Diagnostic Value of a New Myocardial Perfusion Agent, Teboroxime (SQ 30,217), Utilizing a Rapid Planar Imaging Protocol: Preliminary Results

ROBERT C. HENDEL, MD,* BRENDA McSHERRY, CNMT, MOZAFAREDDIN KARIMEDDINI, MD, JEFFREY A. LEPO, MD, FACC
Worcester, Massachusetts

Technetium-99m-labeled agents have advantages over thallium-201 in terms of photon statistics, cost and clinical availability. They have been suggested as an alternative to thallium for myocardial perfusion imaging. Teboroxime is a new boronic acid adduct of technetium dioxime (BATO) compound that demonstrates favorable characteristics in preliminary studies. With use of a novel (seated) patient positioning technique and a rapid dynamic acquisition protocol, 30 patients underwent planar imaging with teboroxime while at rest and after maximal treadmill exercise. Postexercise scans were completed in an average time (mean ± SD) of 4.4 ± 1.6 min, with 4.8 ± 1.5 min for the views at rest.

These results were compared with coronary arteriography or thallium scintigraphy at rest and after stress is an extensively utilized technique for assessing the presence and severity of coronary artery disease. Thallium-201 is the most commonly used myocardial perfusion tracer; however, because it is a cyclotron product, its availability needs to be prescheduled and can be limited. The photon energy (69 to 83 keV) detracts from optimal resolution and the prolonged half-life of 73 h limits the dosage and restricts the ability to perform sequential imaging (1). Therefore, this radiopharmaceutical compound is less than an ideal perfusion imaging agent.

Myocardial perfusion imaging at rest and after stress is an extensively utilized technique for assessing the presence and severity of coronary artery disease. Thallium-201 is the most commonly used myocardial perfusion tracer; however, because it is a cyclotron product, its availability needs to be prescheduled and can be limited. The photon energy (69 to 83 keV) detracts from optimal resolution and the prolonged half-life of 73 h limits the dosage and restricts the ability to perform sequential imaging (1). Therefore, this radiopharmaceutical compound is less than an ideal perfusion imaging agent.

Technetium-99m has photoperiod energy that is well suited to gamma camera imaging. Furthermore, dosimetry and availability enhance its potential clinical utility. Technetium-99m teboroxime or SQ 30,217 (Cardiotec, Squibb Diagnostics), a newly engineered imaging agent, is a boronic acid adduct of technetium dioxime (BATO) compound (2). Initial experience reveals that teboroxime has a high degree of myocardial extraction (2,3) and rapid blood pool clearance (2,4) and correlates well with blood flow (2,4,5). Furthermore, the rapid clearance of teboroxime enables sequential rest and exercise imaging to be done within a brief period (6,7). The kinetics, transport properties and safety of this compound appear promising for its use as a myocardial perfusion agent and have prompted further investigation (2-7).

Preliminary clinical studies (8,9) have demonstrated that the results of imaging with teboroxime correlate well with information obtained from thallium scintigraphy, coronary arteriography, or both. Although there is good agreement with thallium scintigraphy, imaging with teboroxime has potential problems in relation to the inferior wall of the left
ventricle because of extensive hepatic uptake and resultant scatter of this agent (5–7).

Utilizing a novel patient positioning technique during imaging and a rapid dynamic data acquisition protocol, we compared planar imaging with teboroxime and information obtained from thallium scintigraphy or coronary arteriography in 30 patients. Images obtained at rest and after exercise were compared and a description of the important temporal relations of this unique radiopharmaceutical compound are discussed.

**Methods**

**Study patients.** Thirty patients were randomly selected from a group that had undergone cardiac catheterization or exercise testing with thallium scintigraphy within the previous 3 months. All patients were >18 years of age and none had had a myocardial infarction within the 3 months preceding any imaging procedure. All women with child-bearing potential were excluded. Informed consent was obtained from each subject after review and approval by the institutional review board.

**Teboroxime preparation.** Teboroxime was supplied as a single vial kit in a lyophilized powder form. The vial was reconstituted by adding ≤100 mCi of technetium-99m in 1 ml of 0.9% sodium chloride solution. The vial was placed in 100°C water bath for 15 min in a stationary upright position. After the vial was allowed to cool to room temperature, paper chromatography was performed to determine the percent of free pertechnetate and reduced hydrolyzed technetium. Two 1.3 × 11 cm strips of Whatman 31 ET paper were spotted with 1 drop of the preparation. One strip was developed in normal saline solution (percent free pertechnetate) and the other was developed in a 1:1 solution of normal saline/acetone (percent reduced hydrolyzed technetium). As a criterion for injection, the sum of the two percentages could not exceed 10%. The reconstituted product was stored in the original glass vial at room temperature and was transferred to a syringe just before injection. Approximately 45 min was required for preparation of the compound and it remained clinically usable for the next 6 h. Both rest and exercise injections were made from contents of the same vial; the dose of each was between 12 and 20 mCi.

**Thallium scintigraphy.** Maximal symptom-limited exercise testing was performed with use of treadmill exercise and the standard Bruce protocol. On attainment of maximal effort, thallium-201 (2.2 to 2.8 mCi) was injected intravenously and exercise continued for 30 to 60 s. Images were acquired with use of a gamma camera in the 128 × 128 matrix for 7 min in each of three views: 45° left anterior oblique, anterior and left lateral. Redistribution scans were obtained in a similar manner 2.5 to 4 h later. Electrocardiographic (ECG) monitoring of vital signs was done before, during and after exercise.

**Teboroxime scintigraphy.** A similar exercise protocol was performed as described for thallium scintigraphy; however, teboroxime (12 to 20 mCi) was injected at maximal exertion. The subjects were then expeditiously positioned (seated) in front of the gamma camera (29 of 30 patients). An upright position was selected for imaging to minimize the interference by the hepatic uptake of tracer as previously reported (6,7) and to allow rapid patient positioning. Data collection was initiated within 1 min of the discontinuation of exercise. With use of rapid dynamic acquisition with a frame rate of 20 s/frame, data were acquired in a 64 × 64 matrix, initially in the anterior view. Each view was continuously monitored and 40 to 80 s (two to four frames) of data were accumulated in the anterior position after blood pool clearance. The subjects were then sequentially rotated in a chair to the 45° left anterior oblique and later the left lateral position and data were acquired for 40 to 80 s/view. These views were repeated in most subjects for analysis of delayed, (5 to 10 min) postexercise images.

**Imaging was repeated in the same fashion at rest after a second injection of teboroxime.** Postexercise imaging was performed initially in the first 10 patients, with the rest scans collected 1 to 1.5 h later. The next 20 patients were initially studied at rest, followed by postexercise teboroxime imaging performed 1 to 1.5 h after the rest scans. In five patients, images were acquired immediately before the second teboroxime injection to confirm the absence of residual myocardial activity.

Vital signs were obtained and ECG monitoring was performed before, during and after exercise as well as before, during and after injection of teboroxime. Total image collection times were recorded for teboroxime. In addition, urine samples and blood samples (blood count, SMA-12 chemistry values) were collected before and after teboroxime administration. In all cases, no abnormal results were noted.

**Image processing and analysis.** Teboroxime scans were summated with the use of two to three frames for each view (40 to 60 s). Images that showed significant amounts of blood pool activity or motion artifact due to repositioning were excluded.

**The thallium and teboroxime images at rest and during exercise were interpreted by at least two observers who were blinded to patient data.** Disagreements were resolved by consensus after review of discordant interpretations. Each scan was divided into nine segments and a score was assigned corresponding to the number of abnormal segments (0 to 9) as previously described (8). The quality of the teboroxime scans was assessed subjectively as poor, fair or good. Images that revealed abnormalities in the same segment on both rest and exercise scans were considered to demonstrate nonviable infarcted myocardium. A segment that demonstrated an abnormality on the postexercise scan but not on the corresponding rest study was defined as
showing transient myocardial hypoperfusion consistent with ischemia.

Teboroxime scintigrams were compared with thallium studies for determination of normal or abnormal scans. The diagnosis of ischemia or presence of infarction was also correlated between these two imaging techniques. Furthermore, the rest and exercise images immediately after the injection of teboroxime were compared with repeat scans obtained after the collection of the first set of postexercise views. These early repeat scans are referred to as "delayed" teboroxime images. The quality of the delayed scans was also subjectively assessed. Finally, an estimate was made of the time required for the performance of each teboroxime scan based on the time required for blood pool clearance, data acquisition and repositioning of the patient.

Statistics. Paired t test analysis was performed to compare the exercise variables of each scintigraphic study. Fisher's exact test was utilized to determine the significance of the correlation of the teboroxime and thallium scans with regard to the presence or absence of an abnormal scan, transient myocardial ischemia or prior myocardial infarction.

Results

Patient characteristics. Thirty subjects (9 women and 21 men, mean age ± SD 55 ± 13 years) were enrolled in this phase III trial of teboroxime. Prior myocardial infarction was present in 19 patients. A calcium channel antagonist was being taken by 15 subjects and beta-adrenergic blocking medication by 10. No attempt to alter medications was made before either exercise perfusion study.

Coronary arteriography and contrast ventriculography were performed in nine patients, with one patient demonstrating three vessel coronary artery disease, three having two vessel disease, two with one vessel disease and three without significant obstructive lesions in the coronary arteries.

Exercise testing. All patients underwent exercise testing with teboroxime imaging and 28 patients also performed treadmill exercise with thallium scintigraphy. The level of exercise achieved, hemodynamic response and the development of ischemic ECG changes or chest pain are summarized in Table 1. Paired analysis revealed a trend for the total exercise time and percent of maximal predicted heart rate to be higher in the thallium group (0.06 < p < 0.08). The other exercise-related variables (heart rate-blood pressure product, chest pain and ST segment depression on the ECG) were not significantly different.

Several patients had discordant symptoms or ECG abnormalities between the thallium and teboroxime exercise studies. Anginal chest pain was experienced by two patients during the thallium exercise test but not before the administration of teboroxime. Both of these patients exercised for less time and had a lower heart rate and rate-pressure product during the teboroxime exercise test than during thallium imaging. There were five patients with ischemic ECG changes during exercise thallium scintigraphy but not during the teboroxime stress test. A lower maximal heart rate and rate-pressure product were noted in four of the five patients during the teboroxime test. There was no alteration in cardiac medications between the studies in any of the aforementioned patients. All remaining patients who had both teboroxime and thallium exercise scintigraphic imaging demonstrated concordant ECG changes or symptoms.

Teboroxime scintigraphy. The dose of technetium-99m was 15.3 ± 1.8 mCi for images at rest and 16.7 ± 1.6 mCi for postexercise scans. The mean time between the rest and exercise images was 97 ± 33 min. Imaging was completed in an average of 4.8 ± 1.5 min for the rest images and 4.4 ± 1.6 min for postexercise scans. The dynamic images were reviewed to estimate the time required from the initiation of data acquisition until the completion of imaging in the three views. By combining the time required for clearance of the blood pool (40 to 60 s), the one frame (20 s) for repositioning between each view and two to three frames of data acquisition for each projection, we were able to estimate the time required for completion of each study. With these estimations, 3.0 ± 0.4 and 3.2 ± 0.8 min were required to complete imaging at rest and after exercise, respectively.

The quality of the teboroxime images was rated as excellent or satisfactory in 29 of 30 scans at rest and 26 of 30 scans after exercise. Examination for residual myocardial activity was performed in five patients approximately 18 min after imaging at rest. Four of these patients had essentially no detectable myocardial activity and one patient had minimal residual myocardial counts (liver activity much greater than myocardial activity).

Comparison of teboroxime with thallium or angiography. With teboroxime scintigraphy, 10 patients were noted to have normal scans; of these, 9 had thallium scans performed, 8 of which were interpreted as normal (Fig. 1). The discordant thallium study demonstrated a transient defect in one segment. However, this patient underwent cardiac catheterization that failed to demonstrate any significant coronary stenosis, a finding consistent with the teboroxime scan.

Table 1. Comparison of Exercise Testing in 28 Patients

<table>
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<tr>
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<th>Thallium</th>
<th>Teboroxime</th>
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<tbody>
<tr>
<td>Exercise duration (min)</td>
<td>8.3 ± 2.6*</td>
<td>7.6 ± 3.1*</td>
</tr>
<tr>
<td>Maximal predicted heart rate (%)</td>
<td>82 ± 12*</td>
<td>81 ± 13*</td>
</tr>
<tr>
<td>Rate-pressure product (mm Hg x beats/min)</td>
<td>24,200 ± 5,900</td>
<td>23,800 ± 5,100</td>
</tr>
<tr>
<td>Patients with chest pain (no.)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Patients with electrocardiographic changes (no.)</td>
<td>12</td>
<td>8</td>
</tr>
</tbody>
</table>

*0.06 < p < 0.08.
Figure 1. Comparison of thallium (A) and teboroxime (B) scintigraphy. This patient had normal images in both studies. Note the presence of significant hepatic activity in the teboroxime scan. ANT = anterior; LAO = 45° left anterior oblique; LAT = left lateral.

Additionally, there was one thallium scan interpreted as normal in a patient who had an abnormal teboroxime scintigram with a persistent defect in one segment.

Overall, there was excellent correlation between teboroxime imaging and thallium scintigraphy or cardiac catheterization regarding the diagnosis of normal or abnormal myocardial perfusion. With regard to differentiating normal from abnormal scans, 28 of 30 patients demonstrated agreement when teboroxime was compared with thallium or catheterization (p < 0.001), yielding an overall predictive accuracy for teboroxime scintigraphy of 93%. A comparison of teboroxime imaging with coronary angiography revealed concordance for coronary artery disease in all nine patients.

Table 2 summarizes the comparison of findings after thallium and teboroxime administration in the study group. Analysis for the presence or absence of a defect consistent with a myocardial scar revealed agreement between the imaging techniques in 25 of 28 patients (p < 0.0001). Additionally, transient abnormalities (defect present on postexercise studies that was not present on rest images; that is, thallium redistribution) were also concordant in 24 of 28 studies (p < 0.0005) (Fig. 2).

There were 20 teboroxime studies that were abnormal, with the presence of persistent or transient defects, or both. Overall, close correlation between the diagnostic techniques existed in 15 (75%) of the abnormal studies. However, several teboroxime scintigrams revealed more segments showing ischemia than the corresponding thallium study.

Five of the 20 abnormal studies had significant differences regarding the presence or absence of myocardial ischemia or myocardial scar (Table 3). In four of the five studies, the teboroxime scan demonstrated more ischemia than the thallium scan. In fact, three studies had only a persistent defect noted on thallium scintigraphy, with no evidence for myocardial ischemia. The regions of scar on the thallium study were similar to the abnormal regions on the teboroxime scans. An additional discordant study revealed a persistent

Table 2. Diagnostic Correlation of 30 Patients Undergoing Teboroxime Scintigraphy

| Diagnosis | Comparison With Thallium
<table>
<thead>
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<tbody>
<tr>
<td>Abnormal Versus Normal</td>
<td>Ischemia</td>
</tr>
<tr>
<td>No.</td>
<td>30</td>
</tr>
<tr>
<td>Concordance (no.)</td>
<td>28</td>
</tr>
<tr>
<td>Concordance (%)</td>
<td>93</td>
</tr>
<tr>
<td>p value (chi-square)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Teboroxime compared with thallium or coronary angiography.

Table 3. Discordant Segmental Imaging Results in Five Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Thallium*</th>
<th>Teboroxime*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ischemia</td>
<td>Infarction</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>3</td>
</tr>
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<td>8</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>1</td>
<td>2</td>
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</table>

*Number of abnormal segments (0 to 9).
defect in one segment consistent with an apical scar on teboroxime imaging that was not apparent with thallium scanning. The level of exertion, as assessed by total exercise time, percent of maximal predicted heart rate and rate-pressure product, were not significantly different between these discordant thallium and teboroxime exercise studies. With respect to the cumulative totals of abnormal segments, more transient (ischemic) abnormalities were present with teboroxime than with thallium (44 versus 30).

In a subset analysis of patients without prior myocardial infarction, 10 (91%) of 11 studies had diagnostic concordance (abnormal versus normal), with the outlying study revealing a small persistent apical defect after teboroxime injection that was interpreted as normal on thallium scintigraphy. There was also agreement for the presence of ischemia or infarction, or both, in these 10 studies, with the exception of 1 study that showed a persistent and transient perfusion abnormality with thallium imaging, but only a transient defect with teboroxime imaging.

**Delayed postexercise teboroxime scintigraphy.** Repeat images were obtained in 26 of the 30 patients after the initial postexercise teboroxime scans (Fig. 3). There were 15 studies that had abnormal images on the initial scintigrams that could permit comparison with delayed images for possible rapid changes in tracer distribution. Clearly, an initial normal image could not demonstrate a transient-type defect. One repeat study was technically inadequate to allow comparison. The delay between the initial and the delayed postexercise views was 4.2 ± 1.7 min. Of these 14 abnormal early studies, 9 demonstrated differences in the delayed postexercise views compared with those obtained within the first 5 min after teboroxime injection (Fig. 4). All of these delayed images were identical to images on the rest scans. In five patients there were no apparent differences between the early and delayed stress scans. Three of these scans demonstrated only a persistent defect and thus would not be expected to reveal changes from the early to delayed postexercise images. Only two studies revealed a transient defect that failed to have noticeable changes between the two postexercise scans. Thus, 9 of 11 patients with ischemic defects demonstrated this rapid redistributionlike phenomenon within several minutes.

**Discussion**

**Teboroxime versus thallium imaging.** The present study demonstrates the diagnostic utility of teboroxime, a new myocardial perfusion agent, when used with a rapid planar imaging protocol. Although some diagnostic differences exist between thallium and teboroxime imaging, there is close correlation between these techniques. This is true not only for differentiating abnormal from normal scans, but also for the detection of myocardial ischemia and the presence of preexisting myocardial infarction. Thus, this is the first report of a rapid planar imaging technique that yields a high correlation with standard exercise thallium imaging results. In addition, this is the initial report of the presence of early differential washout of teboroxime after postexercise injection.

**Critique of methods.** The methods in the present study differed from previous experience in several ways. First, previous clinical work with teboroxime (7) has utilized a bicycle exercise protocol for teboroxime and treadmill exercise for thallium. Only one study (6) used treadmill exercise testing for teboroxime scintigraphy and then compared the results only with coronary angiography. Therefore, this report represents the first direct comparison of similar exercise protocols for both thallium and teboroxime imaging.

The major technical differences in our study were related to image acquisition. Although different protocols have been utilized previously, all required a minimum of 14 min after blood pool clearance (6,7), which is in sharp contrast to the <5 min required in our study. Rapid repositioning was possible, with the patients being swiveled in a chair while seated. The seated position also theoretically allowed for inferior displacement of the liver, thereby reducing the potential for hepatic interference with the inferior wall, which has previously been described as a problem (6,7). Because our image acquisition time was very brief, all patients were able to tolerate this position without difficulties or significant motion. Since residual myocardial activity was essentially absent at the time of the second study, it appears
that the entire study may be completed within 1.5 to 2 h after the conclusion of exercise.

**Correlation of teboroxime with thallium imaging.** The correlation between the thallium and teboroxime scans was very good and was consistent with the high degree of agreement previously noted between these two techniques (6,7). The teboroxime scans, however, demonstrated more potential ischemic segments than did the corresponding thallium scintigrams.

**Delayed postexercise teboroxime images.** The finding of rapid changes after postexercise teboroxime injection has not been previously described. The majority of images (82%) acquired approximately 5 to 10 min after the teboroxime injection demonstrated the rapid disappearance of defects present on the initial (0 to 5 min) postexercise images. This phenomenon is similar to the description of thallium redistribution where initial defects disappear on the 2 to 4 h delayed scans (9–12).

The mechanism of redistribution after thallium injection may involve the continued extraction of thallium into the ischemic segment from the blood pool (9,10) as well as differential washout from regions of disparate blood flow (11–13). The latter mechanism reflects the more rapid net clearance of thallium from normally perfused myocardium that from an area with reduced flow. Even with thallium, several investigators (9,10) caution against substantial delays (>1 h) after injection of the cation because this may result in a failure to detect ischemic regions as a result of relatively rapid redistribution.

A disparity in net myocardial clearance from ischemic compared with normal areas of myocardium may account for the rapid resolution of ischemic-type defects noted on the delayed postexercise teboroxime scans in this study. Further research on the mechanism of this phenomenon is required. It is apparent, however, that interpretation of teboroxime scans after 5 min may reflect this differential washout and false negative scans for ischemia may result. The slightly diminished diagnostic accuracy of previous studies (6,7) may have been influenced by a more prolonged (≥14 min) acquisition of data and consequently diminished imaging statistics for these final views. Improved diagnostic accuracy has been noted with the use of single photon emission computed tomographic imaging compared with the planar method (6,7); however, given the finding of rapid differential washout of teboroxime, caution should be advised with this imaging technique, when it involves >5 to 10 min of acquisition time.

**Clinical significance and limitations.** The present study has several limitations. Because the first 10 patients had the exercise teboroxime studies performed first and the remaining 20 had rest scans collected before exercise studies, the protocol was not constant. However, there was no significant difference in teboroxime imaging results, except that the quality of the rest study appeared slightly better when it preceded exercise. Because the imaging characteristics and time course were not clearly defined at the onset of the study, data acquisition was more prolonged than necessary. It is now apparent that valid scans can be performed in 3 to 3.5 min and more rapid acquisition of data may be utilized in the future. The lack of quantitative analysis to characterize myocardial clearance of teboroxime was an additional limitation. Although a rapid decrease in myocardial counts was noted in some patients (approximately 5%/min), not all studies were quantitated. Segmental quantitation also was not performed and, therefore, assessment of differential myocardial clearance was not critically analyzed.

**Hepatic uptake of teboroxime is a potential source of image misinterpretation, especially in the left lateral projection (6,7).** Therefore, we used upright positioning of the patients to allow a downward displacement of the liver. Although occasional overlap of the myocardium and liver was present, this did not appear to affect the results of teboroxime scintigraphy. Although tomographic imaging may help alleviate this potential pitfall, the rapid clearance kinetics of teboroxime may limit the application of a single-headed single photon emission computed tomographic system.

**Coronary angiography.** The accepted standard for diagnosis of coronary artery disease, was performed in relatively few patients. However, other studies (6,7) have confirmed the diagnostic correlation of teboroxime and cardiac catheterization. Our study was more concerned with the comparison with thallium scintigraphy because both teboroxime and thallium provide physiologic information regarding the presence or absence of ischemia and myocardial infarction.

In addition, the observed increased incidence of transient (stress-induced) perfusion defects by teboroxime compared with thallium may relate to the imaging techniques utilized. A separate rest and stress thallium study may detect up to 20% more transient defects compared with stress and 4 h redistribution scans (13). It is also possible that 24 h delayed thallium scans or thallium reinjection scans would detect more exercise-induced perfusion defects than the standard 3 to 4 h redistribution images (14). The present study suggests that the rapid imaging protocol involving separate rest and stress injections of teboroxime results in a faster and potentially more sensitive technique to detect stress-induced hypoperfusion than standard thallium (exercise and 3 to 4 h redistribution) imaging. Further investigations of the different thallium and teboroxime protocols are clearly warranted before the superiority of one perfusion imaging method over another can be determined.

**Conclusions.** Teboroxime demonstrates excellent diagnostic correlation with thallium in the diagnosis of abnormal versus normal myocardial perfusion scans as well as close agreement in the detection of myocardial ischemia or infarction, or both. The myocardial kinetics of this new technetium perfusion agent allow both extremely rapid data acqui-
sition and completion of sequential stress and rest scanning within 1.5 to 2 h. There appears to be evidence for rapid differential washout of teboroxime and a rapid disappearance of exercise-induced defects is often noted. Although the initial evidence suggests that these effects may resemble the phenomenon of thallium redistribution, additional research is needed. However, this study does suggest the intriguing possibility that performing an exercise study with teboroxime could permit detection of ischemic heart disease within 10 min after tracer injection.

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References