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Angiocardiography with Iridium-191m

An Ultrashort-lived Radionuclide ($T_{1/2}$ 4.9 sec)

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SUMMARY Iridium-191m is a potential tracer for angiocardiography and may be of particular value in the evaluation of heart disease in children. It possesses a short half-life (4.9 sec), suitable photon energy (129 keV) and may be obtained as a generator product by decay of its long lived (15.3 day) parent ^{191}Os . An $^{191}\text{Os} \rightarrow ^{191m}\text{Ir}$ generator capable of providing 15 mCi of ^{191m}Ir in 1.5 ml of eluant is

described. The separation of ^{191m}Ir from ^{191}Os is achieved by absorbing $^{191}\text{OsCl}_6^{-2}$ on an anion exchange resin. The generator employs an additional resin column which is replaced to prevent ^{191}Os breakthrough to become excessive. By this procedure, the breakthrough may be kept below 0.001% over a period of at least one month and after multiple elutions.

RADIONUCLIDE ANGIOCARDIOGRAPHY is an established method for evaluation of the circulation within the heart, great vessels, and the lungs.¹⁻⁴ Its use in clinical practice is increasing since a large number of hemodynamic parameters can be evaluated nontraumatically following a single intravenous injection of radionuclide. One major use of this technique is in the evaluation of children with congenital heart disease. The information obtained with radio-

angiography is of importance in the diagnosis and management of these patients and, at times, can take the place of a cardiac catheterization. At present, radionuclide angiocardiography is performed with technetium-99m and gamma camera-computer systems.

Within the constraints imposed by modern imaging devices (i.e., limited spatial resolution), a major limitation of the method is the inability to obtain multiple projections within a short period of time because of high background from the initial radionuclide injection. As a consequence, currently employed radionuclides (notably technetium-99m) preclude more detailed anatomical evaluation of the cardiovascular system and study of the effects of exercise or pharmaceutical agents on the hemodynamics. In addition, since the duration of radionuclide angiocardiography is only 20 seconds and the half-life of technetium is six hours, the

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TABLE 1. *Ultrashort-lived Radionuclide Generators for Angiography*

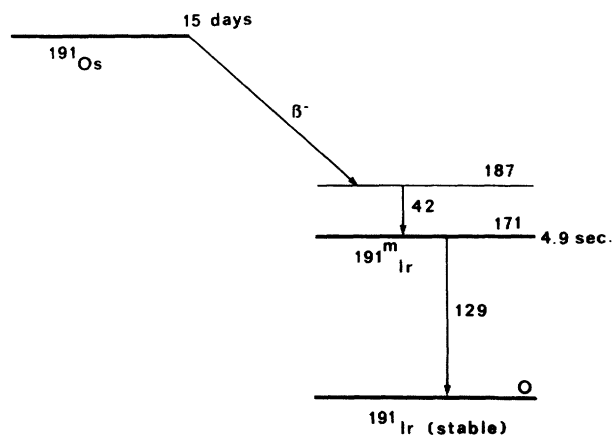
Generator system	T _{1/2}	Decay mode	Production	T _{1/2}	Decay mode	Energy keV
¹³⁷ Cs → ^{137m} Ba	30y			2.5 min		662
⁷⁷ Br → ^{77m} Se	57h	εβ ⁺	⁷⁵ As(α, 2n) ⁷⁷ Br	18 sec	It, e ⁻	162
¹⁰⁹ Cd → ^{109m} Ag	1.3y	ε	¹⁰⁸ Cd(n, γ) ¹⁰⁹ Cd	39.2 sec	It, e ⁻	87
¹⁹¹ Os → ^{191m} Ir	16d	β ⁻ , γ	¹⁹⁰ Os(n, γ) ¹⁹¹ Os	4.9 sec	It	129
⁸¹ Rb → ^{81m} Kr	4.7h	ε	⁷⁹ Br(α, 2n) ⁸¹ Rb	13 sec	It, e ⁻	193

patient continues to be irradiated for a period of time longer than necessary.

Since most of the information on radionuclide angiography is obtained during the initial transit of highly concentrated radionuclide solution, the availability of an ultrashort-lived radionuclide (i.e., with a half-life of a few seconds) with adequate gamma emission for imaging should increase the diagnostic potential of this technique and in addition, result in a significant reduction of the radiation dose. Ultrashort-lived radionuclides can be produced in large variety and quantity in medical centers close to a reactor or a cyclotron and their use is therefore limited to those centers.

Alternatively, a number of ultrashort-lived radionuclide generator systems are possible (table 1).

The advantage of a generator is that it can provide a continuous supply of ultrashort-lived radionuclide in locations remote from the production site. Characteristics of such generator systems in general were pointed out by Yano and Anger.⁶ There are a number of characteristics of ultrashort-lived radionuclide generator systems which are particularly desirable for angiography. The daughter product should decay with emission of low to medium energy gamma rays so that adequate detection and collimation can be accomplished with current gamma camera devices. The generator system should have a long-lived parent radionuclide so that the generator can be transported to hospitals away from the production site. The generator should allow rapid elutions in order that rapid nondiluted radionuclide bolus could be injected. The eluant material must be sterile, non-toxic, and free of pyrogens. The eluant must be of small volume (about 1 ml) and of high specific activity, again to achieve an adequate bolus effect. Finally, the generator must allow multiple elutions safely.

FIGURE 1. *Salient characteristics of osmium-191 decay.*

Method

Radionuclide Generator

Osmium-191 was prepared by reactor irradiation of 98% enriched osmium-190 (Oak Ridge National Laboratory, Oak Ridge, Tennessee) by the reaction ¹⁹⁰Os(n, γ) ¹⁹¹Os (fig. 1). After conversion into hexachloro-osmate,⁸ it was added to a column containing 2 ml of Bio-Rad Ag 1 × 2 anion exchange resin prewashed with 1 M HCl. The generator system is shown in figure 2 and consists of a 2.5 ml glass syringe body in which a polyethylene porous disc (Bel-Art Products, Pequannock, New Jersey) and 0.3 ml of Ag 1 × 4 have been placed at the bottom. The small amount of Ag 1 × 4 resin prevents the loss of appreciable amounts of osmium from the generator by retaining most of that which is released by the Ag 1 × 2 resin.

A millipore filter body containing an 8 μ membrane filter* to allow rapid elutions, and 0.2 ml of Ag 1 × 4 resin in the chloride form is fitted to the bottom of the generator column. An infusion set with short tubing is connected to the bottom of the second column for intravenous injections.

Because the generator is designed for use in radionuclide angiography, the eluant volume was set at 1.5 ml in order to achieve a bolus effect. As a consequence, the iridium yield is approximately 14% of the theoretical maximum. The eluant solution was 1.5 ml of 8.7% sodium chloride (1.5M) at pH 2.2. The second column is changed every five elutions to keep the osmium breakthrough from increasing. A detailed discussion of the chemical aspects pertaining to the development and construction of this and improved generators will be published elsewhere. (Hnatowich DJ, Kulprathipanja S, Treves S: An improved ¹⁹¹Os → ^{191m}Ir radionuclide generator).

The activity on the generator was estimated by counting an aliquot of the solution containing osmium-191 on a Ge(Li) multichannel analyzer system precalibrated for 129 keV gamma ray detection efficiency. The osmium-191 activity on the solution was then determined by correction for the photon-to-internal conversion ratio of 1:4 for 129 keV of iridium. A very small sample of the osmium-191 solution was used to calibrate an NaI(Tl) counter which was used to determine osmium-191 breakthrough in the eluants. The iridium-191m activity in the eluant was estimated by a properly shielded and calibrated survey meter. Readings were taken at the point when the meter reached its maximum reading during rapid elution (2–3 sec) into a vial placed with accurate geometry in front of the survey meter. The activity levels detected this way represented the amount available for angiography. The values of percent indium extraction and percent osmium breakthrough are with respect to the total osmium-191 activity on the column.

*Millipore Corporation, Bedford, Mass.

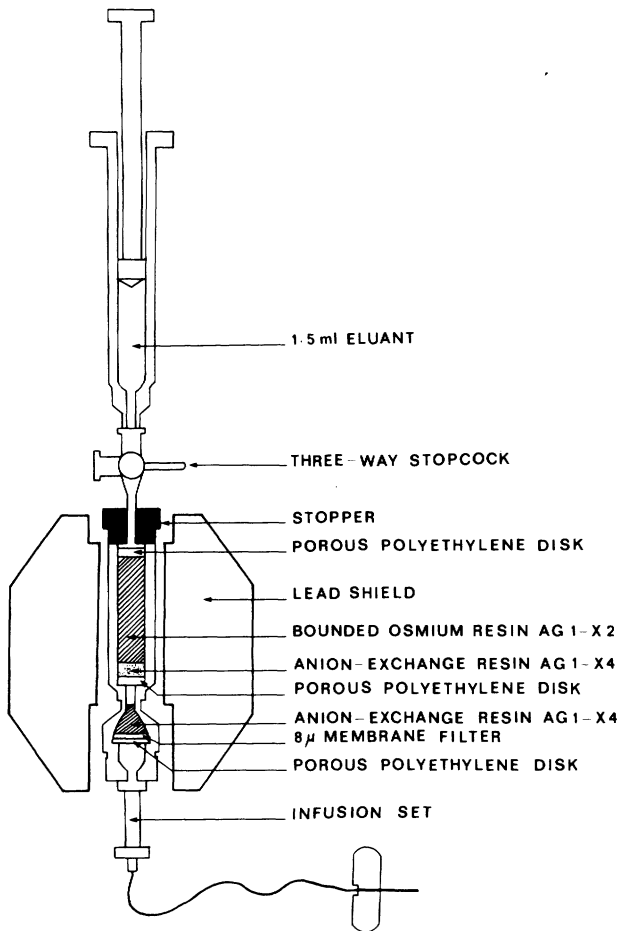


FIGURE 2. Detailed schematic diagram of the osmium-191 — iridium-191m generator.

A generator containing 130 mCi of osmium was initially eluted into a vial which was placed under the gamma camera to assess the amount of radioactivity available at the end of rapid elution. It was estimated that this was about 15 mCi of iridium-191m, which was equivalent to the photon flux of 4 mCi of technetium-99m. The activity in the eluant as a function of time was recorded in the computer (fig. 3).

Results

Multiple radionuclide angiocardiograms were obtained in two anesthetized rhesus monkeys weighing 4.1 and 4.3 kg. Each injection was in a 1.5 ml volume and its duration was less than two seconds. The radionuclide angiocardiograms were obtained in the anterior, oblique, and lateral projections with a gamma scintillation camera*-computer system.†

The radionuclide solution was injected as a bolus directly from the generator into a one-way valve injector,² then into an antecubital vein. The studies were recorded at 10 frames/sec on a 64 × 64 matrix format. A low energy converging collimator was used to achieve magnification since the monkeys were small. The radioactivity was seen as it cir-

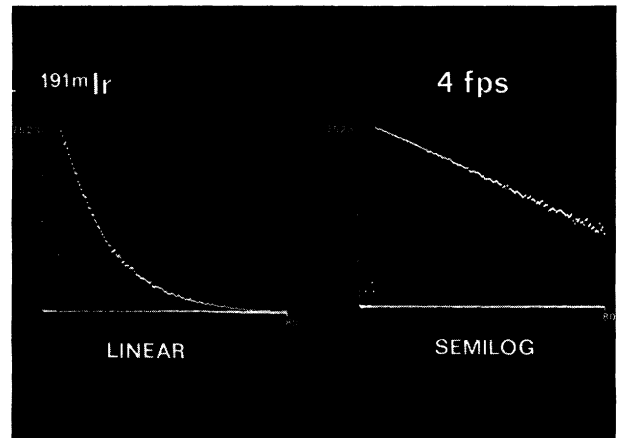


FIGURE 3. Activity as a function of time (4 frames/sec) recorded with the gamma camera-computer system of a vial in which iridium-191m was eluted from the generator. On the left, the linear and on the right, the semilogarithmic graphs are seen.

culated through the superior vena cava, right heart, pulmonary artery, lungs, left heart, aorta and kidneys (fig. 4). Repeat radionuclide angiograms could be performed as early as one minute following the preceding one without interfering background from the previous administration of iridium-191m. The 129 keV photon was adequately collimated with available collimators designed for 140 keV. Time-activity curves were plotted from multiple regions of interest and corrected for radioactive decay (fig. 5). It can be seen that there is greater statistical error in the curves as the isotope decays.

Using the decay corrected pulmonary dilution curve, it was possible to interpolate a gamma variate function and estimate the pulmonary-to-systemic flow ratio in the primate (fig. 6). Twenty and thirty radionuclide angiograms were obtained in each primate, respectively, using three different generator systems. There was no clinically observable toxic or pharmacologic effect during or following the administration of iridium-99m eluant. These animals have been observed for more than five months without any evidence of adverse effects.

Discussion

Of a number of possible ultrashort-lived radionuclide generators (table 1), we chose the osmium-191 — iridium-191m pair. The 129 keV of iridium-191m is well suited for adequate collimation and efficient detection with scintillation cameras. Although the 4.9 sec half-life of iridium-191m may be too short for studies in adults,⁸ it appears acceptable for radionuclide angiocardiography in prematures, newborns, and small infants with their more rapid circulation time and small volume of their cardiovascular system. The parent osmium-191 has a reasonable physical half-life of 15.3 days which allows for transportation of the generator to centers distant from the production sites.

Barium-137m has a physical half-life of 2.6 min suitable for imaging purposes, but its gamma energy (662 keV) is too high for use in conjunction with commonly available gamma scintillation cameras of the Anger type.⁷ Selenium-77m has a physical half-life and energy which makes it quite desirable

*PhoGamma HP Searle Radiographics Inc., Chicago, Illinois.

†Gamma 11 (PDP 11/20) Digital Equipment Corporation, Maynard, Massachusetts.

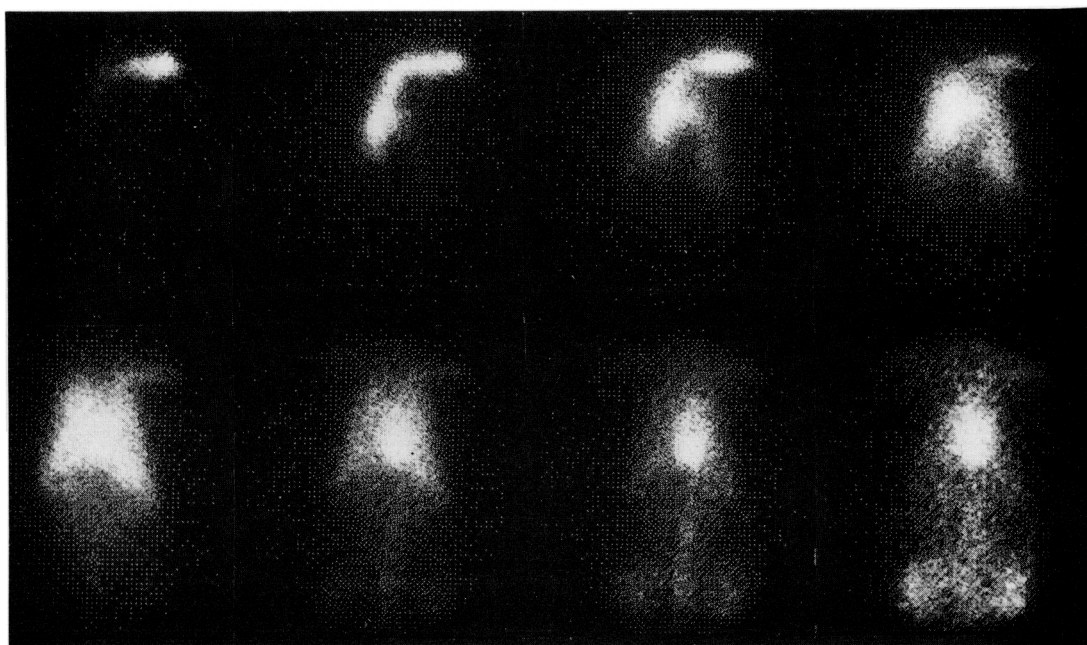


FIGURE 4. Anterior radionuclide angiogram on a rhesus monkey following intravenous injection of a 1.5 ml bolus of about 15 mCi of iridium-191m. The radioactivity is seen (1 frame/sec) as it circulates within the left subclavian vein, superior vena cava, right heart, pulmonary outflow tract (frame 1-3), lungs (frames 3-5), left heart, aorta (frames 5-7), and kidneys (frames 7-8).

for angiocardigraphy, but a generator has not been developed as yet. Silver-109m has the potential difficulty of the 1.26 year half-life of cadmium-109 in case of breakthrough. In addition, silver-109m has only 5% of detectable 99 keV photons. Krypton-81m is well suited for imaging with the

gamma camera for investigation of pulmonary blood flow and ventilation⁷⁻¹² but cannot be used for angiocardigraphy because it is largely eliminated in the lungs during its first pass. In addition, the parent rubidium-81 (half-life 4.7 hours) needs to be produced daily.

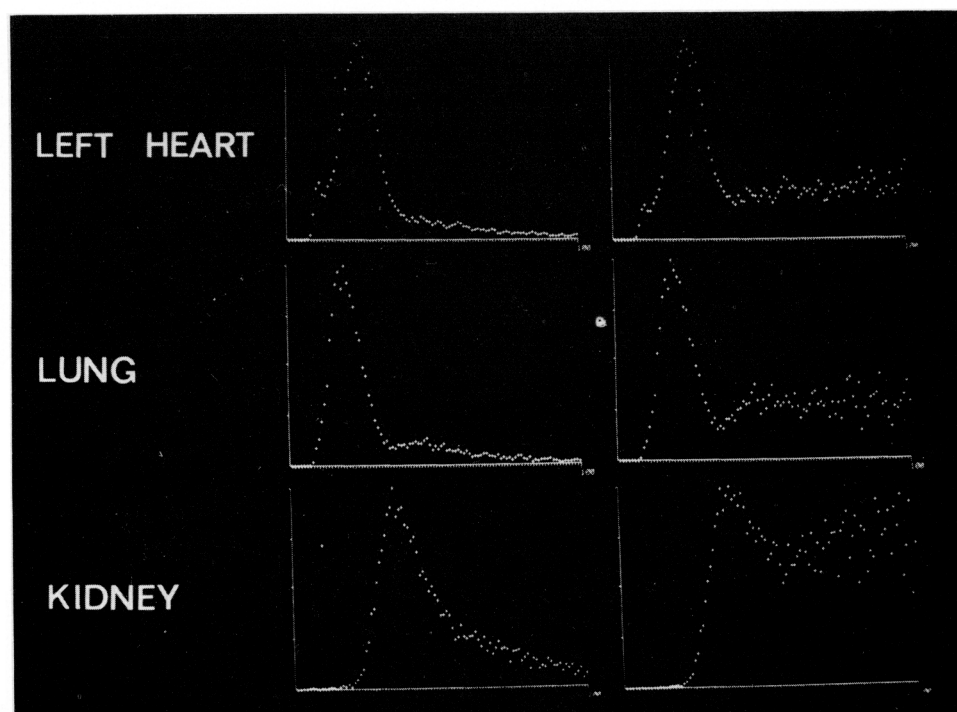


FIGURE 5. Time-activity curves obtained at 4 frames/sec from regions of interest over the left heart, lung, and kidney uncorrected (left) and then corrected (right) for radioactive decay. Note the increase in statistical fluctuation with radioactive decay.

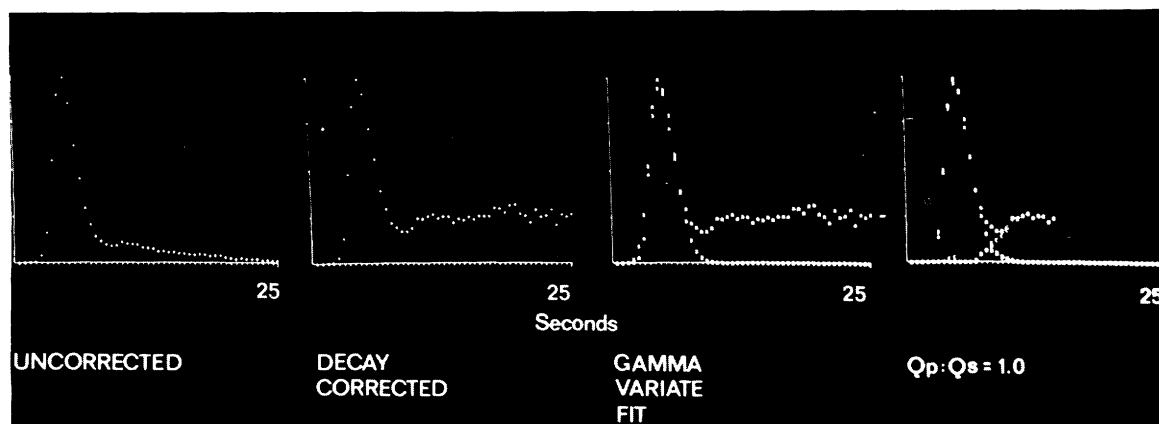


FIGURE 6. Calculation of pulmonary-to-systemic flow ratio ($Q_p:Q_s$) in a rhesus monkey from a pulmonary time-activity curve. The uncorrected curve at 2 frames/sec is corrected for decay. A gamma variate was interpolated and the $Q_p:Q_s$ was calculated by the method of Maltz and Treves.¹

The ^{191}Os - ^{191m}Ir radionuclide generator described in this report provides satisfactory levels of iridium activity when eluted with 1.5 ml of 8.7% NaCl at pH 2.2. Over a period of at least one month, the generator provides 14% of the maximum iridium activity (initially 15 mCi) with less than 0.001% osmium breakthrough (1.3 μCi).

As a result of the 25% photon yield of iridium-191m, the flux density of 15 mCi of this nuclide will be equivalent to about 4 mCi of technetium-99m measured by the gamma camera.

The yield of iridium may be increased by increasing the eluant volume and/or salinity but this will adversely affect the potential usefulness of the generator. Alternatively, the osmium activity on the generator may be increased (preferably by increasing the specific activity of osmium-191). The generators studied in this work contained up to 130 mCi of osmium-191.

Because the volume of each injection is small, the eluant pH and salinity may be easily tolerated. Whereas, the iridium released into the eluant is carrier-free and therefore, nontoxic, the osmium is not carrier-free. Its specific activity is about 1.3 mCi/mg; thus, about 1.0 μg of osmium in a new species, not previously described, will be present in each injection. No osmium tetroxide, which is the known toxic form of osmium, has been found in the eluant by spectrophotometric methods. Toxicity attributed to this new osmium species has not yet been described.

The radiation exposure associated with this procedure has been estimated from the decay scheme of osmium-191^{13, 14} and the MIRD tables of absorbed fraction.¹⁵ The whole body radiation exposure to a 70 kg adult from 15 mCi of iridium-191m is 0.14 mrad while that due to 1.3 μCi of osmium-191 is 3.9 mrad. The whole body radiation exposure to a 10 kg child would be about 21 mrad (iridium-191m and osmium-191). The organ distribution of the osmium compound is presently under study. The estimates of osmium exposure were based on the assumption of infinite retention. However, recent animal distribution studies indicate that a substantial amount of osmium breakthrough appears rapidly in the urine. In this case, the radiation dose will be reduced considerably.

It is expected that with generators of greater activity,

further improvement of radionuclide angiocardiology will be possible. One way of reducing the osmium breakthrough is to increase the osmium activity in the column and increase the amount of resin in the second column. This study demonstrates the feasibility of iridium-191m angiocardiology and shows the potential for improved diagnosis of cardiovascular disorders in infants, prematures, and newborns. In conjunction with mobile (portable) imaging devices, it now becomes possible to offer routine bedside evaluation of these often critically-ill patients both before and after surgery. Moreover, pathophysiologic progression of disease may be defined prior to the onset of signs or symptoms, which have hitherto become manifest only at late stages of decompensation.

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