

Determination of Glomerular Filtration Rate Using Technetium-99m-DTPA with Differing Degrees of Renal Function

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Glomerular filtration rate (GFR) is an important index of renal function. Twenty-four-hour creatinine clearance overestimates GFR in patients with poor renal function. Inulin and iothalamate clearances are accepted reference standards for determining GFR but are expensive and laborious. We have previously reported that GFRs obtained by measuring the disappearance of ^{99m}Tc -DTPA from ultrafiltered (protein-free) samples of plasma were virtually identical to those obtained by the iothalamate method. However, the subjects used in that study had normal to only moderately decreased renal function.

Methods: The accuracy of measuring GFR by plasma clearance of ^{99m}Tc -DTPA was determined in subjects where renal function varied from normal to severely impaired. In all subjects, GFR was established by clearance of ^{125}I -iothalamate from urine and serum and was used as the standard of reference.

Results: For subjects with normal to moderately diminished renal function (GFR > 20 ml/min), the correlation between values of GFR obtained by the DTPA and iothalamate methods was high ($n = 18$, $r = 0.966$). The difference between the pairs of GFR values obtained by the two methods was not statistically significant ($p > 0.1$). In patients with severe renal insufficiency (GFR < 20 ml/min), the correlation between the DTPA and iothalamate methods was poor ($n = 11$, $r = 0.236$), and the GFR values obtained by the two methods were statistically different ($p < 0.01$).

Conclusion: These results suggest that GFR can be determined accurately by plasma clearance of ^{99m}Tc -DTPA in all patients except those with severe renal insufficiency.

Key Words: glomerular filtration rate; technetium-99m-DTPA; iodine-125-iothalamate; renal function; renography

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Glomerular filtration rate (GFR), the volume of plasma ultrafiltered per minute by renal glomeruli, is an important index of

renal function. Twenty-four-hour creatinine clearance, one of the most commonly used methods for inferring GFR, can overestimate GFR in patients with impaired renal function, because the small amount of creatinine secreted by the tubules becomes proportionately more significant as glomerular function drops (1,2). Methods of standard reference for determining GFR include clearance of both inulin and ^{125}I -iothalamate. Both of these methods are expensive, time consuming and technically demanding (3-7). Several simpler methods for deriving GFR from radioisotopic renography have been developed. However, some controversy exists with respect to the consistency and accuracy of GFRs obtained by these methods in humans.

Technetium-99m-diethylene-triaminepentaacetic acid (^{99m}Tc -DTPA) is excreted by glomerular filtration and is commonly used for nuclear medicine renography (8-10). Methods for calculating GFR from clearance of DTPA, which involve the collection of blood and urine samples, have been described (11-13). The GFR can also be inferred by monitoring disappearance of ^{99m}Tc -DTPA from the blood by a radiation detector placed over the precordium (14). A gamma camera-based method for estimating GFR involves the computer analysis of scintigraphic images of the kidneys after a single intravenous injection of ^{99m}Tc -DTPA (15,16).

The methods for determining GFR from nuclear medicine renography have limitations. The accuracy of the camera-based method may be compromised by variability in cameras, technical factors, patient attenuation, renal geometry and extracellular localization of the radionuclide. Methods that measure clearance of radioactivity from the blood are limited by the binding of ^{99m}Tc -DTPA to plasma proteins, which can vary with pharmaceutical preparation and patient-related factors (11,17).

Russell et al. (17,19) circumvented the uncertainty introduced into GFR determinations caused by the protein binding of ^{99m}Tc -DTPA. By the Russell method, ^{99m}Tc -DTPA clearance is determined by measuring the residual radioactivity in samples of plasma obtained 1 and 3 hr after a single intravenous injection of ^{99m}Tc -DTPA. Binding of ^{99m}Tc -DTPA to

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protein is eliminated as a source of error by ultrafiltration of the plasma samples. We have previously reported that GFR obtained by the Russell method was virtually identical to that obtained from clearance of ^{125}I -iothalamate for a group of subjects, most of whom had renal function that ranged from normal to only moderately impaired (20). We describe the results of a study to determine whether the Russell method can also be accurately applied to patients with severe renal insufficiency.

MATERIALS AND METHODS

Subjects

In this study, data from 13 patients with severely impaired renal function were added to those obtained previously from 16 subjects with normal to moderately diminished renal function (20). All examinations were performed after approval by the Institutional Review Board and with informed consent. All subjects were adults (2 women, 27 men) and were either normal volunteers or were patients referred to the nuclear medicine department for renal scans for evaluation of chronic, stable renal insufficiency. In each of these patients, GFR was calculated both by the method of Russell (DTPA method) and by clearance of ^{125}I -iothalamate (iothalamate method). Except for one subject, where the measurements of GFR were made 5 days apart, all others had both tests performed within 48 hr.

Determination of GFR by the Iothalamate Method

Glomerular filtration rate using iothalamate was determined by the method of Sigman et al. (4). After oral hydration with 20 cc water/kg body weight, a bolus of 50 μCi ^{125}I -iothalamate (Glofil-125, ISO-TEX Diagnostics Inc., Friendswood, TX) was injected intravenously. This was followed by a constant intravenous infusion at a rate of 0.5 ml/min of a solution of 50 μCi ^{125}I -iothalamate mixed in 70 cc of 5% dextrose in normal saline. The infusion was continued for 45 min to allow the iothalamate to attain constant plasma levels before beginning collections of urine and blood. In subjects where urinary retention was suspected, the urine specimens were obtained by vesicular catheterization. After 45 min of constant infusion, the bladder was completely emptied, and this first sample of urine was discarded. Two additional complete urine collections were obtained 60 and 105 min after the constant infusion was begun. Immediately after the collection of each urine sample, a sample of blood was also obtained in a heparinized syringe. The constant infusion of iothalamate was continued throughout the collections. All blood samples were obtained from the arm opposite that used for iothalamate infusion. Blood samples were sedimented by centrifugation and the average radioactivity in duplicate 0.5 ml aliquots of plasma and urine was quantified by gamma well counting. GFR was calculated for each collection period based on the formula:

$$\frac{(\text{urine counts per minute}) (\text{urine volume})}{(\text{plasma counts per minute}) (\text{time in minutes})}$$

The reported GFR represented the average of two GFR estimates. All determinations of GFR by iothalamate clearance were performed before DTPA clearance.

Determination of GFR by the DTPA Method

The estimation of GFR using the ultrafiltration of plasma samples after injection of $^{99\text{m}}\text{Tc}$ -DTPA (Sn-complexed, Mediphyics, Paramus, NJ) was performed according to the methods described by Rowell et al. (18) and Russell et al. (19). This examination was performed in conjunction with a standard $^{99\text{m}}\text{Tc}$ -DTPA renal scan. Two aliquots of $^{99\text{m}}\text{Tc}$ -DTPA containing equal activity and volume were prepared, one used as a standard and the other as the patient dose. When the GFR was calculated in conjunction with a renal scan, 10 mCi was used. When the GFR was calculated without a concomitant renal scan, 2 mCi $^{99\text{m}}\text{Tc}$ -DTPA was used. At 60 and 180 min after the injection of the $^{99\text{m}}\text{Tc}$ -DTPA, blood was withdrawn into EDTA tubes from the arm opposite the site of injection. The blood cells were sedimented by low-speed centrifugation for 10 min and the plasma was removed. The plasma was subjected to centrifugation in Centrifree micropartition tubes (Amicon, Danvers, MA) according to the Amicon instructions. The resultant ultrafiltrate is 99% free of plasma protein. Duplicate aliquots of the ultrafiltered samples and an equal volume of a diluted standard (1:10,000) were counted in a gamma well counter. GFR was estimated by the formula (19):

$$[(D \ln (P_1/P_2)/(T_2 - T_1)) \times e^{((T_1 \ln P_2 - T_2 \ln P_1)/(T_2 - T_1))^{0.979}},$$

where D = dose activity, counts/min, T1 = time of collection of first blood sample in 60 min, T2 = time of collection of second blood sample in 180 min, P1 = ultrafiltrate activity (in cpm/ml) at T1, P2 = ultrafiltrate activity (in cpm/ml) at T2.

Statistical Methods

Statistical comparisons of the magnitude of errors was performed by Student's t-tests, using the software STATA (College Station, TX). In Figures 1-4, graphs were generated and linear regression was calculated by the least squares method.

RESULTS

Eighteen of the 29 subjects demonstrated renal function that varied from normal to moderately impaired, defined as a GFR > 20 ml/min by the iothalamate method (assumed to be the true GFR). The remaining 11 subjects had severe renal insufficiency, as defined by a GFR of ≤ 20 ml/min by the iothalamate method. Data for all subjects are shown in Table 1, sorted by low (≤ 20 ml/min) and higher (>20 ml/min) values of GFR based on the iothalamate method. In Figure 1, a comparison between the GFRs obtained by the iothalamate and DTPA methods is shown for subjects with normal to moderately diminished renal function (>20 ml/min by the iothalamate method). In Figure 2, a similar comparison is made for subjects with severely diminished renal function (≤ 20 ml/min). For the subjects with normal to moderately diminished renal function, the iothalamate and DTPA methods for calculating GFR yield virtually identical results [n = 18, r =

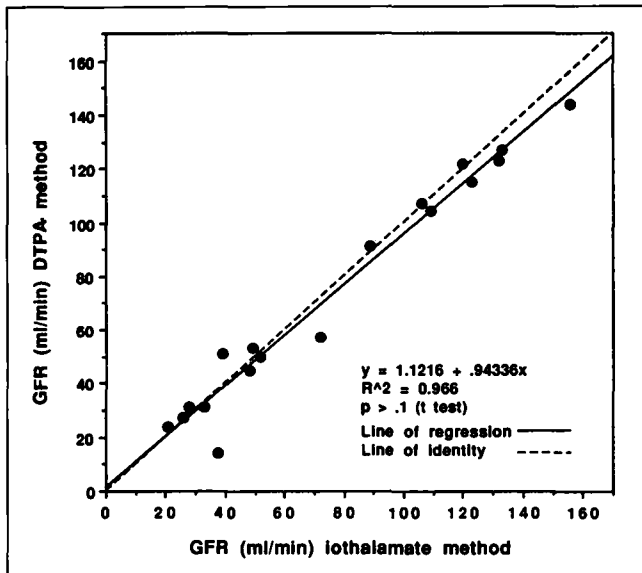


FIGURE 1. Glomerular filtration rate calculated both by clearance of ^{125}I -iothalamate from urine and plasma (x-axis) and by clearance of $^{99\text{m}}\text{Tc}$ -DTPA from two protein-free plasma samples (y-axis). Data have been sorted by the iothalamate method for values of GFR > 20 ml/m. The solid line represents the line of regression, the dashed line is the line of identity.

0.966, $p > 0.1$ (paired Student's t-test). These results agree with those previously published (20). For subjects with severe renal insufficiency (≤ 20 ml/min by the iothalamate method), the GFR as calculated by the DTPA method differs significantly from that by the iothalamate method [$n = 11$, $r = 0.236$, $p < 0.01$ (paired Student's t-test)].

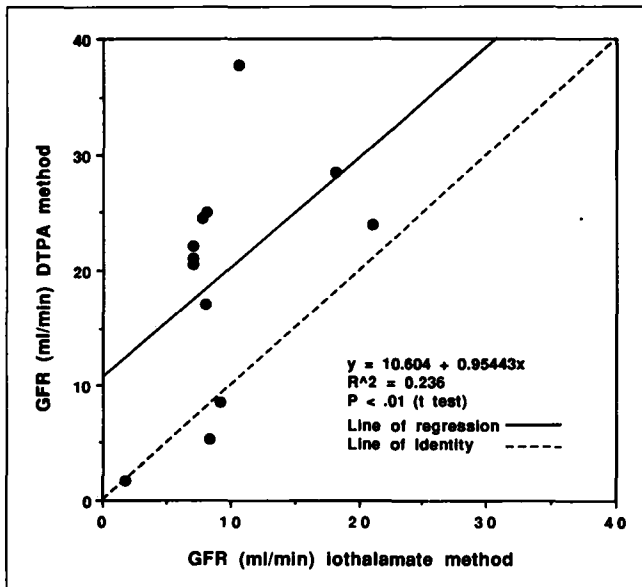


FIGURE 2. Glomerular filtration rate calculated both by clearance of ^{125}I -iothalamate from urine and plasma (x-axis) and by clearance of $^{99\text{m}}\text{Tc}$ -DTPA from two protein-free plasma samples (y-axis). Data have been sorted by the iothalamate method for values of GFR ≤ 20 ml/m. The solid line represents the line of regression, the dashed line is the line of identity.

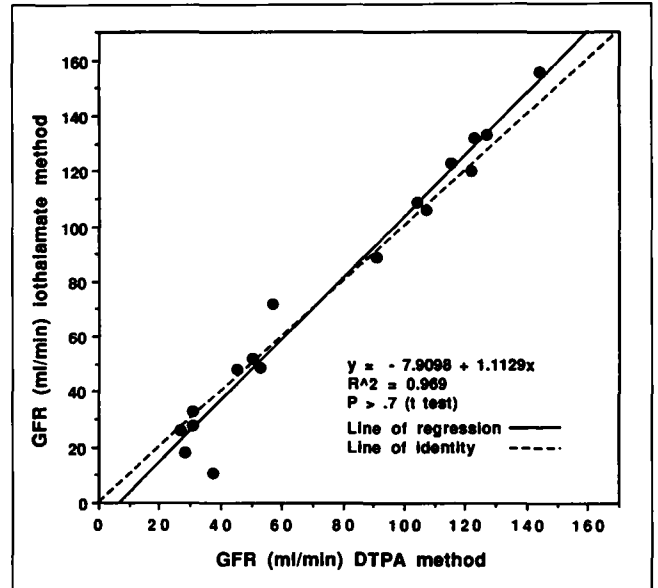


FIGURE 3. Glomerular filtration rate calculated both by clearance of $^{99\text{m}}\text{Tc}$ -DTPA from two protein-free plasma samples (x-axis) and by clearance of ^{125}I -iothalamate from urine and plasma (y-axis). Data have been sorted by the DTPA method for values of GFR > 25 ml/m. The solid line represents the line of regression, the dashed line is the line of identity.

In eight of the 11 subjects (72.7%) with severe renal insufficiency, the GFR as calculated by the DTPA method overestimates that obtained by the iothalamate method by at least 50% (Table 1). The absolute average difference between DTPA and iothalamate methods in the patients with severe renal insufficiency is 11.6 ml/min. The absolute mean percent

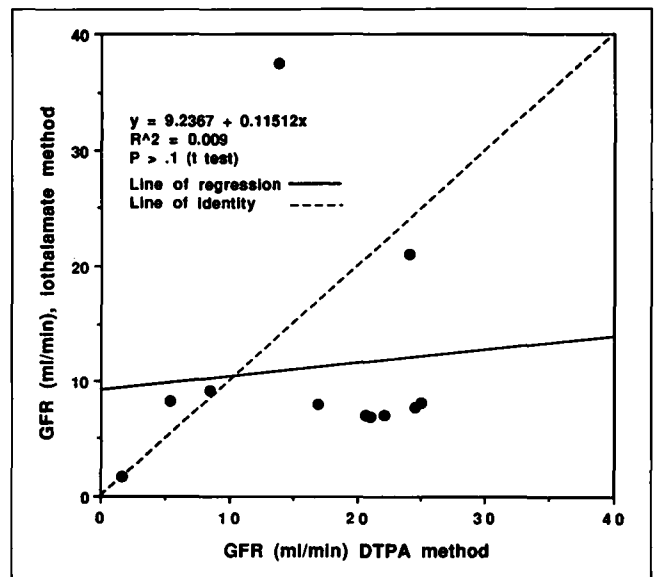


FIGURE 4. Glomerular filtration rate calculated both by clearance of $^{99\text{m}}\text{Tc}$ -DTPA from two protein-free plasma samples (x-axis) and by clearance of ^{125}I -iothalamate from urine and plasma (y-axis). Data have been sorted by the DTPA method for values of GFR ≤ 25 ml/m. The solid line represents the line of regression, the dashed line is the line of identity.

TABLE 1
Comparison of GFR by DTPA and Iothalamate
Methods: Individual Data

Severe Renal Insufficiency				
GFR (ml/m) iothalamate method	GFR (ml/m) DTPA method	Difference (ml/m) DTPA- iothalamate	Percent error	
1.8	1.7	-0.1	-6%	
7.0	21.0	+14.0	+200%	
7.0	22.1	+15.1	+216%	
7.0	20.6	+13.6	+194%	
7.8	24.5	+16.7	+214%	
8.0	17.0	+9.0	+112%	
8.1	25.0	+16.9	+209%	
8.3	5.4	-2.9	-35%	
9.3	8.5	-0.8	-9%	
10.6	37.7	+27.1	+256%	
18.2	28.6	+10.4	+57%	
	Mean absolute error	11.6	Mean absolute percent error	137%
Normal to Moderate Renal Insufficiency				
GFR (ml/m) iothalamate method	GFR (ml/m) DTPA method	Difference (ml/m) DTPA- iothalamate	Percent error	
21	24	+3	+14%	
26	27	+1	+4%	
28	31	+3	+11%	
33	31	-2	-6%	
37	13	-24	-63%	
39	51	+12	+31%	
48	45	-3	-6%	
49	53	+4	+8%	
52	50	-2	-4%	
72	57	-15	-21%	
89	91	+2	+2%	
106	107	+1	+1%	
109	104	-5	-5%	
120	122	+2	+2%	
123	115	-8	-6%	
132	123	-9	-7%	
133	127	-6	-4%	
156	144	-12	-8%	
	Mean absolute error	6.3	Mean absolute percent error	11.3%

error [$100 \times (\text{iothalamate} - \text{DTPA})/\text{iothalamate}$] in subjects with severe renal insufficiency is 137%. In patients with a GFR > 20 ml/min by the iothalamate method, the mean absolute difference between the two methods is 6.3 ml/min, which represents an absolute mean percent error of 11.3%. There is no statistical difference between the mean absolute error of the two groups of patients ($p > 0.05$, unpaired Student's t-test, assuming unequal variance). However, the statistical difference between the absolute mean percent errors of

the two groups is highly significant ($p < 0.01$, unpaired Student's t-test, assuming unequal variances).

If the data are sorted by values of GFR obtained by the DTPA method, rather than by the iothalamate method, a similar pattern emerges. For values of GFR > 25 ml/min by the DTPA method, a high degree of correlation exists between values obtained by the iothalamate and DTPA methods [$r = 0.969$, $p > 0.7$ (paired Student's t-test)] (Fig. 3). For values of GFR ≤ 25 ml/min by the DTPA method, the correlation between the GFR obtained by the DTPA and iothalamate methods is poor, although the difference between the values is not of statistical significance [$r = 0.969$, $p > 0.1$ (paired Student's t-test)] (Fig. 4).

DISCUSSION

Cohen et al. (5) have demonstrated excellent correlation ($r = 0.987$, $s.e. = 5.5$) between clearance of inulin and iothalamate in a substantial series of patients. This correlation was as reliable in patients with very severe renal insufficiency (GFR < 20 ml/min) as in those with normal kidney function. It is justifiable to consider clearance of both inulin and iothalamate as equivalent standards of reference for the determination of true GFR, regardless of the severity of renal dysfunction.

In most patients with normal to moderately diminished renal function, the method described by Russell et al. (19), which predicts GFR by clearance of DTPA from protein-free samples of plasma, is an accurate predictor of true GFR. The DTPA method is relatively simple to perform and avoids the expense and technical difficulties inherent to the iothalamate method. In addition, the DTPA method permits the simultaneous acquisition of a nuclear medicine renogram, which provides useful information regarding differential (split) function and other parameters of renal function. However, in patients with poor renal function, values for GFR obtained by the DTPA method may differ significantly from those provided by the iothalamate method.

The reproducibility of neither the iothalamate nor the two-sample DTPA methods has been reported and may differ from lab to lab. It could be argued that the additive values for the intrinsic error in reproducibility of the iothalamate and DTPA methods could, therefore, contribute to the discordance between the two methods, and that the iothalamate could as easily be a greater source of error than DTPA method. Several indirect lines of evidence suggest that the DTPA value is that which should be held suspect. First, in the Cohen series (5), the values of inulin and iothalamate clearance were very close throughout the range of renal function, supporting the use of iothalamate as a standard of reference. Second, our results suggest that discrepancy between the DTPA and iothalamate methods is likely caused by nonrandom factors. The magnitude of absolute error [$|\text{DTPA method} - \text{iothalamate method}|$] was nearly twice as great for patients with severe renal insufficiency (11.6 ml/min), when compared to those with normal to moderate impairment (6.3 ml/min). In addition, in 75% of our patients with severe renal insufficiency, the GFR by the DTPA method was of a greater magnitude than that determined by

the iothalamate method. Therefore, we believe that it is most prudent to assume that the discrepancy between the DTPA and iothalamate methods in patients with poor renal function is due to an error in the DTPA value.

There are several potential nonrandom sources of discrepancy between the iothalamate and the DTPA GFR methods for patients with severe renal insufficiency. However, the true cause of the discrepancy is unknown and may be multifactorial. DTPA may accumulate in a third space of interstitial fluid. DTPA, with a molecular weight of approximately 500, could diffuse freely into this fluid. Although none of the patients in this study were grossly edematous, the likelihood of increased extracellular water in patients with severe renal insufficiency is greater than that in other patients. That the DTPA method tended to overestimate true GFR in patients with poor renal function is consistent with the third-space theory.

In view of the present data, values obtained by the DTPA method ≤ 25 ml/min should be considered potentially unreliable (Figs. 3, 4). In patients known to have severe renal insufficiency, a GFR by an accepted method of standard reference, such as iothalamate clearance, may be more appropriate. Serial determinations using the DTPA method may provide a trend to determine whether function is improving or deteriorating in patients with severe renal insufficiency, however, the validity of this hypothesis is yet to be tested.

A modified method for calculation of GFR that uses scaling for patient size has been described. The modified method offers advantages for both pediatric and adult patients (21). In our series, there was no significant difference between the GFR obtained by the conventional Russell two-sample method and that predicted by scaling method (data not shown). However, none of the patients examined in our series were children.

Values for GFR less than 25 ml/min obtained by the DTPA method, which uses two or more samples of protein-free plasma, should be considered potentially inaccurate. Although costly and labor intensive, measurements of GFR obtained by clearance of inulin and ^{125}I -iothalamate are suggested, in preference to the DTPA method, for accurate determination of GFR in patients with severe renal dysfunction.

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