Temporal Behavior of Peripheral Organ Distribution Volume in Mammillary Systems. I. A New Tool for In Vivo Tracer Kinetic Analysis

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In complex mammillary compartmental systems, the kinetic solutions for central and peripheral compartments are sums of too many exponentials to be accurately analyzed without very sophisticated mathematical tools. Our data show the peripheral organ distribution volume (PODV) kinetics to exhibit systematic time behavior depending on its mode of relation with plasma: linear increase for irreversible transfer, uniexponential function growing toward an asymptotic value for reversible transfer. Statistical analysis of our kinetic data shows that no other significant information can be extracted at least inside the time and statistical noise limits of our investigation. After intravenous injection of a diffusible tracer, the total activity in any region of interest (ROI) in the body is the sum of various components and, under certain conditions, PODV transformation easily allows their separation. Our simple noncompartmental model provides a useful tool for quantitative tracer analysis in nuclear medicine.

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When a diffusible substance is introduced into the blood stream, it rapidly mixes in the vascular compartment, passively diffuses to the extravascular interstitial spaces, is filtered in the renal glomerulus and eventually excreted in the urines. It may also be actively trapped in any other specific organ for further metabolism. The whole living organism may thus be considered as a complex mammillary system, whose plasma central compartment is either passively or actively cleared by multiple peripheral reversible or irreversible pathways.

The plasma-tracer concentration reflects all these exchanges and its actual value integrates the effects of the multiple metabolic or excretory processes occurring in the various tissues of the whole organism. Thus, at any time, the plasma concentration contains the full history of all the compartments of the system. Complete mathematical description of the plasma curve, which accounts for all the pathways in such complex multicompartmental system, "involves too many exponential terms to be studied with any degree of accuracy" (*1*).

Similarly, tracer kinetics in any peripheral compartment, in mammillary systems, may be expressed by a sum of exponential terms, whose coefficients and arguments are influenced by all the compartments of the system (*2–4*).

Sophisticated compartmental models and computer programs (*5,6*) were proposed for analysis of such complex kinetic data but, if they were extensively used as research tools, their complexity makes their clinical application practically impossible.

The total distribution volume of a tracer is defined as the virtual volume in which the tracer would be uniformly distributed if its concentration was anywhere identical to the plasma reference concentration. The distribution volume concept is usually used at equilibrium (*3*) and, until now, few papers have been devoted to its temporal behavior in complex open systems (*7*).

Riggs (*3*) also defines the distribution volume of a peripheral compartment, i.e., its plasma equivalent space, as the theoretical volume the compartment would occupy if all the tracer it contains was at the same concentration as in plasma. This virtual volume is also usually measured at equilibrium and taken as a reliable index of the concentration gradient which exists between organ and plasma in relative equilibrium state.

The topic of the present paper is the analysis (in mammillary systems) of the temporal behavior of the peripheral organ distribution volume (PODV). The PODV concept is applied to organs reversibly linked to plasma in which relative equilibrium eventually happens and is extended to irreversibly linked organs in which disequilibrium is the rule.

Earlier data (*8,9*) from pertechnetate or iodide kinetic

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studies have shown that the thyroid partial distribution volume has, at least for the first hour after injection of the tracer, a simple systematic behavior. Further observations (*10*) emphasized a similar behavior of the distribution volume in various organs.

The present paper develops the results for various plasma-target organ couples (interstitial fluid, thyroid, and gastric mucosa with technetium-99m-pertechnetate ([^{99m}Tc]pertechnetate), interstitial fluid, and kidneys with ^{99m}Tc-DTPA) and demonstrates that two simple functions are actually necessary and sufficient to represent the PODV time dependence.

MATERIALS AND METHODS

Adult male and female patients referred to the nuclear medicine department for thyroid or gastric (*11*) [^{99m}Tc]pertechnetate uptake studies and for ^{99m}Tc-DTPA (diethylenetriaminepentaacetic acid) separate glomerular filtration rate (GFR) estimation constituted our patient population.

Data Acquisition and Preprocessing

External measurements of the studied organ are performed with a large field of view gamma camera equipped with a general-purpose low-energy parallel-hole collimator (Elscint DYMAX, Boston, MA or Siemens LFOV, Hoffman Estates, IL). Identical syringes containing the tracer doses and the standards are counted, in identical geometric conditions, using a special cylindrical plexiglas holder.

The patient lies in front of the detector, which includes, in its field of view, the organ concerned and the cardiac chambers. The tracer dose is rapidly injected in an antecubital vein and acquisition is started by means of a digital computer (Elscint DYCOM 80 or ADAC-IMAC, Milpitas, CA). Fifteen-second 64 × 64 frames are continuously acquired starting at injection for at least 20 min. Later than the fifteenth minute after injection but before the end of the acquisition period, a blood sample is rapidly withdrawn from a large antecubital vein of the opposite arm for estimation of the plasma-tracer concentration.

Regions of interest (ROIs) are delineated: the studied organ itself, an adjacent zone for tissue background correction, and the heart chambers. After classical background subtraction, corrected organ activity, Q(t), is expressed as fraction of the dose. The heart-activity curve is calibrated in fraction of the dose per liter of plasma, p(t), by reference to the actual plasma concentration measured in the plasma sample.

Various organ-plasma couples have been studied (Fig. 1). Special features such as tracer molecule or patient positioning are, in each case, adapted to the specific organ and described below.

Thyroid Studies. The patient is positioned supine under the camera detector, the neck slightly hyperextended. The [^{99m}Tc]pertechnetate dose is rapidly injected in an antecubital vein and continuous acquisition is generally obtained for 20 min and in some cases up to 120 min. Extra-thyroidal radioactivity is corrected by subtraction of the activity in a large-shoulder ROI normalized to the area of the thyroid ROI. No attenuation correction is performed for gland depth. Eighty-five patients with normal and various thyroid pathologic states are included in the statistical analysis.

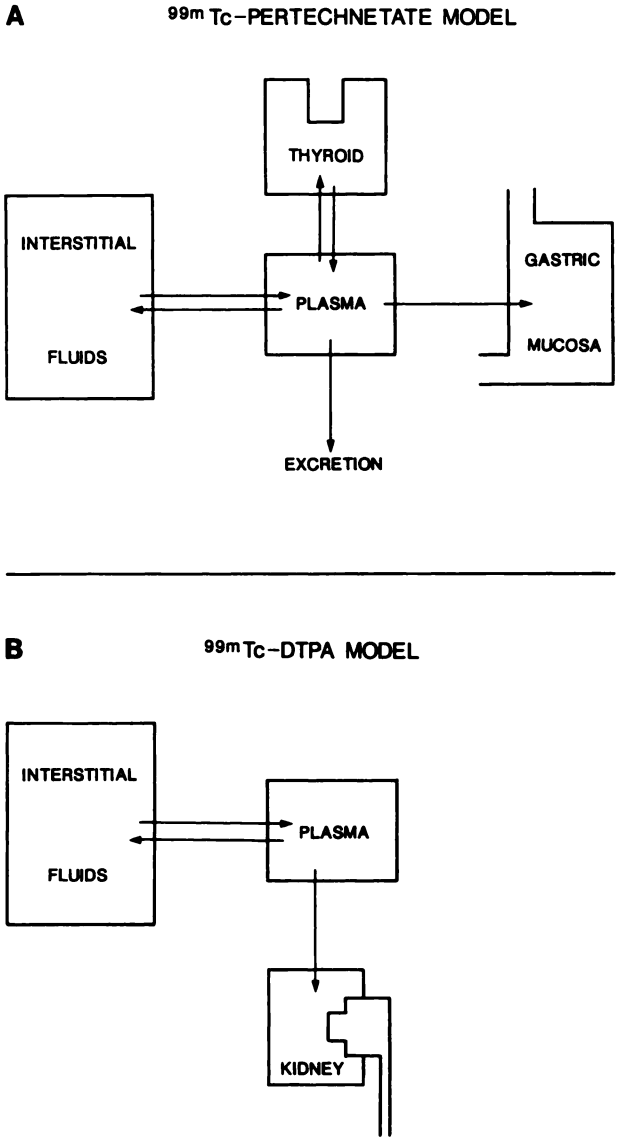

FIGURE 1
Organ-plasma couples studied. (A)[^{99m}Tc]pertechnetate bidirectional (thyroid and interstitial fluids) and unidirectional (gastric mucosa). (B) ^{99m}Tc-DTPA bidirectional (interstitial fluids) and unidirectional (kidney).

Gastric Studies. The patient lies supine under the camera detector, whose field of view includes the whole stomach and the heart. Extra-gastric activity correction is performed by subtracting the activity of an ROI close to the stomach on the left side. The tracer ([^{99m}Tc]pertechnetate) is concentrated by the gastric cell with a relatively long transit time before gastric emptying starts. A left lateral view is acquired at the end of the dynamic acquisition for depth estimation and attenuation correction. Eighty-two patients are included in the statistical analysis.

Kidney Studies. The patient lies supine on a thin plexiglas table, above the camera detector. The field of view includes the two kidneys and the heart. The tracer used is ^{99m}Tc-DTPA. Extrarenal activity is corrected by subtracting the activity of a ROI below each kidney. For attenuation correction, each kidney depth is estimated on left and right lateral views

acquired immediately at the end of the dynamic acquisition. A total of 128 patients, with various renal diseases, are included in the statistical analysis.

Interstitial Fluid Studies. The whole left shoulder-activity curve, taken as background area in thyroid studies with pertechnetate, and the background area of kidney studies with DTPA are used for studying interstitial fluid kinetics. Statistical analysis is performed in a total group of 166 patients with pertechnetate.

Method of Calculation

The PODV curve, V(t) in liters, is calculated for each frame time, as the ratio Q(t)/p(t), where Q(t) and p(t) respectively represent the organ tracer content (in %dose) and the plasma-tracer concentration (in %dose/liter) time-dependent curves.

The graphical plot of V(t), as shown later, essentially exhibits two different kinetics, depending on the type of relationship existing between target organ and plasma. This imposes the choice of two parametric functions to fit the distribution volume curves: an exponential function growing toward an asymptote for bidirectional exchange mode or a linear time dependence for unidirectional transfer.

A multi-parameter non-linear steepest descent least-square's minimization algorithm is used to fit the first mode of data while a least-square's linear regression method is applied to the second. To limit the possible error due to plasma mixing, the lower time limit for the fit has been arbitrarily set to 60 sec. The fitted function parameters are best estimated in the least-square's sense and the adequacy of the fitted curve is validated by the correlation coefficient observed between the experimental data and the parametric function computed values.

For each organ-plasma couple studied, a scatter plot (all patients and all times) of all individual PODV values versus time is drawn. The PODV values in ordinate are corrected for their offset Vo (see Results) and divided by their estimated asymptotic value in case of bidirectional mode. Each corrected PODV value is plotted at an abscissa given by its actual time multiplied by its respective individual exponential rate constant or slope of the linear fit (referred to as "eigentime"). Such a rescaling of the data allows the straightforward comparison of the intrinsic time dependence of the PODV curves of all patients in each group, without interference of the parameter absolute values.

RESULTS

Organ Kinetic Studies

Figure 2 illustrates p(t), the plasma concentration, and Q(t), the organ content obtained, in individual patients, for the various organ-plasma couples: thyroid, interstitial fluid, and gastric mucosa after [^{99m}Tc]pertechnetate injection and kidney after ^{99m}Tc-DTPA injection and V(t), the corresponding distribution volume curve.

Initial Distribution Volume (Vo)

In the four organ-plasma couples presented in Figure 2 (lower panel), the PODV curve, V(t), actually exhibits a two-phase pattern: a rapid initial rise (before 30 sec) followed by a slower component (see next section).

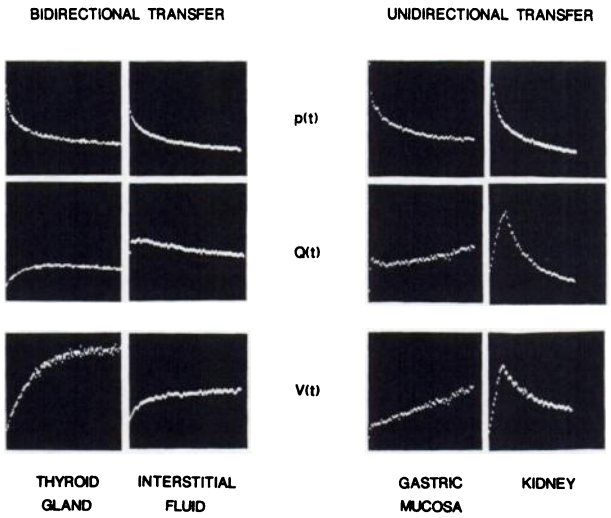

FIGURE 2
Individual patient experimental kinetic curves in the four organ-plasma couples. Organ content Q(t), plasma concentration p(t), and organ distribution volume V(t) = Q(t)/p(t). Thyroid and interstitial fluid studies (50 min), gastric and kidney studies (20 min)

The rapid initial rise is a constant feature both for passive processes such as simple diffusion in interstitial fluids or glomerular filtration and for active processes in thyroid or gastric uptake and is taken into account in the fitting process by introducing an initial value parameter Vo. An example of original data and non-linear fit is shown in Figure 3, in an interstitial fluid study after ^{99m}Tc-DTPA injection.

Systematic Temporal Behavior of the PODV

The scatter plots (Fig. 4) show the systematic temporal behavior of the PODV in the four systems studied.

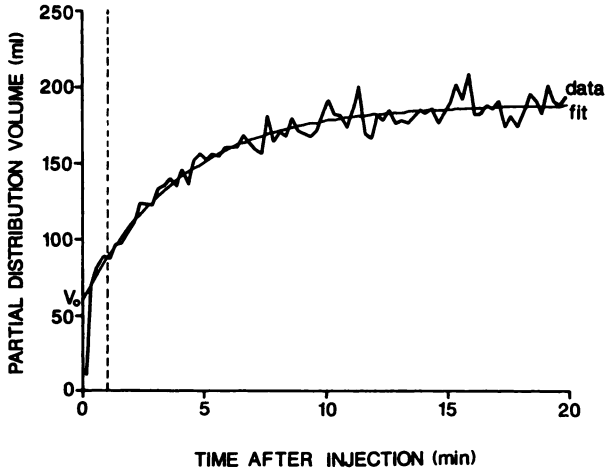

FIGURE 3
Graphic estimation of Vo in an interstitial fluid study with ^{99m}Tc-DTPA. The graph shows the original data and the non-linear fit. The y-intercept, Vo, is the initial distribution volume. Non-linear fit starts from the second minute after injection (dotted line).

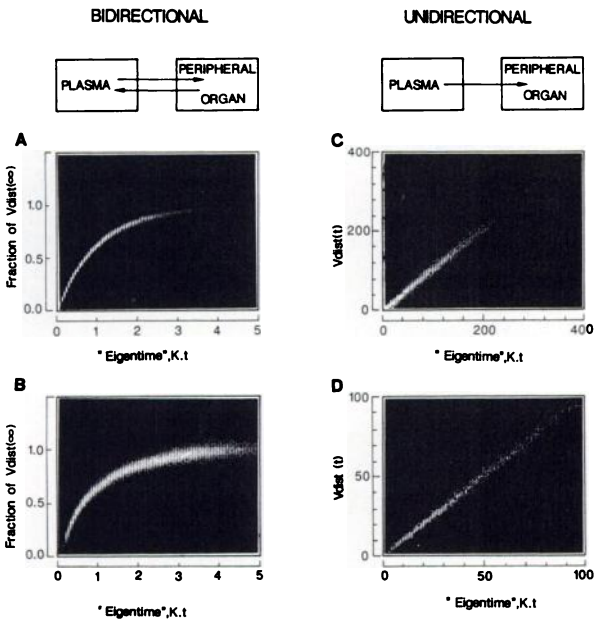

FIGURE 4
Systematic temporal behavior of PODV according to the organ-plasma relationship. Reversible type: (A) thyroid gland (n = 85) and (B) interstitial fluids (n = 166). Irreversible type: (C) gastric (n = 82) and (D) kidney (n = 128). All PODVs are Vo corrected. See text for complete explanation of the x and y scales.

Two different patterns are actually observed: in the case of the thyroid gland and the interstitial fluid, that is in the two bidirectional reversible types of organ-plasma relationship, the PODV follows an exponential function tending toward an equilibrium asymptotic value:

$$V(t) = V_o + (V_\infty - V_o)\cdot(1 - e^{-K\cdot t}), \qquad (1)$$

in which:

V(t) is the PODV at time t
V_o is the initial distribution volume
V_∞ is the relative "equilibrium" PODV
K is the exponential rate constant, $[T^{-1}]$.

As shown in Figure 3 in a typical case, the same pattern is observed in extracellular fluids with DTPA in all cases, but as extensive statistical analysis was not performed, the data are not represented in Figure 4.

The PODV curves are corrected for the initial distribution volume, Vo, as explained above. The x- and y-scales are adapted to emphasize the similarity of the 85 thyroid and the 166 interstitial fluid studies: equilibrium value is set equal to unity and real time on the abscissa is multiplied by the individual exponential rate constant value and referred to as "eigentime."

As pertechnetate is actively concentrated in the thyroid, the data (Fig. 4A) show a lower statistical noise than for the interstitial fluid (Fig. 4B) in which the tracer only passively diffuses.

In the case of the gastric mucosa and the kidney, i.e., in the unidirectional, irreversible type of organ-plasma relationship, PODV kinetics follows a linear law insofar as the minimum transit time is not reached, i.e., before any tracer leaves the organ:

$$V(t) = V_o + K\cdot t, \qquad (2)$$

in which V(t) is the PODV at time t, Vo is the initial distribution volume, and K is the slope (ml/min).

The PODV curves are also corrected for the initial distribution volume, Vo, and the time scale of the abcissa is also normalized to K.t., the "eigentime." The minimum transit time is usually < 10 min in the stomach and < 4 min in the kidney; these are taken as the upper time limit of the abcissa in Fig. 4C (stomach) and Fig. 4D (kidney).

It is important to emphasize that the data plotted in this figure are the experimental data themselves and that the fit parameters are used only to correct for the initial Vo value and to adapt the x- and y-scales.

Statistical Analysis

Distributions of the individual patient PODV model parameters are characterized by their first two moments: mean and s.d. (Tables 1 and 2). In general, s.d. values are large (half to twice the mean values), due to the widespread kinetic behavior in our population.

Correlation coefficients confirm the good fit of experimental values with Equations 1 and 2. Average correlation coefficients, r, given in Table 3, are in no case lower than 0.96 (s.d. < 0.1). An intensive statistical analysis of the relative residual distributions confirms that no additional structure may be identified in our data. However, detailed statistical results are out of the scope of the present paper and the scatter plots of Figure 4 best visualize the local quality of fit not detailed by the global correlation coefficient.

DISCUSSION

Methodologic Aspects

Accurate estimation and kinetic analysis of the PODV actually implie simultaneous measurement of the target organ tracer activity along with the plasma tracer concentration, the latter being the keystone of our model.

TABLE 1
Bidirectional Model—Distribution of the Fit Parameters*

	V_o (liters)		V_∞ (liters)		K (min^{-1})	
Organ	mean	s.d.	mean	s.d.	mean	s.d.
Interstitial fluids	0.88	0.38	1.82	0.67	0.238	0.077
Thyroid gland	0.47	0.45	0.68	1.06	0.147	0.090

* Non-linear fit according to Equation 1.

TABLE 2
Unidirectional Model—Distribution of the Fit Parameters*

Organ	V_o (ml) mean	V_o (ml) s.d.	K (ml/min) mean	K (ml/min) s.d.
Gastric mucosa	127.0	54.1	20.9	11.5
Kidney	18.2	10.5	17.1	10.5

* Linear fit according to Equation 2.

The Plasma Concentration Curve

The true plasma concentration might be measured by frequent plasma sampling but such a method would constitute a major inconvenience for the patient and greatly limit its widespread everyday clinical use.

The cardiac-activity curve obtained by external counting and calibrated with the true concentration of a blood sample withdrawn during in vivo acquisition is used (a technique dating 20 years) as an adequate estimate of the plasma-tracer concentration curve. However, until now, its reliability has not been really validated in man.

As a matter of fact, many factors may actually distort the cardiac-activity curve. Among them, the presence in the cardiac ROI, of a significant amount of interstitial fluid is critical. Kuruc et al. (*12*), in a recent paper, compared, in the rabbit, the calibrated epicardial count rate with the true arterial concentration and demonstrated a systematic distortion in the initial part of the cardiac-activity curve.

The correction for that distortion is presently under study in our department and detailed results will be published in a future paper. However, the problem is difficult because: 1) multiple arterial plasma sampling in man, as proposed by Kuruc et al., is plagued with ethical considerations; and 2) as already shown by McGuire et al. (*13*), our data frequently confirm the unreliability of early venous samples to apply Fleming's correction (*14*) with a sufficient degree of confidence.

However, preliminary results in our department suggest that subtracting or adding relatively large amounts of interstitial fluid to the epicardial-activity curve, even leading to evident distortion, does not significantly influence the PODV temporal behavior, which is the main topic of the present paper.

TABLE 3
Correlation Coefficients

Organ	Tracer	n	Kinetics	mean	s.d.
Thyroid gland	TcO_4	85	Exponential (Eq. 1)	0.983	0.11
Interstitial fluids	TcO_4	166	Exponential (Eq. 1)	0.974	0.06
Gastric mucosa	TcO_4	82	Linear (Eq. 2)	0.965	0.06
Kidney	DTPA	128	Linear (Eq. 2)	0.971	0.08

n = number of cases.

The Organ-Activity Curve

For accurate estimation of target-organ tracer activity, adequate choice of the ROI for background correction is crucial and should be carefully reconsidered for each organ and each tracer. In the present paper, background ROIs have been drawn close to the organ as usually done by others and more discussion is given in part II (*15*) in the particular case of separate GFR estimation.

Photon scattering and attenuation corrections are also critical for quantitative tracer analysis and any error will eventually lead to erroneous kinetic parameters. However, we are more concerned, in the present paper, with the phenomenologic behavior of the PODV, which will not be critically influenced by these factors as far as they remain constant with time during data acquisition.

Data Analysis

The fast initial component of the PODV curve corresponds to the vascular phase and, thus, Vo is mainly related to the plasma volume in the ROI.

Ten years ago, Hays (*16*) developed a mathematical model for pertechnetate-thyroid trap: three compartments (plasma and two thyroidal, "cellular," and "follicular," compartments) were necessary to fit the early observed data. The rapid early thyroidal uptake component was first considered as plasma residual but, as it was shown to be dependent on iodide block, it was considered as part of the trapping mechanism.

In the present data, the rapid initial rise of the PODV curve is a constant feature both for active processes in thyroid or gastric uptake and for passive diffusion in interstitial fluids or glomerular filtration, where no cellular component is actually involved. Hays' hypothesis is thus not necessary and, if we cannot definitely exclude a very rapid "cellular" transient phase in the active processes as thyroid and gastric mucosa uptake, it cannot be kinetically distinguished, in our model from the residual vascular component.

As any active organ has a denser vascular bed than the surrounding tissues, the usual background correction is well known to be insufficient. In the analysis of our kinetic data, the linear or exponential fit of the second component of the PODV curve is thus extrapolated to the origin and its initial value is considered as the distribution volume of the plasma component and no additional compartment is postulated.

This concept is validated in part II (*15*) in the case of renal function study with ^{99m}Tc-DTPA.

The Model

The total distribution volume of a diffusible tracer is the virtual equilibrium volume in which the tracer would be uniformly distributed at a concentration identical to the plasma reference concentration.

The PODV of a tracer in a particular organ may be

defined as the theoretical volume that organ would occupy were the tracer it contains at an equal concentration as in plasma. This theoretical volume is also usually measured at relative equilibrium and no information is available, in the literature, about its transient phase.

The present paper concerns a non-compartmental but phenomenologic approach to the mathematical analysis of in vivo kinetic data; a theoretical volume, the PODV, i.e., the target-organ-tracer content-to-plasma-concentration ratio, exhibits systematic temporal properties.

As a matter of fact, after its rapid initial rise, the PODV curve shows a component whose shape only depends on the type of the relationship between target organ and plasma. Indeed, its analysis in various target organ-plasma couples reveals two simple constant patterns: linear increase with time for unidirectional, irreversible transfer; uniexponential increase tending toward an asymptotic value in the case of bidirectional, reversible transfer.

A statistical analysis of 210 cases of the first type and 251 cases of the second, shows evidence that no other significant information can be extracted from the observed kinetic data, at least inside the time and statistical noise limits of our investigations.

As the clearance concept actually isolates the organ-plasma couple from the whole system and allows the estimation of the overall extraction efficiency, the PODV concept actually integrates the effects of rapid plasma kinetic changes during the uptake phase of the studied organ.

PODV expresses at any time the organ content in fraction of the plasma tracer concentration and actually appears to be equivalent to what the organ tracer content itself would be in a practically impossible experiment in which plasma concentration would be kept constant.

Indeed, the phenomenologically selected function used to fit the PODV curve may be easily shown to be the function which is derived from the convolution of a constant plasma concentration with the unit impulse response function expected for that organ in the underlying compartmental model.

Moreover, constant plasma concentration condition, in a multicompartment mammillary system, would lead to the complete decoupling of all the tracer transfer processes.

Why does the PODV transformation of the organ tracer content result in such a simplification remains to be elucidated and is presently under investigation in our department.

However, such PODV time behavior must be verified by the solutions of any compartmental analysis of mammillary systems to insure better coherence with the experimental data. Incorporated in the model as constraints, the PODV properties will exclude unrealistic solutions.

Clinical Applications

To what extent a tracer is concentrated by an organ has, for many years, been a major concern of nuclear medicine. A high target organ-to-surrounding tissue ratio conditions the scintigraphic image quality. In addition, the organ uptake rate is a metabolic parameter which may, in many cases, lead to differential diagnosis of various disease states.

We initially focused our attention to organ-plasma clearance estimation (*9*). As the PODV is a virtual volume, how is it related to the clearance, a virtual flow? It may be shown that the initial rate of change of the PODV or the time zero value of the derivative of Equation 1 is equal to the organ unidirectional clearance in reversible processes.

It is very difficult, perhaps impossible, to obtain such early in vivo kinetic data due to blood mixing of the tracer. If a simple function could be demonstrated to fit the PODV curve, it could easily be extrapolated to time zero and lead to estimation of the initial clearance.

Preliminary data, obtained in our department, show evidence that:

1. The initial rate of change of the pertechnetate thyroid distribution volume more adequately separates hyperthyroid from euthyroid patients than the usual 20-min uptake value.
2. The gastric pertechnetate clearance is significantly increased by pentagastrin and decreased by anti-H2 compounds therapy. This parameter, as suggested by Taylor (*11*) might be investigated as an index of acid secretion.
3. The rate of increase of the liver distribution volume of ^{99m}Tc-galactosylated albumin appears to be a useful parameter in hepatocyte receptors studies.

However, as previously mentioned, the calibrated epicardial-activity curve, the background, scatter, and attenuation corrections are critical for accurate estimation of absolute kinetic parameters and should be reexamined for each individual organ and tracer for validation as reliable clinical tools.

We have thus actually focused our attention, in this paper, on the temporal behavior of the organ distribution volume in various organ-plasma couples and, in part II (*15*), on a kinetic approach to background correction.

Indeed, after intravenous bolus injection of a diffusible radioactive tracer, the total activity in any ROI in the body is merely the sum of variable proportions of vascular and interstitial components and, when it exists, the trapping organ. This total activity time-dependent curve is a very complex multiexponential function,

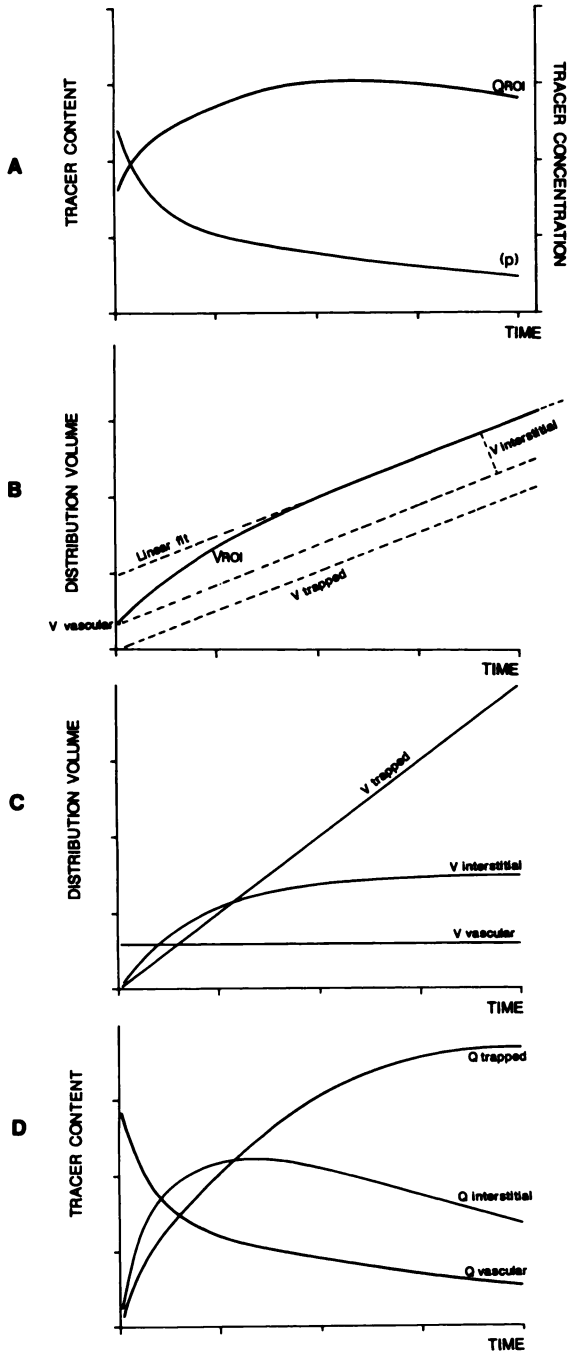

FIGURE 5
Decomposition of an ROI total activity into its basic components based on the kinetic properties of the PODV. (A) Simulated acquisition of the plasma concentration and of a total ROI activity with realistic fractions of vascular, interstitial fluid, and trapping organ components. (B) PODV transformation of the total ROI activity and kinetic decomposition scheme. (C) Plot of the resulting constant (vascular), uniexponential (interstitial), and linear (trapping organ) partial distribution volumes. (D) Inverse transformation: plot of the vascular, interstitial fluid, and trapping organ contents. Y scale has been expanded two-fold in graphs C and D compared to graphs A and B.

which can only be analyzed with sophisticated mathematical techniques.

When the ROI total activity is transformed into PODV, i.e., is divided by the plasma concentration curve p(t), its temporal behavior is reduced to a simple linear combination of independent terms: a constant (vascular), a uniexponential (interstitial fluid), and a linear term (the trapping organ).

Under certain circumstances, depending on the system studied, these terms can be kinetically separated (as shown with simulated data in Figure 5). The kinetics of the net activity of each individual component can thus be approached with good accuracy by the inverse transform that is re-multiplying by the plasma concentration curve.

A practical example of this decomposition and an easy clinical application is presented in part II (*15*): it concerns the decomposition of the ^{99m}Tc-DTPA renographic curve into its various components, i.e., vascular, interstitial fluid, and net kidney components in order to achieve better control of extra-renal activity correction.

It is our feeling that application of this easy phenomenologic approach to other peripheral organs in complex mammillary systems is straightforward and provides a promising tool for quantitative kinetic studies in everyday routine clinical nuclear medicine.

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15 30

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OCTOBER 1975

Clinical Assessment of Left Ventricular Regional Contraction Patterns and Ejection Fraction by High-Resolution Gated Scintigraphy

Daniel S. Berman, Antone F. Salel, Gerald L. DeNardo, Hugo G. Bogren, and Dean T. Mason

Left ventricular ejection fraction and regional myocardial contraction patterns are important parameters of cardiac pump performance, which, until recently, have required invasive procedures for measurement. The Anger scintillation camera has been used in development of the atraumatic technique of radioisotopic angiography. In 1971, Strauss et al. used gated cardiac blood-pool imaging to assess ejection fraction and segmental contraction. Despite the value of these techniques, difficulties with precise delineation of the left ventricular silhouette were evident.

The present study describes improvements in the radionuclide gated blood-pool imaging techniques, which enhance delineation of cardiac margins by using a high-resolution collimator, greater information density, and a phonocardiographic definition of gated intervals of the cardiac cycle. Validity is established by correlation with selective left ventricular cineangiography performed on 27 patients with a variety of cardiac disorders. The practicality and usefulness of this method is illustrated by selected examples from our experience with 79 patients.

In the 27 patients constituting the principal comparative group, the mean absolute difference was 8%. The mean ratio of the radioisotopic and radiopaque determinations was 0.98, indicating a lack of bias. The correlation coefficient was 0.93. In 14 of 22 patients with CAD, gated scintigraphy and cineangiography demonstrated regional abnormalities that were similar in location, nature, and technique. ■

OCTOBER 1960

Evaluation and Management of the Heavily Irradiated Individual

V.P. Bond, T.M. Fliedner, and E.P. Cronkite

Considerable experience with the acute radiation syndrome in man, in varying degrees of severity, has been gained as a result of the exposure of the Japanese at Hiroshima and Nagasaki; of the Marshallese at the Pacific Proving Grounds; of patients given total-body irradiation for therapy of malignant conditions; of workers exposed accidentally in incidents involving fissionable material; and of workers involved in non-nuclear radiation accidents such as the recent Lockport Klystron-tube incident. This degree of experience in human beings, coupled with the vast amount of animal experimentation, removes any justification for surrounding the syndrome with an aura of mystery. The pathogenesis is better understood and handled more effectively than that of many routine clinical conditions seen in the course of medical practice.

The aim of the present paper is to develop guidelines for management of the heavily exposed individual based on the pathogenesis of the acute radiation syndrome and on the use of measures demonstrated to be beneficial. The disorder actually consists of a complex of overlapping syndromes, the presence and severity of which is dependent on the physical dose received. It is quite clear that therapy should not be based on physical dose, however, nor on the category in which a patient has been placed. Therapy is guided only by the daily appraisal of clinical and laboratory findings and should be given only when clearly indicated, and not prophylactically.

With the acute radiation syndrome, non-medical personnel generally expect a precise prognosis and therapeutic outline soon after exposure, in contrast to the usual systematic and continuing analysis of a disease course that is expected of the physician. Radiation exposure should not be considered an extreme emergency. There is no justification for hasty therapeutic procedures done without careful consideration. It will be apparent within hours or days whether the exposure was so low that no therapy will be required, or so high that no therapy will help.

It has been shown that the therapies indicated involve no new principles but simply apply well known principles to physicians with experience in dealing with marrow hypoplasia or aplasia from any source. With vigorous functional replacement therapy, it is felt that human beings may survive a dose of radiation approximately twice that at which they would otherwise die. Such therapy involves, however, constant attention throughout the critical periods and the use of large amounts of antibiotics and fresh blood when indicated. By use of bone marrow, it may be possible for survival to occur at even higher doses; however, the efficacy of bone marrow transplants has not been adequately evaluated as yet.

It will be apparent that adequate care for even a relatively small number of heavily exposed individuals would tax the facilities of most hospitals. Thus, the conditions outlined in this present paper would not be applicable at all under major disaster conditions such as may pertain in the event of a nuclear war. ■