
Left Ventricular Perfusion and Performance from a Single Radiopharmaceutical and One Camera

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To test the hypothesis that a small field of view portable multicrystal scintillation camera can perform stress/rest combined LV function by first-pass and perfusion studies using ^{99m}Tc -teboroxime, 26 patients with positive stress thallium studies within 2 wk and 8 healthy volunteers were studied. A ^{241}Am point source marker over the sternum was used for motion correction. Dynamic dual-isotope ($^{99m}\text{Tc}/^{241}\text{Am}$) acquisition was performed following injection of 15.6 ± 2.3 mCi of ^{99m}Tc -teboroxime at peak treadmill exercise. Two minutes later (blood-pool clearance), while still standing on the flat treadmill, 3-4 40-sec planar images were acquired. One hour later patients were reinjected with 22.7 ± 3.4 mCi of ^{99m}Tc -teboroxime while standing in front of the camera and the same dynamic/static acquisition protocol repeated. The planar images were interpolated from a 20×20 matrix to a 160×160 matrix, a sharpening filter and an interpolative background subtraction algorithm applied. The scans were divided into segments, each scored as normal, reversible and fixed. The agreement with thallium imaging for identifying an abnormal scan was 24/26 (92%) and for identifying abnormal vascular territories was 43/52, (83%). Fourteen patients had exercise LVEF <50% and all had either prior myocardial infarction, myocardial infarction plus ischemia or LAD ischemia. Diagnostic planar perfusion images and exercise LVEF can be acquired in less than 4 min using ^{99m}Tc -teboroxime and a portable multicrystal scintillation camera.

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The prognostic value of the exercise ejection fraction acquired by the first-pass technique during bicycle exercise has been well demonstrated (1,2). Multivariate regression analysis performed on exercise data acquired in a large cohort of coronary patients with long term follow-up on medical therapy demonstrated that the exercise ejection fraction is the single most important variable predicting decreased event-free survival (2).

The technetium perfusion imaging agents offer the opportunity with a single bolus injection of radiotracer to combine measurements of both left ventricular ejection

fraction by the first pass technique and perfusion imaging. Studies combining treadmill exercise first pass using a portable multicrystal scintillation camera with tomographic perfusion imaging using sestamibi, an agent with minimal myocardial redistribution, have been reported (3, 4).

Teboroxime is another new technetium-based myocardial perfusion imaging agent. A member of the BATO (boronic acid adducts of technetium dioxime) complexes, teboroxime is a neutral, lipophilic agent with high myocardial extraction and rapid myocardial washout with a half-time of the predominant component of 5-10 min (5, 6). The tracer is excreted via the enterohepatic route and hepatic activity peaks at about 6 min following injection. Because of these pharmacokinetics, an optimized imaging protocol requires prompt onset of imaging following tracer injection and short image acquisition time (6 min or less).

It was hypothesized that both dynamic first-pass acquisition and planar scans can be acquired without moving the patient from the treadmill belt using a portable multicrystal scintillation camera. Phantom studies were performed to document the resolution of the collimators used for planar acquisitions, and 26 patients who underwent planar thallium perfusion imaging also underwent combined planar perfusion and treadmill exercise left ventricular ejection fraction acquisition following the injection of a bolus dose of ^{99m}Tc -teboroxime.

METHODS

Patient Selection

Twenty-six patients who underwent treadmill thallium stress and redistribution planar and tomographic perfusion imaging underwent combined function and planar perfusion imaging with ^{99m}Tc -teboroxime within 2 wk. All patients had defects on the stress thallium scans. There were 8 women and 18 men with a mean age of 60 ± 11 yr (range 39-77). Sixteen patients had a history of prior myocardial infarction. In addition, eight normal male volunteers with a mean age of 42 ± 5.5 yr (range 32-49) were studied. None had history of chest pain. None had ischemic ST-segment depression to an achieved heart rate of greater than 85% age predicted normal.

Phantom Study

The efficiency and resolution were measured for the 25.4 mm collimator and for the B + C collimator combination (45 mm)

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and the efficiency alone for the B collimator (18 mm) which was used only for dynamic first-pass acquisition. For efficiency measurements, a ^{57}Co flat field source was placed on a 3-in. thick flat foam laid on the collimator face and 60-sec acquisitions were made using a 60-keV window centered over the photopeak of ^{57}Co . Collimator resolution was measured with a line source phantom constructed with capillary tubes and graph paper. Four sources were positioned in a rectangular pattern for spatial calibration with a centered source. Each source contained approximately 450 μCi of [$^{99\text{m}}\text{Tc}$]pertechnetate. The pattern was placed diagonally on the collimator and data were acquired for 100K cts. The phantom images were processed in a similar manner to the planar clinical images. The processed data was displayed in gray scale (256 levels) and each image was "captured" for analysis on a Macintosh computer using the Image 1.41 program (NIH). The image analysis consisted of image rotation, calibration of pixel size, and measurement of five profiles from one source. The efficiencies and values for full width at half maximum (FWHM) for the collimators are shown in Table 1. The line sources were not uniform in displayed intensity, but showed a periodic variation in photon flux. The variations in intensities are sensitive to distance from the detector. Intensities varied by a factor of approximately 31% at 10 cm for the 45 mm collimator and 11% for the 25.4-mm collimator. This is believed to result from crystal separation and the lead septa in the collimators.

A human torso phantom was also imaged. The following concentrations of [$^{99\text{m}}\text{Tc}$]pertechnetate were used: 150 μCi in 350 cc to fill the left and right ventricular cavities, 800 μCi in 200 cc to fill the myocardial compartment into which two circular defects, 2 and 3 cm in diameter were placed, and 1 mCi into the 1-liter mediastinal compartment. These concentrations and ratios of activities were calculated from the known administered dose, myocardial percentage of cardiac output and first pass myocardial extraction of $^{99\text{m}}\text{Tc}$ -teboroxime. The myocardial to background ratios were calculated from patient scans (Fig. 1).

Exercise and Imaging Protocol

Patients and subjects were exercised on a treadmill using a Bruce or modified Bruce protocol. The Sim-400 camera was moved next to the treadmill. For the first 18 patients, a 25.4-mm collimator was used for both dynamic and planar acquisitions. For the remaining patients, a higher efficiency collimator ("B" collimator, 18 mm) was initially affixed to the detector for the first pass acquisition and a second collimator ("C" collimator, 27 mm) clipped onto the "B" collimator between dynamic and planar acquisitions. Prior to the onset of exercise the treadmill angle was increased to the maximal level achieved on the stress thallium study or to the expected level to be achieved by the volunteers (Bruce 4) and the patient asked to stand on the inclined treadmill in front of the camera detector to allow approximate positioning of the detector over the region of the patient's left

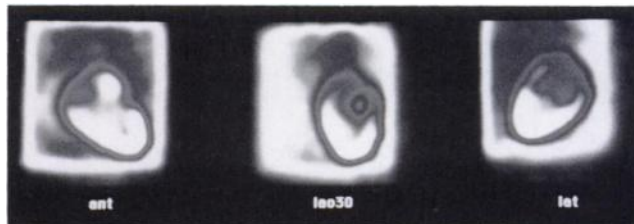


FIGURE 1. Human torso phantom filled with $^{99\text{m}}\text{Tc}$ and imaged in three views using the Sim-400 camera and processed in the same way patient scans were processed with sharpening filter and interpolated background subtraction. Two defects (2 and 3 cm in diameter) were placed in the myocardial compartment adjacent to one another and both can be seen on the phantom image.

ventricle at peak exercise. A ^{241}Am point source mounted onto a plastic clip was affixed on an ECG electrode and positioned over the sternum between the third and fourth intercostal spaces. An 18-gauge angiocatheter was inserted into a large right antecubital vein and attached to connecting tubing, a stopcock and 20 cc syringe filled with 15 cc normal saline.

The computer was set for a dynamic dual isotope acquisition using a 60-keV window centered on the 140-keV photopeak of $^{99\text{m}}\text{Tc}$ and a 40-keV window centered on the 60-keV photopeak of ^{241}Am , to be immediately followed by a series of planar images at 40 sec/image using the technetium window alone. The computer software allows for all the selections to be made and the studies set up before exercise is started.

During exercise the patient was allowed to move his/her upper body freely. Immediately prior to tracer injection, the patient was asked to move up on the belt and bring his/her anterior chest wall close to the detector surface and this position was maintained during bolus injection with the help of a technologist. At peak exercise, 15.6 ± 2.3 mCi of $^{99\text{m}}\text{Tc}$ -teboroxime was injected as a bolus through the angiocatheter using the 15-cc saline flush while dynamic dual-isotope data were acquired at 25 msec/frame for 1000 frames. The treadmill was then slowed and stopped. The "C" collimator was then clipped onto the "B" collimator. Tracer clearance from the blood pool was monitored and upright planar imaging was begun when the blood pool had cleared (less than 2 min after injection). The entire imaging sequence (dynamic first-pass plus planar imaging) was completed in less than 4 min. During this time, continuous 12-lead ECG monitoring was performed.

A heparin lock was attached to the angiocatheter and 1 hr later the patient returned for the rest injection. With the patient standing in front of the detector equipped with the higher efficiency ("B") collimator, 22.7 ± 3.4 mCi of $^{99\text{m}}\text{Tc}$ -teboroxime were injected as a bolus through the antecubital vein and dynamic first pass data acquired using the $^{99\text{m}}\text{Tc}$ window. Following completion of dynamic acquisition, the "C" collimator was added and three to four planar images were acquired for 40 sec per image beginning in the steep LAO projection.

Planar Image Processing and Interpretation

The planar images were processed before interpretation to minimize the effects of scatter from the liver. First, a sharpening filter was applied to the raw data and then an interpolative background subtraction algorithm was applied (Fig. 2) (7). The processed images were then interpreted by consensus of two

TABLE 1
Collimator Efficiencies and FWHM Values

Collimator	Counts (min)	FWHM at 0 cm (mm)	FWHM at 5 cm (mm)	FWHM at 10 cm (mm)
18 mm (B)	1,088,284	—	—	—
25.4 mm	410,903	9.8 ± 0.8	12.8 ± 0.8	18.2 ± 0.8
45 mm (B + C)	135,658	9.8 ± 1.0	12.0 ± 1.0	16.0 ± 1.6

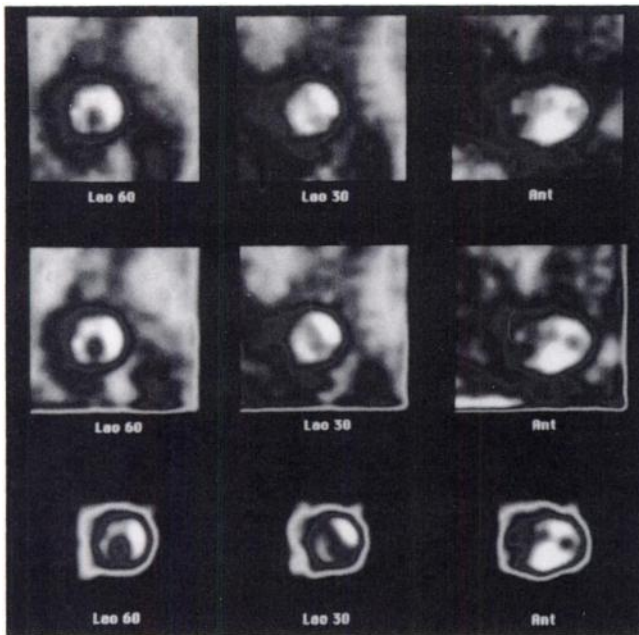


FIGURE 2. Forty-second planar images in three views. Raw images are displayed in the top row. Middle row displays the images that have been processed using a sharpening filter. Bottom row displays images that have undergone final processing step with interpolative background subtraction (see text).

investigators (LJ, RR) without knowledge of the thallium scan results. Planar scans in three views were divided into nine segments which were scored as normal, ischemia or infarction (Fig. 3). The segments were then grouped into two vascular territories, inferoposterior and anterior to better allow comparison between upright teboroxime imaging and supine thallium imaging. Apical defects were assigned to the anterior territory.

Planar thallium scans were divided into the same segments and grouped into the same vascular territories. The two sets of scans were compared with regard to presence, location and reversibility of defects.

First-pass Analysis

Raw first-pass dynamic dual-isotope data were processed using commercially available software. The data were motion corrected using both a point source correction algorithm (8) and a single

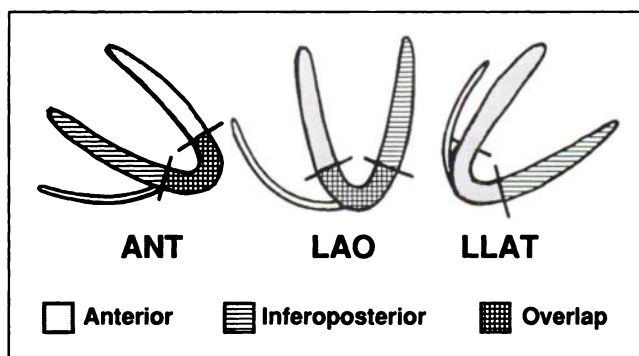


FIGURE 3. Three-view planar images are divided into nine segments for segmental correlation of defect localization and reversibility.

isotope centroid of activity algorithm. The data were temporally smoothed. The ejection fraction was calculated from the left ventricular time-activity curve using standard software. The images used to interpret regional wall motion were superimposed end-diastolic perimeter with end-systolic image and the regional ejection fraction image.

RESULTS

Counting Statistics

The first 18 patients had both planar imaging and dynamic first-pass imaging performed with the same 1" collimator, whereas the last 16 patients had dynamic first-pass acquisition performed using the higher efficiency 18-mm collimator and the planar imaging performed with two stacking collimators (18 + 27 mm). The comparative count data for the two collimators are the following. Total counts in the field of view for the first 40-sec planar image (almost entirely cardiac) using the 1" collimator were $444 \pm 190K$ cps, and for the stacking collimators $179 \pm 53K$ cps. The cps (first-pass acquisition) in the right heart for the 1" collimator were $70 \pm 6K$ and for the "B" (18 mm) collimator $147 \pm 35K$.

In four of the 34 studies, the dynamic exercise study was considered to be uninterpretable due to poor patient positioning or excessive patient motion. The bolus integrity was good in all studies. Corrected end-diastolic counts were low (<5000) for the 1" collimator but only two of these ejection fraction values were under 40%, a range in which the low corrected end-diastolic counts would put the study into a poor statistics range.

Planar Imaging

There was no statistically significant difference between the two treadmill stress tests for any of the following parameters: total treadmill time, peak heart rate or maximal systolic blood pressure. Mean total exercise time was 6.0 ± 2.3 mins for the thallium study and 5.7 ± 1.6 mins for the teboroxime study. Mean double product achieved on the stress thallium study was $23 \pm 6.4 \times 10^2$ and on the stress teboroxime study was $22 \pm 5.0 \times 10^2$. All of the normal volunteers were injected when they reached target heart rate.

There was a good agreement between the two imaging modalities for identifying an abnormal scan (24/26, 92%) and for identifying abnormal vascular territories in CAD patients (43/52, 83%) (Table 2). One patient had a reversible inferior wall defect on thallium imaging and normal perfusion on teboroxime imaging. One patient had normal planar thallium scans but a reversible inferolateral defect on teboroxime scans. Tomographic imaging in this case did show a reversible inferior perfusion defect.

With regard to defect reversibility, five defects that were fixed on thallium scans filled-in on second teboroxime injection. These occurred in three patients, all in territories of prior infarctions. Two defects were fixed on teboroxime scans but showed 4-hr redistribution on thallium scans. This occurred in one patient with no history of infarction

TABLE 2
Correlation of the Two Modalities in Identifying Abnormal Scans and Abnormal Vascular Territories

Anterior	Thallium	
	Normal	Abnormal
Normal Teboroxime	5	0
Abnormal Teboroxime	5	16

Inferoposterior	Thallium	
	Normal	Abnormal
Normal Teboroxime	6	2
Abnormal Teboroxime	2	16

but with reduced LVEF and regional dysynergy on the first-pass scan.

Among the normal volunteers, seven had normal exercise perfusion scans. One volunteer had an unequivocal anteroapical defect seen in the lateral view only that filled in on rest injection. This 46-yr-old man had a very low likelihood for having coronary artery disease because he was asymptomatic with <0.1 mV ST depressions at a peak heart rate of 177 and an exercise LVEF of 80%. In the absence of performing coronary angiography the meaning of this perfusion defect cannot be known, but in combination with other available data it seems most likely to represent a false-positive result.

Ejection Fraction Data

In 4/34 exercise studies, the dynamic first-pass data was uninterpretable due either to poor patient positioning (missing part of the left ventricle) or excessive patient motion and therefore 30/34 studies or 88% could be analyzed. One resting dynamic study was lost due to computer malfunction. LVEF data were divided into normal subjects (8), patients without prior myocardial infarction (9) and patients with history of prior infarction (17). Examples of combined perfusion and ejection fraction studies are displayed in Figures 4 and 5. The mean rest LVEF for the normal subjects was $64.7\% \pm 6.3\%$ (range 57%–72%) and the mean exercise LVEF was $73.0 \pm 4.0\%$ (range 69%–80%). The mean rest LVEF for the patients without myocardial infarction ($n = 9$) was $59.9\% \pm 9.5\%$ (range 40%–70%). The one patient with LVEF <50% (40%) had, in addition to coronary artery disease, chronic renal failure and hypertensive heart disease. The mean exercise LVEF for patients without myocardial infarction ($n = 8$) was $56.6\% \pm 10.9\%$ (range 42%–77%). One patient did not become ischemic either by symptoms or ECG changes, had normal planar thallium and teboroxime perfusion scans and had a normal exercise LVEF response (58%–77%). She was enrolled in the study because of a defect on SPECT thallium perfusion scans and catheterization documented single-vessel coronary artery disease. The mean rest LVEF for patients with prior myocardial infarction ($n = 16$) was $40.8\% \pm 10.5\%$ (range 25%–60%).

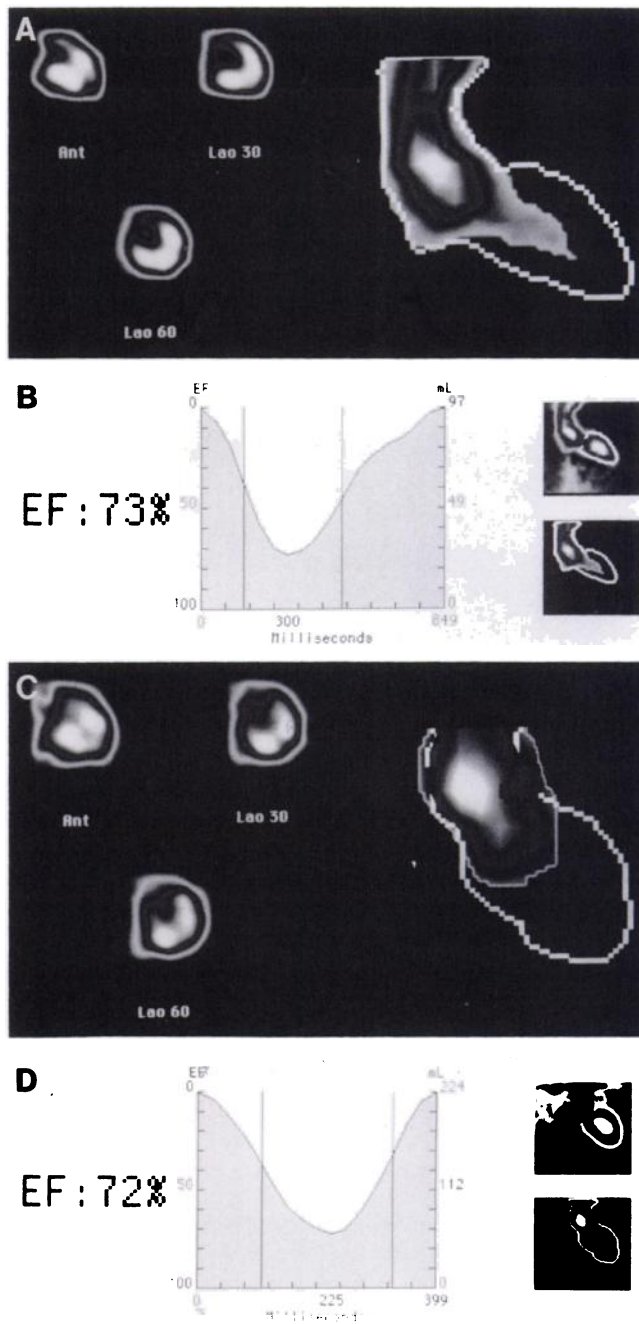


FIGURE 4. (A) Three resting planar images of normal volunteer are displayed on the left and end-diastolic perimeter plus end-systolic image on the right. (B) Time-activity curve plus end-diastolic and end-systolic regions. (C) Three exercise planar images of normal volunteer on left and end-diastolic perimeter plus end-systolic image on the right. (D) Time-activity curve plus end-diastolic and end-systolic regions. Perfusion, wall motion and ejection fraction values are normal.

The mean exercise LVEF ($n = 14$) was $42.5\% \pm 10.7\%$ (range 26%–64%).

Fourteen patients had exercise LVEF values less than 50%. Three of these 14 patients had prior myocardial infarction alone without scan or ECG evidence for ischemia and a rise in LVEF from rest to exercise of more than

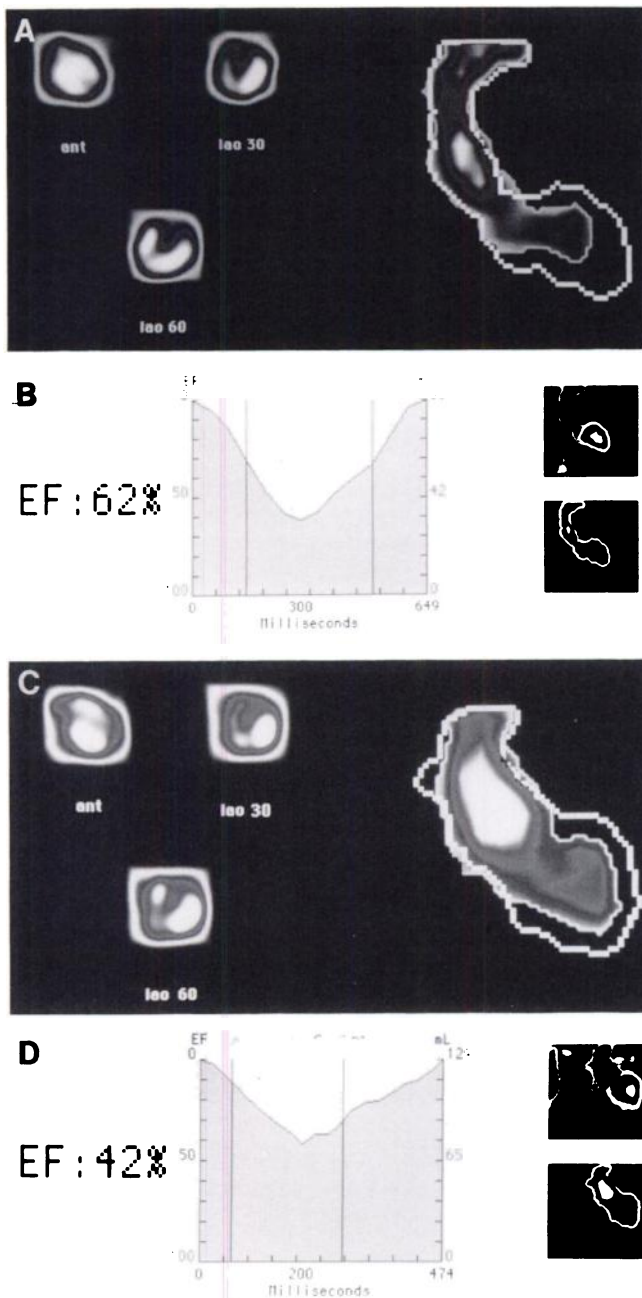


FIGURE 5. Three resting planar images of a patient are displayed on the left and end-diastolic perimeter plus end-systolic image on the right. (B) Time-activity curve plus end-diastolic and end-systolic regions. (C) Three exercise planar images of same patient on left and end-diastolic perimeter plus end-systolic image on the right. (D) Time-activity curve plus end-diastolic and end-systolic regions. Perfusion and wall motion at rest show mild anterior hypokinesis and septal hypoperfusion. With exercise, the anterior perfusion defect and regional dysynergy became more marked and extensive and the LVEF fell from 62% to 42%.

5%. Nine of these 14 patients had infarct and ischemia either in the vascular territory of the prior infarct or in another vascular territory. In eight of the nine patients, the change in LVEF from rest to exercise was less than

5%. One of these 14 patients had LAD ischemia alone and one had co-existing hypertensive heart disease.

DISCUSSION

The technique of bolus injection of [^{99m}Tc]pertechnetate at peak bicycle exercise with dynamic first-pass acquisition using a multicrystal scintillation camera has been pioneered by the group at Duke University (1,2). These investigators followed for a mean of 5.4 yr a large group of medically treated patients with angiographically documented coronary artery disease from the time of bicycle exercise first-pass angiography (2). With use of the Cox regression model, the most important variable among all the exercise data to predict hard cardiovascular events was the exercise ejection fraction. The first-pass technique was further applied to treadmill exercise using a second isotope with a photopeak widely separate from that of ^{99m}Tc for motion correction (7). Borges-Neto et al. reported combined first-pass treadmill exercise ejection fraction measurements and tomographic imaging both in normal volunteers and in patients with coronary artery disease using sestamibi and a portable multicrystal scintillation camera (Sim-400) (3,4).

Teboroxime like sestamibi is a new technetium-based myocardial perfusion imaging agent. However, the pharmacokinetics of teboroxime that determine its optimal imaging protocols are very different from the pharmacokinetics of either sestamibi or ^{201}Tl . Sestamibi washes out of the heart very slowly and unlike thallium shows no clinically significant redistribution (9). Because of the microsphere-like characteristics of sestamibi, imaging is delayed until 30–60 min after injection. It is excreted via the enterohepatic route, but due to the long myocardial residence time, imaging can be delayed until after major clearance of hepatobiliary activity. In contrast, teboroxime has a high first-pass myocardial extraction but a rapid myocardial washout, with a half-time of the major component of the biexponential washout curve (>60%) of 5–10 min (6). The tracer is excreted via the enterohepatic route and liver activity peaks at about 6 min following injection. Upscatter from the liver into the region of the inferior wall of the left ventricle can interfere with interpretation of inferior wall perfusion (6). Optimized imaging protocols therefore include a total imaging time of less than 4 min for planar imaging and less than 6 min for SPECT imaging (10,11). Imaging must be started within 2 min of tracer injection.

A complete dynamic first-pass acquisition at 25 msec/frame for 1000 frames takes at least 25 sec to complete, further shortening the time between treadmill and camera. Therefore, from a practical standpoint, to successfully combine dynamic first-pass acquisition and perfusion imaging from a single injection of teboroxime, it seemed necessary to perform both the dynamic first pass acquisition and perfusion imaging with the same camera.

Initially a single collimator was used for both dynamic

first-pass and planar imaging. The dynamic first-pass studies were count poor, whereas the 40-sec planar scans had high counts. The stacking collimators were then designed to allow rapid change from high efficiency collimation to higher resolution collimation by addition of a clip-on collimator. Subsequent patient and phantom data bore out the superiority of the stacking collimators over the 1-in. collimator for better counting statistics on the dynamic first-pass studies and slightly better resolution of planar images.

The agreement values between teboroxime and thallium planar image interpretation for both patients and vascular territories correlate well with values reported by other investigators using optimized (short) planar imaging protocols (10,12).

In addition to prognostic information provided by the exercise left ventricular ejection fraction, clinically important information may be obtained from the combined planar perfusion and ejection fraction data. Among patients with prior myocardial infarction, the ejection fraction response to exercise in addition to the planar scan results may help differentiate infarct alone from infarct plus ischemia. This short combined perfusion/function test may find a clinical place in evaluating predischarge post-myocardial infarction patients. From a single study, the rest and exercise LVEF, planar scans and treadmill time can be obtained. These are all parameters documented to be prognostically important in the post-myocardial infarction patient (13-16). Other patient groups in whom this combined test may be clinically useful are patients with either exertional dyspnea or exertional hypotension in whom a cardiac etiology must be sought. In addition, this test can help reveal left ventricular dysfunction out of proportion to the degree of coronary artery disease (based on perfusion defects) and point towards coexisting primary myocardial disease.

In summary, this paper describes a method for combining dynamic first-pass ejection fraction data acquisition and planar perfusion imaging from a single injection of a technetium-based myocardial perfusion agent with rapid myocardial washout using a multicrystal scintillation camera. With the use of stacking collimators, high count rate dynamic first-pass statistics were achieved. The rapid addition of a second collimator gave good resolution planar images that were of diagnostic quality and their interpretation compared well with the results of thallium scans

performed within 2 wk. The entire study, including two sets of dynamic and planar images (stress and rest injections), is completed within 1 hr.

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