Myocardial Perfusion Imaging with Technetium-99m SQ30217: Comparison with Thallium-201 and Coronary Anatomy

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Myocardial perfusion in ten normal volunteers and 20 patients with coronary artery disease documented by recent coronary arteriography was studied with ^{99m}Tc-labeled SQ30217 and ^{201}Tl. Plantar ^{201}Tl imaging followed standard treadmill exercise and planar SQ30217 imaging followed upright bicycle exercise, performed to angina, or the same double product achieved on the treadmill test. Upright anterior, 30° left anterior oblique, and 60° left anterior oblique images were obtained for 3, 6, and 9 min, respectively, starting 2 min after injection of 15 mCi of ^{99m}Tc SQ30217. A second 15-mCi dose was injected at rest ~ 2 hr later, and the same imaging protocol was followed. No adverse reactions or laboratory abnormalities attributable to SQ30217 were observed. All scans on the normal volunteers were interpreted as normal. Qualitative readings of both tests were equally sensitive for detecting patients with coronary disease (SQ30217 - 16/20, Tl - 17/20, p=NS) and identifying abnormal vessels (SQ30217 - 19/45, Tl - 21/45, p=NS). Both agents were falsely positive in 1/15 vessels. Ten vascular regions showed persistent abnormalities on resting SQ30217 scans; eight of these were distal to stenoses of at least 90% and three were also abnormal on thallium redistribution images. Hepatic uptake of SQ30217 obscured inferoapical segments in some views in 14/20 patients but did not interfere with abnormal vessel identification.

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Exercise myocardial scintigraphy is a useful tool for diagnosing and assessing the severity of coronary artery disease (CAD) and/or assessing the physiologic significance of a known stenotic lesion. Thallium-201 (^{201}Tl) is currently the most widely used radiopharmaceutical for perfusion scintigraphy. However, thallium is not an ideal agent because of a low gamma photopeak energy that limits resolution, a relatively long half-life that limits the administered dose, and its high cost.

Technetium-99m (^{99m}Tc) has much more favorable imaging and dosimetry characteristics, spurring radiochemists to develop a technetium-labeled myocardial perfusion imaging agent. SQ30217 (Cardiotec, Squibb Diagnostics, Princeton, NJ) is a boronic acid adduct of technetium oxime (BATO), one of a class of neutral lipophilic ^{99m}Tc-labeled compounds. This agent has been shown to have high myocardial extraction, low lung uptake, and rapid blood clearance in a Phase I evaluation of biodistribution and cardiac imaging (*1*). Myocardial uptake was rapid with excellent myocardial visualization at 2 min after injection. Myocardial clearance was also rapid, showing biexponential clearance with half-times of 2 min (68%) and 78 min (32%) (*2*). Blood clearance was rapid with only 9.5% of the dose remaining in the circulation 15 min after injection. Significant uptake was observed in the hepatobiliary system, which is the major route of excretion. Radiation dosimetry showed that the liver and intestine were the target organs.

The purpose of this Phase II study was to compare ^{201}Tl and SQ30217 planar myocardial imaging in normal volunteers and patients with coronary artery disease to compare the two methods for detecting the presence of CAD and for identifying abnormal vessels, and to obtain additional information on myocardial tracer kinetics in man.

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MATERIALS AND METHODS

Patient Population

Thallium exercise and redistribution scans and SQ30217 exercise and rest scans were performed in 33 subjects. All gave informed consent to participate in the study, which had been reviewed and approved by the Institutional Review Board. Ten young healthy male volunteers (mean age 26 yr) without risk factors for CAD served as a normal group. The remaining 23 participants (19 males, four females; mean age 55±9 yr, range 35–68 yr) had ^{201}Tl stress imaging for clinical indications. None had a history of prior infarction. All of the patients except one (who was excluded from further analysis) had coronary arteriography documenting the extent of CAD. The mean time interval between the thallium and SQ30217 studies was 14±21 days. Single plane coronary arteriography was performed in 22/23 of the patients. The mean time between the SQ30217 study and arteriography was 21±21 days.

Exercise and Image Acquisition Protocols

Exercise myocardial perfusion scintigraphy with ^{201}Tl was performed using a treadmill and the Bruce protocol. For normal subjects exercise was limited by fatigue or achievement of 85% of age-predicted maximum heart rate. In the patient group exercise was limited by angina, dyspnea, and/or fatigue. A 2.2 mCi dose of ^{201}Tl was then injected and exercise continued for 1 additional minute. The patient was placed under a gamma camera and 10-min 128×128 pixel images were acquired in the 30° left anterior oblique (LAO), anterior, and 60° LAO projections. Four hours later redistribution images were obtained in the same views with a 14-min acquisition time per view.

Exercise SQ30217 imaging was performed following bicycle exercise. The patient was seated upright on an ergometer table. A gamma camera was positioned in the anterior view using a transmission source to localize the heart. Continuous upright graded bicycle exercise was performed starting at a workload of 150 kpm and increasing in steps of 150 kpm every 3 min until the achievement of the same double product reached on the thallium stress test or to typical angina. At peak exercise 15 mCi of ^{99m}Tc SQ30217 was injected and exercise continued for 90 sec at a reduced work load. Dynamic 128×128 pixel imaging in the anterior projection at 10 sec/frame was started at the time of injection and continued for 5 min. The camera was then repositioned into the 30° LAO projection and a 6-min dynamic acquisition was obtained, followed by a third acquisition of 9 min in the 60° LAO projection. The imaging times were selected to achieve similar left ventricular counts in the three projections, taking into account the myocardial washout rate. The time interval between each of the sequential acquisitions was 30 sec.

Approximately 2 hr after the exercise injection, the subject was again seated on the bicycle. Residual hepatic activity was used as a landmark to position the patient for the initial anterior view. A second 15-mCi injection of SQ30217 was given, and the same imaging protocol as described above was used. Vital signs and ECG were monitored in all subjects before, during, and after SQ30217 imaging.

SQ30217 Preparation

SQ30217 was supplied in kit form as a lyophilized powder in sterile evacuated vials. Seventy-five millicuries of ^{99m}Tc in 1 cc of 0.9% NaCl were added to the contents of the vial. Only eluate from a generator that had been previously eluted at least once was used. The vial was shaken for 1 min, placed in a 100°C water bath for 15 min, and then allowed to cool. Both exercise and rest injections were made from the contents of the same vial. Fifteen millicuries doses were drawn from the vial just prior to each injection.

The presence of free pertechnetate and reduced hydrolyzed technetium species was monitored with paper chromatography. One drop of the preparation was placed on each of two 1.3 cm × 11 cm Whatman 31ET strips. One strip was developed in normal saline while the other was developed in a 50:50 (by volume) normal saline/acetone solution. The criterion for injection was that the sum of free and reduced technetium species be <10%; the mean bound activity in our group was 92.6 ± 2.3 %.

Image Processing and Analysis

The dynamic SQ30217 images were summed, excluding the initial 2 min of blood-pool activity on the anterior view. This process yielded images in the anterior (3-min summation), 30° LAO (5-min summation), and 60° LAO (6-min summation) projections, which were displayed using a linear black-and-white scale. Upper and lower threshold values were individually set for each image so that background activity adjacent to the myocardium was almost completely eliminated and so that the area of the myocardium with the greatest activity was displayed at maximum intensity.

Thallium-201 and SQ30217 exercise and redistribution/rest images were interpreted by three independent observers who were unaware of the results of the other studies. Disagreements in interpretation were resolved by consensus review of the images. Regional perfusion abnormalities seen on the scans were assigned to one of ten wall segments corresponding to the vascular distribution illustrated in Figure 1, and were correlated with the angiographic findings. Paired comparisons between ^{201}Tl and SQ30217 scans were performed using McNemar's test (*3*).

The rate of washout of SQ30217 activity from the myocardium was evaluated by using a myocardial region of interest drawn from the summation image in each view to generate a three-phase (one phase for each view) myocardial time-activity curve. The regions were drawn to exclude overlapping hepatic activity. A sample curve us shown in Figure 2. A monoexponential curve was fitted to the first 3 min of each phase (anterior view, 2–5 min; 30° LAO, 5.5–8.5 min; 60° LAO, 12–15 min) to generate a net clearance half-time for that phase.

RESULTS

Detection of CAD and Vessel Identification

Normal subjects. No abnormalities in myocardial perfusion were seen in either the ^{201}Tl or SQ30217 studies performed on the normal volunteers. Exercise thallium scans showed a mean of 102k counts over the myocardium, dropping to 86k on the redistribution images. Exercise SQ30217 scans had mean myocardial counts of 107k, 143k, and 171k, respectively, for the three summed images, which increased by ~100k counts on the subsequent resting studies. The SQ30217

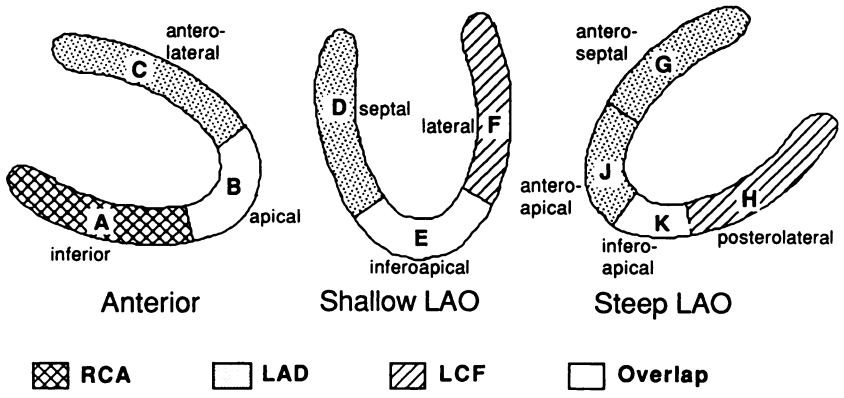

FIGURE 1
Diagram of planar myocardial images showing the wall segments that were evaluated and the corresponding coronary arterial supply.

scans showed increasing hepatic activity over the course of each imaging study and significant residual hepatic activity from the exercise study on the subsequent resting scan (Fig. 3). This activity precluded visualization of 9/100 segments on the exercise scans and 16/100 segments on the rest scans. The nonvisualized segments were in the inferoapical regions on either the shallow or steep LAO view. In all cases the vascular territory involved was visualized on another image.

CAD Patients

Scan data were analyzed for 20 of the 23 patients injected with SQ32017 during exercise. Three patients were excluded from analysis: one patient did not have coronary arteriography; one patient moved during the anterior image acquisition, which was the only projection that showed a thallium perfusion defect; and one patient did not perform sufficient exercise to raise her heart rate above 100 on either the SQ30217 or thallium exercise study. Perfusion abnormalities were seen on the ^{201}Tl studies of 17/20 (85%) patients and on the SQ30217 studies of 16/20 (80%) patients (Fig. 4). This difference was not statistically significant. The exercise studies alone in all cases were sufficient to identify these abnormalities. Relatively intense hepatic uptake obscured inferoapical segments in the SQ30217 studies of 15/21 patients. However, these segments were seen in multiple views and in no case did we fail to identify a vascular abnormality because of an obscured segment.

Coronary arteriography revealed 45 coronary arteries with significant (>70%) stenoses in the patient group analyzed. Three patients had single vessel disease, nine had double vessel disease, and eight had triple vessel disease. Seventeen LAD vessels were abnormal, 15 RCA vessels were abnormal, and 13 LCF vessels were abnormal. The true-positive and false-positive rates for each perfusion agent are shown in Table 1. SQ30217 showed a relatively greater sensitivity for LAD lesions and a

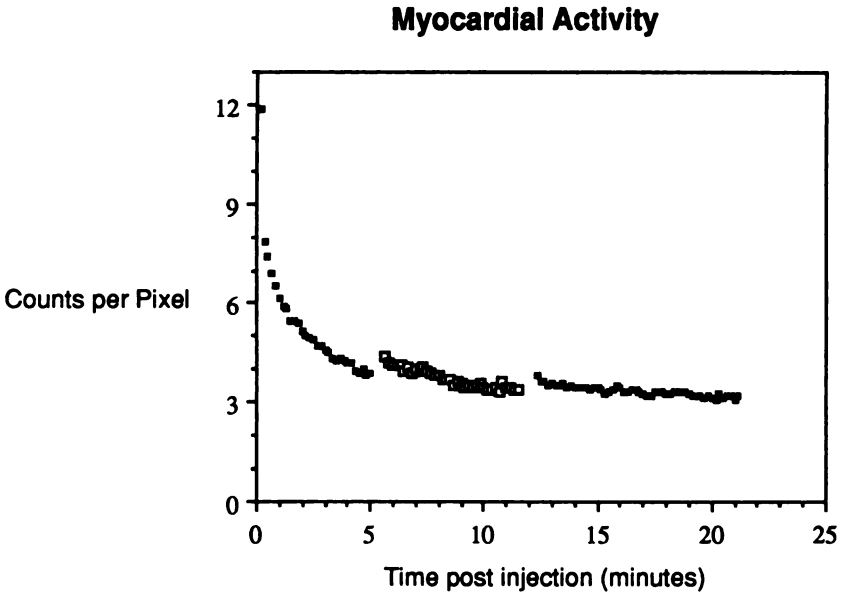

FIGURE 2
Time-activity curve over the myocardium following the injection of ^{99m}Tc SQ30217 during exercise. The points represent counts in each 10-sec interval during the anterior, 30° LAO, and 60° LAO acquisitions. The breaks in the curve (shown by the change in plot symbol) occurred each time the camera position was changed. Following blood-pool clearance and decay of the fast clearance component, the change in myocardial activity is small.

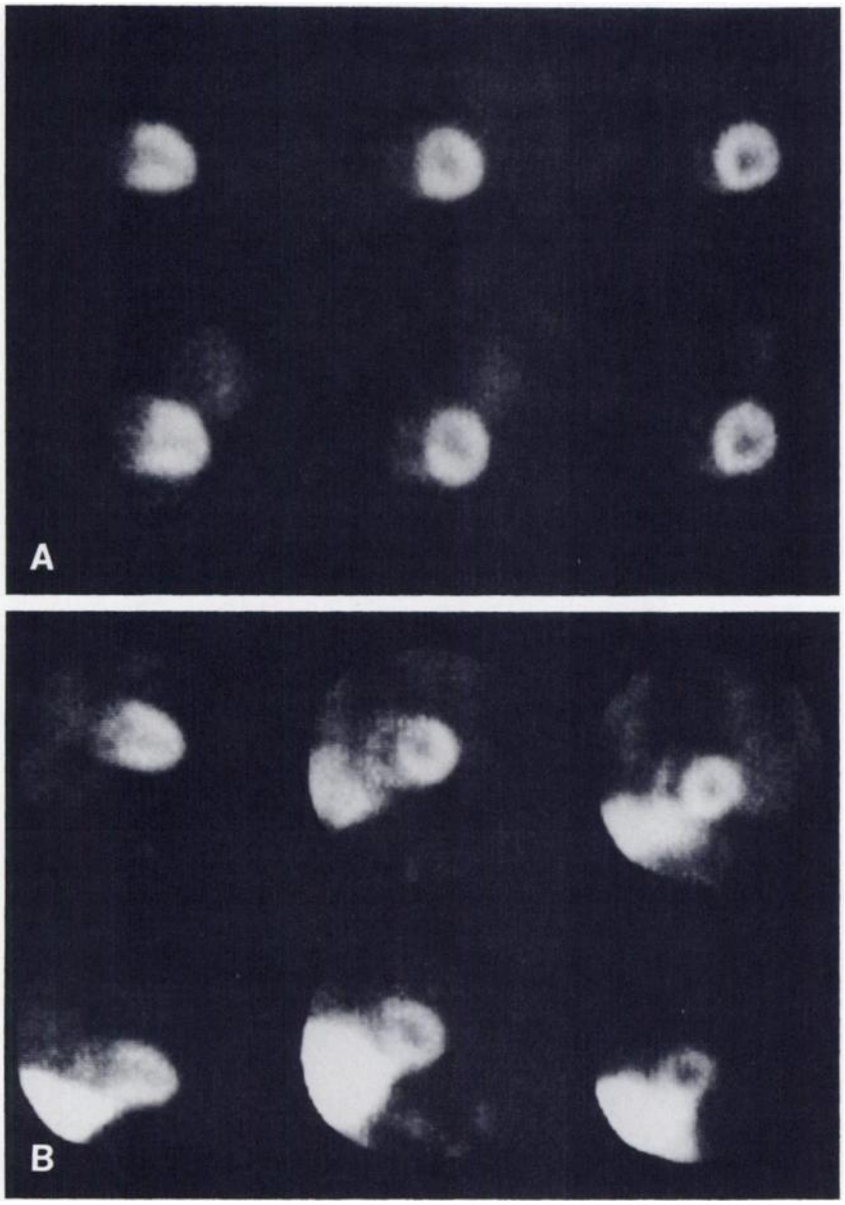

FIGURE 3
A: Normal thallium exercise (top) and redistribution (bottom) images in the anterior, 30° LAO, and 60° LAO views. B: Corresponding normal SQ30217 exercise (top) and rest (bottom) images. The progressive increase in hepatic activity during imaging is evident. Residual hepatic activity from the initial injection makes the liver more prominent on the resting views.

relatively lower sensitivity for RCA and LCF lesions as compared to ^{201}Tl in patients with multivessel disease, but with this small patient sample there were no statistically significant differences between the two agents for the identification of abnormal vessels.

Comparison of Thallium Redistribution with SQ30217 Rest Images

Although none of the patients had history of ECG evidence for prior infarction, three thallium scans showed minimal redistribution and ten SQ30217 scans (which included the three thallium abnormalities) showed persistent perfusion abnormalities on the rest scans ($p<0.05$) (Fig. 4). Eight of these ten persistent SQ30217 abnormalities (including the areas also abnormal by thallium) occurred in vascular territories distal to a stenosis of at least 90%.

SQ30217 Myocardial Washout Rates

Mean myocardial washout half-times for the three exercise and rest views, corresponding to increasing time after injection, are shown in Table 2. There were no significant differences in washout rates between the normal volunteers and the CAD patients except for the last phase of the second (resting) study, for which the CAD patient washout rate was significantly ($p<0.01$) longer than for the normal group (50 min vs. 31 min). For normal volunteers, during the last phase (12–15 min postinjection) of the study there was no significant difference between the exercise and resting washout rates; for the earlier phases exercise washout was significantly faster than rest washout (2–4 min: $p<0.005$; 5.5–8.5 min: $p<0.02$). Exercise washout was significantly faster than rest washout during all phases for the group of patients with CAD.

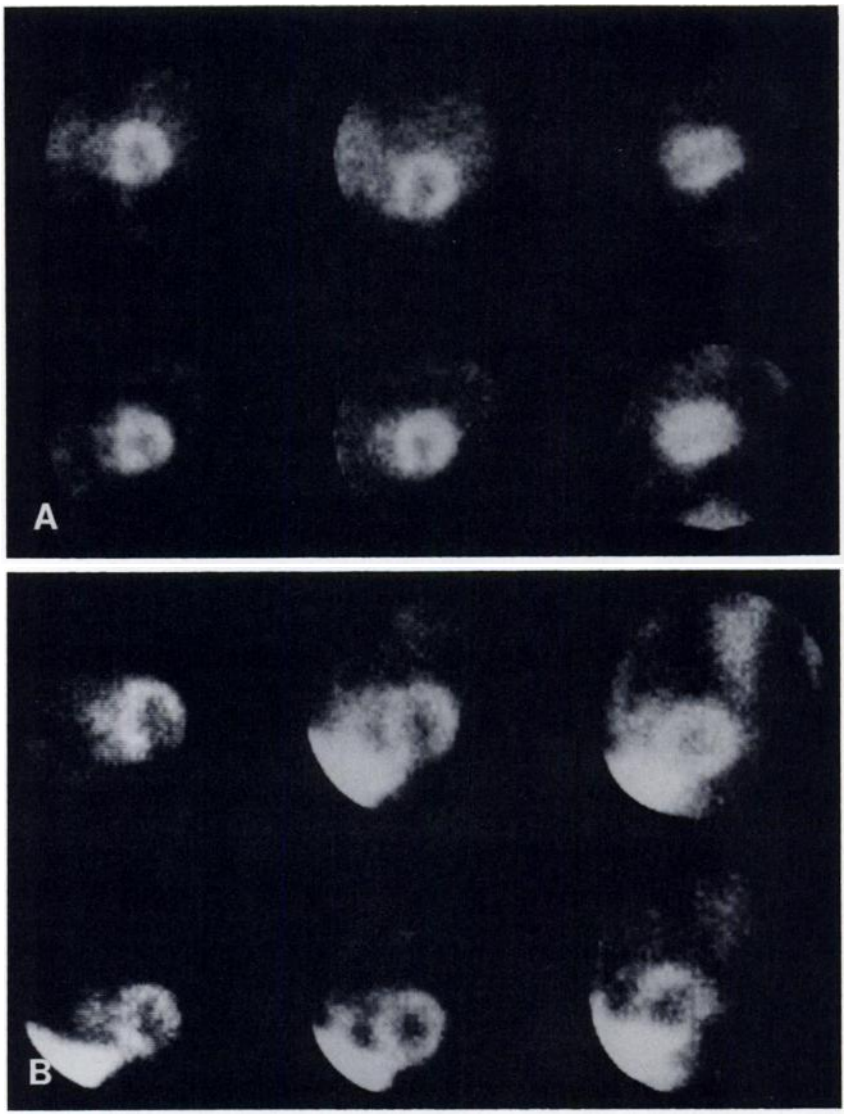

FIGURE 4
A: Thallium exercise (top) and redistribution (bottom) images in the anterior, 30° LAO, and 60° LAO views in a patient with 99% occlusion of the LAD. There is increased lung activity and decreased perfusion of the septum, anterolateral wall, and apex at exercise. A persistent apical defect remains on the redistribution images. B: Corresponding SQ30217 exercise (top) images show the same areas of decreased perfusion. The rest (bottom) images show a apical defect only on the anterior image. Hepatic activity on the steep oblique view obscures the inferoapical segment on the exercise image and the anteroapical and inferoapical segments on the rest image.

Adverse Reactions/Laboratory Parameters

The results of blood chemistry and hematology tests obtained before and after administration of ^{99m}Tc SQ30217 showed no differences that were attributed to tracer administration. Most of the individual postinjection values showed less than a 10% change from baseline measurements. None of the individual postinjection laboratory results were in the abnormal range with the exception of a patient with chronic active hepatitis, whose baseline liver function tests were abnormal, and who showed less than a 10% change postinjection. There also were no significant changes in either the mean or individual values for vital signs. No adverse effects attributable to the radiopharmaceutical were detected. Early in the study, one patient and one subject experienced vasovagal episodes because of the necessity of maintaining an upright posture, sitting on an unpadded bicycle seat for ~40 min. This problem was remedied by padding the bicycle seat and asking the patient to continue to slowly move the bicycle pedals (without ergometer resistance) throughout the imaging.

TABLE 1
Abnormal Vessel Identification

		^{201}Tl	SO30217
LAD	True +	6/17 (35%)	10/17 (59%)
	False +	0/3 (0%)	1/3 (33%)
RCA	True +	9/15 (60%)	5/15 (33%)
	False +	0/5 (0%)	0/5 (0%)
LCF	True +	6/13 (46%)	4/13 (31%)
	False +	1/7 (14%)	0/7 (0%)
ALL	True +	21/45 (47%)	19/45 (42%)
	False +	1/15 (7%)	1/15 (7%)

DISCUSSION

Thallium-201 myocardial perfusion scintigraphy is a valuable means for detecting the presence of significant

TABLE 2
Myocardial Washout Rates

	Normal volunteers	CAD Patients	
Exercise washout $T_{½}$			
Anterior	6.6 ± 0.7*	7.0 ± 1.8*	NS.
LAO 30	15.1 ± 1.9†	14.4 ± 3.7†	NS.
LAO 60	32.2 ± 13.1‡	34.9 ± 21.4†	NS.
Rest washout $T_{½}$			
Anterior	9.1 ± 2.3*	9.4 ± 2.8*	NS.
LAO 30	22.0 ± 7.1†	18.5 ± 5.2†	NS.
LAO 60	30.8 ± 9.5‡	49.7 ± 17.3†	$p < 0.01$

Exercise vs. rest: * $p < 0.005$.
† $p < 0.02$.
‡ p = NS.

myocardial ischemia by comparing exercise and redistribution studies. There are several major limitations to the use of thallium. It has a long physical half-life restricting the total dose that can be administered to patients which limits the count rate that can be achieved, thus requiring relatively long scanning times of from 30 to 45 min. Slow myocardial clearance precludes true exercise and rest imaging studies from being performed on a single day. Redistribution images taken several hours after the exercise scan in most cases approximate the distribution of activity that would be seen on an injection made at rest. However, incomplete redistribution may make it difficult to distinguish between infarction and ischemia, and rapid redistribution may hide ischemic zones before they can be visualized. The necessity for the patient to refrain from eating until the redistribution images are completed and the length of the entire procedure are also undesirable. The principle emitted gamma photon range (Hg x-rays) is not optimal for Anger camera imaging, and the cost of thallium is relatively high.

Technetium-99m has superior imaging and dosimetry characteristics as compared to thallium and is readily available in nuclear medicine/nuclear cardiology labs. Suitable technetium-labeled myocardial imaging agents have been sought after for some time. Some radiopharmaceuticals which showed promise in animal models yielded disappointing results in humans (*4*). More recently, myocardial perfusion images similar to those obtained with thallium have been obtained with a new class of monocationic technetium-labeled pharmaceuticals, the isonitriles, the most promising of which is ^{99m}Tc MIBI (*5*). This agent enters the myocardium by passive diffusion and remains within the myocardium for a prolonged period of time due to binding to intracellular protein. Relatively little redistribution occurs (*6*).

In contrast to these cationic agents, ^{99m}Tc SQ30217 is a neutral lipophilic compound. It is a boronic acid adduct of technetium oxime (BATO), a class of compounds which are formed by template synthesis (*7*). In isolated perfused rabbit hearts, Meerdink et al. have shown that over a wide range of myocardial blood flow rates the myocardial extraction for ^{99m}Tc SQ30217 is significantly higher than that of ^{201}Tl or ^{99m}Tc MIBI (mean 0.76 ± 0.09 vs. 0.62 ± 0.09 vs. 0.30 ± 0.10, $p<0.001$) (*8–10*). In addition, ^{99m}Tc SQ30217 had a significantly greater capillary permeability-surface area product than ^{201}Tl or ^{99m}Tc MIBI, suggesting that it might be a better indicator of myocardial perfusion. These preclinical studies suggested that SQ30217 had the potential to be a good myocardial perfusion imaging agent.

Early Phase I biodistribution studies performed by Coleman et al. (*2,11*) demonstrated myocardial visualization by 1 min postinjection, with peak myocardial uptake of 2.3±0.8% of the injected dose. Blood levels of SQ30217 declined from 39% of the injected dose at 90 sec to 9.5% at 15 min. Myocardial washout followed a biexponential washout pattern with a 2-min fast component and a 78-min slow component. The target organs were the liver (0.12 rad/mCi) and the large bowel (0.11 rad/mCi).

The present study was designed as a trial to evaluate the safety and efficacy of ^{99m}Tc SQ30217 to detect CAD by planar imaging in a larger group of normals and patients with CAD. There were no significant changes in vital signs of laboratory parameters following injection of ^{99m}Tc SQ30217, and no patient or subject noted any adverse symptom. Our protocol used upright bicycle exercise so that we could monitor radiopharmaceutical kinetics by beginning imaging from the moment of injection, while minimizing splanchnic uptake. The high administered dose possible with a ^{99m}Tc-labeled tracer allowed statistically satisfactory images to be obtained from successive 3-, 6-, and 9-min data collection times following clearance of the initial blood-pool activity. We saw no difference between qualitative interpretations of SQ30217 and ^{201}Tl studies in their ability to detect the presence of coronary artery disease. In patients with multivessel disease SQ30217 scans appeared to be superior for detection of LAD lesions while ^{201}Tl detected more RCA and LCF lesions, but these differences did not achieve statistical significance.

Hepatic activity is initially low, but rapidly increases relative to the heart so that hepatic activity is dominant by 5–10 min. In some patients, hepatic activity projecting over the diaphragmatic surface of the heart precluded adequate visualization of the anteroapical and inferoapical segments of the myocardial wall on the steep oblique view. This problem was more pronounced following the second injection of tracer, since a significant amount of residual hepatic activity from the first injection was already present. This limitation did not affect identification of abnormal vessels in our series

since all abnormal vessels produced defects in other, visualized wall segments.

SPECT imaging may decrease hepatic interference with visualization of the myocardium. Cardiac SPECT imaging should not begin until 10 min after exercise because of the changing position of the heart prior to that time ("cardiac creep") (*12*). The short T½ of the fast component of myocardial washout means that almost 95% of the activity remaining at 10 min after injection is due to the slow (78 min) clearance component. The myocardial activity from technetium-labeled SQ30217 would therefore be changing slowly after this time. There would still be a high photon flux (~19k cts/min) as compared to thallium (~10k cts/min) that would permit a short (5–10 min) SPECT acquisition time.

A possible limitation in the use of SQ30217 is the persistence of abnormalities on resting studies following the exercise scans. While these persistent defects do not hinder the detection of the presence of coronary artery disease, it may be difficult to distinguish between ischemia and infarction. This Phase II study was performed employing only an exercise-rest imaging protocol. It is possible that activity from the second (resting) injection was unable to completely mask an initial exercise perfusion defect; 80% of persistent defects in this study were in regions distal to high-grade (>90%) stenoses which would be expected to produce the greatest exercise perfusion deficits. Such results have been reported with same-day exercise-rest MIBI tomographic imaging protocols (*13*), in which rest defects present on the exercise-rest images were not seen when the resting scan was performed first. The longer washout period for the late resting views in the patients with coronary disease may also be due to the influence of residual activity from the initial injection, although in the absence of studies of the mechanisms of uptake and washout of SQ30217 in ischemic myocardium a true pharmacologic effect cannot be excluded.

All three myocardial perfusion imaging agents—SQ30217 thallium, and technetium-labeled MIBI—may find a place in clinical use. The technetium-labeled agents have more favorable imaging and dosimetry characteristics, resulting in a sufficiently high photon flux to permit first transit ventricular function studies with bolus injection of the radiopharmaceutical (*14*). SQ30217 allows more rapid completion of exercise and resting myocardial perfusion studies than thallium, and the use of two independent injections provides greater flexibility in scheduling the exercise and rest imaging studies. This agent may be well suited for use in conjunction with SPECT imaging. SQ30217 may also prove particularly attractive to those laboratories that currently do bicycle exercise ventricular function studies to diagnose ischemia, permitting visualization of myocardial perfusion without major changes in the exercise protocol. The prolonged myocardial residence time of MIBI permits visualization of myocardial perfusion at a time remote from the injection, which could be of particular use in studying acute ischemic syndromes and the effect of interventional procedures. Thallium may still have a role because of the extensive experience with its use for standard treadmill exercise testing with subsequent exercise and redistribution imaging.

In summary, ^{99m}Tc SQ30217 is a new myocardial perfusion imaging agent which has rapid myocardial uptake, allowing imaging to begin within 2 min following injection. Myocardial clearance is relatively rapid, so that a second study can be performed within 2 hr. A planar exercise and rest ^{99m}Tc SQ30217 study can be completed faster than planar exercise and redistribution ^{201}Tl images, and in this limited series using qualitative analysis was equally sensitive for detecting coronary artery disease. Hepatic uptake may interfere with visualization of some myocardial segments, especially on steep oblique views following the second injection. The agent may be well suited for SPECT imaging, which may overcome this hepatic interference with myocardial visualization.

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