Glomerular filtration rate estimated from the uptake phase of 
\(^{99m}\text{Tc-DTPA} \) renography in chronic renal failure

Lars Juhl Petersen\(^1,2\), Jan Roland Petersen\(^2\), Ulrik Talleruphuus\(^2\), Michael Lehd Møller\(^2\), Søren Dastrand Ladefoged\(^1\), Jesper Mehlsen\(^2\) and Henrik Ærenlund Jensen\(^1\)

\(^1\)Department of Nephrology, Hvidovre Hospital, Hvidovre and \(^2\)Department of Clinical Physiology and Nuclear Medicine, Frederiksberg Hospital, Frederiksberg, Denmark

Abstract

**Background.** The purpose of the study was to compare the estimation of glomerular filtration rate (GFR) from \(^{99m}\text{Tc-DTPA} \) renography with that estimated from the renal clearance of \(^{51}\text{Cr-EDTA} \), creatinine and urea.

**Methods.** Fifty patients with reduced renal function (serum creatinine between 150 and 600 \(\mu\text{mol/l} \) ) were enrolled in the study. GFR was estimated from the uptake phase of \(^{99m}\text{Tc-DTPA} \) renography (GFR\(_{\text{DTPA}}\)). The renal clearance of \(^{51}\text{Cr-EDTA} \) (GFR\(_{\text{EDTA}}\)) was used as the reference method. Creatinine clearance (C\(_{\text{Cr}}\)), urea clearance (C\(_{\text{Ur}}\)) and the mean of urea and creatinine clearance (C\(_{\text{Cr}+\text{Ur}/2}\)) were also calculated from urine collected during a period of 24 h. Limits of agreement were used for method comparison.

**Results.** The limit of agreement between GFR\(_{\text{DTPA}}\) and GFR\(_{\text{EDTA}}\) was \(2 \pm 17 \text{ ml/min} \). The mean difference did not deviate significantly from zero. The other clearance techniques had larger limits of agreement and a mean difference significantly different from zero. Furthermore, C\(_{\text{Ur}}\) and C\(_{\text{Cr}+\text{Ur}/2}\) had systematic deviations of the differences, indicating that C\(_{\text{Ur}}\) and C\(_{\text{Cr}+\text{Ur}/2}\) are poor estimates of GFR.

**Conclusion.** The limit of agreement between GFR\(_{\text{DTPA}}\) and GFR\(_{\text{EDTA}}\) are acceptable and, therefore, GFR estimated from \(^{99m}\text{Tc-DTPA} \) renography is acceptable for clinical use in patients with reduced renal function. Furthermore, the method is simple and less time consuming compared with renal techniques.

**Key words:** glomerular filtration rate; renal insufficiency; renography

Introduction

Most simple renal function is evaluated by serum creatinine, but the glomerular filtration rate (GFR) has to be reduced by 30–50% before serum creatinine is elevated above the upper level of normal range [1]. An elevated level of serum creatinine has a 100% specificity but only a 60% sensitivity for reduced renal function [2]. Creatinine clearance is more accurate, but GFR may be overestimated by this method because of a tubular secretion of creatinine which has been shown to be variable [3]. Thus, a direct measurement of GFR gives the best evaluation of renal function. The golden standard for GFR estimation is the renal clearance of inulin [2,4,5], but GFR can also be measured by either renal clearance or plasma clearance of \(^{51}\text{Cr-EDTA} \), \([^{131}\text{I}]\text{diatrizoate}, [^{131}\text{I}]\text{iothalamate}, [^{125}\text{I}]\text{iothalamate} or \(^{99m}\text{Tc-DTPA} \). Plasma clearance of iohexol (an X-ray contrast medium) has also been used for estimating GFR [6,7]. The plasma clearance techniques are inaccurate, when GFR is low or if oedema is present, and renal clearance techniques are time consuming. Thus a simple and reliable method for the estimation of GFR is lacking. Measurement of inulin concentration in urine and plasma is cumbersome and not possible in Denmark due to laboratory environmental problems. Therefore, renal clearance of \(^{51}\text{Cr-EDTA} \) was chosen as the standard method for GFR estimation. Clearance of \(^{51}\text{Cr-EDTA} \) has a close correlation to inulin clearance [8]. In a consensus report of the Radionuclides in Nephrourology group, the renal clearance of \(^{51}\text{Cr-EDTA} \) with a constant infusion technique and urine collection was recommended for research if the GFR is < 30 ml/min [9].

The purpose of the study was to evaluate the estimation of GFR by \(^{99m}\text{Tc-DTPA} \) renography, creatinine clearance, urea clearance and the mean of urea and creatinine clearance as compared with renal clearance of \(^{51}\text{Cr-EDTA} \).

Subjects and methods

**Patients**

Fifty patients (16 women and 34 men, mean age 57 years (range 24–74 years)) with reduced renal function (serum
creatinine between 150 and 600 µmol/l) were enrolled in the study. Renal insufficiency was caused by nephrosclerosis in 14 patients, diabetic nephropathy in 12 patients, glomerulonephritis in 10 patients, interstitial nephritis in three patients, chronic pyelonephritis in two patients and contracted kidneys in eight patients. The study was approved by the local ethics committee, and all patients gave informed consent.

**99mTc-DTPA renography**

Prior to the examination, each patient was hydrated with 750–1000 ml of fluid. Renography was carried out with the patient in a supine position with the gamma-camera placed under the patient’s bed. A dose of 3 MBq of 99mTc-DTPA (International CIS) per kg of body weight was injected as a bolus in an antecubital vein. Frames of 128 × 128 pixels were recorded with an on-line computer, initially at 1 s intervals for 60 s and then at 10 s intervals for 20 min. A region of interest (ROI) over the left ventricle was defined with the same number of pixels for all patients, together with an ROI over the lower part of the right lung. ROIs over the two kidneys were defined on frames summed from 1 to 3 min after injection. Two abdominal background ROIs were defined below the kidneys.

The time activity curves from the ROIs were computed, and corrected for physical decay. The time activity curve from the ROI over the heart was corrected for lung activity. The time activity curves from the ROIs over the kidneys were presumed to be the sum of three factors: (i) filtered activity; (ii) vascular activity in and around the kidney; and (iii) extravascular activity in and around the kidney.

The Uptake Index (UI) was computer estimated automatically by the software as described in the Appendix. From the UIs, single kidney GFR was estimated as:

\[
GFR = \frac{(G_h \times V_h \times G_k \times U_h)}{V_h}
\]

where \(G_h\) = the counting efficiency factor in the ROI over the heart; \(V_h\) = mean plasma volume of the heart ROI; and \(G_k\) = the counting efficiency factor in the ROI over the kidney. The total GFR was estimated as the sum of right and left single kidney GFRs. GFR estimated from 99mTc-DTPA renography will be named GFR\(_{DTPA}\). The reproducibility of the single kidney GFR\(_{DTPA}\) has been published previously as a coefficient of variation of 8% [10].

**51Cr-EDTA clearance**

The GFR was calculated from the clearance rate of 51Cr-EDTA (GFR\(_{EDTA}\)) during constant infusion:

\[
GFR = 1.1 \times \left( \frac{U_{\text{EDTA}} \times V_u}{P_{\text{EDTA}} \times t} \right)
\]

where \(U_{\text{EDTA}}\) = 51Cr-EDTA concentration in the urine; \(V_u\) = urine volume; \(P_{\text{EDTA}}\) = 51Cr-EDTA concentration in the plasma; and \(t\) = time of the clearance period. The factor 1.1 corresponds to the underestimation of GFR by 51Cr-EDTA clearance [8]. A priming dose of 1.38 MBq of 51Cr-EDTA was given as a bolus injection, and was followed by a constant infusion of 0.022 \(\times (C_{C_2}/100)\) MBq/min (\(C_{C_2}\) is the creatinine clearance measured at an earlier visit to the outpatient clinic). The correction of the constant infusion dose with respect to creatinine clearance was used to ensure equal plasma levels of 51Cr-EDTA in all patients. The plasma level of 51Cr-EDTA was measured as the activity in c.p.m. in 2 ml of plasma. The count rate was \(\approx 300\) c.p.m. in most patients. After 1 h of constant infusion, two 30 min clearance periods were performed. In each clearance period, blood samples for measurement of \(P_{\text{EDTA}}\) were taken after 5, 15 and 25 min. \(P_{\text{EDTA}}\) was constant during the clearance periods and no trends toward decreasing or increasing activity were present. The urine collections were timed carefully. Urine concentration of 51Cr-EDTA was also measured as activity in c.p.m. Urine was collected by free voiding; we were unable to perform ultrasonography to confirm bladder emptying. Patients were given 250 ml of fluid to drink every 30 min during the clearance performance, and they were hydrated before examinations as mentioned in the renography section. The 99mTc-DTPA renography was performed during the first hour of infusion before the clearance periods. The patients were in a resting supine position during infusion.

**Creatinine and urea clearance**

Serum and urine levels of creatinine and urea were measured by an autoanalyser (Technicon SMAC 3, Tarrytown, NY). The autoanalyser used a colorimetric method (Jaffe reaction) for creatinine measurement.

Clearance of creatinine (\(C_{Cr}\)) and urea (\(C_{Ur}\)) were calculated as:

\[
C_{Cr} = \frac{(U_{Cr} \times V_u)}{(S_{Ur} \times t)}
\]

\[
C_{Ur} = \frac{(U_{Ur} \times V_u)}{(S_{Ur} \times t)}
\]

where \(U_{Cr}\) = concentration of creatinine in the urine; \(V_u\) = urine volume; \(S_{Ur}\) = serum creatinine; \(t\) = 24 h; \(U_{Ur}\) = concentration of urea in the urine; and \(S_{Ur}\) = serum urea. The mean of creatinine and urea clearance \(C_{(Cr+Ur)/2}\) was estimated as:

\[
C_{(Cr+Ur)/2} = \frac{(C_{Cr} + C_{Ur})}{2}
\]

The urine was collected the day before the renography and the 51Cr-EDTA clearance. Blood samples for urea and creatinine measurements were taken in the morning, the patients were not required to fast.

**Statistics**

For method comparison, the limits of agreement (mean difference ±2 SD) are given [11]. A t-test was used to test whether the mean difference deviated significantly from zero. For graphical illustration, the differences between methods were plotted against the mean value of the two methods [11], as the renal clearance of 51Cr-EDTA is not an unequivocally correct measurement of GFR. For regression analysis, the least squares method was used. A two-sided P-value of 5% or less was considered significant.

**Results**

The mean GFR\(_{EDTA}\) was 30 ml/min (range 9–83 ml/min). In six patients, creatinine clearance and urea clearance could not be calculated due either to inadequate urine collection or to technical problems in the laboratory; in two patients we were unable to calculate urea clearance due to technical problems. GFR\(_{EDTA}\) correlated significantly with GFR\(_{DTPA}\), \(C_{Cr}\), \(C_{Ur}\) and \(C_{(Cr+Ur)/2}\) (Table 1).

Figures 1–4 show the limits of agreement between GFR\(_{EDTA}\) and GFR\(_{DTPA}\), \(C_{Cr}\), \(C_{Ur}\) and \(C_{(Cr+Ur)/2}\). GFR\(_{DTPA}\) had the narrowest limits of agreement, and the mean value of GFR\(_{DTPA}\) that did not differ significa-
Table 1. Correlation between different estimates of GFR and the renal clearance of $^{51}$Cr-EDTA

<table>
<thead>
<tr>
<th>Method</th>
<th>$r$</th>
<th>$P$</th>
</tr>
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<tbody>
<tr>
<td>GFR$_{DTPA}$</td>
<td>0.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C$_{Cr}$</td>
<td>0.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C$_{Ur}$</td>
<td>0.96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C$_{(Cr+Ur)/2}$</td>
<td>0.97</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

GFR$_{DTPA}$ = GFR estimated from $^{99m}$Tc-DTPA renography; C$_{Cr}$ = creatinine clearance; C$_{Ur}$ = urea clearance; C$_{(Cr+Ur)/2}$ = mean of creatinine and urea clearance.

GFR$_{DTPA}$ did not have a significant correlation to the mean value of GFR$_{DTPA}$ and GFR$_{EDTA}$ ($r=0.005; P=0.97$), indicating that the differences between the methods did not deviate systematically with the GFR value. The differences between C$_{Cr}$ and GFR$_{EDTA}$ did not correlate significantly with the mean value of C$_{Cr}$ and GFR$_{EDTA}$ ($r=0.19; P=0.23$). The differences between C$_{Ur}$ and GFR$_{EDTA}$ had a significant correlation to the mean value of C$_{Ur}$ and GFR$_{EDTA}$ ($r=0.76; P<0.001$), suggesting that C$_{Ur}$ is an inappropriate way in which to estimate GFR (Figure 3). The differences between C$_{(Cr+Ur)/2}$ and GFR$_{EDTA}$ also correlated significantly with the mean value of C$_{(Cr+Ur)/2}$ and GFR$_{EDTA}$ ($r=0.40; P=0.009$) (Figure 4).

![Fig. 1. Difference between measured GFR$_{EDTA}$ and GFR estimated from $^{99m}$Tc-DTPA renography (GFR$_{DTPA}$) plotted against the mean value of the two methods. Dotted lines indicate limits of agreement from −15 to 19 ml/min, and the mean difference is 2 ml/min.](image1)

![Fig. 2. Difference between measured GFR$_{EDTA}$ and creatinine clearance (C$_{Cr}$) plotted against the mean value of the two methods. Dotted lines indicate limits of agreement from −24 to 16 ml/min, and the mean difference is −4 ml/min.](image2)

![Fig. 3. Difference between measured GFR$_{EDTA}$ and urea clearance (C$_{Ur}$) plotted against the mean value of the two methods. Dotted lines indicate limits of agreement from −5 to 39 ml/min, and the mean difference is 17 ml/min. The differences correlated significantly with the mean values ($r=0.76; P<0.001$).](image3)

![Fig. 4. Difference between measured GFR$_{EDTA}$ and the mean of creatinine and urea clearance (C$_{(Cr+Ur)/2}$) plotted against the mean value of the two methods. Dotted lines indicate limits of agreement from −12 to 24 ml/min, and the mean difference is 6 ml/min. The differences correlated significantly with the mean values ($r=0.40; P=0.008$).](image4)
Discussion

As expected, we found that all GFR estimates correlated significantly with the chosen standard method. Limits of agreement were large for all methods, stressing the unreliability of estimation of GFR in patients with reduced renal function. GFR_Tc-DTPA showed the narrowest limits of agreement, and only the mean value of GFR_Tc-DTPA did not differ significantly from the mean value of the standard method. No systematic GFR-dependent deviation from GFR was present, and the variation in the differences seems homogenous with respect to different GFR levels. This is an indication of increasing percentage error with decreasing renal function. C_Ur and C_(Cr+Ur)/2, but not C_Cr, had systematic GFR-dependent deviations from GFR. This indicates that C_Ur and C_(Cr+Ur)/2 are poor estimates of GFR in patients with reduced renal function.

When estimating GFR from 99mTc-DTPA renography, the background correction is of great importance. The use of both a vascular and an extravascular background correction, as done in the present study, has been found to improve the GFR estimate and reproducibility as compared with only a vascular background correction [12,13]. In a consensus report, a general consensus on background subtraction could not be reached [9]. In the same consensus report, the use of 99mTc-DTPA is only mentioned for clearance techniques and not for camera techniques [9]. Furthermore, the best plasma activity curve is obtained from a heart ROI, as done in the present study [14]. The stability of different 99mTc-DTPA preparations has been low and the protein binding high, but the preparation used in this study has been validated previously [15].

Previously, a study comparing GFR estimated from 99mTc-DTPA renography with a plasma clearance of 51Cr-EDTA found the SD of the differences to be 10.5 ml/min, indicating larger limits of agreement than in the present study [14]. A recently published study also comparing GFR estimated from 99mTc-DTPA renography with a plasma clearance of 51Cr-EDTA found the SD of the differences to be 10.7 ml/min in a subgroup of patients with GFR <50 ml/min [16]. A thesis including 158 adults found the limits of agreement between GFR estimated from 99mTc-DTPA renography and the plasma clearance of 99mTc-DTPA to be comparable with the present study [17]. Other studies [12, 18–22] evaluating GFR estimated from 99mTc-DTPA renography do not state the limits of agreement but only the standard errors of the estimate, with ranges from 4 to 18 ml/min as compared with 8 ml/min in the present study. Standard error of the estimate is not the correct way to indicate variation, as it only describes the standard error of a y-fit for the mean x-value [23]. Only a few studies on GFR methods state limits of agreement, or report the raw data, allowing the reader to calculate the limits of agreement. Studies [24,25] comparing a renal clearance technique with a plasma clearance technique have broader limits of agreement than the present study. One study [26] comparing a constant infusion plasma clearance technique with a renal clearance technique found the limits of agreement to be very broad. When one plasma clearance technique is compared with another plasma clearance technique, the results are more confusing. Some studies [27,28] with broad limits of agreement were evaluating one-sample techniques, whereas another study [29] with narrow limits of agreement compared a 13-sample technique with several one-sample techniques and a five-sample technique. A newly published study has shown narrow limits of agreement between plasma clearance of iohexol and plasma clearance of 51Cr-EDTA in patients with mild to moderate renal impairment [30]. Close agreement between two plasma clearance techniques is expected, as the major source of error, the extrarenal clearance, is eliminated.

In conclusion, a renal clearance technique is the golden standard for the estimation of GFR, but renal clearance is not simple to perform. Therefore, the plasma clearance technique is widely used, although it may be highly unreliable in patients with reduced renal function. The evaluation of a method for GFR estimation depends on whether the limits of agreement with the standard method are acceptable for clinical use or not. Limits of agreement found for GFR estimated by 99mTc-DTPA renography are large, but these limits of agreement are the narrowest found for a GFR estimate when compared with a standard method of renal clearance. For this reason, we found that estimation of GFR from the uptake phase of 99mTc-DTPA renography is acceptable for clinical use. 99mTc-DTPA renography is simple to perform and is less time consuming than both renal clearance and plasma clearance techniques. Therefore, when a renography is indicated, we recommend performing 99mTc-DTPA renography and obtaining an estimate of GFR as well as other renography data.

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Received for publication: 15.9.98
Accepted in revised form: 5.3.99

Appendix

The activity in the ROI over the kidney could be expressed as a weighted sum of three factors:

$$ C(t) = K(t) + ESF \times B_h(t) + VSF \times H_p(t) \quad (1) $$

$$ C(t) = \text{the time activity curve in the ROI over the kidney; } K(t) = \text{the filtered activity in the kidney; } B_h(t) = \text{the extravascular background activity; ESF} = \text{extravascular subtraction factor (the ratio between the number of pixels in the ROIs over the kidney and the abdominal background); } H_p(t) = \text{the vascular component of the time activity curve over the heart ROI; and VSF} = \text{vascular subtraction factor.} $$

After the first pass phase, it is assumed that the concentration of tracer in the body fluids can be described by a simplified open three compartment system (the plasma, and a fast and a slow equilibrating compartment in the interstitia). From this assumption, a decomposition of the heart curve into $H_p(t)$ and an extravascular component is made. The background activity curve obtained from the subrenal ROIs is assumed to be composed of vascular and extravascular activity. The time courses of these are known from decomposition of the heart curve. Then the extravascular background activity in these regions can be determined from the linear combination of vascular and extravascular activity curves, which best fit to the actually recorded background activity curves.

It is presumed that the heart time activity curve could be expressed as:

$$ H_p(t) = G_h \times V_h \times C_p(t) \quad (2) $$

where $G_h = \text{counting efficiency factor in the heart ROI (counts/Bq)}$, $V_h = \text{mean plasma volume in the heart ROI (ml)}$; and $C_p(t) = \text{the arterial plasma concentration of } ^{99m}\text{Tc-DTPA.}$

Furthermore, it is presumed at time $0 < t < t_{\min}$, where $t_{\min}$ is the shortest parenchymal transit time:

$$ K(t) = G_k \times GFR \frac{t}{G_p(t)} dt \quad (3) $$

where $G_k = \text{counting efficiency factor in the kidney ROI (counts/Bq)}$. By application of equation 3 in equation 1, the following appears:

$$ \frac{C(t) - ESF \times B_h(t)}{H_p(t)} = VSF + \frac{G_k \times GFR \frac{t}{G_p(t)} dt}{H_p(t)} \quad (4) $$

By isolating $C_p(t)$ in equation 2 and putting it into equation 4, the following is derived:

$$ \frac{C(t) - ESF \times B_h(t)}{H_p(t)} = VSF + \frac{G_k \times GFR \frac{t}{H_p(t)} dt}{H_p(t)} \quad (5) $$

The fraction $(G_k \times GFR)/(G_h \times V_h)$ is called the Uptake.
Index (UI) and is substituted in equation 5:

\[
\frac{\text{CK}(t)-\text{ESF} \times B(t)}{H_p(t)} = \text{VSF} + \text{UI} \times \int_0^t \frac{H_p(T) dT}{H_p(t)}
\]

This formula can be solved by simple linear regression (for values of \( t > 1 \) min after bolus maximum count in the heart ROI and \(< t_{\text{min}} \)). Initially, the computer software solves the linear regression in the time period starting 1 min after bolus maximum count in the heart ROI and ending 1 min later. Then the computer software resolves the linear regression in a new time period extended by 10 s (one frame), and the resolving of the linear regression is repeated for each 10 s period until the end of the time period of the renography. Then \( t_{\text{min}} \) is determined as the time ending the period with the largest value of UI and a coefficient of variation of UI < 8%. Previously, the day to day coefficient of variation has been determined to be 8% [10]. VSF is also determined from the same linear regression analysis. After this automatic calculation, it was possible to change this interval interactively.

By isolating GFR in the UI fraction:

\[
GFR = \left( \frac{G_h \times V_h}{G_k} \right) \times UI
\]

The fraction \( \left( \frac{G_h \times V_h}{G_k} \right) \) was presumed constant between patients, and no correction for kidney depth was made. The mean value of \( \left( \frac{G_h \times V_h}{G_k} \right) \) has been measured previously to be 106 ml, the standard error of the mean was 3 ml [10].