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# The Relationship Between Myocardial Retention of Technetium-99m Teboroxime and Myocardial Blood Flow

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*Objectives.* The aim of this study was to define the temporal changes in the relationship between technetium-99m teboroxime tissue retention and myocardial blood flow in a canine model.

*Background.* Technetium-99m teboroxime is a new neutral lipophilic myocardial perfusion agent. It is known to be highly extracted by the myocardium but to have a rapid clearance rate.

*Methods.* A wide range of myocardial blood flow was induced in each experiment by regional coronary occlusion and dipyridamole infusion. Myocardial retention of technetium-99m teboroxime was determined by in vitro tissue counting at 1, 2 or 5 min after injection of the tracer. Tracer retention was correlated with microsphere-determined blood flow and the data were fitted to nonlinear functions.

*Results.* Correlation coefficients for these functions were 0.92, 0.95 and 0.95 at 1, 2, and 5 min, respectively. At 1 min after injection, the relationship of technetium-99m teboroxime retention to blood flow was linear over a wide flow range, becoming nonlinear at flow rates >4.5 ml/min per g. After 5 min the retention-flow relationship was linear only to 2.5 ml/min per g, above which little change in retention was noted. Normalized myocardial retention, expressed as a percent of the retention at 1 ml/min per g, was also calculated. At flow rates of 1, 2, 3, 4 and 5 ml/min per g, normalized retention was 100, 169, 228, 277 and 317% at 1 min and 100, 171, 217, 239 and 237% at 5 min after injection.

*Conclusions.* At 1 min after injection, the relationship of technetium-99m teboroxime myocardial retention to blood flow is well maintained over a wide range of flow. However, after only 5 min, tracer retention underestimates flow changes at moderate and high flow rates. Thus, rapid acquisition protocols are necessary to fully exploit the potential of this promising new tracer in the evaluation of myocardial perfusion.

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Cardiac imaging with radiolabeled perfusion tracers continues to be the most important noninvasive method for the evaluation of myocardial perfusion. In addition to standard exercise imaging protocols, coronary flow reserve can now be assessed clinically with the use of pharmacologic vasodilation (1–5). A four- to fivefold increase in myocardial blood flow can be achieved with these agents in vascular territories with normal coronary arteries (6–8). With this wide range of flow now achievable in the clinical setting, it becomes critical to define the relationship between a given tracer's retention in tissue and blood flow. This relationship is important in determining the accuracy with which myocardial perfusion can be measured by nuclear imaging techniques (9).

Three principal myocardial flow agents are now available for clinical use: thallium-201, technetium-99m sestamibi and technetium-99m teboroxime. Thallium-201 is the most widely used. Its kinetics have been extensively studied (9–15), and its clinical utility and limitations are known.

Thallium-201 has a high extraction fraction by the myocardium in the range of 85% (9–11). However, as flow increases, the extraction and retention decrease (9–11,15). Because thallium-201 has low photon energy and a long physical half-life that limits its suitability as an imaging agent, other flow tracers have recently been developed. Technetium-99m sestamibi is one such agent. It has a lower extraction than that of thallium-201 (9,14) but a greatly prolonged tissue retention (9,14,16,17). As with thallium-201, this tracer also demonstrates a reduction in retention with increasing flow, thus limiting its ability to accurately reflect perfusion at high flow rates (9).

Technetium-99m teboroxime (Cardiotec) represents the most recent flow tracer to be proposed for clinical use (18,19). It is a neutral lipophilic boronic acid adduct of technetium dioxime (BATO) compound that demonstrates a high level of myocardial tissue extraction (15,20,21) with a first pass retention fraction of about 90% (21). After initial

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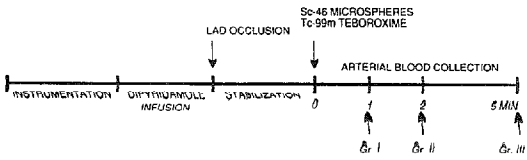


**Figure 1.** Experimental protocol. Gr. = group; LAD = left anterior descending coronary artery; Sc = scandium; Tc = technetium.

uptake, the activity clears rapidly from the myocardium (18,20–25) at a rate proportional to blood flow (21,25). However, there are limited data on the relationship between tissue retention of technetium-99m teboroxime and myocardial blood flow. Given the tracer's stable first pass retention fraction over a wide flow range (21), a linear correlation between retention and flow would be expected. However, with rapid differential tissue clearance this relationship may not be maintained. A more complete understanding of these temporal changes in technetium-99m teboroxime retention is required to fully exploit its potential as a myocardial perfusion tracer.

Thus, this study was designed to define the temporal changes in the relationship between the myocardial retention of technetium-99m teboroxime and myocardial blood flow measured by microspheres during the 1st 5 min after tracer injection. Tissue retention measured by in vitro counting was determined at different times after injection over a wide flow range in open chest dogs.

## Methods

The study protocol was approved by the Committee for Animal Research at the University of Michigan and performed in accordance with the "Position of the American Heart Association on Research Animal Use," adopted November 11, 1984 by the American Heart Association.

**Experimental preparation.** Eleven mongrel dogs weighing 20 to 25 kg were anesthetized with intravenous sodium pentobarbital (30 mg/kg body weight). All dogs were intubated and ventilated with oxygen-enriched room air. A peripheral venous line and central venous line were inserted for intravenous access. Both femoral arteries were catheterized for continuous aortic pressure monitoring and for arterial sampling. The electrocardiogram (ECG) was also monitored continuously. A left thoracotomy was performed and the heart carefully suspended in a pericardial cradle. A left atrial catheter was inserted through the left atrial appendage for microsphere and isotope injection. The position of this catheter in the left atrium was confirmed by a left atrial pressure tracing. The proximal left circumflex coronary artery was isolated. A Doppler flow probe was gently placed around it to measure relative coronary flow velocity in order to continuously monitor flow conditions during the experiment. To produce regional flow differences, the left anterior descending coronary artery was isolated and a snare placed loosely around it for subsequent occlusion.

**Tracer preparation.** The preparation of technetium-99m teboroxime by our laboratory has been previously described (21). Briefly, kits containing vials of teboroxime in a lyophilized form were supplied by Squibb Diagnostics. Sodium pertechnetate technetium-99m was obtained from molybdenum-99/technetium-99m generators that had been eluted within 24 h of radiopharmaceutical preparation. All eluates were used within 6 h, and radionuclide purity, aluminum ion content and pH were determined before use. Each vial was reconstituted with 1 ml of sodium pertechnetate technetium-99m containing 5 to 10 mCi of radioactivity. After reconstitution, each vial was heated for 15 min at 100°C in a boiling water bath. The prepared radiopharmaceutical was cooled to room temperature, and the radiochemical purity of the product was determined with the use of 1.3 × 11-cm Whatman 31 Et chromatography strips developed in normal saline (0.9%) or normal saline/acetone (50:50) solution. The developed chromatograms were air dried and counted. The percent of free technetium-99m, reduced/hydrolyzed technetium-99m and technetium-99m teboroxime was determined. Chromatographic results indicated that the sum of free technetium-99m and reduced/hydrolyzed technetium-99m was routinely <10%, whereas the mean radiochemical purity was 94.5% ± 2.3%.

**Experimental protocol (Fig. 1).** Once blood pressure, heart rate and relative left circumflex coronary artery blood flow were stabilized, 0.2 to 0.56 mg/kg of dipyridamole was administered intravenously over 4 min. At the end of the dipyridamole infusion the left anterior descending coronary artery was occluded by the snare. Once flow and hemodynamics were stable (at least 5 min after occlusion), radiolabeled microspheres and 500 μCi of technetium-99m teboroxime were injected into the left atrium. Arterial blood was then collected for the definition of arterial input function with the use of a Harvard pump for 1 min (group I, n = five dogs), 2 min (group II, n = four dogs) or 5 min (group III, n = two dogs) after tracer injection. For animals in groups II and III, scandium-46–labeled microspheres (half-life 83.8 days) (DuPont-NEN, size 15.0 ± 0.5 μm) were injected simultaneously with the tracer. In group I, microspheres were injected 1 min before the injection of technetium-99m teboroxime. This procedure ensured that all dogs had a minimum 2-min arterial collection for the measurement of

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microsphere blood activity (see under "Measurement of myocardial blood flow").

At the end of blood collection, the dogs were killed with a saturated solution of potassium chloride and the heart was rapidly excised. The left ventricle was cut along the short axis into slices approximately 1 cm thick. Each left ventricular slice was then sectioned to yield samples of approximately 1 g, and each sample of myocardium was individually weighed. The activity in myocardial and blood samples was counted in a well counter (model 5780 Packard). Energy windows were defined for technetium-99m (116 to 160 keV) and scandium-46 (840-1,040 keV). Blood and tissue samples were counted again after 72 h (12 half-lives of technetium-99m) to correct for scandium spillover into the technetium-99m window.

**Measurement of myocardial blood flow.** Myocardial blood flow (MBF, ml/min per g) was determined by using the microsphere technique (26):

$$MBF = (C_t \times F_w)/C_b,$$

where $C_t$ is the activity in myocardium (counts/min per g), $F_w$ is the rate of the withdrawal pump (ml/min) and $C_b$ is the activity in collected blood (counts/min).

**Measurement of technetium-99m teboroxime retention.** Absolute retention (R) (arbitrary units, $g^{-1}$) of technetium-99m teboroxime was calculated as follows:

$$R = C_t/C_{b_c},$$

where $C_{b_c}$ is the blood activity corrected for different withdrawal rates.

**Measurement of percent maximal technetium-99m teboroxime retention.** This measurement of retention with the arterial input function as denominator assumes that technetium-99m teboroxime remains relatively unaltered while it circulates in the blood pool. Because of the very rapid clearance of technetium-99m teboroxime from the blood pool (20,21) (<4% of injected dose present in the blood at 1 min after injection [20]), very little remains available for uptake beyond 1 min after injection. Thus, the correction for the arterial input function appears valid. Alterations that might reduce the availability of technetium-99m teboroxime for myocardial uptake would have to be very marked and occur very early after injection. Even with such changes, there would be little alteration in the blood pool activity after 1 min. Nonetheless, to rule out this possibility as an explanation for any results observed, we also measured the percent maximal retention in each dog, which is equivalent to measuring the percent maximal activity. This measurement also allowed comparison among the groups, because it was independent of each group's different blood collection times. The percent maximal retention ($\%R_{max}$) of the tracer was calculated for each individual heart in the following manner:

$$\%R_{max} = (R \times 100)/R_{max}.$$

Thus, the percent maximal retention is a relative value, which is independent of the blood collection time.

**Statistical analysis.** Blood pressure, heart rate and relative coronary blood flow at baseline, after dipyridamole and before and after injection of the tracer and microspheres were compared by analysis of variance (ANOVA) and expressed as mean value ± SEM. For each dog the absolute myocardial retention of technetium-99m teboroxime for each segment was plotted against the microsphere-determined blood flow. Each retention versus blood flow curve was fitted to a nonlinear function. Then, for each group the myocardial retention of all segments in a given group was plotted against blood flow and also fitted to a nonlinear function. The standard error of the coefficients and the y intercept for the nonlinear function in each group were determined.

As an alternate means of assessing the retention-flow relation, the percent maximal retention for technetium-99m teboroxime was plotted against the myocardial blood flow determined by the microspheres in each dog.

## Results

**Hemodynamic recordings.** At baseline before the dipyridamole infusion, the mean systolic blood pressure and heart rate were 128 ± 6 mm Hg and 150 ± 7 beats/min, respectively. Systolic blood pressure decreased to 108 ± 7 mm Hg ($p < 0.05$) after dipyridamole, whereas the mean heart rate was 146 ± 6 beats/min (p = NS). At the time of tracer injection (at least 5 min after left anterior descending coronary artery occlusion), systolic blood pressure was 102 ± 6 mm Hg and the heart rate was 138 ± 8 beats/min. After the injection of tracer and microspheres, both blood pressure and heart rate remained stable. With dipyridamole, the relative blood flow in the circumflex artery, as measured by Doppler ultrasound, increased significantly over the baseline value. After tracer and microsphere injection, the measured circumflex artery blood flow did not change significantly.

**Microsphere-determined blood flow.** The myocardial blood flow determined by microspheres ranged from 0.01 to 11.71 ml/min per g in group I, 0.01 to 7.48 ml/min per g in group II and 0.02 to 4.88 ml/min per g in group III.

**Myocardial retention of technetium-99m teboroxime.** There were 424 ventricular segments in group I, 308 in group II and 166 in group III. Table 1 shows the nonlinear fit equations and correlation coefficients for all experiments in the three groups. The equations of the curves fitted to the overall data for each group are also shown ($p \leq 0.001$ for each group). Figure 2 shows an individual example from each group of the relationship between technetium-99m teboroxime retention and microsphere-determined blood flow. There is a progressive decline in slope and loss of linearity with time.

**Table 1.** Nonlinear Equations for Retention Versus Myocardial Blood Flow in 11 Dogs

| Time After Injection (min) | Group No./Dog No. | Samples (no.) | Flow Range (ml/min per g) | Nonlinear Fit Equation | Correlation (r) |
|---|---|---|---|---|---|
| 1 | 1/17568 | 108 | 0.15 to 5.63 | $y = -0.005 + 0.332x - 0.0256x^2$ | 0.99 |
| 1 | 1/18185 | 86 | 0.04 to 3.28 | $y = 0.002 + 0.077x - 0.0069x^2$ | 0.98 |
| 1 | 1/19639 | 80 | 0.02 to 1.03 | $y = 0.000 - 0.085x - 0.0314x^2$ | 0.94 |
| 1 | 1/20385 | 86 | 0.07 to 5.93 | $y = 0.003 + 0.063x - 0.0043x^2$ | 0.98 |
| 1 | 1/20368 | 64 | 0.01 to 11.71 | $y = -0.005 + 0.050x - 0.0018x^2$ | 0.98 |
| | All 1-min data ± SE | 424 | 0.01 to 11.71 | $y = 0.017 + 0.065x - 0.0038x^2$ ± 0.003 ± 0.002 ± 0.0002 | 0.92 |
| 2 | 2/16410 | 74 | 0.02 to 7.22 | $y = 0.005 + 0.041x - 0.0021x^2$ | 0.97 |
| 2 | 2/16641 | 98 | 0.03 to 7.48 | $y = -0.002 + 0.046x - 0.0030x^2$ | 0.98 |
| 2 | 2/17340 | 66 | 0.13 to 6.69 | $y = 0.010 + 0.053x - 0.0044x^2$ | 0.87 |
| 2 | 2/17349 | 70 | 0.01 to 1.82 | $y = -0.002 + 0.087x - 0.0180x^2$ | 0.99 |
| | All 2-min data ± SE | 308 | 0.01 to 7.48 | $y = 0.008 + 0.047x - 0.0034x^2$ ± 0.002 ± 0.002 ± 0.0003 | 0.95 |
| 5 | 3/17594 | 84 | 0.02 to 4.88 | $y = 0.002 + 0.029x - 0.0033x^2$ | 0.97 |
| 5 | 3/18527 | 82 | 0.02 to 4.31 | $y = 0.001 + 0.030x - 0.0033x^2$ | 0.93 |
| | All 5-min data ± SE | 166 | 0.02 to 4.88 | $y = 0.001 + 0.030x - 0.0034x^2$ ± 0.002 ± 0.001 ± 0.0003 | 0.95 |

**Percent maximal myocardial retention of technetium-99m teboroxime.** The graphs in Figure 2B depict the relative retention expressed as a percent of the maximum for each example compared with microsphere-determined blood flow. One minute after tracer injection, the increase in relative retention was linear in relation to blood flow over a wide flow range. Above a flow rate of 4.5 ml/min per g the increase was more gradual. In contrast, at 5 min after tracer injection, the data indicate a linear relation only up to a flow rate of 2.5 ml/min per g. Above this flow rate, little change in relative tracer retention was noted.

**Normalized retention of technetium-99m teboroxime.** As a further means of comparison, a normalized tissue retention was also determined (Fig. 3). Myocardial retention values were calculated at flow rates of 1, 2, 3, 4 and 5 ml/min per g based on the fitted equations for individual data in each group. These calculated retention values were then expressed as a percent of the retention determined at a flow rate of 1 ml/min per g. The standard error of the fitted equation for each group was used to determine the error of the normalized retention values. As with the percent maximal retention, the normalized retention measurement is independent of blood input function.

The normalized retention values determined at the five flow rates were 100 ± 7%, 169 ± 11%, 228 ± 15%, 277 ± 20% and 317 ± 25% at 1 min after injection, and 100 ± 12%, 171 ± 20%, 217 ± 30%, 239 ± 43% and 237 ± 56% at 5 min after injection. At 1 min after injection the relative increments in retention between flow rates of 1 to 2, 2 to 3, 3 to 4 and 4 to 5 ml/min per g were 69%, 59%, 49% and 40%, respectively. At 5 min the corresponding values were 71%, 46%, 22% and −2%, respectively. The change in the increments of retention at 5 min showed a dramatic progressive reduction. In comparison, at 1 min this change was much more gradual.

**Assessment of myocardial clearance from the technetium-99m teboroxime retention data.** The determination of retention data at three different times allowed a limited evaluation of technetium-99m teboroxime myocardial clearance. Figure 4 shows the retention data at flow rates of 1, 2, 3 and 4 ml/min per g derived from the fitted curve of each group versus the three time points. This graph demonstrates the differential clearance phenomena. At high flow rates (4 ml/min per g) tracer retention decreases dramatically from 0.218 ± 0.016 to 0.066 ± 0.012 $g^{-1}$ between the 1- and 5-min mark after injection. At lower flow rates (1 ml/min per g) this reduction in retained technetium-99m teboroxime is more gradual, decreasing from 0.079 ± 0.006 to 0.028 ± 0.003 $g^{-1}$ between 1 and 5 min after injection.

## Discussion

**Initial tissue retention of technetium-99m teboroxime and myocardial blood flow.** The principal findings of this study are that initial technetium-99m teboroxime tissue retention has a well maintained relationship to myocardial blood flow over a clinically relevant flow range (0 to 4.5 ml/min per g). However, after 5 min the dynamic range of technetium-99m teboroxime retention is markedly reduced relative to flow. The clinical implication of this observation is a potential loss of sensitivity in determining regional differences in coronary flow reserve. On the other hand, if retention can be mea-

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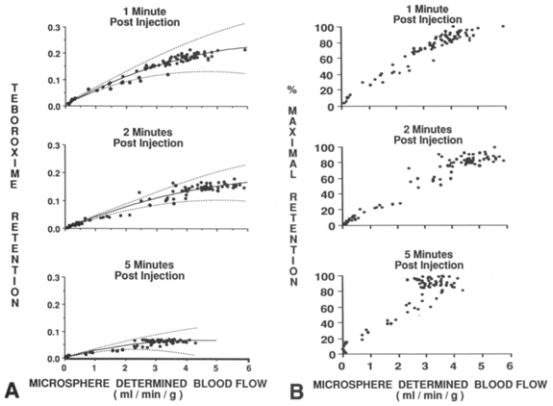
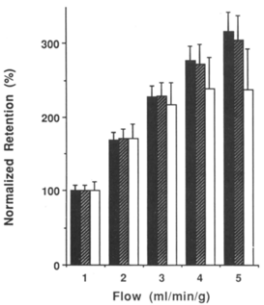



**Figure 2. A,** Examples of technetium-99m teboroxime absolute retention versus microsphere-determined myocardial blood flow at 1 min (Dog 20385), 2 min (dog 16641) and 5 min (Dog 18527) after injection with 95% confidence intervals (equations and correlation coefficients for each example are noted in Table 1). Note the progressive loss of slope and linearity with time. **B,** Percent maximal retention versus microsphere-determined myocardial blood flow for the same examples as in A. At 1 min the relative retention increased linearly in relation to blood flow up to a flow of 4.5 ml/min per g and then became more gradual. At 5 min the relationship was linear up to a flow rate of 2.5 ml/min per g. Above this flow rate there was little change in relative retention, with values between 80% to 100% of the maximum.

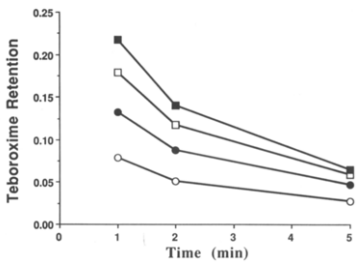
sured early after injection, myocardial blood flow can be determined with a high degree of accuracy. Such early measurement may be clinically achievable with the use of rapid data acquisition by multiheaded single-photon emission computed tomographic (SPECT) systems. Indeed, technetium-99m teboroxime is a promising tracer with the potential for noninvasive evaluation of myocardial perfusion over a wide range of blood flow.

**Figure 3.** Normalized retention at flows of 1, 2, 3, 4 and 5 ml/min per g derived from the retention-myocardial blood flow curve formulas (with retention at 1 ml/min per g assigned a value of 100% in each group). **Error bars** represent the standard error of the equations for each group at the respective flow rates (see Table 1). Technetium-99m teboroxime showed a reasonable increment in retention for increasing flow rates early after injection (1 and 2 min). However, at 5 min these increments decreased progressively in relationship to the increase in flow. ■ 1 min; ▨ 2 min; □ 5 min.




**Validity of this model.** This model combined the use of a pharmacologic vasodilator and a coronary artery occlusion to produce heterogeneous flow rates throughout the myocardium. Blood flow ranged from very low in the occluded territory to very high in the normal region. The border zone around the occluded territory had mild to moderate increases in flow between the two extremes. Maximal induced

**Figure 4.** Teboroxime retention at flows of 1, 2, 3 and 4 ml/min per g derived from the retention-myocardial blood flow relationships versus time after injection. Note the rapid decrease in retention over time at high flow rates. At lower flow rates this change was more gradual. -○- 1 ml/min per g; -●- 2 ml/min per g; -□- 3 ml/min per g; -■- 4 ml/min per g.



flow rates were varied among dogs by using different doses of the vasodilator. This technique was successful, judging by the wide range of microsphere-determined flow rates induced. The use of in vitro tissue counting of a large number of segments in each dog allowed determination of the retention-flow relationship with high statistical power.

Tissue activity was corrected for the integral of the blood activity to calculate absolute tracer retention. Accounting for the arterial input function appears to be appropriate because myocardial uptake of most perfusion tracers continues after their first pass through the coronary circulation. We did not correct for potential metabolic alterations of technetium-99m teboroxime after injection, although such changes could theoretically lead to an overestimation of the true arterial input function. However, a recent study (20) has shown that at 1 min after injection only 1% of injected dose of technetium-99m teboroxime is bound to red blood cells. This observation supports the view that these alterations are not of major importance in the first minutes after injection. In addition, the clearance of technetium-99m teboroxime from the blood pool is so rapid (20,21) that the consequences of later alterations in the compound are probably minimal. In support of our approach, the relative retention data, which are independent of blood collection time, and the absolute retention data yielded similar conclusions regarding the technetium-99m teboroxime retention-blood flow relationships.

The equations for the fitted curves of individual experiments shown in Table 1 were almost identical in group III. However, there was some variability in the equations within groups I and II. This variability does not alter the overall conclusions of this study because all individual curves in group I were also linear over a wide flow range. The individual curve differences may be explained in part by the different ranges of blood flow between experiments. Another possible explanation may be that slight differences in the length of the left atrial catheter and its position within the left atrium may have varied the tracer delivery time to the myocardium between experiments. This could lead to some variability in retention measurements early after injection.

**Technetium-99m teboroxime retention: comparison with previous studies.** Technetium-99m teboroxime is a neutral lipophilic BATO compound. The exact mechanism of its myocardial retention is not known. Given its neutral lipophilic nature, it most likely follows nonionic pathways (20). However, it is not clear whether it enters the cytosol or binds exclusively to the cell membrane lipid bilayer.

Several studies have demonstrated high initial myocardial extraction (15,20,21) and high capillary permeability surface area product (15). Although we did not specifically measure these variables, our data support these previous studies by demonstrating that retention accurately reflected blood flow over a wide range early after injection.

Our data also support previous work from our laboratory (21) that showed a stable first-pass retention fraction over a wide range of blood flow and suggested that retention would be almost linearly related to flow. Indeed, the present study supports this hypothesis, although the relation between tracer retention and flow changed over the 1st 5 min after injection.

Using isolated heart preparations with a multi-indicator dilution technique, Leppo et al. (15) showed that the peak extraction, capillary permeability and net extraction (= retention) were all higher for technetium-99m teboroxime than for thallium-201. They also reported a tendency for the peak extraction to decrease with increasing blood flow. Both tracers showed an inverse linear relation between flow and peak extraction fraction and a linear relation between capillary flux and coronary perfusion, confirming our observations. However, Leppo et al. (15) demonstrated a diffusion limitation at a relatively low flow rate of 2.5 ml/min per g tissue in the blood-perfused isolated rabbit heart. In addition to obvious species differences, there are important methodologic differences between their work and our present study. The multi-indicator dilution technique derived variables based on the continuous recovery of activity from the venous effluent of the isolated heart. Comparison of kinetics of a vascular tracer (radiolabeled albumin) and technetium-99m teboroxime allowed the instantaneous characterization of tracer extraction. In contrast, our data are based on tracer tissue retention at various times after injection in the intact animal. However, the different results of the two studies suggest there is less diffusion limitation at comparable blood flows for technetium-99m teboroxime in our model, which may reflect maintained integrity of vascular coupling in an intact animal.

The clearance kinetics of technetium-99m teboroxime have been well studied. Rapid myocardial clearance has been demonstrated in cell culture models (22), animal models (20,21,23,25) and human studies (18,24). The clearance rate has been shown to correlate with blood flow (21,25), and rapid disappearance of exercise defects has been observed in a clinical study as well (19). We did not examine the tracer clearance directly in this study; however, we did observe a progressive reduction in the slope of the retention-flow relation and a loss of linearity over time. Tracer tissue retention decreased more rapidly at higher flow rates (Fig. 4), an effect consistent with the differential clearance property of this tracer.

**Implications for imaging protocols.** Our results indicate that clinical imaging protocols must incorporate the rapid acquisition of data after technetium-99m teboroxime injection. This is in order to 1) capitalize on the excellent early relation of tracer retention to blood flow, and 2) to prevent the potentially reduced sensitivity in detecting flow reserve differences by delayed data acquisition. Given the time course of routine SPECT imaging, single-headed tomographic systems may be of limited use with this agent. Normal regions with high flow after a given stress will already have had significant clearance of activity during image acquisition and thus may be difficult to differentiate from regions distal to a coronary artery stenosis where the

clearance of technetium-99m would be more gradual. In a canine model with coronary stenosis, Li et al. (23) showed that both 12-min and 5-min SPECT acquisitions initiated early (1 min) after technetium-99m teboroxime injection led to underestimation of relative microsphere-determined flow deficits after dipyridamole administration. The investigators attributed this underestimation to residual activity from a preceding injection. However, the results of our study suggest that the underestimation observed by Li et al. (23) may also have been related in part to a loss of sensitivity due to the differential clearance accompanying a wide flow range.

An additional problem with routine SPECT imaging is the acquisition of myocardial tracer activity that is rapidly changing over time. This factor could potentially lead to image artifacts and thus interfere with data interpretation (27,28). The problem is compounded when tracer distribution is changing at different rates (23), as would be the case when there are regional differences in flow. Because of these problems, clinical studies (18,19) to date have principally involved planar acquisition protocols. However, even planar imaging involves projections acquired at different times with potentially different tracer distribution.

On the other hand, the newer multiheaded SPECT systems may provide sufficient temporal resolution to overcome the drawbacks of standard imaging techniques with this tracer. Nakajima et al. (24) used a dynamic triple-headed SPECT acquisition with 30 sets of 1-min projections beginning at the time of injection in six patients at rest. Excluding the 1st min, which had blood pool artifact, good image quality was achieved and time-activity data acquired. According to these investigators (24), the minimal time for a continuous rotation is 10 s with the triple-headed SPECT camera they describe. The potential for dynamic data acquisition with such systems may permit the absolute quantification of blood flow by applying tracer kinetic models to time-activity data. Such a tracer kinetic model for technetium-99m teboroxime could utilize both the excellent early retention-flow relationship, as well as the relationship of clearance rate to blood flow (21,25).

The present study used dipyridamole to maintain stable experimental conditions over a prolonged period. Clinically, however, it may be advantageous to utilize the rapid decrease in myocardial blood flow that occurs after cessation of either exercise or an adenosine infusion (5,29). Use of a short-acting vasodilator or exercise may prolong the linear relation of retention to flow by delaying the clearance in segments with high flow rates, thus permitting longer data acquisition times with a more stable tracer distribution.

**Conclusions.** Technetium-99m teboroxime demonstrates unique kinetics among available gamma-emitting myocardial flow tracers. Our study shows that a delay in acquiring technetium-99m teboroxime retention data may lead to significant underestimation of regional blood flow differences at moderate to high flow rates. This effect may limit the differentiation of regions with different levels of coronary flow reserve. In contrast, early after injection there is a well maintained relationship between technetium-99m teboroxime tissue retention and myocardial blood flow over a clinically relevant flow range. Thus, there appears to be promise for this agent in the use of rapid acquisition protocols and the development of a kinetic model for the estimation of regional myocardial blood flow.

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