An Optimized Protocol for Detection of Coronary Artery Disease Using Technetium-99m-Sestamibi

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This is the second article in the four-part series on "New Radiopharmaceuticals." Upon completion of this article the reader should be able to: (1) identify imaging characteristics of technetium-99m-sestamibi and (2) understand the reconstruction and processing protocol.

Thallium-201 (^{201}Tl) has been the agent used in imaging myocardial perfusion. To circumvent the physical limitations of ^{201}Tl (low-energy photons, long half-life), technetium-99m-(^{99m}Tc) labeled myocardial perfusion agents have been sought. Technetium-99m-sestamibi* (Cardiolite, Du Pont de Nemours, N. Billerica, MA) was found to exhibit properties which offer several advantages over ^{201}Tl for myocardial perfusion imaging. These include higher energy emission, shorter half-life, higher administrable activity and absence of significant redistribution several hours after injection (*1*). In addition, these properties make it possible to assess not only myocardial perfusion, but also function (including first-pass ejection fraction) with a single injection (*2*).

The superior imaging characteristics of ^{99m}Tc-sestamibi over ^{201}Tl are only fully realized if the technical aspects associated with single-photon emission computed tomography (SPECT) of the myocardium are optimized. Our institutions have developed image processing parameters to fully utilize the improved imaging qualities of ^{99m}Tc-sestamibi (Fig. 1).

Acquisition parameters for single-detector camera systems were developed by using phantom studies. Reconstruction parameters were initially defined using phantom studies and then refined further by using clinical data. By employing first-pass acquisition (both at rest and during exercise), wall motion and ejection fraction information is obtained, improving the diagnostic interpretation of the patient's study. A same-day protocol as well as a two-day protocol are compared in this article.

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Imaging sequence can be particularly flexible in that both same-day or two-day protocols can be used. The radiopharmaceutical dose depends upon which protocol is employed. Preparation and quality control of ^{99m}Tc-sestamibi are shown in Table 1.

MATERIALS AND METHODS

Optimization of the acquisition parameters for single-detector camera systems was performed using phantom studies where the contrast of simulated perfusion defects and uniformity of normal slices were used as parameters for evaluating imaging characteristics. The optimal parameters determined for the rest and exercise studies included the use of a 20% symmetric energy window centered on the 140 keV photopeak, a high-resolution collimator, and a circular 180° acquisition with 64 projections (from a 45° RAO to a 45° LPO) (*3*). In addition, preliminary studies, using actual patient data, indicated that a 64 × 64 matrix is preferable to a 128 × 128 matrix (*4*). Both provide similar image uniformity, but the 64 × 64 matrix better conserves computer disc space and computer processing time. The above image acquisition parameters can be used for both the same-day and two-day protocols. To further optimize image quality, patients are instructed to drink 8 oz of whole milk (or a light fatty meal, (e.g., doughnuts in patients with intolerance to dairy products) immediately after both rest and stress injections. This procedure promotes tracer clearance from the gallbladder which otherwise may obscure the inferior wall of the left ventricle (*5*).

The post-exercise image acquisition is ECG-gated using eight frames/cardiac cycle. This resting wall motion information provided by the gated display may be useful for evaluation of artifacts and assists in the assessment of myocardial viability. That is, segments with perfusion defects and normal wall motion represent viable myocardium, whereas segments with perfusion defects and akinesis represent scar (*6*). The subsequent quantitative analysis of myocardial perfusion involves the comparison of regional myocardial counts

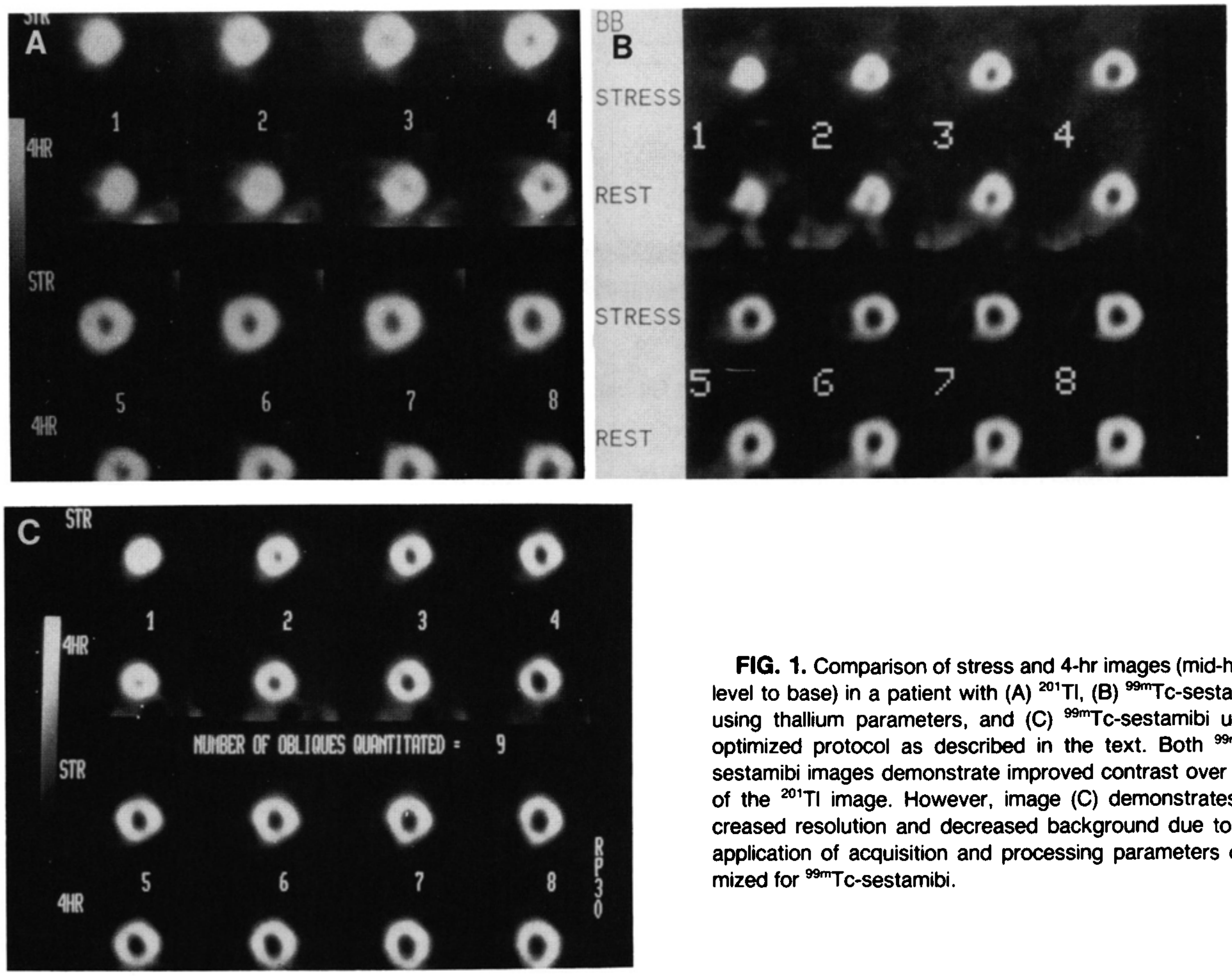

FIG. 1. Comparison of stress and 4-hr images (mid-heart level to base) in a patient with (A) ^{201}Tl, (B) ^{99m}Tc-sestamibi using thallium parameters, and (C) ^{99m}Tc-sestamibi using optimized protocol as described in the text. Both ^{99m}Tc-sestamibi images demonstrate improved contrast over that of the ^{201}Tl image. However, image (C) demonstrates increased resolution and decreased background due to the application of acquisition and processing parameters optimized for ^{99m}Tc-sestamibi.

from the summed images (of all the eight gated frames) to a previously established normal limits profile.

The patients are exercised in the fasting state using symptom-limited treadmill or bicycle exercise. A first-pass study is obtained at peak stress using a special first-pass scintillation camera designed with a small detector head. The activity injected (at least 8 mCi) is sufficient to obtain reliable wall motion and ejection fraction information from a first-pass acquisition. The patient continues to exercise for 1–2 min following tracer injection. Integration of the functional information from a rest/stress first-pass study, along with the rest/stress perfusion information should result in the improvement of the diagnostic accuracy for coronary artery disease (*7*).

Imaging the patient in the prone position has been investigated. Cardiac tomographic acquisition in this position offers the advantage of reduced diaphragmatic attenuation over supine imaging, resulting in noticeable reduction of attenuation in the inferior wall (*8–10*). However, the effects of attenuation due to the scan table must be considered. One approach to overcome table attenuation is to use a specially designed imaging table with a cut-out for the cardiac region (*8,9*). Another approach is to correct for the photon attenuation due to the scan table by using tomographic transmission imaging of a ^{99m}Tc-filled flood source obtained in air and through the scanning table. However, studies are in progress to determine the clinical significance of prone versus supine imaging. At the present time, tomographic imaging in the supine position is recommended.

Patient Protocol and Acquisition Parameters: Resting Study

1. The patients are prepared for a resting first-pass study (Table 2).
2. With the patient standing in the anterior position, ^{99m}Tc-sestamibi is loaded into the extension tubing. If using a same-day protocol, 8–9 mCi should be injected. If using a two-day protocol, a 22–25 mCi dose is injected.
3. The first-pass camera is set for a dynamic study, 25 msec/frame for 1,000 frames.
4. Start the first-pass camera and immediately flush the tubing with 40 cc of saline. The patient's arm should be relaxed and placed by his side.
5. The patient is asked to drink 8 oz of whole milk.
6. After 1 hr, position the patient for the SPECT study.
   a. Collimator: high resolution
   b. Window: 20% symmetric
   c. Orbit: 180° circular
   d. Projections: 64
   e. Matrix: 64 × 64

TABLE 1. Preparation and Quality Control of ^{99m}Tc-Sestamibi

1. With a sterile-shielded syringe, aseptically obtain additive-free sterile, nonpyrogenic sodium pertechnetate ^{99m}Tc injection [max: 925–5550 MBq (25–150 mCi)]. The activity should be such that the volume is no more than 3 ml.
2. If volume is less than 3 ml, add normal saline (0.9%) QS to 3 ml.
3. Aseptically add the sodium pertechnetate ^{99m}Tc injection to the vial of sestamibi in a lead shield. Without withdrawing the needle, remove an equal volume of air to maintain atmospheric pressure within the vial.
4. Swirl the contents of the vial for a few seconds.
5. Using appropriate lead shielding, place the vial in a boiling water bath for 10 min. Timing for 10 min is begun as soon as the water begins to reboil.
6. The shielded vial is then cooled for 15 min.
7. Inspect the vial for particulates and/or discoloration.
8. A dried Baker-Flex aluminum oxide-coated plastic TLC plate #1B-F is pre-cut to 2.5 cm × 7.5 cm.
9. Apply one drop of 95% ethanol using a 1-ml tuberculin syringe 1.5 cm from bottom of the plate. The spot should not be allowed to dry.
10. Add two drops of ^{99m}Tc-sestamibi side by side on top of the ethanol spot. Return the plate to the desiccator and allow the same to spot dry. This takes ~15 min.
11. Develop the plate in ethanol for a distance of 5 cm from the point of application.
12. Cut the TLC plate 4 cm from the bottom and measure the ^{99m}Tc activity in each piece.
13. Calculate the % ^{99m}Tc-sestamibi as:

$$\% \ ^{99m}\text{Tc-sestamibi} = \frac{\mu\text{Ci top piece}}{\mu\text{Ci both pieces}} \times 100$$

14. The dose should contain ^{99m}Tc-sestamibi ≥90%. Do not use if it is <90% bound.

f. Time/projection: 25 sec (same-day); 20 sec (two-day)
g. ECG-gated: No

7. Planar studies may also be obtained. We image for 5 min in the anterior, LAO 45°, and LAO 75° projections.

Patient Protocol and Acquisition Parameters: Stress Study

1. Prepare patients for a standard 12-lead ECG test, as well as an exercise first-pass study (Table 2).
2. Position the patient in front of the camera so that the patient is touching the collimator. The ^{241}Am source is used to assure correct cardiac positioning in the field of view as well as for motion correction.
3. At peak stress, the patient's chest is pressed gently against the camera (straight anterior view, with no tilt applied to the camera in any angle). Using the same bolus technique and imaging parameters as the rest study, inject 22–25 mCi of ^{99m}Tc-sestamibi.
4. The patient continues to exercise for 1–2 min (preferably 2 min).
5. The patient is asked to drink 8 oz of whole milk.
6. After 30 min, position the patient for the SPECT study. As in the resting study, 5-min planar images may be obtained.

a. Collimator: high resolution
b. Window: 20% symmetric
c. Orbit: 180° circular
d. Projections: 64
e. Matrix: 64 × 64
f. Time/projection: 20 sec
g. ECG-gated: using 8 frames/cycle, and an R-to-R window of 100%.

Time Considerations for Same-Day and Two-Day Protocols

Logistics of scheduling ^{99m}Tc-sestamibi studies are of particular importance, as time slots will not be the same as those employed for ^{201}Tl stress redistribution imaging. If employing the same-day protocol, the rest image should be performed first, followed by a 3-hr minimal wait before the stress test begins. Taillefer et al. (*5*) reported that some reversible defects have appeared fixed when exercise was performed first. Although the time interval between the rest/stress ^{99m}Tc-sestamibi imaging is essentially the same as that of a ^{201}Tl stress/redistribution study (3–4 hr), stress studies are performed in the afternoons. Inaccessibility of supervising physicians for the stress testing in the afternoon could be a deterrent to using this protocol, although from the patient's point of view, the time consideration is the same.

Two-day protocols require a patient to return to the testing site on two separate days. The length of time spent is ~2 hr for the rest study and 2.5 hr for the stress study. One advantage of using this protocol is that stress studies could be performed in the morning, therefore, the protocol does not interrupt the attending physicians' schedule.

Reconstruction and Processing Protocol

The acquired projections of the rest and exercise studies are corrected for radioactive decay from the start of image acquisition and prefiltered using a two-dimensional Butterworth filter (*4*). Different filter parameters are used for the different count densities of the rest and exercise studies in order to generate tomograms of comparable image texture. The lower the cut-off frequency and the higher the power of the filter, the more the images will be smoothed.

TABLE 2. First-Pass Patient Preparation

1. Insert 18-g i.v. catheter in right medial antecubital vein.
2. Attach 20-in. i.v. extension tubing filled with saline. A three-way stopcock is placed at the end of the tubing. Patency of this i.v. set-up as well as security should be assured.

3A. Stress injection: Prepare patient for standard 12-lead ECG. In addition, place an ECG pad on the sternum between leads V1 and V2. This is for the placement of a 12-mCi ^{241}Am point source which is secured on an ECG lead. It is used for motion correction during the exercise first pass study.

3B. Resting injection: Motion correction is not needed for the resting injection. However, for positioning purposes, the ^{241}Am point source may be used.

The transaxial tomograms are reconstructed one-pixel thick (6.2 mm) using a Ramp filter and reoriented along the vertical long-axis, the horizontal long-axis and the short-axis of the left ventricle. Once reoriented, the 6.2-mm slices are combined two frames at a time, incremented by one frame each, resulting in a thickness of 12.8 mm every 6.4 mm of length. This reframing results in slices of twice the count density per pixel, with equal spatial resolution along all directions. The processing protocol for stress and rest is shown in Table 3.

Processing of the first-pass studies to obtain rest and exercise ejection fraction is according to the manufacturers' recommendation, employing motion correction parameters for the exercise study (Fig. 2).

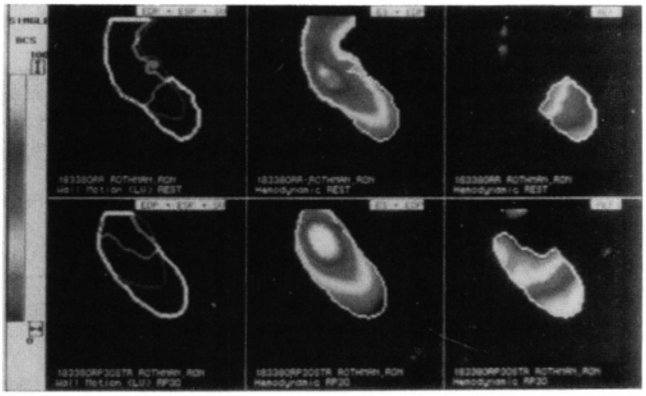

FIG. 2. ^{99m}Tc-sestamibi first-pass study both at stress and at rest demonstrating normal wall motion and ejection fraction.

CONCLUSION

Data from ^{99m}Tc-sestamibi studies obtained using suboptimal acquisition, reconstruction and processing protocols, previously demonstrated diagnostic accuracies for evaluation of coronary artery disease which were as good as ^{201}Tl stress imaging (*9,11,12*). We have presented an optimized protocol which considers the superior physical characteristics of ^{99m}Tc-sestamibi. Clinical application of such a protocol is likely to increase the diagnostic capabilities of the ^{99m}Tc-sestamibi study for the detection and localization of coronary artery disease. Because ^{99m}Tc-sestamibi does not significantly redistribute, exact adherence to time of imaging following injection is not necessary and can be broadened to take into account particular circumstances that relate to individual nuclear cardiology imaging laboratories or patient availability. If employing a same-day protocol, it is necessary that the resting acquisition be performed prior to the exercise acquisition (*5*). If using a two-day protocol, it is suggested that the stress image be performed on day one, as clinical results could either eliminate the need for the resting study (*6*), or elicit prompt medical attention (due to a severely abnormal stress image).

TABLE 3. Processing Protocol

	Rest	Exercise
Preprocessing		
Projections:	decay-corrected	decay-corrected
Filter:	2-D Butterworth	2-D Butterworth
System 1		
Cutoff frequency (% of Nyquist)	0.50	0.66
Order	5	2.5
System 2		
Cutoff frequency (cycles/cm)	0.4	0.52
Power	10	5
Reconstruction		
Filter	Ramp	Ramp
Oblique slices		
Thickness	12.8 mm	12.8 mm
Increment	6.4	6.4

As different manufacturers' systems use various definitions for the parameters of the Butterworth filter, insure that individual selections correspond appropriately. These filter parameters are specific for two different computer systems (Microdelta/Maxdelta, Siemens Gammasonics, Des Plaines, IL and Starport, General Electric, Milwaukee, WI). Two-day processing protocols for rest and exercise utilize the same parameters as the same-day exercise parameters listed above.

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