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Comparison of Technetium-99m Teboroxime Tomography With Automated Quantitative Coronary Arteriography and Thallium-201 Tomographic Imaging

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Technetium-99m (Tc-99m) teboroxime is a new perfusion tracer that is highly extracted and rapidly cleared by the myocardium. To determine the feasibility of Tc-99m teboroxime imaging in the diagnosis of patients with suspected coronary artery disease, 30 patients underwent single photon emission computed tomography imaging with Tc-99m teboroxime (25.2 ± 1 mCi) at peak exercise and again 60 min later at rest. All patients underwent either a thallium stress test (n = 26) or automated quantitative coronary arteriography (n = 25), or both, without intervening revascularization or infarction. Images were reviewed by two investigators who had no knowledge of clinical data. Coronary lesions with ≥50% diameter narrowing by quantitative coronary arteriography were considered significant.

Both thallium and Tc-99m teboroxime detected disease in all patients with two or three vessel disease. One vessel disease was detected with Tc-99m teboroxime in 9 of 10 patients and with thallium in 8 of 10 (p = NS). In patients without angiographically significant disease, Tc-99m teboroxime demonstrated normal perfusion in six of eight patients and thallium in three of five (p = NS). Overall, when presence or absence of disease detected by Tc-99m teboroxime or thallium was compared with quantitative coronary arteriography, there was no difference between Tc-99m teboroxime and thallium. These results suggest that Tc-99m teboroxime is comparable to thallium as an imaging agent. The rapid biologic half-life, 5.3 min, allows studies to be completed in 60 to 90 min.

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Thallium imaging is a useful adjunct for the diagnosis of coronary artery disease. However, thallium-201 is limited as a tracer by a low photon energy (80 keV), which contributes to problems with attenuation and a long half-life (73 h) that precludes higher doses. Accordingly, several radiopharmaceuticals based on technetium-99m (Tc-99m) have been developed for perfusion imaging. Compared with thallium, Tc-99m has a shorter physical half-life (6 h) and higher photon energy (140 keV), which allows higher count rates to be obtained with use of increased doses and decreased tissue attenuation.

Tc-99m teboroxime (SQ30217) is a lipophilic compound derived from a boronic acid adduct of technetium oxime (BATO). It has a myocardial extraction of >90% over a wide range of coronary blood flow (1–3). After uptake, the tracer clears the myocardium rapidly (biologic half-life of 5.3 min) and then concentrates in the hepatobiliary system (4–6). Good cardiac images have been reported in clinical studies (7,8) performed with planar imaging initiated approximately 3 min after administration of the tracer, although liver activity obscured the inferior wall of the heart in some patients. The purpose of the present study was to determine the feasibility of single photon emission computed tomography (SPECT) imaging with Tc-99m teboroxime and its relation to the anatomic severity of the stenosis as determined by quantitative coronary arteriography. Imaging was started within 2 min of injection to minimize scatter from the liver. In addition, the results of Tc-99m teboroxime studies were compared with those of stress SPECT thallium imaging.

Methods

Study patients. Thirty subjects suspected of having coronary artery disease and undergoing either a thallium stress test or coronary arteriography, or both, were enrolled in the

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Table 1. Clinical Characteristics of 30 Patients

Pt. No.	Age (yr)/Gender	MI	Collat	EF (%)	PTCA
1	52/M	Sub	+	56	–
2	45/M	–	+	50	–
3	42/M	Sept	–	43	LAD
4	62/F	–	–	65	–
5	65/M	Sub	+	50	–
6	72/F	–	–	60	–
7	55/M	Inf	–	81	LAD
8	57/M	–	–	55	–
9	55/F	–	–	60	–
10	64/M	LBBB	+	NA	–
11	57/M	–	+	63	–
12	44/F	Sub	–	NA	RCA
13	44/F	Ant	–	68	–
14	69/F	Inf	–	70	RCA
15	57/M	Sept	+	65	–
16	62/M	Inf	+	60	–
17	30/F	–	NA	60	–
18	65/M	–	–	60	–
19	60/M	–	NA	NA	–
20	84/M	–	+	64	–
21	65/M	Inf	–	60	–
22	64/F	–	–	65	–
23	45/F	–	–	65	–
24	59/F	–	NA	NA	–
25	41/F	–	NA	NA	–
26	56/M	–	NA	NA	–
27	45/F	–	–	NA	–
28	53/M	Inf/ Sept	–	40	–
29	37/M	Lat	–	62	LAD
30	53/M	Sub	+	74	–
Mean	55.3	232		60.7	
±SD	11.3	54		9.2	

Ant = anterior; Collat = collateral vessels; % EF = ejection fraction by contrast ventriculography; F = female; Inf = inferior; Lat = lateral; LAD = left anterior descending coronary artery; LBBB = left bundle branch block; M = male; MI = myocardial infarction; NA = not available; Pt. = patient; PTCA = percutaneous transluminal coronary angioplasty; RCA = right coronary artery; Sept = septal; Sub = subendocardial; – = none (MI, Collat) or not performed (PTCA); + = present.

study from July 1989 to March 1990. Patients who had a history of cardiomyopathy, severe valvular disease, unstable angina, pregnancy or morbid obesity or who had a myocardial infarction, angioplasty or bypass surgery between studies were excluded. All patients signed a consent form approved by the University of Texas-Houston Institutional Review Board for the Protection of Human Subjects. There were 18 men and 12 women (mean age 55.3 years) (Table 1). All 30 patients underwent Tc-99m teboroxime SPECT imaging, 26 thallium SPECT imaging, 25 coronary arteriography and 21 all three studies. In patients who had prior angioplasty, perfusion scans were compared with the postangioplasty arteriogram.

Each study was performed in the fasted state. There was an average of 16 ± 28 days between nuclear studies and all three studies were completed within a mean of 21 ± 31 days. Complete blood chemistry determinations, blood count and urinalysis were performed before and within 24 h of the Tc-99m teboroxime injection. There were no significant abnormalities in any of these values after Tc-99m teboroxime imaging.

Coronary arteriography. Coronary arteriography was performed with the Judkins technique. Multiple simultaneous biplane views were obtained after contrast injection with standard doses of either Hypaque or Isovue (3 to 10 ml). Filming was performed at 30 frames/s. The resolution of the cine system was 4 to 5 line pairs/mm, with both pincushion and magnification correction carried out in the quantitative coronary arteriographic analysis according to the methods of Brown et al. (9). Selected end-diastolic cine frames were digitized by a Spatial Data System frame grabber (640 × 480 matrix) with optical magnification so as to obtain a spatial resolution of approximately 0.1 mm/pixel. Subsequent image processing (border recognition, magnification correction and determinations of stenosis morphology were performed with previously validated software (10–12) running on a DEC VAX 11/780 computer. Hard-copy reports were generated on a Tektronics 4207 graphics terminal. Stenosis severity was measured as percent diameter stenosis. Lesions ≥50% were considered significant.

Thallium studies. Stress thallium studies were obtained in conjunction with treadmill exercise with use of a standard Bruce protocol. Exercise was continued until limited by symptoms (angina, shortness of breath, fatigue, leg pain), ischemic changes on the electrocardiogram (ECG) (>1 mm ST segment depression) or until >85% of maximal predicted heart rate was reached. Approximately 1 min before cessation of exercise, 3 mCi of thallium-201 was injected intravenously. Patients were continuously monitored for changes in blood pressure, heart rate and ECG until pre-exercise values returned. SPECT images were obtained with a General Electric 400 AC/Starcam camera. A total of 32 acquisitions were obtained at 40 s, each over 180°, with use of a 64 × 64 matrix. Images were processed with a Hanning filter with a cutoff frequency of 0.83 Hz and a multipurpose collimator. Standard backprojection techniques were used to obtain the transaxial tomograms. Images were then reoriented in short-axis and vertical and horizontal long-axis views. Redistribution images were obtained 4 h later with use of the same imaging procedure.

Preparation of Tc-99m teboroxime. Teboroxime was prepared within 4 h of patient administration. The lyophilized product was reconstituted with 0.5 to 1.0 ml of sterile pyrogen-free Tc-99m generator eluate, which did not contain >100 mCi of Tc-99m pertechnetate as indicated in the manufacturer's protocol (Squibb Diagnostics). The solution was then heated in a water bath for 15 min at 100°C. The mixture was then cooled to room temperature and kept in a glass vial until ready for injection.

The percent of Tc-99m pertechnetate and reduced hydrolyzed Tc-99m was determined by paper chromatography

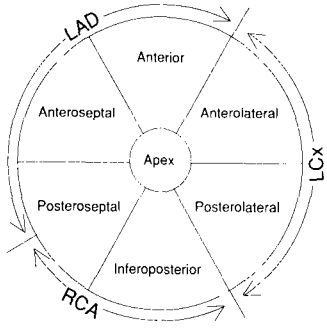

Figure 1. Regions of interest for perfusion interpretation are shown with the corresponding arterial distributions. Assignment of the posterior circulation and apex was verified by review of the coronary angiograms. Regional assessment of perfusion was based on multiple slices. Bullseye reorientation was not performed. LAD = left anterior descending artery; LCx = left circumflex artery; RCA = right coronary artery.

immediately after drug preparation. All preparations contained <10% Tc-99m pertechnetate.

Teboroxime imaging protocol. The same exercise protocol used for the thallium stress studies was used for teboroxime imaging. However, exercise was not continued for 1 min after administration of tracer as with thallium; instead, it was stopped immediately after Tc-99m teboroxime injection and SPECT imaging was begun within 2 min. The average dose of Tc-99m teboroxime was 25.2 ± 1 mCi. Teboroxime SPECT imaging was also performed with use of a GE 400 AC/Starcam camera at 15 s per 6° arc over 180°. Images were reoriented in a manner similar to that of thallium studies with use of a Hanning filter with a 0.83 Hz cutoff and multipurpose collimator. Acquisitions required 10 min to complete. In two subjects, imaging was performed for 5 s per view. The shorter acquisition time produced images that were judged to be adequate for interpretation but of lesser quality than the 15 s acquisitions. Rest images were obtained approximately 1 h later, at the same dose used for the stress study.

SPECT image interpretation. Two experienced observers (R.G., H.T.) interpreted the perfusion images without knowledge of the clinical and angiographic data. Images were randomly reviewed as stress and rest (redistribution) pairs independently and at a different time from the interpretation of the other tracer study. Readers did not know the results of the perfusion images previously evaluated. Regional perfusion was scored on a continuous scale from 0 to 5, where 0 was considered to be definitely normal and 5 a severe perfusion defect. The results from the two graders were averaged and used to determine the presence of disease. Values from 0 to 2 were classified as negative and values from 3 to 5 as positive for disease. Regions of interest were matched to the arterial supply (native or graft) as illustrated in Figure 1 and independently verified (R.F.). The apex was matched to the culprit artery. Interobserver variability, defined as the difference between observer perfusion scores for a region, was also determined. Agreement was complete if both observers graded a region identically; disagreement was complete if the scores differed by 5 points.

Table 2. Results of Exercise Testing in 30 Patients

	Thallium-201	Teboroxime
Maximal heart rate (beats/min)	132 ± 13	132 ± 15
Rate-pressure product*	22,523 ± 4,010	22,099 ± 4,513
Exercise ECG response		
Positive (%)	13 (50)	11 (42)
Negative (%)	13 (50)	15 (58)
Angina during exercise (%)	9 (30)	8 (31)

*Maximal systolic blood pressure × maximal heart rate. Values are mean values ± SD. p = NS for all variables.

Statistical methods. Chi-square analysis with correction for continuity was used to determine whether there was a statistically significant difference between tracers versus quantitative coronary arteriography. Differences between thallium and Tc-99m teboroxime exercise tests were evaluated using a Student's *t* test for paired data. Values are expressed as mean values ± SD.

Results

Comparison of thallium and teboroxime imaging with quantitative coronary arteriography. Table 2 lists the results of the ECG and hemodynamic measurements obtained with the thallium and teboroxime exercise stress tests. There were no differences in the rate-pressure product achieved, presence of angina or development of significant ST segment abnormalities. All patients exercised to a symptom-limited or target heart rate end point.

The results of coronary arteriography and perfusion imaging in each patient are listed in Table 3.. The prevalence of disease in the 25 patients with arteriography was 68%. Ten patients had angiographic evidence of significant one vessel disease, six patients of two vessel disease and one patient of three vessel disease. Eight patients had no significant coronary disease. There were no differences between the two tracers versus arteriography for specific arterial distributions (Table 4). Results of imaging were abnormal in 9 of the 10 patients with one vessel disease who underwent teboroxime imaging and in 8 of the 10 with thallium imaging (p = NS). In every case where two or three vessel disease was present by arteriography, thallium and Tc-99m teboroxime images were abnormal. In patients without arteriographic evidence of disease, six of eight Tc-99m teboroxime studies were interpreted as normal versus three of five thallium studies (p = NS). When overall presence of disease was evaluated, there was no significant difference between arteriography and Tc-99m teboroxime or thallium imaging. With Tc-99m teboroxime imaging, 6 patients had reversible defects (19 segments) and 17 had fixed defects (39 segments). Similarly, with thallium imaging, reversible defects were present in 9 patients (31 segments) and fixed defects in 10 patients (23 segments).

Table 3. Comparison of Anatomic Measures of Coronary Stenosis Severity With Perfusion Imaging in 30 Patients

Pt. No.	RCA			LAD			LCx		
	%D	T1-201	Tebo	%D	T1-201	Tebo	%D	T1-201	Tebo
1	4	1	0	6	2	4	16	0	2
2	56	4	5	82	5	1	4	2	0
3	48	4	3	52	5	4	35	2	4
4	64	0	0	45	0	1	29	0	2
5	100	4	4	58	2	0	100	4	4
6	99	5	4	19	1	0	11	0	0
7	41	4	5	64	3	4	36	0	3
8	38	2	0	51	0	3	42	0	2
9	4	0	0	6	4	1	16	2	1
10	0	0	0	100	5	4	46	3	1
11	47	4	0	79	4	3	45	2	0
12	43	0	0	18	0	0	7	0	0
13	13	5	2	47	1	2	18	0	2
14	16	0	4	48	0	0	11	0	0
15	25	0	0	100	5	5	39	1	0
16	100	5	3	36	0	2	63	4	0
17	—	1	2	—	4	5	—	3	2
18	59	4	4	68	0	0	43	2	0
19	—	2	0	—	0	1	—	0	1
20	100	5	4	12	2	2	65	0	1
21	59	5	4	100	3	2	37	0	4
22	9	—	0	4	—	2	15	—	2
23	34	—	0	38	—	2	10	—	2
24	—	0	0	—	2	4	—	0	0
25	—	4	4	—	2	5	—	0	4
26	—	1	2	—	1	2	—	0	0
27	22	—	1	36	—	1	9	—	0
28	37	—	5	99	—	5	99	—	5
29	46	4	0	71	5	5	37	0	4
30	40	4	4	72	5	5	21	3	1

Perfusion images were evaluated with a scale from 0 to 5 with ≥3 defined as ischemia. Values presented from perfusion images represent the highest mean score during stress within the arterial distribution. LCx = left circumflex artery; %D = percent diameter stenosis; Tebo = teboroxime; T1-201 = thallium-201; — = no available data/not done. Other abbreviations as in Table 1.

Two patients had false positive and two had false negative thallium studies. Two patients had a false positive and one patient had a false negative Tc-99m teboroxime study. One with a false positive teboroxime study who had a history of an inferior myocardial infarction had undergone angioplasty of the right coronary artery, which left a residual stenosis of 16%. Teboroxime images showed an inferoposterior defect that, although consistent with the old myocardial infarction, was classified as a false positive result because of arteriographic findings. The thallium images of this patient were interpreted as normal and thus considered to be a true negative result. This case illustrates the difficulty in comparing anatomy with perfusion, particularly in patients with prior infarction. There was no apparent reason for the other false positive finding or the false negative result.

On a regional basis, there were many false positive results for both Tc-99m teboroxime and thallium in the right coronary artery distribution (Table 4). Although false positive thallium defects are common because of attenuation from overlying diaphragm, these results suggest that a similar problem may be present for Tc-99m teboroxime despite the higher photon energy of Tc-99m.

Direct comparison of thallium and teboroxime perfusion. Thallium and teboroxime perfusion studies were in agreement for the presence or absence of disease in 65% of posterolateral, 77% of anterior or septal (or both) and 85% of inferoposterior segments. Interpretation of Tc-99m teboroxime perfusion regions agreed with arteriographic data on the presence or absence of disease in 57 (76%) of 75 segments, and thallium studies were concordant in 46 (73%) of 63 segments (p = NS). The overall concordance between thallium and teboroxime studies for the presence or absence of disease was 77%.

Interobserver agreement for stress and rest images obtained with thallium and Tc-99m teboroxime are summarized in Figure 2. In the stress images, there was absolute agreement in 131 of 208 thallium studies and 133 of 240 Tc-99m teboroxime studies (p = NS). Similar results were obtained with redistribution thallium images (126 of 208) and rest Tc-99m teboroxime images (138 of 240).

Table 4. Sensitivity and Specificity of Thallium and Teboroxime Imaging When Compared With Automated Quantitative Coronary Arteriography

Thallium			Teboroxime		
Overall disease presence					
	QCA			QCA	
	+	−		+	−
Tl +	14	2	Tebo +	16	2
Tl −	2	3	Tebo −	1	6
Specific arterial distributions					
	RCA			RCA	
	+	−		+	−
Tl +	7	6	Tebo +	7	5
Tl −	1	7	Tebo −	1	12
	LAD			LAD	
	+	−		+	−
Tl +	9	1	Tebo +	9	1
Tl −	3	8	Tebo −	4	11
	LCx			LCx	
	+	−		+	−
Tl +	2	2	Tebo +	2	4
Tl −	1	16	Tebo −	2	17

QCA = quantitative coronary arteriography; Tebo − and Tebo + = disease absent or present by teboroxime imaging; Tl − and Tl+ = disease absent or present by thallium; other abbreviations as in Tables 1 and 3.

Discussion

Thallium versus teboroxime for perfusion imaging. The ideal tracer for perfusion imaging would be 100% extracted on first pass at all flow rates and retained in the myocardium for a long enough period to allow collection of accurate statistical information. It would also have a short physical or biologic half-life, or both, so that rest and stress studies could be performed in rapid succession. At present, the only single photon tracer available for perfusion imaging is thallium-201. Thallium-201 has diffusion-limited extraction, a long half-life and low photon energy. In contrast, Tc-99m teboroxime has a high first-pass extraction, rapid clearance and the higher energy and shorter half-life of technetium-99m. These characteristics would be expected to improve sensitivity. However, Stewart et al. (6) demonstrated in dogs that the rate of washout is directly proportional to flow. Therefore, one concern about Tc-99m teboroxime is whether this rapid clearance of activity would allow diagnostic studies using standard single head, rotating SPECT cameras. One might expect that early images would show greater differences in activity between high and low flow regions than would later acquisitions. These changes might degrade the regional information obtained during reconstruction and increase the number of false negative studies. Another potential problem with Tc-99m teboroxime is that scatter from the liver could increase apparent inferior wall activity and increase the number of false negative studies.

The results of the current study suggest that Tc-99m teboroxime SPECT imaging is comparable diagnostically to thallium tomographic imaging for assessment of coronary artery disease. There was no difference between the tracers on determination of disease in a given arterial distribution. In particular, there was no difference between the tracers for assessment of inferior wall perfusion. Interobserver variability for stress and rest/redistribution studies was similar for both tracers and these values were similar to values obtained by others (13) for thallium.

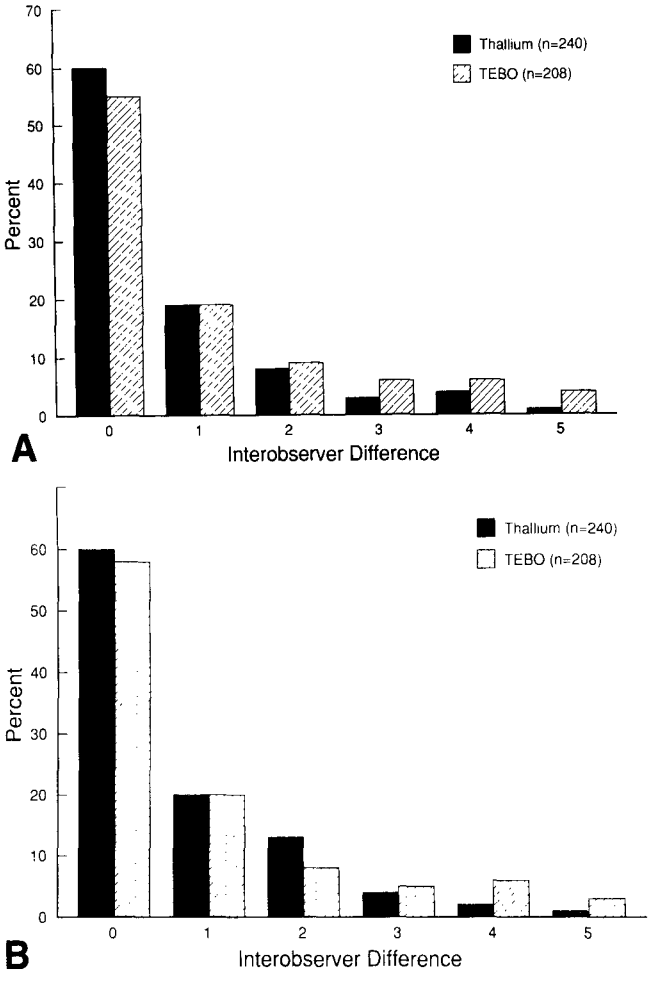

Figure 2. Interobserver variability for stress (**A**) and redistribution/rest (**B**). Perfusion defects were graded on a scale from 0 (normal) to 5 (severe defect). The abscissa is the absolute difference between segments scored by the two readers and the ordinate is the percent of segments for each difference in interpretation. TEBO = teboroxime.

Considerations for Tc-99m teboroxime imaging. To minimize the contribution of liver activity and optimize myocardial counts, image acquisition was started within 2 min of Tc-99m teboroxime injection. The transfer of the patient from the treadmill to the SPECT camera was rehearsed before stress so that proper alignment could be achieved quickly. Unlike the procedure in thallium studies, the tracer was injected at peak exercise and the treadmill was then stopped. A possible alternative is use of pharmacologic stress with intravenous dipyridamole or adenosine.

Teboroxime stress and rest image acquisitions were each completed in approximately 10 min. The entire study re-

quired 90 min to 2 h (total setup and processing time). The shorter time necessary for Tc-99m teboroxime imaging should increase the daily number of procedures that can be performed by a camera and be more convenient for the patient.

Study limitations. In this study, acquisitions were performed using a "stop and shoot" approach, with each 15 s image followed by a 2 to 3 s dead time loss for the camera head to be repositioned. This resulted in a 10% to 15% loss of available activity. Image content would be expected to improve with continuous acquisition programs available on some instruments.

In addition, no attempt was made to correct images for clearance of the tracer. The use of a multihead SPECT unit that is capable of rapid sequential scans should allow washout information to be incorporated into the images and may improve sensitivity and specificity.

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