Imaging Considerations for a Technetium-99m Myocardial Perfusion Agent

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Myocardial perfusion imaging with ^{201}Tl chloride suffers from a number of physical, geometric, and dosimetric constraints that could be diminished if an agent labeled with ^{99m}Tc were available. The cationic complex ^{99m}Tc hexakis-(t-butylisonitrile)technetium(I) ([^{99m}Tc]TBI) has been shown to concentrate in the myocardial tissue of both animals and humans, with preliminary clinical studies demonstrating a number of technical attributes not possible with ^{201}Tl. Technetium-99m-TBI is a promising myocardial imaging agent that may permit high quality planar, gated, and tomographic imaging of both myocardial ischemia and infarction with reduced imaging times and improved resolution.

Myocardial perfusion imaging with ^{201}Tl is an established technique for the diagnosis of cardiovascular diseases. Thallium-201 suffers under a number of constraints such as the low energy of the mercury x-ray emissions (69–83 keV), significant tissue attenuation, a relatively long half-life (73 hr), and high cost (*1,2*). Although ^{201}Tl imaging has been used in a variety of clinical settings, it has only been through advancements in instrumentation that the drawbacks of this radionuclide have been tolerated. Thinner NaI(Tl) crystals, increased numbers of photomultiplier tubes, and single-photon emission computed tomography (SPECT) have all contributed to improved imaging of ^{201}Tl. These advances, however, still do not overcome the problems of limited dose administration, lengthy imaging times, and expense.

A myocardial imaging agent incorporating the radionuclide ^{99m}Tc, the optimal emitter to date, would alleviate a number of these drawbacks, particularly with respect to photon yield, efficiency of detection, and ready availability. The development of a myocardial perfusion agent based on ^{99m}Tc has, however, remained elusive. A number of ^{99m}Tc-labeled agents show promise in animal models (*3–5*), but they present disappointing results in humans (*6,7*). Jones, et al., (*8–10*), have recently reported that one of the isonitrile complexes of technetium (I), the ^{99m}Tc hexakis-(t-butylisonitrile) technetium(I) cation ([^{99m}Tc]TBI) demonstrates viable uptake in the human heart, yielding planar, gated, and tomographic images of excellent technical quality (*10*). In this report, we will describe the preparation and imaging considerations of the myocardial perfusion agent [^{99m}Tc]TBI.

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MATERIALS AND METHODS

The preparation of [^{99m}Tc]TBI involves a ligand exchange/reduction reaction between t-butylisonitrile and ^{99m}Tc-glucoheptonate produced from a standard glucoheptonate kit. In order to facilitate the handling of the volatile (fast evaporating) isonitrile, the clinical preparation uses the zinc bromide adduct, [$ZnBr_2$ (^{t}BuNC)$_2$]. This adduct retards evaporation and produces a more water-soluble solution. Sterile pyrogen-free kits are prepared by dissolving the zinc adduct in 0.9% saline and dispensing 0.22-μm filtered 1-ml aliquots of the solution into sterile vials precooled in liquid nitrogen. The kits are kept frozen until ready for use.

Injectate Preparation

Technetium-99m generator eluate (75–120 mCi in ~ 0.5 ml of 0.95 saline) is added to a standard glucoheptonate kit, followed by 0.8 ml of solution from a thawed zinc bromide/t-butylisonitrile solution. The mixture is shaken and then placed in a boiling water bath for 15 min. After cooling, the fluid contents of the vial are withdrawn and discarded, and the container is rinsed twice with 10 ml of sterile water for injection. This leaves 30–60% of the required TBI complex essentially free of all the other constituents of the reaction mixture that may adhere to the walls of the vial. The [^{99m}Tc]TBI is then

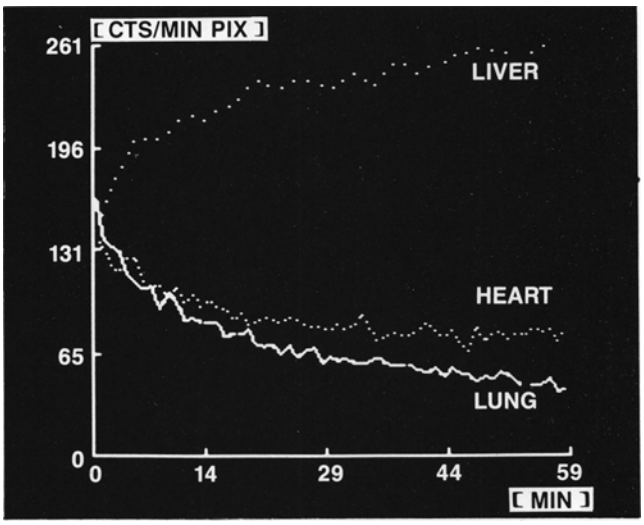

FIG. 1. Typical washout characteristics of [^{99m}Tc]TBI 1 hr after i.v. injection of a normal subject at rest.

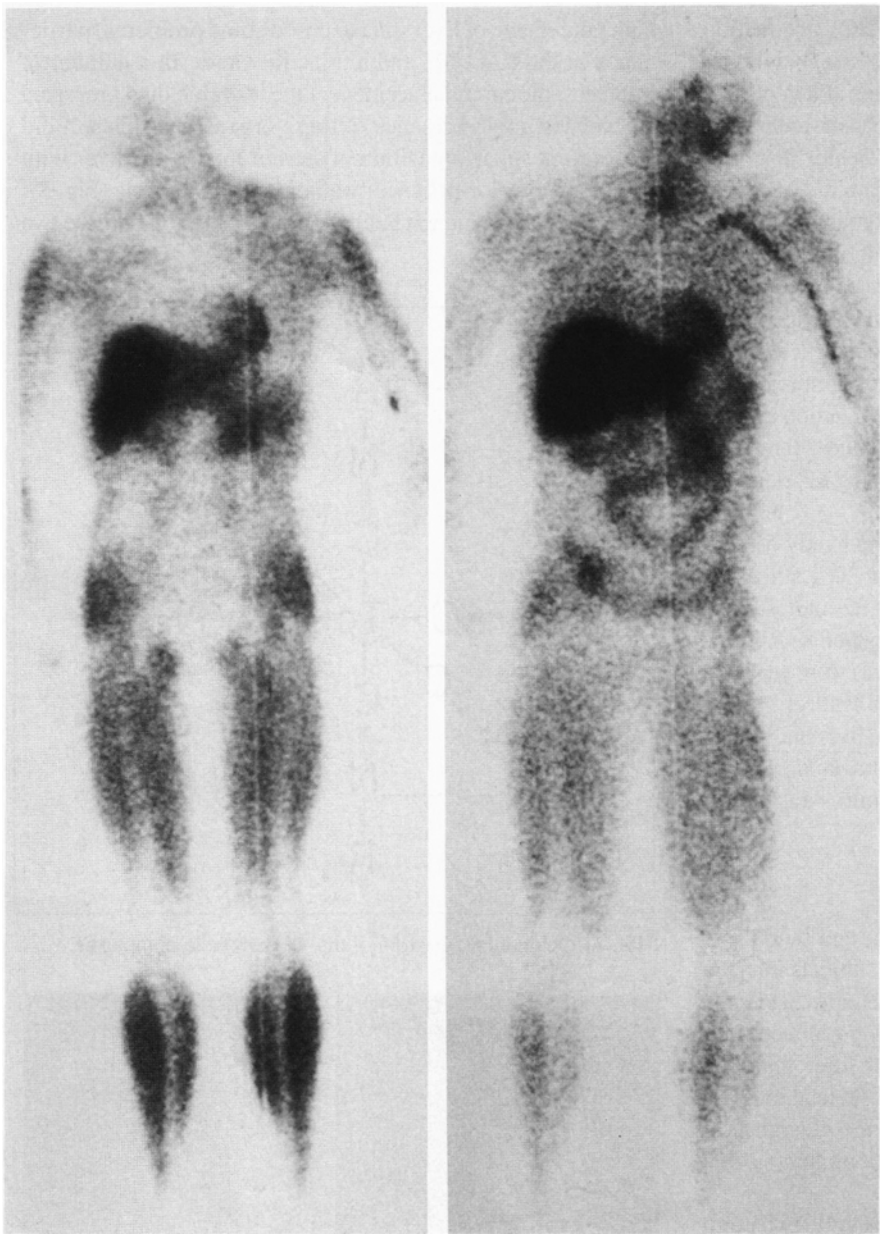

FIG. 2. Whole body distribution of [^{99m}Tc]TBI (left) imaged 5 hr after i.v. injection during exercise, illustrating increased muscle uptake.

FIG. 3. Twenty-four-hr whole body image of [^{99m}Tc]TBI (right) demonstrating intestinal activity.

dissolved in 0.75 ml dehydrated ethanol for injection and diluted with 2.25 ml of 0.9% sodium chloride for injection to give the final injectate which is 25% v/v in ethanol and contains > 10 mCi/ml of [^{99m}Tc]TBI.

Although seemingly complicated, the preparation of [^{99m}Tc]TBI is actually a straightforward two-step preparation which, within 30 min, produces the tracer radiopharmaceutical essentially free of starting materials and reaction byproducts. A simple thin layer chromatography assay* has been developed to confirm the radiochemical purity of the product.

Biodistribution of [^{99m}Tc]TBI

The distribution of [^{99m}Tc]TBI was studied in both normal patients and in patients with coronary artery disease, at rest and exercise under conditions and procedures previously reported (*10*). After i.v. injection of 5–10 mCi of [^{99m}Tc]TBI, dynamic imaging of the chest and upper abdomen was performed in the anterior projection, at a rate of 1 frame per min for 60 min. Time-activity curves were generated, from 0–60 min for the average counts per pixel in regions of interest (ROIs) over the liver, heart, and lung areas.

Imaging Techniques

Planar images of the myocardium were performed 1 hr after injection in order to minimize lung interference, and consisted of standard anterior, 30° left anterior oblique (LAO), 70° LAO, and left lateral views. Images were acquired in a supine position, with a 20% window centered over the 140 keV photopeak of ^{99m}Tc. Data were collected for a 300 sec duration and stored on a 128 × 128 matrix with a 1.5 zoom magnification. A lead shield was positioned over the liver and spleen to increase the myocardial information density.

Upon the completion of planar images, SPECT acquisition was performed using 64 projections in a 180° arc, beginning in the 45° right anterior oblique (RAO) position. Each projection was collected for 20 sec with a 1.0 zoom factor, and stored on a 64 × 64 matrix. To reduce target to detector distance, the patient's left arm was raised above the head, and the table was elevated above the centroid of the circle of rotation. Projections were collected with a 41-mm thick, hexagonal-hole, low energy general-purpose collimator, and corrected extrinsically for uniformity variations that utilized methods previously reported (*11*). Each completed data set was reconstructed with a 1-pixel slice thickness (0.63 mm), a Ramp-Hanning filter kernel of 0.50, a Y-directional filter, and no attenuation correction. Upon the formation of the transaxial slices, long-axis ("cucumber") slices were reconstructed utilizing a 3-point reconstruction plane.

Planar gated imaging was performed immediately following SPECT acquisition in the anterior, LAO 30°, and LAO 70° positions. Data were acquired on a 32 × 32 matrix, with a 15% R-R tolerance window, for 24 frames per R-R interval. Acquisition was terminated when 2K counts were acquired in a 2 × 4-pixel ROI placed on one isolated wall of the left ventricle. A lead sheet was positioned over the liver and spleen to prevent premature pixel overflow. Planar images were processed with a Fourier filter to provide dynamic wall motion studies.

RESULTS

Liver uptake rises steadily after injection, and by 60 min the liver to heart ratio is ~ 3.4:1 (Fig. 1). In subjects injected at rest and during exercise, heart and lung activities remained the same, but the liver activity is substantially reduced after exercise. Whole body images obtained 5 hr after injection showed uptake in the heart, liver, spleen, and skeletal muscles (Fig. 2); 24-hr whole body images suggest the clearance of [^{99m}Tc]TBI primarily throughout the hepatobiliary system into the small bowel (Fig. 3).

In subjects studied for 4 hr, there appeared to be two components to the lung clearance: 1) a fast compartment with a half time of 10 min; and 2) a slower compartment with a half time of 4 hr. Assuming a two-compartment model, the faster compartment would comprise 60% of the total initial lung uptake. This lung washout rate will have implications regarding optimal imaging times.

The alkylisonitrile complexes of technetium in the (+1) oxidation state are octahedral structures with six isonitrile ligands (RNC) carbon-bonded to the central metal atom (Fig. 4). The R group on each ligand can be readily varied, producing changes in the size and shape of the inner coordination sphere of the resulting technetium complex sphere, in density and lipophilicity, and hence in the biologic properties. The t-butyl-isonitrile complex, for example, could be regarded as a charged ball with 18 methyl groups on the periphery of the molecule, resulting in a very lipophilic material (*9*).

Excellent quality images were obtained with all three imaging techniques within 1 hr (Figs. 5–7). In planar imaging, the high percentage of liver uptake posed some problems, particularly in the LAO 70° and left lateral views. In a number of instances, the careful placement of the lead shielding prevented an overwhelming presence of these organs, but this still did not prevent superimposition of the left lobe of the liver with that of the inferior-posterior wall of the left ventricle (Fig. 8). On the LAO 70° and left lateral views, separation of these two

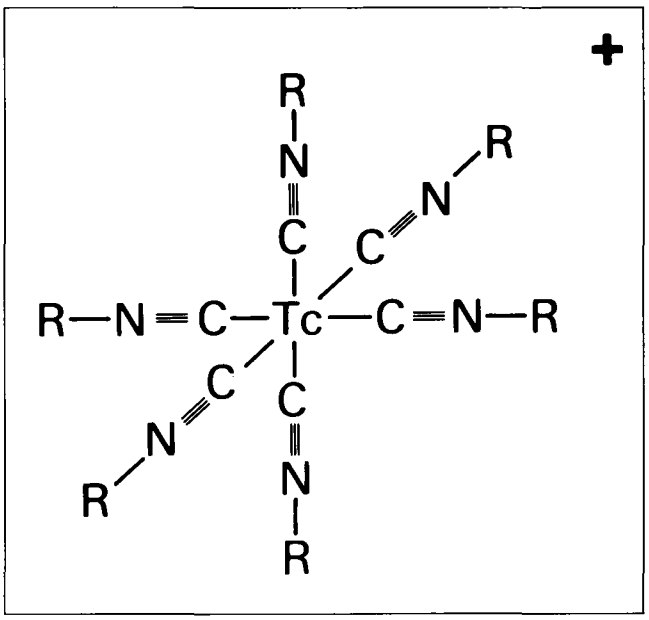

FIG. 4. Octohedral structure of the alkylisonitrile complexes.

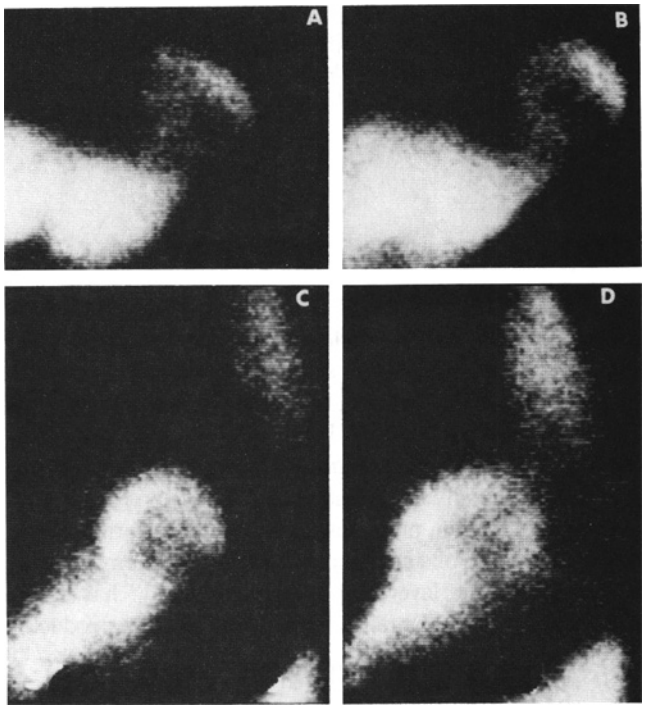

FIG. 5. Planar images obtained after injection of [^{99m}Tc]TBI during exercise in patient with prior diagnosis of infarct. Decreased uptake in the septum and apex on images 1 hr postinjection correlate with previous thallium study.

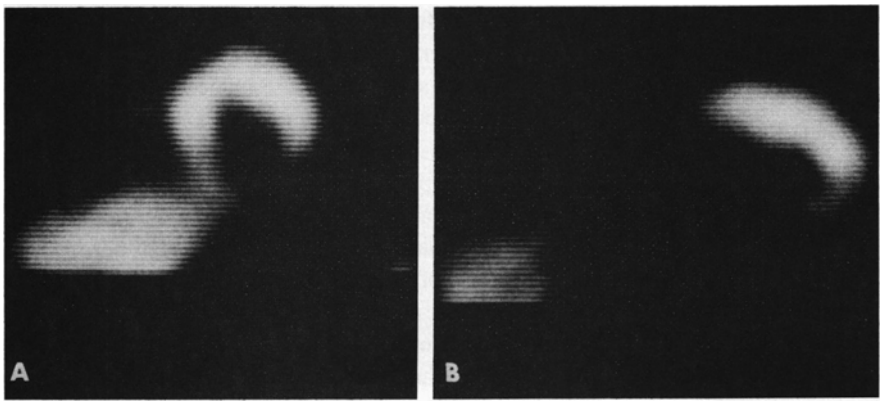

FIG. 6. SPECT images of decreased [^{99m}Tc] TBI distribution in patient's posterior wall. Cucumber (short axis) yields high contrast image with minimal liver interference. A sagittal (long axis) slice highlights posterior wall defect.

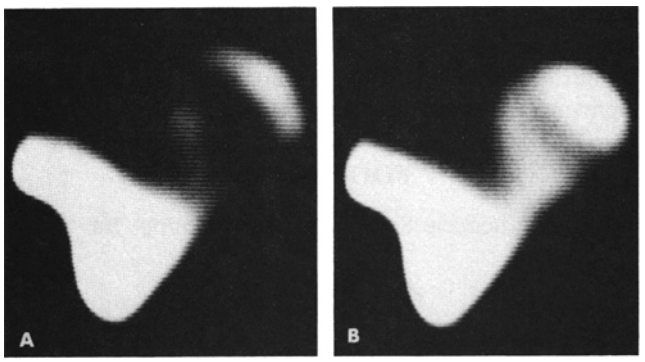

FIG. 7. Planar, anterior gated images of [^{99m}Tc]TBI distribution in diastolic and systolic phase, illustrating minimal wall motion in apex region. Increase of activity in systolic image demonstrates a compression of myocardium toward center pixels of left ventricle.

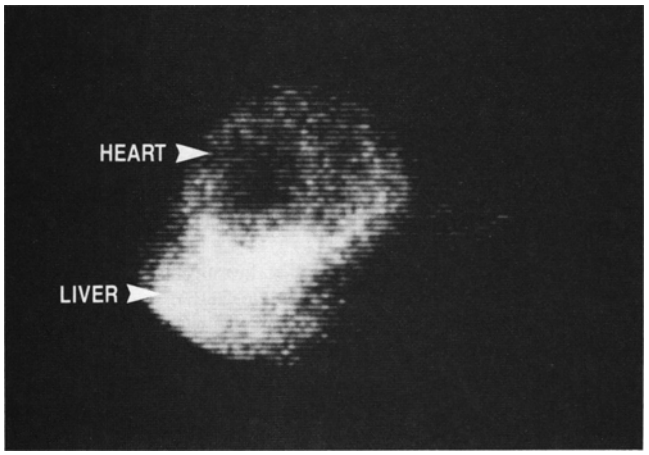

FIG. 8. 70° LAO static image illustrating liver interference (arrow) with myocardial distribution of [^{99m}Tc]TBI.

structures was often accomplished with a 5–15 ° cephalead tilt of the detector, and in some other cases, separation occurred after the patient had eaten a full meal, with a resultant expansion of the stomach and elevation of the diaphragm (Fig. 9).

DISCUSSION

The photon yield from a 10-mCi dose of [^{99m}Tc]TBI generates an average of 3 times the counts of a 2-mCi dose of

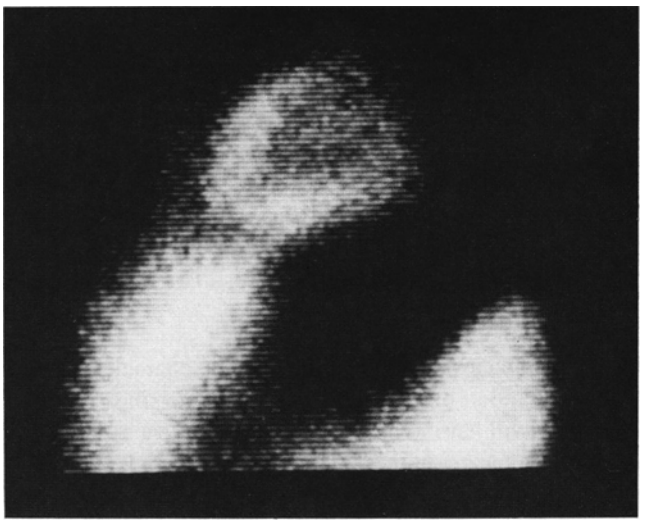

FIG. 9. 70° LAO static image of patient's heart after a meal, demonstrating elevated diaphragm and resultant liver/myocardium separation.

^{201}Tl for equivalent acquisition times and a superior energy resolution. This increase in count rate allows a reduction of 40–50% in SPECT acquisition times and short acquisition times for gated studies. In comparison with ^{201}Tl, a higher photon yield is possible because higher doses of [^{99m}Tc]TBI can be injected, which reduces the impact of tissue photon attenuation. Gated studies, which are not practical with ^{201}Tl, were acquired in less than 15 min per view. Currently, gated imaging is used to provide qualitative information about regional and global ventricular functions. Quantitative wall motion evaluation may also be possible. One of the major obstacles in formulating an ejection fraction index (or any "numerical" wall motion evaluation) is that the change in counts per pixel is the inverse of a labeled erythrocyte study. Utilizing standard ROIs encompassing end-diastolic and end-systolic images creates an inverted curve of the cardiac cycle because counts are never removed from the area but compressed toward the center. Utilizing the internal wall diameter produces a semblance of an ejection fraction curve but will require further careful study to determine its reliability, correlation, and usefulness. Wall motion evaluation from radial histograms are also possible (Fig. 10).

Whereas the technical benefits of a ^{99m}Tc-labeled myocar-

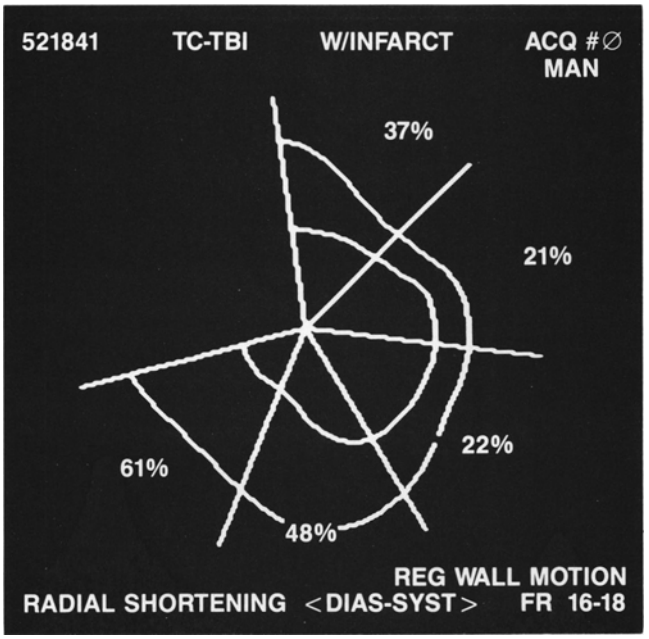

FIG. 10. Radial histogram of [^{99m}Tc]TBI processed wall motion study, illustrating contours of left ventricle during diastolic/systolic phases, and resultant % changes in motion.

dial perfusion agent surpasses the imaging characteristics of ^{201}Tl, a number of chemical and biologic constraints of [^{99m}Tc]TBI will have to be resolved. The present preparation of the radiopharmaceutical, for example, is not suitable for routine clinical use. The objective in the first scientific studies was to provide a tracer solution of the ^{99m}Tc complex free of reactants; for this reason the yield considerations became secondary. A standardized kit formulation would obviously need to be simpler. In addition, the prolonged lung activity and intense liver uptake require considerable time, effort, and care during patient/detector positioning, and high liver to heart ratios can generate considerable difficulties when transferring digital images to hardcopy.

Despite the proven value of myocardial perfusion scintigraphy in the early detection and localization of myocardial infarction, it has found little place in the routine emergency assessment of patients with suspected infarction. This occurs primarily because the current agent, ^{201}Tl, is only available commercially as a product which poses practical problems of storage and availability. Thus, it is more suited for use on an advanced schedule basis. Technetium-99m-TBI can be prepared from a nonradioactive kit and from ^{99m}Tc that is readily and cheaply produced from widely available generator systems. Therefore, [^{99m}Tc]TBI may be available on demand and has considerable potential for routine use in the initial evaluation of patients with suspected acute myocardial infarction. In this situation, it would not only provide a valuable adjunct to current methods of diagnosing acute myocardial infarction, but could potentially provide unique early information on the extent of infarction and ischemia, and the functional state of the myocardium. In addition, the technique may permit the accurate evaluation of pharmacologic and physical methods of acute intervention aimed at limiting infarct size.

The work of Jones, et al. (*8–10*) has shown that the biological behavior of these technetium complexes varies considerably with the substitute (R) group in the isonitrile (RN=C) ligand. Further studies with newer derivatives may thus yield other technetium compounds that have, for example, more rapid lung and liver clearance than [^{99m}Tc]TBI. Pending this, however, it is obvious that [^{99m}Tc]TBI is an important development in improving myocardial perfusion scintigraphy.

FOOTNOTE

*Whatman Chemical Separations, Inc., Clifton, NJ.

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