CONTINUOUS RADIONUCLIDE GENERATION. II. SCINTIGRAPHIC DEFINITION OF CAPILLARY EXCHANGE BY RAPID DECAY OF ^{81m}Kr AND ITS APPLICATIONS

Ervin Kaplan, Lewis W. Mayron, W. Earl Barnes, Lelio G. Colombetti,* Arnold M. Friedman, and James E. Gindler

Veterans Administration Hospital, Hines, Illinois and Argonne National Laboratory, Argonne, Illinois

Specific theoretical considerations of the properties of the radionuclide ^{81m}Kr are presented as preliminary to the application of a new method of selective scintigraphic angiography. This technique proposes defining the size, configuration, and location of infarcts; vascular insufficiency; and other physiologic and pathologic sites of absent, increased, or decreased circulatory exchange. An ^{81}Rb-^{81m}Kr radionuclide generator has been constructed to produce, at a constant rate, ^{81m}Kr, a water-soluble gas, diffusible through capillary membranes, emitting a monoenergetic gamma ray, and decaying with a half-life of 13 sec. This gas in solution may be infused at a constant rate intra-arterially into an organ or anatomic region. Infusion may be sustained until equilibrium conditions prevail. In this steady state intravascular radioactivity remains constant as it is replaced by newly generated ^{81m}Kr. The gas that diffuses into the extracapillary space exchanges more slowly than the intravascular activity. The rapid decay produces a heterogeneity of distribution of radioactivity which depends on the diffusion time. A static image produced by a scintillation camera will detect, record, and display this heterogeneity and may be processed to define the adequacy of capillary exchange. The built-in clock of rapid decay will define the kinetics of exchange in a steady state with a single image. Applications of the ^{81m}Kr generator delivery system are described.

A functional generator which will continuously produce ^{81m}Kr at a rate equal to the 4.7-hr decay of the parent radionuclide ^{81}Rb has been described and evaluated by the authors (*1–3*). The generator will deliver the ^{81m}Kr as a gas or in liquid solution in water or 5% dextrose-in-water. The 0.190-MeV monoenergetic gamma emission, the 13 sec half-life, and the high output of the generator render it ideal for on-line use with the Anger scintillation camera. Its use results in the production of well-resolved images while employing an intense gamma flux with relatively low radiation exposure to the patient and minimal environmental contamination. This radionuclide possesses unique properties for the study of vascular kinetics. The characteristics of ^{81m}Kr are similar to ^{133}Xe except for gamma energy, lesser liquid solubility, and the extremely short half-life of ^{81m}Kr.

METHODS

In vivo imaging of the distribution of ^{81m}Kr when administered by inhalation, ingestion, and intravenous and intra-arterial infusion is described. Images were produced using a Picker Dynacamera II and an 1100 parallel-hole collimator designed for a maximum of 0.525-MeV gamma energy or a model 2C Dynacamera 2700 parallel-hole collimator designed for a maximum energy of 0.225 MeV. Use of a parallel-hole collimator designed for a maximum of 0.140-MeV energy gamma rays showed significant evidence of septal penetration.

Ventilation lung scintigrams were produced using normal human volunteers. After being positioned in relation to the detector, the subjects inhaled one breath of air through a mouthpiece from a plastic bag into which the catheter tip from the generator had been placed. For these experiments, the generator pump eluted the generator with air. The image was

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For reprints contact: Ervin Kaplan, Nuclear Medicine Service, Veterans Administration Hospital, Hines, Ill. 60141.

* Current address: Michael Reese Hospital, Chicago, Illinois.

produced by exposure for a 20-sec period during which the breath was held. The total number of detected counts during such exposure was approximately 100,000.

Intravascular administration was accomplished using as experimental animals 20-kg male dogs anesthetized with Nembutal. The lumen of the vein or artery was entered with a 16-gage 1½-in. needle. The catheter was then threaded through the needle and into the vessel, the needle then being withdrawn around the catheter (*1*). Activity was continuously delivered intravascularly by elution with isotonic 5% dextrose-in-water solution. The catheter could be advanced along the vessel under view of the scintillation camera detector. The ^{81m}Kr activity was plainly discernible on the persistent monitor scope of the camera. Positioning the catheter tip without fluoroscopy was readily accomplished by an unskilled operator. The level of activity being delivered was adjustable by using the Cole-Parmer constant speed control unit to regulate the pump motor rpm. When the catheter was appropriately placed and the activity being delivered at the desired level, equilibration occurred in 2 min or less. A very stable, high gamma flux image would persist so long as the ^{81m}Kr was being delivered. It was possible to reposition the animal for optimal imaging by direct observation while continuous flow of ^{81m}Kr was maintained.

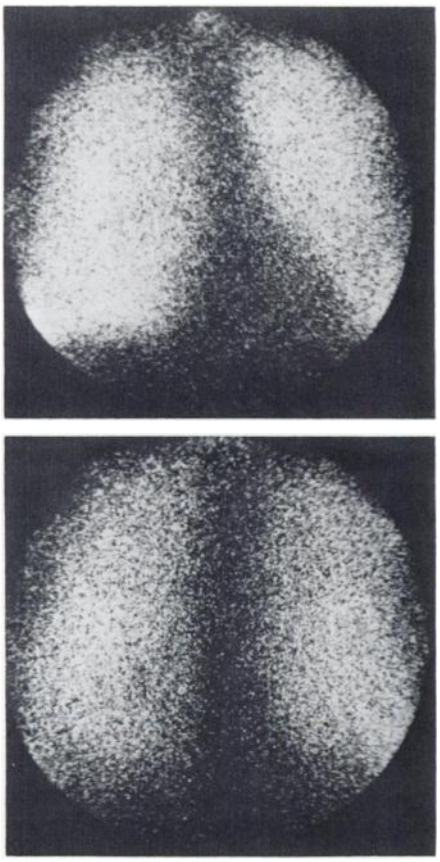

FIG. 1. Scintigraphic images of lungs of normal 50-year-old man: (top) anterior view, (bottom) posterior view. These pictures were produced after inhalation of single breath of ^{81m}Kr. No diaphragmatic motion artifacts are present as images were made as breath was held for 20 sec. Each image contains 100,000 counts for that period of time. Higher counting rates are possible with rebreathing.

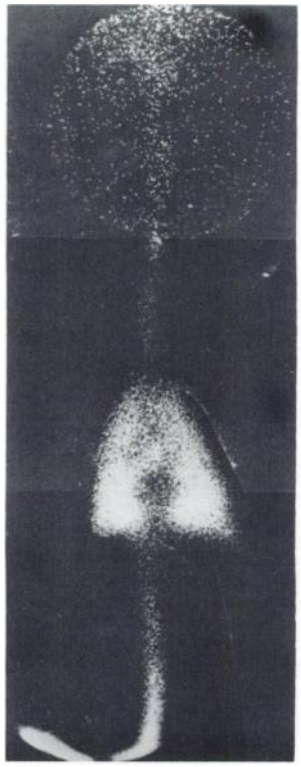

FIG. 2. Composite scintigram of distribution of ^{81m}Kr in 20-kg dog obtained during continuous intravenous administration in right rear leg. Activity decreasing with decay may be seen in inferior vena cava. Right heart and lungs show constant unchanging image during steady-state conditions. Activity may be seen in airway. Wedge of activity at top of image represents ^{81m}Kr being emitted from dog's nostrils.

RESULTS

The ventilation lung scans produced by single-breath inhalation and breathholding for 20 sec may be seen for anterior and posterior views (Fig. 1 A,B). These scans are rapidly produced; the environmental contamination is of little significance as the ^{81m}Kr decays almost immediately upon exhalation, and the delivery of the gaseous radionuclide may be stopped between administrations by turning off the pump. A large number of subjects may be examined sequentially; time requirements are not significantly different than for an x-ray film of the chest. The constant generation of ^{81m}Kr is of adequate levels for an entire working day.

The intravenous insertion of the catheter in the dog permitted visualization of the proximal venous

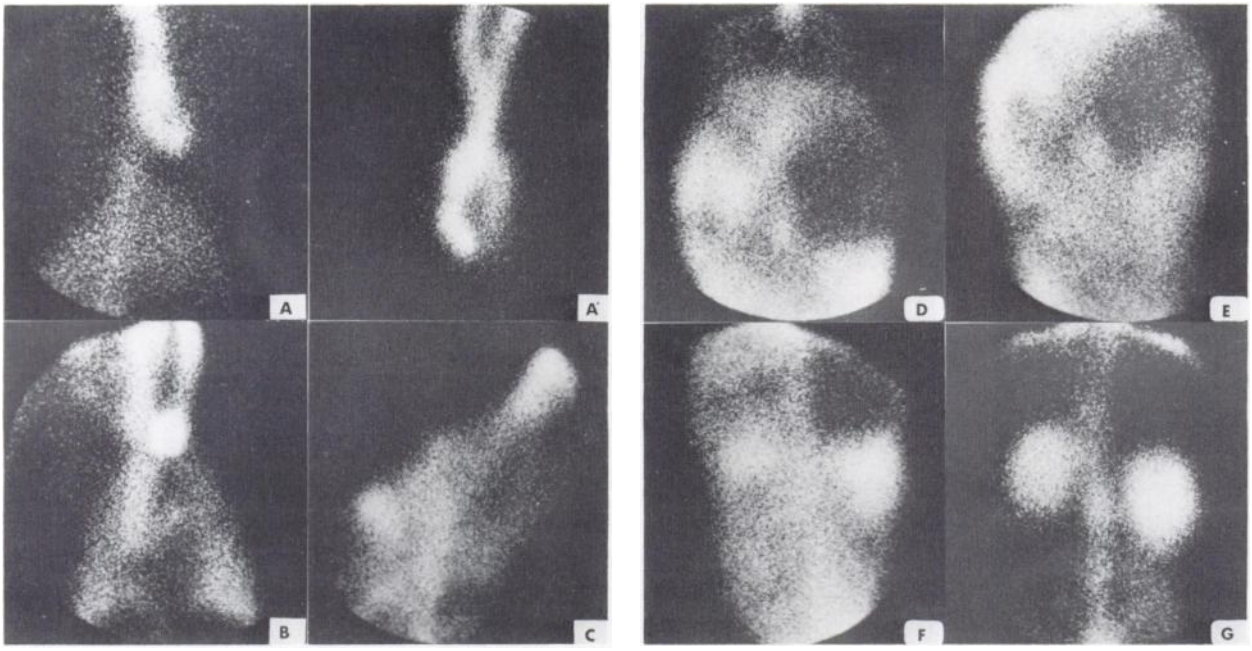

FIG. 3. Series of scintigraphic images obtained in 20-kg male dog under steady-state conditions of ^{81m}Kr administration following retrograde catheterization of right external carotid artery. (A) Catheter tip is in aortic root. In second view, in another dog, (A') an undefined portion of coronary artery circulation is seen; in addition, thoracic and abdominal aorta and liver are visible. (B) Catheter tip is in arch of aorta; greater part of activity is entering carotid circulation. Venous return through superior vena cava is seen, as is also right heart and lungs. Comparison should be made with inferior vena cava return in Fig. 2. (C) Right lateral view of dog's head is seen with catheter tip in aortic arch. (D) Catheter tip is in distal thoracic aorta. Liver is visualized while characteristic "cold" focal area of gallbladder within liver is obvious. Abdominal aorta and portion of mesenteric circulation is visible. (E) With catheter tip as in (D) above, moving detector inferiorly reveals an additional region of superior mesenteric artery circulation. (F) Catheter tip is in superior portion of abdominal aorta. Liver is visualized as well as abdominal aorta. Renal circulation is receiving a significant contribution as is inferior mesenteric artery. In Figs. 3(D) through (F), splenic and gastric arteries are receiving little activity. (See Fig. 4.) (G) Catheter tip is in aorta above renal arteries. Kidneys are optimally visualized with little contribution to inferior mesenteric artery.

draining, the right heart, and the perfusion of the lungs as well as activity in the trachea, the distal airways, and the exhaled breath. Such a composite image is seen in Fig. 2.

The catheter was inserted in the carotid artery and advanced proximally to the aortic arch and then distally along the thoracic and abdominal aorta. The flow rate was maintained at a flow of 1.5 ml/min. As the catheter tip was advanced and allowed to equilibrate at each stop, the proximal image would decay and a new distal image would appear. All regions of the body are accessible to imaging by this technique. Examples of various images produced may be seen in Fig. 3 A–G. When arteries to specific organs are entered, the rapid decay and washout in adjacent areas result in an unimpaired image of the organs in question. The pancreas and spleen are examples of such specific visualization (Figs. 4 and 5).

Catheterization of the femoral artery in the dog with retrograde passage was particularly efficacious for visualizing the kidneys. The mechanics of deglutition and the configuration of the esophagus and stomach are readily seen when a human volunteer subject swallows water saturated with ^{81m}Kr (*4*). Although the resolution of fluoroscopy is lacking, the radiation exposure is so minimal that repeated studies may be undertaken. The images referred to in this paragraph were obtained with the Picker Dynacamera 2C system using a 2700 parallel-hole collimator designed for a maximum gamma energy at 0.225 MeV.

DISCUSSION AND THEORETICAL CONSIDERATIONS

The production of a ^{81m}Kr generator and delivery system for human application would appear technically feasible with a pyrogen-free, sterile version of the generator, free of toxic radiolytic products of the exchange resin. The production of ventilation and perfusion scintigrams of the lungs using a radioactive noble gas would be significantly simplified. The performance of selective arterial scintigraphic angiography can be accomplished without fluoroscopy. This procedure could be accomplished with minimal radiation exposure, additionally reduced by the 13-sec half-life of the ^{81m}Kr despite the high gamma photon flux. The availability of ventilation exhaust systems are not required with ^{81m}Kr as the major component of decay occurs in vivo; what minimal quantities are exhaled are dissipated by the exceedingly rapid decay.

Decay in a closed compartment. Constant production and intra-arterial infusion of a radioactive gas solution with a 13-sec half-life represents a unique set of conditions not previously studied for biologic purposes. A quantity of ^{81m}Kr placed in a closed compartment will decay as defined by the formula

$$A_t = A_0 e^{-\lambda t} \quad (1)$$

in which A_t is the activity remaining at time t, A_0 is the initial activity, and λ is the physical decay constant.

Decay in a replenished open compartment. If activity is produced at a constant rate and flows in solution through an open, uniform diameter, cylindrical compartment at constant velocity, for any discrete segment of that compartment the activity remains constant. For any increment of activity entering the segment at time zero (A_0) and leaving the segment at time (t), the activity will diminish by decay and is defined as (A_t) as in Eq. 1. The constant average level of activity at equilibrium ($\bar{A}_{eq}$) may be approximated for periods significantly less than a physical half-life.

$$\bar{A}_{eq} = A_0 e^{-\lambda t/2} \quad (2)$$

The more exact definition of $\bar{A}_{eq}$ for any time is

$$\bar{A}_{eq} = (A_0/t)(1 - e^{-\lambda t}) \quad (3)$$

In either equation t is the time of transit through the segment. For the purpose of this example, the entrance of the segment is the orifice of a catheter in an artery at the site of entering an organ and the exit is the average location where activity passes through the capillary wall and enters the extracapillary compartment. A_0 is activity at the time of entry and A_t is activity at the time of exit from the segment. For pragmatic reasons, variations in velocity and cross-sectional area are not considered. The intravenous activity beyond the arterial–capillary segment is considered a special case of extrasegmental activity.

Since $\bar{A}_{eq}$ in the described constantly replenished open compartment never changes, the conditions of

$$A_t = A_0 e^{-\lambda t} \quad (1)$$

are modified in reference to the total average activity in the cylindrical compartment such that steady-state conditions exist and

$$\bar{A}_t = \bar{A}_0 \quad (4)$$

Thus the average activity at any time ($\bar{A}_t$) is a constant equal to the initially established average activity ($\bar{A}_0$).

Equilibration with the extracapillary compartment. Krypton-81m distributes in a manner similar to ^{133}Xe when infused into an artery at a constant rate by penetrating the extracapillary compartments. As each atom of ^{81m}Kr decays, an atom of ^{81}Kr appears. The total Kr, the sum of ^{81m}Kr and ^{81}Kr, will distribute at homogeneous concentration within the accessible extracapillary volumes, which will approximate the con-

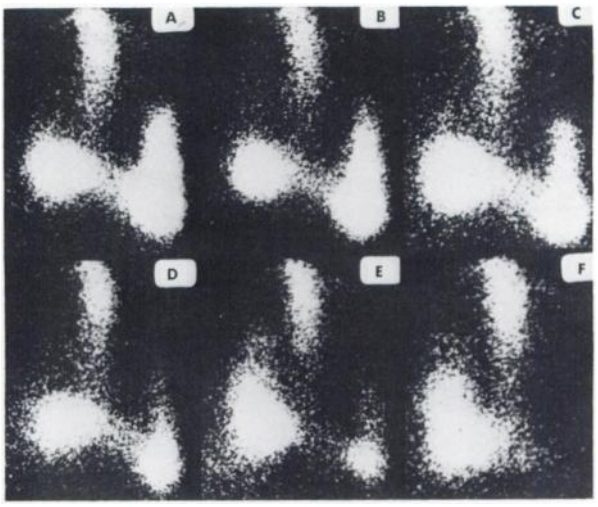

FIG. 4. (A–F) Catheter tip is in splenic artery. (A) shows pancreas and spleen in steady-state condition. This image had been maintained for several minutes. (B to F) show image sequence following intravenous administration of epinephrine. Splenic image is seen to fade while pancreatic image persists.

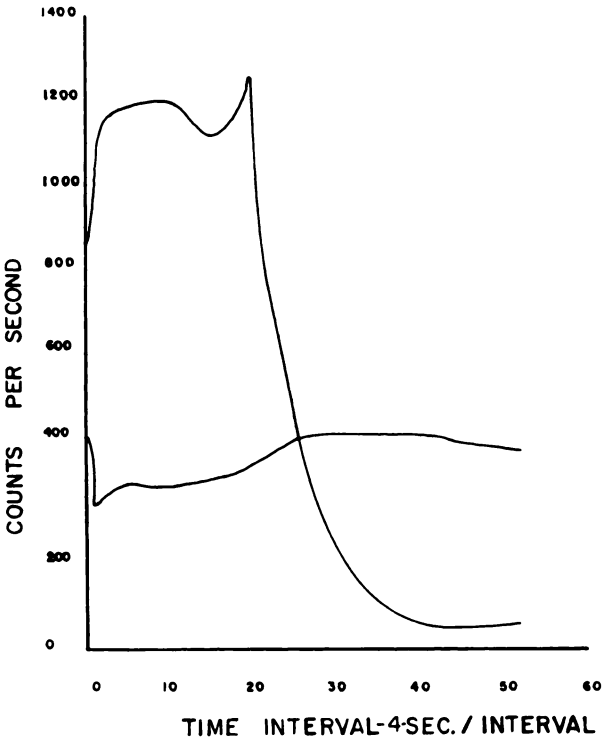

FIG. 5. Profile shows quantitated activity in spleen (top curve) and pancreas at 4-sec intervals as influenced by i.v. administration of epinephrine.

centration within the capillary at the time of equilibration. Homogeneous solubility of ^{81m}Kr is assumed despite the well-known differences in solubility of Kr in lipid as compared with water. The delivery and exchange of krypton is at a steady state in the system described.

Decay in the extravascular compartment as compared to decay in vasculature. The ^{81m}Kr is detectable by scintillation events because of its rapid decay. Krypton-81 is relatively without activity with a half-life of 200,000 years. The exchange with the pericapillary compartments occurs following transit through the vascular segment and has undergone decay during transit. Therefore, each component of the extracapillary compartment contains a lesser concentration of ^{81m}Kr than the vascular segment. Movement of Kr through the extracapillary compartments takes place outside of the vascular flow and occurs at lesser velocity than blood flow. The time of transit may be of significantly greater duration than within the vasculature. The ^{81m}Kr is the only detectable radionuclide in the system. Its actual and specific activity relative to total Kr is constantly decreasing as it diffuses away from the capillary. Its concentration decreases as it diffuses into a larger volume. Finally, a portion of the ^{81m}Kr diffuses back into the capillary prior to decay into ^{81}Kr. Significant changes in intravascular or extravascular volume will produce changes which will be measurable only after allowing appropriate time for re-equilibration.

Heterogeneity in the extravascular compartment during steady state. The distribution of ^{81m}Kr is heterogeneous, being low in regions of minimal exchange with long equilibration time and approaching the intravascular activity in compartments of rapid exchange. Known washout times would indicate extracapillary exchange times compatible with generating significant heterogeneity when the physical half-time of ^{81m}Kr is 13 sec.

Scintigraphic measurement of heterogeneity. The production of a scintigraphic matrix image at the time of equilibration would illustrate the heterogeneity of ^{81m}Kr distribution. It may be assumed that at the time equilibrium conditions are obtained, the accumulation of information using a scintillation detector may continue for sufficient time to satisfy all statistical requirements of adequate image production. Employing a diffusible radionuclide with a half-time of 13 sec, any extracapillary space requiring 130 sec, or ten half-lives, for equilibration would contribute a counting rate of only 0.1% of the intravascular activity. Considering the precision of the detecting instruments, equilibration may be assumed within 2 min of perfusing an organ or region at constant rate. It is then assumed that detectable counts in an area of interest of a scintigram are proportional to the activity, variability due to distance and self-absorption not being considered. The measurable activity in the image matrix originates in both the vascular and extravascular compartments. Observed heterogeneity would indicate relative concentrations in both compartments. The average intravascular activity $\bar{A}_{eq}$ has been defined in Eqs. 2 and 3. The average extravascular activity for any area of interest is designated $\bar{A}'_{eq}$ and will be more definitely defined below.

Differentiating the vascular and extravascular compartments. Differentiating the two compartments is viewed as a solvable problem. This solution is based upon the relative rates of washout of intravascular ($\bar{A}_{eq}$) and extravascular ($\bar{A}'_{eq}$) ^{81m}Kr activity. To determine the extravascular-to-blood ratio ($\bar{A}'_{eq}/\bar{A}_{eq}$), the level of activity being viewed by the detector during steady-state conditions is sequentially recorded as a series of digital matrices. The ^{81m}Kr component of the glucose solution being delivered is abruptly interrupted. That fraction representing intravascular activity will be rapidly replaced (*5*). The extravascular activity will wash out less rapidly and at various rates. After correction for the very rapid physical decay, the value for $\bar{A}_{eq}$ and $\bar{A}'_{eq}$ may be determined by extrapolation of each component of the curve to zero time, the time of interruption of ^{81m}Kr delivery, and subtracting the value of either intercept from the total activity (A). $\bar{A}'_{eq}$ values will be relatively less in those areas with prolonged exchange time. It has been demonstrated that recirculation is not a significant factor due to rapid decay and elimination from the lungs. An alternative method of differentiating the vascular and extravascular compartment is predicated upon the use of a nondiffusible intravascular marker. Human serum albumin labeled with ^{99m}Tc may be employed. Differentiating the ^{99m}Tc and the ^{81m}Kr by pulse-height analysis and subtracting the vascular component may be a more practical approach (*6*).

Complexity of exchange between blood and tissue. The rate of exchange between the two compartments is influenced by volume and shape of the specific exchange compartments, hydrostatic and osmotic pressure, the area of capillary membrane, spatial distribution of capillaries in relation to the extravascular compartment, heterogeneity of tissue components, solubility of krypton, the diffusion constant of krypton, and various additional factors. It is not possible to measure these factors in a complex biologic system; therefore, these factors in conventional diffusion formulas cannot be used to define capillary exchange time.

Calculation of exchange time in the tissue compartment. It is possible to determine transit time in the extravascular space by the rationale described above in a single-frame scintigraphic matrix image obtained under steady-state conditions. The factors to be measured to make the determination in any area of interest in the matrix image are the total activity (Z) in the area and the contribution of the blood and extravascular components. The rapid decay of ^{81m}Kr is of the same order of magnitude as the extracapillary exchange time and is the built-in clock which generates the heterogeneity of activity to be measured.

To calculate exchange time (t) for any extravascular area of interest, the area is defined in relation to its location in the total matrix, the X and Y dimension, and the total count content (ΣZ) of the area of interest. The sum of Z of each matrix display point within the area of interest is especially determined per unit time during steady-state conditions (ΣZ_{eq})

$$\Sigma Z_{eq} = \bar{A}_{eq} + \bar{A}'_{eq} \qquad (5)$$

and is equal to the total vascular and extravascular activity. When ^{81m}Kr delivery is interrupted, the resulting zero intercept of the rapid and slow component $\bar{A}_{eq}$ and $\bar{A}'_{eq}$ may be determined and corrected for decay following interruption.

The half-transit time through the vascular compartment is defined below as the half-time of the rapid component corrected for decay in the equation.

$$\bar{A}_{eq} = \bar{A}_0 e^{-\lambda t/2} \qquad (2,3)$$

The activity in the extravascular compartment

$$\bar{A}'_{eq} = \bar{A}_{eq} e^{-\lambda t} \qquad (6)$$

Since $\bar{A}_{eq}$ and $\bar{A}'_{eq}$ are derived from Eq. 5 and λ is known, extravascular exchange time (t) for any area during steady state may be determined.

$$t = \ln(\bar{A}_{eq}/\bar{A}'_{eq})/\lambda \qquad (7)$$

While the above value for extravascular transit time is determined for the half-time of intravascular transit and the extravascular exchange begins at the end of transit to the capillary, appropriate corrections may be made if the difference is significant.

Advantage of steady-state measurement. The heterogeneity of activity will remain static so long as the steady-state condition remains or conditions of vascular exchange are not modified. This can be defined by the rectilinear scanner or scintillation camera within the technical limitations of these instruments. A very high photon flux may be used without undue exposure of the patient considering the entire period of decay. Krypton-81m decays 1660 times more rapidly than ^{99m}Tc, ordinarily considered a radionuclide that can be safely employed in high dosage. It is estimated that very high levels of activity capable of blocking scintillation camera function can be used without dangerous patient exposure. This level of activity would indicate the scintillation camera as the instrument of choice. Satisfactory static images capable of the above kinetic interpretation can be easily obtained in less than 1 min, permitting multiple views under steady-state conditions.

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