Myocardial Clearance Kinetics of Technetium-99m-Teboroxime Following Dipyridamole: Differentiation of Stenosis Severity in Canine Myocardium

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The purpose of the current study was to determine whether teboroxime clearance kinetics are useful in differentiating the severity of coronary artery flow restriction. **Methods:** Groups of dogs received stenoses of the left circumflex coronary artery as follows: nine dogs received a mild-to-moderate stenosis (Group 2) and eleven dogs received severe stenoses (Group 3). In three control dogs (Group 1), there was no stenosis. Using miniature cadmium-telluride radiation detectors, myocardial teboroxime activities were continuously monitored in both the control and stenosed zones following dipyridamole infusion. **Results:** A significant difference in fractional myocardial clearance between the control zones (0.69 ± 0.01, n = 26) versus mild-to-moderate (0.61 ± 0.06, $p < 0.05$, n = 9) and severe (0.57 ± 0.03, $p < 0.01$ versus control, $p < 0.05$ versus mild-to-moderate, n = 11) flow-restricted zones was observed over a 1-hr period. Significant differences between normal and both stenosed zones became apparent after 7 min of clearance. Significant differences in myocardial clearance between mild-to-moderate and severe groups were detected within 15 min. **Conclusion:** Thus, in this canine model using dipyridamole, miniature probe-determined teboroxime myocardial clearance can differentiate among normal myocardium, myocardium distal to a mild-to-moderate stenosis and myocardium distal to a severe stenosis.

Key Words: teboroxime; stenosis; differential clearance; dipyridamole

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Technetium-99m-teboroxime has been approved for clinical nuclear cardiology perfusion imaging in patients. Among the unique kinetic properties of teboroxime are a high extraction fraction and rapid myocardial washout compared to ^{201}Tl and ^{99m}Tc-MIBI (*1–3*).

Prior research has indicated that teboroxime is an excellent flow marker even at flows which are several times that of normal (*4*). In a previous study in our laboratory, a rest canine stenosis model was employed which produced a heterogeneous range of hemodynamic severity. Rapid early differential teboroxime clearance kinetics were observed in this model (*5*). Specifically, very early myocardial clearance kinetics of ^{99m}Tc-teboroxime were significantly delayed in flow-restricted myocardium relative to normal myocardium due to flow restriction.

In the present study, the primary aim was to determine whether coronary stenoses of differing severity could be further differentiated using dipyridamole and miniature radiation detectors to record regional teboroxime clearance kinetics in a canine model.

METHODS

Surgical Preparation

Twenty-three adult mongrel dogs (mean weight 23.2 kg, range 15–24 kg) were anesthetized with sodium pentobarbital (26 mg/kg, intravenous bolus). Supplemental anesthetic was administered throughout the experiment as necessary. The dogs were intubated and placed on a respirator with 95% oxygen. Vinyl catheters were inserted into both femoral arteries and the carotid artery to monitor arterial pressure, to provide a site for microsphere reference blood withdrawal, and to obtain specimens of blood for the determination of arterial hydrogen ion concentration, partial pressure of CO_2, and partial pressure of oxygen. Appropriate adjustments were made as necessary to maintain these parameters within a normal physiologic range. Arterial oxygen partial pressure was maintained above 100 mmHg throughout the experiment. Vinyl catheters were also inserted into both femoral veins as sites for the infusion of supplemental anesthetic and fluids as required.

The heart was exposed via a left thoracotomy at the fifth intercostal space and suspended in a pericardial cradle. A vinyl catheter was inserted into the left atrial appendage in order to monitor left atrial pressure and provide a site for the injection of radiolabeled microspheres. A Swan-Ganz thermodilution catheter was inserted into the left jugular vein and passed through the right side of the heart until its tip rested in the pulmonary artery. This

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catheter was subsequently used for the measurement of cardiac output.

The left circumflex (LCx) coronary artery was then carefully dissected free near the origin and a 2.0–2.5 mm electromagnetic flow probe was placed around the artery. A snare occluder was loosely positioned distal to the electromagnetic flow probe. A stiff 22-gauge, 8-inch catheter was inserted retrograde into a small branch of the left circumflex coronary artery for monitoring pressure distal to the snare occluder.

Mean or phasic systemic arterial pressure, left atrial pressure, distal left circumflex artery pressure, left circumflex coronary artery flow and lead II of the electrocardiogram were continuously monitored throughout the protocol on an 8-channel stripchart recorder.

Two pairs of ultrasonic dimension crystals were placed across the wall of the left ventricle in order to record regional wall thickness. One pair was placed in an area of the myocardium which was perfused by the left circumflex coronary artery and the other pair was placed in an area which was perfused by the left anterior descending coronary artery. The pinger of each pair was located on the epicardial surface and the receiver was located on the endocardial surface of the ventricle. The dimension crystals were connected to a four-channel sonomicrometer. Regional wall thickening was monitored throughout the experiment in the normal and flow-restricted zones.

Finally, miniature cadmium-telluride (Cd-Te) radiation detectors were positioned against the epicardium of the left ventricular anterior and posterior walls in close proximity to the sonomicrometer crystals and sutured in place. These detectors were connected through preamplifiers to a multichannel analyzer operating in multi-channel scaling mode and allowed continuous monitoring of regional myocardial ^{99m}Tc activity in the ischemic and nonischemic regions of the heart. The physical characteristics of these detectors have been previously reported (*6*).

Dipyridamole Preparation

Dipyridamole was supplied by Boehringher Ingelheim Pharmaceuticals, Inc. of Ridgefield, CT. One ampule of dipyridamole (2 ml, 5 mg/ml) was diluted in saline to a final volume of 4 ml and infused intravenously into the left jugular vein over 4 min at an infusion rate of 0.08 mg/kg/min.

Preparation of Teboroxime

Kits for the preparation of teboroxime were supplied in a lyophilized form by Squibb Diagnostics (Princeton, NJ). A vial of teboroxime was reconstituted by addition of 25 mCi of ^{99m}Tc pertechnetate. The vial was then heated for 15 min at 100°C using a heating block. After cooling to room temperature, paper chromatography was performed to determine the percentage of soluble contaminants and reduced hydrolyzed Tc. Whatman 31 ET chromatography strips (1.3 × 11 cm) and two individual mobile-phase solvent systems were used to determine the radiochemical purity of the prepared product. The developed chromatographs were air-dried and counted (*7*). The results indicated that radiochemical purity was 94.0% ± 0.4%. Just prior to injection, a volume of the vial having 5 mCi of activity was withdrawn into a lead shielded syringe.

Experimental Protocol

Figure 1 illustrates the experimental protocol. Baseline hemodynamic measurements were recorded during a 15 min period following instrumentation in all 23 dogs. Following the baseline period, 2–3 million 11-micron radiolabeled microspheres were

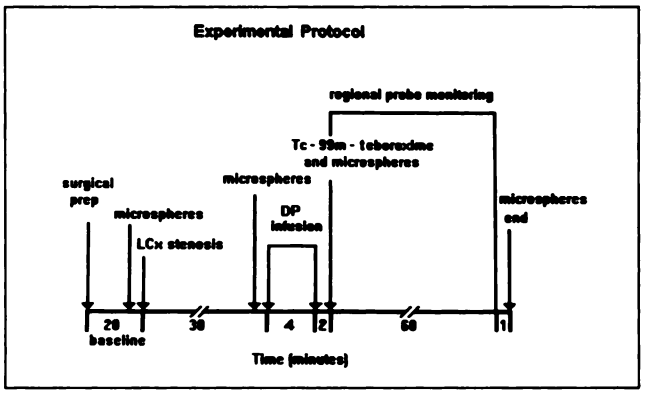

FIGURE 1. Experimental protocol. Diagram showing order of events and time spans in the experimental protocol. LCx = left circumflex coronary artery, DP = dipyridamole.

injected into the left atrium to determine regional myocardial blood flows. The occluder on the left circumflex coronary artery was then partially tightened in 20 dogs with a stainless steel, arterial screw clamp occluder to provide either a mild to moderate or severe resting flow reduction, as indicated by flow probe. In three control group dogs, no stenosis was created in order to observe the effects of dipyridamole alone on all parameters. A second microsphere blood flow measurement was made following the determination that the stenosis was stable to document the resting poststenosis coronary flow.

Thirty minutes later, dipyridamole (0.08 mg/kg/min) was infused into the left jugular vein over 4 min. Two minutes later, 5 mCi of ^{99m}Tc-teboroxime was injected into the left femoral vein and a third microsphere blood flow determination was simultaneously made. A thermodilution cardiac output determination was also made at this time.

Normal and stenosed zone regional myocardial ^{99m}Tc activities were continuously monitored over 1 hr using the miniature Cd-Te radiation detectors and recorded on a multichannel analyzer. An example of these recordings illustrating the relative lack of system noise is shown in Figure 2.

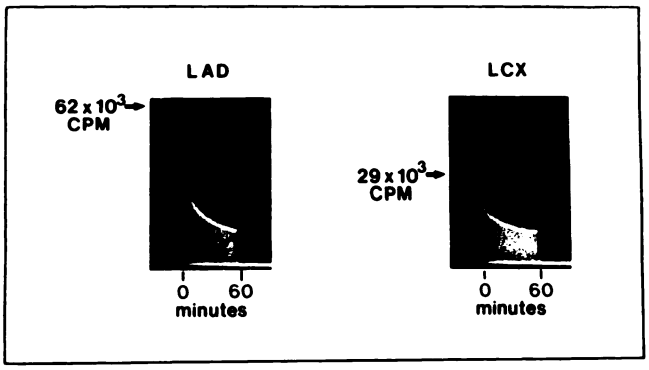

FIGURE 2. Multichannel analyzer displays. Teboroxime myocardial clearance curves as recorded by miniature Cd-Te probes are shown. The left panel illustrates clearance from a left anterior descending artery (LAD) control zone, while the right panel displays the paired left circumflex artery (LCx) stenosis zone from a severe stenosis experiment. Note the lower peak uptake in the stenosis zone compared to that of the control zone.

To measure blood ^{99m}Tc activity over the 1-hr study period, 1.0 ml serial arterial blood samples were collected at 30-sec intervals during the first 2 min and then at 2, 4, 6, 8, 10, 20, 30 and 60 min after injection. At the end of 1 hr, a final myocardial blood flow determination was made by injecting a fourth set of microspheres into the left atrium and a final cardiac output determination was made. The dogs were then killed.

Microspheres were labeled with either ^{113}Sn, ^{103}Ru, ^{95}Nb or ^{46}Sc. The order in which the microspheres were injected was randomized across experiments. Microsphere reference blood collection was begun 10 sec prior to each microsphere injection and continued for 2 min following the injection. The microsphere technique has been used extensively in our laboratory and has been previously described (*8*).

After the dogs were killed, their hearts were quickly removed and the area of the myocardium from each zone was divided into 24 transmural samples per zone and weighed (0.9–1.1 g/sample). Within 12 hr of collection, the ^{99m}Tc serial blood samples and the transmural myocardial tissue samples were counted for 3 min each in a gamma well counter with a window setting of 120–160 keV to detect ^{99m}Tc activity. These count data from the gamma counter were corrected for background and radioactive decay. The next day, the microsphere reference blood samples and the same transmural myocardial tissue samples were again counted for 5 min each. Appropriate window settings were chosen for each microsphere isotope (^{113}Sn was counted within a 350–435 keV window, ^{103}Ru within a 450–550 keV window, ^{95}Nb within a 660–800 keV window, and ^{46}Sn within a 810–1200 keV window). A computer was used to correct for both background and spillover of activity from one window into another and to calculate regional transmural myocardial blood flow using proprietary software developed for this purpose. Regional transmural myocardial blood flow was expressed as ml/min/g of tissue as calculated from the microsphere count data and tissue sample weights. Myocardial blood flow ratios were calculated by dividing the flow in the left circumflex (stenosis) zone by the flow in the left anterior descending (no stenosis) zone.

All experimental animals were handled in accordance with the guiding principles of the "Position of the American Heart Association on Research Animal Use" and by the Institutional Animal Care and Use Committee of the University of Oklahoma Health Sciences Center.

Data Analysis and Statistical Methods

Dogs were categorized following analysis of transmural microsphere flow data as having mild to moderate (0.4–1.0 ml/min/g flow) or severe (0–0.3 ml/min/g flow) stenoses based on the post-dipyridamole LCx coronary artery flow at the time teboroxime was injected.

The first blood sample in each experiment was discarded, as the activity of this sample was lower than that of the 30-sec sample due to inadequate time for complete mixing of teboroxime in the blood pool. Then, background and decay-corrected serial blood sample data representing individual activity versus time curves for each dog were modeled using a nonlinear estimation.

Myocardial clearance data was recorded from the Cd-Te probes and multichannel analyzer at 1 min intervals and corrected for initial background activity and ^{99m}Tc decay. Fractional myocardial clearance was defined as the difference between the initial and final counts divided by the initial counts, expressed in percent and was calculated from the background and decay corrected, non-normalized data from the normal and stenosed zones.

All results were expressed as mean ± 1 s.d. from the mean. The significance of mean differences among groups was assessed using a one-way repeated measures analysis of variance. Post-hoc comparisons were made using t-tests with Newman-Keuls procedure for multiple comparisons. Temporal comparisons were made using a paired t-test. Correlation coefficients reported are Pearson r values. Linear regression analysis was performed using TableCurve 2D software. Probability values of less than 0.05 were considered significant.

RESULTS

Hemodynamics

Complete hemodynamic data for the 23 dogs are presented in Table 1. There were no significant differences in mean arterial pressure among the three groups during the control period, following stenosis, at the time of ^{99m}Tc-teboroxime administration or at the end of the experiment. Following administration of dipyridamole and at the time of ^{99m}Tc-teboroxime injection, all groups had significant reductions in mean arterial pressure. The reduction in mean arterial pressure for all groups was approximately the same and did not differ significantly following dipyridamole. Mean heart rate and mean cardiac output did not vary significantly among the groups at any time during the experiment. Mean distal pressure was not significantly different among the groups during the control period. Following stenosis, mean pressure distal to the stenosis was significantly lower than initial values in the severe stenosis group and remained so throughout the experiment indicating that the stenoses were sustained. Reductions in distal pressure occurred in all three groups following administration of dipyridamole. Mean left atrial pressure was not significantly different among the groups at any time during the experiment.

Regional Myocardial Function

Wall thickening fractions as shown in Table 1, were calculated from sonomicrometer-determined end-systolic and end-diastolic wall thicknesses for each dog during the control period, following stenosis, at teboroxime administration and at the end of the experiment. Wall thickening, an index of regional contractile function, did not change significantly in the control group or in the mild-to-moderate stenosis group. Significant decreases in wall thickening were observed in the flow-restricted zone compared to the normal zone in the severe stenosis group at every time following stenosis, indicative of the severity of ischemia in this group. No significant changes in wall thickening occurred from the time at which teboroxime was administered until the end of the study in any group.

Blood Clearance Kinetics

Serial blood samples taken during each experiment were counted in a gamma well counter to obtain ^{99m}Tc activities. The activity at each time point for each dog was normalized by expression as a percent of maximal activity for that dog. Then, means were derived at each time point and analyzed as group data. Teboroxime cleared rapidly from

TABLE 1
Hemodynamic Parameters

	Control	Post-Stenosis pre-DP	^{99m}Tc injection post-DP	Final
MAP (mmHg)				
Group 1	109.3 ± 19.7	102.0 ± 5.3	78.0 ± 7.2	93.3 ± 2.3
Group 2	100.8 ± 6.8	98.4 ± 5.0	76.5 ± 15.1	95.3 ± 11.6
Group 3	105.2 ± 6.5	101.6 ± 6.2	75.2 ± 9.6	100.4 ± 6.4
HR (bpm)				
Group 1	134.3 ± 8.7	125.0 ± 5.0	121.0 ± 1.7	111.7 ± 10.4
Group 2	126.0 ± 15.6	123.5 ± 18.2	115.5 ± 17.8	107.6 ± 18.1
Group 3	124.8 ± 14.7	122.2 ± 14.5	115.8 ± 13.7	112.6 ± 13.7
CO (liter/min)				
Group 1	1.9 ± 0.7	1.9 ± 0.7	2.0 ± 0.8	1.8 ± 0.5
Group 2	1.9 ± 0.6	1.7 ± 0.5	2.1 ± 0.6	1.7 ± 0.4
Group 3	1.6 ± 0.2	1.5 ± 0.3	1.7 ± 0.4	1.7 ± 0.6
DsP (mmHg)				
Group 1	94.0 ± 22.5	90.7 ± 16.8	58.0 ± 7.2	75.3 ± 6.4
Group 2	96.0 ± 12.2	62.0 ± 28.1	38.6 ± 23.9	51.8 ± 27.9
Group 3	96.6 ± 13.4	35.6 ± 17.3*	23.4 ± 14.7*	33.0 ± 14.4*
LAP (mmHg)				
Group 1	4.0 ± 1.0	4.7 ± 2.1	5.0 ± 1.0	3.7 ± 0.6
Group 2	4.4 ± 1.0	5.8 ± 3.1	5.5 ± 2.9	5.5 ± 2.7
Group 3	3.6 ± 1.0	4.8 ± 1.5	5.7 ± 1.8	6.4 ± 1.9
Wall Thickening Fraction (%)				
Group 1				
LAD	22.3 ± 5.3	22.3 ± 5.3	22.7 ± 7.2	20.3 ± 4.5
LCx	17.7 ± 6.1	18.3 ± 4.6	17.6 ± 7.6	16.8 ± 5.4
Group 2				
LAD	20.3 ± 6.3	21.5 ± 6.9	21.6 ± 8.9	21.9 ± 7.9
LCx	16.6 ± 5.3	17.2 ± 3.2	18.1 ± 3.4	15.6 ± 2.8
Group 3				
LAD	19.9 ± 7.4	24.6 ± 6.8	27.8 ± 7.8	25.5 ± 5.6
LCx	16.9 ± 3.3	15.2 ± 4.8†	13.6 ± 4.1†	13.3 ± 5.6†

mean ± sd; Group 1 = control (no stenosis), (n = 3); Group 2 = mild-to-moderate stenosis, (n = 9); Group 3 = severe stenosis, (n = 11); *p < 0.05 (from control group); †p < 0.05 (from LAD).

CO = cardiac output; DsP = distal left circumflex coronary artery pressure; HR = heart rate; LAD = left anterior descending coronary artery; LAP = left atrial pressure; LCx = left circumflex coronary artery; MAP = mean arterial pressure; DP = dipyridamole.

the blood during the first 5 min, with slower clearance over the remaining period of study. Blood clearance was modeled and found to be biexponential in all groups. Postdipyridamole blood clearance at 60 min was 0.96 ± 0.01 in Group 1 (control), 0.94 ± 0.03 in Group 2 (mild-to-moderate stenosis) and 0.95 ± 0.02 in Group 3 (severe stenosis). There were no significant differences in teboroxime blood clearance among these groups.

Myocardial Blood Flow

Flows increased from resting values in all of the left anterior descending coronary artery (LAD) zones as would be expected. Mean flows in the LCx zone of the mild-to-moderate group increased from a mean post-stenosis value of 0.59 ± 0.14 ml/min/g to 0.77 ± 0.34 ml/min/g (p = ns) following dipyridamole. Seven of nine experiments demonstrated this increase in flow. In contrast, 10 of 11 experiments in the severe group showed a significant decrease in LCx flow from a mean of 0.28 ± 0.16 ml/min/g to 0.16 ± 0.09 ml/min/g (p < 0.005) following dipyridamole. Mean LCx flows were significantly lower in the severe group when compared to the mild-to-moderate group both following stenosis (0.28 ± 0.16 ml/min/g versus 0.59 ± 0.14 ml/min/g, respectively; p < 0.005) and following dipyridamole (0.16 ± 0.09 ml/min/g versus 0.77 ± 0.34 ml/min/g, respectively; p < 0.0001). Postdipyridamole regional myocardial blood flows determined by radiolabeled microspheres for each experiment are shown in Table 2.

Flow-restricted to normal ratios were calculated for each dog studied during four time periods and are shown in Figure 3. During the control period, flow ratios were near unity and were not significantly different among the three groups. Following stenosis, the severe group mean flow ratio (0.39 ± 0.28), but not the mild-to-moderate group mean flow ratio (0.92 ± 0.20), was significantly reduced compared to the control group mean flow ratio (1.10 ± 0.03; p < 0.05 versus severe group). Following administration of dipyridamole, both stenosis groups had significantly reduced mean flow ratios (mild-to-moderate = 0.36 ± 0.20;

TABLE 2
Transmural Myocardial Flows and Flow Ratios

	LCx flow (ml/min/g) Tc Inj Post-DP	LAD flow (ml/min/g) Tc Inj Post-DP	Flow ratio (LCx/LAD) Tc Inj Post-DP
Group 1			
B104	0.56	0.98	0.57
B105	0.42	2.49	0.17
B106	0.88	3.22	0.27
B107	0.98	1.27	0.77
B108	0.69	3.94	0.18
B109	0.62	2.82	0.22
B110	1.22	2.60	0.47
B111	0.94	1.38	0.68
B124	1.03	2.08	0.49
mean ± sd	0.82 ± 0.26	2.31 ± 0.98	0.43 ± 0.23
Group 2			
B100	0.22	1.30	0.17
B101	0.24	2.30	0.10
B102	0.26	1.45	0.18
B103	0.30	2.40	0.13
B112	0.20	0.65	0.31
B117	0.11	2.43	0.05
B118	0.05	4.20	0.01
B120	0.05	2.24	0.02
B121	0.05	0.93	0.05
B122	0.06	2.51	0.02
B123	0.20	2.82	0.07
mean ± sd	0.16 ± 0.09	2.11 ± 0.99	0.10 ± 0.09

Group 1 = mild-to-moderate stenosis, Group 2 = severe stenosis, LCx = left circumflex coronary artery, LAD = left anterior descending coronary artery, DP = dipyridamole.

$p < 0.05$ and severe = 0.10 ± 0.09; $p < 0.05$) compared to the control group (0.93 ± 0.07). Note that the administration of dipyridamole revealed a flow disparity in the mild-to-moderate stenosis group which was not apparent at rest. At the end of study, the mean flow ratios of both stenosis groups had returned toward post-stenosis, pre-dipyridamole values (mild-to-moderate = 0.82 ± 0.17, severe = 0.29 ± 0.16). Notice also that the stepwise progression of decreasing flow ratios with increasing severity of stenosis was maintained throughout the experiment. Mean peak absolute flows in control zones increased from 0.79 ± 0.08 at rest to 2.2 ± 0.28 ml/min/g following administration of dipyridamole, representing an average increase of 278%.

Figure 4 illustrates the microsphere-determined flow ratio (flow-restricted to normal) at the time of ^{99m}Tc teboroxime administration compared to the gamma well counter-determined myocardial tissue-Tc ratio, at the end of 1 hr. Both stenosis groups had significantly lower mean flow ratios compared to final tissue-Tc ratios (mild-to-moderate = 0.36 ± 0.20 versus 0.77 ± 0.08; severe = 0.10 ± 0.09 versus 0.47 ± 0.19; $p < 0.05$), indicating that a substantial amount of differential clearance of teboroxime occurred over one hour.

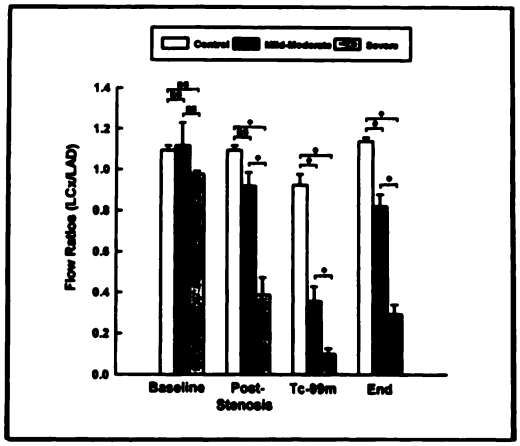

FIGURE 3. Myocardial blood flow ratios. This bar graph illustrates microsphere-determined myocardial blood flow ratios for the control and both stenosis groups studied at 4 times: (1) prestenosis baseline, (2) post-stenosis (pre-dipyridamole), (3) post-dipyridamole and simultaneously with teboroxime administration, and (4) end of study. DP = dipyridamole, *$p < 0.05$, ns = not significant, control group (n = 3), mild-to-moderate group (n = 9), severe group (n = 11).

Myocardial Clearance Kinetics

In order to compare the myocardial clearance kinetics between the normal and stenosis zones, the clearance curves from the miniature probes for each dog were corrected for background and radioactive decay, normalized to 100% maximal activity and averaged at each time point, see Figure 5. There was a similar pattern of myocardial clearance in both stenosis zones with a rapid early phase followed by a slow late phase. Significantly delayed myocardial clearance from both flow-restricted zones compared to the control flow zones became apparent as early as 7 min following teboroxime administration and was

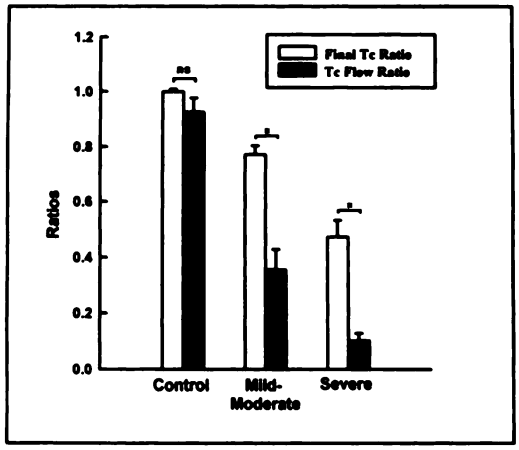

FIGURE 4. Technetium ratio versus flow ratio. This bar graph illustrates significantly lower microsphere-determined flow ratios at the time of teboroxime administration compared to the gamma well counter-determined myocardial tissue Tc ratio at the end of 1 hr for both stenosis groups. This is indicative of differential clearance. *$p < 0.05$, ns = not significant, control group (n = 3), mild-to-moderate group (n = 9), severe group (n = 11).

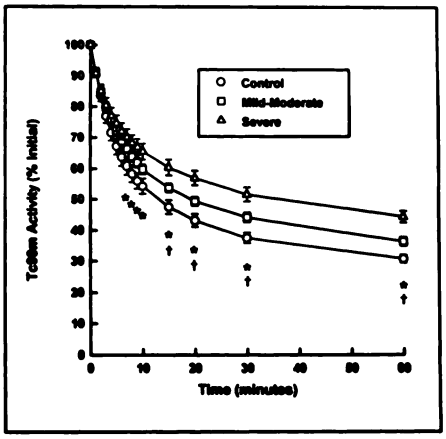

FIGURE 5. Time course of myocardial clearance. Decay-corrected time activity curves for normal, mild-to-moderate and severe stenosis zones are displayed. Delayed myocardial clearance from both flow-restricted zones compared to the normal flow zones, became significant at 7 min following isotope administration. *$p < 0.05$ from control zones, †$p < 0.05$ from mild-to-moderate stenosis zones, control zones (n = 26), mild-to-moderate stenosis zones (n = 9), severe stenosis zones (n = 11).

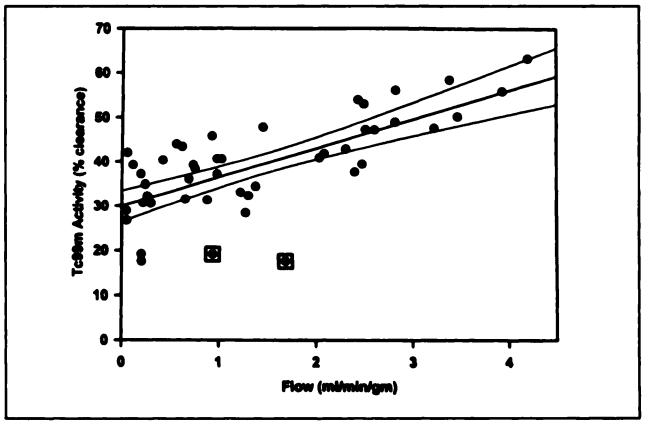

FIGURE 6. Myocardial flow and teboroxime clearance. This scatterplot displays microsphere-determined transmural myocardial flow for each of 46 myocardial zones studied versus miniature probe-determined fractional myocardial clearance of ^{99m}Tc-teboroxime for those zones. These data represent the relationship between flow and clearance at 9 min postinjection of teboroxime. Solid lines shown on either side of the best fit linear regression line represent 95% confidence intervals. The two points shown in boxes are statistical outliers.

maintained throughout the remainder of the experimental period. Delayed myocardial clearance from severe stenosis zones compared to the mild stenosis zones became significant by 15 min and was maintained throughout the remainder of the experiment.

Mean fractional myocardial clearance at 60 min in the normal zone was 0.69 ± 0.01 compared to 0.61 ± 0.06 in the mild-to-moderate flow-restricted zone ($p < 0.05$). The severe stenosis group flow-restricted zone clearance was 0.57 ± 0.03 ($p < 0.01$ from control; $p < 0.05$ from mild). Thus, 1 hr fractional myocardial clearance was significantly less in both flow-restricted zones compared to control zones and was significantly less in severe compared to mild-to-moderate flow-restricted zones.

A regression plot of microsphere-determined transmural flow versus miniature probe-determined myocardial clearance for all 46 zones at 9-min postinjection of teboroxime is shown in Figure 6. Myocardial teboroxime clearance increased as flow increased. The correlation coefficient between fractional clearance and transmural flows at the time of teboroxime administration across all zones was r = 0.71 ($p = .0001$, n = 46). Two points which are outliers appear within small boxes near the lower left margin of this figure. The correlation between flow and clearance improved to r = 0.78 ($p = 0.0001$, n = 44) with removal of these 2 points which are from nonstenosed control (LAD) zones.

A regression plot of microsphere-determined transmural flow ratios versus probe-determined clearance ratios is shown in Figure 7. Clearance ratios clearly increased as flow ratios increased. The correlation of these ratios is r = 0.73 ($p < 0.0001$, n = 23). Thus, a significant positive relationship between flow and clearance following dipyridamole has been established whether single-zone or dual-zone ratios are used.

DISCUSSION

This study uses miniature radiation probe techniques to determine regional myocardial teboroxime clearance kinetics following dipyridamole. This study confirms previous gamma camera imaging studies which have shown decreased clearance from flow-restricted zones. However, this study also examined the utility of teboroxime clearance rates in differentiating stenoses of differing severity.

Technetium-99m-teboroxime has been approved for

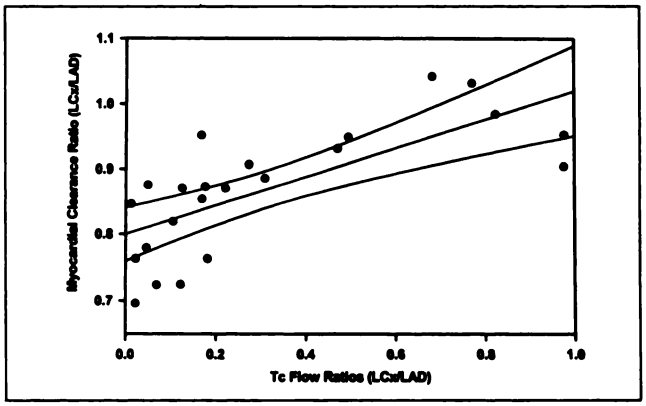

FIGURE 7. Myocardial flow ratio and teboroxime clearance ratio. This scatterplot displays microsphere-determined transmural myocardial flow ratios at the time of teboroxime administration versus miniature probe-determined fractional clearance ratios of ^{99m}Tc-teboroxime at 1 hr. The solid line represents the least squares best fit linear regression line through these 23 data points. Solid lines shown on either side of the regression line represent 95% confidence intervals.

clinical nuclear cardiology perfusion imaging in patients. Most clinical studies have utilized this agent in conjunction with exercise or dipyridamole stress. Teboroxime washout has been noted to be quite rapid after exercise. Therefore, dipyridamole stress has some potential advantages over treadmill exercise since imaging can begin immediately after tracer administration.

In this study, dipyridamole was used in conjunction with fixed stenoses of known severity over a wide range of flow restriction in order to test the hypothesis that teboroxime myocardial clearance kinetics could be used to detect even mild-to-moderate stenoses and to differentiate more severe stenoses from mild-to-moderate stenoses.

Hemodynamics

The pattern of hemodynamic alterations observed was consistent with stenosis of a major coronary artery, i.e., reduction of coronary artery pressure distal to the stenosis with elevation of left atrial pressure in the most severe stenosis group. Injection of dipyridamole produced similar reductions in mean arterial pressure and distal pressure in all groups with no other hemodynamic alterations. The pattern of hemodynamic response to intravenous dipyridamole in the present study was similar to that previously reported in open-chest anesthetized dogs including a decrease in systemic arterial pressure, decrease in coronary artery pressure distal to the stenosis and no significant changes in heart rate, cardiac output and left atrial pressure (*9–13*). Technetium-99m-teboroxime injection produced no observable hemodynamic changes during these experiments.

Blood Clearance Kinetics

Teboroxime blood clearance was rapid with 90% of the radiotracer being cleared in the first 5 min. There were no significant differences in blood clearance among the groups studied. A biexponential model provided the best fit to these data.

Myocardial Flow and Flow Ratios

Previous work in control dogs has shown increases in coronary artery flow with intravenous dipyridamole of 35%–400% depending upon the concentration. Normal zone microsphere determined flows in the present study were increased to 278% of control flow across all three groups.

The reductions in flow and flow ratios distal to a severe coronary artery stenosis observed in the present study following administration of dipyridamole were consistent with previous data (*10–15*). The explanation for this phenomenon could be that a reduction in distal pressure secondary to a falling mean arterial pressure resulted in reduced flow beyond the stenosis. Alternatively, this phenomenon could be due to coronary steal. Administration of dipyridamole did unmask a flow disparity in the mild-to-moderate stenosis group which was not apparent at rest and which is also consistent with previous work from this laboratory (*16–18*).

Teboroxime has been shown to have a high extraction fraction over a wide range of flows (*4,19,20*). Stewart et al. (*4*) found that mean first-pass retention fraction after intracoronary injection of teboroxime in intact dogs was stable over a wide flow range of 0.3–7.7 ml/min/g.

Myocardial Clearance Kinetics

Previous studies have shown teboroxime clearance kinetics to be rapid in normal myocardium (*4,5*) at rest. Early clearance kinetics in ischemic myocardium have been shown to be delayed relative to normal myocardium, in part as a result of reduced flow (*5,21,22*). Previous data from our laboratory indicated that very early clearance kinetics, i.e., during the first 5 min, differentiated between normal and ischemic zones at rest, while later clearance kinetic parameters did not (*5*). Early myocardial clearance of teboroxime is thought to be primarily but not solely dependent upon blood flow (*4*). Thus, increased flows due to dipyridamole would be expected to produce increased myocardial clearance of teboroxime in normal zones compared to flow-restricted zones. Accordingly, dipyridamole was used to expand the range of flows in order to magnify the differences in teboroxime clearance between normal and flow-restricted zones.

Marshall et al. (*20*) described myocardial clearance kinetics as being more rapid in normal isolated rabbit hearts due to increased coronary flow associated with administration of dipyridamole. This finding of accelerated clearance following dipyridamole in normal tissue is also supported in canine studies (*4,21,23*). Seldin et al. (*24*) have confirmed this finding in clinical studies which showed an accelerated early clearance component following dipyridamole in normal myocardium.

Stewart et al. used gamma camera images to demonstrate delayed 30-min clearance distal to a relatively severe partial (>90%) occlusion following dipyridamole. Gray and Gewirtz also used scans to demonstrate delayed 7-min clearance distal to an 80% stenosis following dipyridamole. The current study produced clearance curves which were increasingly delayed with increasing stenosis severity. Thus, clearance curves derived from regional probes differentiated between normal, mild-to-moderate and severe flow-restricted myocardium after dipyridamole.

Further Support for Differential Clearance

The final gamma well counter determined tissue Tc-ratio (ischemic to normal) was significantly greater than the microsphere-determined blood-flow ratio (ischemic to normal) at the time of ^{99m}Tc-teboroxime administration which indicated that differential clearance occurred in both stenosis groups. Furthermore, the final Tc ratios of the two stenosis groups were significantly different (0.77 ± 0.1 mild-to-moderate versus 0.47 ± 0.2 severe). Peak uptake was less in the severe zones than in those of mild-to-moderate which in turn were less than those of the control zones. Thus, clearance curves for the three groups start at different points as a result of reduced uptake and are sub-

jected to differential post-stenotic delays in clearance. These observations lead to the following speculations:

1. The differences between these values may be large enough to be perceived on images.
2. The differential clearance of the mild-to-moderate group approaches normal such that this defect would appear to resolve over time on an image.
3. Apparent redistribution due to differential clearance was not complete in the severe group, which would appear on an image as a partially persistent defect. Thus, the analysis of differential myocardial clearance of teboroxime may provide useful diagnostic information.

Differential clearance resulting in apparent redistribution on images has been reported in patients (*25,26*) and also observed in animal studies (*21,22*). The investigation of Gray and Gewirtz reported an increase in ischemic to normal zone teboroxime activity between the 30 sec and 7 min scans. Early differential clearance is thought to represent differences in regional flow reserve between normal and ischemic zones as well as ongoing differences in flow during imaging (*22*). Dipyridamole exacerbates these differences in flow and consequently the differences in myocardial clearance, thus exposing differences in coronary flow reserve.

Therefore, quantitative information from the miniature probes was confirmed by evidence from the gamma well counter from the current study and are consistent with scan data from other studies. These data taken together support the concept of differential myocardial clearance of teboroxime from flow-restricted zones compared to normal zones. Further, the greater the flow restriction, the more delayed will be the clearance of teboroxime.

Clinical Implications

The present study and others have demonstrated rapid myocardial uptake and clearance of ^{99m}Tc-teboroxime following dipyridamole (*21,22*). Thus, imaging of teboroxime must begin soon after injection to detect initial defects. Rapid imaging protocols of 15–20 min or less allow for immediate determinations of myocardial perfusion and would allow for multiple measurements within a short span of time. Fortunately, clearance from the blood pool is quite rapid, which permits the commencement of imaging within minutes of injection.

In patients with single-vessel coronary artery disease, the depth of the initial defect compared to the normal zone may correlate with the severity of flow restriction (*22*). However, in patients with multivessel coronary artery disease such an approach may not be possible due to the lack of a normal control zone. In such patients, a technique for determining the severity of flow restriction of any given coronary distribution based on an analysis of clearance from that area of myocardium alone would be useful. In the current study, postdipyridamole teboroxime clearance rates distal to a stenosis progressively decline with increasing flow restriction. The correlation coefficient for probe-determined clearance and blood flow for all zones studied was 0.71. Significant differences were observed after only 7 min of clearance. This relatively high correlation between clearance and flow allows for the possibility that flow-restricted zones could be distinguished in the absence of a normal zone for comparison. However, before these data can be extrapolated to a clinical situation, the limitations noted below would need to be addressed.

A similar approach has been investigated for ^{99m}Tc-MIBI and ^{201}Tl. However, prior research has shown that sestamibi clearance kinetics cannot be used to distinguish poststenotic myocardium from normal myocardium (*18*). Thallium clearance after dipyridamole is slower and up to 2 hr of imaging may be necessary to detect significant differences in clearance.

Limitations of the Study

The limitations of the study include the fact that dipyridamole produced an increase in flow in the normal zone which was less than three times normal. Adenosine is capable of producing far greater increases in flow which might be more useful in allowing differentiation of flow disparities between zones. Furthermore, adenosine is more rapid acting, and therefore may be better suited to the rapid clearance characteristics of teboroxime.

Another practical limitation stems from the fact that the open-chest dog model chosen for this study represents an ideal situation of well-controlled conditions. The use of miniature radiation detectors represent an accurate method of monitoring tracer kinetics in experimental animal models. Even with such a monitoring technique, the correlation of flow versus teboroxime clearance was 0.71. Furthermore, if these study results are to be clinically useful, images would be required to corroborate these results. Undoubtedly, more advanced image analysis software and imaging techniques will need to be developed.

Conclusions

Our results show that after 7 min, myocardial teboroxime clearance is significantly different between normal and mild-to-moderate stenosis zones following dipyridamole. After 15 min, myocardial teboroxime clearance is significantly different between mild-to-moderate and severe stenosis zones. Moreover, a significant correlation was found between blood flow and early myocardial teboroxime clearance across all zones.

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EDITORIAL

Myocardial Clearance Kinetics of Technetium-99m-Teboroxime Following Dipyridamole Injection

This issue of the *Journal* contains an article by Johnson et al. concerning myocardial clearance kinetics of ^{99m}Tc-teboroxime in the setting of a coronary artery stenosis and dipyridamole administration (*1*). The principal conclusion of the article is that stenosis severity can be determined by serial imaging of ^{99m}Tc- teboroxime following coronary vasodilation with dipyridamole. The results of the study are consistent with earlier related investigations (*2–4*) and commentary (*5*). To their credit, the authors of the present study acknowledge that their open chest canine model with implanted radiation detectors confers a number of important advantages which may not be available under clinical conditions. Accordingly, it is appropriate to consider if clinically useful information regarding the functional severity of a coronary arterial stenosis can be obtained with standard gamma camera imaging (either SPECT or planar) of ^{99m}Tc- teboroxime myocardial clearance kinetics and if this approach has any potential advantages over conventional, defect-oriented image analysis.

The answer to the second question is more interesting than it would appear at first glance and is thus worthy of some consideration. In particular, since conventional myocardial perfusion imaging with single photon tracers is relativistic in nature, by definition at least one region of the heart must be "normal" when the principal end-point for recognition of coronary artery disease is a defect in the stress perfusion scan. Though extent of uptake abnormality is often used to determine if multivessel coronary disease is present, it should be noted that an extensive perfusion defect, particularly one that involves the apex of the left ventricle, may project into the vascular territory of more than one artery even though it reflects either ischemia or infarction from a single coronary lesion (usually proximal LAD). While such patients may also have circumflex and right coronary disease, these vessels actually represent innocent bystanders in the above scenario and their detection by stan-

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