Planar Myocardial Perfusion Imaging with Technetium-99m-Teboroxime: Comparison by Vascular Territory with Thallium-201 and Coronary Angiography

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Myocardial perfusion agents labeled with ^{99m}Tc offer improved physical imaging properties compared to ^{201}Tl. Teboroxime is a new ^{99m}Tc-labeled compound for myocardial perfusion imaging that shows a high myocardial extraction and rapid clearance. Sixty-seven patients underwent planar teboroxime imaging with a rapid acquisition protocol. Agreement of teboroxime and ^{201}Tl for the presence or absence of disease occurred in 56/65 patients (86%). There was agreement (normal or abnormal) between the two agents in 156/195 vessels (80%) and 457/585 segments (78%). When abnormal segments (ischemia or infarction) were compared, teboroxime showed significantly more ischemic segments (89/135, 66%) than did ^{201}Tl (73/135, 54%, $p < 0.05$). Teboroxime offers accuracy comparable to ^{201}Tl for the diagnosis of coronary artery disease and may improve the detection of ischemic or viable myocardium. In addition, its rapid myocardial clearance permits stress/rest imaging in 60–90 min.

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Myocardial perfusion imaging with ^{201}Tl is a well established technique for the evaluation of coronary artery disease that demonstrates good sensitivity and specificity for the diagnosis of coronary stenoses when compared with coronary angiography (*1–3*). However, despite its widespread use and proven utility, thallium has several deficiencies as an imaging agent. The low photon energy of 80 keV is not ideal for Anger camera imaging and results in soft-tissue attenuation artifact. In addition, the relatively long half-life of ^{201}Tl limits the patient dose, which results in lower photon fluence.

Technetium-99m has physical properties that are well suited to Anger camera imaging, while its short half-life allows a high administered activity. Recently two ^{99m}Tc-labeled myocardial perfusion agents, sestamibi and teboroxime, have been released for clinical use. Sestamibi is a hexakis isonitrile compound that has a prolonged myocardial retention, while teboroxime is a BATO compound that has a very high myocardial extraction and rapid myocardial clearance (*4–6*).

The rapid myocardial clearance of teboroxime permits serial stress-rest imaging in as little as 60–90 min (*7,8*). To evaluate the utility of this compound for the detection of coronary artery disease, we compared myocardial perfusion imaging with teboroxime and thallium in a group of patients being evaluated for coronary artery disease.

MATERIALS AND METHODS

Patients

Sixty-seven patients were recruited from those undergoing cardiac catheterization or thallium scintigraphy within the preceding 3 mo. Patients were greater than 18 yr of age, and women with child-bearing potential were excluded. Informed consent was obtained from each patient after the study was approved by the Human Studies Review board at the University of Massachusetts Medical Center. Sixty-five patients underwent both ^{201}Tl and teboroxime imaging, with 25 of these patients also undergoing coronary angiography. Two additional patients underwent teboroxime imaging and coronary angiography without ^{201}Tl imaging. When patients had both ^{201}Tl and teboroxime imaging, ^{201}Tl was performed first.

Technetium-99m-Teboroxime Preparation

Teboroxime was obtained as a lyophilized kit from Squibb Diagnostics, Princeton, NJ. A maximum of 100 mCi [^{99m}Tc] pertechnetate in 1 ml of saline was added to each vial. The vial was placed upright in a 100°C water bath for 15 min and allowed to cool to room temperature. Radiochemical purity was checked with paper chromatography as previously described (*7*). Radiochemical purity exceeded 90% in all cases.

Thallium-201 Scintigraphy

All patients underwent a maximum symptom-limited treadmill exercise test using the standard Bruce protocol. Electrocar-

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diograms, blood pressures and heart rates were recorded during each stage of exercise and cardiac rhythm was continuously monitored. At peak exercise 2.0–2.8 mCi of ^{201}Tl were injected intravenously and exercise continued for 30–60 sec. Planar Anger camera imaging using the 80 keV photopeak of ^{201}Tl was performed with images acquired in a 128 × 128 matrix. The 45° left anterior oblique (LAO), anterior and left lateral views were obtained for 7 min each. Delayed ^{201}Tl imaging was performed 3–4 hr later in a similar manner.

Teboroxime Scintigraphy

Exercise testing, as described for ^{201}Tl scintigraphy, was performed. At peak exercise, 17 to 25 mCi ^{99m}Tc-teboroxime were injected followed by planar myocardial imaging. Patients were then rapidly positioned (seated or standing) in front of the gamma camera. Patient imaging was begun within 1 min of the discontinuation of exercise.

The first 45 patients underwent planar imaging using a dynamic acquisition protocol. The heart was continuously monitored on the video display of the gamma camera, and images were acquired in dynamic acquisition mode in a 64 × 64 matrix at 20 sec/frame. Patients were rotated in a chair or while standing, and 40–80 sec (2–4 frames) of data were obtained in the anterior, 45° LAO and left lateral positions after blood-pool clearance. A similar imaging protocol was repeated at rest after a second injection of teboroxime.

The next 22 patients underwent planar teboroxime imaging using a static imaging protocol. The 45° LAO, anterior and left lateral images were acquired in static mode in a 128 × 128 matrix with 45 sec/image. Similar imaging was also performed at rest after a second injection of teboroxime.

The imaging sequence varied, with 46 patients undergoing stress imaging first and 21 patients undergoing rest imaging followed by stress imaging. In all patients, images were collected within 5 min of teboroxime injection. Because of the rapid myocardial clearance of teboroxime, there was no apparent difference between the two imaging sequences. In addition, no differences were noted in the correlation of the teboroxime images from dynamic or static studies, so all studies were combined. All images were considered to be of diagnostic quality. Of note, the static images appeared of slightly higher visual quality than the summated dynamic frames. The stress/rest teboroxime studies were completed within 1–2 hr as opposed to the 3–4 hr required for stress/redistribution ^{201}Tl imaging.

Image Analysis

Both the teboroxime and the ^{201}Tl scans were analyzed on a computer display and on film by at least two observers who were blinded to patient data. Each scan was divided into nine segments (three segments/view), and the activity in each segment was visually assessed. Segments that were abnormal with stress imaging were visually assessed for improvement with rest imaging. Those segments that showed no change from stress to rest were considered to represent myocardial infarct while segments that showed definite improvement from stress to rest were interpreted as ischemia. Segmental perfusion abnormalities were assigned to the three coronary artery territories as shown in Figure 1. Segments 1, 4 and 9 were assigned to the left anterior descending artery, segments 3, 5 and 7 to the right coronary artery and segment 6 to the left circumflex artery. Isolated apical defects (segments 2 or 8) were interpreted as diagnostic for coronary artery disease, but were nonspecific for vessel territory.

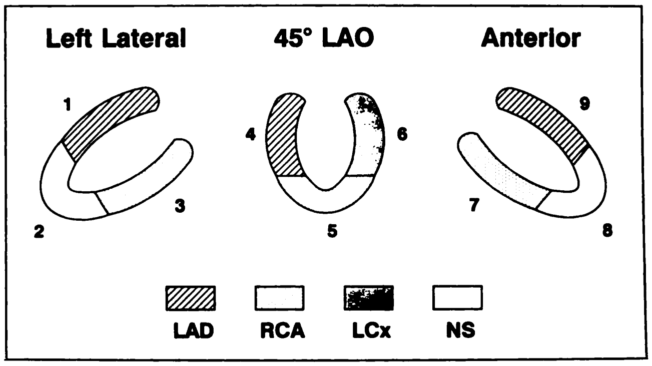

FIGURE 1. Diagrammatic representation of planar perfusion scan illustrating assignment of ventricular segments to vessel territories. LAO = left anterior oblique; LAD = left anterior descending artery; RCA = right coronary artery; LCX = left circumflex artery; NS = nonspecific territory.

Teboroxime and ^{201}Tl studies were compared for the determination of normal or abnormal scans, and individual segments were compared for the presence of ischemia, infarction or normal perfusion. A comparison of teboroxime and ^{201}Tl for each coronary artery territory was also performed.

Cardiac Catheterization

A subgroup of 27 patients underwent coronary angiography. In this group of patients, teboroxime and ^{201}Tl imaging were compared with angiography for the presence of coronary disease and for detection of disease in individual coronary arteries. Significant angiographic coronary artery disease was defined as ≥50% reduction in luminal diameter.

Statistics

Data are reported as mean ± s.d. Sensitivity was defined as the number of true-positive tests multiplied by 100 and divided by the sum of the true-positive and false-negative tests. Specificity was defined as the number of true-negative tests multiplied by 100 and divided by the sum of the true-negative and false-positive tests. Accuracy was defined as the sum of the true-positive and true-negative tests multiplied by 100 and divided by the total number of tests. Comparisons of means for the exercise variables were made with paired Student's t-test. Frequency data were compared using McNemar's test. Agreement of thallium and teboroxime scans was assessed using the Kappa (K) statistic. A K value of <0.40 shows poor agreement, a value of 0.40 to 0.75 represents fair to good agreement, and a value of >0.75 represents excellent agreement (*9*). Statistical computations were performed with the SAS or BMDP software (*10,11*).

RESULTS

Patient Population

The 67 patients included 53 men and 14 women with a mean age of 58 ± 12 yr. Thirty-six patients (54%) had a history of myocardial infarction, 29 (43%) were treated with beta antagonists and 30 (45%) were treated with calcium antagonist medications. Medications were not routinely discontinued before the exercise tests.

Exercise Parameters

The comparative exercise variables for stress ^{201}Tl and teboroxime tests (Table 1) showed similar final exercise stage, exercise

TABLE 1
Comparison of Exercise Testing in 65 Patients

	Teboroxime	^{201}Tl
Exercise stage	3.0 ± 1.0	3.1 ± 0.9
Exercise duration (min.)	8.1 ± 2.8	8.4 ± 2.7
% Maximum predicted heart rate	81 ± 3	86 ± 12*
Double product (mm Hg × bpm)	22,928 ± 7303	24,360 ± 7428
Chest pain	11/64 17%	16/64 25%
ECG ST-depression ≥1 mm	16/65 25%	25/65 38%*

* $p < 0.05$, teboroxime vs. ^{201}Tl exercise tests.

duration and heart rate-blood pressure product. Slightly more patients had ECG ST-depression at a higher mean percentage of maximum predicted heart during the ^{201}Tl exercise tests than during the teboroxime tests.

Detection of Coronary Artery Disease

Stress teboroxime and ^{201}Tl imaging were concordant for the presence of coronary artery disease in 56/65 patients (86%, K = 0.62). Agreement was 85% in patients with a history of myocardial infarction and 87% in those without. The overall sensitivity by planar teboroxime imaging was 90% (19/21) and 90% (18/20) by ^{201}Tl for the detection of coronary artery disease in the subgroup of patients who underwent coronary angiography. In the few patients who did not have coronary artery disease by coronary angiography, the specificity was 50% (3/6) by teboroxime imaging and 40% (2/5) by ^{201}Tl imaging. Only nine patients with coronary angiography had no history of myocardial infarction. In this subgroup, the sensitivities of teboroxime and ^{201}Tl were 71% and 86%, while the specificities were both 50%.

Detection of Disease in Individual Coronary Vessels

In the 65 patients with both teboroxime and ^{201}Tl imaging, disease in individual coronary arteries was diagnosed using the patterns in Figure 1. The overall agreement of teboroxime and ^{201}Tl (Table 2) for the presence of disease in individual coronary arteries was 80% (K = 0.56). This agreement ranged from 75% for disease in the left anterior descending artery to 83% for disease in the left circumflex artery. The sensitivities and specificities of teboroxime and ^{201}Tl imaging for the detection of disease in individual vessels in the subgroup of patients who underwent coronary angiography are shown in Table 3. There was no significant difference between the sensitivity or specificity of teboroxime versus ^{201}Tl in any of the individual vessel territories. Both teboroxime and ^{201}Tl tended toward lower sensitivity (28%, 28%) and higher specificity (85%, 82%) for left circumflex disease than for disease of the left anterior descending or right coronary arteries. However, when comparing detection of disease in individual coronary arteries, only the difference in sensitivity of teboroxime imaging for disease in the left anterior descending artery versus the left circumflex artery was significant.

TABLE 2
Agreement of Teboroxime and ^{201}Tl for Disease in Individual Vessels

Vessel*	Agreement	%
LAD	49/65	75
RCA	53/65	81
LCX	54/65	83
Overall	156/195	80, K = 0.56

* LAD = left anterior descending; RCA = right coronary artery; LCX = left circumflex.

Segmental Analysis

Perfusion in each of the nine segments (Fig. 1) was compared in the 65 patients who had both teboroxime and ^{201}Tl images. There was good agreement for normal versus abnormal perfusion (Fig. 2) with concordance in 457/585 segments (78%, K = 0.51). However, when the pattern of uptake (normal, ischemia, infarct) of teboroxime and ^{201}Tl was compared (Fig. 3), there was concordance in 407/585 segments (70%, K = 0.40) indicating only fair agreement. Because preliminary data suggested that more abnormal segments were interpreted as ischemia with teboroxime than with ^{201}Tl imaging (*7*), the pattern of abnormality was further analyzed in the abnormal segments. When only the segments which were abnormal by both teboroxime and ^{201}Tl were compared (Fig. 4) for the type of abnormality (ischemia or infarction), there were significantly more ischemic segments on the teboroxime images than on the ^{201}Tl images ($p < 0.05$). A patient example (Fig. 5) illustrates the greater areas of ischemia seen on a teboroxime scan compared to a ^{201}Tl scan.

DISCUSSION

Teboroxime is a lipophilic BATO compound that demonstrates both a higher myocardial extraction and less diffusion limitation than ^{201}Tl over a wide range of coronary flows (*4,12*). However, in the range of increased coronary blood flow caused by exercise, both teboroxime

TABLE 3
Sensitivity and Specificity of Teboroxime and ^{201}Tl for Angiographic Coronary Artery Disease by Vessel

	Sensitivity (%)		Specificity (%)	
Vessel*	Teboroxime	^{201}Tl	Teboroxime	^{201}Tl
LAD	70	62	60	55
RCA	67	50	67	54
LCX	28†	28	85	82
Overall	56	45	71	64

* LAD = left anterior descending; RCA = right coronary artery; LCX = left circumflex.
† $p < 0.05$ vs. teboroxime LAD sensitivity.

		Thallium-201 Abnl	Thallium-201 Nl
Teboroxime	Abnl	135	59
	Nl	69	322

Agreement 457/585 (78%)
Kappa=0.51

FIGURE 2. Segmental agreement of teboroxime and ^{201}Tl for the presence of stress defects. Abnl = abnormal segments with stress defects and Nl = normal segments.

and thallium can accurately assess regional perfusion, suggesting that the two agents would show comparable results with stress exercise perfusion imaging (*13*).

The results of this study indicate that teboroxime and ^{201}Tl give comparable diagnostic information with planar exercise perfusion imaging. The two agents were concordant for the presence of coronary artery disease in 56/65 patients (86%). In the subgroup of patients who underwent coronary angiography, teboroxime and ^{201}Tl showed a similar (90%) sensitivity for the detection of coronary artery disease.

In addition to diagnosing the presence of coronary artery disease, ^{201}Tl imaging can determine the particular vessels that are abnormal (*2*). In this study, ^{201}Tl and teboroxime imaging were in agreement about the individual coronary vessels with disease in 80% of the 195 coronary arteries. When compared in the subgroup with coronary angiography, there was no difference in the sensitivity or specificity of teboroxime versus ^{201}Tl for the detection of diseased vessels. Both agents showed a similar tendency toward a lower sensitivity for detection of disease in the left circumflex coronary artery. This lower sensitivity for circumflex disease has been reported in previous studies of planar ^{201}Tl imaging (*14,15*). It may be related to the overlap of myocardium that occurs with planar imaging or to our image analysis which required a defect in one specific segment (posterolateral) for the diagnosis of circumflex disease. Although SPECT ^{201}Tl imaging offers greater accuracy for detection of disease in specific coronary vessels,

		Thallium-201 Inf	Thallium-201 Isch	Thallium-201 Nl
Teboroxime	Inf	29	17	23
	Isch	33	56	36
	Nl	17	52	322

Agreement: 407/585(70%)
Kappa=0.40

FIGURE 3. Segmental agreement of teboroxime and ^{201}Tl for the classification of perfusion. Inf = infarct; Isch = ischemia; Nl = normal.

		Thallium-201 Infarct	Thallium-201 Ischemia
Teboroxime	Infarct	29	17
	Ischemia	33	56

Ischemic Segments
Tebo 89/135(66%)*
Tl-201 73/135(54%)
* p<0.05 vs. Tl-201

FIGURE 4. Segmental agreement of teboroxime and ^{201}Tl for pattern of perfusion abnormality. Tebo = teboroxime.

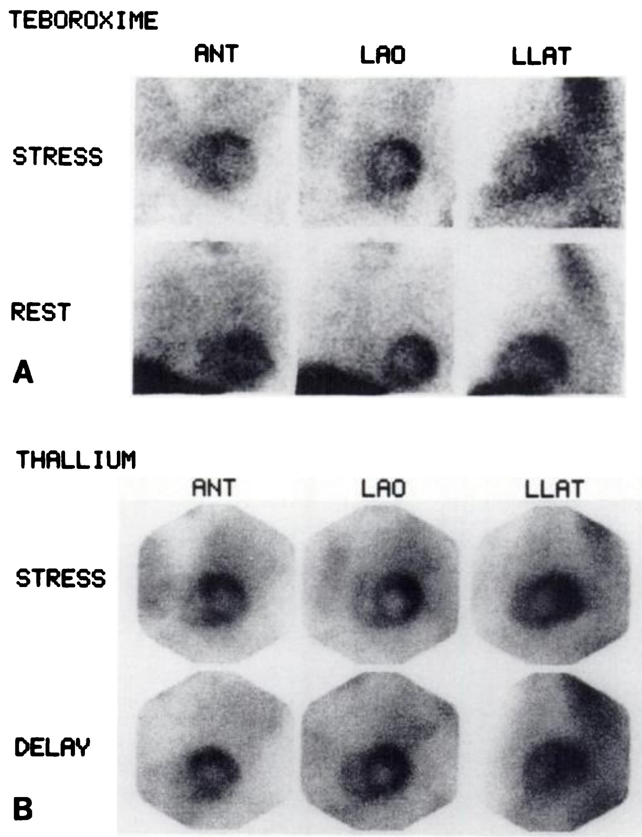

FIGURE 5. Teboroxime (A) and ^{201}Tl (B) scans from the same patient illustrating a greater number of transient defects with teboroxime than with ^{201}Tl. This is apparent in the inferior and apical walls of the anterior view and the distal anterior and apical walls of the left lateral view. LAO = left anterior oblique; ANT = anterior; LLAT = left lateral.

the rapid myocardial clearance of teboroxime may pose a difficulty with SPECT imaging systems (i.e., single-head, step-and-shoot systems) that are designed to collect ^{201}Tl scans.

A comparison of perfusion in each myocardial segment showed a good agreement for the presence of an initial stress defect (normal versus abnormal) between teboroxime and ^{201}Tl. However, when segments were classified as normal, ischemia or infarct, the agreement between teboroxime and ^{201}Tl was only fair. An analysis of the segments classified as abnormal by both agents indicates that teboroxime imaging classifies significantly more segments as ischemic (versus infarcted) than does stress/rest ^{201}Tl. The segmental detection of a transient stress defect with teboroxime but infarct with ^{201}Tl may be the result of separate stress and rest teboroxime injections. Separate stress and rest studies with ^{201}Tl or studies utilizing reinjection can demonstrate more ischemic segments than a single stress injection followed by redistribution imaging (*16,17*).

The high extraction and rapid washout of teboroxime may also result in a higher detection of ischemic segments by allowing completion of teboroxime imaging in 5–10 min versus 20–25 min for ^{201}Tl. This results in a stress image that is free of any contribution by the pattern of rest blood flow during image acquisition. Although teboroxime imaging might also diagnose more areas of ischemia by more accurately reflecting a wider range of coronary flow than ^{201}Tl, that property appears less important in this study. Most of the patients achieved relatively low heart rates (perhaps due to antianginal therapy or to underlying coronary disease), which would result in less than maximal regional flow disparity. The stress ^{201}Tl and teboroxime images of coronary blood flow during exercise detected similar defects (Fig. 2). The higher percentage of maximal heart rate and increased incidence of chest pain (Table 1) after the ^{201}Tl stress may have been due to a training effect since ^{201}Tl was performed first. This could only have increased the detection of ischemic segments on the ^{201}Tl stress studies. Therefore, the linearity of myocardial teboroxime uptake over low to high coronary flow rates is probably less important in accounting for the greater number of ischemic segments detected with teboroxime imaging. Further studies comparing teboroxime imaging with ^{201}Tl reinjection are clearly warranted to assess whether the tracer (teboroxime) or the protocol (separate stress/rest injections) accounts for the improved detection of transient defects.

There are several limitations to this study. Although all patients underwent planar teboroxime imaging, the protocol varied with both stress/rest and rest/stress studies performed. Both dynamic and static acquisition studies were also performed. However, despite these variations in the protocol, all patients underwent rapid planar imaging that was completed within 5 min of teboroxime injection, and there were no systemic differences noted in any of the subgroups. We are currently using the static acquisition protocol because of a subjective assessment of improved image quality.

Not all patients underwent coronary angiography, and almost all who did had coronary disease suggesting a strong selection bias in our study. Such a selection bias may inflate perfusion imaging sensitivity and lower apparent specificity (*18*).

CONCLUSIONS

Teboroxime and ^{201}Tl perfusion imaging give comparable diagnostic information in patients undergoing exercise testing for assessment of coronary artery disease. However, the rapid myocardial clearance of teboroxime allows much faster patient throughput than standard ^{201}Tl imaging. The separate stress/rest tracer injections of teboroxime also result in a higher detection of ischemic segments than does stress and delay ^{201}Tl imaging. Our results, as well as the possible prognostic significance of enhanced ischemia detection, warrant further study of teboroxime myocardial perfusion imaging.

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