INVESTIGATIVE NUCLEAR MEDICINE

Iridium-191 Angiocardiography for the Detection and Quantitation of Left-to-Right Shunting

S. Treves, C. Cheng, A. Samuel, R. Lambrecht, B. Babchyck, R. Zimmerman, and W. Norwood

Harvard Medical School, The Children's Hospital Medical Center, and Massachusetts Institute of Technology, Boston, Massachusetts, and Brookhaven National Laboratory, Upton, New York

An osmium-191 → iridium-191 generator that can deliver multiple doses of Ir-191m for first-pass radionuclide angiography has been developed. Iridium-191m has a physical half-life of 4.96 sec and decays with emission of 65-keV and 129-keV photons in 58 and 30% abundance, respectively. Using a gamma camera, Ir-191m radionuclide angiography was carried out, in dogs and ten patients, for the detection and quantitation of left-to-right shunting. In a one-year-old patient, 25 mCi of Ir-191m results in a whole-body radiation absorbed dose of 35 mrad. Multiple Ir-191m angiograms can be performed, seconds to minutes apart, without interference from background. The 15.4-day half-life of Os-191 permits transportation of the generator to centers far from the production facility. With the low radiation dose, high information density, and the ability to repeat studies with Ir-191m, clinical use of radionuclide angiography should be expanded.

J Nucl Med 21: 1151–1157, 1980

First-pass radionuclide angiography is well established for the detection and quantitation of shunts and in the evaluation of cardiac function (*1–8*). Technetium-99m is used almost exclusively in this method because of its easy availability and nearly ideal photon energy (140 keV) for imaging with gamma scintillation cameras. However, its physical half-life (6 hr) is too long for first-pass radionuclide angiography, since this is carried out in 20–30 sec following intravenous injection. Consequently, Tc-99m angiography exposes the patient to radiation for a much longer time than necessary. In addition, multiple Tc-99m angiograms repeated at short intervals are compromised by the high residual background from previous injections.

Iridium-191m, with a physical half-life of 4.96 sec, is potentially advantageous for radionuclide angiography (*9–14*). It emits x-rays at about 65 keV and a 129-keV gamma photon; these are in 58 and 30% abundance, respectively. Both photons can be imaged with modern gamma scintillation cameras. Because of the short physical half-life of Ir-191m, relatively large amounts of activity can be administered to the patient with much lower radiation exposure than with relatively smaller doses of Tc-99m. The high photon flux available with Ir-191m permits rapid imaging with high information density. Serial studies in the same patient only a few seconds apart are possible with Ir-191m without interfering background from previous administrations. In this way, the heart and great vessels can be evaluated in a variety of conditions.

Iridium-191m is the product of β^- decay of osmium-191, which has a physical half-life of 15.4 days. An Os-191 → Ir-191m generator system, which can deliver multiple doses of Ir-191m for rapid intravenous injection, has been developed in our laboratory (*15*). In this manuscript, we describe our initial experience in the use of Ir-191m for first-pass radionuclide angiography in patients referred for detection and quantitation of shunts.

Received April 18, 1980; revision accepted July 21, 1980.

For reprints contact: S. Treves, MD, Div. of Nuclear Medicine, The Children's Hospital Medical Ctr., 300 Longwood Ave., Boston, MA 02115.

METHODS

Radionuclide generator. This is described in detail in the companion paper (*15*). It is eluted, in less than 2 sec, with 1 ml or less of 0.9% NaCl at pH 1. The eluent is rapidly diluted and flushed with 1–10 ml of a buffer solution (25% 0.05 *M* Na_2HPO_4 and 75% normal saline) at pH 8.4. Since the flushing solution is injected simultaneously with the generator eluate, the lowest pH in the injected solution is 3.5. The generator eluate is sterile, free of pyrogens, and nontoxic even at pH 1 (*15*). The Ir-191m yield in 1 ml of eluate is 7–10% of the Ir-191m in the column, and the Os-191 breakthrough is 0.003–0.005%. The Ir-191m yield and Os-191 breakthrough remain essentially constant throughout multiple elutions over 3 or more weeks.

The maximum administered dose of Ir-191m to the patients in this study was 80 mCi and the minimum was 25 mCi. Knowing the elution profile (activity/ml) of the generator, the dose of Ir-191m can be adjusted by selecting the volume of eluate injected.

Imaging technique. A small source of Os-191 is used to calibrate the scintillation camera. Osmium-191 does not itself emit photons, thus the only two photopeaks detected are the photons from Ir-191m. Two 20% windows in the dual pulse-height analyzer are set over the 65- and 129-keV peaks. Modern gamma scintillation cameras can image both energies and 3 mm lead bars spaced 3 mm apart can be resolved. (Fig. 1)

In patients, Ir-191m angiography produced true maximum count rates at ~150,000 cps. This counting rate resulted in significant count loss due to system dead time. The loss was measured using a small shielded source of Os-191 placed near the edge in the field of view of the gamma camera while the radioangiogram was carried out. As the count rate to the rest of the field increased beyond the linear response of the system, the apparent count rate of the small source decreased (Fig. 2). Correction for count losses was carried out in the following way. An average value (A) of the counts from the point source before deadtime occurred was calculated. A correction factor (CF) was calculated for each frame of the study using the formula: CF = A/RC, where RC is the recorded count rate of the point source in that frame. The corrected counts were obtained by multiplying the number of counts in the region of interest by the correction factor. Correction for radioactive decay was applied to all the angiograms done with Ir-191m (cf. Fig. 2B). The correction factor is $\exp(T - T_0)\ln 2/T_{1/2}$, where exp is the exponential function, T is the time (sec) from the beginning of the study, T_0 is the time (sec) at which the activity first appears, and $T_{1/2}$ is the physical half-life of Ir-191m (4.96 sec) (*16,17*).

The observed time-activity curves were corrected for the shape of the input bolus using deconvolution analysis.

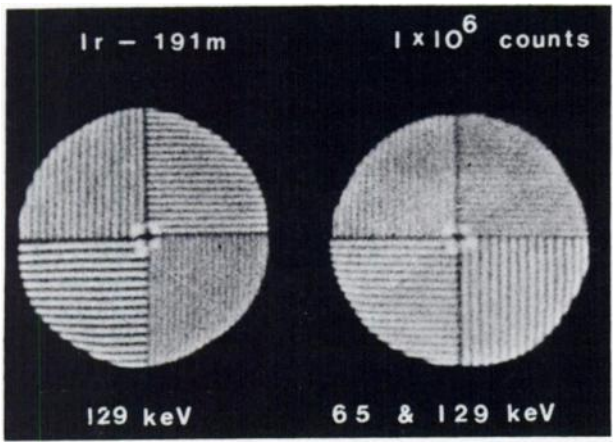

FIG. 1. Intrinsic resolution (Searle LEM) of bar phantom exposed to small source of Ir-191m 6 ft away from detector. Each image contains 1 million counts. Left image is taken with 129-keV photon alone. Right image includes both photons. Smallest lead bars are 3 mm wide.

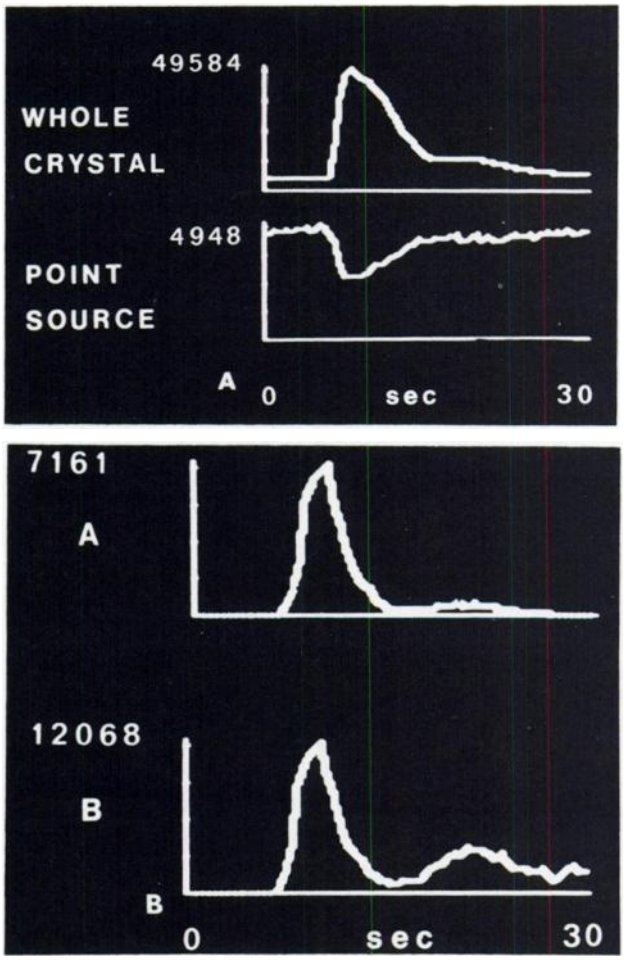

FIG. 2. (A) Time-activity curves as recorded during first-pass radionuclide angiogram, recorded at 2 frames/sec for 30 sec. Top: count rate over whole field of view of camera. Maximum recorded rate = 49,584 cps. Bottom: rate from point source, 4,940 cps and apparent decrease due to system deadtime. (B) A: Uncorrected Ir-191m pulmonary time-activity curve from patient JL, who had no shunt. Radioactive decay is evident. B: Same curve as above after correction for radioactive decay and count loss.

TABLE 1. Ir-191m ANGIOGRAPHY IN PATIENTS*

Name	Sex	Age	Site of injection	Diagnosis	Qp:Qs	Area study performed
JL	M	3 yr	Right atrial catheter	Post op ASD	1.05	Intensive Care Unit
BBL	M	26 d	Right wrist	PDA	1.5–1.7	Special Care Nursery
BG	M	20 yr	Right jugular vein	Traumatic VSD	1.2	Nuclear Medicine
BGD	M	24 d	Right arm	Post op PDA	1.3	Special Care Nursery
ML	M	16 yr	Right arm	PVO, VSD	1.5	Nuclear Medicine
LC	F	23 yr	Left jugular vein	? VSD	1.2–1.3	Nuclear Medicine
CC	F	7 m	Right jugular vein	Post op truncus	1.8	Nuclear Medicine
TD	M	8 m	Left jugular vein	? PDA	2.3	Nuclear Medicine
MB	F	5 yr	Left jugular vein	VSD	1.3	Nuclear Medicine
GC	M	4 d	Left foot	VSD	3.0	Intensive Care Unit

* M = male; F = female; ASD = atrial septal defect; PDA = patent ductus arteriosus; VSD = ventricular septal defect; PVO = pulmonary vascular obstruction; and Qp:Qs = pulmonary-to-systemic flow rate.

This was performed by the method of discrete Fourier transforms (*18–21*), and the resulting curves were filtered using a low-pass digital filter to remove high-frequency components. The pulmonary-to-systemic flow ratio (Qp:Qs) was determined by analysis of pulmonary dilution curves using a method developed in our laboratory (*7*).

Animal studies. In order to confirm the effectiveness of Ir-191m for detection and quantitation of left-to-right shunting, we performed Ir-191m and Tc-99m angiography in two normal dogs and in three dogs with experimental atrial septal defects. The animals were anesthetized with sodium pentobarbital and studied in the supine position. One milliliter of Ir-191m eluate was rapidly injected into one external jugular vein with simultaneous flushing using the buffer solution. Five to seven sequential Ir-191m angiograms (30 to 80 mCi) were followed by one or two Tc-99m angiograms (5 and 10 mCi). The studies were recorded using a gamma scintillation camera and a computer at 12 frames per sec for 15 sec, on a 64- × 64-word matrix format. The radionuclide angiograms were evaluated visually and regions of interest were marked, including the superior vena cava, right lung, left lung, and point source. Time-activity curves were calculated for these regions and for the entire field of view of the camera. The curve from the superior vena cava served to evaluate the shape and integrity of the bolus, and as an input signal for deconvolution analysis. The curves from the lungs were used for detection and quantitation of left-to-right shunting. The values on the curve from the point source were used to correct for count loss.

Angiography in patients. Ten patients ages 4 days to 23 years had first-pass Ir-191m angiography for detection and quantitation of shunts (Table 1). Consent for the studies was obtained from the patient and/or parent or guardian in each case.

All the patients were studied in the supine position. The gamma camera, fitted with a collimator designed for low energies was positioned above the chest of the patient. A 21- or 23-gauge "butterfly" needle was inserted intravenously and the tubing was connected to a special injector in the form of a "T" connector (*5*). The eluate (0.6–1 ml) containing the Ir-191m was injected into one branch of the "T" connector while the buffer solution (1–5 ml) was injected simultaneously into the other branch. The injection lasted less than 2 sec. All injections were adequate and no adverse reactions were detected in any of the patients studied. The radionuclide angiograms were recorded on a computer at 12 frames per sec for 25 sec. The studies were analyzed visually and quantitatively as described above.

RESULTS

Animal studies. The estimated Qp:Qs with Ir-191m in normal animals varied between 1.09 and 1.13 ($\bar{x}$ = 1.11 ± 0.02 s.d.). After deconvolution the range was from 1.07 to 1.17 ($\bar{x}$ = 1.12 ± 0.04 s.d., Table 2).

The Qp:Qs estimated using Ir-191m and Tc-99m angiograms in the dogs with experimental atrial septal defect were in close agreement. Slightly less variability

TABLE 2. PULMONARY-TO-SYSTEMIC FLOW RATIO (Qp:Qs) IN TWO NORMAL DOGS

Experiment	Original pulmonary curve	Deconvoluted pulmonary curve
1	1.13	1.12
2	1.09	1.11
3	1.08	1.07
4	1.13	1.17
5	1.10	1.14
	$\bar{x}$ 1.11	1.12
	s.d. 0.02	0.04

TABLE 3. RADIONUCLIDE DETERMINATION OF PULMONARY-TO-SYSTEMIC FLOW RATIO (Qp:Qs) IN DOGS WITH ATRIAL SEPTAL DEFECT

Dog no.		Qp:Qs Original pulmonary curve	Qp:Qs Deconvoluted pulmonary curve
1	Tc-99m	1.95	2.14
	Ir-191m	2.08	1.79
		2.14	2.05
		1.88	2.12
		2.10	2.14
		1.83	1.97
	$\bar{x}$	2.01	2.01
	s.d.	0.14	0.14
2	Tc-99m	1.69	1.47
		1.72	1.67
	Ir-191m	1.82	1.63
		2.24	1.17
		2.36	1.77
		1.73	1.70
		1.77	1.60
	$\bar{x}$	1.98	1.68
	s.d.	0.29	0.07
3	Tc-99m	1.28	1.33
		1.12	1.25
	Ir-191m	1.34	1.38
		1.45	1.25
		1.26	1.28
		1.18	1.37
		1.47	1.27
		1.47	1.27
		1.52	1.38
	$\bar{x}$	1.38	1.31
	s.d.	0.13	0.06

among the Qp:Qs estimates was seen when the deconvoluted pulmonary curves were used (Table 3).

Patient studies. Patient JL, a 3-year-old boy, was evaluated in the intensive-care unit because of a residual systolic murmur following closure of an atrial septal defect. The estimated pulmonary-to-systemic flow ratio in this patient was 1.05 (Figs. 3A and B). Three patients with the diagnosis of patent ductus arteriosus were studied. A 26-day-old male (BBL), receiving assisted ventilation in the special-care nursery, had a Qp:Qs of 1.5–1.7. It was felt that his major problem was related to the pulmonary disease. A 24-day-old female (BGD), with a residual murmur after ligation of a patent ductus arteriosus, had a Qp:Qs of 1.3. The shunt was judged to be hemodynamically insignificant and probably related to a patent foramen ovale. A third patient (TS), with the diagnosis of patent ductus arteriosus, was an 8-month-old male who had a Qp:Qs of 2.3.

Five patients with the diagnosis of ventricular septal defect were studied. A 20-year-old man (BG), with a traumatic ventricular septal defect, was evaluated for possible spontaneous closure of the defect. The Qp:Qs was 1.2, unchanged 1 yr after a previous study. A 16-year-old male (ML), with pulmonary vascular obstructive disease and ventricular septal defect, had a Qp:Qs of 1.5 on room air and also 1.5 after breathing oxygen for 15 min. This failure to increase the Qp:Qs after oxygen was consistent with advanced pulmonary vascular obstructive disease. A 23-year-old woman was evaluated because of transient "ischemic attacks" and a murmur of ventricular septal defect. The left-to-right shunt was hemodynamically insignificant. A 5-year-old girl (MB) was evaluated to document spontaneous closing of her ventricular septal defect. She had a Qp:Qs of 1.3. A 4-day-old male (CG) was studied in the intensive-care unit following surgical closure of a ventricular septal defect. A Qp:Qs greater than 3 substantiated the diagnosis of patch detachment, and a new operation was done. A 7-month-old female (CC) was evaluated following surgery of a truncus arteriosus. A residual left-to-right shunt with a Qp:Qs of 1.8 was detected (Figs. 4A and B).

DISCUSSION

First-pass radionuclide angiography has demonstrated its potential for noninvasive evaluation of a variety of congenital and acquired cardiovascular disorders in children (*5*). In some cases this method provides useful complementary information, and in others it serves as a definitive diagnostic procedure.

There are certain limitations with current first-pass radionuclide angiography. Some are related to the radiopharmaceutical (Tc-99m) and some to the available instrumentation.

The limitations related to the use of Tc-99m include the following.

1. The patient is irradiated for much longer time than necessary, since the recording time for the study is from 15 to 30 sec.

2. It is not possible to obtain adequate serial angiograms within a short period of time due to high body background from previous administrations. Multiple injections may be necessary in a variety of circumstances. For example, to determine the anatomic relationships of the chambers of the heart and of the great vessels; to locate shunts; or for measurement of ventricular function. Similarly multiple angiograms are necessary for the evaluation of the effect of exercise, drugs, or oxygen on the shunt flow, pulmonary resistance, or cardiac function. Also, in case of technical failure, a repeat injection may be necessary.

3. With currently accepted dosimetry, Tc-99m yields relatively low photon flux for high-frequency recording. Low photon flux limits temporal and anatomic resolution, which in turn limits accuracy in measurements of ventricular function.

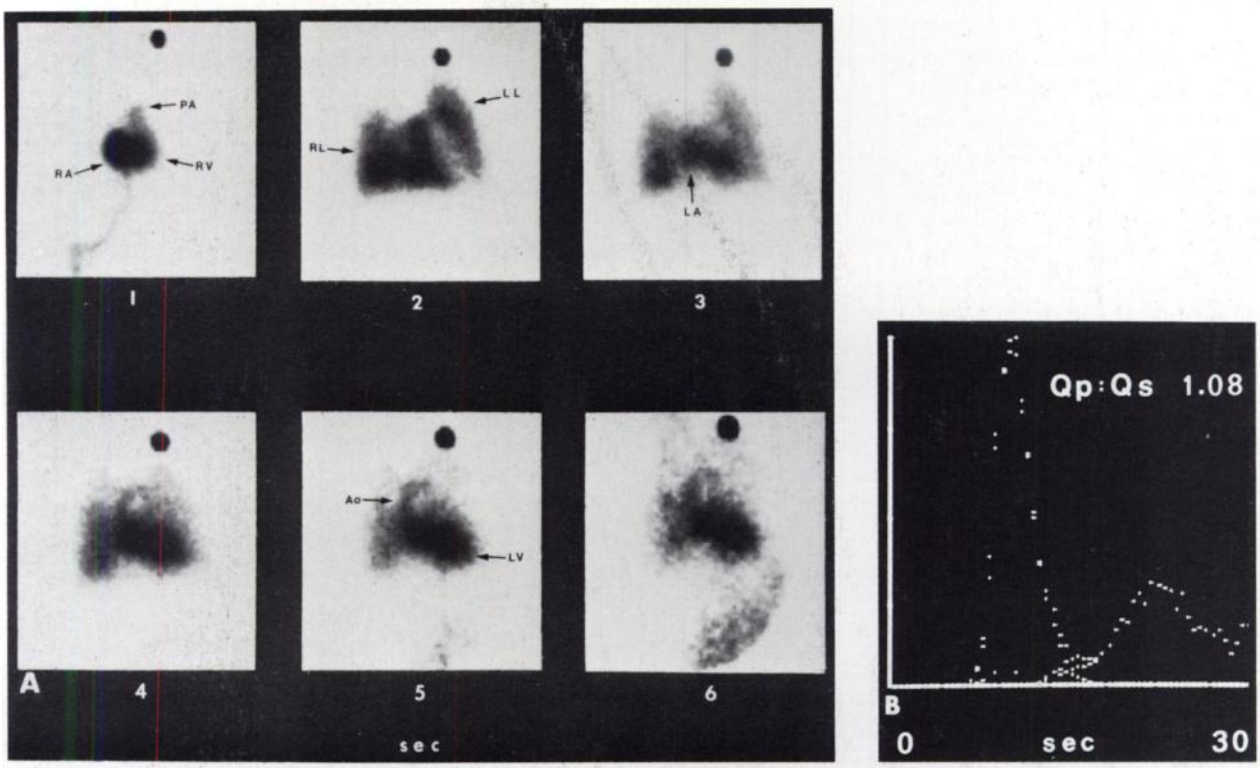

FIG. 3. (A) Normal Ir-191m angiogram. Anterior view, Patient JL. Each image shown represents 1.0 sec. Tracer was injected into transcutaneous right-atrial catheter. Radioactivity is seen as it circulates into catheter, right atrium, right ventricle, pulmonary artery, lungs, left atrium, left ventricle, and aorta. Dot of activity in upper part of each frame is small shielded source of Os-191, used to measure count loss (see Fig. 2). (B) Normal pulmonary time-activity curve obtained from right lung of same patient. Curve has been corrected for count loss and radioactive decay, and has been analyzed by method of Maltz and Treves for determination of pulmonary-to-systemic flow ratio (Qp:Qs). In this case Qp:Qs = 1.08 or essentially normal.

With the new generator and tracer, on the other hand, our angiograms were of excellent quality. Iridium-191m results in low radiation dose to the patients. For example, a 25-mCi dose of Ir-191m given to a one-year-old patient results in a whole-body radiation absorbed dose of 35.4 mrad: 0.4 mrad due to Ir-191m and 35 mrad due to the Os-191 breakthrough. The critical organ with Ir-191m is the vein receiving the injection, and its maximum extimated absorbed dose is less than 500 mrad. In comparison, 3 mCi of Tc-99m, administered as sodium

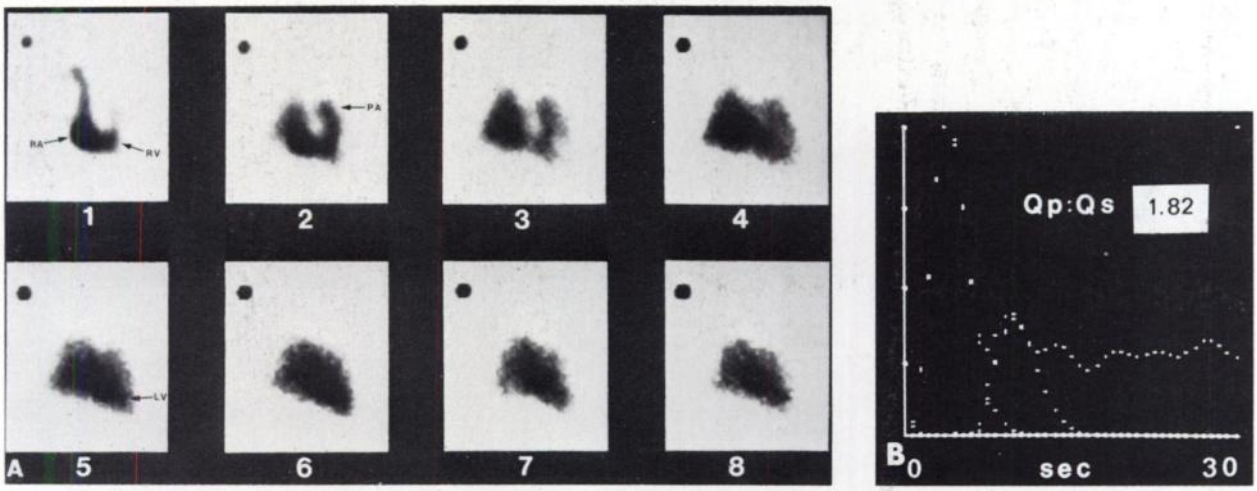

FIG. 4. (A) left-to-right shunting. Patient CC, a 7-month-old female studied after surgical correction of truncus arteriosus. Each image lasts 1 sec. Tracer was injected in right external jugular vein. Series of images shows radioactivity circulating in superior vena cava, right atrium, pulmonary artery, lung, left side of heart, and aorta. Early pulmonary recirculation, due to left-to-right shunt, is evident. (B) Pulmonary time-activity curve on same patient reveals early recirculation due to left-to-right shunting. Curve was corrected for radioactive decay and count loss. Estimated Qp:Qs = 1.82.

pertechnetate to a 1-year-old patient, results in a whole-body dose of 195 mrad and a critical organ (intestine) dose of 1,900 mrad.

In 1973 we developed and validated (*4*) a method of radionuclide angiography for the detection and quantitation of left-to-right shunting in children. Others have confirmed the validity of this method in patients (*22*) and in dogs with experimental atrial septal defects (*23*). We have performed multiple successive Ir-191m and Tc-99m radionuclide angiograms in normal dogs and dogs with experimental atrial septal defect. The two tracers provided essentially identical estimates of pulmonary-to-systemic flow ratios (Qs:Qs).

We have determined that multiple studies done immediately, one after the other, are possible with Ir-191m without interference from background. Correction for radioactive decay of the Ir-191m time-activity curves can be done on any nuclear medicine computer system.

Another limitation of present first-pass radionuclide angiography is the count loss due to instrument dead time. Correction for such losses is dependent on scatter and window setting. To measure the count loss, we placed a small shielded source of Os-191 at the edge of the field of view. All the commercial Anger cameras that we tested showed a linear response up to about 20,000 counts per second, beyond which point deadtime began to cause problems. Studies using phantoms with Ir-191m reached peak (corrected) count rates of about 300,000 counts per second in air. Iridium-191m studies in patients reached count rates of about 150,000 cps. Thus it is evident that although current scintillation cameras can be used for imaging Ir-191m, they do not take full advantage of the count rate available with this radionuclide. Modification of these cameras or the development of alternative imaging detectors (multiwire proportional chambers or solid-state cameras) is desirable. Not only would these two concepts provide better response to high count rates than current cameras, but also both detectors should be reasonably efficient at low energies, such as the 65 keV derived from Ir-191m. Spatial resolution with Ir-191m is best with the most modern scintillation cameras, which have been optimized for low energies. With these cameras, phantoms of lead bars 3 mm wide can be easily resolved.

Our Os-191 → Ir-191m generator system has been designed for first-pass radionuclide angiography in children. Since the circulation in children is rapid and their intravascular volume is small, the 4.9-sec half-life of Ir-191m is quite satisfactory, as our studies demonstrate. We found, however, that the method can also be used effectively in older children and young adults (patients BG, ML, LC). Recently we have performed Ir-191m angiograms in an additional 49 patients (9 days to 67 years of age) including five patients more than 40 years of age. All studies were technically adequate, permiting visualization of the right and left chambers of the heart. Preliminary results show that Ir-191m allows quantitation of right and left ventricular function in children and adults.

Other potential applications of Ir-191m angiography include: (a) measurement of ventricular volumes; (b) detection of left-to-right and right-to-left shunts; (c) evaluation of renal perfusion; (d) evaluation of pulmonary arterial perfusion; (e) venography, diagnosis of superior or inferior vena caval obstruction, or evaluation of other venous drainage; (f) evaluation of cerebral perfusion; and (g) evaluation of blood flow to organs and tumors by selective arterial infusion.

The 15.4-day physical half-life of Os-191 permits transportation of the generator to centers distant from the production site. The Os-191 → Ir-191m generator should result in more widespread use of radionuclide angiography, since the study can be done with minimal radiation exposure.

ACKNOWLEDGMENTS

This work was supported by grants from the Fannie Ripple Foundation, DOE Contract No. EY-76-S-4115, and NIH Grant No. 2-P50-6M-18674-07.

REFERENCES

1. DONATO L: Basic concepts of radiocardiography. *Semin Nucl Med* 3:111-130, 1973
2. KURTZ D, AHNBERG DS, FREED M, et al: Quantitative radionuclide angiocardiography. Determination of left ventricular ejection fraction in children. *Br Heart J* 38:966-973, 1976
3. WEBER PM, DOS REMEDIOS LV, JASKO IA: Quantitative radioisotopic angiocardiography. *J Nucl Med* 13:815-822, 1972
4. MALTZ DL, TREVES S: Quantitative radionuclide angiocardiography: determination of Qp:Qs in children. *Circulation* 47:1049-1056, 1973
5. TREVES S, COLLINS-NAKAI RL: Radioactive tracers in congenital heart disease. *Am J Cardiol* 38:711-721, 1976
6. MCILLMOYLE G, AHNBERG D, LAFARGE G, et al: Localization of left-to-right shunts by radionuclide angiocardiography. In *Dynamic Studies with Radioisotopes in Medicine*. Vienna, IAEA 2:251-261, 1975
7. RABINOVITCH M, ROSENTHAL A, AHNBERG DS: Cardiac output determination by radionuclide angiography in patients with congenital heart disease. *Am J Cardiol* 39:309, 1977 (abst)
8. WESSELHOEFT H, HURLEY PJ, WAGNER HN, JR, et al: Nuclear angiocardiography in the diagnosis of congenital heart disease in infants. *Circulation* 45:77-91, 1972
9. YANO Y, ANGER HO: Ultrashort-lived radioisotopes for visualizing blood vessels and organs. *J Nucl Med* 9:1-6, 1968
10. YANO Y: Radionuclide generators: Current and future applications in nuclear medicine. In *Radiopharmaceuticals*. Subramanian G, Rhodes BA, Copper JF, Sodd VJ, Eds., New York, Society of Nuclear Medicine, 1975, pp 236-245
11. TREVES S, KULPRATHIPANJA S, HNATOWICH DJ: Angiocardiography with Iridium-191m. An ultrashort-lived radionuclide ($T_{1/2}$ 4.9 sec). *Circulation* 54:275-279, 1976
12. HNATOWICH DJ, KULPRATHIPANJA S, TREVES S: An improved ^{191}Os-^{191m}Ir generator for radionuclide angiocar-

diography. *Radiology* 123:189-194, 1977

13. KULPRATHIPANJA S, HNATOWICH DJ, TREVES S: The hydrolysis and radiolysis of Os-191 Hexachloroosmate (IV). *J Inorg Nucl Chem* 39:933-935, 1977
14. KULPRATHIPANJA S, HNATOWICH DJ, DAVIS MA, et al: Radionuclide angiography with Iridium-191m ($T\frac{1}{2}$ - 4.9s). An improved osmium-191-iridium-191m generator, Vienna, IAEA, 2:53-59, 1977
15. CHENG C, TREVES S, SAMUEL A, et al: A new osmium-191 → iridium-191m generator. *J Nucl Med* 21:1169-1176, 1980
16. SORENSON JA: Deadtime characteristics of Anger cameras. *J Nucl Med* 16:284-288, 1975
17. ULLMANN V, HUSAK V, DUBROKA L: Dead-time correction in dynamic radionuclide studies by computer. *Eur J Nucl Med* 3:197-202, 1978
18. LIN CL, LIN JWS: *Linear Systems Analysis.* New York McGraw-Hill, Inc., 1975
19. ALDERSON PO, DOUGLASS KH, MENDENHALL KG, et al: Deconvolution analysis in radionuclide quantitation of left-to-right cardiac shunts. *J Nucl Med.* 20:502-506, 1979
20. WILLIAMS DL; Improvement in quantitative data analyses by numerical deconvolution techniques. *J Nucl Med* 20: 568-570, 1979
21. NIEMI AJ: On discrete deconvolution. *Med Biol Eng* 14: 582-584, 1976
22. ALDERSON PO, JOST RG, STRAUSS AW, et al: Detection and quantitation of left-to-right cardiac shunts in children: A clinical comparison of count ratio and area ratio techniques. *J Nucl Med* 16:511, 1975 (abst)
23. ALDERSON PO, GAUDIANI VA, WATSON DC, et al: Quantitative radionuclide angiocardiography in animals with experimental atrial septal defects. *J Nucl Med* 19:364-369, 1978