Myocardial Perfusion Imaging with Technetium-99m-Teboroxime

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Technetium-99m-teboroxime is a myocardial perfusion imaging radiotracer that, although not widely used in clinical practice, has the potential to provide valuable diagnostic information. Teboroxime's high myocardial extraction and rapid in vivo myocardial clearance make stress/rest studies possible using very short imaging protocols. In addition, differential washout of ^{99m}Tc-teboroxime produces defect fillin on early delayed images in a high percentage of patients, potentially eliminating the need for a second rest injection. Finally, because of its rapid myocardial clearance, serial injections of ^{99m}Tc-teboroxime in an acute myocardial infarction (MI) setting can provide information on infarct vessel patency based on defect size and can help document the success or failure of reperfusion therapy.

Key Words: myocardial perfusion imaging; technetium-99m-teboroxime

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Since the two ^{99m}Tc-labeled radiotracers for myocardial perfusion imaging became commercially available in 1990, ^{99m}Tc-sestamibi (Cardiolite®, DuPont) has become far more commonly used than ^{99m}Tc-teboroxime (Cardiotec®, Squibb). Although ^{99m}Tc-teboroxime has rapid in vivo myocardial clearance (*1*), it has been difficult to develop practical protocols for this radiotracer since image acquisition must begin so soon after injection. Despite this disadvantage, ^{99m}Tc-teboroxime is finding a niche as a perfusion agent with interesting and unique potential applications in cardiovascular imaging.

PHARMACODYNAMICS

Teboroxime is chemically very different from sestamibi (a cationic compound) or ^{201}Tl (a cationic element). Teboroxime is a boronic acid (BATO) compound; the radiolabeled compound is neutral and highly lipophilic (*2*).

The extraction fraction of ^{99m}Tc-teboroxime is very high—higher than that of ^{201}Tl or ^{99m}Tc-sestamibi—over a wide range of flow rates (*3*). Myocardial uptake of ^{99m}Tc-teboroxime parallels flow in a linear fashion, without "roll-off" at high flow levels, even when myocardial blood flow is increased to four times the level of resting blood flow, which can be achieved with adenosine infusion. In addition, ^{99m}Tc-teboroxime uptake parallels myocardial blood flow under both ischemic and nonischemic conditions (*4*). In animal studies, the correlation between count ratios of radiotracer uptake in ischemic-to-nonischemic zones and microsphere transmural flow ratios is better for ^{99m}Tc-teboroxime than for ^{201}Tl (*4*).

Uptake and retention of ^{99m}Tc-teboroxime do not appear to involve active metabolic processes (*5*). When myocytes are damaged by metabolic poisons, the uptake of both ^{201}Tl and ^{99m}Tc-sestamibi decreases, whereas ^{99m}Tc-teboroxime uptake remains unchanged, even when myocardial protein content decreases by nearly 50% (*5*). A decrease in temperature, however, does result in decreased ^{99m}Tc-teboroxime uptake (*5*). These cell culture studies support the premise that ^{99m}Tc-teboroxime is incorporated passively into the cell membrane and does not reach the intracellular space.

Rapid Washout

Following myocardial uptake, ^{99m}Tc-teboroxime shows rapid biexponential myocardial washout in vivo. The half-time for the early washout phase (60% to 70%) has been measured at 5.0 to 6.0 min in patients at rest; and 2.5 to 3.0 min in patients during exercise or pharmacologic stress (*1*). The faster clearance during stress indicates that blood flow affects the clearance rate of ^{99m}Tc-teboroxime. Increased blood flow results in more rapid washout, and decreased blood flow results in more gradual washout.

Differential Washout

Because the rate of blood flow influences the clearance rate of ^{99m}Tc-teboroxime, there is differential washout of the radiotracer in the distribution of stenotic versus normal coronary arteries (*6*). The clearance of ^{99m}Tc-teboroxime at rest is much slower in the myocardium subtended by an occluded vessel when compared to washout from myocardium supplied by a normal vessel. The global heart washout is a combination of both slow and rapid washout. With pharmacologic stress, the differential washout between myocardium supplied by stenosed and nonstenosed vessels is enhanced (Fig. 1).

The mechanism for "redistribution" of ^{99m}Tc-teboroxime is different than the mechanism for ^{201}Tl redistribution. Differential washout alone accounts for ^{99m}Tc-teboroxime redistribution, whereas differential washout *and* reuptake of ^{201}Tl from the blood account for ^{201}Tl redistribution. Immediately after injection, ^{99m}Tc-teboroxime is completely bound to proteins and there is no

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further myocardial extraction (7). Reversible protein binding of ^{99m}Tc-teboroxime may also explain the rapid myocardial washout.

IMAGING PARAMETERS

The unique pharmacokinetics of ^{99m}Tc-teboroxime determine the prerequisites for successful myocardial perfusion imaging. When performing treadmill testing with ^{99m}Tc-teboroxime, the gamma camera has to be ready to acquire images before stress begins. After completion of exercise, the patient must be moved quickly from the treadmill to the camera.

With pharmacologic stress, the protocol is simpler because adenosine or dipyridamole can be infused while the patient is positioned under the camera. Because of the high myocardial blood flows achieved with adenosine, there is even faster myocardial washout of the radiotracer. The advantage of this faster washout is that two injections can be made in close temporal sequence without the second scan being influenced by residual myocardial activity from the first scan (*8,9*). When using dipyridamole, with its longer duration of action, there was a theoretical concern that it would be necessary to administer aminophylline immediately after ^{99m}Tc-teboroxime injection to reverse the effect. In practice, however, it has been shown that dipyridamole can be substituted for adenosine without using aminophylline; diagnostic scans can be acquired with a triple-headed SPECT camera before radiotracer activity disappears from the heart.

In cardiac phantom studies designed to mimic the situation in which radiotracer concentrations change during tomographic acquisition, results indicated that when total image acquisition time is less than twice the washout rate (8 to 10 min for ^{99m}Tc-teboroxime), artifacts due to changing activity will not be produced (*10*). However, this study did not take into account differential washout. Subsequent phantom studies, which included differential washout in the design, found that image acquisition should be completed within 4 to 5 min after ^{99m}Tc-teboroxime injection (*11,12*). After this 5-min window of opportunity, differential washout begins to introduce artifacts. If image acquisition takes too long, perfusion defects can redistribute before acquisition is complete, resulting in an underestimation of the number and severity of ischemic segments.

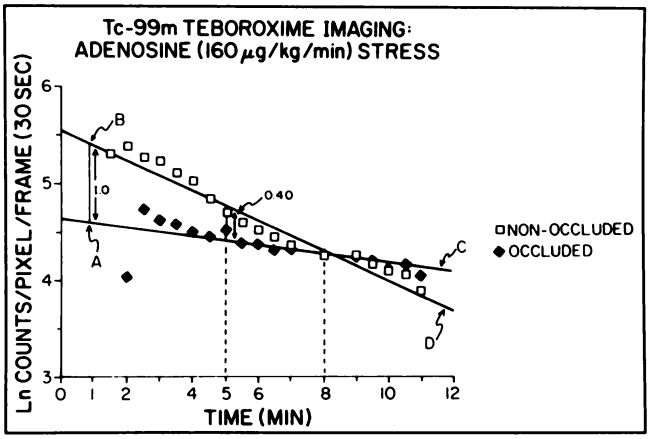

FIGURE 1. Study documenting differential washout of ^{99m}Tc-teboroxime in an animal model. Log transform of myocardial clearance of ^{99m}Tc-teboroxime during adenosine stress from normal zone (curve B–D) and from zone in distribution of severe coronary artery stenosis (curve A–C). The clearance half-time in the non-occluded zone was faster (4.9 min) than in the zone subtended by the stenotic vessel (10.5 min), causing the curves to intersect at 8 min following ^{99m}Tc-teboroxime injection. Reprinted with permission from Reference 6.

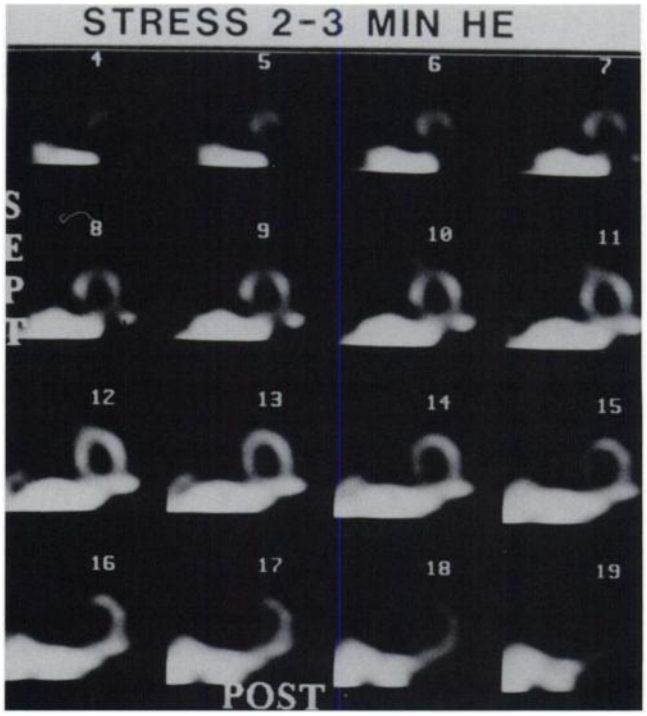

FIGURE 2. Study demonstrating that hepatic uptake of ^{99m}Tc-teboroxime, which is more intense when injected during pharmacologic stress, can produce nondiagnostic images in some patients. Short-axis slices are displayed from apex to base. The apparent defects in the inferior wall could not be read with certainty because the intense liver uptake can lead to artifactual decrease in inferior wall counts. Courtesy of Hosen S. Kiat, MD, Cedars-Sinai Medical Center.

With a single-headed SPECT camera, it may be difficult to acquire the tomogram in sufficient time before radiotracer washout affects defect delineation unless continuous acquisition, rather than "step and shoot" is used. Triple-headed SPECT, which can complete image acquisition in 3 to 4 min, is best suited for ^{99m}Tc-teboroxime imaging.

Another aspect of ^{99m}Tc-teboroxime pharmacokinetics adversely affecting image quality is enterohepatic clearance and consequent liver uptake, which is most intense following pharmacologic stress (Fig. 2) (*8,9*). With intense activity adjacent to and "blossoming" into the inferior wall, filtered back-projection can oversubtract activity from this region, creating a defect. Proposed methods to correct for liver activity include volume masking (particularly with adenosine) and/or interpolative background subtraction. One method uses volume masking on the projection images before filtered backprojection is done (*13*).

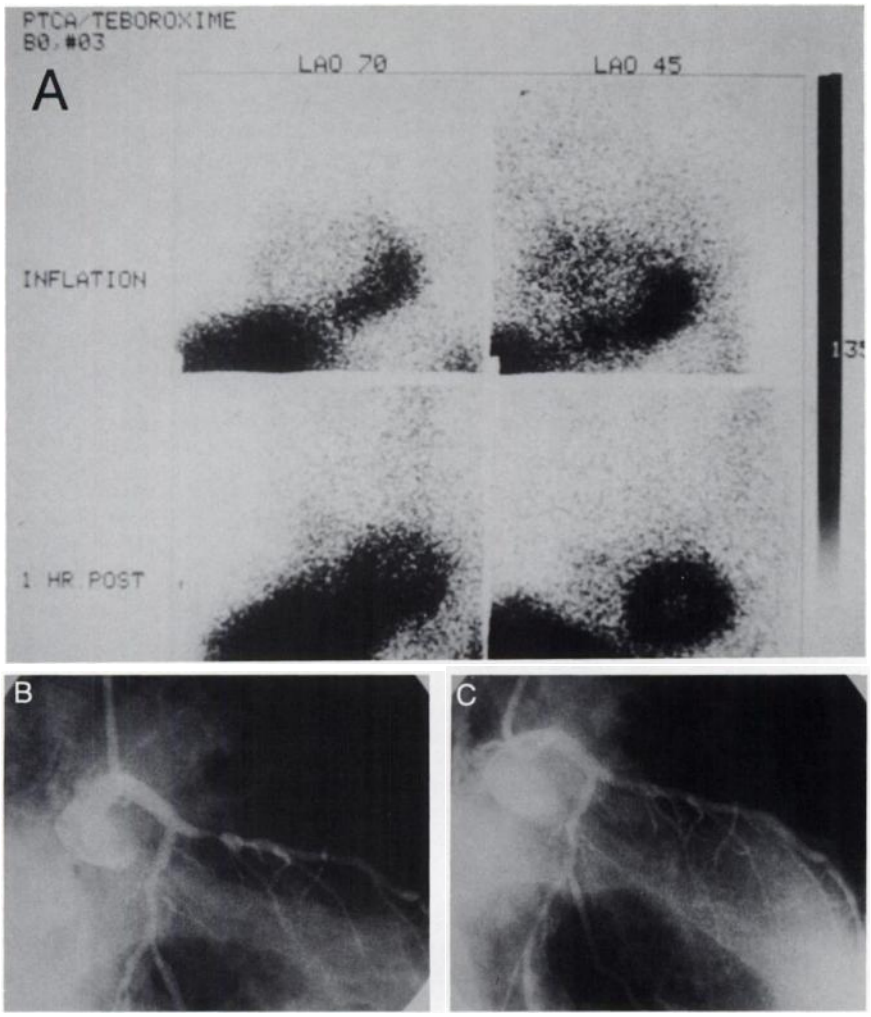

FIGURE 3. Because of its rapid myocardial washout, serial injections and imaging with ^{99m}Tc-teboroxime can be used to document coronary vessel patency. (A) Forty-second planar images obtained in the 70° and 45° LAO projections during balloon inflation (top row) and 1 hr after PTCA (bottom row). Anteroapical and anteroseptal defects in the distribution of the occluded LAD are gone when the radiotracer is reinjected and the patient is reimaged one hour later. The LAO stenosis is demonstrated before (B) and after (C) angioplasty. Reprinted with permission from the American College of Cardiology (*Journal of the College of American Cardiology* 1993;21:1319–1327).

Mean counts are obtained from a region adjacent to the inferior wall, and this value is then subtracted from a 10-pixel band under the heart. All of these image processing methods have limitations. Intense liver uptake of ^{99m}Tc-teboroxime leads to clinically uninterpretable scans in a small, but significant, number of patients (*9*).

CLINICAL APPLICATIONS

The pharmacokinetics of ^{99m}Tc-teboroxime make myocardial perfusion studies with this radiotracer uniquely indicated for several clinical applications. Further studies are needed to validate the accuracy of ^{99m}Tc-teboroxime data in these clinical situations.

One-Dose Stress/Delay Protocol

Because of ^{99m}Tc-teboroxime's differential washout, it may be possible to develop a clinically useful protocol that uses one ^{99m}Tc-teboroxime dose to obtain a complete stress/delay study within minutes of injection. Since ^{99m}Tc-teboroximе clears and redistributes so rapidly in the myocardium, a delayed image can be acquired very soon after the stress image is acquired. In a study of 68 patients, delayed planar ^{99m}Tc-teboroxime images obtained 5 to 10 min after exercise showed radiotracer redistribution in 22 of 46 (48%) patients who had transient defects (*14*). It appears feasible, in some patients, to obtain a stress/rest study with one injection and two image acquisitions spaced minutes apart.

To further investigate this possibility, Phillips et al. studied 102 consecutive patients with dipyridamole-teboroxime SPECT imaging (*15*). Two-minute serial ^{99m}Tc-teboroxime images were obtained with a triple-headed SPECT camera. Images from the first 4 min were combined and compared with images from the next 6 min (the early delayed images). A second dose of ^{99m}Tc-teboroxime was injected for the rest scans. Twenty-four of 28 perfusion defects were reversible on the rest studies, and 20 of these 24 (83%) showed reversibility on the early delayed images. These authors concluded that poststress delayed images, if obtained in all patients, can preclude the need for a separate rest injection in most of them. Dipyridamole-teboroxime imaging with a triple-headed camera can also significantly enhance patient throughput.

Evaluating Success of Reperfusion Therapy

Perfusion imaging with ^{99m}Tc-teboroxime may be uniquely capable of evaluating infarct vessel patency after reperfusion therapy (*16*). To salvage myocardium, reperfusion must occur within 6 hr of the onset of chest pain.

Thrombolytic therapy typically results in 75% to 80% infarct vessel patency, 85% at best (*17,18*). Noninvasive evaluation of the success or failure of thrombolytic therapy is clinically important. Various noninvasive techniques—such as realtime ST-segment monitoring, peak CK-MB isoenzyme, CK isoforms, and myoglobin measurements—have been evaluated, but with disappointing results (*19*).

Experimental data from the work of Villegas et al. indicate that serial ^{99m}Tc-teboroxime scans may be capable of providing this information (*20*). In one study using a rabbit model, a coronary artery was ligated, microspheres were injected, then the ligature was removed. Two hours after reperfusion, ^{99m}Tc-teboroxime was injected, and the animal was killed. Count data demonstrated that normalized ^{99m}Tc-teboroxime correlated linearly with reperfusion flow as measured by microspheres. In addition, the average defect size on ^{99m}Tc-teboroxime images correlated well with normalized reperfusion flow. The investigators concluded that ^{99m}Tc-teboroxime uptake following acute experimental MI reflects myocardial blood flow independent of tissue viability.

During balloon angioplasty, balloon occlusion of a coronary artery delineates the risk region for that vascular territory. After flow is restored, normal perfusion returns. Imaging with ^{99m}Tc-teboroxime has been performed during and after angioplasty to visualize the risk region (Fig. 3) (*21*). This situation is comparable to an acute MI treated with a thrombolytic agent. When a patient arrives in the emergency room with signs and symptoms of acute MI due to acute coronary artery occlusion, ^{99m}Tc-teboroxime studies would show the maximal perfusion defect. Following thrombolytic therapy or primary percutaneous transluminal coronary angioplasty (PTCA), ^{99m}Tc-teboroxime imaging could provide information on the success of therapy, i.e., infarct vessel patency, based on presence or absence (or size) of a perfusion defect.

With more clinical documentation, this technique could emerge as an exciting clinical application for ^{99m}Tc-teboroxime.

CONCLUSION

Although ^{99m}Tc-teboroxime is not widely used for myocardial perfusion imaging, this radiotracer has the potential to provide stress/rest studies with one injection and a very short image acquisition time. In addition, ^{99m}Tc-teboroxime studies could provide valuable diagnostic data in a rapid sequential imaging mode. The rapid myocardial washout of ^{99m}Tc-teboroxime permits sequential injections within a short time frame and, since defect size correlates with regional perfusion, scan results offer information on infarct vessel patency and success of reperfusion therapy with thrombolytic agents or primary PTCA.

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