Continuing Education Series

Developing Radiopharmaceuticals

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This is the second of a series of continuing education articles on radiopharmaceuticals. After reading and studying this article, the nuclear medicine technologist will be able to: (1) identify the clinical utility of each new radiopharmaceutical described; and (2) discuss technical considerations, such as amount of activity administered, imaging times, radiation dosage, and pitfalls of each. New radiotracers will play an important role in the future of nuclear medicine. This article discusses the technical aspects and potential clinical efficacy of three new radiotracers: gold-195m, iodine-123 amphetamines, and technetium-99m DTPA aerosols.

Gold-195m Cardiac Studies

Radionuclide evaluation of ventricular performance by the first-pass technique is well established (*1*). The inherent advantages of the first-pass method compared to the multigated equilibrium technique are two-fold: rapid assessment of cardiac performance over 3–5 cardiac cycles, which is advantageous for assessing changes in cardiac function with exercise or drug intervention, and the spatial and temporal separation of the cardiac chambers, which allows analysis of right and left ventricular function.

Although Tc-99m is routinely used for first-pass radionuclide angiocardiography, there are substantial limitations. Multiple sequential studies are difficult because of several factors: (1) the physical and biologic half-lives of Tc-99m radiopharmaceuticals increase the patient's radiation burden, (2) the potential radiopharmaceuticals that can be used are restricted to those excreted via the kidneys or reticuloendothelial system, (3) only about three studies can be performed using 10 mCi each, and (4) the time interval between sequential studies needs to be maximized to reduce residual background activity (for example, 10 min). Therefore, to be fully realized, the first-pass technique for sequential measurements of ventricular performance requires a radiotracer with a short half-life and a detectable radiation emission, reducing both radiation dose and residual background activity (*2–4*).

Several short-lived radiotracers, such as tantalum-178 (half-life = 9.3 min) and iridium-191m (half-life = 4.9 sec) have been tested for this purpose by other investigators (*2,3*). Tantalum-178 with gamma emissions in the range of 55–65 keV as well as 500 keV is not optimally suited for detection by conventional scintillation cameras. Although iridium-191m has a gamma emission of 129 keV, its 4.9 second half-life is too short to allow routine use in adults.

Gold-195m (half-life = 30.5 sec) is an alternative to Tc-99m for first-pass radionuclide angiocardiography (*4–7*). Its short physical half-life and gamma ray emission (262 keV) even allow simultaneous dual energy imaging of ventricular function and perfusion with Tl-201.

Imaging Considerations: Gold-195m is obtained by elution from a sterile, pyrogen-free generator column containing mercury-195m (half-life = 41.6 hr). Mercury-195m, along with Hg-195, is cyclotron produced by proton bombardment (p, 3n) of stable gold-197 with 20.5 MeV protons. Forty-six percent of the Hg-195m (Fig. 1) decays by electron capture to Au-195 with Au-195m as an intermediate step. Mercury-195m also decays by isomeric transition (54%) to Hg-195. This mercury isotope decays completely by electron capture to Au-195. Gold-195 (half-life = 183 days) decays to stable platinum-195. Since Hg-195m and Au-195m are in a state of equilibrium, the 262-keV emission of Hg-195m (32%) represents the major radiocontaminant in this generator system. The higher energy gamma rays from Hg-195 (half-life = 9.5 hr) ranging up to 1.2 MeV may represent another potential radiocontaminant (*8*).

The prototype Hg-195m/Au-195m generator (Byk Mallinckrodt, Petten, Holland) has a 40-mm lead housing surrounding a 5 × 1 cm glass column with appropriate inlet and outlet for elution. This design makes this generator suitable for bedside

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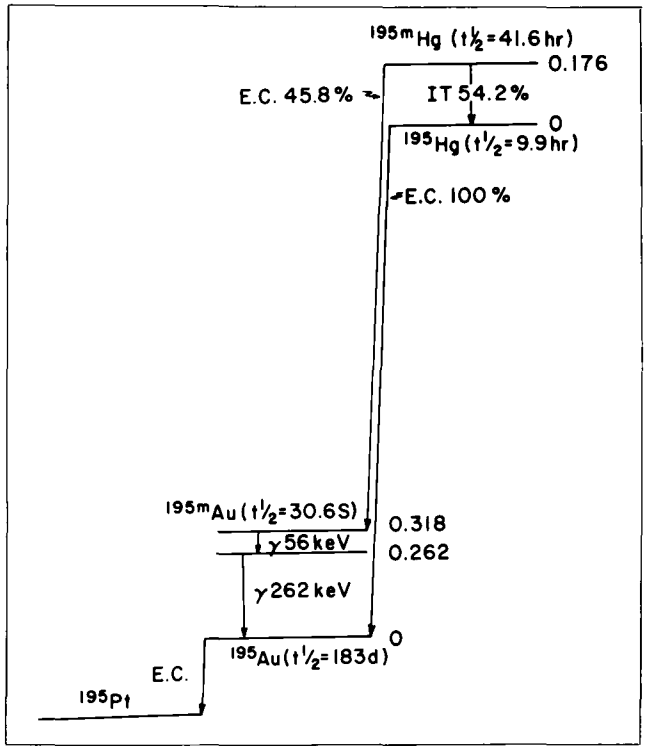

FIG. 1. Decay scheme of Hg-195m.

use. The Hg-195m is loaded on the glass column with an inorganic material. The column is flushed with an aqueous sodium thiosulfate/sodium nitrate buffer (eluent). A typical prototype generator contains approximately 170 mCi of the parent; the expected yield of Au-195m is 35–40% of the Au-195m on the column (Fig. 2).

Strict quality control procedures must be performed with each generator before it can be used for patient studies. The generator initially is flushed with at least 40 ml of the eluent in order to wash off the Hg-195m and Hg-195 accumulated through radiolysis. Subsequent 2-ml elutions are measured in a standard dose calibrator for Au-195m and Hg-195m breakthrough. The activity of Au-195m should be measured 15 seconds after elution since this represents the approximate time at which the tracer would be injected into the patient. In addition, the Hg-195m activity should be measured 15 min after elution. In order to limit the radiation dose to the target organ (kidneys) to 5 rads, the maximal activity that can be delivered to a patient is 295 μCi of Hg-195m. By calculating the amount of Hg-195m breakthrough for each individual generator, the total number of allowable injections of eluate can be determined. This approach permits definition of the proper patient dose.

The radiation dose at the surface of a generator is not more than 0.25 mR/hr. Weekly exposure rates for generator assembly and operation are calculated to be not more than 9 mrem and 22 mrem, respectively (*9*). Comparing Au-195m with Tc-99m diethylene-triamine pentaacetic acid (DTPA), there is a demonstrable decrease in patient radiation exposure with Au-195m (Table 1).

Along with its inherent high count rate capability, the crystal thickness and collimation of the computerized multicrystal camera (Baird System 77, Bedford, MA) make it suitable for detection of the 262-keV gamma emission of Au-195m. Routine single crystal Anger cameras have a limited count rate capability and will need to be modified in the future to take advantage of the full potential of the Au-195m generator. Placement of the generator sufficiently away from the field of view is necessary to decrease the scattering of the high energy emission of Hg-195m. A field flood using Hg-203 (279 keV) should be acquired for uniformity correction.

The radiotracer is injected by using an 18-gauge, 1¾ in. angiocatheter and a large right medial antecubital vein. This catheter is connected to the outlet of the generator with an extension tube (3-ml capacity) flushed with normal saline or 5% dextrose. The generator is flushed rapidly with 2 ml of the eluent, and the eluate is input directly into the extension tube. A bolus injection is performed with the use of a separate 20-ml flush

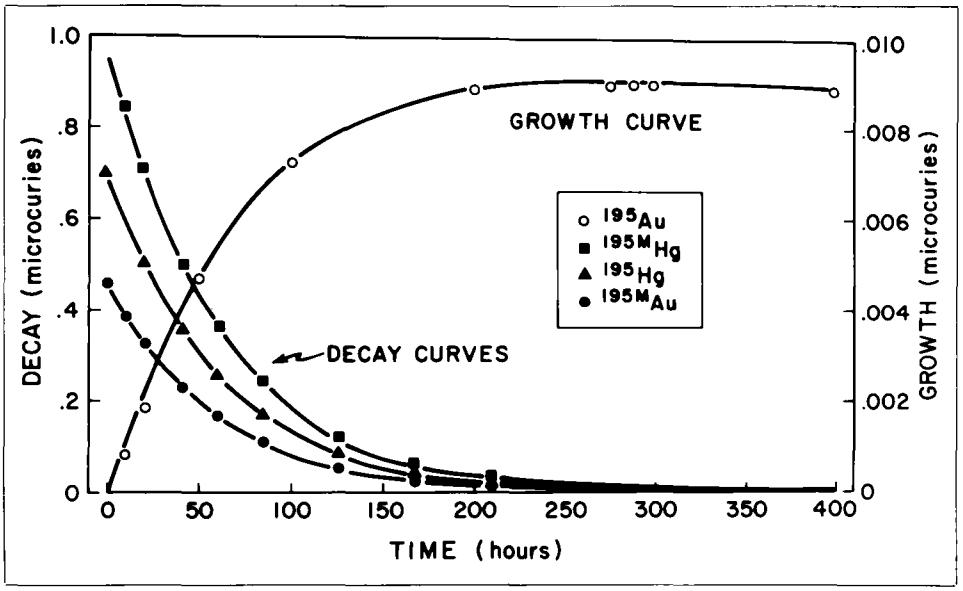

FIG. 2. Activities of Hg-195m and daughter products in generator eluate containing 1-μCi Hg-195m.

TABLE 1. Estimated Radiation Dose* from Hg-195m/Au-195m and Tc-99m for First-Pass Radionuclide Angiocardiography

Organ	Radiation dose (rad/study)	
	Hg-195m/Au-195m†	Tc-99m‡
Kidney	0.340	1.45
Liver	0.070	0.090
Spleen	0.086	0.213
Ovaries	0.003	1.34
Testes	0.001	0.85
Total body	0.007	0.39

*MIRD calculation
†2-ml eluate containing 20-μCi and 20-mCi Au-195m is injected per study
‡20-mCi Tc-99m DTPA

connected to the extension tubing via a three-way stopcock. The time between elution and injection should be within 7–10 seconds.

Data are acquired at 50 msec/frame and 25 msec/frame for rest and exercise studies, respectively. Using the multicrystal camera, the raw data are corrected for dead time, uniformity, and ambient background. Radioisotope decay correction and temporal smoothing also are applied. Left ventricular ejection fraction (LVEF) is determined from a background-corrected, summed, representative cardiac cycle generated by a region of interest selected over the left ventricle.

Clinical Applications: Studies using Au-195m should be of excellent technical quality and indistinguishable from those obtained using Tc-99m. In 166 studies performed in our laboratory, the mean count rate uncorrected for decay in the entire field of view using Au-195m during the left ventricular phase was 211,128 ± 13,271 counts per second as compared to 182,462 ± 12,260 counts per second for Tc-99m. The decay and background-corrected mean count rate at end diastole for Au-195m was 9,326 ± 1,056 counts compared with 4,260 ± 728 counts for Tc-99m. The residual background during sequential studies using Au-195m ranges from 3–12% of end diastolic counts.

The results of LVEF determination using Au-195m and Tc-99m in 18 patients correlated well (r = 0.93; mean LVEF for Au-195m 47 ± 14% vs 47 ± 14% for Tc-99m). The absolute mean interstudy difference was 4 ± 4%.

In 29 patients who underwent multiple consecutive studies using Au-195m, LVEF determinations were reproducible (r = 0.96), with a mean study difference of 4 ± 2% (*10*).

In 20 of 25 patients with suspected coronary artery disease studied both at rest and exercise, abnormal left ventricular function at exercise was observed. However, several patterns of change in ejection fraction during stress were observed—highlighting the diagnostic potential of serial imaging during exercise.

Combined Au-195m and Tl-201 imaging appears to be feasible and may be useful in simultaneous assessment of ventricular function and perfusion at the same exercise level (hopefully providing more information about functional capacity in coronary artery disease than either study alone), and minimization of the cost of the imaging procedure by only requiring a single exercise test. Medium energy collimation is necessary

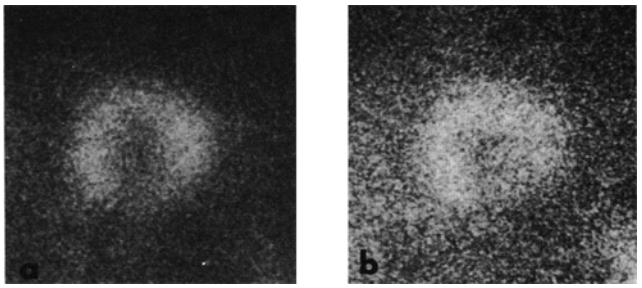

FIG. 3. (A) Standard exercise Tl-201 left anterior oblique (LAO) view. (B) Repeat LAO image after 12 injections of Au-195m. Reproduced with permission, reference (10).

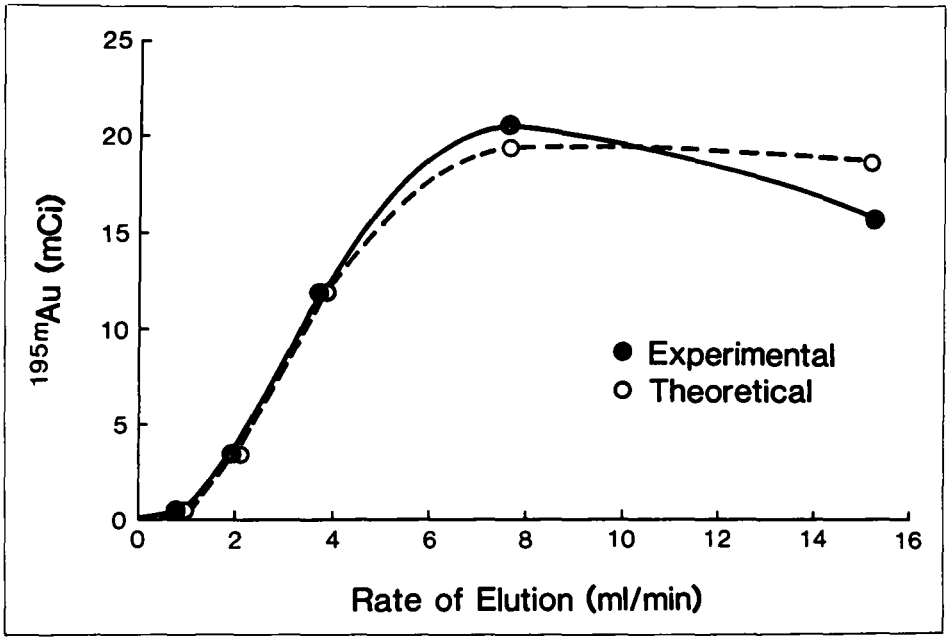

FIG. 4. Au-195m activity steady state and rate of elution.

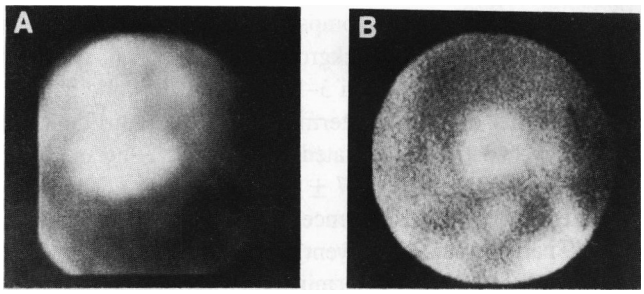

FIG. 5. (A) Multigated equilibrium LAO image with Au-195m. (B) Alternating rest Tl-201 image.

to minimize higher energy background contamination from Hg-195m into the Tl-201 window (approximately 380 counts per min/μCi in the entire field of view) (*10*) (Fig. 3).

Multigated equilibrium studies can be reliably performed using continuous infusion of Au-195m. By continually eluting the generator at a rate of 7.5 ml/min, a maximum yield and steady state of Au-195m can be obtained (Fig. 4). Mercury-195m breakthrough was also determined to be constant and relatively independent of elution rate. Again, measurements of Hg-195m breakthrough should be done first in order to determine the maximal volume of eluate that can be delivered without exceeding the 295 μCi limit. From our experience the volume was usually 40 ml with maximum infusing time being usually 5 min.

In 15 patients, we compared the multigated equilibrium technique using Au-195m and Tc-99m labeled red blood cells. Left ventricular ejection fraction correlated well (r = .80) (*10*)

Using a 5-min acquisition, end diastolic counts with Au-195m were 11,122 $\pm$ 4,837 counts (*10*). Typically, the images demonstrated more activity in the right ventricle than in the left ventricle with minimal background activity. Definition of the ventricular chamber edges was adequate to allow interpretation of regional wall motion, comparable to the Tc-99m studies. Alternating infusion of Au-195m with Tl-201 imaging is also easily performed—providing an alternative method of assessing function and perfusion (*11,12*) (Fig. 5).

Studies with Au-195m thus far have involved a relatively limited number of patients and prototype generators manufactured in Europe. The early work clearly has demonstrated the potential clinical utility of this new technique. With the planned broader availability of generators in the United States, it is likely that this new radiopharmaceutical will become more widely used; it could become the tracer of choice for radionuclide angiocardiography. Hopefully, forthcoming versions of the generator will have even lower Hg-195m breakthrough to minimize the radiation burden to the patient further.

Brain Scintigraphy Using Radiolabeled Amines

Until recently, brain imaging in nuclear medicine has been dependent on the breakdown of the blood-brain barrier for definition of abnormal results. The introduction of x-ray computed tomography with its superior structural definition replaced the conventional radionuclide brain scan, and encouraged the search for compounds that would provide measurements of regional physiology. New agents have to meet two criteria to make these measurements. They must be able to cross the normal as well as abnormal blood-brain barrier, and be retained in the brain parenchyma. Significant achievements were made in this area with positron-emitting compounds (*13*); however, cost and limited availability prohibited their widespread use. Recently a family of amines—single photon radiopharmaceuticals—has been introduced that meet both of the above criteria. They are also cost-effective and routinely available.

There are two tracers within the family of amines, the monoamine (IMP) and the diamine (HIPDM), that have shown much promise in brain imaging. Amines serve an important function in their own right, as chemical mediators of brain function. They affect transport and uptake of brain metabolites, rates of synthesis, and metabolism. It is likely that many neurologic diseases, and some functional disorders may be the result of altered amine kinetics and function. Several of the amines have been synthesized and labeled with I-123. It is the ability of these labeled amines to cross the blood-brain barrier, and remain in the brain cortex for long periods of time (up to 4 hr), that permits not only promising planar images, but also detailed tomographic studies.

Currently, two amphetamine analogs are being actively investigated, the diamine N,N,N′-trimethyl-N′-(2-hydroxyl-3-methyl-5-iodobenzyl)-1,3-propane diamine (HIPDM), and N-isopropyl-p-iodo-amphetamine (IMP). Holman et al. have reported that the distribution in man is initially in the lung, with approximately 50% maximum for HIPDM, and 30% for IMP (*14*). While the brain uptake of IMP is approximately 30–40% greater than HIPDM, the uptake rate of HIPDM is higher. In both compounds, however, brain activity is unchanged between 30 to 60 min. Liver activity is 2.5 times greater than brain activity for HIPDM, and 4.3 times greater for IMP.

Both HIPDM and IMP are still investigational; HIPDM is supplied in kit form (Benedict Nuclear, Golden, CO) and IMP is supplied already labeled (Medi-Physics, Emeryville, CA).

Imaging Considerations: As with any radiopharmaceutical, both the biological characteristics and physical properties must be considered when preparing imaging protocols. With radiolabeled amines, the favorable biologic distribution of the agents removes most of the time constraints encountered with the Tc-99m brain agents. Because of the rapid uptake and prolonged parenchymal retention, high statistic planar and tomographic images may be collected without loss of physiologic information. Image collection may be conducted 10–20 min postinjection, and the need for delayed studies is eliminated.

The physical characteristics of I-123 pose a more formidable problem. Much of the available I-123 is produced by the Te-134(p,2n) I-123 reaction, yielding 2.1 to 4.6% contamination of I-124. The I-124 impurity in the (p,2n) I-123 yields several high energy photons that contribute to background scatter and resolution degradation (*15*). One method of reducing the high energy I-124 photons is the use of I-123 produced by the indirect method, which results in only a small amount of I-124 impurity (usually less than 0.4%). Unfortunately, this production method is very limited in the United States.

From the technical point of view, the acquisition of standard

planar views follows those established for brain imaging with Tc-99m compounds. The primary exception is the use of the 159-keV gamma peak of I-123. With a 20% window, a 5-mCi dose will usually yield a count rate of 1,000 counts per second in the normal adult.

Clinical Applications: Patients with a normal x-ray CT scan, and without central nervous system disease, demonstrate a bilateral, symmetrical pattern of distribution in both planar (Fig. 6) and tomographic modes (Fig. 7). In cases of cerebral infarction, decreased perfusion is demonstrated in those regions supplied by the involved artery. These results will appear immediately upon the onset of symptoms using single photon radiopharmaceuticals and emission computed tomography; the CT scan may not demonstrate a defect for three to four days (*16*).

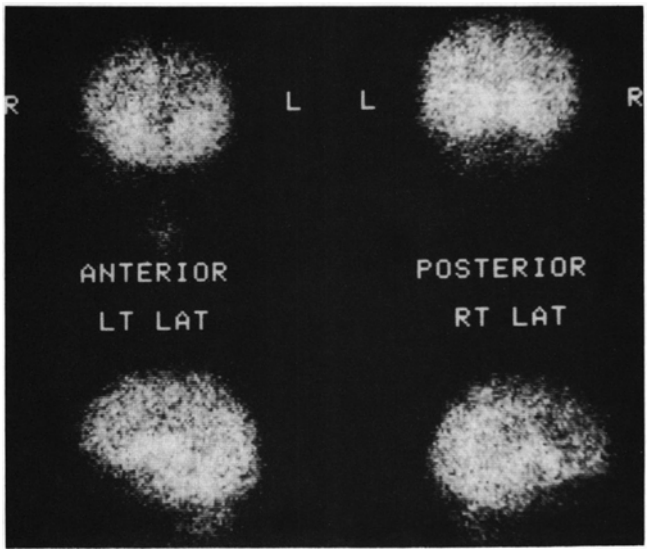

FIG. 6. Normal distribution of I-123 IMP in standard planar views.

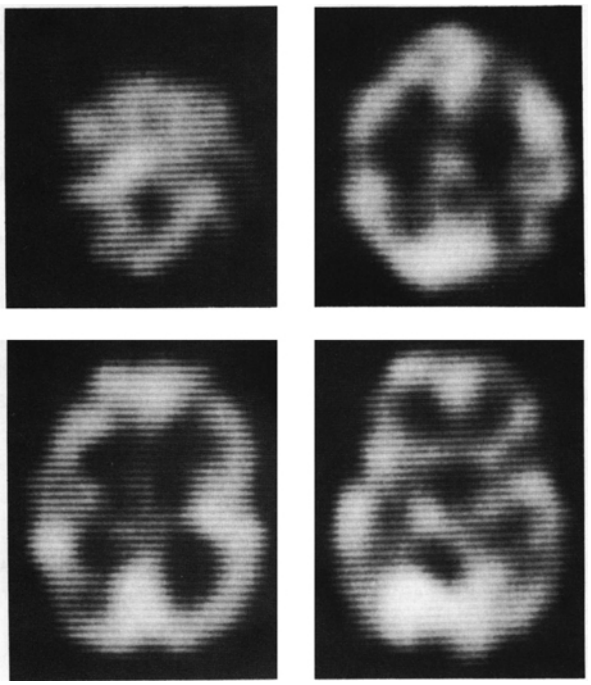

FIG. 7. Normal distribution of I-123 IMP in transaxial projections.

Investigation of the utility of radiolabeled amines is not simply limited to the onset of stroke symptoms, but encompasses a variety of brain disorders. Holman et al. (*17*) have reported that ECT and radiolabeled amines appear useful in a number of neurologic conditions. Their work has entailed studies of cerebral infarction, pre- and post-endarterectomy, epilepsy, and those patients with ambiguous clinical patterns, where CT does not provide a diagnosis. It is anticipated that with increased clinical experience, improved instrumentation, and tomographic software, the list of clinical indications for this procedure will increase substantially.

Technetium-99m-DTPA Aerosol

Functional assessment of the lungs for detection of pulmonary embolus requires the interpretation of both ventilation and perfusion functions. The most specific criterion for high probability of pulmonary embolism is ventilation perfusion "mismatch." Xenon-133 is well established as an effective radiopharmaceutical for evaluation of ventilation. Yet many hospitals, especially smaller community hospitals, are not equipped or may not be licensed to use Xe-133 and, until recently, there have been few suitable alternatives.

The inherent limitations of Xe-133 as an imaging agent and its inconveniently long half-life have presented problems in nuclear imaging. The 80-keV gamma rays emitted by Xe-133 are quite suitable for imaging with the scintillation cameras used at virtually all centers today but, unfortunately, are significantly lower in energy than the 140-keV gamma rays emitted by the Tc-99m commonly used in macroaggregated albumin or microsphere preparations for perfusion imaging. This obviously necessitates that the ventilation scan be performed first, and the physical properties of Xe-133 gas usually limit the study to a single projection. It would be far more desirable to perform the ventilation scan *after* the perfusion scan in the projection(s) that show perfusion defects best. A patient with a normal perfusion study would require no ventilation scan, thus limiting patient radiation dose, cost, and maximizing camera utilization time.

An alternative to Xe-133 is an aerosol preparation of Tc-99m. Since the same isotope is used for the perfusion scan, aerosolized Tc-99m is not subject to the limits imposed by the lower energy gamma rays of Xe-133.

When the aerosol technique was first introduced in 1965 (*18*), problems with control and uniformity of particle size caused precipitation of large particles (greater than 3 microns) in the large central airways, producing confusing "hot spots." Small particles (less than 1 micron) have no significant upper airway deposition, and virtually all particles less than 0.5 microns are exhaled immediately (*19*). Control of particle size and uniformity has been the most significant factor limiting the use of aerosol preparations of Tc-99m.

A prototype aerosol system (Synaco, Palo Alto, CA) has been under evaluation to test the efficacy of a Tc-99m labeled aerosol for ventilation imaging.

Three independent studies have evaluated the production

of uniform size particles by this system (Syntevent) and were in close agreement (1.58 microns ± 1 SEM) with one another (*20,21*). All show control of particle size to be well within acceptable limits.

Technetium-99m diethylene-triamine pentaacetic acid (DTPA), when inhaled, crosses the alveolar membrane and is cleared from circulation by the kidneys in the same manner as an intravenously administered dose of the same compound (*22*). The radiation dose compares with that of Xe-133.

Imaging Considerations and Clinical Application: The Syntevent aerosol delivery system is designed to be simple and easy to use and is disposable after a single use. The system consists of two major components: a reservoir (a nebulizer) and a yoke. The nebulizer consists of a venturi tube and a fitting for connecting the system to a source of compressed oxygen. Liquids placed in the nebulizer are forced through the venturi tube by a jet of compressed air or oxygen to generate the aerosol (*23*). The second component of the system, the yoke, is fitted with a mouthpiece and includes a bacterial filter, which traps expired air passing through the return side of the yoke (Fig. 8). This entire system is shielded.

Technetium-99m DTPA is prepared from a commercial kit (Medi-Physics). The compound was reconstituted with 30 mCi of [^{99m}Tc] pertechnetate in a total volume of 3 ml. The activity in the aerosol system actually delivered to the lungs represented only 100,000 counts per 10 min in the entire field of view. By changing the dose to 45 mCi in 3 ml, 100,000 counts in 5 min can be obtained.

It is advisable to let the patients practice breathing through the system before beginning the actual study. A nose clip is used to insure that the patient only breathes through the mouthpiece of the system. It is important to remember that the oxygen flow rate is approximately 8 l per min.

Aerosol is distributed in the lungs by normal tidal breathing and the depth of inspirations has little effect on particle distribution. The patient is allowed to breath through the system for 3–5 min after which the oxygen flow is terminated and the patient is instructed to take 5 breaths before removing the mouthpiece, thus insuring that no particles are exhaled outside the closed system.

Image acquisition is terminated after 100,000 counts, usually requiring approximately 5 min using a large field of view camera with a low energy all purpose collimator. Standard views are identical to those obtained for a perfusion scan and consist of six projections: anterior, posterior, both posterior obliques, and both laterals. After completion of the aerosol study a perfusion study is performed in the usual manner

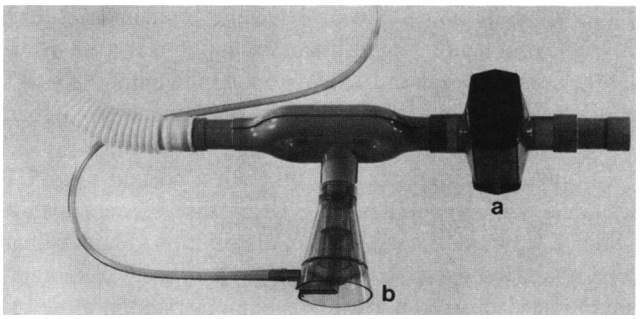

FIG. 8. Aerosol delivery system (Synaco Corp.) with yoke (A) and nebulizer (B).

(4-mCi Tc-99m macroaggregated albumin administered intravenously). The same views are acquired for 300,000 counts with the exception of the lateral views, which are acquired for 200,000 counts. The second lateral view is imaged for the same time as the first.

Ventilation studies with Xe-133 gas on a closed spirometer system can also be performed on patients receiving aerosol and perfusion studies. The Xe-133 study should be completed before the other studies as necessitated by the higher energy gamma rays emitted by Tc-99m. The normal distribution (Fig. 9) demonstrates homogeneous uptake throughout the lungs with Xe-133, Tc-99m DTPA aerosol, and Tc-99m macroaggregated albumin. Ventilation/perfusion mismatch (Fig. 10) can be demonstrated well using either Xe-133 gas or Tc-99m DTPA aerosol.

Dosimetry calculations are based upon the assumption that a maximum dose of 200 μCi of Tc-99m DTPA is delivered to the lungs. With an oxygen flow of 8 l per min, 3 min of tidal breathing would deposit 9.3 ± 2.5 μl of the aerosol preparation in the lungs. A concentration of 15 mCi/ml will deliver a 139.5 μCi dose to the lungs with an assumed maximum dose of 200 μCi, allowing for variability in lung size and total volume. A 20-mCi dose of Tc-99m DTPA administered intravenously will deliver 35.2 mrad to the lung as compared with the 13.25 mrad dose from the aerosol study (Table 2). Other organs also receive much lower radiation doses from inhaled aerosol than they do from intravenous administration of comparable doses.

The half-life of Tc-99m DTPA in the lungs when aerosol particles of 2 microns are inhaled is 59 min for nonsmokers and 20 min for smokers. This interesting disparity may related to increased alveolar permeability in smokers. Since the inhaled Tc-99m DTPA remains in the lung, it is therefore possible to "breathe" the patient in another room, thereby increas-

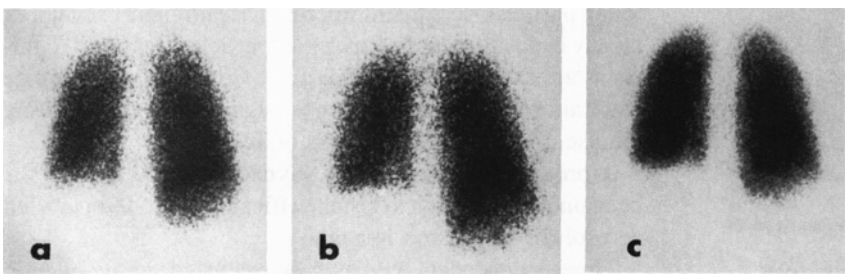

FIG. 9. Posterior images of a normal study: (A) aerosol, (B) Xe-133, and (C) Tc-99m MAA perfusion.

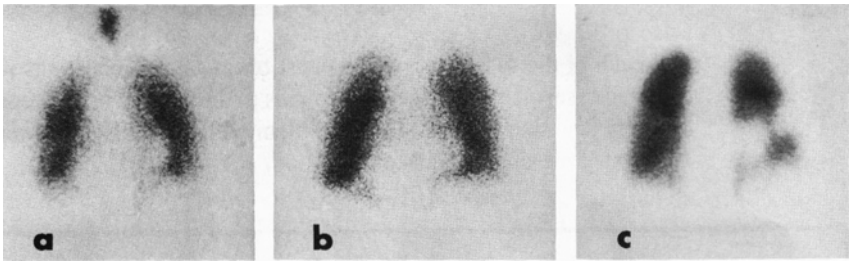

FIG. 10. Posterior images showing a peripheral mismatch defect on the lateral aspect of the right lung: (A) aerosol, (B) Xe-133, and (C) Tc-99m MAA perfusion.

TABLE 2. Estimated Radiation Dose Following Uptake of 200-μCi Tc-99m DTPA in Lungs

Organ	mRad/200 μCi
Bladder	126.46
Lungs	13.25
Kidneys	7.75
Ovaries	6.16
Testes	3.76
Total body	1.91

ing camera utilization in a very small or busy department.

Two technical problems encountered during the study were: higher count rates achieved when the dose was increased from 30 mCi to 45 mCi, and improper assembly of the delivery system causing incomplete alveolarization of the liquid. In order to avoid another potential problem it is important to turn the compressed air on gradually to 8 l per min, avoiding the disassembly of the tubing from the nebulizer.

Since we have initiated our study, the aerosol system has been slightly modified and we are now able to acquire 100,000 counts in 2–3 min using a 20-mCi dose of Tc-99m DTPA and breathing the patient on the system for only 3 min. These and future improvements will hopefully promote widespread use of this technique.

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