
A Review of Cardiac Imaging with Sestamibi and Teboroxime

Jeffrey A. Leppo, E. Gordon DePuey, and Lynne L. Johnson

Department of Nuclear Medicine and Department of Medicine (Cardiology), University of Massachusetts Medical Center, Worcester, Massachusetts; Department of Radiology, Division of Nuclear Medicine, St. Luke's-Roosevelt Hospital Center and Columbia University College of Physicians and Surgeons, New York, New York; and Department of Cardiology and Nuclear Medicine, Columbia University, New York, New York

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The goal of this review is to characterize the basic properties of the recently approved technetium-labeled agents and to outline the indications and protocols for their clinical use.

The noninvasive study of myocardial perfusion has benefitted from the development of standard nuclear cardiology techniques which have provided valuable medical insight into coronary perfusion with the use of single-photon tracers. Although ^{201}Tl is the most widely used clinical myocardial perfusion agent, $^{99\text{m}}\text{Tc}$ -labeled perfusion agents offer several advantages. Technetium-99m is readily available, its energy (140 keV) is ideal for standard gamma imaging, and its improved radiation dosimetry and much shorter half-life compared to ^{201}Tl permit the injection of ten times as much radioactivity. Consequently, it is clear that the use of $^{99\text{m}}\text{Tc}$ -labeled perfusion agents will significantly expand the possibilities for diagnostic nuclear cardiology studies.

We have not addressed the issues of quantitation. However, several observations deserve mention. The background subtraction algorithms employed for analysis of ^{201}Tl imaging must be modified for the technetium labeled tracers. Use of the algorithms without modification may cause an artifactual decrease in inferior wall activity. Aside from this change, the enhanced count density and higher photon energy of the technetium images requires the establishment of new normal ranges for each agent. Finally, the changing distribution of the non-cardiac activity (in the case of sestamibi) and cardiac activity (in the case of teboroxime) will make it necessary to define the time of imaging after injection.

CARDIAC TRANSPORT

Diffusible radiolabeled compounds can image myocardial perfusion because the injected tracer distributes in the tissue in proportion to regional blood flow. This means that regions with

higher blood flow at the time of the tracer injection will receive a higher concentration of the injected isotope and, consequently, will appear brighter on scintigrams when compared to adjacent regions having lower flow. As with all diffusible compounds, peak extraction tends to fall as blood flow increases. This is due, in part, to the increase in transit time as the isotope traverses the capillary network. However, the decrease in extraction is more than compensated for by the large increases in blood flow so that the total amount of transcappillary exchange of the tracer still tends to increase as blood flow increases. At some point of increased blood flow, a diffusion barrier tends to be reached and the transport of the tracer across the capillary barrier becomes severely limited. It is clearly important to know at what point this diffusion barrier is reached for each particular perfusion agent that is employed in clinical studies. A thorough knowledge of the cellular uptake, distribution and retention, as well as the physiologic factors that effect capillary-tissue exchange are important for the accurate interpretation of perfusion images. These parameters are outlined in Table 1 for the two new technetium-labeled compounds (sestamibi and teboroxime) as well as for thallium.

Sestamibi is an isonitrile and is a cation like thallium (1). In contrast, teboroxime, which is a boronic acid adduct of technetium dioxime (BATO), is neutral (2). Both of the technetium compounds have much greater lipophilicity than does thallium and their effective dose equivalents, as determined by the ICRP (International Committee on Radiation Protection) guidelines, are fairly similar but teboroxime is about 70% greater. The target organ (upper GI tract) for the technetium compounds is different from thallium (kidneys and bladder), due to different routes of excretion.

At flow levels ranging from ischemic to hyperemic, the transport parameters of extraction demonstrate that teboroxime has the greatest first-pass extraction of any of the compounds and sestamibi has the lowest (3-9). Consequently, teboroxime has less diffusion limitation and can more reliably track higher flow levels than the other two compounds. The effect of coronary reperfusion on the extraction of these compounds is shown by arrows that display the directional change (if any) in extraction. When coronary flow is held constant before and after reperfusion, the extraction of sestamibi appears to rise, compared to control levels, while the effect on thallium is a slight decrease (7) and there is no significant change for teboroxime

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For reprints contact: Jeffrey A. Leppo, MD, Department of Nuclear Medicine, University of Massachusetts Medical Center, 55 Lake Ave. North, Worcester, MA 01655.

TABLE 1
Physiologic and Pharmacokinetics Properties of Sestamibi, Thallium and Teboroxime

| | Sestamibi (Isonitrite) | ²⁰¹ Tl | Teboroxime (BATO) |
|---------------------------------------|---------------------------|-------------------|----------------------|
| Charge | Cation | Cation | Neutral |
| Lipophilicity | High | Low | Very high |
| Effective dose equivalent | 1.06 rem/30 mCi | 1.05 rem/3 mCi | 1.78 rem/30 mCi |
| Target organ | Upper GI | Kidney | Upper GI |
| Extraction (Peak) | | | |
| Variable flow | 0.40–0.60 | 0.75–0.85 | 0.80–0.90 |
| Coronary reflow effect | ↑ | sl ↓ | — |
| Ouabain effect | sl ↑ | sl ↓ | — |
| Net Retention | | | |
| Early (2–5 min) | 0.40 | 0.50 | 0.55 |
| Late (>10 min) | — | ↓ | ↓ |
| Coronary reflow effect | ↑ | ↓ | sl ↓ |
| Diffusion limitation (ml/min/g) | 2–2.5 | 2.5–3.0 | >4.0 |
| Myocardial clearance t _{1/2} | >6 hr | 3–4 hr | 10–15 min |
| Redistribution | Minimal | Yes | Yes |
| Cellular "Uptake" | | | |
| Metabolic cellular dysfunction | | | |
| Mild (reversible) | sl ↑ | sl ↓ | — |
| Moderate (some damage) | ↑ | ↓ | — |
| Severe (cell death) | ↓ | ↓ | ↓ |
| Ouabain effect | — | ↓ | — |
| Mitochondria inhibition | ↓ | — | — |

—, no effect; ↑, increase; ↓, decrease; sl, slight; n/a = not available.

(10). The specific effect of coronary reperfusion was evaluated in situations where coronary flow was held constant so that the effect of cellular damage could be evaluated independent of blood flow. In a separate series of evaluations, ouabain has been infused into the perfusion system (at constant flow) and the ability to extract thallium was depressed when compared to control but was unchanged for the technetium compounds (10).

Another common parameter to assess myocardial transport is a measurement of net retention (4,6,7). This parameter evaluates what fraction of the injected dose remains in the myocardium and reflects both the initial, first-pass extraction as well as any degree of backdiffusion from the cellular compartment. When looking at the relatively early values of this calculation (between 2 and 5 min after injection), it is clear that teboroxime remains the highest and sestamibi has the lowest value. However, the overall difference in net retention among these compounds is less marked than might be expected given the disparity in peak extractions. This relatively smaller difference among the three compounds is related to the relatively faster back diffusion of teboroxime and thallium in comparison to sestamibi. This kinetic effect eventually results in a late (>10 min) net retention, which tends to favor sestamibi since it has very little decrease in activity over time as compared to a much more rapid loss for teboroxime and, to a lesser extent, for thallium (4). The effect of coronary reperfusion on net retention results in an enhancement of sestamibi net retention while thallium and, to a lesser degree, teboroxime are somewhat

depressed (7,10). Given all of these parameters, the myocardial clearance times for the three compounds are quite different. Teboroxime clearly has the fastest clearance time of the three tracers and sestamibi has the slowest (3,4,8,9). From these kinetic parameters, it is predictable that thallium and teboroxime can show appreciable redistribution of the tracer based on differential regional kinetics and washout while these types of changes are fairly minimal when imaging with sestamibi.

In a series of experiments (10–14) involving cell culture preparations and evaluation of cellular "uptake," several characteristics of the three tracers have also been noted. When there is mild and reversible metabolic cellular inhibition, there is apparently a slight increase in uptake of sestamibi which is not seen with the other two agents. In fact, thallium tends to show a slight to more marked decrease in relative uptake during reversible and moderate cellular inhibition whereas the uptake of teboroxime is not significantly affected in either of those two conditions. With more profound cellular damage, resulting in 100% cell death, sestamibi clearly shows a great loss in cellular uptake, whereas thallium and teboroxime continue to show similar types of changes seen with moderate damage. When cells are exposed to ouabain, only thallium shows any significant decrease in uptake and, during experiments simulating mitochondrial inhibition, only sestamibi demonstrates significant inhibition in cellular uptake.

All three agents show linear distributions of tracer uptake related to flow increase but, at elevated levels of coronary flow, as seen with vasodilators, sestamibi would show the most

impairment from diffusion limitation, while teboroxime would have the least amount of limitation. It would also appear that teboroxime has the least degree of sensitivity to cellular dysfunction compared to the other agents and may therefore result in images that more consistently display effects of blood flow as opposed to possible enhancements or depression of uptake related to cellular dysfunction, reperfusion or effects of hypoxia and ATPase inhibition.

SESTAMIBI IMAGING PROTOCOLS

Following ^{99m}Tc -sestamibi injection with the patient at rest, initial tracer concentration in the liver is nearly twice that in the heart. Subsequently, there is minimal change in concentration in the heart, while there is progressive hepatobiliary excretion from the liver into the gallbladder and gut, which may be facilitated by having the patient drink 8 oz of milk or eat a fatty meal. The heart-to-liver ratio is approximately 1:1 by 120 min (15). There is also progressive tracer clearance from the lungs and spleen (Fig. 1). Following tracer injection during exercise, the heart-to-liver ratio is immediately greater than 1.0 and progressively increases over the next 3 hr (Fig. 2). Taking into account the 6-hr ^{99m}Tc half-life, the optimal time postinjection for sestamibi imaging has been determined to be 60-90 min for resting studies and 30-60 min for exercise studies. Whereas with planar imaging the longer times are preferable in order to allow for maximal liver clearance, with the improved contrast resolution of SPECT, the shorter times are feasible.

Since ^{99m}Tc -sestamibi does not appreciably redistribute, separate resting and exercise injections are required to identify and differentiate myocardial scar and ischemia. The most straightforward approach is to perform the stress study with exercise or pharmacologic vasodilatation on one day and the resting study on a subsequent day. Each study is performed using 15-30 mCi of ^{99m}Tc -sestamibi. This two-day protocol avoids any "crosstalk" between the two sets of images and may readily accommodate the laboratory and patient's schedules since the

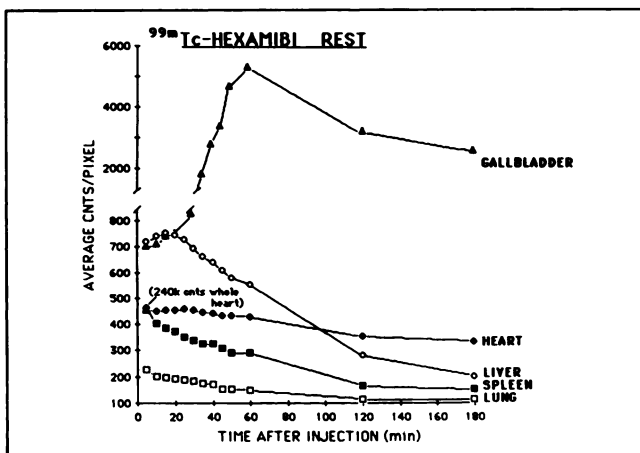


FIGURE 1. Organ time-activity curves after ^{99m}Tc -sestamibi injection at rest in five normal volunteers (mean \pm s.d.). Data are normalized to myocardial activity at 5 min postinjection. (Reproduced with permission from reference 15.)

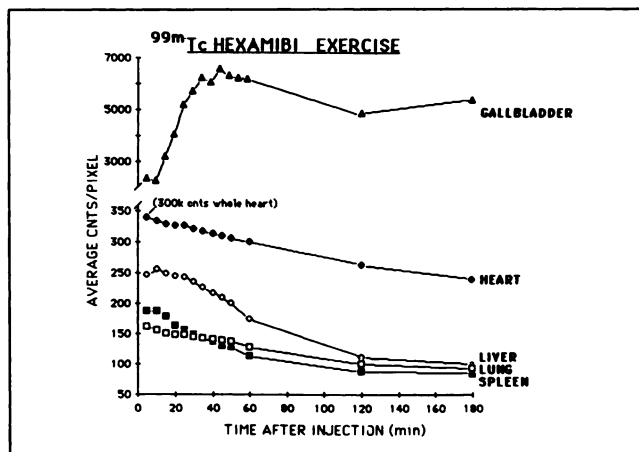


FIGURE 2. Organ time-activity curves after ^{99m}Tc -sestamibi injection at peak treadmill exercise in five normal volunteers (mean \pm s.d.). (Reproduced from reference 15.)

second-day resting study can be canceled if the stress study is entirely normal.

However, logistic circumstances (preoperative evaluation, patient from out of town, etc.) frequently arise, necessitating completion of the entire myocardial perfusion study in one day. Under these circumstances, the injected dose must be adjusted to avoid having the patient leave the imaging laboratory with greater than 30 mCi. Imaging is first performed 60-90 min following a resting injection of 9 mCi (doses are adjusted upward according to body weight: Rest dose = (patient weight in kg/70) \times 9, to a maximum of 13 mCi. Stress dose = (patient weight in kg/70) \times 22, to a maximum of 32 mCi). A stress injection of 22 mCi is subsequently given 0-4 hr after the resting images are completed, with stress imaging performed 30-60 min postinjection. The patient should void the urinary bladder before leaving the laboratory to decrease the accumulated dose.

Taillefer et al. compared the diagnostic accuracy of ^{99m}Tc -sestamibi imaging in 15 patients undergoing a same-day protocol to results in the same patients also undergoing a separate-day protocol (16). Both protocols demonstrated the same number of ischemic (52/225) and fixed (19/225) defects. Moreover, the normal-to-ischemic wall ratios were nearly identical for the same-day (1.33 ± 0.12) and separate-day (1.28 ± 0.10) protocols. A minor disadvantage of the same-day protocol is that the stress test must be performed late in the morning or early in the afternoon. Although many laboratories have averted this potential problem by performing resting injections very early in the morning (7:30 a.m.), thus allowing the stress testing to begin at 9:30 a.m., the total number of patients may be more limited than with the present early morning thallium exercise protocols.

An alternate same-day ^{99m}Tc -sestamibi protocol, which circumvents the above limitations, is to perform a stress study with a low (9 mCi) dose, wait 3-4 hr, and perform a separate resting study with a higher (22 mCi) dose. However, Taillefer et al. prospectively compared one-day protocols using the rest-stress and stress-rest sequences in 18 patients (17). Although there was agreement with regard to normalcy, scar, or ischemia

TABLE 2
Planar ^{99m}Tc-Sestamibi Acquisition Protocol

| | |
|---------------|---|
| Collimator | GAP or high-resolution |
| Field of view | Full 10 in.; or LFOV 15 in. with 1.2–1.5 zoom |
| Matrix | 128 × 128 |
| Window | 20% centered on 140 keV |
| Gating | Optional 16 frames/cardiac cycle |
| Imaging time | 5–8 min/view (10 min/view with gating) |
| Image counts | At least 1 million |

in 283/324 (87.3%) segments, in 7.4% of segments abnormalities were judged to be ischemic using the rest-stress sequence but misinterpreted to be fixed with the stress-rest sequence. This significant underestimation of ischemia was felt to be due to crosstalk from the earlier stress dose, with failure to recognize reversibility in the later resting study. Therefore, the stress-rest same-day protocol should be used cautiously and may be best applied to patients with a relatively low pre-test likelihood of disease in whom a normal initial stress study is anticipated.

Because ^{99m}Tc-sestamibi does not redistribute and provides high photon flux, image acquisition and processing protocols have been designed to obtain the highest possible resolution images, limited only by the radiopharmaceutical dose and patient tolerance (Tables 2–5). This is in contrast to myocardial perfusion imaging with ^{99m}Tc-teboroxime, where it is critical to begin imaging immediately following injection and to complete the acquisition within 6 min, before the tracer has significantly washed out or redistributed. An additional advantage of ^{99m}Tc-sestamibi afforded by its lack of redistribution is the ability to repeat image acquisition in the event of positioning error, patient motion, or instrument malfunction.

DIAGNOSIS OF CORONARY ARTERY DISEASE

The higher photon energy, decreased attenuation and scatter, and improved count rate afforded by ^{99m}Tc-sestamibi compared to ²⁰¹Tl, yield images with lower background and better defini-

TABLE 4
SPECT ^{99m}Tc-Sestamibi Separate-Day Acquisition Protocol

| | Exercise | Rest |
|--------------------|-----------------|----------|
| Energy window | 20% symmetric | Same |
| Collimator | High resolution | Same |
| Orbit | 180°, circular | Same |
| No. of projections | 64 | Same |
| Matrix | 64 × 64 | Same |
| Time/projection | 20 sec | Same |
| Total time | 25 min | Same |
| ECG gated | Optional | Optional |
| Frames/cycle | 8 | 8 |
| R-to-R window | 100% | 100% |

tion of the myocardium (Figs. 3 and 4). Studies to date using either planar or SPECT methodology and interpretation by blinded expert observers have shown equivalent diagnostic accuracies for ^{99m}Tc-sestamibi and ²⁰¹Tl imaging performed in the same patients (15,18–21). For detecting individual coronary stenoses, one study, by Kahn et al., demonstrated an improved sensitivity of ^{99m}Tc-sestamibi SPECT (79%) compared to ²⁰¹Tl (69%) ($p < 0.05$) (18). A significant improvement in interobserver agreement in planar image interpretation has been reported for ^{99m}Tc-sestamibi (96%) compared to ²⁰¹Tl (88%) (22). This advantage is most likely attributable to the improved image quality with ^{99m}Tc-sestamibi.

Evaluation of right ventricular perfusion is also feasible with ^{99m}Tc-sestamibi (23). Although the ratio of counts in the right ventricle compared to the left is similar to ²⁰¹Tl, the improved spatial resolution afforded by ^{99m}Tc-sestamibi allows evaluation of right ventricular perfusion at rest and during exercise in most patients.

IDENTIFICATION AND SIZING OF ACUTE MYOCARDIAL INFARCTION

Infarct identification and sizing with ^{99m}Tc-sestamibi has been compared to other invasive and noninvasive methods for iden-

TABLE 3
Same-Day Acquisition Protocol: Single-Head Camera

| | Sestamibi | | Teboroxime* | |
|---------------------|-----------------|----------|--|----------|
| | Rest | Exercise | Rest | Exercise |
| Energy window | 20% symmetric | Same | 20% symmetric | Same |
| Collimator | High-resolution | Same | Leap or high resolution | Same |
| Orbit | 180°, circular | Same | 180°, circular | Same |
| No. of projections | 64 | Same | 32 step and shoot 64 continuous | Same |
| Matrix | 64 × 64 | Same | 64 × 64 with masking | Same |
| Time/projection | 25 sec | 20 sec | 10 sec† | Same |
| Total time | 30 min | 25 min | 6–7 min | Same |
| ECG gated | No | Yes | No | Same |
| Frames/cycle | 1 | 8 | 1 | Same |
| R-to-R window | 100% | Same | 100% | Same |
| Mode of acquisition | Step and shoot | Same | Step and shoot (con- tinuous preferred) | Same |

* Protocol suggested by Dr. Jonathan Links.

† Live plus step and shoot time should be <7 min total.

TABLE 5
Same-Day Acquisition: Three-Head Camera

| | Teboroxime | | Sestamibi | |
|--------------------|-----------------|----------|-----------------|--------------|
| | Rest | Exercise | Rest | Exercise |
| Energy Window | 15% symmetric | Same | 15% symmetric | Same |
| Collimator | High resolution | Same | High resolution | Same |
| Orbit | 360° elliptical | Same | 360° elliptical | Same |
| No. of projections | 90 | Same | 60 or 120 | Same |
| Matrix | 64 | Same | 64 | Same |
| Time/projection | 8* sec | Same | 45 or 30 sec | 60 or 40 sec |
| Total time | 4 min | Same | 15 or 20 | 20 or 27 |
| ECG gated | No | No | No | Yes |
| Frames/cycle | 1 | 1 | 1 | 8-16 |
| R-to-R window | 100% | 100% | 100% | 100%† |

* Sum of 4 sec counter-clockwise and 4 sec clockwise.

† 10% window bat-beat rejection.

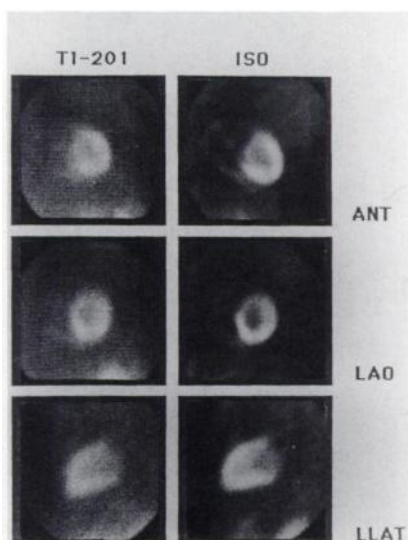
tifying myocardial necrosis. When correlated with coronary angiography, planar sestamibi imaging identified 91% of infarcts, compared to 85% for ^{201}Tl ($p = \text{ns}$) (24). When compared to other noninvasive markers of infarction, including electrocardiographic Q-waves and wall motion abnormalities on equilibrium radionuclide angiography, a 96% concordance with $^{99\text{m}}\text{Tc}$ -sestamibi imaging was reported (25). The severity of the myocardial perfusion defect has been shown to correlate well with the severity of regional left ventricular dysfunction. In a study by Rocco et al., 91/100 defects with $<50\%$ of maximal myocardial uptake demonstrated regional akinesis or dyskinesia (26). In a canine model, infarct size determined by $^{99\text{m}}\text{Tc}$ -sestamibi SPECT imaging correlated very closely ($r = 0.95$) with actual infarct size measured from TTC-stained heart slices (27). Thus, $^{99\text{m}}\text{Tc}$ -sestamibi provides an accurate noninvasive means to identify and size myocardial infarcts. If the radiopharmacy can be made operational on a 24-hr schedule, sestamibi has advantages (compared to thallium) in the management of patients with suspected acute myocardial infarction.

APPLICATIONS IN ACUTE ISCHEMIC HEART DISEASE

The lack of sestamibi redistribution permits $^{99\text{m}}\text{Tc}$ myocardial perfusion imaging in patients with acute ischemic syndromes. The patient can be injected when acutely symptomatic and imaged later when stable. Tracer distribution at the time of imaging reflects blood flow at the time of injection (time zero). When a patient is admitted to the hospital with acute chest pain, it is important to make an accurate diagnosis of coronary ischemia since appropriate treatment can reduce morbidity and mortality. Clinical symptoms are often misleading and the electrocardiogram, even when performed during chest pain, may be insensitive and nonspecific. In contrast, the exclusion of coronary ischemia as a cause of chest pain directs the patient to other appropriate diagnostic modalities and decreases cost by minimizing the time spent in the coronary care unit. Gregoire and Theroux injected 26 patients without prior myocardial infarction with $^{99\text{m}}\text{Tc}$ -sestamibi during spontaneous episodes of chest pain suggestive of unstable angina (28). Patients then underwent SPECT imaging when they were clinically stable. When compared to angiographic evidence of coronary artery stenoses, $^{99\text{m}}\text{Tc}$ -sestamibi SPECT was 96% sensitive and 76% specific for detection of significant coronary artery disease. Not only the presence, but also the location and severity of ischemia was identified. In contrast, an electrocardiogram performed during chest pain was only 35% sensitive (29). Normalization of the myocardial perfusion image pattern following a second injection of tracer when the patient is asymptomatic reinforces the diagnosis of coronary ischemia and differentiates acute ischemia from prior myocardial infarction. Administration of nitroglycerine prior to the second injection may further aid in differentiating scar from ischemia by decreasing the likelihood of asymptomatic, resting ischemia.

If patients with acute myocardial infarction are injected with $^{99\text{m}}\text{Tc}$ -sestamibi at the time of presentation to the hospital, subsequent imaging after the patient has been stabilized and treated will reflect not only the area of acute infarction, but also surrounding and adjacent areas of ischemic, jeopardized myocardium. Several investigators have used this new radiophar-

FIGURE 3. Planar myocardial perfusion images obtained in the anterior (ANT), left anterior oblique (LAO), and left lateral (LLAT) views in a normal subject with ^{201}Tl (left) and $^{99\text{m}}\text{Tc}$ -sestamibi (ISO) (right). Note the considerable improvement in image quality with $^{99\text{m}}\text{Tc}$ -sestamibi. Image provided courtesy of Frans. J. Wackers, MD, Yale University.



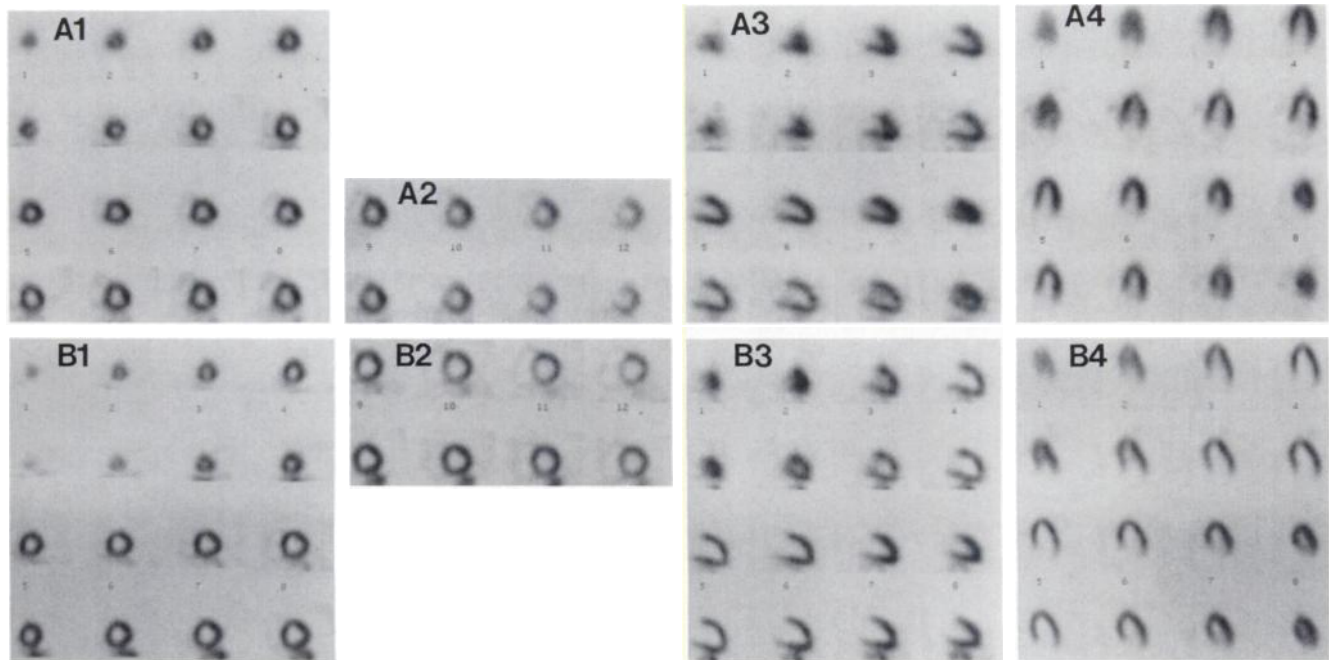


FIGURE 4. Normal SPECT myocardial perfusion images obtained with ^{201}Tl (A) and $^{99\text{m}}\text{Tc}$ -sestamibi (B). Sestamibi images were acquired and processed using parameters outlined in the text and Tables 2 and 3. Stress and 4-hr delayed or resting images are paired for each tomographic slide with the stress images immediately above the corresponding delayed or resting images. Six millimeter thick short-axis slices are shown in A-1 and A-2 for ^{201}Tl and B-1 and B-2 for $^{99\text{m}}\text{Tc}$ -sestamibi, proceeding from the apex to the base (1-12) of the left ventricle. Vertical long-axis slices are shown in A-3 and B-3, proceeding from the lateral wall to the septum (1-8). Horizontal long-axis slices are shown in A-4 and B-4, proceeding from the anterior to the inferior wall.

maceutical to determine the amount of myocardium salvaged following thrombolytic therapy (27,30–35) by quantifying serial perfusion scans. Patients are injected upon admission, thrombolytic therapy is given and imaging is then performed, usually at the bedside, within 4 hr. These initial images identify regions of jeopardized plus infarcted myocardium. A repeat study performed later in the patient's hospital course or prior to discharge identifies only infarcted tissue. The amount of salvaged myocardium can be estimated by comparing the initial and late studies. Using quantitative planar imaging, Wackers et al. demonstrated that patients with a patent infarct-related artery post-successful thrombolysis had a significant decrease ($-51\% \pm 38\%$) in defect size compared to those with persistent coronary occlusion ($-1\% \pm 26\%$) ($p = 0.001$) (30).

EVALUATION OF VENTRICULAR FUNCTION

A final advantage of the $^{99\text{m}}\text{Tc}$ -based perfusion agents compared to ^{201}Tl is the ability to assess both myocardial perfusion and function using a single injection of tracer. Left ventricular ejection fraction (LVEF) correlates inversely with myocardial perfusion defect size. In a study by Borges-Neto et al. using $^{99\text{m}}\text{Tc}$ -sestamibi first-pass imaging with a multicrystal camera, this inverse relationship was demonstrated for both resting ($r = -0.77$) and exercise studies ($r = -0.79$) (36). Measurement of ejection fraction provides additive prognostic information to perfusion imaging, particularly in patients with diffuse, small-vessel disease and cardiomyopathy in whom discrete, segmental perfusion defects may not be present. Exercise ejection fraction

is an important variable which was significantly correlated with both patient survival and event-free status (37).

Another way to evaluate myocardial perfusion and function with a single injection of $^{99\text{m}}\text{Tc}$ -sestamibi is by means of electrocardiographic gating of the perfusion images. Since the patient is at rest during image acquisition, only resting ventricular function can be assessed in combination with either the stress or resting perfusion distribution of tracer. The simultaneous evaluation of exercise perfusion and resting function is a particularly attractive option since inferences regarding myocardial viability may be made. An exercise perfusion defect with preserved regional wall motion implies ischemia, whereas regional akinesis could be associated with either scar or severely ischemic or stunned myocardium. With the newer generation three-headed SPECT systems, 24-frame per cardiac cycle gated acquisition is possible. Wall motion can be assessed by evaluating endocardial excursion. It also has been demonstrated that the increase in myocardial count density during systole is proportional to wall thickening (38). The imaging protocols recommended for planar and SPECT $^{99\text{m}}\text{Tc}$ -sestamibi imaging are included in Tables 2–5. Computer processing should be performed with a prefilter (two-dimensional Weiner or Butterworth) and ramp filtered backprojection, but the specific parameters will depend on the camera model utilized.

TEBOROXIME IMAGING: GENERAL CONSIDERATIONS

The high photon flux from 20 to 30 mCi of $^{99\text{m}}\text{Tc}$ plus the high first-pass myocardial extraction of teboroxime combines

to produce very high myocardial counts within 2 min following radiotracer injection. However, there is also rapid myocardial washout. This can be seen as a two-edged sword. On the one hand, by 60 min after an injection of teboroxime, residual myocardial activity is negligible, which permits serial tracer injection within a relatively short time period. On the other hand, imaging must be started within 2 min of tracer injection and quickly completed. The major component of myocardial washout has a half-life of 5–10 min. The second major factor that sets a limit on the length of acquisition is hepatic uptake, which peaks at about 6 min after injection. The rapidity and intensity of liver uptake appears to be multifactorial and depends in part on patient position, splanchnic blood flow and, related to the latter, status of left ventricular function. Following high-level exercise in a patient with normal left ventricular function and imaging in the upright posture, a set of three planar images can be acquired before hepatic activity is apparent. Conversely, following low-level exercise in a patient with compromised left ventricular function, the liver can be apparent at the onset of imaging. Pharmacologic stress also appears to accentuate early hepatic uptake. In addition, the supine position increases anatomic overlap between the liver and heart.

Therefore, the requisites for optimal image quality include a short (less than 2 min) interval between injection and onset of imaging, and a short total acquisition time, with completion by 6–9 min postinjection. When combined with exercise stress, either the bicycle or treadmill may be used. If bicycle exercise is to be combined with planar imaging, the patient can pedal with his/her chest close to the gamma camera detector and planar imaging is begun within 2 min of injection while the patient is still seated upright on the bicycle. A positioning mode should be used to identify the earliest point of blood-pool clearance to begin imaging. If the camera has high count rate capability, the planar scans can be combined with first-pass acquisition for ejection fraction measurement.

When teboroxime injection is combined with treadmill exercise, the acquisition parameters, whether planar or SPECT, must be set up before exercise is begun. The radiotracer is injected at peak exercise, the treadmill slowed and stopped, and the patient then is moved quickly under the camera, which is set to go. This protocol works best if the treadmill and camera are in the same or adjacent rooms. Continuous ECG monitoring for the first 4 min of recovery should be maintained.

PLANAR IMAGING

One useful protocol for planar imaging was developed by Hendel et al. (39). The patient is injected with 15–20 mCi of ^{99m}Tc -teboroxime at peak exercise and then moved rapidly from the treadmill to the camera. The patient either stands or sits in a swivel chair in front of the detector of a standard Anger camera. Imaging is begun in the steep LAO or lateral projection, in which there is greatest anatomic overlap with the liver, to acquire these images before liver activity peaks. Dynamic imaging is performed at 20 sec/frame or rapid static imaging is completed in 45–60 sec per view. The technologist can either stop the acquisition when adequate counts are achieved in the

left ventricle and quickly reposition and restart the static collection or wait 2–4 frames (40–80 sec) before repositioning the patient during a dynamic collection. Counts in the left ventricle in the first planar image are in the range of 200–400K and the images are diagnostic. The patient is reinjected at rest 1 hr later and the same imaging protocol repeated. The correlation with planar thallium exercise and redistribution imaging was excellent (39). An example of this imaging protocol is seen in Figure 5. This patient also provides an example of early “redistribution” (differential washout) of teboroxime.

An alternative method of combining treadmill exercise and planar imaging, as well as acquiring first pass data for LVEF measurements and maintaining continuous ECG monitoring in the early recovery period is to use a portable high count rate multi-crystal camera (Sim-400) (40). A positioning source is attached to the patient’s chest (americium-241) for motion correction. At peak exercise, 15–20 mCi of Tc-teboroxime is injected as a bolus and dynamic dual isotope ($^{99m}\text{Tc}/^{241}\text{Am}$) acquisition is performed for 50 sec using a high-efficiency collimator. The treadmill is slowed and stopped. A second, high-resolution collimator is attached to the detector and planar imaging is begun in less than 2 min from the time of injection. Imaging is performed while the patient is still standing on the treadmill and still monitored, beginning with the steep LAO projection, for 40 sec per view. Counts in the first image (almost all myocardial) using this camera/detector/acquisition combination are in the range of 200K. The patient returns in 1 hr and the same dynamic first-pass followed by rapid three-view planar imaging is repeated using a slightly higher dose of Tc-teboroxime (25–30 mCi). The combined dose does not exceed 40 mCi. The patients are required to void before leaving the laboratory. An example of this type of imaging protocol is shown in Figure 6.

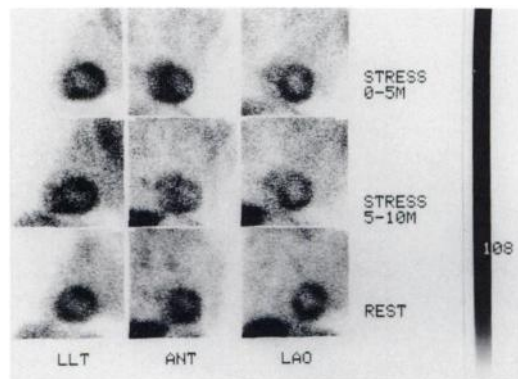


FIGURE 5. Planar teboroxime images in a patient with two vessel disease (LAD and LCx). The left lateral (LLT), anterior (ANT) and left anterior oblique (LAO) views are shown for the initial stress (0–5 min postinjection), delayed stress (5–10 min postinjection) as well as the same views for the separate rest injection 1.5 hr later. The patient shows anterior, anterior-lateral, posterior-lateral, and apical defects on the initial stress images with some “redistribution” after 5 min in the anterior-lateral and apical areas. The rest images show extensive improvement in all of the initial defect areas.

The prognostic value of the exercise LVEF has been well demonstrated by Jones and colleagues (37). In 571 stable medically treated patients with documented coronary artery disease who underwent upright bicycle exercise with measurements of exercise LVEF by the first-pass technique and 5.4-yr clinical follow-up, exercise LVEF was the single most important descriptor of left ventricular function predicting hard cardiovascular events, including infarction and death. Using life table analysis, survival fell off below an exercise value of 50%. The survival became significantly worse at lower exercise LVEF values. Therefore, protocols that can take advantage of the ability to acquire exercise LVEF from dynamic acquisition following bolus injection of Tc-teboroxime offer significantly more clinical information with no increment in test time and with modest increase in technical time, equipment, and software.

SPECT IMAGING

SPECT imaging of teboroxime must also be performed rapidly for the reasons stated above. In addition, artifacts in reconstructions may be induced by changing activity of tracer in the organ being imaged. Phantom experiments have demonstrated that, if the total acquisition time is equal to or less than the tracer half-time in the organ, there is minimal distortion due to changing tracer activity (41). The half-life for the first and major component of myocardial washout is 11 min and total SPECT acquisitions are under 10 min. There is variability in camera deadtime among manufactured single-headed cam-

eras. To get the greatest number of counts in a tomographic mode, either the camera deadtime must be short or the camera must have the option for continuous step and shoot acquisition. Either a general all-purpose collimator or a high-resolution collimator may be used. A suggested acquisition protocol (Tables 3 and 5) is continuous acquisition or step and shoot with total livetime plus stepping time less than 7 min, beginning in the LPO and finishing in the RAO projection. The image quality is comparable to SPECT thallium. Processing should be performed, preferably using a two-dimensional Weiner or two-dimensional Butterworth prefilter and ramp filtered backprojection and including volume masking to ensure that the slices will be normalized to myocardial activity.

Because of the need to record data in a very short time frame following teboroxime injection, a three-headed camera is uniquely suited for teboroxime SPECT imaging. Corbett et al. (Table 5) have used a three-headed SPECT camera to image teboroxime, beginning within 2 min of injection, using continuous rotation acquisition for 4 sec per projection and 30 projections per head for completion of the total acquisition in 2 min (42). Dynamic SPECT can be performed with a total of six to eight acquisitions alternating clockwise and counterclockwise rotations. Reconstructed slices from either the first 2-min acquisition alone or from the sum of the first four 2-min acquisitions can be interpreted. An acquisition completed 2 min following an exercise injection shows no appreciable hepatic uptake. Interpretation can be performed on the initial 2-min SPECT or on the sum of the first four 2-min acquisitions. A potential advantage in reading the short serial SPECTs is to see regional differences in myocardial tracer concentration over this short period. Preliminary observations have been made of both early "fillin" and, in some segments, appearance of defects over the first 8 min (42).

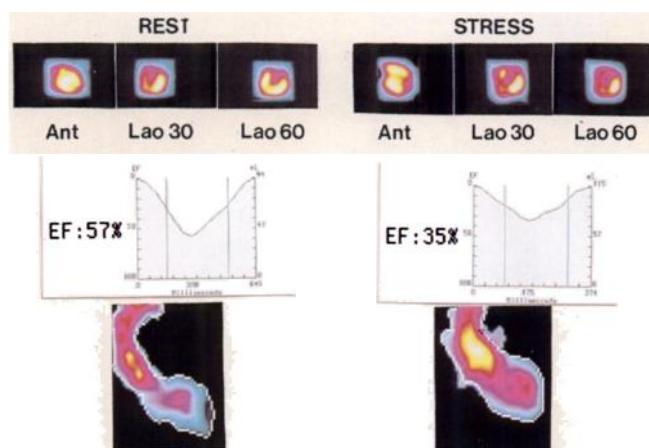


FIGURE 6. Rest data displayed on the left panel, stress on right. Three 40-sec planar teboroxime images are on the top of each panel, the time-activity curve from the first-pass acquisition in the middle, and the wall motion image from the first-pass acquisition on the bottom (end-diastolic perimeter and end-systolic images superimposed). The color scale is based on counts, with the highest count density displayed as yellow, through red, purple, blue, green to black. The patient has documented proximal LAD stenosis without prior infarction. The resting-perfusion scans and function study were interpreted as normal. The stress-perfusion scans were interpreted to show an anteroseptal, apical defect, and the stress-wall motion study to show anteroapical hypokinesis.

CLINICAL INDICATIONS

The diagnostic accuracy of teboroxime imaging was shown to be high in 177 patients in whom the results of the teboroxime scans (either planar or SPECT) were compared to the overall clinical impression based on the results of all other invasive and noninvasive cardiovascular diagnostic studies (cardiac catheterization and/or stress thallium). The patient population studied comprised patients with chronic stable ischemic heart disease and excluded patients with acute ischemic syndromes. When the scan results of teboroxime were compared against overall clinical impression, the sensitivity was 84%, specificity 91%. Since these figures are not significantly different than those reported in the literature for planar thallium imaging and the specificity is higher than that reported for SPECT thallium, then teboroxime imaging may be used in place of ^{201}Tl in this outpatient population with chronic ischemic heart disease or as a diagnostic test to evaluate patients with chest pain.

In a patient with either high pretest probability for coronary disease or objectively documented disease, the exercise stress-teboroxime test can be ordered to address the same clinical questions as stress thallium tests. Specifically, stress-teboroxime imaging can confirm a diagnosis, evaluate the region at risk,

gauge the success of interventions (such as revascularization or medical therapy), or assess flow limitations of angiographically-documented lesions. In patients with prior myocardial infarction, either recent or remote, the test can be used to assess perinfarct ischemia or ischemia remote from the infarction in the distribution of another vessel (multi-vessel disease). The major advantage of stress-teboroxime imaging over that of thallium is the shorter test duration. The total time for stress and redistribution thallium imaging is about 5–7 hr and this time can be increased with late redistribution or reinjection. In contrast, because of rapid myocardial washout, stress and rest teboroxime injections can be performed within 1 hr of one another and, because the acquisition times are short for both planar or SPECT, the total test time is usually 1.5–2 hr.

In patients with prior myocardial infarction, stress-teboroxime imaging, especially when combined with rest and exercise LVEF, may be superior to stress and 4-hr redistribution thallium imaging for patient evaluation. Whether scans following two separate injections of a technetium perfusion imaging agent at stress and rest are better than thallium stress and 4-hr redistribution scans for differentiating reversible (ischemic) defects from fixed (scar) defects is yet unresolved. Hendel et al. reported good agreement between the two imaging modalities for identification of the presence or absence of a defect consistent with myocardial scar (39). These same investigators found that teboroxime scintigraphy identified a significantly greater number of ischemic segments than thallium scintigraphy. The addition of the exercise LVEF can be of further help in this group because of the prognostic importance of exercise LVEF value. In addition, the LVEF response to exercise combined with regional wall motion analysis may help distinguish between patients with infarct alone (fixed wall motion abnormality, rise in LVEF with exercise) from patients with predominant ischemia (ejection fraction fall with exercise, increase in size, location or severity of wall motion abnormality). Other patient groups in whom combined perfusion and left ventricular function from stress and rest teboroxime injections and imaging are useful clinically are those in whom symptoms suggest a component of ventricular dysfunction during exercise such as exertional dyspnea (differential anginal equivalent versus lung disease) or exertional fall in blood pressure (differential global ischemia versus autonomic dysfunction).

As noted above, thallium or sestamibi have been used to access the region at risk and/or to assess the efficacy of thrombolytic therapy in acute ischemic syndromes (35,43). Although teboroxime imaging is so quick that it would not significantly delay therapy, only those hospitals having a portable gamma camera in the emergency room or coronary care unit and an imaging technologist immediately available on an emergency basis will be able to perform teboroxime studies in these clinical settings. For these practical reasons, teboroxime will probably find less use in evaluating patients with acute ischemic syndromes than will sestamibi.

SPECIAL CLINICAL CONSIDERATIONS

The unique pharmacokinetic properties of teboroxime, including high extraction at high myocardial blood flow and rapid

myocardial washout, present several opportunities where teboroxime imaging may either be superior to thallium or sestamibi, or offer information neither of the other agents can provide. These two areas include differential washout and pharmacologic stress.

Because of its neutral, lipophilic properties, teboroxime comes close to being a freely diffusible tracer similar to ^{133}Xe . The myocardial washout is biexponential and the first rapid component is the major component (>60%) with a half-life of 5–10 min. Because there is probably little re-uptake of teboroxime into the heart following the initial high first-pass extraction, “redistribution” to teboroxime is due to differential washout alone (44). Regional differences in myocardial washout of teboroxime have been observed in dynamic planar imaging (39) (Fig. 5) and with dynamic SPECT imaging using a three-headed camera (42). Imaging of early redistribution may obviate the need for a second rest injection in some cases, further shortening an already very short test. Washout rate has been shown to relate to myocardial blood flow in experimental animals. Although absolute values for regional left ventricular myocardial blood flow probably cannot be quantitated from teboroxime washout, it may be possible using a three-headed camera to estimate myocardial flow reserve by comparing baseline regional myocardial washout rates with washout rates at maximal coronary vasodilatation induced by adenosine infusion.

With the exception of regional washout analysis, quantitation based on count profiles, similar to those available for thallium and teboroxime, are not presently available for teboroxime and may never have the same applicability. In addition to rapidly changing myocardial activity, background scatter from the liver changes from image to image and the rate of this change varies among patients. Even a small delay in time interval between injection and imaging could affect count profiles due to rapid washout. For all of these reasons, quantitation is more likely to be based on regional washout analysis than circumferential count profiles.

Pharmacologic stress using either dipyridamole or adenosine infusion combined with teboroxime imaging is now being performed at several institutions. The advantages of this combination include the pharmacokinetic properties of teboroxime of high myocardial extraction at maximal myocardial blood flow induced by adenosine, rapid imaging, and avoiding the logistic difficulties of rapidly moving a patient from treadmill to camera since the infusion can be performed with the patient lying on the SPECT table during stress and tracer injection. Iskandrian and co-workers have combined adenosine infusion with teboroxime-SPECT imaging, using a single-head detector, in more than 20 patients who also underwent exercise SPECT thallium imaging (45). The protocol they used included a 6-min adenosine infusion, according to the recommendations of Verani et al. (46) with injection of tracer during the last minute of infusion and imaging after blood-pool clearance of teboroxime with a single-head camera at 10 sec/stop \times 32 stops for a total imaging time of 7.8 min. In the majority of patients imaged to date, the image quality is excellent and the sensitivity

and specificity for diagnosing CAD and identifying abnormal vessels are comparable to stress-thallium studies. In two patients, teboroxime uptake in a prominent left lobe of the liver interfered with visualization of the inferior wall. Because of the short stress, short imaging, and short time between stress and rest injections, this entire protocol can be completed within 1 hr. It may also be possible to shorten the test time further by using a three-headed camera for acquisition and performing the rest-injection 10 min following the stress acquisition. Imaging was begun 1 min following injection using high-resolution collimators with a 64 × 64 matrix from four 1-min acquisitions. Pharmacologic stress tests are frequently ordered for preoperative evaluation for urgent surgery. To have results available in such a short time frame would find high approval among physicians ordering these tests.

SUMMARY

Overall, it is clear that the two new technetium-labeled compounds can provide diagnostic myocardial perfusion imaging both at stress (exercise and pharmacologic) and rest, but they have very different mechanisms of transport in comparison to each other and to thallium. Therefore, new imaging protocols will need to be developed and refined by practical experience as the use of these agents expands. Further investigative work needs to be done to optimize protocols and computer processing of images. In addition, special clinical situations will become associated with the use of these new compounds. Nuclear cardiology will continue to advance during this time of great changes and challenges if informational exchange on these topics continues to flourish and critical clinical trials are completed.

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