Clinical Usefulness of Ultrashort-Lived Iridium-191m from a Carbon-Based Generator System for the Evaluation of the Left Ventricular Function

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Ultrashort-lived ^{191m}Ir (4.96 sec; 63–74 and 129 keV photons) is potentially advantageous for first-pass radionuclide angiocardiography, offering the opportunity to perform repeat studies with very low absorbed radiation dose to the patient. Left ventricular (LV) first-pass studies were performed in 72 patients with ^{191m}Ir from a new bedside 1.3 Ci (48.1 GBq) $^{191}Os/^{191m}Ir$ generator system using an activated carbon support that offers high ^{191m}Ir yields (15–18%) and consistent low ^{191}Os breakthrough ($2–4 \times 10^{-4}$%/bolus). Using a single crystal digital gamma camera, uncorrected end-diastolic counts in the left ventricular representative cycle ranged from 10 up to 30 k counts. The reproducibility of repeated LV ejection fraction (LVEF) determination at 2-min intervals in 50 patients was r = 0.97, mean diff. = 2.08 ± 1.55 EF units. Comparison between ^{191m}Ir (80–120 mCi; 2,960–4,400 MBq) and ^{99m}Tc (20–25 mCi; 750–925 MBq) LV count rates indicates a 3 wk useful shelf life of this new generator system for cardiac studies. Iridium-191m determined LVEF correlated closely with ^{99m}Tc determined LVEF in 32 patients (r = 0.96, mean diff. = 1.87 ± 1.23 EF units). Parametric images for LV wall motion analysis were comparable with both isotopes. We conclude that rapid, repeat, and reproducible high count rate first-pass left ventricular studies can be obtained with ^{191m}Ir from this new $^{191}Os/^{191m}Ir$ generator system using a single crystal digital gamma camera.

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Ultrashort-lived radionuclides, including gold-195m (^{195m}Au) (T½ = 30.5 sec), tantalum-178 (^{178}Ta) (T½ = 9.3 min), krypton-81m (^{81m}Kr) (T½ = 13.3 sec), and iridium-191m (^{191m}Ir) (T½ = 4.96 sec) are potentially useful for first-pass radionuclide angiocardiography. They offer the opportunity to perform rapid, repeat, high photon flux studies of the heart with a substantial reduction in absorbed radiation dose to the patients. Unfortunately, the conventional gamma cameras are not optimal for ^{178}Ta and ^{195m}Au whereas ^{81m}Kr cannot be utilized for left ventricular studies as it is completely cleared from the blood pool during its first transit through the lungs.

Iridium-191m has many advantageous nuclear characteristics. It decays by isomeric transition to stable ^{191}Ir with emission of three x-rays (63, 65, and 74 keV) and a low-energy photon (129 keV). The reactor-produced osmium-191 (^{191}Os) parent decays by β^- emission with a half-life of 15.4 days that is sufficiently long to facilitate generator construction, quality control, and clinical use far from production facility centers.

Although the description of an $^{191}Os/^{191m}Ir$ separation by ion exchange techniques was published in 1956 (*1*), the first $^{191}Os/^{191m}Ir$ generator system available for radionuclide angiographic investigations in humans was reported in 1980 (*2*). The system employed the AGMP-1 resin and a pyrocatecol "scavenger" column

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to trap the majority of the ^{191}Os breakthrough. Iridium-191m obtained from this system has been used effectively for the evaluation of intracardiac shunts in children (*3*) and for the determination of right and left ventricular ejection fraction in adults (*4*). Because of the rather complicated fabrication and the limitations of the AGMP-1 generator system (*5*), other potential ^{191}Os/^{191m}Ir generator systems have been evaluated (*5–8*).

An ^{191}Os/^{191m}Ir generator based on the adsorption of ^{191}Os on an activated carbon support that offers good ^{191m}Ir yield (15–18%) and consistent low ^{191}Os breakthrough ($2–4 \times 10^{-4}$%/bolus) over a 3-wk period has been recently described (*7*). The present study reports our experience with ^{191m}Ir from this new generator system for the evaluation of global and regional left ventricular ejection fraction using a single crystal digital gamma camera.

MATERIALS AND METHODS

Osmium-191/Iridium-191m Generator Preparation and Use

The ^{191}Os parent was produced by neutron irradiation of 98% enriched metallic ^{190}Os at a neutron flux of $\sim 2.5 \times 10^{15}$ $n \cdot cm^{-2} \cdot sec^{-1}$ in the High Flux Isotope Reactor at Oak Ridge National Laboratory (Oak Ridge, TN, USA) or at 8.5×10^{14} $n \cdot cm^{-2} \cdot sec^{-1}$ in the BR2 Reactor in Mol (Belgium) with subsequent fusion in a mixture of KOH-KNO_3. The method of ^{191}Os production and the separation of ^{192}Ir formed during the irradiation have been published elsewhere (*9*).

The generator is based on the adsorption of K_2OsCl_6 on 140–230 mesh heat-treated activated carbon. The preparation of the generator has been previously described in detail (*7*).

Nine consecutive generators loaded with 1.2 to 1.8 Ci (44.4–66.6 GBq) of ^{191}Os (average 1.6 Ci-59.2 GBq) were used in this clinical study. Generator construction, quality controls, and transportation to the clinical investigation center last 5 to 7 days resulting in a decay of the ^{191}Os activity on the column to ~1.3 Ci (48.1 GBq). Iridium-191m elution yield has been experimentally proved to be dependent upon the volume of KI passed through the carbon column, reaching an optimal yield of 15% to 18% after ~250 ml of the eluent solution. Increasing ^{191m}Ir at the beginning compensates, at least partially, the decay loss of ^{191}Os.

The ^{191}Os/^{191m}Ir generators were eluted at a flow rate of 120 ml/min with 2.5 to 3.0 ml of a pH2 0.9% NaCl solution containing 0.25 g/potassium iodide (KI). The eluent was neutralized to physiologic pH and isotonicity with 0.3 ml of a pH 8.4 Tris buffer (0.13*M*) immediately prior to intravenous injection. Elution and neutralization were performed in <2 sec using an automatic pump device. The ^{191m}Ir bolus was manually injected into the patient, through a 0.22-Millipore filter, using 15 to 20 ml of normal saline solution (Fig. 1). An acute toxicity study conducted in rats and in rabbits with the tris-buffered saline ^{191}Os generator eluate produced no pathologic changes in the animals studied by body weight, hematology, blood chemistry, and necropsy.

Careful quality control, including sterility, apyrogenicity, and isotonicity of the generator eluent, and analysis of performance of each individual generator were performed before clinical use. Apyrogenicity, breakthrough, and pH of the generator eluent were measured routinely, at least once a day.

Gamma Camera

Radionuclide angiocardiographic studies were performed with a small field-of-view (20 cm) single crystal digital gamma camera connected to the dedicated minicomputer (APEX 215M, Elscint, Inc., Boston, MA). Data were acquired in the "fast" mode (only the first 400 nsec of the scintillation are integrated) with a very high sensitivity, low-energy, parallel hole collimator.

Iridium-191m emits a gamma photon (129 keV, abundance 26%) and three x-rays (63 keV - 16%, 65 keV - 28%, 74 keV - 12%) that cannot be resolved with the NaI crystal. X-rays appear thus as one single peak at 69 keV. For ^{191m}Ir studies, the pulse-height analyzer (PHA) was set either over the apparent ^{191m}Ir x-ray using a 50–100 keV window, or over the ^{191m}Ir photon using a 100–150 keV window, or over the apparent ^{191m}Ir x-ray and the ^{191m}Ir photon using a 50–150 keV window.

The performance of this gamma camera system in detecting high ^{191m}Ir photon flux was determined using the following decaying source method. The ^{191}Os/^{191m}Ir generator was eluted and ^{191m}Ir was collected in a 100-ml beaker placed on the collimator. Data were acquired in dynamic mode, 25 frames per second, for 40 sec. Count rates were first corrected for camera deadtime using a reference shielded source of ^{191}Os placed in the field of view of the gamma camera during acquisition (*10*). Adopting a 1% deviation as criteria, the limits of the linearity response of the system were determined by back-extrapolation of the corrected data fitted with the theoretical exponential decaying curve of ^{191m}Ir ($\lambda = 0.140$ sec^{-1}). The linearity response of the gamma camera was successively determined for the above-mentioned PHA windows.

The spatial resolution of the gamma camera for ^{191m}Ir was determined by calculating the full width at half maximum (FWHM) of an ^{191}Os point source in the above-mentioned PHA windows.

Patient Studies

253 ECG gated first-pass radionuclide angiocardiographic studies of the left ventricle with ^{191m}Ir from nine generators were performed in 72 patients (55 males and 17 females) with proved or suspected coronary artery disease (CAD). Mean age of the group was 56 yr, ranging from 38 to 67 yr. Informed consent was obtained from each patient.

In 50 patients, the reproducibility of sequential ^{191m}Ir left ventricular ejection fraction (LVEF) measurements was determined from two successive first-pass studies acquired in the anterior view at 2-min intervals. In 32 patients, ^{191m}Ir LV studies were compared to ^{99m}Tc LV first-pass studies [20–25 mCi (750–925 MBq)] technetium-99m diethylenetriamine-pentaacetic acid ([^{99m}Tc]DTPA) performed a few minutes after the last ^{191m}Ir injection, without moving the patient from the camera. In 14 patients with acute myocardial infarction, repeated ^{191m}Ir LV first-pass studies were acquired in multiple views (anterior, 30° right anterior oblique and 40° left anterior oblique projections). Regional wall motion analysis was compared to the multigated equilibrium ^{99m}Tc red blood cell ventriculography.

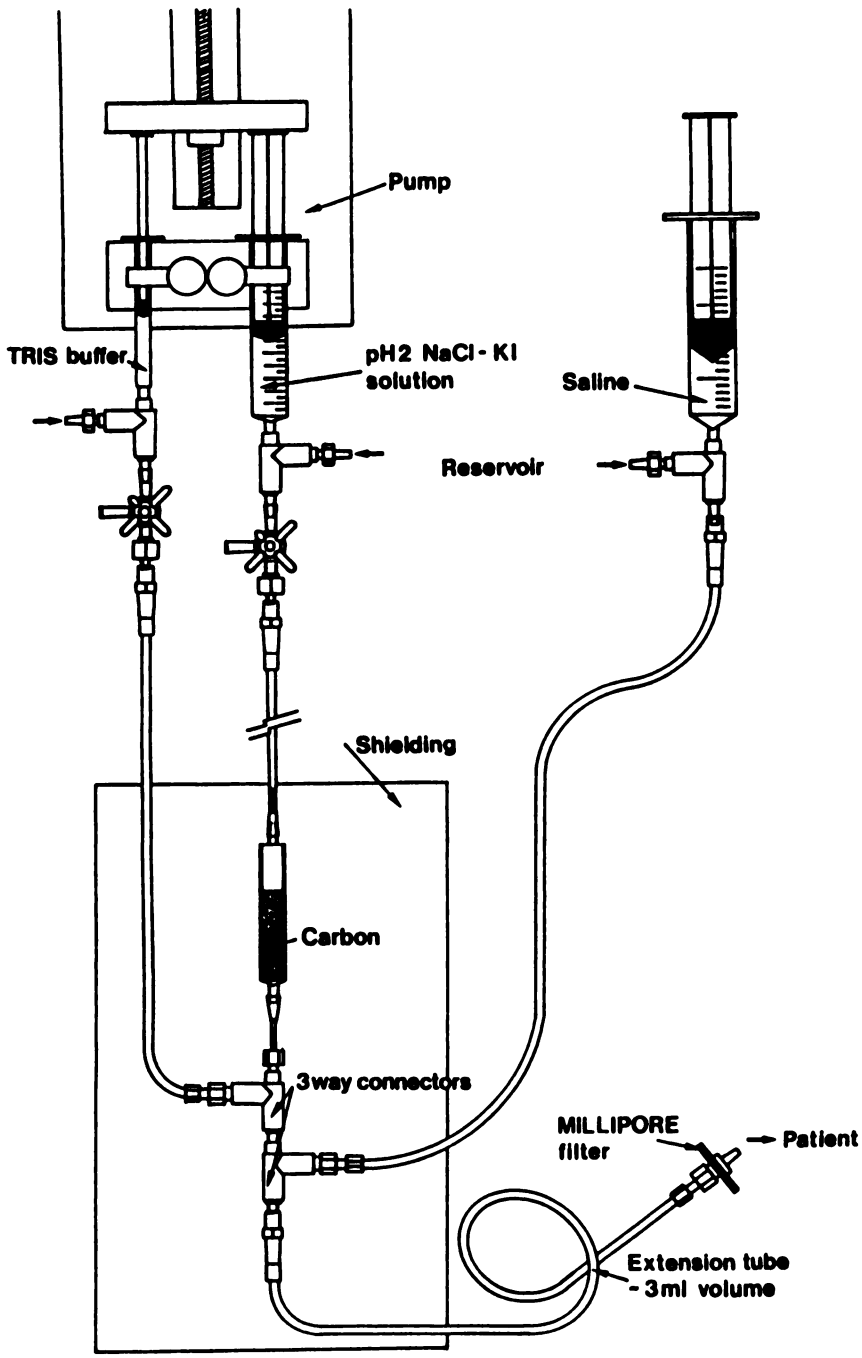

FIGURE 1
Schematic drawing of the generator system.

Data Acquisition and Processing

All clinical studies were acquired with the 50–150-keV window including the apparent ^{191m}Ir x-rays and the ^{191m}Ir gamma photon. Data were collected in frame mode (25 frames per sec) in a 32x32 matrix for 30 sec. Bolus integrity was assessed from the pulmonary time-activity curve. Studies from three patients with prolonged pulmonary transit time were rejected.

A representative left ventricular cardiac cycle was constructed from five consecutive beats selected on the descending portion of the LV time-activity curve using the ECG signals recorded during acquisition. Extra beats were rejected. Separate left ventricular end-diastolic (ED) and end-systolic (ES) regions of interest (ROIs) were drawn taking care of the displacement of the aorto-ventricular valve plane during heart contraction. Background was calculated from a background ROI surrounding the left ventricular cavity. End-diastolic and end-systolic counts were subsequently corrected for the camera deadtime (using the attenuation factor of the small reference source placed in the field of the camera) and for the radionuclide decay. Global left ventricular ejection fraction was calculated as $LVEF = 1 - (ES_{counts}/ED_{counts})$. Regional wall motion was analyzed from the gated representative cycle displayed in cine format, the superposition of ED and ES isocount lines, the Fourier first harmonic amplitude and phase images as well as from the regional ejection fraction image.

Statistical Methods

Standard linear regression analysis was performed on the ejection fraction values from ^{191m}Ir and ^{99m}Tc studies and on sequential data. Results are expressed as mean ± s.d.

RESULTS

Generator Elution Yield, ^{191}Os Breakthrough, Sterility and Dosimetry

The ^{191m}Ir activity and ^{191}Os breakthrough values as a function of the age of the ^{191}Os/^{191m}Ir generators are given in Figure 2. The clinical studies were performed from Days 5–7 until ^{191m}Ir activity in the eluate was too low to obtain sufficient count rates in the LV, usually on Days 21–25 when ^{191m}Ir activity was <80 mCi (2,960 MBq) per bolus. The ^{191m}Ir activity averaged ~120 mCi (4,440 MBq) per bolus during the first week of clinical trial, 100 mCi (3,700 MBq) during the second week, and 80 mCi (2,960 MBq) during the third week. Osmium-191 contamination in the eluate decreased from 4.11 ± 1.89 μCi (152 ± 70 kBq) per bolus (3.2 ± 1.5 × 10^{-4} %/bolus) to 1.70 ± 0.93 μCi (63 ± 34 kBq) per bolus (2.6 ± 1.4 × 10^{-4} %/bolus) according to the physical half-life of ^{191}Os.

Based on the tissue distribution data in female Fisher rats for ^{191}Os and on the values of transit times in humans for ^{191m}Ir, the absorbed radiation dose from a typical 100 mCi (3,700 MBq) ^{191m}Ir bolus with a 5-μCi (185-kBq) ^{191}Os breakthrough was approximated to be 50 mrad (500 μGy) for the heart, 20 mrad (200 μGy) for the lungs, and 10 mrad (100 μGy) for the kidneys. The effective dose equivalent calculated following the ICRP recommendations was ~13 mrem (130 μSv). On the other hand, the source of radiation to personnel was limited to the bolus of ^{191m}Ir passing through the tubing from the generator to the patient, and the ^{191m}Ir in the patient. The radiation at the surface of the collecting tube was measured at 0.2 mrad (2 μGy) per bolus of 100 mCi (3,700 MBq) ^{191m}Ir which gave ~0.006 mrad (0.06 μGy) at 50 cm.

The pH values of the ^{191m}Ir generators eluate ranged

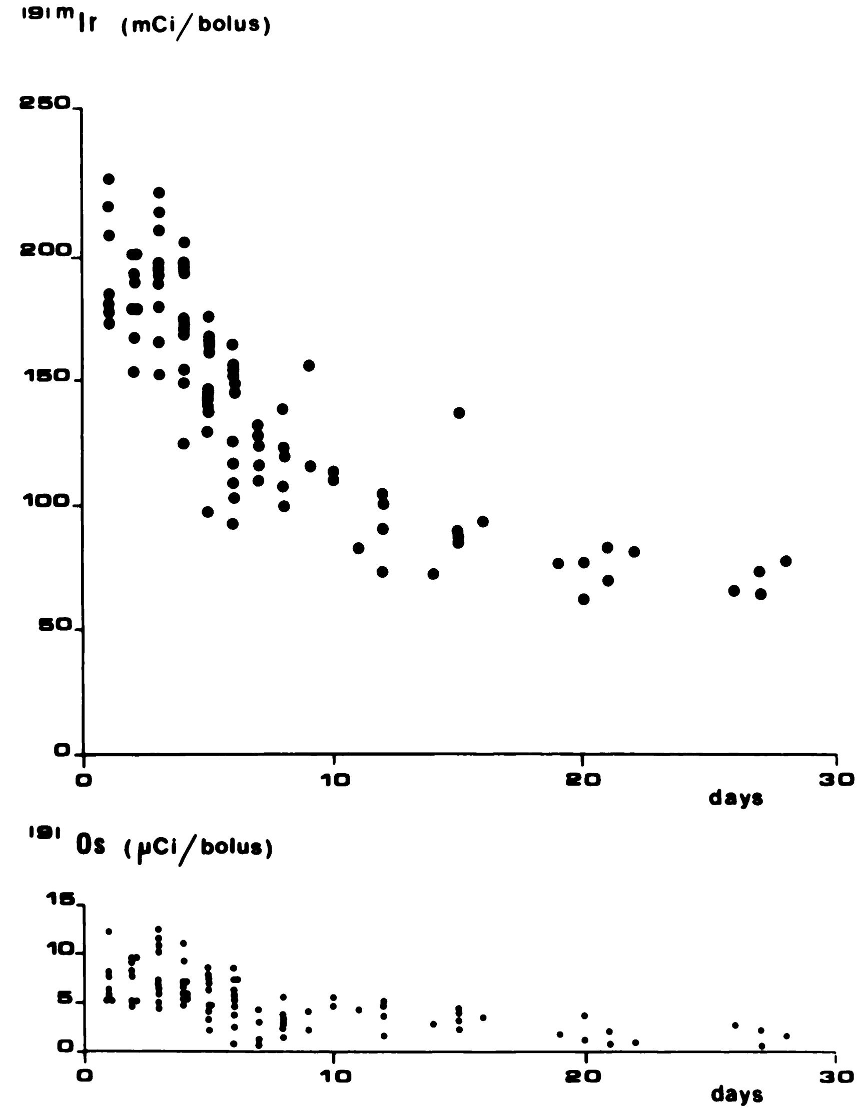

FIGURE 2
Iridium-191m activity (upper panel) and ^{191}Os contamination in the eluate (lower panel) as a function of the age of the generators. Generators were loaded on Day 0 with 1.2–1.8 Ci (44.4–66.6 GBq) of ^{191}Os.

from 5.6 to 7.2. All samples tested were sterile and pyrogen-free.

Gamma Camera Performance

The saturation count rate of the gamma camera occurred in the "fast" acquisition mode at 410 kcps when the pulse-height analyzer windows were set over the two ^{191m}Ir photopeaks, 275 kcps when the pulse-height analyzer windows were set over the apparent ^{191m}Ir x-ray and 125 kcps when the PHA windows were set over the ^{191m}Ir gamma photon. Using a small ^{191}Os reference source, the nonlinearity response of the camera was corrected with an error of <1% up to 320 kcps measured in the 50–150 keV window, 210 kcps measured in the 50–100 keV window and 105 kcps measured in the 100–150 keV window. The spatial resolution (FWHM) in the "fast" mode were 10.3 mm, 9.0 mm, and 7.3 mm, respectively. The spatial resolution of the system was 7.3 mm for ^{99m}Tc.

Clinical Studies

No immediate or delayed adverse reaction was observed in any of the 72 patients (253 first-pass studies) performed with ^{191m}Ir from this new ^{191}Os/^{191m}Ir generator system.

Counting Efficiency

The highest count rates in the whole field-of-view of the camera measured during the left ventricular transit of the bolus was within the limits of linearity correction of the camera, ranging in our patient population from 100 to 250 kcps. Uncorrected left ventricular counts in the 40 msec end-diastolic image of the ECG gated representative cycle averaged 14,789 counts (range 5,257–30,337 counts).

Reproducibility Studies

The reproducibility of sequential ^{191m}Ir determined LVEF was evaluated from two successive LV angiocardiographic studies performed at 2-min intervals. No background activity from the first study was detected during the second study. The correlation coefficient between study 1 and study 2 was 0.97 (Fig. 3). The slope of the linear regression equation was 0.91. The mean absolute difference between the first and second measurement was 2.08 ± 1.55 EF units.

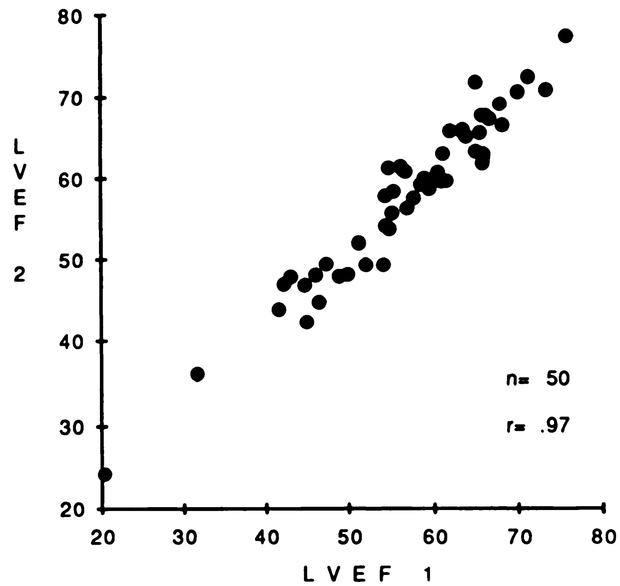

FIGURE 3
Reproducibility of two successive LVEF measurements performed in the same patient at 2-min interval with ^{191m}Ir.

Comparison with ^{99m}Tc

In 32 patients, ^{191m}Ir left ventricular first pass studies were compared to [^{99m}Tc]DTPA first-pass studies performed a few minutes later in the same projection. Visually, the left ventricular end-diastolic and end-systolic images obtained with ^{191m}Ir were comparable to the images obtained with ^{99m}Tc. A typical example of a 100 mCi (3,700 MBq) ^{191m}Ir left ventricular study in comparison with a 22 mCi (814 MBq) [^{99m}Tc]DTPA study is illustrated in Figure 4. Uncorrected left ventricular counts in the 40 msec end-diastolic image of the ECG gated representative cycle averaged 15,258 counts (range 5,257–28,704 counts) with ^{191m}Ir and 10,161

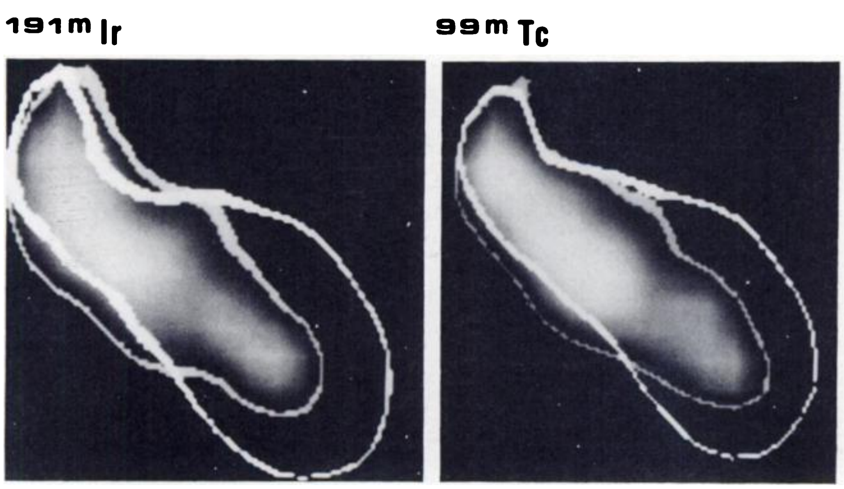

FIGURE 4
Comparison of ^{191m}Ir (left) and ^{99m}Tc (right) images from a patient with normal left ventricular function. The end-systolic frame is shown with the end-diastolic perimeter superimposed.

counts (range 3,555–22,067 counts) with ^{99m}Tc. In this patient study group, LVEF ranged between 0.34 and 0.79 (Fig. 5). The correlation coefficient between the ^{191m}Ir and ^{99m}Tc studies was 0.96. The slope of the linear regression equation was 0.92. The mean difference between the ^{191m}Ir and ^{99m}Tc studies was 1.87 ± 1.23 EF units with a maximal deviation of 4.3 EF units.

Regional Wall Motion Analysis

The parametric images from ^{191m}Ir LV studies were of good quality and comparable to the ^{99m}Tc studies. In addition, regional wall motion analysis from multiple views ^{191m}Ir studies in patients with acute myocardial infarction was in good agreement with the extent of contractility impairment determined from the multigated equilibrium ^{99m}Tc RBC ventriculographic studies (Fig. 6).

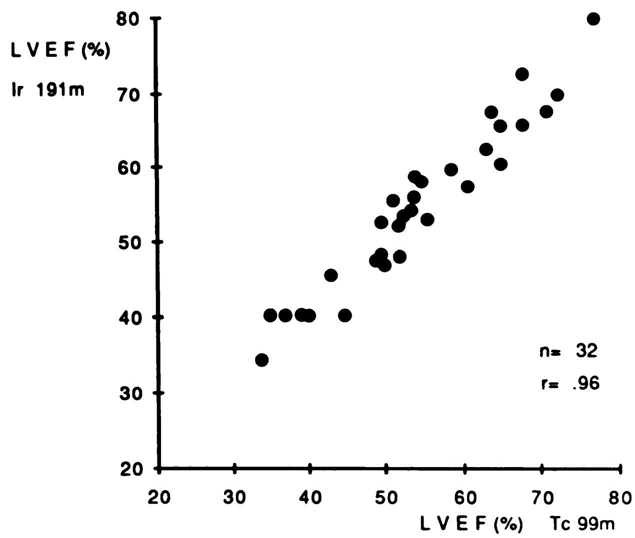

FIGURE 5
Comparison of left ventricular ejection fractions from ^{191m}Ir and ^{99m}Tc first-pass studies obtained in the same patient.

DISCUSSION

A new $^{191}Os/^{191m}Ir$ generator system, based on the adsorption of ^{191}Os on an heat-treated activated carbon support has recently been available for clinical applications. The activated carbon support was found to be an excellent generator adsorbent and to retain these properties for 2–3 wk. Consistently high ^{191m}Ir activities from the nine consecutive generators utilized in this study were obtained during prolonged periods, up to 3 wk, with multiple daily elutions. Osmium-191 breakthrough in the generator eluates was very low, ranging from 2 to 4 × 10^{-4}% of the ^{191}Os activity in the column, and remains constant throughout the entire period. This compares very favorably with other $^{191}Os/^{191m}Ir$ generator systems (*2,8*).

Iridium-191m, in comparison with ^{99m}Tc, offers many advantages for first pass angiocardiographic studies including the ability to perform rapid, repeat high photon flux studies of the heart with very low absorbed radiation dose to the patient, ~50 times lower than conventional 20 mCi (740 MBq) [^{99m}Tc]DTPA bolus.

Because of this marked reduction in patients dosimetry, the magnitude of the injected dose of ^{191m}Ir is primarily limited by the count rate performance of the camera. We have shown that saturation count rate of the APEX 215M system occurs at about 420 kcps with the PHA set over the two ^{191m}Ir photopeaks and that correction for count losses as a result of camera deadtime can be accurately carried out up to 320 kcps by measuring count losses of a reference source of ^{191}Os placed in the field of view of the camera during acquisition. In our patients studies, peak count rates during the left ventricular phase were clearly under this limit. As expected, the highest effective count rate capacities were obtained with the largest window including the two ^{191m}Ir photopeaks compared to the x-ray window

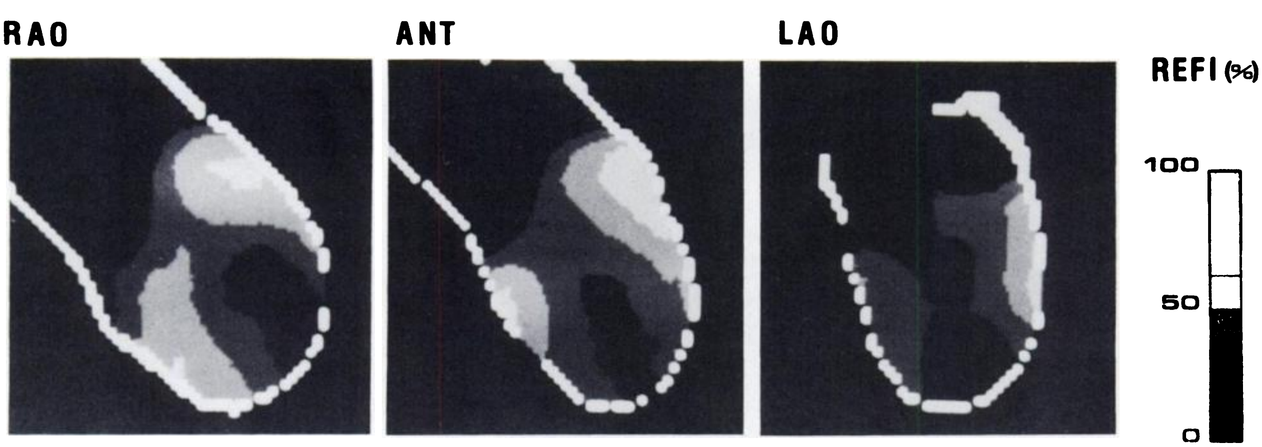

FIGURE 6
Regional ejection fraction images from a patient with anterior myocardial infarction obtained with ^{191m}Ir successively in the 30° right anterior oblique projection, the anterior and the 40° left anterior oblique projection.

or the gamma window alone. Because accuracy in global and regional first pass radionuclide angiocardiographic measurements are primarily depending on count rates, clinical studies were performed with the PHA windows set over the two photopeaks.

Concerning the feasibility in performing left ventricular studies with ^{191m}Ir from this new ^{191}Os/^{191m}Ir generator system, we demonstrated that sufficient ^{191m}Ir activity was provided by this new generator system to give statistically reliable measurements of the left ventricular function in adults when the radioactive bolus was injected in a peripheral vein. Iridium-191m left ventricular studies were of high quality except in three patients with prolonged pulmonary transit time resulting from poor bolus quality injection (two patients) or from impairment of right ventricular function (one patient). Iridium-191m left ventricular ejection fractions were highly reproducible and correlated closely to ^{99m}Tc left ventricular ejection fractions. Images of the left ventricular representative cycle and the parametric images utilized for regional wall motion analysis were comparable with both isotopes.

In conclusion, this new bedside ^{191}Os/^{191m}Ir generator system can be used for 2–3 wk, providing sufficiently high ^{191m}Ir activities to assess left ventricular function. Iridium-191m is as reliable as ^{99m}Tc for first-pass studies in adults. The major advantage is related to its ultrashort half-life offering the unique opportunity to conduct rapid, repeat first-pass studies of the cardiovascular system under different conditions, such as varying levels of exercise, with marked reduction in the radiation exposure to both patient and personnel.

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