The Technetium-99m-DTPA Renal Uptake-Plasma Volume Product: A Quantitative Estimation of Glomerular Filtration Rate

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An image-based method for estimating quantitative renal glomerular filtration rates (GFR) by calculating the product of the renal uptake rate and plasma volume is presented. By using the relationship GFR = F·PV/t, F represents renal ^{99m}Tc-DTPA uptake after bolus injection, PV is the plasma volume and t is time. This GFR evaluation was carried out on 96 patients and compared to GFR values determined in the same patients using radiotracer blood clearance techniques relying on two venous blood samples. When estimating patient plasma volumes using patient's weight and measured hematocrit values, the image-based method for calculating GFR accurately approximates the values obtained from blood samples (linear regression slope = 1.03; y-intercept = −2.81 ml/min). The two techniques correlate with a value of r = 0.89.

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The interest in radioisotopic quantitation of renal function has led in recent years to the use of gamma camera images for the estimation of the glomerular filtration rate (GFR) (*1–7*). Generally, these methods require an accurate estimation of the renal uptake of ^{99m}Tc-diethylenetriamine pentaacetic acid (DTPA) during the early part of the renogram. Different approaches are then applied, requiring, in various combinations, the calibration of cardiac time-activity curves with a blood sample (*2,3*), the processing of cardiac and renal time-activity curves (*6*) or the use of regression equations (*4*). The latter assumes a simple linear relationship between renal uptake and GFR. Following the determination of the renal uptake, the patient's GFR can be calculated using a regression equation generated from a reference data base correlating the two quantities. The uptake value (typically expressed as fraction of injected dose) is then transformed into a physiologic parameter (GFR) with the units of ml/min.

Based on established quantitative renal clearance models (*5,6*), we calculated GFR from the product of the renal uptake and an estimate of the volume in which the injected dose is distributed. We investigated this concept by comparing the clearance of ^{99m}Tc-DTPA obtained from two blood samples to the clearance derived from our ^{99m}Tc-DTPA renal uptake-plasma volume product (RUPV), assuming that the volume of distribution at the time of measurement is the plasma volume.

MATERIALS AND METHODS

The population studied was comprised of 96 patients referred to nuclear medicine for evaluation of renovascular disease. There were an equal number of male and female patients, ranging from 29 to 84 yr of age (mean and standard deviation, 60 ± 13 yr).

The study was performed with the intravenous administration of approximately 520 MBq of ^{99m}Tc-DTPA (Squibb Inc., Princeton, NJ). Chromatography was done (using Whatman 31ET paper with acetone solvent and ITLC SG-media with water solvent) in order to assure complete binding. The patients were imaged in the supine position with a gamma camera positioned underneath the imaging table. Dynamic data was collected in a 64 by 64 matrix, on a PCS-512/Gamma-11 computer (Picker International, Highland Heights, OH) at a rate of one frame every 3 sec for 120 sec, followed by 1 frame every minute for 30 min.

For quantitative analysis, camera sensitivity was determined before each study by imaging a source of approximately 40 MBq placed at 30 cm from the collimator face. Point source geometry and camera settings were the same as those used for the patient acquisitions.

Calculation of GFR

For an ideal glomerular filtration tracer, the quantity of tracer filtered is:

$$Q(t) = GFR \cdot c(t)dt, \qquad \text{Eq. 1}$$

where Q(t) is the total activity, expressed in MBq, filtered by the kidneys. The GFR is expressed in milliliters of plasma/minute, c(t) is the concentration of the radiotracer in the plasma in MBq/ml and t is time in minutes. By assuming that the GFR remains constant and by integrating the above equation, we can write:

$$\int Q(t)dt = GFR \cdot \int c(t)dt. \qquad \text{Eq. 2}$$

By assuming that the concentration of activity in plasma (c(t)) remains constant in the early part of the study, the equation can

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be simplified to:

$$Q = GFR \cdot C \cdot t, \quad \text{Eq. 3}$$

where C is the constant plasma concentration and t is the time over which the observation is carried out.

If we assume that for the early part of the study all the administered tracer is confined to the vascular compartment (i.e., the tracer is diluted in a volume equal to the plasma volume), then the plasma concentration (C) is given by the total injected dose (D) divided by the plasma volume (PV):

$$C = D/PV. \quad \text{Eq. 4}$$

If the measurements are limited to the pure parenchymatous phase of the renogram, (i.e., no tracer yet excreted into the urine), the following equation is valid:

$$GFR = Q/D \cdot PV/t, \quad \text{Eq. 5}$$

where Q/D represents the fractional renal uptake, which we label F, and write

$$GFR = F \cdot PV/t. \quad \text{Eq. 6}$$

F is obtained from the image corresponding to the first 3 min of the renogram by positioning an elliptical region of interest (ROI) over each kidney. A larger ROI is positioned around each renal ROI and the background is determined by calculating the average counts per pixel found in this annular region (Fig. 1). The fractional renal uptake (F) is determined from the following relationship:

$$F = (K_b/e^{-\mu x})/D, \quad \text{Eq. 7}$$

where K_b is the background corrected counts in the kidney. The injected dose (D) is expressed as total injected counts using the camera sensitivity to convert the units. The estimated kidney depth (x) is calculated according to Tønnesen (*8*), where the attenuation coefficient (μ) for ^{99m}Tc is taken to be 0.153 cm^{-1}.

Total blood volumes are estimated by the following relationships (*9,10*):

$$BV1 = 95.7\ W - 274 \quad \text{Eq. 8}$$

$$BV2 = 0.366\ H^3 + 0.0322\ W + 0.604, \quad \text{Eq. 9}$$

where BV1 and BV2 are two independent estimates of the total blood volume in milliliters, W is body weight in kilograms and H is the patient height in meters. Plasma volume (PV) can be obtained by multiplying the total blood volume by (1- hematocrit).

A third method directly estimates plasma volume:

$$PV3 = 84.5\ W^{0.80635}. \quad \text{Eq. 10}$$

The exponential 0.80635 is the average of the results from Cropp (*11*) as used by Shore et al. (*12*).

The GFR was also determined for each patient using a two-blood sample clearance technique developed by Russell (*13*). Two blood samples were obtained from each patient at 45 and 180 minutes post injection by drawing 10 cc (for each sample) into heparinized sealed vials from the arm contralateral to the injection. The samples were centrifuged for 15 min at 2000g and duplicate 1-cc samples were counted in a well counter (Thyro-Count, Kemble Instruments Inc., Hamden, CT). The total injected dose was obtained by converting the total injected activity in MBq to counts using the sensitivity of the well counter. The plasma activity at time zero is obtained by extrapolation, and the rate of disappearance is computed from the logarithmic slope.

RESULTS

A plot of the GFR calculated from two blood samples versus the renal uptake of ^{99m}Tc-DTPA (F) measured by

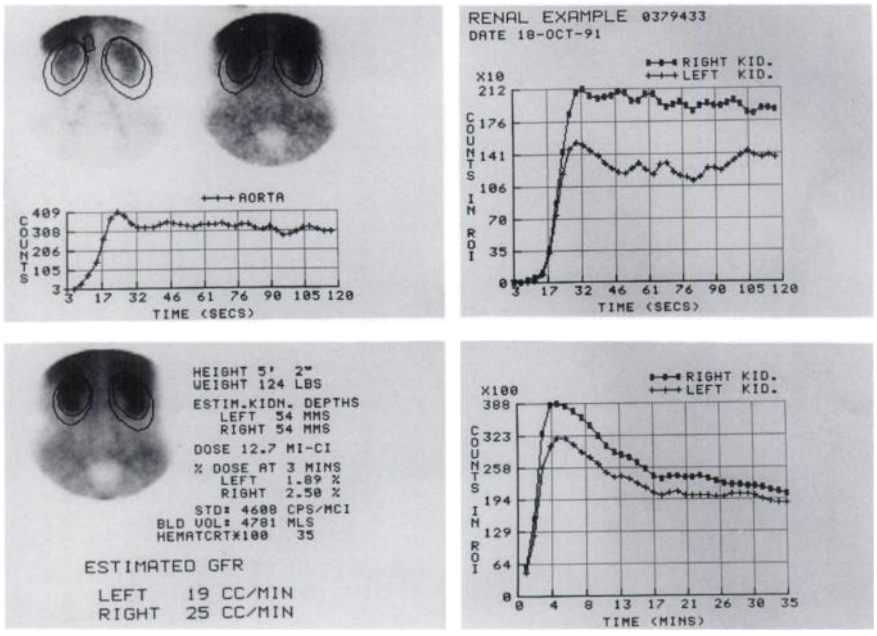

FIGURE 1. Computer display for quantitative renogram and RUPV calculation. The upper portion displays the ROIs and time-activity curves for the first 2 min of the study acquired at a rate of 1 frame every 3 sec. The lower portion shows the analysis of the final 35 min of the dynamic scan (acquired at 1 frame every minute). The lower left quadrant shows patient information, including dose administered, renal uptake, estimated blood volume, as well as calculated GFR.

scintigraphy is shown in Figure 2. The correlation coefficient of R = 0.82 indicates that fitting a linear relationship between uptake and GFR could give an acceptable method of predicting GFR from renal uptake.

Figures 3 through 5 show the GFR calculated with the RUPV product for three plasma volumes estimations (RUPV1, RUPV2, RUPV3) plotted against the reference GFR obtained with the two-blood samples technique. Plasma volume estimates PV1 and PV2 were obtained by using Equations 8 and 9 respectively and correcting for hematocrit. Plasma volume PV3 was calculated directly using Equation 10. RUPV1 (Fig. 3) provides the best prediction of the plasma clearance of ^{99m}Tc-DTPA, since the regression slope is very near to 1.0 (y = 1.034 [SE 0.054]x − 2.812). The lower and upper 95% confidence values for the slope are 0.927 and 1.142 respectively and s.e. = 0.054 is the standard error of the slope. The RMS residual for RUPV1 is 16.1 ml/min with a correlation coefficient of r = 0.89.

Figure 4 shows the comparison of RUPV2 to the plasma clearance of ^{99m}Tc-DTPA (y = 0.712 [s.e. 0.04]x + 2.851). The lower and upper 95% confidence values for the slope are 0.633 and 0.791, respectively. The RMS residual for RUPV2 is 11.8 ml/min with a correlation coefficient of r = 0.88.

RUPV3 (Fig. 5) gives the best correlated results (r = 0.90); however, the regression slope, similar to RUPV2, is less than unity (y = 0.744 [s.e. 0.038]x − 2.364). The lower and upper 95% confidence vales for the slope are 0.669 and 0.819 respectively and the RMS residual is equal to 11.2 ml/min. The PV3 plasma volume calculation has the added advantage of not requiring a hematocrit determination. Both RUPV2 and RUPV3 underestimate the expected GFR value.

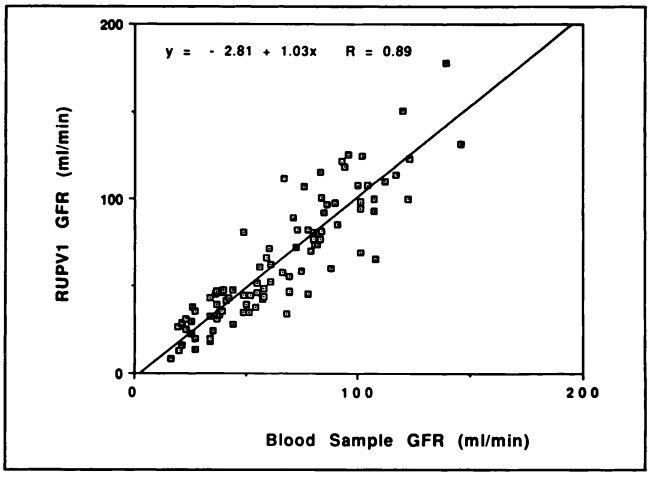

FIGURE 3. GFR estimated using the RUPV1 method plotted against GFR calculated from plasma clearance of ^{99m}Tc-DTPA. The RUPV1 calculation represents the fractional uptake multiplied by an estimate for the plasma volume. The plasma volume is obtained from PV1 = (95.7 W − 274)·(1 − hematocrit).

DISCUSSION

We have shown that the product of the renal uptake of ^{99m}Tc-DTPA, calculated from scintigraphic images, and plasma volume, estimated from patient height and weight and hematocrit, (RUPV), has a good correlation with an independent measurement of the plasma clearance of ^{99m}Tc-DTPA. The renal uptake is the fraction of injected tracer taken up by the kidneys from the circulating plasma over a given time period. The product of fractional uptake and plasma concentration of ^{99m}Tc-DTPA represents the milliliters of plasma cleared by the kidneys during that time.

The volume of distribution of an intravenously injected bolus enlarges until complete uniform mixing with the

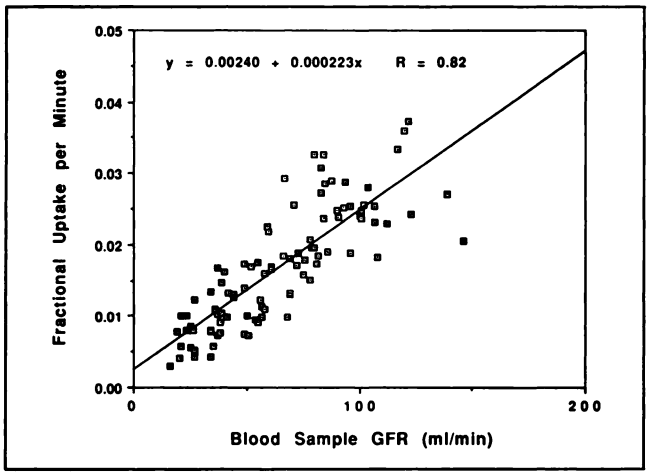

FIGURE 2. The fractional uptake of radiopharmaceutical in the kidney during the first 3 min (F) is shown plotted versus the GFR calculated from two blood samples. Fractional uptake was determined by applying background subtraction and patient attenuation.

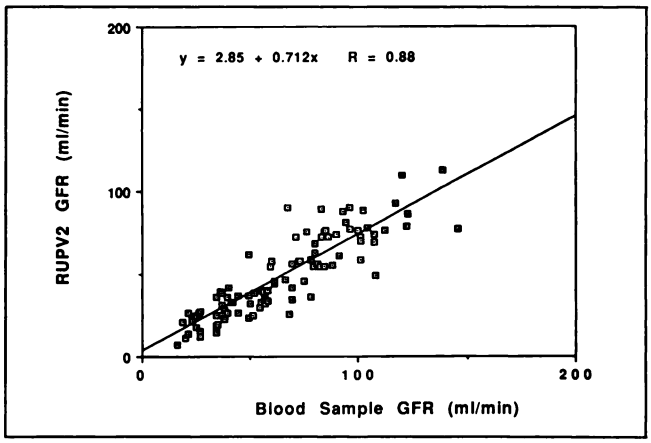

FIGURE 4. GFR estimated using the RUPV2 method plotted against GFR calculated from plasma clearance of ^{99m}Tc-DTPA. The RUPV2 calculation represents the fractional uptake multiplied by an estimate for the plasma volume. The plasma volume is obtained from PV2 = (0.366 H^3 + 0.0322 W + 0.604)·(1 − hematocrit).

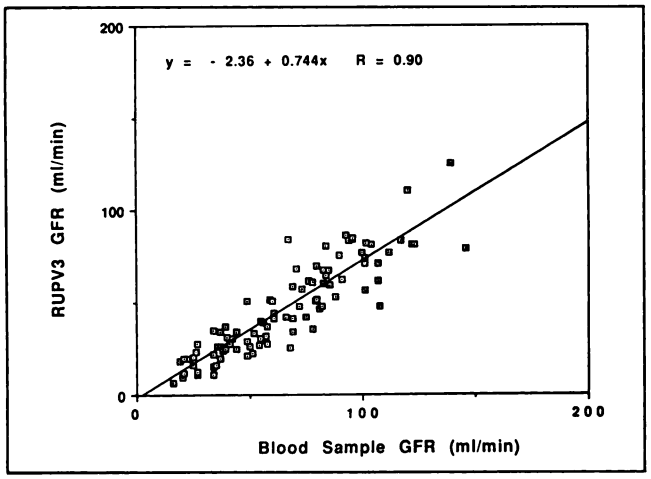

FIGURE 5. GFR estimated using the RUPV3 method plotted against GFR calculated from plasma clearance of ^{99m}Tc-DTPA. The RUPV3 calculation represents the fractional uptake multiplied by an estimate of the plasma volume. The plasma volume is obtained from $PV3 = 84.5\ W^{0.80635}$.

final volume of distribution is achieved. If there were no loss of tracer during equilibration, the plasma concentration of the tracer should be constant. After mixing is completed, the tracer concentration declines at a rate that equals the rate of elimination from the vascular compartment. It is important to note that the renal uptake of DTPA is calculated when the tracer is not evenly distributed within the intra- and extravascular spaces while the plasma concentration is continuously changing.

While the volume of distribution of DTPA at equilibrium is larger than the plasma volume, the volume of distribution in the first 3 min is necessarily much smaller, possibly within the range of the intravascular plasma space. Similar assumptions were used by Peters et al. (*14*) in their analysis of background corrections for the estimation of renal uptake. Therefore, the 3-min renal uptake is the renal cumulative activity drawn from plasma tracer concentrations which are higher than those found after equilibration. If this hypothesis is correct, a measure of GFR can be obtained by using renal uptake and plasma volume as the volume of distribution of the tracer. Our results seem to confirm the validity of this assumption.

It can be argued that the loss of tracer to extravascular spaces invalidates the basic assumption that equates plasma volume to the early volume of distribution, since it effectively makes the volume of distribution larger than the plasma volume. The magnitude of this third compartment in the first 3 min has not been estimated but is probably very small for most patients. Nevertheless, the use of the body weight to estimate plasma volume accounts for third space losses of the tracer by overestimating the true plasma volume. In effect, the predicted volume in those cases may not be an exact estimation of plasma volume but rather a volume that includes some of the extravascular space. This estimated plasma volume is, however, closer to the volume in which the tracer is actually diluted.

The rationale for renal uptake being representative of glomerular filtration is based on the assumption that after injecting a GFR tracer, all the activity observed within the kidneys during the parenchymal phase (earlier than 3 min postinjection) has been filtered. The tracer, however, is present in the afferent arterioles and glomeruli (tracer to be filtered) as well as in postglomerular structures within the efferent arterioles and veins (tracer that was not filtered). Furthermore, the renal image also includes radioactive blood perfusing nonfunctional renal and extrarenal tissue (*14*). Overestimation of GFR can result when the post-glomerular and other renal activities are unaccounted for during background correction. This error may be more significant in abnormal kidneys where the extraction efficiency of the tracer declines.

In this study, we used the blood sample method as the reference measurement for GFR. While the method is acceptable for clinical use, it is not without errors. Of particular interest for this evaluation is the overestimation of GFR when there is a significant extravascular space. These conditions will affect the plasma sample techniques to a greater extent than the scintigraphic methods. With the RUPV method, data collection over the kidneys is limited to the initial 3 min. We assume that this is hardly enough time to lose enough tracer to a third space to alter the plasma concentration of the tracer. In contrast, the blood sample methods rely on concentration measurements (taken at 45 and 180 min) when the tracer has had more time to diffuse into this third compartment. When the extrarenal losses are significant, an overestimation of GFR can result. It is expected that some discrepancy between the blood sample technique and the RUPV method can be traced to those factors and that the RUPV method may have an advantage over blood sample techniques in evaluating patients with edema or anasarca.

The approach proposed by Gates (*4*) requires the use of regression data that converts renal uptake into GFR. Ideally, a reference data base comparing renal uptake with an independent GFR determination, which is generated at the same institution, should be used with this method. This is unlikely to happen in nonacademic centers or even in academic centers that do not emphasize this line of research. Recent publications have shown significant differences between camera-based GFR calculation and blood sample techniques, supporting the need for exercising caution when using these methods (*15,16*). Therefore, while the linear relationship between renal uptake and glomerular filtration has been demonstrated, the appropriateness of using methods based on foreign regression data should be treated with care.

In conclusion, we have shown that the ^{99m}Tc-DTPA RUPV method gives a close estimation of the plasma clearance of ^{99m}Tc-DTPA without the need of taking blood samples. The plasma volume necessary for the calculation

can be derived from the patient's weight, height and hematocrit, or simply from an equation that derives plasma volume directly. The best method is based on the calculation of total blood volume from body weight and correcting for the hematocrit. Further improvement in background correction of the renal images should result in even more accurate GFR estimations. The RUPV method is simple and can be performed at any nuclear medicine facility equipped with a gamma camera and a computer.

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