Rapid Method for the Measurement of Differential Renal Function: Validation

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Evaluation of renal function requires the determination of the glomerular filtration rate (GFR) and, in some cases, of the effective renal plasma flow (ERPF). The standard techniques for determination of these parameters necessitates continuous intravenous administration of adequate substances, with multiple blood and urine analysis, and does not allow measurement of separate renal function. Schlegel et al. and Gates described isotopic methods for the measurement of global and unilateral GFR and ERPF based on the determination by scintillation camera of the fraction of the injected dose ([99mTc]DTPA-[131I]hippuran) present in the kidneys 1–3 min after its administration. These methods require counting of the injected dose and correction for attenuation, but no blood or urine sampling. We have validated these techniques by simultaneous infusion of inulin and PAH in patients with various levels of global renal function (anuric to normal). To better define unilateral renal function we have also studied nine kidneys in patients either nephrectomized or with a nephrostomy enabling unilateral function measurement. A good correlation between inulin or PAH clearances and fractional uptake of [99mTc]DTPA or [131I]hippuran by the kidney was observed. Very good reproducibility of both isotopic techniques was shown. We conclude that determination of the fractional uptake of [99mTc]DTPA and [131I]hippuran between 1 and 3 min allows good and reproducible prediction of global and especially of unilateral kidney function with great rapidity and simplicity, rendering this technique suitable for clinical practice.


METHODS

Twenty-four adult patients with various levels of renal function, ranging from normal to anuric (two patients on hemodialysis), were studied after informed consent for simultaneous measurement of standard and isotopic measurements.
of global renal function. Their age ranged from 27 to 77 yr (12 females and 12 males). All the patients, except the two
anuric, were well hydrated orally (20 ml/kg, 1–2 hr before the
study followed by 1 ml/kg/hr during the study). A catheter
was placed in a superficial vein of each forearm for inulin and
PAH perfusion and for blood sampling. At the beginning of
the study, a priming dose solution of inulin (25%) and PAH
(20%) was given through the catheter over a 3-min period,
followed by a maintenance infusion of inulin (25%) and PAH
(20%) at a rate calculated to maintain a constant serum
concentration of 200 mg/l inulin and 25 mg/l PAH. Forty-
five minutes were allowed for equilibration before two to three
urine collections were started. Blood samples were withdrawn
at the mid- and end-point of each period for the determination
of inulin and PAH concentrations. Urine samples were ob-
tained by spontaneous voiding. Our results showed the coef-
ficient of variation of inulin clearance to be 10% and of PAH
clearance to be 11%. Inulin measurement was done according
to a micromodification of the technique of Von Führ et al.
(10) described by Hilger et al. (11), and PAH measurements
were performed by a micromodification of the technique of
Bratton and Marshall (12), described by Deetjen and Sonnen-
berg (13).

During the first or second period 3 mCi of $[^{99m}Tc]$DTPA
(freshly prepared from a constant source) followed at 15-min intervals by 250 µCi of $^{131}$I-labeled sodium iodohippurate were
injected intravenously in the catheter. The injected dose was
measured by counting the syringe on the gamma camera under
standardized geometry (at 20 cm). Renal data acquisition
was also performed with the gamma camera (GE 400 AT)
equipped with a ½ in. crystal and a 300-keV parallel hole
collimator, with the patient in supine position over the camera.
The data was recorded in computer memory every 15 sec
during 10 min for $[^{99m}Tc]$DTPA and 20 min for
$[^{131}I]$hippuran. Data acquisition was initiated at the moment
of injection and was analyzed at the end of the study, after
outlining each kidney in a region of interest. In practice, 3–4
min for each measurement is sufficient, as described by Schle-
gel et al. (5–7), Brodkey et al. (8), and Gates (9); however, we
increased the duration of the study in order to visualize the
urinary tract and renogram. To calculate ERPF and GFR the
relative and fractional uptake were first determined by the
computer (6,9) then related to the clearance values (6,9):

$$\text{relative uptake (}\!^{[131]}\text{I} \!\text{hippuran}) 1–2 \text{ min}$$

$$= \frac{\text{kidney counts} - \text{background}}{\text{counts of injected dose}} \times Y^2 \times 100,$$

where $Y$ is the renal depth calculated according to Tonnesen
(14); left kidney depth = 13.2 (weight/height) + 0.7, right
kidney depth = 13.3 (weight/height) + 0.7 (9).

$$\text{fractional uptake (}\!^{[99m}Tc\!)\text{DTPA}) 2–3 \text{ min}$$

$$= \frac{\text{kidney counts} - \text{background}}{\text{counts of injected dose}} \times e^{-\mu Y} \times 100,$$

where $Y$ is renal depth and $\mu$ is the attenuation coefficient for
$^{99m}$Tc in tissue equivalent ($\mu = 0.153$). Relative and fractional
uptake were related to clearance value by the following empiric
regression equations (6,7,9):

$$\text{ERPF} = 5.029 \times \text{BSA} \times \text{return}.$$

$$\text{BSA} \times \text{return} = 0.3698707 \times \text{relative uptake (}\!^{[131]}\text{I})$$

$$- 2.31476 \times 10^{-4} \times \text{relative uptake (}\!^{[131]}\text{I})^2,$$

where BSA is body surface area.

$$\text{GFR} = \frac{\text{fractional uptake (}\!^{[99m}Tc\!)\text{DTPA}}{9.75621 - 6.19843} \times 100.$$
TABLE 1
Correlations Observed in Renal Function Determination

<table>
<thead>
<tr>
<th>Global renal function</th>
<th>% Uptake $^{99m}$Tc-DTPA versus C inulin (2)</th>
<th>y = $a + bx$</th>
<th>s.e.e.</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24 y = $-6.5173 + 8.9885 X$</td>
<td>17.2538</td>
<td>0.9073</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>35 y = $-6.1984 + 9.7562 X$</td>
<td>8.6245</td>
<td>0.9436</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C creatinine versus % uptake $^{99m}$Tc-DTPE (Gates)</th>
<th>23 y = $70.6244 + 1.0453 X$</th>
<th>94.7292</th>
<th>0.7887</th>
<th>&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative uptake $^{131}$I-hippuran versus CAPH (1)</td>
<td>23 y = $65.4171 + 19.6001 X$</td>
<td>104.4201</td>
<td>0.7418</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% Uptake $^{131}$I-hippuran versus CPATH (2)</td>
<td>23 y = $69.5435 + 16.4140 X$</td>
<td>100.6401</td>
<td>0.7631</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% Uptake $^{131}$I-hippuran versus CPATH (3)</td>
<td>23 y = $58.1454 + 17.0499 X$</td>
<td>92.2031</td>
<td>0.8058</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Separate renal function</th>
<th>% Uptake $^{99m}$Tc-DTPA versus inulin (2)</th>
<th>y = $-14.4861 + 11.0301 X$</th>
<th>23.6742</th>
<th>0.8622</th>
<th>&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative uptake $^{131}$I-hippuran versus CPATH (1)</td>
<td>9 y = $4.2586 + 1.7008 X$</td>
<td>97.6284</td>
<td>0.8493</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>% Uptake $^{131}$I-hippuran versus CPATH (2)</td>
<td>9 y = $-69.1017 + 37.1564 X$</td>
<td>96.0315</td>
<td>0.8546</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>% Uptake $^{131}$I-hippuran versus CPATH (3)</td>
<td>9 y = $-62.0351 + 32.6569 X$</td>
<td>86.8472</td>
<td>0.8829</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

A good correlation was observed between inulin clearance and GFR calculated by Gates' formula, with an r value of 0.88 ($y = 0.85 x +10.38$, s.e.e. = 19.01) for global and an r value of 0.91 ($y = 0.66 x + 15.89$, s.e.e. = 14.47) for unilateral renal function. The calculated line is not significantly different from the line of identity. The correlation between PAH clearance and ERPF measured by Schlegel's formula was also good ($y = 0.84, y = 0.88 x + 38.25$, s.e.e. = 87.15, for global, and $r = 0.86, y = 0.66 x + 47.28$, s.e.e. = 72.71 for separate renal function, respectively).

The mean inulin clearance was 52.74 ± 8.36 for global and 36.28 ± 15.39 ml/min for separate renal function. The mean isotopic GFR was 56.17 ± 33.37 ml/min for global and 131.5 ± 53.47 ml/min for separate renal function. The mean isotopic ERPF was 251.1 ± 34.39 ml/min and 151.3 ± 47.13 ml/min, respectively.

![Fractional Uptake $^{99m}$Tc-DTPA (2-3) vs Inulin Clearance (ml/min)](image-url)
The reproducibility of isotopic GFR \((r = 0.91, y = 0.82x + 6.93, \text{s.e.e.} = 7.38, t \text{ paired} 0.775, 19 \text{ df}, \text{N.S.})\) and ERPF \((r = 0.95, y = 0.90x + 15.9, \text{s.e.e.} = 20.4, t \text{ paired} 0.416, \text{df} 19, \text{N.S.})\) determination is excellent. The calculated lines are not significantly different from the line of identity. Finally, the reproducibility of the processing (kidney outlining and creation of semilunar background region of interest) by successive analysis of renal function 3 mo apart is good \((r = 0.99, y = 0.90x + 5.15, \text{s.e.e.} = 2.48, t \text{ paired} -1.51, 19 \text{ df}, \text{N.S.} \text{ for GFR and} r = 0.96, y = 0.92x + 19.76, \text{s.e.e.} = 17.85, t \text{ paired} -1.25, 19 \text{ df}, \text{N.S. for ERPF). The isotopic estimation of the filtration fraction (GFR/ERPF) is also reproducible and independent of the observer determination (Table 3). The means and standard error of the means of these determinations are given in Table 3.

**DISCUSSION**

Although in experimental physiology, the quantitative measurement of renal function using inulin for GFR and PAH for ERPF does not raise serious problems, this is not the case in clinical practice. The various difficulties in performing clearance determination in humans are well known, and the technique is so time-consuming, that only specialized centers can utilize them routinely. Indeed, inulin, which fulfills all the requirements proposed by Smith (15) for the measurement of GFR, is not an endogenous substance and necessitates intravenous infusion with repeated urine collections and blood sampling. PAH, commonly used in the measurement of ERPF and considered to be the "classical" noninvasive reference, compared with A-V catheterization, unfortunately has the same disadvantages as inulin.

The clearance of endogenous creatinine, very commonly used in clinical practice, may under- or overestimate renal function depending on the level of this function. Both a secretory (2) and a reabsorptive mechanism (16) have been described for creatinine. For these reasons and because of frequently incomplete urine collection, it is generally felt that creatinine clearance is not satisfactory for the correct estimation of GFR.

In vitro isotopic methods for evaluating GFR (17–20) and ERPF (21–23) have been described by many investigators. The most widely used single injection methods are: the two compartments method (17–18) for GFR and (22) for ERPF that requires multiple blood sampling; the one compartment "slope intercept" method (18,19) for GFR and (21) for ERPF with two delayed blood collections, and the simplified method proposed by Tauxe et al. (23) and Russell et al. (20), which correlates the plasma volume of distribution of

**TABLE 2**

| Influence of Kidney Depth on the Correlations Observed in Renal Function Determination |
|----------------------------------|-------|-----------|-----|--------|
| % Uptake \(^{99m}Tc\)DTPA versus C inulin (Tonnesen) 15 | \(y = -11.4180 + 9.2934x\) | 20.5152 | 0.8825 | <0.001 |
| % Uptake \(^{99m}Tc\)DTPA versus C inulin (measured) 15 | \(y = -21.0380 + 8.2626x\) | 23.7716 | 0.8385 | <0.001 |

\(y = \text{GFR or ERPF.}\)

\(X = \% \text{ Uptake of the isotope injected into the kidneys.}\)
the injected dose at a given time to the clearances. These methods are easier to perform than standard clearance techniques with continuous infusion, but unless ureteral catheterization or simultaneous in vivo determination by imaging of the relative kidney uptake are performed, they measure only global renal function. The measurement of separated renal function is important in many clinical situations, such as unilateral pyelonephritis with renal atrophy, unilateral congenital hypoplasia, or renovascular hypertension, and can be performed by an imaging in vivo isotopic method. Most of the isotopic techniques that measure differential in vivo renal function (24–34) for instance Bianchi’s stop flow (30) and Piepsz methods (28), require blood and/or urine collections. Furthermore, Bianchi’s technique (30) requires separate determination of global and separated renal function and the use of a technique of external compression to stop the flow of urine between the kidney and the bladder. Piepsz et al.’s (28) technique also is based on a theoretically sound foundation, although they use several assumptions that are difficult to fulfill. The authors recognize that the precordial curve cannot entirely be equated to a plasma disappearance curve. Furthermore, the intrarenal vascular activity cannot be entirely corrected for by the standard background correction techniques and are responsible for errors in the calculation. In contrast, due to the empiric nature of Gates’ (9) and Schlegel’s (6) methods (as discussed below), the intrarenal vascular activity does not have to be excluded entirely but is accounted for in the regression analysis. The vascular activity unrelated to filtration or secretion phenomena [in part caused by the small fraction of tracer bound to plasma proteins (35)] probably explain the positive intercept in all the relations between the fractional uptake and the reference clearance data.

The techniques devised by Schlegel et al. (6) and Gates (9) for the determination of global and unilateral GFR and ERPF require no blood or urine sampling. Although theoretically less accurate, these methods are gaining popularity because of their ease and rapidity. These empiric techniques are based on the direct scintigraphic determination of the fractional radionuclide accumulation within each kidney, occurring at a specified time interval after radionuclide renal appearance (2–3 min for Gates, 1–2 min for Schlegel et al.). The tracers used are [99mTc]DTPA and 131I-labeled sodium iodo-hippurate. These authors validated their techniques with creatinine (9) and PAH (6) clearances only for global renal function [except for two patients with nephrostomy in Brodkey et al.’s study (8)]. As already mentioned, the 24-hr creatinine clearance is not the most precise way of determining GFR. Comparison with isotopic measurements performed at different

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times and in different positions is also difficult. Moreover, the hydration of these patients was different during creatinine, PAH clearances, and scintigraphic determinations. The role of diurnal rhythm, position, and especially hydration on renal function is well known (36) and need not be discussed here. It was important in our opinion, therefore, to validate simultaneously and under similar hydration conditions these now widely used isotopic techniques against the admitted references, to reevaluate the s.e.e. and the factors contributing to data dispersion, and to provide an easier formula for ERPF measurement that correlates linearly the fractional uptake of [131I]hippuran to PAH clearance in both global and unilateral renal function (because the original formula would not allow the use of [123I]hippuran). A positive correlation between global GFR measured by isotopic methods and fractional uptake [99mTc]DTPA by the kidneys already has been shown by other authors (37—39).

The results we observed in this study also show good correlation between inulin clearance and fractional uptake of [99mTc]DTPA. The regression equation that correlates the abovementioned parameters (Table 1) is comparable with the one given by Gates for global renal function (9). A smaller correlation and a larger s.e.e. were shown in this study, despite simultaneous measurement of isotopic GFR and inulin clearance. A regression equation is also given for unilateral renal function. In these patients the adequacy of the kidney, and especially background regions of interest determination, can be assessed without the compounding influence from the other kidney.

We showed a good correlation between the fractional uptake of [131I]hippuran and PAH clearance. A simple linear regression equation that correlates the fractional uptake of [131I]hippuran to PAH clearance is given for both global and unilateral renal function. The rather large s.e.e. we observed is in accordance with the results of Fine et al. (40) in the absence of blood sampling.

Despite these s.e.e., the very good reproducibility of both isotopic techniques and the good reproducibility of the observer determinations of GFR and ERPF (Table 3) render these techniques of renal function measurement useful in clinical practice.

Several factors interfere with the fractional uptake determination and calculation of the renal clearances. Recently, Ginjaume et al. (41) found no correlation between global GFR measured by the one injection-two blood samples technique of Brochner-Mortensen (42) and [99mTc]DTPA fractional uptake, concluding that the Gates method for GFR determination in both adults and children was unreliable. For this author (41), kidney depth, calculated by Tonnesen's formula (14), is the major source of error. By contrast, in our study even though echographic evaluation of renal depth could be more precise, good correlation was observed in the adults studied between inulin clearance and the fractional uptake of [99mTc]DTPA by the kidneys already has been shown by other authors (37—39).

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et al.'s (41) study not enough information is provided concerning the study protocol and the subjects tested, to critically assess their results.

In conclusion, on the basis of our results, we suggest that the determination of the fractional uptake of $[^{99m}Tc]$DTPA and $[^{131}I]$hippuran between 2 and 3 min allows in adults with normal cardiac output and vascular volume good and mainly reproducible determination of global and especially of unilateral kidney function with great rapidity and simplicity, rendering this technique useful in clinical practice, and suitable to critically assess their results.

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