Temporal Behavior of Peripheral Organ Distribution Volume in Mammillary Systems. II. Application to Background Correction in Separate Glomerular Filtration Rate Estimation in Man

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An original approach to background subtraction is presented for ^{99m}Tc-DTPA separate glomerular filtration rate (SGFR) estimation in man. The method is based on the properties of the peripheral organ distribution volume (PODV) in mammillary systems. These PODV properties allow easy separation of the components of the renogram, i.e., interstitial fluid, plasma and renal activities. The proposed algorithm takes advantage of the linear time dependence of the kidney distribution volume, during the renal uptake phase, to correct for the plasma residual activity, which always remains after classical background correction. Theoretically, the ratio between kidney uptake and SGFR should be identical for both left and right kidneys, even for very asymmetrical kidney functions. This is best verified when the proposed plasma residual activity correction is applied.

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Technetium-99m-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) separate glomerular filtration rate (SGFR) estimation by external counting, with a scintillation camera, is, since Piepsz's first paper (*1*) in 1977, a widely used nuclear medicine procedure.

Whatever algorithm is used, adequate correction of non-renal activity counted in the renal region of interest (ROI) is a crucial step of data processing. The ideal background ROI should consist of the same plasma and interstitial fluid proportions as the kidney ROI in order to adequately estimate the net renal tracer content but no such perfect background ROI a priori exists.

The present paper is concerned with the kinetic separation of the various components in both renal and non-renal areas of interest in order to achieve a better control of background correction.

Our original method is based on the properties of the peripheral organ distribution volume (PODV) in complex mammillary systems already reported in part I of the present paper (*2*).

RATIONALE FOR BACKGROUND CORRECTION

Technetium-99m-DTPA complex is not significantly bound to plasma proteins and, after its rapid intravenous injection, the externally recorded activity over any ROI in the body is the sum of different components, in variable and a priori unknown proportions from one area to another: plasma, interstitial fluid, and, if it exists, the trapping organ. Moreover, most active organs, for example the kidney, have a much denser vascularity than the surrounding tissues.

The diagram of Figure 1 displays the total-body plasma, interstitial fluids, and kidney compartments. ROI 1 and ROI 2, respectively, represent the kidney and background ROIs and are shown, delineated by dotted lines, to emphasize the compartment overlap.

The measured time-activity curve in the renal ROI, at time t, is a weighted sum of three components:

$$\text{Kmeas}(t) = \text{Knet}(t) + \alpha \cdot \text{P}(t) + \beta \cdot \text{I}(t), \quad (1)$$

where

Kmeas(t)	=	activity in renal ROI (%dose).
Knet(t)	=	net kidney activity (%dose).
P(t)	=	total plasma activity (%dose).
α	=	actual fraction of P(t) in the renal ROI.
I(t)	=	total interstitial fluid activity (%dose).
β	=	actual fraction of I(t) in the renal ROI.

Extra-renal activity curve, from a second ROI (BGROI) adjacent to the kidney is a weighted sum of

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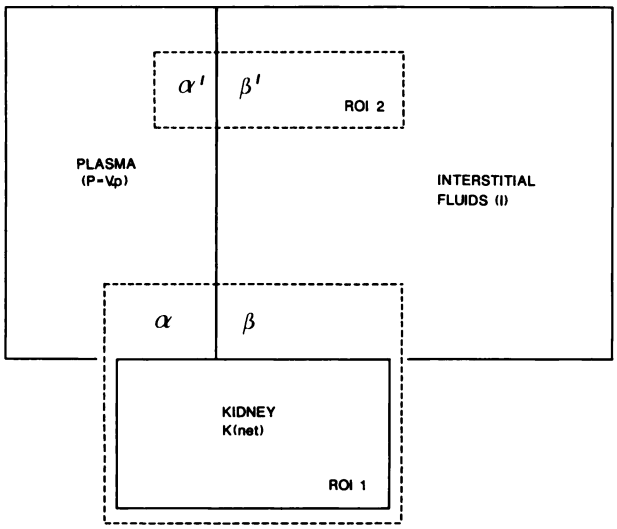

FIGURE 1
Diagram of total plasma, interstitial fluid, and kidney compartments. The dotted lines delineate the renal (ROI 1) and background (ROI 2) ROIs (see text).

two components (after size equalization with the renal ROI):

$$\text{BGmeas}(t) = \alpha' \cdot P(t) + \beta' \cdot I(t), \quad (2)$$

where

BGmeas(t) = activity in BGROI (%dose).
α' = actual fraction of P(t) in the BGROI.
β' = actual fraction of I(t) in the BGROI.

In an ideal BGROI, α' and β' should be equal respectively to α and β of the renal ROI but no ROI can simultaneously fulfill such criteria.

In the present paper, we assume that a BGROI drawn immediately below the kidney ROI will fulfill one of the criteria, that is $\beta' = \beta$, but not the other as it is well known that the vascular network in the kidney is much denser than in the surrounding tissues, that is $\alpha' < \alpha$. The classical background subtraction, with such a BGROI, may thus adequately correct for the interstitial fluid activity but will actually leave a significant amount of uncorrected plasma activity (*3*). However, kinetic properties of the PODV (*2*) are easily used for adequate correction of this plasma residual activity.

The PODV Approach

The Decomposition Algorithm. The interstitial fluid is seen as a peripheral compartment, its activity results from bidirectional exchange process with the plasma central reference compartment. By definition (*2*), and as P(t) is equal to plasma volume, V, times plasma concentration at time t, p(t), its PODV is:

$$\frac{\text{BGmeas}(t)}{p(t)} = \frac{\beta' \cdot I(t)}{p(t)} + \alpha' \cdot V \quad (3)$$

whose initial value, $\alpha' \cdot V = \text{VBGo}$ is determined from the uniexponential fit (*2*).

The BGROI is thus decomposed in its two kinetic components as:

$$\beta' \cdot I(t) = \text{BGmeas}(t) - \text{VBGo} \cdot p(t) \quad (4)$$

$$\alpha' \cdot P(t) = \text{VBGo} \cdot p(t) \quad (5)$$

Subtracting Equation 4 from Equation 1, assuming $\beta' = \beta$, leads to a partially corrected kidney content:

$$K\text{"corr"}(t) = \text{Knet}(t) + \alpha \cdot P(t). \quad (6)$$

Applying PODV transformation to Equation 6, i.e., dividing by p(t), leads to:

$$\frac{K\text{"corr"}(t)}{p(t)} = \frac{\text{Knet}(t)}{p(t)} + \alpha \cdot V. \quad (7)$$

Kidney uptake, before tracer excretion, is a unidirectional process, its PODV linear fit (*2*) initial value VKo estimates the $\alpha \cdot V$ constant.

The three components of Equation 1 are thus given by:

$$\text{Knet}(t) = K\text{"corr"}(t) - \text{VKo} \cdot p(t) \quad (8)$$

$$\alpha \cdot P(t) = \text{VKo} \cdot p(t) \quad (9)$$

and $\beta \cdot I(t)$ given by Equation 4, assuming $\beta = \beta'$.

The Renogram Background Correction

For background correction purpose only, Equation 2 is subtracted from Equation 1 (assuming $\beta' = \beta$), leading to a kidney "corrected" curve analogous to Equation 6:

$$K\text{"corr"}(t) = \text{Knet}(t) + (\alpha - \alpha') \cdot P(t). \quad (6a)$$

Linear fit of its PODV transform estimates the plasma residue $(\alpha - \alpha') \cdot P(t)$, giving Knet(t).

The Initial Value of the PODV Time Function

From the PODV definition, its initial value Vo is easily interpreted as the early distribution volume of the tracer. In compartmental models, the instantaneous mixing of the tracer is assumed before any significant uptake occurs in any peripheral compartment. Therefore, VKo, after the complete decomposition process, is indeed an estimate of the plasma volume seen in the renal ROI, i.e., it is related to the vascular volume of the kidney. If a blood-pool tracer is injected, Knet(t) and $\beta \cdot I(t)$ of Equation 1 and $\beta' \cdot I(t)$ of Equation 2 are nonexistent and the two equations simplify to the plasma components, $\alpha \cdot P(t)$ and $\alpha' \cdot P(t)$ only. The α and α' fractions obtained from a blood-pool agent study should be identical to those calculated by the decomposition process after DTPA injection.

Validation of the PODV Approach

For unidirectional processes, such as the kidney early uptake, the linear system convolution theorem reduces

to a proportionality between uptake and clearance. The proportionality factor is common for both kidneys, in any particular individual, even with very asymmetrical kidney functions:

$$\frac{LK(t)}{LSGFR} = \int_0^t p(\tau)\, d\tau = \frac{RK(t)}{RSGFR}, \qquad (10)$$

where

LK(t) = left kidney uptake at time t.
RK(t) = right kidney uptake at time t.
LSGFR = left kidney SGFR.
RSGFR = right kidney SGFR.

A validation of the PODV approach may thus be based on this identity, which must be best verified with adequate background correction.

MATERIALS AND METHODS

Adult female and male patients, referred to the department of nuclear medicine for total or separate GFR estimation, constitute our patient population; normally functioning kidneys and various pathologies are included such as chronic renal insufficiency, diabetes, lithiasis, pyeloureteral junction stenosis, or suspected renovascular hypertension.

Standard Data Acquisition

Data acquisitions were performed with a large field of view gamma camera (Elscint DYMAX or Siemens LFOV), equipped with a general-purpose low-energy parallel-hole collimator.

Identical syringes, tracer dose, and standard were counted in identical geometric conditions and corrected for counting nonlinearity of the camera.

The well-hydrated patient emptied his bladder before data acquisition and was positioned supine on a thin plexiglas table. The camera detector, placed underneath, simultaneously views parts of the heart chambers and the two kidneys.

The ^{99m}Tc-DTPA (Mallinckrodt-Holland) dose of 2.5 MBq/Kg body weight (BW) is rapidly injected in a large antecubital vein and 15-sec 64 × 64 frames are recorded for 20 min. Between 15 and 20 min after injection (the sampling time is accurately recorded), a blood sample was withdrawn from a large vein of the opposite arm.

After completion of the dynamic acquisition, static left and right lateral views are acquired for depth attenuation correction. Injected dose counts were corrected for postinjection residue by a second syringe counting. Patient's height and weight are measured at the time of investigation in order to estimate the body surface area (BSA) from Dubois's formula.

Data Processing

ROI Selection and Curve Generation. Two composite images were obtained: the first (Fig. 2A), by adding frames near the maximal renal activity, is used to draw the left and right renal and background ROIs, the second (Fig. 2B) by adding early frames near the left ventricular peak activity to visualize the cardiac chambers and draw the epicardial ROI. After drawing ROIs as shown in Figure 2, left and right renal and background activity curves, Kmeas(t) and BGmeas(t), respectively, were generated (Fig. 3A) as well as a cardiac-activity curve.

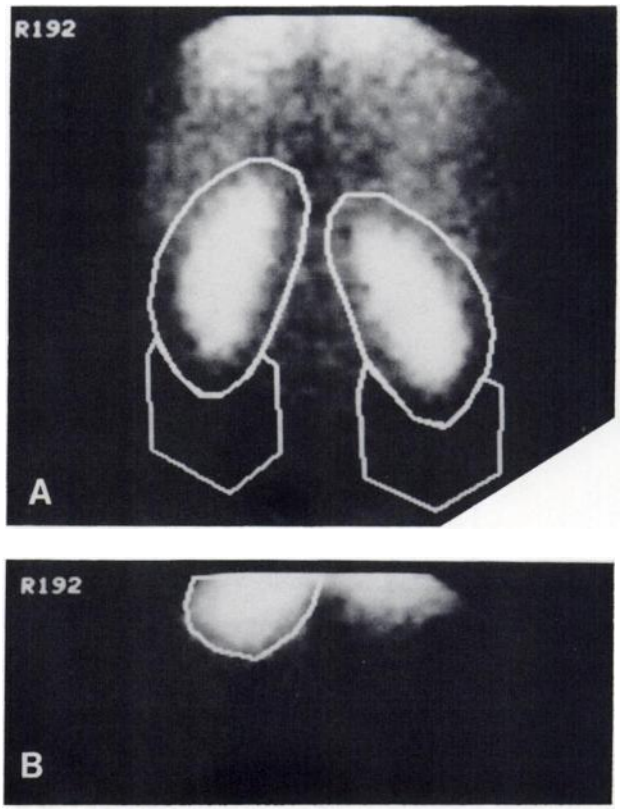

FIGURE 2
Posterior view of the renal region showing the renal and background ROIs (A) and the cardiac ROI (B).

The kidney activity time curves were corrected (Eq. 6a) by subtracting homolateral background activity (after size equalization of the ROIs). Renal curves are corrected for attenuation with an experimentally measured coefficient of 0.115/cm and expressed in percent of the injected dose (Fig. 3B). The left and right, 2–3 min, non-Vo corrected kidney uptakes were derived.

The cardiac activity time curve was calibrated in plasma tracer concentration (Fig. 3B) by setting its value, at blood sampling time, equal to the actual value measured in a plasma volume of 1 ml and expressed in percent of the dose per liter.

Correction for Residual Plasma Activity. Each kidney PODV time curve (Fig. 3C) was fitted linearly in the limited time interval ranging from the beginning of the second minute to the end of the third minute after injection, before any filtered activity is excreted to the bladder. The y-intercept (VRESo) of the PODV fit was subtracted from both experimental and fitted curves.

Clearance and Net Uptake Calculation. The VRESo corrected fitted curve, after PODV inverse transformation, i.e., multiplication by the plasma concentration curve, p(t), leads to a vascular-free activity curve Kfit(t) matching the net kidney activity curve, Knet(t), in the interval of fit. The time derivative of Kfit(t) was divided by the plasma concentration curve and led to a true but "noisy" plateau (Fig. 3D), the average of which is the kidney SGFR. This result was then normalized to a standard BSA of 1.73 m^2.

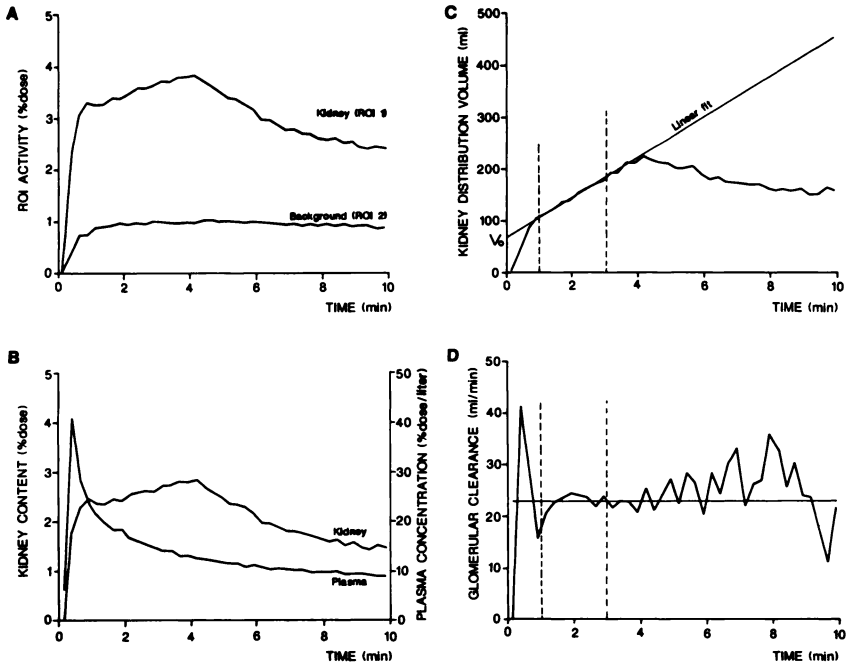

FIGURE 3
Main steps of the procedure used for GFR estimation (see text for detailed explanation). Intervals of fit are shown by dotted lines. In the figure, kidney data are not corrected for depth.

The VRESo-corrected kidney PODV time curve is also PODV inverse transformed and net, 2–3 min, Vo corrected, left and right kidney uptakes were calculated in percent of the injected dose.

The Convolution Integral

The convolution integral was independently estimated, as in Equation 10, from left and right data, in a group of 101 patients, without and with correction of the vascular residue by dividing the 2–3 min renal uptake by the corresponding SGFR. The patient group consisted of 55 females and 46 males, aged 14 to 87 yr, with total GFRs ranging from 14 to 185 ml/min. Asymmetrical renal function was frequently encountered in our population (left to right SGFR ratio varying from 0.19 to 7.2).

The Kidney Vascular Component

VKo and VBGo were estimated in a 20-patient group after ^{99m}Tc-DTPA injection and their ratio VKo/VBGo was calculated. In 10 other patients, receiving ^{99m}Tc-HSA (human serum albumin) for cardiac angiography, the activities were measured at blood-pool equilibrium, in renal (QK), and background (QBG) ROIs, similar to those used for SGFR estimation, and their ratio QK/QBG was calculated.

RESULTS

Decomposition of the Renogram

Figure 4A illustrates, in a case of normal GFR, the decomposition of the kidney activity curve into its three components, i.e., vascular, interstitial, and renal components. Figure 4B demonstrates the result of the procedure in a case of impaired kidney function (30% of normal) and emphasizes the critical need of adequate background correction (66% of total renal ROI activity at the time of maximum kidney uptake).

It has to be noticed that these two cases might give the impression that full background correction, despite its influence on the net renal uptake, has no effect on the shape of the uptake phase of the renogram and consequently on the SGFR results: this fact is actually fortuitous.

The Convolution Integral

Figure 5 illustrates the relationship between the left and right uptake to SGFR ratios (Eq. 10), calculated without VRESo correction of the uptakes: considerable scattering is observed ($Y = 49.9 + 0.49X$; $r = 0.55$).

Figure 6 shows the same relationship after VRESo correction of the uptakes: no significant difference can be seen with the identity line; regression parameters are $Y = 1.1 + 0.98X$, with a correlation coefficient $r = 0.99$.

The Kidney Vascular Component

Table 1 shows, separately for left and right kidneys, a comparison of the ratio between VKo and VBGo estimated in kidney and background ROIs and the ratio between the vascular activity measured in similar ROIs, QK and QBG, after HSA injection. There is no significant difference on either side: on the left, the ratio is 1.49 ± 0.14 for DTPA and 1.46 ± 0.13 for HSA; on the right, the ratio is 1.56 ± 0.17 for DTPA and 1.48 ± 0.13 for HSA.

DISCUSSION

Since Piepsz et al (*1*), proposed in 1977 the first method to estimate ^{99m}Tc-DTPA SGFR in man from data recorded with a gamma camera by external counting, many alternative methods have been proposed (*4–10*). An extensive review of these methods has been recently published by Russel (*11*).

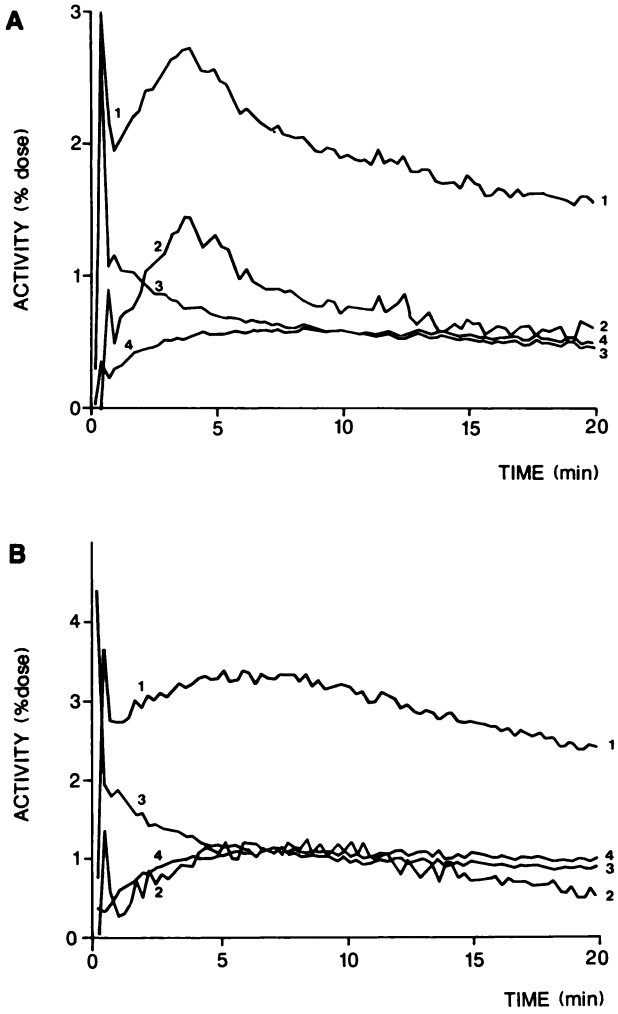

FIGURE 4
Renal ROI activity curve (1) decomposition into its net renal (2), vascular (3) and interstitial (4) components. (A) Normal kidney function. (B) Impaired kidney function.

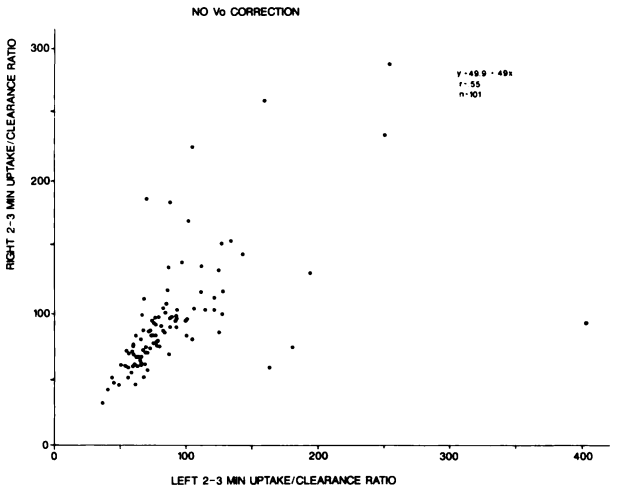

FIGURE 5
Correlation between left (abcissa) and right (ordinate) renal uptake to SGFR ratios without plasma residual correction of the uptakes.

Classification of Background Correction Methods

Choice of the BGROI for extra-renal activity correction, i.e., a BGROI in which the plasma and interstitial fluid components are identical to those of the kidney ROI, currently remains a wide matter of debate.

In fact, published methods are based on various assumptions, all of them being concerned with the fractions α, β, α' and β' of Equations 1 and 2. Most of these methods may be classified into three groups: 1) empirical methods attempting to simultaneously equalize α and β to α' and β'; 2) methods whose main purpose is to equalize the vascular fractions α and α'; and 3) methods which try to equalize β and β' for partial correction in a first step and correction of the vascular residue in a second step.

Empirical Methods Assuming $\alpha = \alpha'$ and $\beta = \beta'$. In their paper (*1*), Piepsz et al. drew a narrow BGROI surrounding each kidney and found reasonable GFR values in the expected range. Peters et al. (*12,13*) showed the perirenal BGROI to be appropriate. In a recent paper, Gruenewald et al. (*14*) used ROIs above and below each kidney without discussing their choice. Other background ROIs have been considered, suprarenal or between the upper or lower kidney poles, these choices have not been explicitly validated (*15*).

There is an evident inter-patient difference in the two component fractions because of the high variability of the spleen or liver overlap with the kidney and background ROIs. Thus, such background ROIs must be

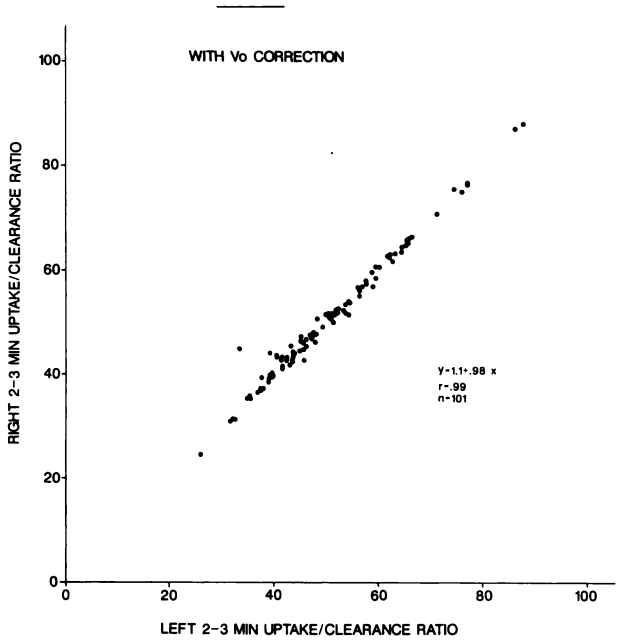

FIGURE 6
Correlation between left (abcissa) and right (ordinate) renal uptake to SGFR ratios after plasma residual correction of the uptakes.

TABLE 1
Initial Distribution Volume and Intravascular Activity

	Left kidney		Right kidney	
	VKo/VBGo DTPA	QK/QBG HSA	VKo/VBGo DTPA	QK/QBG HSA
n	21	10	20	10
mean	1.49	1.46	1.56	1.48
s.d.	0.14	0.13	0.17	0.13

n = number of patients.

empirically adapted to every single patient without real control.

Vascular Methods Assuming $\alpha = \alpha'$ Only. Rehling et al. (*10*) assumed that the heart curve activity was proportional to the background activity of the kidney. Similarly, Delcourt et al. (*6*) assumed that the background-to-kidney ROI ratio after ^{99m}Tc-HSA injection may be used to normalize the background ROI activity after ^{99m}Tc-DTPA injection.

By this assumption, both methods probably approach the vascular component with good accuracy but, due to the denser vascularity of the kidney, they actually overestimate the interstitial fluid component to be subtracted and consequently underestimate the GFR.

Two-Step Methods Assuming $\beta = \beta'$ Only. Gates (*4, 5*), from a comparison of the 2–3-min kidney uptake with creatinine clearance, derived a linear regression formula to estimate GFR. However, the parameters of his regression line actually depend on the area of interest used for background correction. First, he found a better correlation using a semilunar BGROI somewhat lateral at the lower pole of the kidney than with a circumferential ring-shaped ROI. This has recently been confirmed by other authors (*16*). Second, the underestimation of the vascular component with his BGROI is taken into account by the linear regression formula (positive Y intercept).

Gates' regression formula is dependent on the choice of the BGROI and its parameters have to be adapted if another BGROI is used. It is thus surprising that Guinjaume et al. (*8*) and Chachati et al. (*9*) did not actually specify the BGROI they used for validation of their respective methods using Gates' algorithm.

The PODV Approach

The original PODV method, proposed in the present paper may be classified in the third group. It uses a large BGROI located below the kidney—its width is that of the kidney ROI and its surface is as large as possible to obtain a good count rate and thus decrease Poisson's noise.

Indeed, the interstitial spaces seen in the renal ROI, where ^{99m}Tc-DTPA diffuses, mostly consist of the muscular masses of the posterior wall of the abdomen. These are not significantly different behind or below the normally positioned kidneys and such BGROI adequately approximates the interstitial fluid component of the renal ROI activity curve. However, the vascular component is significantly underestimated but is adequately corrected by VRESo subtraction in the PODV approach.

Rutland (*17,18*) previously published a two-step kinetically based background correction. The vascular residual activity is also estimated by a linear regression algorithm but from a completely different theoretical approach. This method is used by Piepsz in a recent paper (*19*).

Validation of the PODV Approach

The convolution integral provides, as in Equation 10, an identity relation between left and right kidney uptake to SGFR ratios. These ratios are actually very sensitive to background correction.

Underestimation of the plasma component of the renal ROI has opposite effects on the uptake and SGFR values: uptake increases and SGFR decreases proportionally to the plasma residue. As background corrections are independently performed on left and right kidney curves, the probability to verify Equation 10 identity is low unless both background corrections are adequate.

This identity is valid even for very asymmetrical kidney functions and might constitute a very strong test for checking any background correction method. The PODV approach presented in this first application fulfills this condition.

The proposed method for background correction is easily usable in everyday practice and gives highly confident results even in case of very low GFR values. Moreover, complete kinetic separation of the three components of the renal ROI activity curve becomes simple through PODV properties.

The next part of this work is in preparation and will illustrate the predictive value of our PODV model with ^{99m}Tc-DTPA. When extrapolated to 20 min, the 2–3-min renal PODV linear fit not only allows accurate estimaton of the 20-min bladder activity but also gives its true time behavior over the whole study. This last property confirms our original PODV model as an adequate tool for quantitative tracer analysis in clinical nuclear medicine.

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