Continuing Education

Technetium Myocardial Perfusion Agents: An Introduction

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This is the third in a series of four Continuing Education articles on developing radiopharmaceuticals. After reading this article, the reader should be able to: 1) understand the basic concepts of myocardial perfusion imaging; and 2) discuss the advantages of the technetium myocardial perfusion complexes over thallium-201.

The assessment of cardiovascular performance using radionuclides dates back to 1927, when Blumgart and Weiss measured radon gas for intravascular transit times (*1*). These early studies, while appearing crude by today's technology, laid the foundation for the established techniques common to most community imaging centers. But scintigraphic images so common today are the accumulation of decades of research and development in both radiopharmaceutical and instrumentation technology. Fifteen years ago, myocardial perfusion imaging or gated blood pool analysis was a methodology available only to those centers with advanced computers and instrumentation.

Myocardial perfusion imaging with thallium-201 (^{201}Tl) is an established technique for the diagnosis of cardiovascular disease (*2*). But in the early 1970s this imaging technique was out of the reach of most nuclear medicine centers. The radiopharmaceutical companies that sold ^{201}Tl distributed a gold-195 (simulated ^{201}Tl) line phantom (Fig. 1), to assure a minimum standard in gamma camera performance prior to the sale of the agent. Those hospitals with 19-photomultiplier-tube cameras soon found that their cameras were obsolete and could not be used in myocardial perfusion scintigraphy.

Even now, use of thallium-201 suffers from 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 (*2,3*). 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 tolerable. 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.

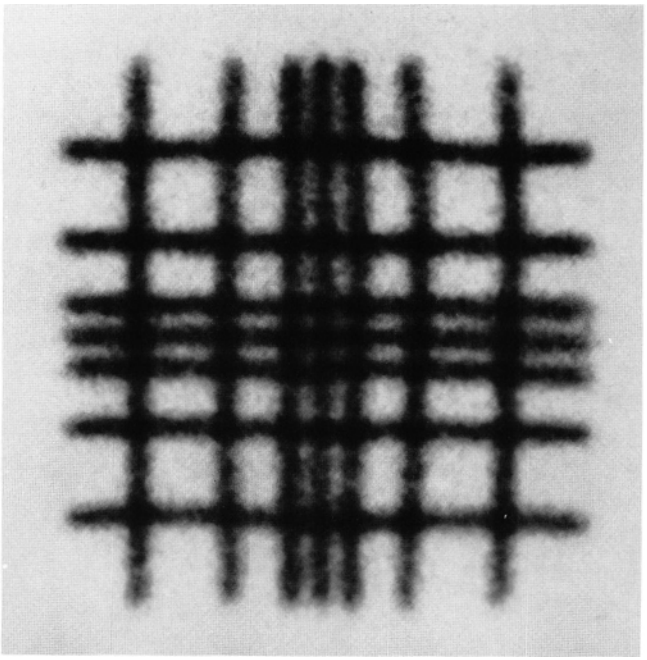

FIG. 1. Scintigraphic pattern of a gold-195 (simulated ^{201}Tl) phantom to evaluate camera performance.

A myocardial imaging agent incorporating the radionuclide ^{99m}Tc, the optimal single photon emitter in nuclear medicine today, would alleviate a number of these drawbacks, particularly photon flux, efficiency of detection, and ready availability. Availability is a real problem with ^{201}Tl; it is not only expensive, but also unavailable except for routine scheduled procedures. As a result, large metropolitan institutions with around the clock cardiac care may not always be able to use myocardial imaging for acute care. With the ready availability of the ^{99m}Tc generator, a ^{99m}Tc-labeled myocardial imaging agent has far-reaching potential.

THALLIUM-201

In the latter part of the 1970s, nuclear medicine lost a number of routine studies to other imaging modalities. While there

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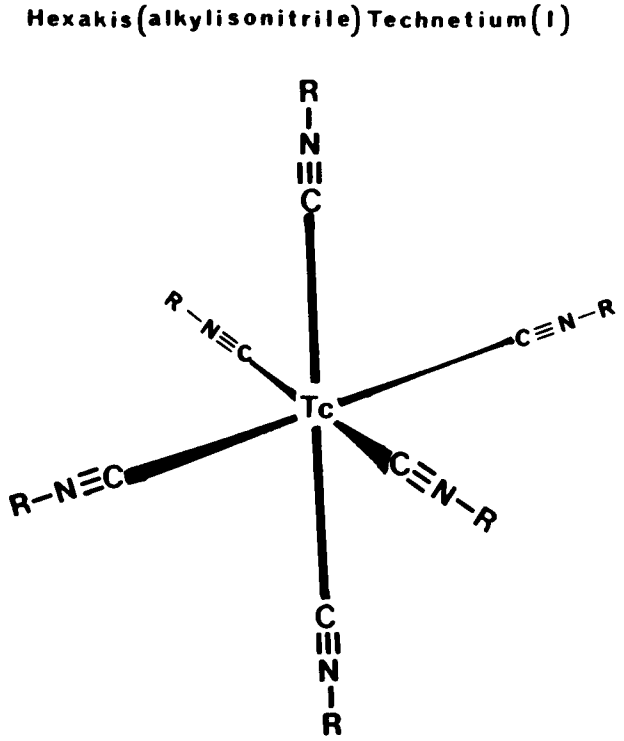

FIG. 2. The basic hexakis-(alkylisonitrile) technetium(I) structure with six isonitrile ligands (RNC) carbon-bonded to a central technetium metal atom.

was a decrease in emphasis on radionuclide imaging, the increasing popularity of exercise thallium imaging resulted in a steady growth of gamma cameras and personnel. Radionuclide scintigraphy of the heart provides a noninvasive, safe tool for the evaluation of myocardial perfusion. Although the need for a ^{99m}Tc myocardial perfusion agent is apparent, myocardial scintigraphy with ^{201}Tl has become a routine part of the clinical evaluation of patients with coronary artery disease.

The ideal myocardial perfusion agent should have the following properties:

1. No pharmacologic effects
2. Distribution proportional to myocardial blood flow over the physiologic range
3. Rapid blood clearance
4. No myocardial clearance or redistribution
5. Imageable gamma ray energy
6. Low absorbed dose
7. Short effective half-life
8. Ready availability
9. Reasonable cost

It would be wishful thinking to expect that any tracer in the forseeable future will meet all these criteria. The ionic tracers used in the past (potassium, rubidium, thallium) are usually carrier free, and have extraction efficiencies of 70% to 90% (*3*), with only 3% to 4% of the activity remaining in the heart at rest or after exercise. The rapid blood clearance after intravenous injection results in a satisfactory target-to-background ratio for scintigraphic imaging.

Additionally, the turnover of the intracellular pool in the myocardium influences the concentration of the tracer. For example, after an intracoronary injection, potassium has a biologic half-life in the myocardium of about 90 min (*3*). Thallium, however, has a half-life of about 7 hours after an intravenous injection. Aside from altering the imaging statistics, this intracellular turnover results in a redistribution of the tracer that no longer reflects blood flow at the time of injection. It is for this reason that imaging of thallium is performed immediately after exercise tolerance testing (ETT).

From the technologist's point of view, the physical charac-

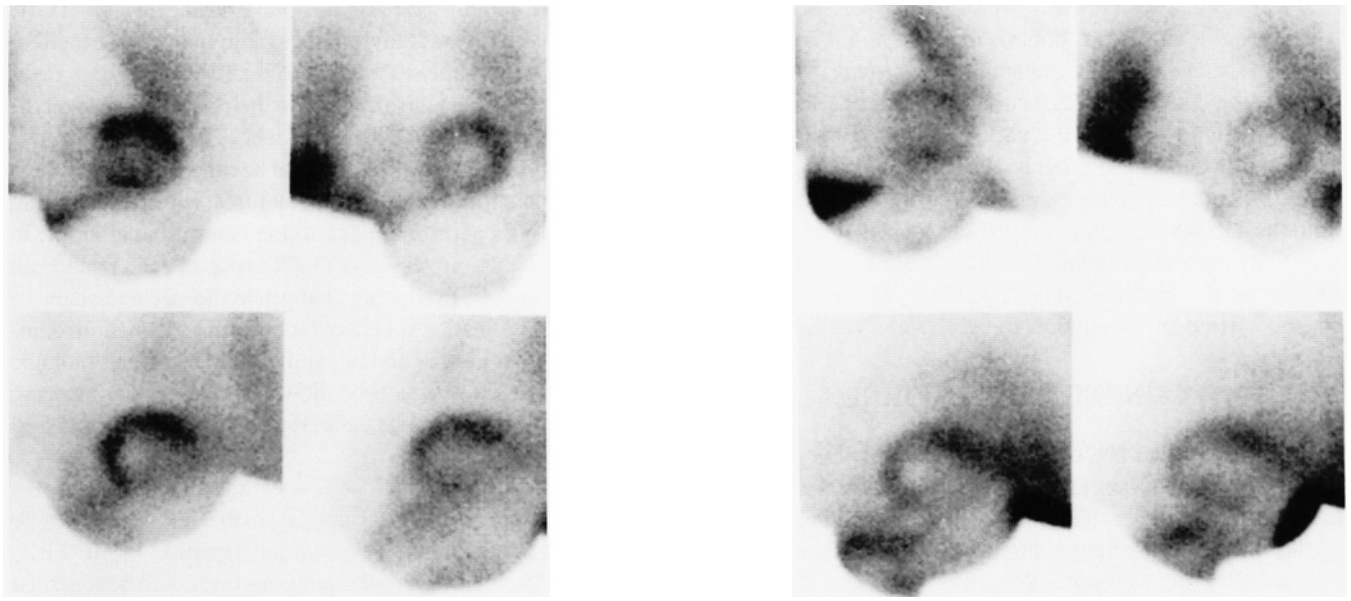

FIG. 3. Planar views of the 1 hr post-ETT (left) and 1 hr post-resting distribution (right) of ^{99m}Tc TBI, demonstrating high lung and liver activity. (Clockwise from upper left the views are anterior, LAO-30, LAO-45, and LAO-70).

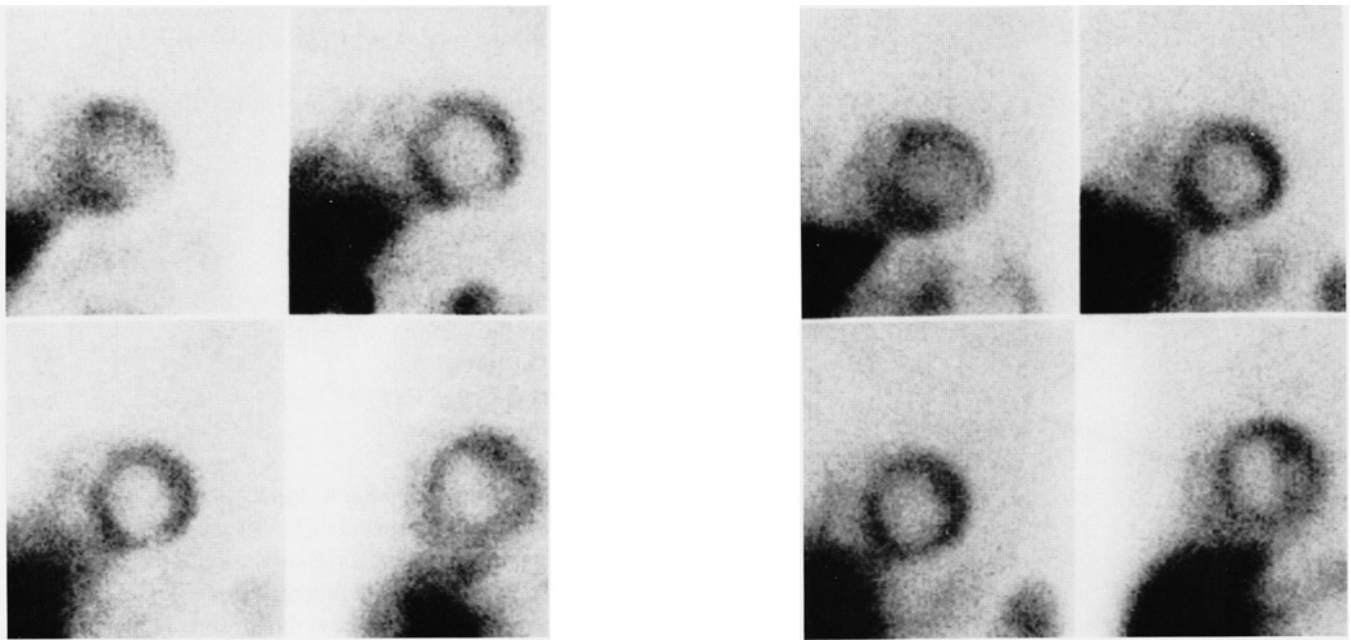

FIG. 4. Planar views of the 1 hr post-ETT (left) and 1 hr post-resting distribution (right) of ^{99m}Tc CPI demonstrating high myocardial uptake with reduced lung activity but substantial liver retention.

teristics of the radionuclide have a direct influence on an imaging instrument's performance, with a resultant effect on image quality. Since spatial resolution of the imaging system is a function of two primary parameters, photon energy and collimation, ^{201}Tl is less than optimal for routine use. The mercury x-ray peak is near the low end of the scale for resolution with scintillation cameras; furthermore, the x-ray emission causes a wide spectrum stretching from 69 to 83 keV, yielding a less than satisfactory energy resolution. As a result, the use of high resolution collimation is almost mandatory. This results in a loss of sensitivity extending the imaging time, which increases problems of evaluating rapid redistribution of the radiopharmaceutical.

There are a number of options that one might consider to preserve spatial resolution and increase sensitivity. The administered dose could be increased, but at the expense of increasing the radiation dose to the patient and increasing the cost of the tracer. A second option is using all the ^{201}Tl photopeaks, collecting counts from the mercury x-ray (95% abundance) and both the 135 keV (2%) and the 167 keV (8%), and increasing sensitivity without an additional radiation burden to the patient. Of course the most reasonable solution to the resolution/sensitivity tradeoff problem is to use ^{99m}Tc as the radiotracer.

TECHNETIUM COMPOUNDS

Technetium-99m BATO. The boronic acid adducts of technetium oxine complexes (BATOs) are neutral ^{99m}Tc complexes. In early patient studies this complex exhibited high myocardial uptake in the first minutes after injection, with continued visualization up to 20 min. This compound demonstrates a biphasic washout characteristic with approximately one-half the radiotracer clearing with a 3–4 min half-time, and the remainder exhibiting a half-life of about 2 hr (*4*).

This rapid washout time requires immediate data collection (*5*). Although increased dosages would reduce imaging times, the margin for error or complications markedly reduces the practical implementation of this agent. For example, those patients experiencing long post-ETT recovery periods may also experience compromised imaging collections. This agent is unacceptable for SPECT data acquisition due to the rapid changes in tracer distribution.

A number of ^{99m}Tc-labeled agents have shown promise in animal models (*6–8*), but were disappointing in human studies (*9,10*). The last few years have seen the development of a number of technetium-labeled derivatives of the isonitrile complexes that demonstrate useful uptake in the human heart, yielding planar, gated, and tomographic images of excellent quality (*11–13*). While still in an investigative stage, these myocardial perfusion agents may add to the role of nuclear medicine in cardiac care and management.

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, in this case technetium (Fig. 2). The R group of each ligand can be readily varied, producing changes in the size and shape of the inner coordination sphere of the resulting technetium complex altering its density and lipophilicity, and hence its biologic properties. As a result, this allows for the bio-engineering design changes that produce the isonitrile derivative discussed further in this text.

Technetium-99m TBI. The first of the isonitrile complexes to demonstrate myocardial uptake in the human was ^{99m}Tc hexakis-(t-butylisonitrile) technetium(I) cation (^{99m}Tc TBI). The t-butylisonitrile complex, for example, could be regarded as a charged ball with 18 methyl groups on the periphery of the molecule, resulting in this case in a very lipophilic material (*14*). The preparation of this agent involves a ligand exchange

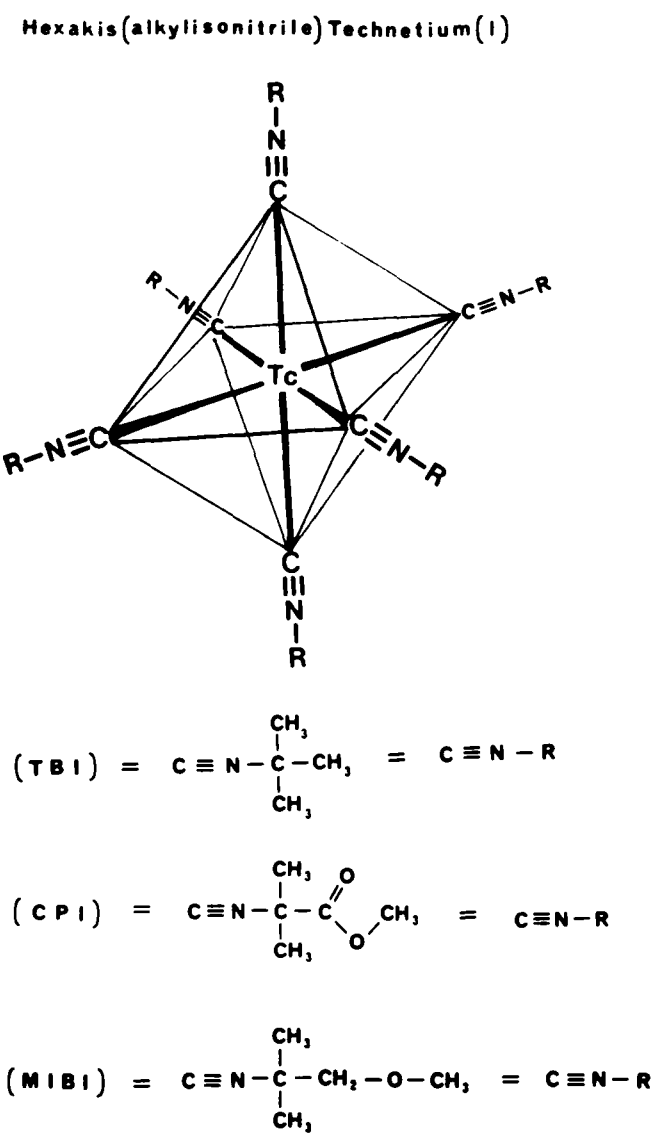

FIG. 5. The basic hexakis-(alkylisonitrile) technetium(I) structure and corresponding alterations that produce ^{99m}Tc TBI, ^{99m}Tc CPI, and ^{99m}Tc MIBI.

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 a zinc bromide adduct, $[ZnBr_2(tBuNC)_2]$. 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.

The distribution of ^{99m}Tc TBI has been studied in both normal patients and patients with coronary disease at rest and during exercise (*11*). After a 10-mCi IV injection of ^{99m}Tc TBI, the liver demonstrates a steady rise in activity, achieving a liver-to-heart ratio of 3.4:1 at 60 min. Heart and lung activity are similar whether the injection is made at rest or after exercise, but liver activity is substantially reduced with exercise. Technetium-99m TBI is cleared primarily through the hepatobiliary system into the small bowel.

The disadvantages of ^{99m}Tc TBI—1) redistribution, 2) high lung uptake and retention, and 3) high liver uptake and retention (Fig. 3)—led to alterations of the basic isonitrile complex that would provide for more favorable biologic characteristics.

Technetium-99m CPI. Based on preliminary data derived from animal studies, ^{99m}Tc carbomethoxyisopropyl isonitrile (^{99m}Tc CPI) appeared to have more favorable biologic characteristics than ^{99m}Tc TBI, with avid accumulation in normal myocardium and rapid clearance from the lung and liver (*12*). Holman et al. (*12*) reported equally impressive results with ^{99m}Tc CPI in the normal human and in those with coronary artery disease.

The preparation of ^{99m}Tc CPI is similar to that for ^{99m}Tc TBI. Following IV injection in the normal subject, the radiotracer clears quickly from the lung and accumulates in the liver and heart (Fig. 4). The heart-to-lung activity ratio has been reported as 1.7:1 at 10 min, and 2.4:1 at 60 min. The liver activity peaks at 10 to 15 min, and clears slowly through the hepatobiliary system with resultant gallbladder and small bowel activity.

In preliminary studies, ^{99m}Tc CPI demonstrated high myocardial uptake with no evidence of myocardial redistribution into zones of transient ischemia for several hours after exercise. The myocardial activity, however, does clear from the heart. Because myocardial redistribution does not occur, reinjection 3–4 hr later of the tracer is necessary to obtain a resting study.

Technetium-99m CPI represents the biologic improvements that were sought with changes in the ligand structure. While demonstrating low lung activity, ^{99m}Tc CPI does appear to have myocardial clearance with rest redistribution, as well as high liver activity. In the liver, however, unlike ^{99m}Tc TBI, ^{99m}Tc CPI presented substantial gallbladder and bowel activity in the early phases of imaging.

Technetium-99m MIBI. The second analog of ^{99m}Tc TBI to be developed was the methoxyisobutyl isonitrile or ^{99m}Tc MIBI. This further step in ligand alteration (Fig. 5) has retained the myocardial uptake benefits of its sister compounds while increasing the clearance characteristics in the blood, lung, and liver. Although the activity to the heart appears to be somewhat lower than ^{99m}Tc TBI or CPI, the superior heart-to-lung and heart-to-liver ratios offer a marked improvement in image contrast (Fig. 6).

The altered isonitrile ligand that has produced ^{99m}Tc MIBI has resulted in a compound that appears to have low lung and liver activity, and myocardial uptake that remains unchanged for long periods of time. This consistency in myocardial distribution, as a function of time, allows for a number of variations in myocardial perfusion imaging with exercise tolerance testing. Post-ETT recovery time need not be compromised because of redistribution, and the addition of SPECT and gated imaging may be implemented without concern to altered biodistribution.

CLINICAL EXPERIENCE

The class of cationic technetium compounds, the hexakis-(alkylisonitrile) technetium(I) complexes, has several members

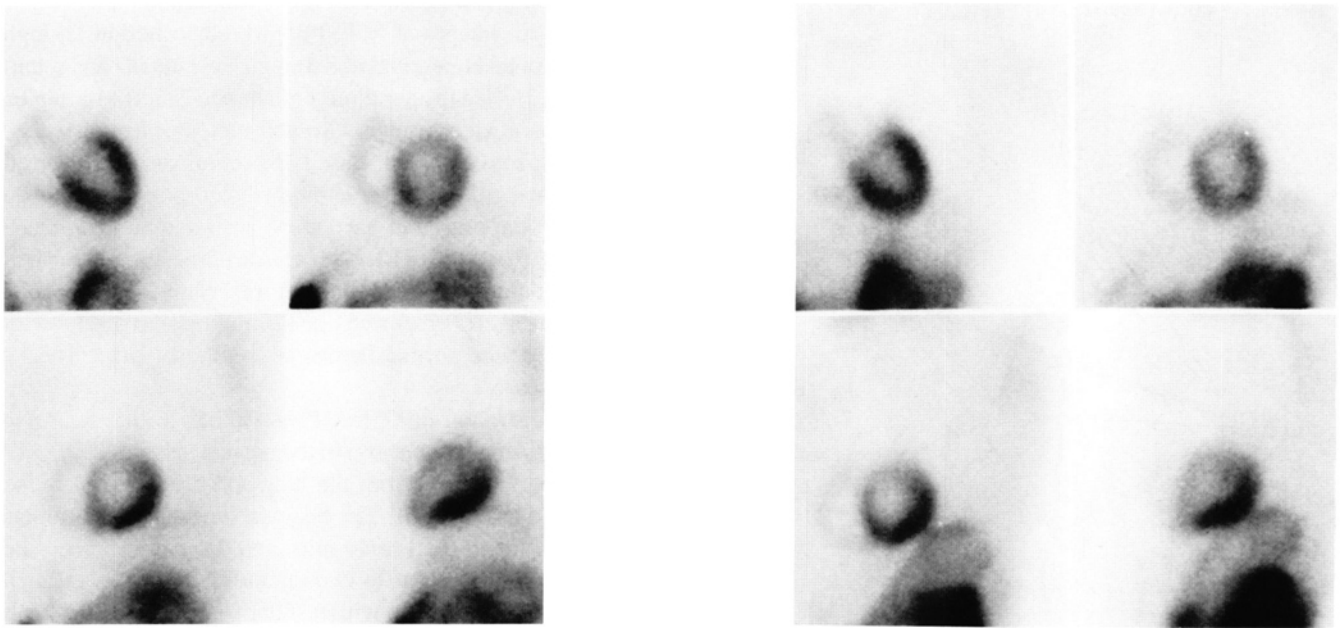

FIG. 6. Planar views of the 1 hr post-ETT (left) and 1 hr post-resting distribution (right) of ^{99m}Tc MIBI, demonstrating a high myocardial-to-background ratio, and reduced liver activity. (Clockwise from upper left the views are anterior, LAO-30, LAO-45, and LAO-70).

that accumulate in the human heart with sufficient avidity to result in the photon flux necessary for high technical quality planar, SPECT, and gated studies. Before these complexes can be used clinically, they must be shown to be comparable to ^{201}Tl, particularly in the identification of transient and irreversible ischemia.

The first isonitrile studied in humans, ^{99m}Tc TBI, failed this test of comparability because of high lung and liver uptake. The slow clearance from these organs coupled with the redistribution of the tracer resulted in only a fair correlation with ^{201}Tl for the identification of transient ischemia. Technetium-99m CPI proved to be comparable to ^{201}Tl, but was limited by rapid myocardial clearance that limited the time after injection during which optimal imaging could be achieved. Technetium-99m CPI also has slow liver clearance with resulting overlap of the liver by the heart, particularly in the high degree LAO projections. The third complex, ^{99m}Tc MIBI, appears to be ideal for myocardial scintigraphy because of its high correlation with ^{201}Tl for the identification of ischemia, rapid lung and liver clearance, and resultant low radiation burden.

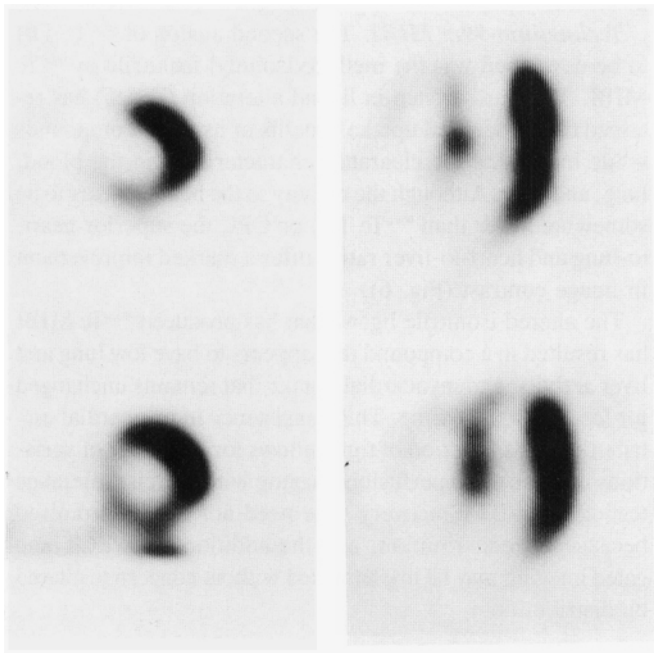

FIG. 7. Post-exercise (top) SPECT short axis (left) and long axis (right) slices demonstrate large perfusion defects in the septal region, and comparable slices (bottom) presenting minimal redistribution after resting injection of ^{99m}Tc MIBI.

Sia et al. report that ^{99m}Tc MIBI and ^{201}Tl are at least comparable with regard to the detection of ischemia (Sia BST, Holman BL, Lister-James J, manuscript submitted for publication), and that in some cases ^{99m}Tc MIBI scintigraphy demonstrates the ischemic zones more clearly than comparable images obtained with thallium. It thus becomes appropriate to discuss the attributes of ^{99m}Tc MIBI that would extend the current applications of myocardial scintigraphy.

Technetium-99m is the least expensive, most widely and readily available radionuclide in current use. Most scintillation cameras have come to be designed around its favorable energy characteristics, and its short half-life of 6 hr. Its favorable dosimetry allows for higher administered doses with a resultant increase in photon flux. The high count rate, improved energy resolution, and lower photon attenuation, when compared to ^{201}Tl, result in improved spatial resolution for planar and gated imaging, and for SPECT. In addition to the ideal physical factors, the possibility of an easily prepared ^{99m}Tc myocardial perfusion kit provides for the around the clock scintigraphic documentation of the acute myocardial infarction (MI).

The absence of redistribution and relatively unchanged biodistribution of ^{99m}Tc MIBI have major implications for its

potential clinical applications. Resting studies would need to be performed at least 4 hr after the first injection, or on a different day. The stable intramyocardial distribution of this complex and higher photon flux improve the quality and accuracy of SPECT imaging (Fig. 7), because data acquisition requires at least 20 to 30 min. Early redistribution of ^{201}Tl has been a serious concern (*15*). The unchanged distribution and sufficiently long retention of ^{99m}Tc MIBI allows for optimal SPECT acquisition, without the concern of redistribution. Because the tracer does not redistribute, imaging can be delayed for hours after injection. Thus, this compound could be administered during an acute event such as chest pain or asymptomatic ST depression, at the bedside in the coronary care unit or emergency room, and with imaging up to 4 hr later when the patient is stable. This flexibility also allows for the pre and post imaging of those patients undergoing some form of treatment intervention such as percutaneous coronary angioplasty, or some form of clot dissolving (i.e., thrombolysis) protocol.

The greater photon flux obtained with ^{99m}Tc MIBI allows for the serious investigation of software refinements that draw from SPECT data. For example, "bullseye" or circumferential profile programs, or gradient shading techniques may provide a new approach to myocardial perfusion interpretation. Distance weighted shading programs can also be used to reproject isocontours of a transaxial data set. The transaxial slices are, in effect, molded into one form that represents, when rotating, a three-dimensional portrayal of the left ventricle.

DISCUSSION

Despite the proven value of myocardial perfusion scintigraphy in the early detection and localization of myocardial ischemia and infarction, ^{201}Tl imaging has found little place in the emergency assessment of patients with suspected infarction. Technetium-99m MIBI can be prepared from a nonradioactive kit, using the ^{99m}Tc radionuclide readily available from commercial generator systems. Therefore, ^{99m}Tc MIBI is available on demand and has considerable potential for routine use in the initial evaluation of patients with suspected acute myocardial infarction.

Two directions may be taken regarding resting studies. The first is simply to perform the resting study on another day. An alternative would be to use a 5-mCi dose at exercise, and re-inject a 10-mCi dose 3–4 hr later. Because of ^{99m}Tc MIBI's favorable dosimetry and physical characteristics (i.e., its short half-life), use of mixed doses is a viable alternative.

Since ^{201}Tl and ^{99m}Tc MIBI correlate well for the identification of transient ischemia, ^{99m}Tc MIBI will provide early information on the extent of infarction and ischemia, and the functional state of the myocardium in patients with acute symptoms and in patients with known or suspected coronary artery disease. In addition, the technique may permit the accurate evaluation of pharmacologic and physical methods of acute intervention aimed at limiting infarct size.

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