6 (9%) and 2 (3%).

Accuracy for Detection of Coronary Artery Disease

Coronary arteriographic data were available in 59 patients. Among them, 11 patients (19%) had either normal coronaries or insignificant coronary stenosis. Forty-eight patients (81%) had significant coronary artery disease: 27 patients (46%) had

TABLE 2
Agreement between Technetium-99m-Tetrofosmin SPECT and Coronary Angiography to Assess Coronary Artery Disease

		^{99m}Tc-Tetrofosmin SPECT		
		Normal	Abnormal	Total
Angiography	Normal	6	5	11
	Abnormal	7	41	48
	Total	13	46	59

Exact agreement: 80%; kappa = 0.38.

single-vessel disease, 13 patients (22%) had double-vessel disease and 8 patients (14%) had triple-vessel disease.

Among the 59 patients with coronary arteriography, 13 had normal ^{99m}Tc-tetrofosmin SPECT, 35 had partially (n = 27) or completely (n = 8) reversible defects and 11 had fixed defects.

The agreement between ^{99m}Tc-tetrofosmin SPECT and coronary angiography is summarized in Table 2. With coronary angiography as the gold standard, the sensitivity and specificity of ^{99m}Tc-tetrofosmin SPECT to assess coronary artery disease were 85% and 55%, respectively. An example of an abnormal study is shown in Figure 3. The sensitivity was 78% (21 of 27) in the patients with single-vessel disease and increased to 95% (20 of 21) in the patients with multivessel disease.

Among the 48 patients without prior coronary artery bypass surgery, ^{99m}Tc-tetrofosmin SPECT had a sensitivity of 81% (30 of 37) and a specificity of 55% (6 of 11). The sensitivity was 76% (19 of 25) in patients with single-vessel disease compared to 92% (11 of 12) in patients with multivessel disease.

Accuracy for Detection of Individual Coronary Stenoses

In the overall population with coronary arteriography, 100 arteries were either normal or had insignificant stenosis, and 77 had significant stenoses. The stenoses involved the left descending artery in 26, the left circumflex artery in 25 and the right coronary artery in 26 patients. The overall sensitivity and specificity of ^{99m}Tc-tetrofosmin SPECT for detection of coronary artery disease in individual arteries was 53% (41 of 77) and 72% (72 of 100), respectively. The sensitivity of ^{99m}Tc-tetrofosmin SPECT for detection of coronary artery disease in individual vessels was 48% (13 of 27) in the 27 patients with single-vessel disease and 56% (28 of 50) in the 21 patients with multivessel disease. The sensitivity and specificity of ^{99m}Tc-tetrofosmin SPECT for detecting left anterior descending, left circumflex and right coronary artery disease are summarized in Figure 4.

Among the 48 patients without prior coronary artery bypass surgery, the sensitivity and specificity of ^{99m}Tc-tetrofosmin SPECT for detection of coronary artery disease in individual vessels were 54% (29 of 54) and 80% (72 of 90), respectively (Table 3).

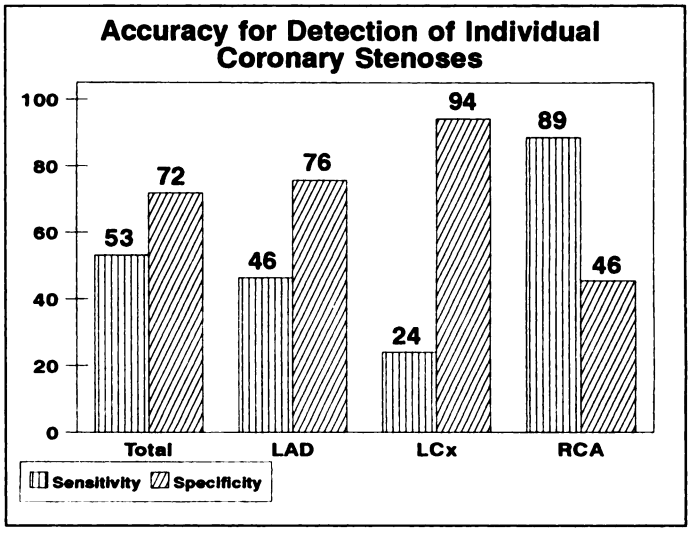

FIGURE 4. Sensitivity and specificity of ^{99m}Tc-tetrofosmin SPECT imaging for detection of any coronary artery disease (total), left anterior descending (LAD), left circumflex (LCx) and right coronary artery (RCA) disease.

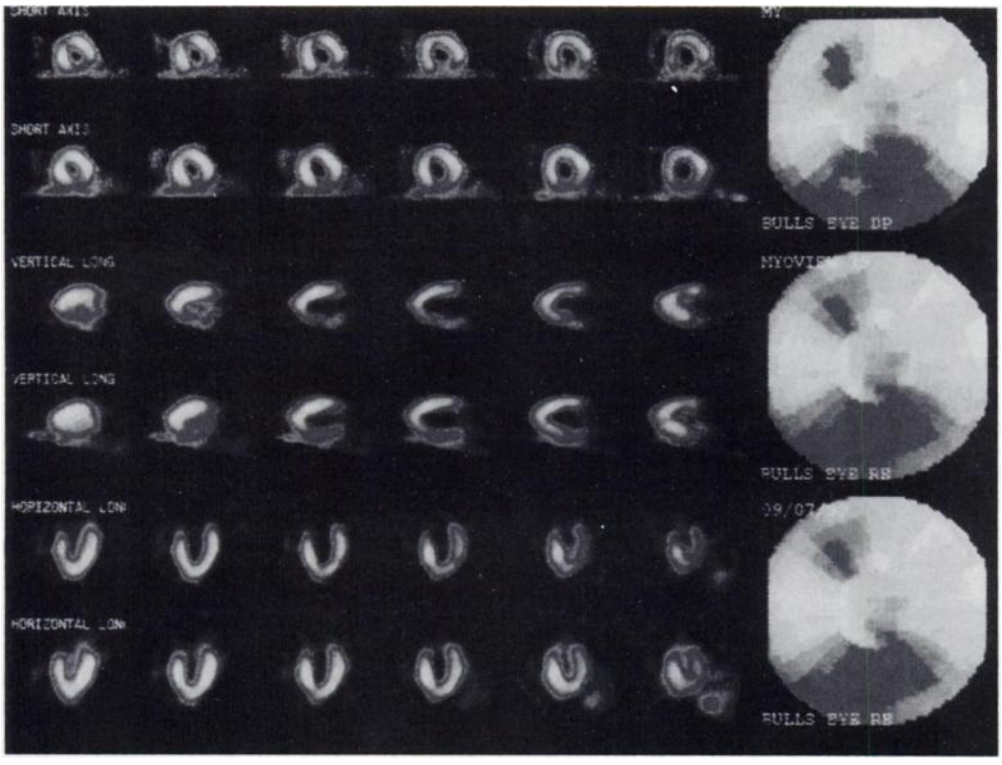

FIGURE 3. Technetium-99m-tetrofosmin SPECT after dipyridamole administration in a 47-yr-old man demonstrated moderate perfusion defects of the inferior and posterior walls, which were reversible in the rest study. Coronary arteriography demonstrated right coronary artery occlusion with collaterals filling the distal artery.

TABLE 3
Sensitivity and Specificity of Technetium-99m-Tetrofosmin SPECT for Individual Coronary Stenoses*

	LAD	LCx	RCA	Total
Sensitivity				
One-vessel disease	53% (8/15)	33% (2/6)	75% (3/4)	52% (13/25)
Two- or three-vessel disease	28% (2/7)	30% (3/10)	92% (11/12)	55% (16/29)
Overall	45% (10/22)	31% (5/16)	88% (14/16)	54% (29/54)
Specificity	92% (24/26)	97% (31/32)	47% (15/32)	80% (72/90)

LAD = left anterior descending artery; LCx = left circumflex artery; RCA = right coronary artery.
*Patients with prior coronary artery bypass surgery were excluded.

DISCUSSION

Radionuclide myocardial perfusion imaging is a well-established modality for assessing myocardial perfusion and viability (*1*). A wealth of information demonstrates that stress ^{201}Tl myocardial imaging is reliable and more accurate than other diagnostic modalities for detecting coronary artery disease. Several ^{99m}Tc-labeled myocardial perfusion agents recently have been developed. The clinical value of myocardial imaging using these agents is already established or is under investigation.

Technetium-99m-Labeled Compounds

Previous studies have demonstrated that stress ^{99m}Tc-sestamibi myocardial scintigraphy has high sensitivity and specificity for detection of angiographic coronary artery disease (*22*). Several studies have shown that the sensitivity and specificity of myocardial images with ^{99m}Tc-sestamibi and ^{201}Tl during either exercise (*22*) or pharmacological stress (*13*) were similar for assessment of coronary artery disease. Technetium-99m-sestamibi also allows assessing ventricular function using either first-pass radionuclide angiography or a gated SPECT technique. Moreover, gated myocardial SPECT using ^{99m}Tc-labeled tracers may assist in differentiating true perfusion defects from artifacts (*23*).

Sinusas et al. (*6*) have shown that myocardial ^{99m}Tc-tetrofosmin activity 15 min after injection correlated linearly with microsphere flow during pharmacologic vasodilation in dogs. In comparison with microspheres-determined flow, myocardial tetrofosmin activity underestimated flow at flows exceeding 1.5–2.0 ml/min/kg and overestimated flow at low flows, in a similar fashion as ^{201}Tl and ^{99m}Tc-sestamibi.

Previous studies have demonstrated that ^{99m}Tc-tetrofosmin imaging is accurate for detecting coronary artery disease (*24–27*). A large phase III multicenter trial demonstrated that tetrofosmin planar imaging had a sensitivity of 77% and specificity of 58% for diagnosing coronary artery disease, compared to 83% and 48%, respectively, by ^{201}Tl imaging (*10*). Gated myocardial SPECT with ^{99m}Tc-tetrofosmin has been shown to correlate well with cine MRI for assessment of regional left ventricular wall motion abnormalities (*28*). Technetium-99m-tetrofosmin has some potential advantages over sestamibi: its preparation is easy because it does not require boiling, and imaging can be started as early as 15 min after injection. Tetrofosmin imaging may be useful for assessment of acute myocardial ischemia (*29*), but its value in this realm needs to be validated further.

Vasodilation Compared with Exercise Stress

Both dipyridamole and adenosine can cause inhomogeneous myocardial blood flow distribution in patients with coronary artery disease, which results in myocardial perfusion defects (*30*). Previous studies have demonstrated that the accuracy of myocardial perfusion imaging during pharmacologic vasodilation is similar to that of exercise in combination with either ^{201}Tl or ^{99m}Tc-sestamibi (*11,20,31*). Myocardial imaging using dipyridamole stress is more accurate than that during exercise for detection of coronary artery disease in patients with left bundle branch block (*12,14,17*). Therefore, dipyridamole and adenosine have become increasingly popular alternative stressors for myocardial perfusion imaging, particularly in patients unable to exercise.

The present study is the first to demonstrate that one-day dipyridamole/rest ^{99m}Tc-tetrofosmin SPECT imaging is moderately accurate for assessment of coronary artery disease, with a sensitivity of 85%. The relatively low specificity (55%) of ^{99m}Tc-tetrofosmin SPECT in this study may be attributed to a selection bias. Technetium-99m-tetrofosmin SPECT imaging during vasodilation with dipyridamole had a sensitivity of 53% and a specificity of 72% for localization of coronary artery disease to individual vessels, with the lowest sensitivity (24%) for detection of left circumflex disease, which is consistent with previous studies using ^{201}Tl and sestamibi (*20,31*). The low sensitivity of ^{99m}Tc-tetrofosmin SPECT for detecting coronary artery disease in individual vessels may be due to a low myocardial extraction fraction during high flow states (*32*). This is a physical limitation that is shared by both sestamibi and tetrofosmin. Although the diminished extraction during high flow conditions raises valid concerns about the sensitivity of these agents when used in combination with vasodilator stress, published results of ^{99m}Tc-sestamibi in combination with dipyridamole (*33*) and adenosine (*34*) have shown good clinical results. Our present results indicate comparable results with ^{99m}Tc-tetrofosmin during dipyridamole stress.

Nonetheless, it is conceivable that a decreased extraction may be related to the relatively lower sensitivity for detection of all individual coronary stenoses, as opposed to only the most severe ones. This limitation may be of special importance when one studies patients with only mild to moderate stenoses, which may not be uncovered by a pharmacologic stress.

Study Limitations

First, the study cohort had a high prevalence of coronary artery disease (48 of 59 patients). As discussed above, this patient selection bias may contribute to a low specificity and enhanced sensitivity. Second, subjects with a low likelihood of disease have not been included, hence the normalcy rate of dipyridamole tetrofosmin imaging could not be evaluated. Another limitation is that qualitative, rather than quantitative, analysis was used in the interpretation of tetrofosmin imaging. Finally, the sensitivity for correct localization of individual coronary stenoses was relatively low. It is quite conceivable that this sensitivity would be enhanced by quantitative analysis, as previously shown for both thallium and sestamibi tomography (*20,31*).

CONCLUSION

One-day stress-rest ^{99m}Tc-tetrofosmin myocardial perfusion tomography during dipyridamole-induced coronary vasodilation is moderately accurate for detection of coronary artery disease. Further study directly comparing tetrofosmin imaging during exercise and pharmacologic stress would be of interest.

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