Krypton-81m Imaging of the Right Ventricle

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We report the development of a method for obtaining right-ventricular radionuclide angiograms using continuous peripheral intravenous infusion of the ultra-short-lived nuclide krypton-81m. This tracer has a half-life of 13 sec, emits a single 190-keV photon, and is extremely insoluble. During infusion into a peripheral vein, Kr-81m achieves stable count rates over the right heart, and it is essentially completely cleared by the lungs during its initial pulmonary transit. Thus no interfering activity is present in the systemic circulation. Initial studies provide excellent data on right-heart anatomy and function.

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Pulmonary hypertension, and its sequelae of cor pulmonale and right-ventricular failure, may occur in many diseases. Unfortunately, reliable measurements of pulmonary arterial pressure and right-ventricular performance require catheterization of the right heart, an invasive and costly procedure. Thus there is considerable interest in the search for an accurate, noninvasive, radiotracer method for examining the pulmonary circulation.

The inability to separate the right ventricle (RV) from the adjacent cardiac structures (*1*) has detracted from RV radionuclide angiography using Tc-99m blood-pool agents in a gated equilibrium modality. First-pass techniques permit temporal separation of the right and left hearts, but allow only a few beats to be analyzed. Moreover, at least with Tc-99m and standard gamma cameras, rapid sequential studies to assess the effects of drugs or exercise are usually not possible and would subject the patient to an excessive radiation burden.

Krypton-81m has several properties suggesting that it would be an ideal tracer for selective radionuclide imaging of the right heart. It is a nearly insoluble inert gas and is essentially completely cleared from the blood by the lungs during its initial pulmonary transit. It decays by isomeric transition to stable Kr-81, emitting 65%-unconverted 190-keV gamma photons that allow excellent imaging with a standard gamma camera (*2*). Its 13-sec half-life minimizes both radiation exposure to the patient and risk to hospital and technical staff, while allowing multiple studies to be performed in rapid sequence (*3,4*). In addition, Kr-81m infusions permit one to obtain lung perfusion images that correlate closely with those obtained using standard macroaggregated albumin (*5*).

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METHODS

Before use of this nuclide in people, approval was obtained from the Food and Drug Administration and the appropriate committees at our Center and the University of California. Our Kr-81 generator uses the 4.6-hr parent, rubidium 81, which decays by electron capture and positron emission to the Kr-81m daughter, with a 96% transient equilibrium yield for Kr-81m. The carrier-free Rb-81 was adsorbed onto Dowex 50 macroporous cation-exchange resin contained in a sterile, glass column through which sterile 5% dextrose in water was passed as an eluent. Each generator was prepared sterilely in a laminar-flow hood, and generator eluates were tested and certified periodically by standard methods for apyrogenicity and sterility, and by germanium spectroscopy for any potential radioactive contaminants. The Rb-81 parent was produced by the (*p*,*2n*) reaction in a cyclotron, by proton bombardment of Kr-79 in a sealed gas target; possible radioactive contaminants would be mainly Rb-81, Rb-82m, and Kr-83m, all of which were found to be insignificant. Most of the generators contained approximately 10–15 mCi of the rubidium parent.

For this pilot study, we examined 15 normal subjects,

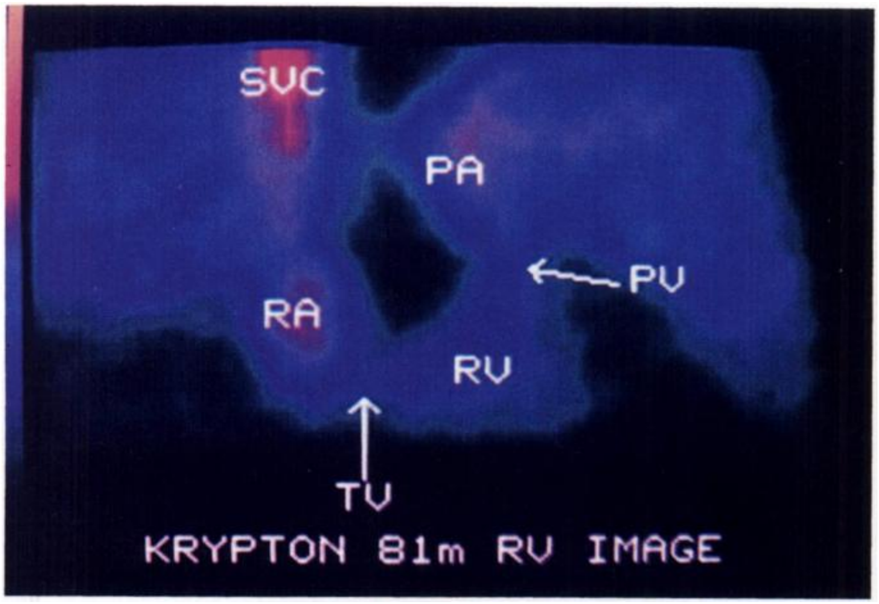

FIGURE 1
Krypton-81m image of right heart during systole, in 15° right anterior oblique projection. Note excellent delineation of right-heart structure. Abbreviations: SVC = superior vena cava, RA = right atrium, RV = right ventricle, TV = tricuspid valve, PV = pulmonic valve, PA = main pulmonary artery

all nonsmokers with normal physical examinations and no symptoms of cardic or pulmonary disease. Chest radiographs were not obtained.

The Kr-81m was infused through a vein in the right antecubital fossa, using a rotary peristaltic pump capable of continuously variable infusion rates of 1-999 ml/hr. The eluate from the generator was delivered through microbore tubing (1 ml/m, i.d. 1.13 mm) with a 0.2-μ Millipore filter in the line. This was essential to minimize the tubing's dead space and thus the transit time from the generator to the venous infusion site. For gated right-ventricular imaging, infusions were typically run at 10 to 15 ml/min. The large-field gamma camera (half-in. crystal, 61 PM tubes) was equipped with a medium-energy collimator. Patients were studied supine, in the anterior or slight (15°) right anterior oblique view. The camera orientation was selected to minimize lung overlap of the right ventricle, to separate the RA and RV throughout the cardiac cycle, and to optimize definition of right-heart anatomy (Fig. 1). Data were acquired in a dedicated minicomputer system in an EKG-gated list-mode format with 1-msec timing markers. Typically 500-800 heart cycles were acquired over 5-8 min for each resting study. The data were then transferred to a second computer system for specialized processing.

First, a histogram of the R-to-R intervals was constructed and displayed. The mean and most frequent R-R intervals were determined. An operator-selected R-R interval (usually the mean value) with a user-defined window (usually ±5%) was then used to frame the list-mode data into 16 temporally equal, 64- by 64-word composite frames over the predetermined cardiac cycle. All beats within the window were accepted for the framed images. The framing algorithm used a variation of forward-backward breakup, which attempts to compress or expand the individual cycle during its diastasis period to fit the selected R-R framing-time interval. The ejection phase and the rapid-filling phase of each beat within the acceptable R-R window were framed precisely in time, while the mid portion (during diastasis) was either compressed or expanded to fit the selected composite R-R interval.

Next, the images were temporally filtered using a Fourier filter with a raised cosine attenuation function for frequencies above 6-8 Hz. The images were then spatially filtered with a nine-point centrally weighted smoothing algorithm. The data were displayed in real time in an endless-loop movie format.

Perfusion lung scans were obtained in some cases, usually in both supine and upright positions. For such studies, the infusion was continued at 10-15 ml/min and 500,000 counts were collected over ~2 min for each view in the standard fashion. These data were also stored in computer memory as 64-by-64 digital matrices to allow determination of apex-to-base perfusion distributions in the various positions.

RESULTS

Supine, resting right-ventricular radionuclide angiograms have been acquired in 15 normal adults ranging in age from 23 to 62 yr. Right-heart structures—including the right atrium, tricuspid-valve plane, right ventricle, pulmonic-valve plane, and the pulmonary outflow tract—were clearly visible (Fig. 1). Scatter activity was present, essentially, only in the left-heart region. Significantly, the tricuspid valve could be seen throughout the cardiac cycle, allowing RA and RV to be visualized individually.

Right-ventricular ejection fractions (RVEFs) were calculated in the 15 normal subjects. End-diastolic and end-systolic regions of interest were manually assigned using a light-pen, with no background corrections. The mean RV ejection fraction for the normal group averaged (48.3 ± 5.7%), with a range of 39% to 58%.

We have also had the opportunity to study several patients with pulmonary disease. Two patients with restrictive lung disease, one mild and one moderately severe, had resting RVEFs of 68% and 45%. Two other patients, with severe COPD and clinically apparent cor pulmonale, manifested grossly enlarged, hypokinetic right ventricles by scintigram. Their resting RVEFs measured 39% and 27%.

Supine and upright perfusion lung scans, which can be used as an index of pulmonary arterial pressure (*6*), were obtained in several subjects (Fig. 2). The normal shift in perfusion away from the lung apices upon assumption of the upright position was easily seen. Computer analysis of these perfusion distributions potentially allows simultaneous estimation of the pulmonary arterial pressure (RV afterload).

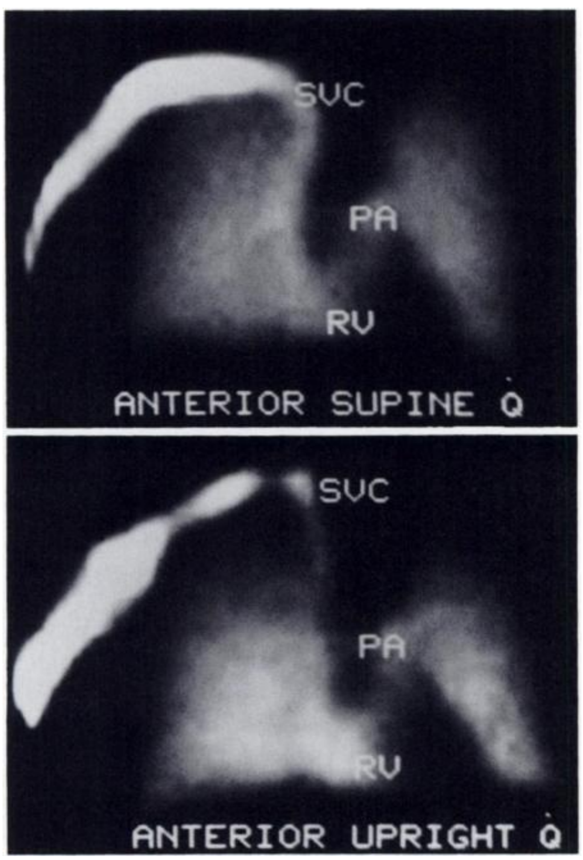

FIGURE 2
Supine (top) and upright (bottom) Kr-81m perfusion lung images demonstrating normal postural shift in perfusion away from apices of lung, upon assumption of upright position

DISCUSSION

Our preliminary investigations suggest that Kr-81m is an ideal tracer for the noninvasive study of right heart and pulmonary hemodynamics. Excellent images of the right heart can be obtained without interference from radioactivity in the systemic circulation. Additionally, the very short half-life and rapid pulmonary elimination should permit serial investigations to assess the effects of exercise or pharmacologic intervention. The ability to acquire perfusion lung scans in various positions concomitantly may yield clinical information regarding the cause of a patient's lung disease as well as an estimate of the pulmonary arterial pressure (*6*). This latter measurement is vital for the proper interpretation of the right-heart radionuclide angiogram.

The values for RVEF in our group of normal subjects are in agreement with those obtained using other radionuclide techniques (*7*) as well as preliminary data with Kr-81m (*8*). We feel, however, that there remains no "gold standard" for the right ventricle, since the unusual geometry of this structure makes even angiographic measurements difficult. Thus, the problem of validation of this technique remains. Krypton-81m is potentially a standard of measurement for RV function because of its unique ability to image the right heart over many cardiac cycles without spillover from the adjacent cardiac chambers. Moreover, Kr-81m imaging avoids the problematic geometric assumptions that make contrast angiography a suboptimal method for the RV. The reproducibility and intraobserver variability of this technique remain to be determined. Our images should be amenable to computerized interpretation algorithms, which certainly could minimize subjective variation in image interpretation and quantitation.

Several problems with Kr-81m imaging have become apparent. First, the 13-sec half-life demands a very efficient infusion system with low transit time. The generator column, filters, and micro-bore tubing create significant resistance to flow, necessitating the use of special infusion pumps similar to the one described. Also, unless cameras and collimators with high counting efficiency are used, count rates over the right heart will be very low. Finally, the 4.58-hr half-life of the parent rubidium-81 limits the useful life of a 10-mCi generator to about 5–6 hr for these studies.

Many important clinical studies await the refinement of this imaging method. The effects of COPD, pulmonary hypertension, mechanical ventilation, etc., on the right ventricle remain to be defined with a noninvasive technique. In addition, many therapeutic modalities for cor pulmonale of various origins could be evaluated periodically without the need for invasive serial right-heart catheterization (*9*). Finally, radionuclide imaging with Kr-81m may permit early detection of right-heart dysfunction and pulmonary hypertension, conditions that usually are not diagnosed until late in their course.

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