Three-Hour Volume of Distribution Method: An Accurate Simplified Method of Glomerular Filtration Rate Measurement

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Eight hundred studies of glomerular filtration rate (GFR) measurements were performed by the standard slope-intercept method using [^{99m}Tc]DTPA and results were compared with a simultaneous measurement of the 3-hr tracer volume of distribution. A wide range of human renal function was studied and a nonlinear relationship between GFR and the volume of distribution resulted with an excellent correlation ($r = 0.989$). Agreement between the two measured parameters was not constant for all levels of renal function with the greatest accuracy being found for GFR = 60 to 100 ml/min.

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There have been a large number of radionuclide methods described for the measurement of glomerular filtration rate (GFR) in the relentless search for more simplified techniques. Constant infusion has been replaced by single injection, urine sampling has been dispensed with, multiple blood sampling has been modified to two blood samples or less and, even more recently, bloodless techniques have been described. There has been increasing reliance on assumptions and approximations with each simplification of the original methods. In a recent comparative assessment of the simplified techniques performed simultaneously in 50 patients, we found that in addition to the two-sample, slope-intercept method, only the single-injection, volume of distribution method could be recommended as having sufficient accuracy for clinical use (*1*).

Three hours following the injection of a glomerularly filtered agent technetium-99m diethylenetriaminepentaacetic acid ([^{99m}Tc]DTPA), a single blood sample is obtained and the administered dose divided by the plasma concentration at 3 hr to give an apparent volume of distribution. From this value, the GFR is calculated using an experimentally obtained regression equation.

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In this paper, we describe our experience and results in 800 studies of the volume of distribution method when compared with our reference method of [^{99m}Tc]DTPA renal clearance.

PATIENTS AND METHODS

A retrospective examination was made of total renal function studies from the previous 3 years. This yielded a total of 800 GFR measurements of which 150 involved renal transplant patients.

Technetium-99m DTPA was freshly prepared from [^{99m}Tc]pertechnetate using a generator* and a lyophilized stannous DTPA kit† according to the manufacturers' instructions. The [^{99m}Tc]DTPA had an in vitro protein binding of <5% and had previously been found suitable as a GFR agent. The patient dose of [^{99m}Tc]DTPA 1.5mCi (~60 MBq) was accurately assayed in a dose calibrator‡ which was calibrated daily for sensitivity against a reference isotope source. The net activity injected intravenously to the patient was determined by assaying the dose in a plastic syringe before and after injection together with any extension tubing. The injection site was imaged with a gamma camera onto Polaroid film in order to verify that no extravasation of the injectate had occurred and the time of injection noted. Venous blood samples were drawn from the contralateral arm into heparinized specimen tubes at 2 and 3 hr postinjection, with exact times being noted.

The blood samples were centrifuged (10 min at 1,000 *g*)

and duplicate 1,000-μl aliquots of plasma were pipetted (using a calibrated pipette and disposable tips) into disposable plastic counting tubes. The plasma samples were assayed for ^{99m}Tc activity in an automated well counter (LKB Ultrogamma 1280) for a sufficient time to obtain 0.5% counting precision. The sensitivity of the well counter with respect to ^{99m}Tc activity, as measured in the dose calibrator, was determined by a standard dilution technique. The long-term sensitivity of the well counter was checked on each occasion of use by counting a calibrated cobalt-57 source (calibrated at the time of the standard dilution above).

The ^{99m}Tc activities were background and decay corrected to a common time and converted to compatible units. The plasma clearance of ^{99m}Tc was calculated (assuming monoexponential kinetics) from the formula:

$$\text{clearance (ml/min)} = \frac{I\lambda}{A_0}, \quad (1)$$

where I = injected activity, λ = exponential slope of the clearance curve, A_0 = initial plasma tracer concentration by extrapolation of the clearance curve. The 3-hr volume of distribution (V_3) was calculated from the formula:

$$V_3\ (l) = \frac{I}{A_3}, \quad (2)$$

where I = injected activity (MBq), A_3 = 3-hr plasma tracer concentration (MBq/l). The results were subject to a least squares regression analysis to produce a regression equation.

RESULTS

Figure 1A displays the 800 measurements as a plot of the plasma clearance of tracer (ml/min) against the 3-hr volume of distribution (l) and we were surprised to find an uneven scatter of the results. There appears to be a boundary condition such that for each volume of distribution there exists a maximum clearance value. There is also less scatter of results over the range of clearance values 60 to 100 ml/min. Figure 1B shows the lines of the boundary condition, the regression equation and Constable's original equation superimposed on the results. The equation of the boundary condition from the graph is:

$$\text{clearance} = 2.05\ V_3, \quad (3)$$

and for the line of best fit by least squares regression analysis is

$$\text{clearance} = 31.94(V_3 + 16.92)^{½} - 161.7, \quad (4)$$

where the regression coefficient r = 0.989. Quadratic and cubic polynomial expressions could also be fitted to the data, however, least squares analysis showed that these expressions offered no significant improvement on the square root function of Eq. (4). Extrapolation of the quadratic and cubic equations soon produce misleading results whereas the square root function continues to be meaningful—thus the preference for the equation shown.

A rigorous statistical analysis necessary to provide confidence intervals when the data is so clearly not normally distributed is beyond the scope of this publication. Instead the raw data is presented (Fig. 1A) to allow a visual inspection of the data spread.

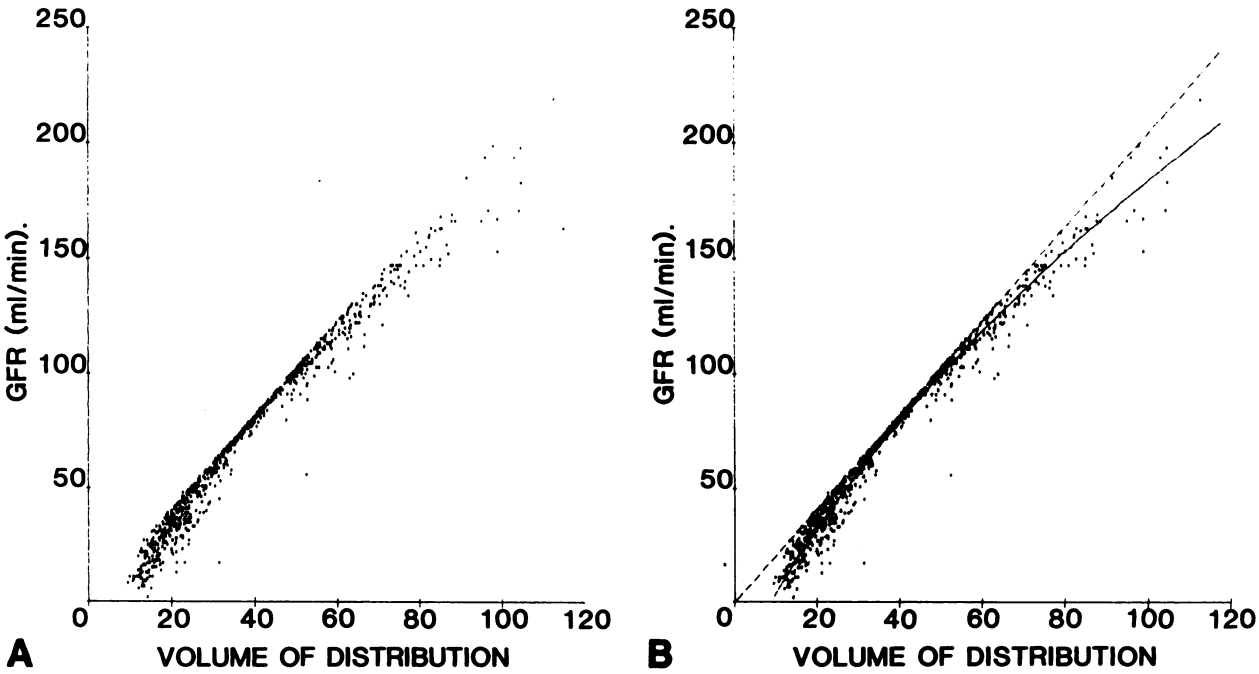

FIGURE 1

A: GFR measured from two plasma samples and the slope-intercept method versus the 3-hr volume of distribution for 800 measurements. B: Data as for Figure 1A with curves. (—) Regression line. GFR = $31.94(V_3 + 16.92)^{½} - 161.7$; (· · ·) Constable curve. GFR = $24.5(V_3 - 6.2)^{½} - 67$; (- - -) Boundary condition. GFR = $2.05\ V_3$.

The equation relating the plasma clearance rate to the volume of distribution originally proposed by Constable and based on chromium-51 ethylenediaminetetraacetic acid ([^{51}Cr]EDTA) data, appeared to slightly underestimate renal function in our study.

DISCUSSION

Chelates of radioactive atoms are today the most widely used compounds for measurement of GFR. Chromium-51 EDTA (*2*) is the best known of these radiopharmaceuticals, but [^{99m}Tc]DTPA has also been shown to be a useful GFR agent (*3*) if attention is paid to the source of the DTPA and the extent of protein binding (*4*). We have previously demonstrated the reliability of locally prepared [^{99m}Tc]DTPA† by comparing [^{99m}Tc]DTPA clearance with that of [^{51}Cr]EDTA clearance in both rabbits and normal human volunteers. No significant difference was found between the GFR calculated using these two agents (*5*).

The reference value for [^{99m}Tc]DTPA clearance was calculated in this study from the single exponential derived from the results of blood samples at 2 and 3 hr after injection without adjustment for the patient's height and weight. No other corrections were made. It has previously been shown (*6*) by external monitoring of plasma clearance with a cadmium telluride detector that clearance between 2 and 3 hr is a single exponential, except in cases of very severely reduced total function. Compared with more frequent blood sampling and calculation by a double exponential formula, this method, has been shown to give a slight overestimation of ~15% (*7*).

Several publications have already reported empirical relationships involving only GFR and apparent volumes of distribution of the radiotracer at some fixed time after injection (*8,9*). Other publications have reported the errors involved in the single-sample method and the two-sample monoexponential method when compared with a multisample biexponential reference method (*10,11*). They indicated the very close agreement between the two-sample monoexponential method and the more detailed biexponential method. However, owing to their small sample sizes (49 studies and 40 patients, respectively), normal scatter was assumed for their results. A larger study has more recently found nonuniform scatter of results when comparing the volume of distribution with renal function (*12*).

By assuming that plasma clearance of [^{99m}Tc]DTPA is monoexponential by the time that blood samples are taken at 3 hr postinjection, i.e.,

$$A_3 = A_0 e^{-3\lambda} \quad \text{and also} \quad \lambda = \ln 2/T_{½} \qquad (5)$$

and by combining Eq. (1) and (2) it can be shown that:

$$\text{clearance (l/hr)} = \lambda(e^{-3\lambda})V_3$$

or in more conventional units:

$$\text{clearance (ml/min)} = \frac{1{,}000\ \lambda(e^{-3\lambda})V_3}{60}, \qquad (6)$$

whereas before λ = exponential slope of clearance curve (hr^{-1}) and V_3 = 3-hr volume of distribution (l). Equation (6) shows that the clearance is not solely a function of the volume of distribution. The term $\frac{1{,}000\ \lambda(e^{-3\lambda})}{60}$ reaches a maximum value of 2.044 when λ = ⅓ hr^{-1} giving a linear equation for the boundary condition of slope 2.044 and passing through the origin in good agreement with the experimental result of slope 2.05 and origin intercept. Table 1 lists calculated values of this term for varying values of the biologic clearance half-times of [^{99m}Tc]DTPA found in man and shows that this term is approximately constant over the range of $T_{½}$ values from 90 min to 175 min. In our experience, this typically occurs in patients with clearance rates of 60 ml/min to 130 ml/min. Hence, the often reported observation (*8,10–13*) that for the greatest accuracy by the single sample technique, the optimum time of sampling is 3 hr postinjection for typical patient renal function. Watson (*14*) (1986) has also observed in 22 patients the near constancy of a term similar to that described above.

As renal function progresses below 60 ml/min or above 130 ml/min in our experience, it becomes less and less probable that the biologic $T_{½}$ will lie in the range 90–175 min causing the results to be scattered further and further from the linear boundary condition. Equation (6) then adequately explains the existence of the observed boundary condition and the clustering of results towards the boundary as the biologic $T_{½}$ approaches 125 min (i.e., λ = ⅓ hr^{-1}).

Similarly it can be shown that a single blood sample at 2 hr postinjection will provide the greatest accuracy

TABLE 1
Typical Biologic Clearance Half-Times of [^{99m}Tc]DTPA in Man and Corresponding Value of Function $f(T_{½}) = \frac{1{,}000\ \lambda\ (e^{-3\lambda})}{60}$

$T_{½}$ (min)	f ($T_{½}$)
50	1.14
60	1.44
70	1.67
80	1.82
90	1.93
100	1.99
125	2.044
150	2.01
175	1.94
200	1.86
300	1.52
500	1.08
1,000	0.61

when the biologic half-time is 83 min (which, in our experience, most frequently occurs in patients with clearance rates of ~150 ml/min) whereas the single sample would need to be delayed until 6 hr postinjection to provide the greatest accuracy in patients with biologic half-times of 250 min which often accompany clearance rates of ~20 ml/min. A single 3-hr sample can provide good accuracy by the volume of distribution method when the renal function is > ~50 ml/min but when precision is required at lower levels of renal function (such as for monitoring the function of a kidney transplant or the residual function of dialysis patients) rather than using a very delayed single sample, the more expedient two-sample-slope intercept method is to be preferred.

NOTES

* Mallinckrodt, Inc., St. Louis, MO.
† Pentastan, Australian Atomic Energy Commission.
‡ CRC10RB, Capentec, Inc., Ramsey, NJ.

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REFERENCES

1. Fawdry RM, Gruenewald SM, Collins LT, et al. Comparative assessment of techniques for estimation of glomerular filtration rate with 99mTc-DTPA. *Eur J Nucl Med* 1985; 11:7–12.
2. Stacy BD, Thorburn GD. Chromium-51 ethylene diaminetetraacetate for estimation of glomerular filtration rate. *Science* 1966; 152:1076–1077.
3. Klopper JF, Hauser W, Atkins HL, et al. Evaluation of 99mTc-DTPA for the measurement of glomerular filtration rate. *J Nucl Med* 1972; 13:107–110.
4. Carlsen JE, Moller ML, Lund JO, et al. Comparison of four commercial 99mTc-(Sn)DTPA preparations used for the measurement of glomerular filtration rate. *J Nucl Med* 1980; 21:126–129.
5. McHugh M, Carrick D. Validation of 99mTc-DTPA as an agent for measurement of GFR. *Aust NZJ Med* 1982; 12:660.
6. Rossing N, Bojsen J, Fredericksen PL. The glomerular filtration rate determined with 99mTc-DTPA and a portable cadmium telluride detector. *Scand J Clin Lab Invest* 1978; 38:23–28.
7. Rootwelt K, Falch D, Sjokvist R. Determination of glomerular filtration rate by analysis of capillary blood after single shot injection of 99mTc-DTPA. *Eur J Nucl Med* 1980; 5:97–102.
8. Fisher M, Veall N. Glomerular filtration rate estimate based on a single blood sample. *Br Med J* 1975; 3:542.
9. Constable AR, Hussein MM, Albrecht MP, et al. Single sample estimates of renal clearances. *J Urol* 1979; 51:84–87.
10. Smart R, Trew P, Burke J, et al. Simplified estimation of glomerular filtration rate and effective renal plasma flow. *Eur J Nucl Med* 1981; 6:249–253.
11. Russell CD, Bischoff PG, Kontzen FN, et al. Measurement of glomerular filtration rate: Single injection plasma clearance method without urine collection. *J Nucl Med* 1985; 26:1243–1247.
12. Tauxe WN. Glomerular filtration. In: Tauxe WN, Dubovsky EV, eds. Nuclear medicine in clinical urology and nephrology. Norwalk, CT: Appleton-Century-Crofts, 1985:61–76.
13. Morgan WD, Birks JL, Sivyer A, et al. An efficient technique for the simultaneous estimation of GFR and ERPF involving a single injection and two blood samples. *Int J Nucl Med Biol* 1977; 4:79–83.
14. Watson WS. Glomerular filtration rate-calculation from blood samples alone [Lett]. *Eur J Nucl Med* 1986; 11:373–374.