Myocardial Technetium-99m-Teboroxime Uptake during Adenosine-Induced Hyperemia in Dogs with Either a Critical or Mild Coronary Stenosis: Comparison to Thallium-201 and Regional Blood Flow

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Experimental studies have shown ^{99m}Tc-teboroxime to have a higher first-pass myocardial extraction, exceeding that of ^{201}Tl with nearly linear initial myocardial uptake over a wide range of coronary flows. The goal of this study was to quantitatively compare teboroxime with ^{201}Tl for the assessment of a regional coronary flow imbalance when administered during adenosine vasodilation in dogs with either critical or mild LAD stenoses. **Methods:** Twenty-four anesthetized dogs with either critical (n = 10) or mild (n = 14) LAD stenoses were given an i.v. infusion of adenosine (300 μg/kg/min). When LCx flow was maximal, ^{201}Tl, teboroxime and microspheres were simultaneously injected and the dogs were killed either 2 or 4 min later. Regional ^{201}Tl, teboroxime activities and myocardial blood flow were determined by gamma well counting and ex vivo imaging of ^{99m}Tc-teboroxime activity in myocardial heart slices was performed. **Results:** In both the critical and mild stenosis groups, the LAD/LCx zone ratios in dogs killed 2 min after tracer injection for both ^{201}Tl (0.31 ± 0.07, 0.63 ± 0.05) and teboroxime (0.38 ± 0.09, 0.72 ± 0.04) significantly underestimated the microsphere flow ratio (0.18 ± 0.05, 0.43 ± 0.05) ($p \leq 0.01$), but the degree of underestimation was greater for teboroxime compared with Tl ($p \leq 0.05$). **Conclusion:** In dogs with either critical or mild LAD stenoses, as early as 2 min after tracer injection, the ^{201}Tl activity ratio more accurately assessed the adenosine-induced regional flow heterogeneity than did teboroxime. These results highlight the importance of an ultra-fast imaging protocol when using teboroxime with pharmacologic stress.

Key Words: thallium-201; teboroxime; adenosine; hyperemia; coronary stenosis

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Technetium-99m-teboroxime is a neutral, lipophilic member of a class of complexes known as boronic acid adducts of technetium dioximes, or BATOs, that was developed for use as a myocardial perfusion imaging agent (*1–3*). In vitro and in vivo animal studies have demonstrated a high first-pass myocardial extraction over a wide range of coronary flows (*4*). In addition to its high extraction, teboroxime also undergoes rapid biexponential washout which has been shown to be flow dependent (*5–9*). In experimental studies reporting nearly linear myocardial uptake of teboroxime versus microsphere flow, the animals were killed almost immediately after the tracer injection. Flow dependent myocardial clearance would suggest that in the presence of a coronary stenosis, teboroxime would clear more rapidly from nonstenotic regions of myocardium, resulting in the loss of defect contrast over time, especially at the high flow rates achieved with pharmacologic vasodilation.

The goals of this study were: (1) to quantitatively compare teboroxime with ^{201}Tl when administered during adenosine-induced hyperemia in dogs with either mild or critical LAD stenoses with respect to stenotic zone/normal zone activity ratios versus the flow ratio and (2) to determine the influence of time after teboroxime injection on the estimation of the magnitude of the regional flow heterogeneity.

METHODS

Surgical Preparation

Twenty-four fasted adult mongrel dogs (23 kg ± 1 kg) were anesthetized with sodium pentobarbital (30 mg/kg), intubated and ventilated on a respirator with 4 cm of positive end-expiratory pressure. Arterial blood gases were monitored throughout the experiment and pH, PO_2, PCO_2 and HCO_3 levels were maintained at physiologic levels. Lead II of the electrocardiogram was mon-

itored continuously. The right femoral vein was cannulated with an 8F polyethylene catheter for the administration of fluids, medications, ^{201}Tl and ^{99m}Tc-teboroxime. Both femoral arteries were isolated and cannulated with 8F polyethylene catheters and served as sites for the collection of arterial blood samples and for microsphere reference blood withdrawal. A 7F cathether was placed in the right femoral artery for continuous monitoring of systemic arterial pressure.

A thoracotomy was performed at the level of the fifth intercostal space and the heart was suspended in a pericardial cradle. A flare-tipped polyethylene catheter was inserted into the left atrial appendage for continuous left atrial pressure measurements and as a site for the injection of radiolabeled microspheres. The left anterior descending (LAD) coronary artery was then dissected free of the epicardium and an ultrasonic flow probe and a snare ligature was placed around the vessel. A similar flow probe was placed around the left circumflex (LCx) artery.

The hemodynamic parameter heart rate, systemic arterial and left atrial pressures and LAD and LCx flows were continuously recorded on an 8-channel stripchart recorder throughout each protocol. All experiments were performed with the approval of the University of Virginia Animal Research Committee in compliance with the position of the American Heart Association on use of research animals.

Reconstitution and Quality Control of ^{99m}Tc-Teboroxime

Technetium-99m-teboroxime was obtained in a lyophilized kit form by Squibb Diagnostics, Princeton, NJ. A kit was reconstituted by adding 30 mCi of ^{99m}Tc pertechnetate in 1 ml of saline to the vial and heating for 15 min in boiling water. Care was taken to prevent inversion of the vial and contact with the rubber stopper. The vial was then cooled for 20–25 min. Paper chromatography was performed immediately after reconstitution to determine the percentage of ^{99m}Tc labeled soluble contaminants and the amount of reduced/hydrolyzed ^{99m}Tc. Whatman 31 ET chromatography strips (1.3 cm × 11 cm) and two individual mobile-phase solvent systems (saline, acetone/saline) were used to determine the purity of the radiopharmaceutical. In all cases, the radiochemical purity exceeded 90%. The reconstituted product was stored in the original glass vial until immediately prior to the injection time.

Experimental Protocols

The protocol is shown schematically in Figure 1. Prior to setting the LAD stenosis, baseline recordings were made of heart rate, arterial and left atrial pressures and LAD and LCx flows. A radioactive microsphere was injected into the left atrial catheter to measure baseline myocardial blood flow. The reactive hyperemic flow response of the nonstenotic LAD was then measured by briefly occluding the LAD for 10 sec and then releasing the occlusion. The maximal flow response was recorded on the stripchart recorder.

In Group I, the snare occluder was adjusted to produce a critical LAD stenosis. A critical stenosis was defined as the point where baseline flow was unchanged, however, the reactive hyperemic response was completely abolished. A second microsphere was then injected into the left atrium. Next, an intravenous infusion of adenosine was begun at a rate of 300 μg/kg/min and continued until LCx flow was maximal. This dose of adenosine was chosen to produce high coronary flow without decreasing systemic arterial pressure below 85 mmHg. At the point where LCx flow was maximal, 18.5 MBq (0.5 mCi) ^{201}Tl and 185 MBq (5.0 mCi) of ^{99m}Tc teboroxime were injected into the femoral vein

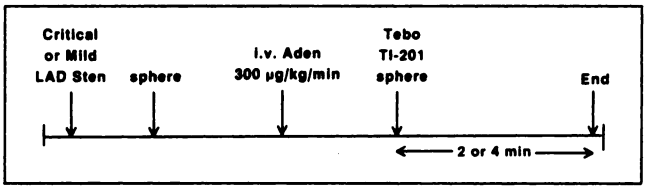

FIGURE 1. Experimental Protocol. LAD Sten = left anterior descending coronary artery stenosis, sphere = radioactive microsphere, Aden = adenosine, Tebo = ^{99m}Tc-teboroxime.

catheter and microspheres were simultaneously injected into the left atrium. One subgroup of these dogs (Ia, n = 5) were killed 2 min after tracer injection, whereas a second subgroup (Ib, n = 5) of dogs were killed 4 min after injection.

An identical protocol was performed in Group II. In this group, however, the snare occluder was adjusted to produce a mild LAD stenosis. A mild stenosis was defined as one producing no change in baseline flow, but 50% reduction in the reactive hyperemic response. Two subgroups of dogs were studied. One subgroup (IIa, n = 9) was killed at 2 min after tracer injection, and the second subgroup (IIb, n = 5) at 4 min after injection.

Ex Vivo Slice Imaging

Hearts were then removed and sliced into 4 approximately 1 cm thick rings from apex to base. The slices were trimmed of excess fat and adventitia and placed on a thin piece of cardboard covered with cellophane wrap. Slices were imaged directly on the collimator of a conventional planar gamma camera for maximal count time (1638 sec). The slices were imaged using a 20% window centered on the ^{99m}Tc photopeak and image quantification was performed on a nuclear medicine computer system (Sopha Medical Systems). Regions of interest (ROI) were drawn on the defect area visible in the antero-apical region of the left ventricular wall and on the normal posterior wall of the teboroxime images. Quantification was performed on the two center slices since the basal slice was always above the stenosis and therefore always normal, whereas the apical slice lacked a quantifiable normal region. The defect magnitude was calculated as the ratio of the average counts in the LAD ROI divided by the average counts in the normal LCx ROI. Because of spilldown of ^{99m}Tc into the ^{201}Tl window, quantitation of ^{201}Tl defect magnitude was not performed.

Quantification of Myocardial ^{201}Tl, ^{99m}Tc-Teboroxime and Microsphere Flow

To measure ^{201}Tl, teboroxime activities and microsphere determined the flow in the myocardial tissue samples, each of the four myocardial slices were divided into eight sections which were then further subdivided into epicardial, midwall and endocardial segments; resulting in a total of 96 myocardial segments for each dog. The myocardial tissue samples were counted in a gamma well scintillation counter for both ^{201}Tl and ^{99m}Tc activities within 24 hr of collection. The tissues were recounted for microsphere flow 2 wk later when the ^{201}Tl and ^{99m}Tc had decayed. The window settings on the gamma counter were ^{201}Tl: 50–100 keV, ^{99m}Tc: 130–170 keV, ^{103}Ru:450–550 keV, ^{95}Nb:640–840 keV and ^{46}Sc: 842–1300. Tissue counts were corrected for background, decay and isotope spillover according to the method of Heymann et al. (*10*), and regional myocardial blood flow was calculated using specialized computer software (PCGERDA, Packard Instruments, Downer's Grove, IL). Transmural activity and flow values

TABLE 1
Hemodynamic Parameters

Group	Heart rate (bpm)			Arterial pressure (mmHg)			Left atrial pressure (mmHg)		
	Base	Sten	Aden	Base	Sten	Aden	Base	Sten	Aden
I (n = 10)	132 ± 7	131 ± 8	136 ± 6	123 ± 7	123 ± 6	101 ± 6*	8 ± 1	8 ± 1	8 ± 1
II (n = 14)	118 ± 5	117 ± 6	124 ± 6*	113 ± 4	114 ± 3	105 ± 6*	8 ± 1	8 ± 0	7 ± 1

*$p \leq 0.02$ vs. Sten.
Group I = critical left anterior descending artery stenosis; Group II = mild LAD stenosis; Base = baseline; Sten = stenosis; Aden = adenosine.
mean ± s.e.m.

were calculated as the weighted average of the corresponding epicardial, midwall and endocardial samples.

Data and Statistical Analysis

All statistical computations were made using SYSTAT software (SYSTAT Inc., Evanston, IL). The results were expressed as the mean ± s.e.m. Differences between two means within a group were assessed using a paired t-test with p values < 0.05 considered significant. Differences between groups were assessed using one-way analysis of variance. Hemodynamic parameters were compared using a repeated measures ANOVA.

RESULTS

Hemodynamics

Mean heart rate, systemic arterial pressure and left atrial pressure measured at baseline, after setting the LAD stenosis, and at the peak adenosine response when the tracers were administered, are shown in Table 1. As shown, setting either a critical (Group I) or mild (Group II) LAD stenosis had no effect on heart rate, arterial pressure or left atrial pressure. During adenosine infusion, mean arterial pressure fell from 123 ± 6 to 101 ± 6 mmHg and from 114 ± 3 to 105 ± 6 mmHg in Groups I & II, respectively ($p \leq 0.02$). A reflex rise in heart rate from 131 ± 8 to 136 ± 6 BPM and from 117 ± 6 to 124 ± 6 BPM, respectively, was observed in Groups I and II, although the increase in Group I did not quite reach statistical significance ($p = 0.068$). No significant difference was observed between the critically stenotic and mildly stenotic dogs for any of these hemodynamic parameters.

Coronary Flows

In Group I dogs with a critical stenosis, ultrasonically measured mean LAD flow was 21 ± 2.0 ml/min at baseline and was unchanged after setting the critical stenosis (20 ± 2 ml/min). As shown in Figure 2, during the adenosine infusion, LAD flow in the critically stenotic LAD did not increase during adenosine infusion (21 ± 5 ml/min). LCx flow during adenosine administration increased approximately four-fold, from 28 ± 4 to 108 ± 13 ml/min ($p \leq 0.01$). Thus, at the time when teboroxime and ^{201}Tl were administered, there was a 5:1 disparity in flow between the LCx and LAD coronary beds.

In the mild stenosis dogs, LAD flow remained unchanged after setting the mild stenosis (19 ± 2 ml/min) compared with its baseline value (24 ± 3 ml/min). As shown in Figure 2, LAD flow increased during infusion of adenosine to 42 ± 5 ml/min ($p \leq 0.01$), whereas LCx flow increased from 29 ± 3 to 113 ± 8 ml/min ($p \leq 0.01$), resulting in a nearly three-fold difference in flow between the LAD and LCx coronary beds. Thus, in Group II dogs, the mild LAD stenosis permitted some increase in LAD flow, although flow reserve was significantly reduced compared to LCx flow during adenosine infusion.

Comparison Between Myocardial ^{99m}Tc-Teboroxime and ^{201}Tl Activities with Regional Myocardial Blood Flow

Table 2 summarizes the mean microsphere determined regional myocardial blood flows (ml/min/g) in the LAD and LCx zones from the Group I and Group II dogs. As shown, there was no significant change in baseline flow in the LAD zone upon setting either the critical or mild LAD stenosis. In the Group I dogs with critical LAD stenoses, there was no significant change in LAD flow with adenosine, however, there was a four-fold increase in LCx flow in the epicardial, midwall and endocardial regions ($p < 0.05$). In the Group II dogs with mild LAD stenoses there was a two-fold increase in LAD flow and a nearly 5-fold increase in LCx flow ($p < 0.01$ vs LAD) transmurally with adenosine.

Figure 3 shows ^{201}Tl and teboroxime activity versus

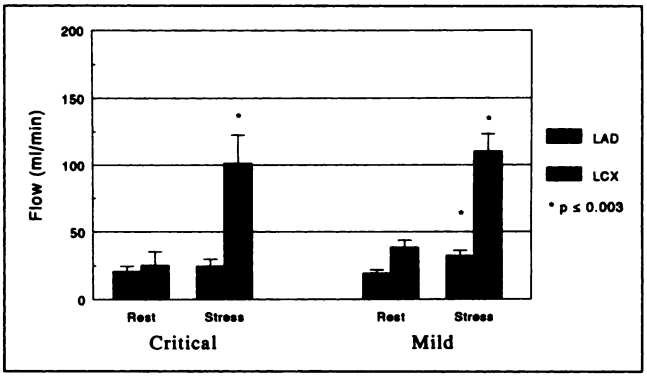

FIGURE 2. Ultrasonically measured flow (mean ± s.e.m.) in dogs with critical (Group I, n = 10) and mild (Group II, n = 14) left anterior descending coronary artery stenoses at rest and after intravenous adenosine infusion. LAD = left anterior descending coronary artery, LCx = left circumflex coronary artery.

TABLE 2
Regional Myocardial Blood Flows (ml/min/g, mean ± s.e.m.)

Group I: Critical LAD Stenosis

	Baseline	LAD stenosis	Adenosine	Baseline	LCx stenosis	Adenosine
Epi	0.99 ± 0.12	1.04 ± 0.11	1.09 ± 0.22	0.82 ± 0.08	0.92 ± 0.09	4.27 ± 0.44*
Mid	0.91 ± 0.07	1.00 ± 0.12	0.71 ± 0.14	0.86 ± 0.06	0.93 ± 0.09	4.42 ± 0.44*
Endo	0.90 ± 0.08	0.95 ± 0.12	0.62 ± 0.20	0.93 ± 0.06	1.05 ± 0.09	3.71 ± 0.48*
tm	0.93 ± 0.09	1.00 ± 0.11	0.81 ± 0.15	0.86 ± 0.07	0.97 ± 0.10	4.20 ± 0.38*

Group II: Mild LAD Stenosis

	Baseline	LAD stenosis	Adenosine	Baseline	LCx stenosis	Adenosine
Epi	1.05 ± 0.10	1.01 ± 0.08	2.58 ± 0.29*+	0.88 ± 0.05	0.91 ± 0.08	5.17 ± 0.42*
Mid	0.94 ± 0.09	0.92 ± 0.09	2.05 ± 0.32*+	0.93 ± 0.08	0.93 ± 0.08	4.91 ± 0.43*
Endo	1.02 ± 0.18	0.95 ± 0.11	1.54 ± 0.29*+	0.99 ± 0.10	1.00 ± 0.09	3.94 ± 0.44*
Tm	1.00 ± 0.11	0.96 ± 0.09	2.09 ± 0.27*+	0.93 ± 0.07	0.94 ± 0.08	4.78 ± 0.40*

*$p < 0.05$ vs. stenosis time point.
+$p < 0.05$ Group I vs. Group II.
LAD, LCx = left anterior descending, left circumflex coronary arteries; epi, mid, endo, tm = epicardial, midwall, endocardial and transmural regions. All values are mean ± s.e.m.

microsphere flow curves from a representative dog with a critical LAD stenosis killed 2 min after tracer injections. Teboroxime activity falls below that of ^{201}Tl at flows above 2–2.5 ml/min/g as early as 2 min after injection.

Figure 4 displays the mean stenotic zone: normal zone ratios for microsphere flow and for ^{201}Tl and teboroxime activities in both the critical and mild LAD stenosis groups of dogs that were killed 2 min after tracer injection. In the critical stenosis group, the stenotic zone: normal zone ratios for both ^{201}Tl (0.31 ± 0.07) and teboroxime (0.38 ± 0.09) significantly underestimated the actual microsphere flow ratio (0.18 ± 0.05) ($p = 0.01$). In addition, the degree of underestimation was greater for teboroxime compared with ^{201}Tl ($p \leq 0.05$). Similarly, in the mild stenosis group, the stenotic zone: normal zone ratios for both ^{201}Tl (0.63 ± 0.05) and teboroxime (0.72 ± 0.04) significantly underestimated the microsphere flow ratio (0.43 ± 0.05) ($p < 0.01$) and, again, the degree of underestimation was greater for teboroxime than for ^{201}Tl ($p < 0.05$).

Figure 5 displays the stenotic zone: normal zone microsphere flow ratio and tracer activity ratios from the dogs that were killed 4 min after teboroxime and ^{201}Tl injection.

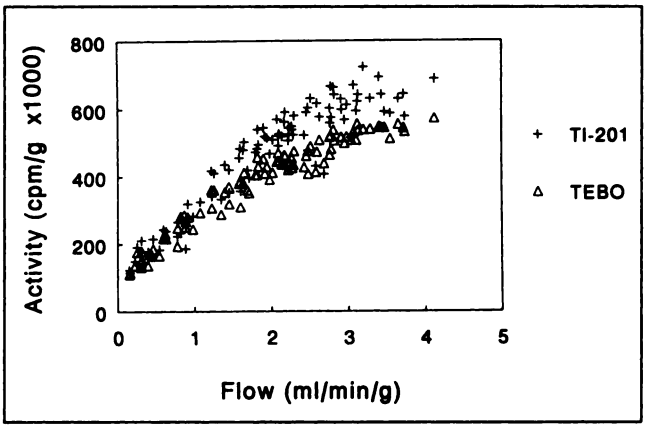

FIGURE 3. Thallium-201 and teboroxime activity versus microsphere flow curves from a representative dog with a critical LAD stenosis. The tracers were administered during adenosine infusion and the dog was killed 2 min later. The data points represent all 96 myocardial segments. TEBO = teboroxime.

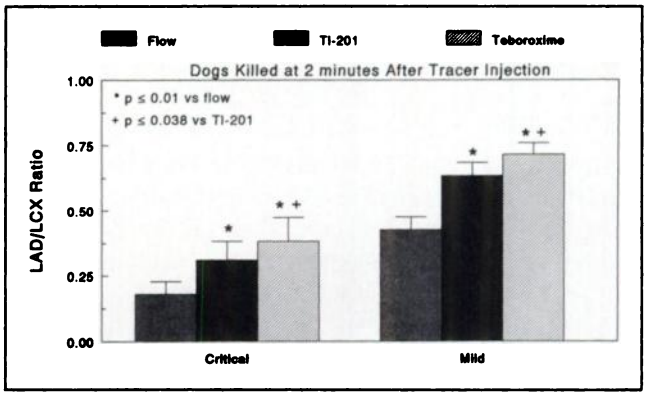

FIGURE 4. Mean microsphere flow, ^{201}Tl and ^{99m}Tc-teboroxime activities expressed as the LAD:LCx ratio for both the critical and mild stenosis groups of dogs killed 2 min after tracer injection. In both groups, ^{201}Tl and teboroxime significantly underestimated flow, but the degree of underestimation was greater for teboroxime.

As seen in dogs killed at 2 min after tracer injection, the stenotic zone: normal zone ^{201}Tl activity ratio (0.31 ± 0.05) and teboroxime activity ratio (0.50 ± 0.07) significantly underestimated the flow ratio (0.17 ± 0.03; $p \leq 0.01$) in dogs with a critical stenosis killed 4 min after tracer injection. Similarly, the stenotic zone:normal zone ^{201}Tl activity ratio (0.61 ± 0.04) and teboroxime activity ratio (0.78 ± 0.02) significantly underestimated the flow ratio (0.43 ± 0.06) in dogs with a mild stenosis killed at the later time point. The degree of underestimation was greater in both groups for teboroxime compared with ^{201}Tl ($p = 0.02$).

Comparing the teboroxime activity ratio in the Group I dogs with critical LAD stenoses killed 2 min after tracer injection (0.38) with the teboroxime activity ratio in the Group 2 dogs killed at 4 min (0.50), there was a clear trend towards an increase in the activity ratio over this time period (i.e., lessening of the defect magnitude), although this change did not reach statistical significance. In the dogs with mild LAD stenoses, there was no significant change in the teboroxime activity ratio from 2 min (0.71) to 4 min (0.73).

Image Defect Ratios on Myocardial Slice Imaging

In Group I dogs with critical LAD stenoses, the mean ischemic/normal ^{99m}Tc-teboroxime count ratios from quantification of myocardial slice images were 0.44 ± 0.05 and 0.51 ± 0.05 in the subgroups of dogs killed at either 2 or 4 min, respectively (p = ns). These data, determined using an independent technique for quantiying tracer activity, were not significantly different from the ^{99m}Tc-teboroxime activity ratios determined by gamma well counting of myocardial tissue segments reported above (0.38 and 0.50). Although the change in teboroxime defect magnitude from 0.44 to 0.51 over 2 min did not reach statistical significance, there was a clear trend towards a lessening of the defect magnitude (i.e., increased count ratio) over this time period. In Group II dogs with mild LAD stenoses, the ischemic/normal ^{99m}Tc-teboroxime count ratios were 0.71 and 0.73 at 2 min versus 4 min (p = ns). Again, the teboroxime ischemic/normal count ratios determined by imaging were not significantly different from those determined by gamma well counting (0.72 and 0.78), and thus, confirm these results.

DISCUSSION

The results of the present study demonstrate that myocardial teboroxime activity was significantly less than ^{201}Tl activity as early as 2 min after both radionuclides were injected during adenosine-induced flow heterogeneity in dogs with either critical or mild LAD stenosis. In the dogs with critical LAD stenosis, the stenotic/normal ratio of teboroxime uptake four min after tracer injection in the underperfused LAD bed was 0.50, which significantly underestimated the stenotic/normal flow ratio which was reduced to 0.17. The stenotic/normal ^{201}Tl activity ratio of 0.31 more closely approximated the reduction in flow distal to the LAD stenosis during adenosine infusion. Above 2-times normal flow, ^{201}Tl activity in the myocardium exceeded teboroxime activity, whereas ^{201}Tl and teboroxime activities relative to flow were comparable in the lower flow ranges (Fig. 3). Since defect magnitude derives from measuring the ratio of activity in the stenotic zone to the hyperemic normal zone, a lower teboroxime concentration in the normal zone compared to ^{201}Tl would yield a milder teboroxime defect. The same findings were observed in the mildly stenotic dogs in which the stenotic zone: normal zone activity ratio for ^{201}Tl better reflected the flow reduction than the teboroxime activity ratio.

Relationship to Prior Experimental Studies

At first glance, the data summarized above may seem in conflict with the widely held concept that because of a high first-pass extraction, teboroxime uptake by the myocardium after intravenous injection better reflects the regional flow pattern than does ^{201}Tl, particularly at high flow rates. Some prior experimental studies have shown a high initial myocardial extraction for teboroxime and less of a plateau in uptake versus flow than seen with ^{201}Tl or sestamibi. Stewart et al. reported a first-pass myocardial retention fraction of teboroxime averaging 90% after the direct intracoronary injection of the tracer in open chested dogs (*5*). They found no diminution in retention fraction with myocardial blood flows over flow values of 0.3 to 7.7 ml/min/g. Dipyridamole was used to determine teboroxime kinetics over a wide flow range in this study. Li et al. reported a good agreement between perfusion defect severity measured by teboroxime tomography in dogs and microsphere blood flow after dipyridamole infusion (*11*). Tomographic images were begun one minute after teboroxime injection.

Gray and Gewirtz found a strong correlation between the ischemic/normal zone flow ratio during adenosine/phenylephrine stress in swine with an experimental coronary stenosis and the ischemic/normal zone defect ratio of teboroxime on images acquired one to two minutes after

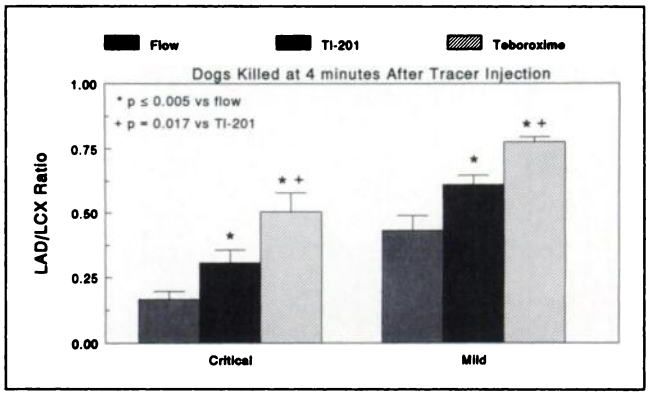

FIGURE 5. Mean microsphere flow, ^{201}Tl, and teboroxime activities for both the critical and mild LAD stenosis groups of dogs killed 4 min after injection. As was shown for the dogs killed at 2 min (Fig. 3), both ^{201}Tl and teboroxime significantly underestimated flow and the degree of underestimation was greater for teboroxime. Note that waiting an additional 2 min resulted in a lessening of the magnitude of the flow disparity measured by teboroxime, but not by ^{201}Tl.

teboroxime injection (*8*). The teboroxime ratio (0.50) better approximated the flow diminution in the stenotic zone (0.45) than did the simultaneously measured ^{201}Tl scan ratio (0.62). The experimental stenoses were more severe in the pig model employed by Gray and Gewirtz (*8*) than in the model employed in the present study. Flow was reduced at baseline prior to adenosine infusion in their experiments. This basal flow diminution resulted in a ^{99m}Tc-teboroxime of 0.65 at rest with no adenosine infusion. Also, gamma well scintillation counting of ^{201}Tl and ^{99m}Tc activities was not performed in that study.

Marshall et al. found an average peak myocardial extraction of 0.67 for ^{201}Tl and 0.62 for teboroxime in the isolated blood-perfused rabbit model (*6*). Peak first-pass extraction significantly decreased with increasing flow rates for ^{201}Tl but not for teboroxime. Using single-pass experiments in rats, Di Rocco et al. found that teboroxime and ^{201}Tl were comparable in their relationship to myocardial blood flow after adenosine-induced vasodilation (*12*). Both underestimated microsphere flows by the same degree. It should be pointed out that rats were killed 6 sec after tracer injection into the left ventricle. In a multiple-pass open chested canine model with an LAD stenosis, these investigators again found that myocardial uptake of teboroxime and ^{201}Tl were comparably related to coronary flows up to 4–6 ml/min/g induced by adenosine (*12*). These dogs were killed 70 sec from the start of the isotope injection into the left atrium.

The experimental data cited above suggest that immediately after intravenous injection, the myocardial activity of teboroxime is more linearly related to flow than ^{201}Tl. This yields defect magnitudes on teboroxime imaging of animals with experimental coronary occlusions more reflective of the degree of hypoperfusion than ^{201}Tl defect magnitudes. The explanation for the observed greater ^{201}Tl than teboroxime uptake in the myocardium in the present study, despite a higher Emax and Enet for teboroxime (*4*) and a more linear relation of tracer uptake to regional flow, is related to differences in clearance kinetics between the two radionuclides. Teboroxime exhibits rapid tissue clearance after a high initial myocardial extraction. Johnson et al. found that myocardial clearance of teboroxime was biexponential over one hr (*14*). The $t_{1/2}$ for the washout from normal myocardial zones averaged 4.5 min for the first exponential phase. Stewart et al. found that 67% of retained activity cleared with a $t_{1/2}$ of 2.3 ± 0.6 min (*5*). Marshall et al., using an isolated blood-perfused rabbit model, found that increasing coronary flow rate was associated with more rapid teboroxime clearance from the myocardium (*6*). Beanlands et al. examined the relationship between myocardial retention of teboroxime and myocardial blood flow at one, two or five min after injection of the tracer in a canine experimental model (*9*). At one min after injection, the relationship of teboroxime retention to flow was linear over a wide range, becoming nonlinear at flows above 4.5 ml/min/g. After five min, the myocardial uptake of the tracer versus flow was linear only to 2.5 ml/min/g, which is consistent with the findings of the present study. Thus, there is significant back diffusion of teboroxime from the myocardial cellular compartment despite a high peak extraction in the regions of hyperemic coronary blood flow.

Clinical Implications: Vasodilator Stress Imaging

There are some clinical implications of the present findings to pharmacologic stress teboroxime imaging with dipyridamole or adenosine for detection of CAD. Defect magnitude should be maximal the ealier images are acquired. A limitation of imaging immediately after teboroxime administration is that some scintigrams are difficult to interpret because of intense liver uptake causing scattered activity into the inferior wall and inferoapical region. This problem is more prevalent with vasodilator stress imaging than with exercise imaging, similar to what is observed with dipyridamole or adenosine ^{201}Tl imaging. Nevertheless, some recent reports indicate that teboroxime imaging with dipyridamole or adenosine is feasible and permits detection of coronary artery stenoses. Labonte et al., utilizing a planar imaging technique, found a good correlation between dipyridamole ^{201}Tl and teboroxime imaging for CAD detection (*15*). Seventy-three percent of stenotic arteries were detected by ^{201}Tl dipyridamole imaging and 64% by dipyridamole teboroxime imaging. Iskandrian et al. began acquiring teboroxime SPECT images as soon as an adenosine infusion was completed (*16*). With a total imaging time of 7.8 min, teboroxime images were abnormal in 94% of patients with CAD. By segmental analysis, although there was an 80% agreement between adenosine teboroxime images and exercise images, 29 segments interpreted as normal on teboroxime images showed redistribution defects of ^{201}Tl scans. Only 8 segments judged to be normal on ^{201}Tl images corresponded to reversible defects on teboroxime images. Marked hepatic uptake was seen on adenosine teboroxime images which contributed to false positive fixed defects in the inferior wall in two patients.

Chua et al. performed back to back adenosine stress/rest teboroxime SPECT using a triple-detector camera and found that images acquired in a 1 to 2 min time frame had a high proportion of low quality images associated with residual blood-pool activity on the projection data (*17*). Sensitivity and specificity for CAD detection were 95% and 71%, respectively for 2 to 3 min and 2 to 5 min summed raw imaging data of 1 min continuous rotations. Liver interference was considered severe or moderate in 32% of the imaging studies. The ability to detect physiologically significant stenoses with teboroxime and adenosine stress using a rapid imaging protocol is consistent with the findings of the present experimental study. None of these prior clinical studies separated out the sensitivity of vasodilator teboroxime imaging for detection of mild versus severe stenoses.

Exploiting the Rapid Clearance Kinetics of Teboroxime

It may be possible to exploit the rapid myocardial clearance of teboroxime for detection of reversible stress-induced ischemia. Experimental data (*7,8,14*) have shown that differential washout of teboroxime between zones of reduced flow and normal zones can result in defect resolution similar to delayed ^{201}Tl redistribution. In the clinical setting, Chua et al. reported a significantly slowed teboroxime washout in ischemic myocardium on SPECT images obtained serially after adenosine induced hyperemia in 33 catheterized patients (*18*). In this study, 51% of ischemic, noninfarcted territories had abnormal teboroxime washout compared with 7% of normal territories. Weinstein et al. performed immediate poststresss and 5 min delayed teboroxime imaging in 68 consecutive patients with known or suspected CAD (*19*). Rapid teboroxime redistribution was observed in 48% of scintigrams judged to be ischemic by conventional stress-rest comparison. Defect magnitude improved from 0.79 to 0.88 at early delay which was statistically significant. This redistribution was attributed to disparate washout rates from ischemic and normal myocardial regions.

Study Limitations

In vivo SPECT imaging could not be performed logistically in these animal experiments and comparisons of teboroxime and ^{201}Tl stenotic: normal activity ratios are derived solely from from in vitro well counting on myocardial specimens from stentic and normal zones. Therefore, the influence of such variables as scatter and attenuation on relative defect magnitudes could not be assessed. A group of dogs was not killed immediately after injection of teboroxime and ^{201}Tl, and prior to any significant teboroxime washout, to confirm that teboroxime uptake is more linearly related to flow values after adenosine infusion than observed at the two and four minute timepoints examined in this study. Nevertheless, it is unlikely that any rapid imaging protocol in the clinical setting could be completed within 30 sec to 1 min after teboroxime injection. The time points chosen to measure stenotic: activity ratios in the present study are relevant to the clinical situation. Finally, a higher infusion concentration of adenosine than employed in clinical imaging studies was utilized. Nevertheless, the dose selected resulted in the greatest degree of hyperemia in the normal myocardial zones permissible without reducing mean arterial pressure below 85 mmHg.

CONCLUSIONS

This experimental study shows that when ^{201}Tl and teboroxime are simultaneously administered during adenosine-induced hyperemia in the setting of either a critical or mild LAD stenosis, the stenotic zone: normal zone activity ratio in the myocardium for ^{201}Tl better reflects the heterogeneity in flow than does the teboroxime activity ratio. This difference favoring ^{201}Tl was seen as early as two min after tracer injections. The loss of defect severity over time is due presumably to the rapid clearance of teboroxime from high flow myocardial regions immediately following the extraction phase of uptake. The clinical implication of these findings, and those of others reported in the literature, is that an ultra-rapid image acquisition protocol is required to optimize the detection of coronary artery stenoses when teboroxime is employed in conjunction with dipyridamole or adenosine imaging. Also, the results of this study suggest that mere reliance on first-pass extraction data for a tracer, or initial immediate myocardial uptake versus microsphere flow data to predict an advantage over other diffusible tracers such as ^{201}Tl or sestamibi for clinical imaging, is not warranted. Thallium-201, sestamibi, teboroxime and other radionuclide perfusion agents each have positive and negative attributes for detection of ischemia and/or determination of myocardial viability. Knowledge of basic myocardial uptake and clearance kinetics of these tracers is mandatory for optimizing the appropriate imaging technique for each in the clinical setting.

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