Comparison of $^{99m}$Tc-Teboroxime With Thallium for Myocardial Imaging in the Presence of a Coronary Artery Stenosis

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Background. This study tested the hypotheses in the setting of a coronary artery stenosis that 1) planar $^{99m}$Tc-teboroxime myocardial scans are capable of providing a good estimate of relative coronary flow reserve, and 2) delayed washout of the tracer from the myocardium is a marker of reduced myocardial blood flow and, in certain cases, myocardial ischemia.

Methods and Results. Experiments were conducted in eight closed-chest domestic swine prepared with an artificial stenosis that reduced diameter of the left anterior descending coronary artery by 80%. Measurements of hemodynamics, regional myocardial blood flow, oxygen, and lactate metabolism were made 1) at baseline, 2) after 5 minutes of intravenous infusion of adenosine and neosynephrine ("stress"), and 3) at recovery 2 hours after discontinuing the adenosine/neosynephrine infusion. Simultaneous intravenous injection of teboroxime (~9 mCi) and thallium (~3.5 mCi) was made at peak stress, and serial planar teboroxime imaging began 1–2 minutes later. Scans were made in dynamic mode for 30 seconds each for 7 minutes after which a stress thallium scan (7 minutes acquisition) was obtained. A redistribution thallium scan was made 2 hours later after which a repeat teboroxime injection followed by serial imaging for 7 minutes was performed. The animal was then killed, and the heart removed for determination of microsphere activity. Under baseline conditions, transmural myocardial blood flow (ml/min/g) distal to the stenosis (1.06±0.17) was reduced (p<0.01) compared with the normally perfused circumflex zone (1.50±0.31). In response to intravenous infusion of adenosine/neosynephrine, flow increased (p<0.01) compared with baseline in both distal (2.00±0.84) and circumflex (4.67±1.55) zones. However, the distal:circumflex flow declined (0.45±0.17) compared with baseline (0.73±0.17; p<0.01). Two hours later flow had returned to baseline levels in both zones, and lactate production during stress (~41.7±37.5 µmol/min/100 g) had reverted to consumption (13.6±7.7; p<0.05). Analysis of stress teboroxime scans demonstrated 1) an increase (p<0.01) in the ischemic: normal zone (IZ: NZ) count between 30-second (0.50±0.14) and 7-minute scans (0.61±0.11); 2) a good correlation between the 30-second scan IZ: NZ count and the stress distal:circumflex flow (0.45±0.17; r=0.74; p<0.05; slope=0.90; intercept=0); and 3) a close correlation between the IZ: NZ count of the 7-minute scan (0.61±0.11) and the recovery distal:circumflex flow (0.69±0.21; r=0.89; p<0.01). The IZ: NZ count also increased (p<0.01) between 30-second (0.65±0.15) and 7-minute (0.72±0.14) scans following rest injection of teboroxime. As anticipated, serial thallium scans demonstrated evidence of redistribution between stress (IZ: NZ count =0.62±0.08) and recovery (IZ: NZ count =0.75±0.06; p<0.01) time points. The stress thallium scan IZ: NZ, however, was greater than that of the 30-second teboroxime scan as well as that of the stress distal:circumflex flow.

Conclusions. Accordingly, the data indicate that 1) myocardial imaging with $^{99m}$Tc-teboroxime is valuable in the noninvasive assessment of relative coronary flow reserve and that 2) delayed washout of the tracer from the myocardium reflects reduced myocardial blood flow and, under conditions comparable to those of the present study, may be a marker of myocardial ischemia. (Circulation 1991;84:1796–1807)
A new technetium-labeled boronic acid adduct of technetium dioxime, $^{99m}$Tc-teboroxime, recently has been introduced for myocardial perfusion imaging and appears to have a number of important properties that make it a useful agent for the noninvasive assessment of relative coronary flow reserve. In particular, data from isolated heart preparations indicate that myocardial capillary permeability surface area of teboroxime is greater than that of thallium at any given flow.\(^1\) In addition, although teboroxime extraction by the myocardium may decline with increasing blood flow, the decline is less than that observed for thallium.\(^1\) Taken together, the observations indicate that teboroxime should be useful in providing a noninvasive estimate of relative coronary flow reserve and may be superior to thallium in this regard. Data from an intact canine model also suggest that myocardial clearance of teboroxime is flow dependent, and, thus, measurement of teboroxime washout may be of value in identifying transiently ischemic myocardium and/or regions of persistently reduced myocardial blood flow.\(^2\)

While in vitro studies have provided important data regarding potentially useful imaging characteristics of teboroxime, there is only limited information available regarding the applicability of these findings to actual myocardial imaging with teboroxime in the presence of a coronary artery stenosis. Accordingly, the present study was performed to test the hypotheses that 1) planar teboroxime myocardial scans are capable of providing a good estimate of relative coronary flow reserve; and 2) that differential myocardial washout of teboroxime can be detected on serial planar scans, is an indicator of reduced myocardial blood flow, and may be a marker of myocardial ischemia. Experiments were performed in sedated, closed-chest domestic swine instrumented with an intraluminal coronary artery stenosis that reduced vessel diameter by 80%.\(^3,4\) Teboroxime and thallium scans were obtained in each animal. Myocardial imaging results were referenced to an appropriate "gold standard," namely, transmural myocardial blood flow (radioactive microspheres), and, as will be shown, support the hypotheses proposed.

**Methods**

**Animal Preparation**

Farm-bred domestic swine ($n=8$; mean weight, 47.3 kg; range, 42–64 kg) were premedicated with ketamine (25 mg/kg i.m.) and sodium thiamylol (total dose, 0.5–1.0 g i.v.), intubated, and anesthetized with halothane (0.5–1.5%) and nitrous oxide (60:40 mixture with oxygen). The animals were ventilated with a volume-cycled respirator through which supplemental oxygen was delivered at 2–3 l/min mixed with room air and anesthetic gases. Arterial blood gases were monitored frequently and were maintained at appropriate levels ($pH$ 7.40–7.47, $PCO_2$ at 37–48 mm Hg, and $PO_2$ at 98–148 mm Hg) throughout each study. After induction of anesthesia, each animal was anticoagulated with heparin (225 IU/kg i.v.). Full anticoagulation was maintained by administering approximately half the initial loading dose every 2–3 hours.

The animal was instrumented for the study as follows. A 7F pigtail catheter was advanced under fluoroscopic control into the left atrium. This catheter was used to administer radioactive microspheres for measurements of regional myocardial blood flow. Another 8F catheter was positioned in the aorta to monitor arterial blood gases and for reference withdrawal for microsphere determinations of regional myocardial blood flow. The femoral veins were cannulated bilaterally to administer fluids and medications during the study. A 3F angioplasty catheter was positioned in the mid-distal third of the anterior interventricular vein as described previously.\(^3,4\)

A plastic stenosis (7.5-mm long; outer diameter, 3.5 mm; inner diameter, 0.625 mm) was then placed in the proximal one third of the left anterior descending artery.\(^3,4\) The stenosis contained a second lumen into which the distal end of a 1.4-mm-diameter, 70-cm-long catheter had been attached before placement of the stenosis. The distal end of the catheter was open to the distal end of the stenosis and was used to record pressure from the distal arterial bed.

After placement of the coronary arterial stenosis, halothane and nitrous oxide were discontinued, and the animal was permitted to awaken sufficiently to breathe spontaneously and exhibit modest tremulousness. A constant intravenous infusion of sodium thiamylol was begun at 5–25 ml/hr (20 mg/ml) to maintain sedation and ensure that the animal was free of pain.

**Study Protocol**

After instrumentation, the animal was placed in the right lateral decubitus position for the duration of the study. The head of a portable gamma camera was positioned horizontally over the animal so that the apical impulse was in the center of the image field. With this arrangement, images corresponding to a 70° left anterior oblique view in humans were obtained (Figure 1). Once established, the positions of the camera and animal were kept constant throughout the study.

After a 30-minute stabilization interval, the experimental protocol was begun. Baseline measurements of hemodynamics, regional myocardial blood flow, arterial and anterior interventricular vein blood gases, oxygen content, and lactate were obtained. Next, an intravenous infusion of adenosine (~35 mg/min) was begun and gradually increased until a systemic blood pressure response was noted; a decline in mean arte-
FIGURE 1. Panel A: Teboroxime scans obtained at rest and during intravenous adenosine (Ado) plus phenylephrine infusion in a pig without coronary artery stenosis. Each scan is a composite of 14 30-second images obtained in dynamic mode over 7 minutes. Modest apical thinning is apparent in both scans. Panel B: A 7-minute static thallium image obtained at rest immediately following the rest teboroxime scan in Panel A. Apical thinning is apparent and is somewhat more prominent than that observed in the teboroxime images.

Mean arterial pressure of approximately 20–30 mm Hg was obtained in all animals. At that point, an intravenous infusion of phenylephrine (~0.35 mg/min) was started and gradually increased until the mean arterial pressure returned to baseline. The “stress” condition was maintained in a steady-state fashion for 5 minutes, at which time repeat measurements of all experimental parameters were obtained.
Next, thallium (~3.5 mCi) and $^{99m}$Tc-teboroxime (~9 mCi) were given intravenously in rapid succession. The adenosine and phenylephrine stress was continued for 1–2 minutes after isotope injection and then stopped. Serial teboroxime scans (Figure 2A), were obtained over a 7-minute time period after which the pulse height analyzer of the gamma camera was reset for thallium, and a stress thallium scan obtained (Figure 2B). Details of image acquisition and analysis are provided below.

Two hours later with the animal in a baseline state, thallium imaging as described above was repeated, followed by measurements of hemodynamics, regional myocardial blood flow, and metabolism. Next, a second teboroxime injection (~9 mCi i.v.) was given and imaging began 1–2 minutes later. Marker microspheres were then injected through the stenosis catheter to delineate the ischemic area.

After completion of the protocol, the animal was given a large bolus dose of sodium thiamylol and then killed 5 minutes later with an intravenous bolus of concentrated KCl. The heart was then removed and sectioned for determination of microsphere activity. The protocol for this study was approved by the Institutional Animal Care and Use Committee.

Image Acquisition and Analysis

Planar teboroxime and thallium scans were obtained with a Picker Dynamo portable gamma camera equipped with a general all-purpose collimator and interfaced with a Technicare computer system. Images were acquired in a $128\times128\times16$ matrix using a 20% window centered on the thallium photopeak (~80 keV) and a 15% window centered on the technetium photopeak (~140 keV). Teboroxime scans were obtained in dynamic mode at 30 seconds/frame for 7 minutes, beginning 1–2 minutes after each injection. Thallium scans were acquired in static mode for 7 minutes each. Because of rapid clearance of teboroxime from the myocardium, thallium scans were always obtained at a time when technetium activity in the heart was low and thus did not interfere with the thallium image (Figures 1 and 2).2

Thallium and teboroxime scans were analyzed objectively with computer assistance as follows. Operator defined regions of interest (ROI) were placed over the anterior wall defect (ischemic zone, IZ) and the normally perfused inferior/posterior wall of the left ventricle (normal zone, NZ). Since both the gamma camera and animal did not move during the study, a single ROI for each normal and ischemic zone was employed for the teboroxime and thallium scans of each animal. Normal and ischemic areas, however, were defined separately for thallium and teboroxime images to optimize ROI placement for each tracer. Counts per pixel were determined for ischemic and normal zones for stress and redistribution thallium scans and for each of the 14 teboroxime images obtained following stress and rest injection. Numeric data were derived from unprocessed images without background correction.

Imaging in vitro of pure standards at an activity ratio of technetium:thallium of 3:1 was performed with appropriate Lucite scatter material to determine the extent of spillover of each isotope into the window of the other. Data obtained demonstrated that ~80% of counts in the thallium window were from thallium and more than 99% of counts in the technetium window were from technetium. Because, as will be shown, technetium activity declined by approximately half at the time thallium imaging was completed, the myocardial technetium:thallium ratio at the time of stress imaging was closer to 1.5:1; thus, by proportion at least 90% of thallium counts in the thallium window were from thallium. Correction for spillover of technetium counts into the thallium window was not performed since subtraction of a constant fraction of total thallium counts per pixel from each pixel of an image would not influence either IZ:NZ count ratios or time–activity curves.

Hemodynamics

Heart rate and arterial, left atrial, and distal coronary artery pressures were monitored continuously throughout the study and recorded on chart paper with a Hewlett-Packard eight-channel recorder (model 5588A, Palo Alto, Calif.). Intravascular and intracardiac pressures were recorded from fluid-filled catheters connected to Hewlett-Packard force transducers (model 1280A).

Regional Myocardial Blood Flow

For each experimental condition, approximately $4\times10^6$ radiolabeled microspheres (15-μm diameter; 85–105 μCi total radioactivity) were injected through the left atrial catheter to determine regional myocardial blood flow.2 A different isotope was chosen at random for each flow determination. Details of microsphere methods used in our laboratory have been previously published.6

Since the purpose of this study was to compare results of myocardial imaging with measurements of myocardial blood flow, myocardium bordering the region directly distal to the stenosis was included in the distal zone. This was done to ensure that imaging data, which of necessity included a contribution from the border region, could be correlated more accurately with microsphere measurements of flow.

Regional Myocardial Oxygen Metabolism

Paired samples (2–3 ml) of arterial and anterior interventricular venous blood were obtained for determination of oxygen content (Lex-O2–CON Instrument, Lexington Instruments, Waltham, Mass.) as noted in the study protocol. Oxygen content (vol%) was determined in duplicate for each sample, and values were accepted only when the difference between them was less than 0.2 ml O2/dl. Regional myocardial oxygen consumption (ml/min/100 g) was calculated as the product of transmural regional myocardial blood flow distal to the stenosis and the arterial and anterior interventricular venous oxygen difference.
**Figure 2.** Panel A: Sequential 30-second images obtained following teboroxime injection during adenosine plus phenylephrine infusion in a pig with an 80% stenosis in the left anterior descending coronary artery. A dense anterior wall defect is present in the initial scan (upper left corner). The defect is less intense in the final scan (bottom right corner) primarily because of more rapid washout of tracer from the normally perfused posterior wall of the left ventricle. Scans are shown in sequential order reading from left to right along the rows. Panel B: Static stress and redistribution thallium scans for one of the animals used in the study. An anterior wall defect is clearly evident with definite redistribution apparent in the 2-hour scan.

**Regional Myocardial Lactate Metabolism**

Lactate concentration in arterial and anterior interventricular vein blood was determined by a spectrophotometric method with commercially available kits (Calbiochem Rapid Lactate Reagents, Calbiochem-Behring, La Jolla, Calif.). Samples of blood (5 ml) were immediately deproteinized by placing them in cold perchloric acid (8% vol/vol). The samples were centrifuged, and the supernatant was frozen for subsequent analysis in duplicate. Regional lactate consumption was calculated as the product of transmural regional myocardial blood flow distal to the stenosis
TABLE 1. Regional Myocardial Blood Flow

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Stress</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal zone (ml/min/g)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Endocardium</td>
<td>0.86±0.18*</td>
<td>1.48±0.18†</td>
<td>0.79±0.24</td>
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<td>Epicardium</td>
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<td>2.19±0.75‡</td>
<td>1.02±0.45</td>
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<td>Transmural</td>
<td>1.06±0.17*</td>
<td>2.00±0.84‡</td>
<td>0.98±0.36</td>
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<td>Circumflex zone (ml/min/g)</td>
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<tr>
<td>Endocardium</td>
<td>1.60±0.30</td>
<td>4.28±1.36‡</td>
<td>1.58±0.40</td>
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<tr>
<td>Epicardium</td>
<td>1.31±0.34</td>
<td>4.02±1.52‡</td>
<td>1.24±0.43</td>
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<tr>
<td>Transmural</td>
<td>1.50±0.31</td>
<td>4.67±1.55‡</td>
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<td>Distal:circumflex ratio</td>
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</tr>
<tr>
<td>Endocardium</td>
<td>0.57±0.22</td>
<td>0.35±0.17‡</td>
<td>0.52±0.16</td>
</tr>
<tr>
<td>Epicardium</td>
<td>0.88±0.17</td>
<td>0.58±0.20‡</td>
<td>0.85±0.25</td>
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<tr>
<td>Transmural</td>
<td>0.73±0.17</td>
<td>0.45±0.17‡</td>
<td>0.69±0.21</td>
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</table>

Values are mean ± SD; n=8.
* p<0.01 vs circumflex zone.
† p<0.05 vs. baseline.
‡ p<0.01 vs. baseline.

and the arterial and anterior interventricular vein lactate difference.

Statistics
All data are expressed as mean±SD. The significance of differences between group mean values was assessed by means of a blocked one-way analysis of variance and the Newman-Keuls multiple comparison test. Paired t tests also were employed when appropriate to evaluate hypotheses proposed prior to data acquisition and analysis. Correlations between variables were assessed using linear regression analysis. Values of p<0.05 were considered statistically significant.

Results

Hemodynamics
Heart rate and mean aortic pressure did not change significantly compared with baseline (115±26 mm Hg and 99±9 mm Hg, respectively) during the study. Mean pressure distal to the stenosis also did not change significantly (55±16 mm Hg), compared with baseline (59±8 mm Hg) in response to stress although both values were less (p<0.01) than that at the recovery (2 hours) time point (77±8 mm Hg). Mean left atrial pressure increased significantly (p<0.05) from its baseline value (7±3 mm Hg) at peak stress (13±5 mm Hg) and remained unchanged at the 2-hour time point (11±7 mm Hg).

Regional Myocardial Blood Flow
Under baseline conditions, distal zone endocardial and transmural blood flows were reduced (p<0.01) compared with respective circumflex zone values. Baseline epicardial flow did not differ significantly between the two zones. Endocardial, epicardial, and transmural blood flows in both distal and circumflex zones increased significantly (p<0.01) compared with baseline levels during peak stress and returned to control levels 2 hours following stress. The distal:circumflex zone blood flow ratios for all layers were significantly lower (p<0.01) during peak stress compared with both baseline and 2-hour recovery. There was no difference in distal:circumflex flow ratios in any layer between baseline and 2-hour recovery (Table 1).

Regional Myocardial Oxygen Metabolism
Arterial oxygen content increased modestly but significantly (p<0.05) compared with baseline in response to stress and then returned to baseline at the 2-hour measurement point. In contrast, anterior interventricular vein oxygen content during peak stress was significantly greater (p<0.01), and myocardial oxygen extraction significantly less (p<0.01).

TABLE 2. Regional Myocardial Oxygen Metabolism

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Stress</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen (ml/dl)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ART</td>
<td>12.8±0.6</td>
<td>14.2±0.9*</td>
<td>12.5±1.2</td>
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<tr>
<td>AIV</td>
<td>1.4±0.3</td>
<td>5.2±1.6†</td>
<td>1.6±0.4</td>
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<tr>
<td>Extraction (%)</td>
<td>88.7±2.3</td>
<td>63.5±11.4†</td>
<td>87.0±2.6</td>
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<tr>
<td>Consumption (ml/min/100 g)</td>
<td>10.7±1.2</td>
<td>10.5±2.1</td>
<td>9.2±2.1</td>
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</table>

Values are mean±SD; n=8.
ART, artery; AIV, anterior interventricular vein.
* p<0.05 vs. baseline.
† p<0.01 vs. baseline.
than either baseline or 2-hour recovery values. Myocardial oxygen consumption, however, did not change control during the study (Table 2).

Regional Myocardial Lactate Metabolism

Arterial lactate concentration remained unchanged compared with baseline during the study. In contrast, AIV lactate concentration increased significantly ($p<0.01$) compared with baseline during stress but then returned to control levels at the 2-hour recovery point. Consequently, both lactate extraction and consumption declined ($p<0.05$) compared with baseline and became frankly negative (that is, production occurred) during stress. At the 2-hour recovery point, both extraction and consumption were significantly ($p<0.01$) improved compared with stress (Table 3).

Teboroxime and Thallium Image Analysis

Teboroxime scans. Time–activity curves generated over ischemic and normal zones of serial images obtained after stress and rest injection demonstrated delayed tracer clearance from the ischemic area compared with the normal area (Figure 3A, Table 4). Thus, ischemic zone activity at 7 minutes declined to 78±6% of peak (i.e., 30-second scan) following stress injection compared with 61±7% in the normal zone ($p<0.01$). The $T_{1/2}$ of tracer clearance from the normal zone (assuming monoeponential decay) was ~10 minutes, a value that agrees closely with that reported by others (~13 minutes) under comparable experimental conditions. Following rest injection, ischemic zone activity at 7 minutes declined to 82±11% of maximum compared with 73±9% in the normal zone ($p<0.05$).

An inverse relation also was apparent between transmural blood flow and retained teboroxime activity (% initial scan) following stress and rest injection (Figure 3B). The correlation coefficient ($r$) was 0.63 (n=32 data pairs; $p<0.01$). However, both normal and ischemic zone activity in one animal after stress injection and in another after rest injection exhibited residual activity in relation to blood flow, which was out-of-keeping with the remaining data pairs (circled points, Figure 3B). The reason for this is uncertain. Upon exclusion of these points (each of which was more than 2.5 times the standard error of the estimate of $y$ [average = 3.5 times]), the correlation coefficient was 0.86 (Figure 3C; n=28 data pairs; $p<0.001$).

Since teboroxime washed out of the ischemic zone more slowly than the normal zone following stress injection, the IZ:NZ count ratio increased significantly ($p<0.01$) between 30-second (0.50±0.14) and 7-minute scans (0.61±0.11) (Figure 4). The same was true following rest injection. The IZ:NZ ratio at 7 minutes (0.72±0.14) was significantly ($p<0.01$) greater than that at 30 seconds (0.65±0.15). It also should be noted that 1) the IZ:NZ ratio of the 7-minute stress scan (0.61±0.11) did not differ significantly from that of the 30-second rest scan (0.65±0.15) obtained 2 hours later, and 2) in seven of eight animals, the average difference between stress (7-minute scan) and rest (30-second scan) IZ:NZ ratios was 5±4%. The difference was larger (~20%) in the remaining animal.

The IZ:NZ transmural blood flow ratio and the IZ:NZ count ratio for data obtained at peak stress (that is, stress flow compared with 30-second scan) correlated well, as shown in Figure 5 ($r=0.74; p<0.05$; IZ:NZ microspheres=0.90; IZ:NZ scans, +0.0). In addition, the mean value of the IZ:NZ transmural blood flow ratio at stress (0.45±0.17) did not differ significantly from that of the IZ:NZ count ratio for data obtained at peak stress

### Table 3. Regional Myocardial Lactate Metabolism

<table>
<thead>
<tr>
<th>Lactate (mM)</th>
<th>Baseline</th>
<th>Stress</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART</td>
<td>1.1±0.3</td>
<td>1.2±0.3</td>
<td>1.0±0.3</td>
</tr>
<tr>
<td>AIV</td>
<td>1.2±0.4</td>
<td>1.6±0.5*</td>
<td>0.8±0.3</td>
</tr>
<tr>
<td>Extraction (%)</td>
<td>−7.4±32.1</td>
<td>−32.9±30.0*</td>
<td>19.7±13.3*</td>
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<tr>
<td>Consumption (µmol/min/100 g)</td>
<td>−5.1±32.3</td>
<td>−41.7±37.5*</td>
<td>13.6±7.7*</td>
</tr>
</tbody>
</table>

Values are mean± SD; n=8.

* $p<0.05$ vs. baseline.

$fp<0.01$ vs. baseline.

$p<0.01$ vs. stress.

The IZ:NZ transmural blood flow ratio and the IZ:NZ count ratio for data obtained at peak stress (that is, stress flow compared with 30-second scan) correlated well, as shown in Figure 5 ($r=0.74; p<0.05$; IZ:NZ microspheres=0.90; IZ:NZ scans, +0.0). In addition, the mean value of the IZ:NZ transmural blood flow ratio at stress (0.45±0.17) did not differ significantly from that of the IZ:NZ count ratio for data obtained at peak stress

### Table 4. Imaging Data

<table>
<thead>
<tr>
<th>Teboroxime scan</th>
<th>Count ratio (IZ:NZ)</th>
<th>30 seconds</th>
<th>7 minutes</th>
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<tbody>
<tr>
<td>Stress</td>
<td>0.50±0.14</td>
<td>0.61±0.11*</td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>0.65±0.15</td>
<td>0.72±0.14*</td>
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</table>

<table>
<thead>
<tr>
<th>Counts/pixel (% 30 second scan)</th>
<th>7 minutes: IZ</th>
<th>7 minutes: NZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress</td>
<td>78±6†</td>
<td>61±7</td>
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<tr>
<td>Rest</td>
<td>82±11‡</td>
<td>73±9</td>
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<table>
<thead>
<tr>
<th>Thallium scan</th>
<th>Count ratio</th>
<th>Stress</th>
<th>Redistribution</th>
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<tbody>
<tr>
<td>(IZ:NZ)</td>
<td>0.62±0.08</td>
<td>0.75±0.06§</td>
<td></td>
</tr>
</tbody>
</table>

Results are mean±SD; n=8.

IZ, ischemic zone; NZ, normal zone.

* $p<0.01$ vs. 30-second scan.

† $p<0.01$ vs. 7 minutes NZ.

‡ $p<0.05$ vs. 7 minutes NZ.

§ $p<0.01$ vs. stress.
Graph A: Time-activity curves (expressed as % initial activity) for group mean (±SD) data for ischemic (IZ) and normal (NZ) zones following injection of teboroxime (TEBO) at stress. Initial activity has been set to 100% for both zones. Values at 7 minutes are significantly reduced (p<0.01) compared with 30 seconds. Note that minutes after TEBO takes time zero as the start of TEBO imaging that was 1–2 minutes after TEBO injection.

Graph B: Activity (% initial) in normal and ischemic zones of the final teboroxime scan obtained after stress and rest injection as a function of transmural blood flow for all data pairs (n=32). An inverse relation between flow and percent initial activity is apparent (r=0.63, p<0.01). Four "outliers" are circled (see text and graph C). Graph C: The data shown are the same shown in panel B except for exclusion of four outliers. The difference between the expected value of percent initial activity derived from linear regression analysis and the measured value for excluded points averaged 3.5 times the standard error of the estimate of y (range, 2.7–3.8).

(0.50±0.14). Similar results were obtained on comparison of the 2-hour IZ:NZ transmural blood flow ratio and the IZ:NZ count ratio for data obtained at 7 minutes after stress injection (r=0.89; p<0.01; IZ:NZ microspheres=1.61, IZ:NZ scans, -0.29) (Figure 6.)

Thallium scans. The thallium scan IZ:NZ count ratio, as anticipated, increased significantly (p<0.01)
between stress (0.62±0.08) and 2-hour redistribution (0.75±0.06) images (Figure 2B, Table 4). Also as expected, the redistribution scan IZ:NZ count ratio (0.75±0.06) was greater (p<0.01) than that of the stress IZ:NZ transmural blood flow ratio (0.45±0.17). The extent of redistribution (absolute or relative change in IZ:NZ count ratio from stress to redistribution images), however, did not correlate with either the IZ:NZ transmural flow ratio at stress or rest, or with absolute levels of transmural flow in either the ischemic or normal zones. These results are consistent with observations reported previously from our laboratory⁸ and others.⁹ Finally, the IZ:NZ count ratio for the 2-hour teboroxime scan (7-minute image=0.72±0.14)

**Figure 4.** The ischemic:normal (IZ:NZ) count ratio for stress and rest teboroxime injections. The ratio increased significantly (**=p<0.01) between 30-second and 7-minute scans following both stress and rest injection.

**Figure 5.** The relation between ischemic:normal (IZ:NZ) zone blood flow ratio at stress and the IZ:NZ count ratio of the first teboroxime (TEBO) scan made 1–2 minutes following injection of the tracer during stress. The dashed line is the line of identity. A strong correlation is apparent between the two variables (see text for regression equation).

**Figure 6.** The relation between ischemic:normal (IZ:NZ) zone blood flow ratio at recovery and the IZ:NZ count ratio of the final teboroxime scan made following injection of the tracer during stress. The dashed line is the line of identity. A strong correlation is apparent between the two variables (see text for regression equation).
did not differ significantly from that of the redistribution thallium scan (0.75±0.06).

In contrast to teboroxime, the thallium IZ:NZ count ratio of the stress scan did not correlate well with the stress IZ:NZ transmural blood flow ratio (r=0.55; p=NS). Further, the IZ:NZ count ratio of the stress thallium scan (0.62±0.08) was significantly (p<0.01) greater than that of the 30-second teboroxime scan (0.50±0.14) and thus did not provide a good estimate of the true IZ:NZ flow ratio (0.45±0.17 by radioactive microspheres) (Figure 7).

**Discussion**

The objectives of this study were to test the hypotheses that 1) ⁹⁹ᵐTc-teboroxime planar scans of the myocardium obtained after injection of the tracer during pharmacological vasodilation provide a good estimate of relative coronary flow reserve and 2) delayed washout of teboroxime from the myocardium is an indicator of reduced myocardial blood flow and may be a maker of myocardial ischemia. The first hypothesis is based on earlier in vivo work that indicates myocardial teboroxime uptake closely parallels flow up to levels of 4–5 ml/min/g. In contrast, previous studies have shown that thallium uptake by the myocardium underestimates flow above levels of 2–3 ml/min/g. Data obtained in an earlier study, however, were based primarily on in vitro and non-imaging counting measurements and were not designed to determine if comparable ischemic compared with normal zone differences could be detected with conventional gamma camera images of the myocardium. Similarly, there are no data available in a clinically relevant animal model to link delayed teboroxime clearance from the myocardium with reduced myocardial blood flow and/or ischemia.

Results obtained in the present study demonstrate in the setting of a coronary arterial stenosis that the IZ:NZ count ratio of teboroxime scans made within 1–2 minutes of injection during pharmacological coronary vasodilation provides a good measure of the true IZ:NZ flow ratio, as determined by radioactive microspheres. Further, the IZ:NZ ratio assessed from teboroxime images correlated better with the true IZ:NZ flow ratio than did thallium scans obtained at the same time. Accordingly, the ability of uncorrected planar teboroxime scans to provide a reliable estimate of the true IZ:NZ flow ratio during stress demonstrates the imaging agent offers a useful measure of relative coronary flow reserve under clinical conditions.

While the thallium scan IZ:NZ count ratio would have been lower had background been subtracted, the same also applies for the teboroxime scans. Further, conventional background correction for thallium images is largely empirical and known to be subject to error, particularly in cases with high splanchic and hepatic activity as often occurs with pharmacological vasodilation. In addition, residual low levels of technetium activity that caused some scatter into the thallium window, if anything, should have tended to lower the IZ:NZ thallium ratio because technetium activity in the liver was greater adjacent to the inferior and posterolateral walls of the left ventricle (the normal zone) than in the lung and thorax adjacent to the defect (Figures 1 and 2). It also should be noted in this regard that the ratio of technetium to thallium employed in these experiments (~2.5:1) is less than that commonly employed in dual isotope studies of the thyroid and parathyroid glands (~3.3:1). Finally, apical thinning was more prominent in thallium than teboroxime scans that also should have helped to lower the IZ:NZ count ratio of the thallium images (Figure 2A).

Serial teboroxime images obtained after stress or rest injection of the tracer demonstrated a progressive increase in the IZ:NZ count ratio over the 7-minute acquisition period (Figure 4). The increase in the count ratio occurred because of delayed washout of teboroxime from relatively hyperperfused myocardium (Figure 3A) and was flow dependent (Figures 3B and C). Thallium images obtained in these same animals also demonstrated redistribution (Figure 2B). Thus, it is appropriate to consider if “redistribution” observed in the teboroxime scans (Figure 2A) means the same thing as it does in thallium images of the myocardium.

Thallium redistribution may be observed following tracer injection during pharmacological or exercise.
stress testing\textsuperscript{16–20} or at rest in patients with ischemic heart disease.\textsuperscript{21} The phenomenon requires a region with viable myocytes\textsuperscript{22,23} and depends heavily on the rate of decline of thallium levels in the blood.\textsuperscript{22,24–26} Difference in regional myocardial blood flow and flow reserve is essential only in creating an initial thallium defect but does not, as demonstrated in this and earlier studies, influence the extent of redistribution.\textsuperscript{18,27} Redistribution in thallium images is widely regarded as a sign of myocardial viability (and in some cases ischemia), although lack of redistribution in clinical scans certainly does not rule out viability.\textsuperscript{28–30} Indeed, the viability information in thallium imaging appears to be related more to the capacity of the myocytes to retain the tracer than to redistribution per se.\textsuperscript{23,30} Retention of thallium in turn is a function of cell membrane potential and integrity and the modest level of metabolic activity (\textendash{}20\% of basal myocardial oxygen consumption\textsuperscript{11}) required to sustain it.

Initial teboroxime defects also reflect differences in regional coronary flow reserve. Data obtained in the present study, however, indicate that teboroxime washout is flow dependent (Figure 3B and C). Thus, serial teboroxime scans would be expected to demonstrate redistribution only if regional flow differences present at the time of tracer administration persist while imaging is continued. Since redistribution implies persistent flow deficit, the myocardial zone imaged could correspond to a viable region with reduced resting flow plus an additional stress induced flow deficit (relative or absolute) as was demonstrated in the present study. Alternatively, similar findings could be observed in a region of myocardial infarction. The extent and intensity of the initial defect may be helpful in distinguishing between the two. Equalization of flow soon after tracer injection, on the other hand, may well be associated with equalization of washout rates. Under such conditions, an initial defect might fail to demonstrate redistribution. Absent redistribution in serial teboroxime scans, however, would be no more indicative of myocardial scar than absence of redistribution in serial thallium scans. Indeed, the opposite would be the case in teboroxime images since equalization of flows soon after discontinuing stress would strongly imply viability in the defect zone. This hypothesis can be verified under clinical conditions by scanning the patient after injection of the tracer at rest. The scan obtained should demonstrate resolution of the defect. Finally, although it is retained only briefly in the heart, teboroxime binds to lipid membranes so myocardial uptake provides an indirect marker of viability under steady-state conditions.\textsuperscript{32} This may not be true, however, under conditions of acute coronary occlusion with reperfusion.

In the present study, evidence of myocardial ischemia was documented by lactate production during stress despite the increased myocardial blood flow distal to the stenosis. A disproportionate increase in myocardial oxygen demand caused by both left ven-

tricular dilation (mean left atrial pressure increased significantly) and the positive inotropic effects of phenylephrine likely was responsible.\textsuperscript{33} Subsequent reversal of lactate production with return to consumption during the recovery phase of the study is consistent with myocardial adaptation to prevailing oxygen supply/demand conditions and has been demonstrated previously.\textsuperscript{3,4}

Teboroxime redistribution was observed both at stress when lactate production occurred and at recovery when lactate production did not occur. The fact that lactate production was observed simultaneously with thallium redistribution in this study reflects that both imaging techniques are sensitive to stress-induced differences in regional coronary flow even though the mechanisms responsible for redistribution differ between the two. Further, results in humans, which indicate that teboroxime redistribution is frequently associated with thallium redistribution, suggest these differences in regional myocardial blood flow may persist for at least several minutes after discontinuing exercise stress testing.\textsuperscript{34} Viability information in the teboroxime scan, however, may not be indicated by redistribution but more by the level of tracer uptake in the initial scan as well as resolution of the defect after injection of the tracer with the patient at rest. In this regard, the teboroxime study resembles thallium since cardiac uptake by each is a marker of what likely is at least the minimal level of flow required to maintain myocardial cell membrane integrity. It is important, however, to recognize the physical and technical limitations of conventional gamma camera imaging in inferring viability from apparent myocardial uptake of either tracer, particularly in regions adjacent to areas of high background activity.

In summary, results of this study demonstrate in the setting of a severe coronary arterial stenosis that 1) teboroxime scans obtained after tracer injection at peak stress are capable of providing a good estimate of relative coronary flow reserve; and 2) differential washout of isotope on serial teboroxime scans obtained after stress or rest injection is related to differences in regional myocardial blood flow and flow reserve. Although additional research is necessary, initial observations suggest that differential washout of teboroxime may result in defect resolution in serial myocardial images and may, under certain conditions, reflect the presence of ischemic or chronically hypoperfused (hibernating\textsuperscript{3,35,36}) myocardium. A persistent defect in serial teboroxime images obtained after stress, however, does not necessarily mean scar. Indeed, such defects may be related to rapid post-stress equalization of myocardial blood flow and hence may be a marker of myocardial viability under chronic steady-state conditions. A repeat injection of teboroxime with the patient at rest should demonstrate defect resolution under these circumstances.

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