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# Radioisotopic Measurement of Glomerular Filtration Rate in Severe Chronic Renal Failure

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In order to determine the best method for routine measurement of glomerular filtration rate (GFR) in severe renal failure, we compared simultaneously the urinary clearances of [ $^{99m}\text{Tc}$ ] diethylenetriaminepentaacetic acid (DTPA) (UD), [ $^{125}\text{I}$ ]iothalamate (UI), 24-hr creatinine clearance (UC) and plasma clearance of [ $^{99m}\text{Tc}$ ]DTPA (PD), based on three plasma samples. In 60 studies in 22 patients with serum creatinine values of 2 to 8 mg/dl, UD and UI were almost identical:  $\text{UD} = 0.358 + 0.976 \text{ UI} \pm 0.87 \text{ ml/min}$ ,  $r = 0.990$ . However, PD overestimated UD by a large and variable extent:  $\text{PD} = 11.3 + 0.843 \text{ UD} \pm 5.5 \text{ ml/min}$ ,  $r = 0.694$ , and was inconsistent in sequential measurements in individual patients. UC also overestimated urinary isotope clearance:  $\text{UC} = 4.2 + 0.95 \text{ UI} \pm 3.9 \text{ ml/min}$ ,  $r = 0.865$ . Sequential measurements of GFR in five patients with severe but stable renal failure (mean GFR 5.9 ml/min) showed an average standard deviation of only 0.83 ml/min. Thus both UD and UI appear to be reliable and precise measures of GFR in severe renal failure.

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Measurement of glomerular filtration rate (GFR) in patients with chronic renal failure has assumed increasing importance in recent years as attention has been directed towards assessing the rate of progression of renal insufficiency and attempting to slow it. A practical technique for estimating GFR sequentially in such patients is needed.

Inulin clearance requires constant infusion and the analytical methods are tedious. Endogenous creatinine clearance overestimates GFR to an increasing degree as renal failure becomes more severe (1). The average of 24-hr clearances of urea and creatinine has been reported to be close in inulin clearance but the variability in tubular secretion of creatinine and in tubular reabsorption of urea make it unlikely that these two processes could always be equal and opposite in magnitude (1).

Radiopharmaceuticals, including chromium-51 ( $^{51}\text{Cr}$ )EDTA, iodine-125 ( $^{125}\text{I}$ )iothalamate and technetium-99m diethylenetriaminepentaacetic acid ([ $^{99m}\text{Tc}$ ]DTPA) have been widely used to measure GFR, either on the basis of plasma clearance or urinary clearance. For urinary clearance to measure GFR, tubular secre-

tion, tubular reabsorption and plasma protein-binding must be negligible and urine flow must be sufficient to avoid collection errors. Urine flows adequate for the measurement of urinary clearance are often difficult to obtain in patients with severe renal failure. Plasma clearance measures GFR only if extrarenal clearance is negligible. While an extrarenal clearance of 5 ml/min, for example, is a tolerable error in a subject with a GFR of 120 ml per min, it is a significant error in a subject with severe renal failure, particularly for serial measurements. Few measurements of extrarenal clearances of these isotopes in patients with severe or moderately severe renal failure have been reported.

As discussed below, published reports are conflicting as to whether plasma clearance or urinary clearance is superior in patients with renal failure, and as to whether plasma clearance overestimates renal clearance of radio-nuclides. The most reliable plasma clearance determinations require multiple blood samples (1) and are therefore not well suited to routine use, especially if several patients are studied on the same day.

In the present study, clearances of both [ $^{99m}\text{Tc}$ ]DTPA and [ $^{125}\text{I}$ ]iothalamate have been measured in patients with chronic renal failure. Iodine-125 iothalamate was given by subcutaneous injection (2) with an aim to measuring urinary clearance, but not plasma clearance. Technetium-99m DTPA was given intravenously by

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single injection so as to measure plasma clearance and urinary clearance. We used only three blood samples to estimate plasma clearance because we felt that a technique requiring more samples would not be acceptable for routine use.

## Materials and Methods

### Patients

Twenty-two patients with renal insufficiency, 15 male and seven female, with serum creatinine values of 2.0 to 8.0 mg/dl were selected. Sixty studies were performed over a 10-mo interval in these subjects. Forty 24-hour creatinine clearances were determined on the day before the isotope study.

### Protocol

On the morning of the day of the study, after an overnight fast, the subjects took five drops of a saturated solution of potassium iodide. An oral water load of 10 to 15 ml/kg was ingested to initiate diuresis. Throughout urine collection periods, urine output was measured and an equal volume of water was ingested.

An i.v. injection of 100  $\mu$ Ci of [ $^{99m}$ Tc]DTPA was administered and a subcutaneous injection of 35  $\mu$ Ci of [ $^{125}$ I]iothalamate. After at least 60 min of equilibrium a timed spontaneous void was obtained and discarded. Three spontaneous timed urinary collections of 30–45 min duration were then obtained. Timed venous blood samples were drawn immediately following each voiding. Periods in which urine flows were less than 0.8 ml/min were excluded from the study. Only five periods were excluded on this basis.

Urinary clearances of [ $^{125}$ I]iothalamate and [ $^{99m}$ Tc]DTPA were calculated for each collection period as urine activity times urine flow divided by average plasma activity. Average plasma activity was calculated by summing the two values of plasma radioactivity as measured immediately before and after each urinary collection period and dividing by two. These values were then averaged for the three collection periods.

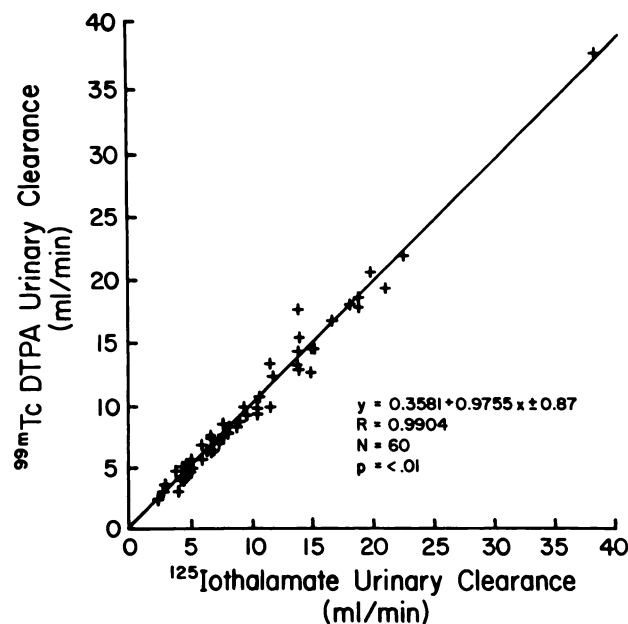
Plasma clearance of [ $^{99m}$ Tc]DTPA was measured from four timed samples for 180 to 200 min as the product of the volume of distribution at time zero and the regression slope of the monoexponential plot (3,4).

Technetium-99m DTPA was used immediately after preparation. Radiochemical purity was evaluated within 15 min of injection by thin layer chromatography using acetone as a solvent. Mean % bound was 99.1% (range 97.8–99.7%).

## RESULTS

When [ $^{125}$ I]iothalamate urinary clearance is compared to [ $^{99m}$ Tc]DTPA urinary clearance (Fig. 1) a slope of 0.9755, an intercept of 0.36 ml/min and an *r* value of 0.990 is obtained. Plasma clearance of [ $^{99m}$ Tc]DTPA exceeded the urinary clearance of [ $^{99m}$ Tc]DTPA by a large and variable amount. Extrarenal clearance, calculated as the difference between plasma clearance and urinary clearance varied from 2 to 30 ml/min, and was also inconsistent on repeat studies in individual patients (Fig. 2).

In five patients with severe but stable renal failure

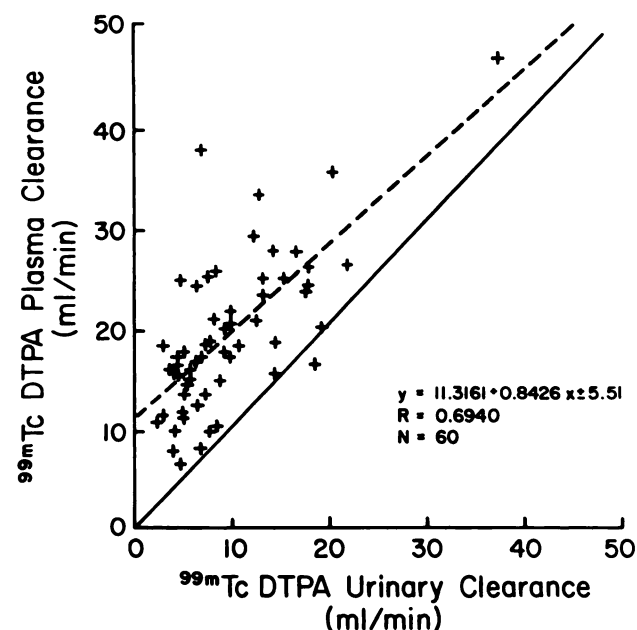


**FIGURE 1**

Comparison of the urinary clearances of [ $^{125}$ I]iothalamate and [ $^{99m}$ Tc]DTPA in 60 studies in 22 patients with chronic renal failure.

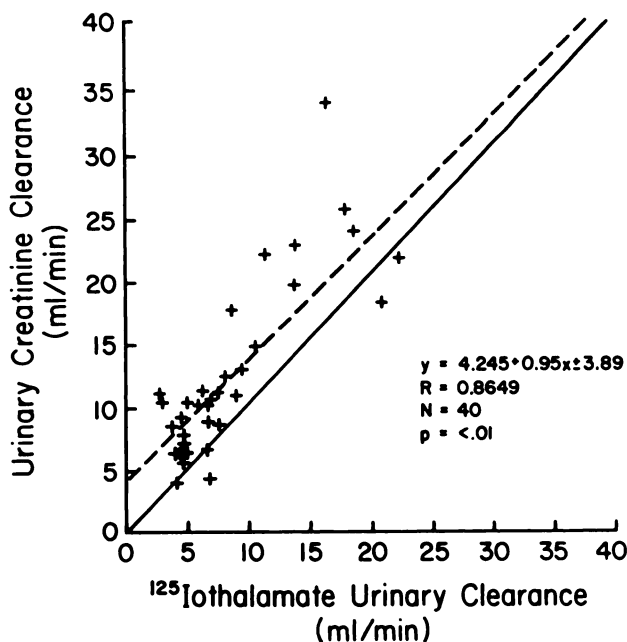
(mean GFR 5.9 ml/min), five to seven sequential measurements of the mean urinary clearances of the two isotopes showed an average standard deviation of 0.83 ml/min. Thus, in severe renal failure, this technique can determine GFR within 2 ml/min.

Creatine clearance also exceeded urinary isotope clearance (Fig. 3) in most studies, by up to 18 ml/min.



**FIGURE 2**

Comparison of [ $^{99m}$ Tc]DTPA plasma clearance and [ $^{99m}$ Tc]DTPA urinary clearance. The regression line (dotted) and line of identity (solid) are shown.



**FIGURE 3**  
Comparison of 24-hr creatinine clearance and  $^{125}\text{I}$ -iothalamate urinary clearance. The regression line (dotted) and the line of identity (solid) are shown.

## DISCUSSION

Several authors have measured GFR in patients with chronic renal failure by radioisotopic methods and a brief discussion of their findings will allow our above results to be placed in the proper context. Skov (5) found near equality of urinary  $^{125}\text{I}$ -iothalamate and inulin clearance in patients with severe and very severe renal failure, using collection periods of up to 170 min. For this reason we chose not to repeat Skov's validation work with inulin.

Bianchi et al. (6) showed that GFR measured by urinary clearances of  $^{99\text{m}}\text{Tc}$ ]DTPA was 8% lower than urinary clearance of  $^{131}\text{I}$ ]diatrizoate, but only six of 21 patients had GFRs below 60 ml/min. They obtained urine by vesical catheterization. Hagstam (7) et al. reported that urinary clearance of  $^{51}\text{Cr}$ ]EDTA slightly underestimated inulin clearance. Only five of the 60 patients had GFRs below 40 ml/min. Our study focused on more severe renal failure and used timed voiding samples following hydration and exact fluid replacement of a volume of water equal to their voided sample volume.

Rehling et al. (8) reported that plasma clearance of  $^{99\text{m}}\text{Tc}$ ]DTPA after i.v. injection was similar to renal clearance of inulin in subjects with GFRs of 25–80 ml/min. Plasma clearance was calculated from the area under the plasma concentration curve, using 13 plasma samples between 5 and 300 min after injection. Later, Rehling et al. (9) reported that GFR could be measured

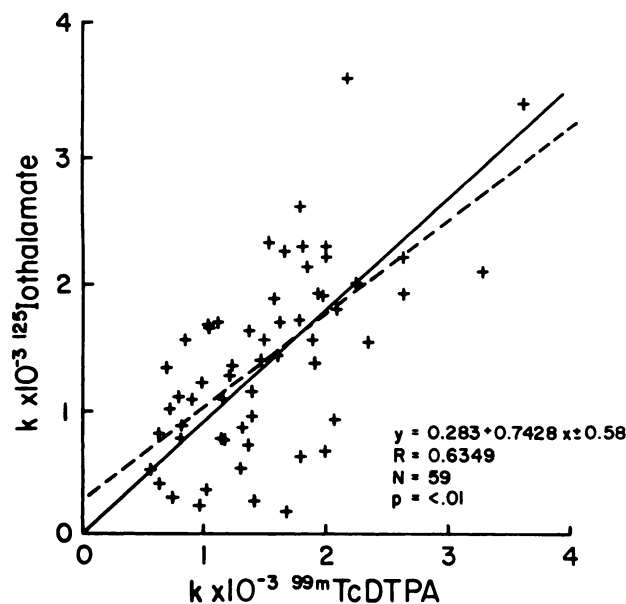
by gamma-camera renography of both kidneys after injecting  $^{99\text{m}}\text{Tc}$ ]DTPA, without determining the injected dose or collecting urine or blood samples, in subjects with GFRs from 4 to 172 ml/min. However, the coefficient of variation was 8.3 ml/min (at a GFR of 50 ml/min), a value so large as to preclude the use of this technique for following patients with severe or moderately severe renal failure.

Manz et al. (10) measured GFR in children with severe renal failure and observed that  $^{51}\text{Cr}$ ]EDTA plasma clearance (by a two-compartment model) overestimated inulin clearance by 36% and was not significantly correlated with inulin clearance. Carlsen et al. (11) reported that plasma clearances of  $^{99\text{m}}\text{Tc}$ ]DTPA and  $^{51}\text{Cr}$ ]EDTA were similar and concluded that  $^{99\text{m}}\text{Tc}$ ]DTPA can be used to measure GFR. However, they did not collect urine and therefore both methods may have overestimated GFR owing to extrarenal clearance. We agree that plasma EDTA or DTPA overestimates GFR and, in part, was why we performed this investigation.

Ott and Wilson (2) reported that urinary clearance of subcutaneously injected  $^{125}\text{I}$ -iothalamate was equal to inulin clearance, with a standard deviation around the regression of 6.4 ml/min, in subjects with GFRs of 10–140 ml per min. They also report that plasma  $^{125}\text{I}$ -iothalamate concentration, in patients with GFRs <33 ml/min, did not decrease between 30 and 180 min after subcutaneous injection. However, their data show a high degree of variability in plasma levels further supporting the need for a more rigorous and less variable GFR determination by urinary clearance especially at lower GFRs.

The close correlation of urinary clearance of DTPA and iothalamate in our study, in light of the studies cited above, indicates that either method is acceptable in the setting of moderate to severe renal failure. To our surprise, the exponential decline of plasma  $^{125}\text{I}$ -iothalamate levels was very similar (on the average) to the decline of intravenously injected  $^{99\text{m}}\text{Tc}$ ]DTPA levels. Therefore the slopes of these two isotopes were compared (Fig. 4). Plasma clearances could not be directly compared because we did not measure accurately the dose of injected  $^{125}\text{I}$ -iothalamate. However, the comparison of slopes gives a reasonable estimate of the relationship between the plasma clearances of these two radionuclides. The extrarenal clearances were correlated, but are not identical.

Combining the information from Figures 2 and 4 we can conclude that the plasma clearances of both radiopharmaceuticals, determined from three plasma samples, overestimate GFR, indicating a substantial and variable extrarenal clearance. In contrast to other reports (2, 12) we found that iothalamate plasma concentration fell monoexponentially after subcutaneous administration without epinephrine. We also observed



**FIGURE 4**  
Slopes of [ $^{125}\text{I}$ ]iothalamate plasma disappearance versus [ $^{99\text{m}}\text{Tc}$ ]DTPA plasma disappearance. The regression line (dotted) and line of identity (solid) are shown.

that 24-hr creatinine clearance overestimates GFR and confirm that it is a poor measure of renal function in patients with severe renal failure. Thus, the urinary clearances of [ $^{99\text{m}}\text{Tc}$ ]DTPA and [ $^{125}\text{I}$ ]iothalamate have a strong correlation and are reliable and precise measurements of GFR in severe renal failure.

#### ACKNOWLEDGMENTS

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