RADIOCHEMISTRY AND RADIOPHARMACEUTICALS

Gold-195m, An Ultra-Short-Lived Generator-Produced Radionuclide: Clinical Application in Sequential First Pass Ventriculography

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Gold 195m (Au-195m) has a half-life of 30.5 sec and can be produced at the bedside from the parent mercury-195m ($T_{1/2}$ = 41.6 hr). The generator produced sterile pyrogen-free Au-195m with mercury breakthrough of 0.75 ± 0.09 (s.e.m.) μCi per mCi of Au-195m. Approximately 20 to 25 mCi of Au-195m was produced per elution from a generator containing 155 mCi of Hg-195m. We compared first-pass resting Tc-99m angiograms with Au-195m angiograms in 28 patients. The correlation coefficient between the two studies was 0.92 over an ejection-fraction range from 0.22 to 0.83. In addition, we tested the reproducibility of Au-195m first-pass angiograms by performing two studies 3 min apart. In 25 patients with ejection fractions ranging from 0.20 to 0.78, the correlation coefficient between such pairs was 0.93. The nuclide is reliably and reproducibly produced, and its short half-life allows the performance of background-free sequential first-transit studies with unusually low radiation exposure to the patient.

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An ultra-short-lived single-photon-emitting radionuclide has many potential advantages in clinical nuclear medicine. An ultra-short half-life offers a marked reduction in radiation exposure to the patient. It also permits frequent sequential studies.

Krypton-81m, a rare gas with a 13-sec half-life, was developed primarily for studies of lung ventilation and has been used for cardiovascular examinations (*1*). However, such applications are limited to evaluation of right-ventricular function or they require intra-arterial injections, since intravenous injection of the gas is followed by its escape through the lung (2,3). Iridium-191m is an ultra-short-lived (4.9 sec) nuclide that is useful for the evaluation of cardiac shunts in newborns (*4*). Its half-life, however, is so short that it has limited utility in adult studies of cardiovascular function.

We previously reported the physical characteristics of the eluate of a gold-195m generator (*5,6*). Gold-195m (Au-195m, $T_{1/2}$ = 30.5 sec) is a single-photon emitter that can be produced at the bedside. The parent is cyclotron-produced mercury-195m, with a half-life of 41.6 hr. This paper reports the performance of the Au-195m generator.* In addition, the clinical findings of first-pass left ventriculography, performed after bolus injection of Au-195m, and the reproducibility of these measurements, are compared with similar studies using pertechnetate (Tc-99m).

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MATERIALS AND METHODS

Production of Au-195m. Stable Au-197 is transmuted to both Hg-195m and Hg-195 by the $p,3n$ reaction during cyclotron bombardment with 20.5-MeV protons. About half (45.8%) of the Hg-195m decays to Au-195 through electron capture with Au-195m as an intermediate step, while 54.2% of the Hg-195m decays to Hg-195 by isomeric transition. All Hg-195 decays through electron capture to Au-195 without contributing appreciably to the formation of Au-195m. Gold-195 decays

with a half-life of 183 days to stable platinum-195. Figure 1 shows the decay scheme for the parent Hg-195m ($T_{1/2}$ = 41.6 hr).

During decay, Hg-195m emits 261.75-keV gamma photons with 32.3% abundance, due to the Au-195m activity in equilibrium with Hg-195m (*7,8*). Thus, Hg-195m represents the major potential contaminant in the generator eluate. Therefore, optimal imaging of Au-195m requires that it be relatively free of the high-energy radiation from Hg-195m, including the 560-keV photons. Likewise, Hg-195, with energies ranging up to 1.171 MeV and a $T_{1/2}$ of 9.5 hr, is another potential contaminant that may appear.

Description of the drug. The drug is administered by intravenous injection, and contains Au-195m in the form of a complex with thiosulfate, $Na_3Au(S_2O_3)_2$. The established chemical name based on NF XII is: gold sodium thiosulfate Au-195m. The drug is obtained by elution from a sterile, pyrogen-free generator column in which Hg-195m is adsorbed and subsequently decays to Hg-195 and Au-195m.

Gold-195m can be available from a bedside generator. The generator column consists of silica gel coated with ZnS. The mercury isotopes obtained during cyclotron production are loaded on the column as mercuric nitrate, pH 5–6. Subsequently the generator is washed with thiosulfate solution and sterilized by autoclaving. The yield of Au-195m obtained from the generators at the present stage of development is 28–30% of the theoretical equilibrium activity of Au-195m, which in turn is 45.8% of the Hg-195m activity present on the generator.

Because of the very short half-life of Au-195m, it is obtained just before administration by the aseptic elution of the Au-195m generator with a thiosulfate solution. Elution intervals of 3–5 min can be accomplished easily. Roughly 20 mCi of Au-195m can be obtained with a 2-ml elution from a 155-mCi generator.

At the time of the study, a method to measure the amount of Au-195m actually eluted from the generator at the bedside was not available. The statements about performance of the generators used in this study are based on the observation that very good reproducibility was obtained from generators derived from the same production batch. These data were reported by the manufacturer during the preclinical trial period and were confirmed by the performance of generators retained by the manufacturer from the batches used in this study. At least two generators out of batches of five were retained by the manufacturer for analysis. They were eluted in a manner and at times analogous to the clinically used generators. Yields of Au-195m were measured with a Ge(Li) crystal with known calibration factors for 262 keV. The readings are extrapolated to t_0 = start of elution (*9*).

Clinical evaluation of the elution yields. Ten consecutive generators were evaluated for reproducibility of

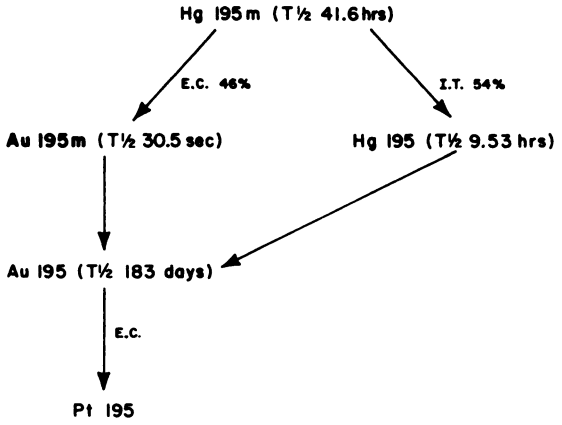

FIG 1. Production of Au-195m.

PRINCIPAL GAMMA EMISSIONS

				keV
Hg-195m	GAM	.7	32.3%	262
	GAM	.16	2.3%	388
	GAM	.30	7.5%	560
Au-195m	GAM	.7	68%	262

(Abbreviations: E.C. = electron capture; I.T. = isomeric transition)

Au-195m production as well as for assessment of contamination with Hg-195m. We eluted the generators with 2 ml of a solution consisting of 2.98 g% of sodium thiosulfate and 1.0 g% sodium nitrate. The generator was flushed sequentially every 3 min for 10 consecutive elutions. Immediately after the last elution, the eluate was diluted in 1,000 ml, and a one-ml aliquot was counted in a spectrometer with a 10% window set for the 260-keV peak. Sequential 6-sec counts were performed every 30 sec and continued for 7 min. After 7 min, a 1-min count was obtained. The results were expressed in counts per 6 sec on a semilogarithmic plot, extrapolated to zero time, and the $T_{1/2}$ calculated. The counts remaining after 7 min were considered to originate from Hg-195m (Fig. 2).

The toxicity of the eluting solution (aqueous thiosulfate) was studied with acute experiments in mice and rabbits. The cardiovascular safety of eluates was established in dogs. In mice, single eluate doses up to 800 times the single clinical dose were tolerated without observable effect; 1,600 times the single clinical dose produced minor transient reactions. Similarly, in rabbits, no untoward effects were seen after maximum volume doses equivalent to 300 times the single clinical dose. In dogs, no effects on the cardiovascular system were encountered with doses up to 64 times the single dose. Both the eluting solution and the eluates obtained from the generator are nontoxic and have no known pharmacological action on the cardiovascular system.

Radiation protection for clinical studies. Radiation protection measures must be taken during use of a Au-195m generator at the bedside. These involve shielding

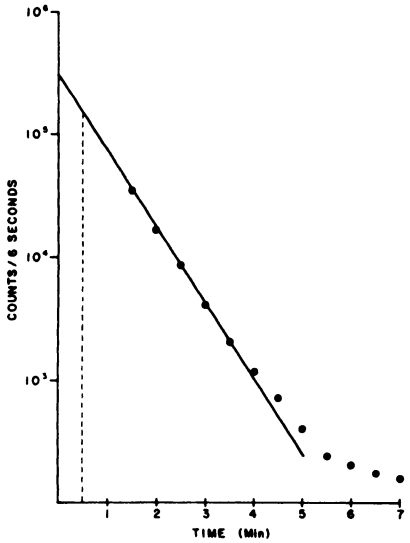

FIG. 2. Decay of Au-195m. Semi-log plot of Au-195m activity (in counts/6 sec) versus time (min). The $T_{1/2}$ of Au-195m is 30.5 sec (dashed vertical line). Solid line represents exponential, least-squares fit of initial curve. Residual activity at 6 and 7 min is presumed to represent Hg-195 activity.

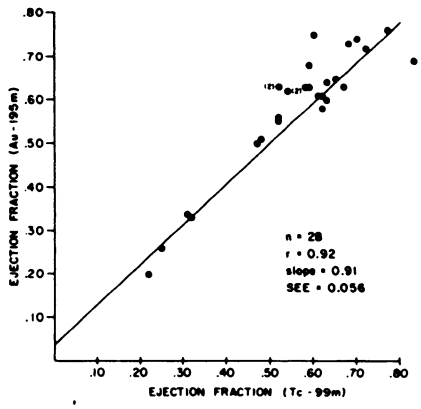

FIG. 3. Comparison of ejection fractions: Studies were obtained in same patients using Tc-99m and Au-195m as imaging agents.

the generator with approximately 8 cm of lead on all sides.The radiation at the surface of the installed generator in its shielding is not more than 0.25 mR/h. Under proper installation and handling conditions, the source of radiation to persons other than the patient is the bolus of Au-195m passing through the tubing from the generator to the patient, together with the Au-195m in the patient. Measurements at a 30 cm from the tubing and patient gave levels of 100 mR/h immediately after injection, 20 mR/hr at 1 min after injection, and 1 mR/hr at 2 min after injection.

The radiation dose to a person who installs and disassembles the generator is calculated to be not more than 9 mrem/wk. A person who performs elutions from the generator for 1 wk (25 patients with 6 studies per patient) would receive not more than 22 mrem/wk. These calculations are based on TLD badge readings obtained during a separate experimental animal study.

Patient studies: Determinations of ejection fraction. Right anterior oblique first-pass studies were obtained in 34 subjects after obtaining informed consent. Twenty patients had coronary artery disease, six had nonischemic heart disease, and eight subjects were normal volunteers. Two 30° RAO first-transit studies were obtained using Au-195m, with injections performed 3 min apart. The patients were seated, upright. Three minutes after the last Au-195m angiogram, a 1-min count over the patient's back was obtained to assess the presence of any 262-keV radiation from the kidney (presumably reflecting Hg-195m breakthrough).

The patient was then repositioned in the 30° RAO upright position, and a repeat left ventriculogram was obtained with a bolus injection of 15 mCi of pertechnetate (Tc-99m).

Instrumentation. Continuous on-line determinations of the reproducibility of the Au-195m elution were performed with a heavily shielded 1- by ½-inch sodium iodide detector with a 1-cm opening in the collimator. This collimator was placed 20 cm from the outlet of the Au-195m generator on an intravenous line connected to the patient.

A single-crystal, large-field-of-view camera with a 260-keV high-sensitivity collimator was used. The camera was interfaced to a dedicated computer. The maximal counts/sec in the total field were recorded immediately after an intravenous bolus injection of Au-195m.

The left-ventricular ejection fraction and wall motion were determined by our procedure (*3*), with modifications including determination of valve planes with phase analysis and the amplitude image (*10*). In brief, data are acquired in list mode, corrected for decay, then formatted into 1-sec frames. After background subtraction, the left-ventricular region of interest was outlined and a time-activity curve generated. Four cardiac cycles were summed and displayed in cine format for evaluation of wall motion, with a 35% isocount line superimposed on each frame.

RESULTS

Sterility and pyrogenicity. Samples of the eluate were obtained after the first elution of Au-195m from seven generators. In two of them the first elution and the final elution of Au-195m approximately 48 hr thereafter were evaluated. All samples were submitted to a reference laboratory unaware of the sequence in which the samples were obtained. All tests for pyrogenicity and sterility were negative.

Purity and dosimetry of Au-195m. Mercury-195m breakthrough in the eluates of the Au-195m generator

was measured in ten generators over 3 days. The average of 50 measurements revealed a mercury breakthrough of 0.75 ± 0.09 μCi per mCi of Au-195m. There was no statistically significant increase in mercury breakthrough when values obtained 24 and 72 hr after the initial elution were compared. Based upon these data and those of Ackers et al. (*11*), the absorbed radiation dose from a 20-mCi bolus of Au-195m would be: heart 0.78 mrads/mCi and kidneys 0.16 mrads/mCi. (Table 1). Exposure from Hg-195m is a function of the fractional leakage from the generator. Assuming roughly 1 μCi of Hg-195m/mCi of Au-195m, a 20-mCi injection of Au-195m would result in 240 mrads to the kidney, or 1.5 rads to the kidneys after six consecutive injections (*11*).

In contrast, the absorbed doses from a first-pass study with 15 mCi Tc-99m as pertechnetate are 0.17 rad whole body, approximately 1.9 rad each to the thyroid and large intestines, and 0.45 and 0.13 rad to ovaries and testes respectively (*12*).

Reproducibility of elution. The reproducibility of the eluent from the Au-195m generator was evaluated in 81 sequential measurements obtained on-line from the intravenous tubing carrying the patient injections. The coefficient of variation for the amount of Au-195m in the eluents was (2.5 ± 0.3)%. While the coefficient of variation was quite acceptable, a portion of the variation may nonetheless be the result of inaccuracies in the volume measurement of the eluting solution, which were performed with 3-ml syringes.

Counting efficiency. The counting efficiency for a 20-mCi bolus of Au-195m injected intravenously was evaluated during each of the 32 patient studies. The maximum total-field count rate achieved with this dose of Au-195m was 41,000 ± 3,700 cps. A 15-mCi bolus of technetium-99m resulted in 54,000 ± 3,900 cps.

The lower count rate obtained using Au-195m is due to a lower percentage yield of gamma photons as well as a lower crystal sensitivity. The calculated crystal absorption efficiency of Tc-99m is 91% using a ⅜ inch NaI crystal and a 140-keV setting. The crystal absorption for Au-195m at a 260-keV setting is 50%. The relative crystal absorption efficiency for Au-195m is, therefore, 55% compared with that for Tc-99m (*13*).

TABLE 1. DOSIMETRY OF Au-195m (Ref. *11*)

	Au-195m mrad/mCi	Hg-195m (incl. Hg-195) mrad/μCi
Heart wall	0.78	
Kidneys	0.16	12.4
Gonads	0.05	0.8
Lungs	0.56	0.8
Liver	0.12	1.1
Spleen	0.03	1.4
Total body	—	0.6

Comparison of resting left-ventricular ejection fraction (Tc-99m vs. Au-195m). Twenty-eight patients had both Tc-99m and Au-195m resting ejection fraction determinations. The EF ranged from 0.22 to 0.83 with a mean of 0.56 ± 0.028 (s.e.m.) with Tc-99m, and 0.2–0.76 with a mean of 0.58 ± 0.027 during the first of the two Au-195m resting studies. The correlation coefficient between the studies with the two nuclides was 0.92. The slope of the linear regression equation was 0.91, and the standard error of the estimate was 0.056 EF units (Fig. 3). This compares favorably with the data we have previously reported correlating first-pass radionuclide ventriculography with contrast angiography during cardiac catheterization (*3*). We previously reported a correlation coefficient of 0.97 (s.e.e. = 0.041 EF units) between contrast angiography and radionuclide angiography using pulmonary-artery injections of technetium.

The reproducibility of sequential Au-195m angiograms was also evaluated. These studies, performed 3 min apart, were obtained in 25 patients. The correlation coefficient between the two studies was 0.93 over an EF

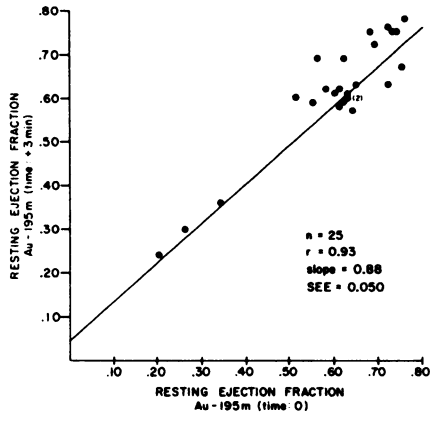

FIG. 4. Reproducibility of EF in same patient. Studies were performed 3 min apart with Au-195m as imaging agent. First study is termed "time 0" and second study 3 min later is "+3 min".

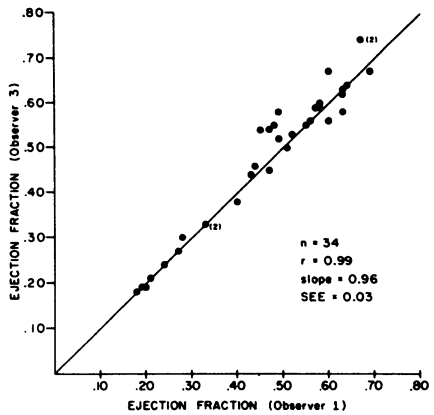

FIG. 5. Reproducibility of ejection-fraction determinations (interobserver variability).

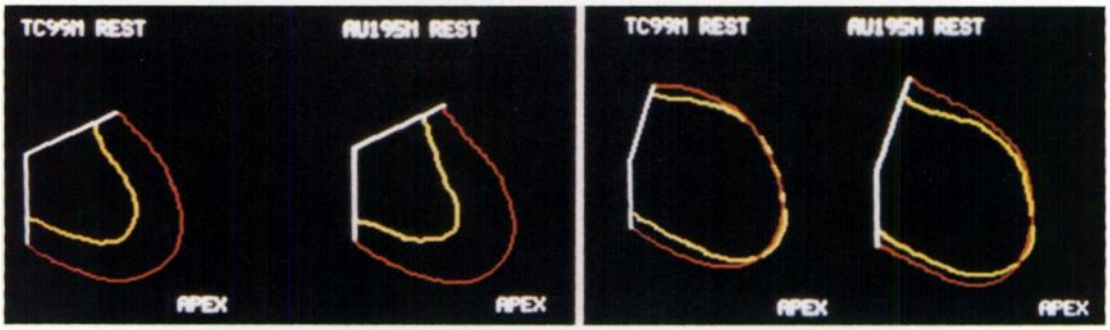

FIG. 6. Comparison of wall motions using Tc-99m and Au-195m as imaging agents. End-diastolic/end-systolic image of normal subject are displayed in left-hand panel (valve plane determined from amplitude and phase image). In this normal subject, symmetrical contraction is noted in both studies. In right-hand panel, studies of patient with prior infarct are displayed; diffuse hypokinesis and an apical aneurysm are noted with both tracers.

range from 0.20 to 0.78. The slope of the regression line was 0.88, and the standard error of the estimate was 0.050 absolute EF units (Fig. 4).

The reproducibility of our technique for determining the left-ventricular EF was evaluated by three operators using the same semi-automated computer algorithms to generate the left ventricular EF and a hard-copy display of the wall motion. The correlation coefficient for Observer 1 vs. Observer 3 was 0.99, with a standard error of the estimate of 0.03 EF units (Fig. 5). Wall motion was similar whether Au-195m or Tc-99m was used (Fig. 6).

Residual Hg-195 activity. Mercury breakthrough was evaluated during a 1-min count over the renal region 3 min after the last Au-195m ventriculographic study. In the 1-min counting period, the average 262-keV count rate was always less than 1,000 cps. Background activity with the generator in the imaging room was 600 cps. This is assumed to arise in residual Hg-195m activity and would represent approximately 0.1% mercury breakthrough during these patient studies.

DISCUSSION

With the currently available procedures, the Au-195m generator appears to provide stable yields with highly reproducible elution results. Preliminary reports from other laboratories agree with our findings (*14–16*).

The present study was performed using commercial collimators and a commercially available single-crystal digital camera. Since modern digital gamma cameras can process count rates in the order of 95,000 cps in the 260-keV energy range, with a 30% window and a 20% coincidence loss, even higher yields of Au-195m can easily be accommodated.

The experimental and clinical evaluation of the Au-195m generator presented herein demonstrates the feasibility and potential usefulness of its short-lived product, whose 30.5-sec half-life has many obvious advantages. As opposed to other short-lived radionuclides, Au-195m can be produced at the bedside, as this study shows. The radiation dose to the patient is substantially reduced when this agent is used, compared with technetium-99m, the conventional imaging agent. Based on the data presented in this evaluation, between six and eight sequential Au-195m first-transit studies can be performed with a radiation dose roughly equivalent to a single injection of 15 mCi of Tc-99m (*11,12*). The advantage of such a six- to eightfold reduction of radiation exposure would become even more critical in pediatric cardiology.

The availability of frequent, background-free determinations of left-ventricular function would open up additional uses for the evaluation of the left-ventricular ejection fraction and volume indices. Rapid acquisition at varying levels of exercise, frequent assessment of pharmacologic and physiologic interventions, and instantaneous acquisition of data using more than one tracer become readily feasible with agents such as Au-195m.

FOOTNOTE

* The Au-195m generators were produced by the Research Department of Byk Mallinckrodt CIL, Petten, The Netherlands, and were not commercially available at the time of the study.

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