Estimation of Extracellular Fluid Volume from Plasma Clearance on Technetium-99m DTPA by a Single-Injection, Two-Sample Method

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A simple method is presented for estimating extracellular fluid volume from the plasma clearance of [^{99m}Tc]DTPA or [^{169}Yb]DTPA. Two plasma samples are required, at 1 and 3 hr, following a single intravenous injection. (The same plasma samples can be used for measurement of glomerular filtration rate.) Using the complete plasma clearance curve as a reference (eight samples at 10 to 240 min), the error of the two-sample method in 40 patients was 1.5 l for [^{99m}Tc]DTPA, 2.1 l for [^{169}Yb]DTPA (residual standard deviation).

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In our clinic, glomerular filtration rate (GFR) measurement is used chiefly as a research tool. For routine clinical measurement of renal function, we measure instead the effective renal plasma flow (ERPF), which requires less time (*1*). GFR is estimated from two plasma samples obtained 1 and 3 hr after a single injection of technetium-99m diethylenetriaminepentaacetic acid ([^{99m}Tc]DTPA) (*2*). Investigators using this method have asked whether we could simultaneously estimate extracellular fluid volume (ECV) using methods similar to those of Brøchner–Mortensen (*3*). Here we present such a method. Unlike the method of Brøchner-Mortensen, sample collection is completed in 3 hr and only two samples are required.

METHODS

Plasma clearance curves corrected for protein binding were obtained in a previous study that was described in detail elsewhere (*2*). Forty patients were studied, having a range of GFR from essentially 0 to 150 ml/min. Briefly, eight plasma samples were drawn from 10 to 240 min after simultaneous injection of [^{99m}Tc]DTPA and ytterbium-169 DTPA and counted separately for ^{99m}Tc and ^{169}Yb. In the case of [^{99m}Tc]DTPA, the counts were corrected for binding by plasma proteins. Forty patients were studied, having a range of GFR from essentially 0 to 150 ml/min.

Data Processing

Reference values were obtained for GFR and ECV by fitting the 8-point plasma clearance curves to the open linear two-compartment model of Sapirstein (*4*). In that model, Compartment 1 was the compartment that included blood plasma and from which glomerular filtration occurs, and Compartment 2 represented the less accessible portion of the creatinine space. Compartment 2 was assumed to exchange tracer with Compartment 1 at a rate directly proportional to the concentration of tracer in each compartment, with proportionality constant alpha. V_1 represented the volume of Compartment 1 and V_2 the volume of Compartment 2.

A simpler estimate of ECV was also obtained, using only the two points at 1 and 3 hr. The method was analogous to that for GFR (*2*). Of the four parameters describing the two-exponential clearance curve, two (ECV and GFR) were regarded as unknowns and found by Newton's method, while "average" values (chosen for best fit to total group of 40 patients) were used for the other two parameters (α/V_1, α/V_2). A standard Gauss-Newton method was used for nonlinear curve fitting in which a subroutine representing the two compartment model served as the "curve" to be fitted.

Some authors have expressed compartment volumes in liters of plasma, while others have used liters of water. The small correction (0.94 liter water/liter plasma) is rarely important. In this paper, liters of plasma are used.

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Corrections For Donnan Effect and Plasma Protein Binding

Estimated corrections for the Donnan effect and for protein binding almost exactly cancelled each other and were therefore omitted. Technetium-99m DTPA has an ionic charge of −2 at physiologic pH (*5*). Its negative charge is repelled by the negative charge on plasma proteins so that [^{99m}Tc]DTPA tends to concentrate on the opposite side of a semipermeable membrane. The Donnan factor for plasma is 1.05^z, where z is the ionic charge (*6*). Thus, the concentration of [^{99m}Tc]DTPA in ultrafiltrate (or in glomerular filtrate or in interstitial fluid) is 10% higher than in plasma.

This correction was overlooked in our previous report (*7*), but we have recalculated our data with appropriate corrections. The bound fraction measured by ultrafiltration is 14.4 ± 0.7%; measured by gel filtration, 3.8 ± 0.5%. Gel filtration disrupts binding equilibrium and measures irreversibly bound material, while ultrafiltration preserves equilibrium and measures total (reversible + irreversible) binding. The difference between the two numbers, 10.5 ± 0.9%, thus represents the reversibly bound fraction. This reversible binding of [^{99m}Tc]DTPA has previously been unrecognized. However, it is almost identical to that reported for a related agent, chromium-51 (^{51}Cr) EDTA (*8*). If the net charge on [^{169}Yb]DTPA is assumed to be −2, as stated without documentation in the manufacturer's package insert, then our data (*7*) leads to the value of 8.8 ± 0.9% for the reversible binding of [^{169}Yb]DTPA. In both cases, the effect of the Donnan factor, 10% for a dinegative ion, essentially cancels the effect of protein binding.

RESULTS

The computer model proved capable of estimating ECV from two points of the plasma curve, as shown in Figure 1, in which ECV computed from measurements at 1 and 3 hr is plotted against the entire 8-point plasma curve. However, the parameters giving the best estimate of ECV (Table 1) differed slightly from those giving the best estimate of GFR (*2*).

Using the validated computer model as a guideline, we next sought a method for estimating ECV that could be used without a computer. Different formulas could be used by adjusting the constants in each formula to achieve best fit. We assumed, however, that the search could stop as soon as a formula was found with accuracy comparable to the physiologic model used by the computer. While other formulas might work as well, it was unlikely that one would work better, since the best curve fitting methods are generally those based (like the computer model) on *a priori* knowledge of the general form of the curves to be fitted. This strategy led to the following formulas, which had accuracy comparable to the computer model (Table 2).

$$V = 0.81\ V' - 0.056\ F' + 4.1 \quad \text{for [}^{99m}\text{Tc]DTPA}$$
$$V = 0.83\ V' - 0.054\ F' + 3.7 \quad \text{for [}^{169}\text{Yb]DTPA} \qquad (1)$$

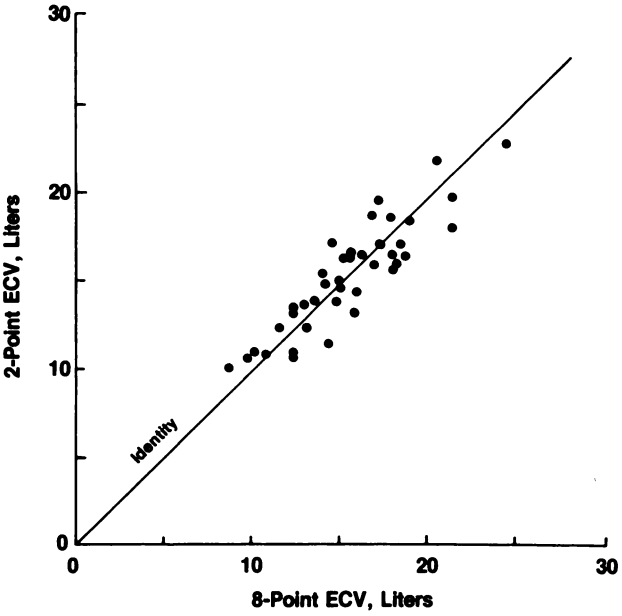

FIGURE 1
Extracellular fluid volume estimated from two plasma samples at 1 and 3 hr versus that calculated from the entire 8-point [^{99m}Tc]DTPA clearance curve. Correlation coefficient = 0.90.

where V is the ECV (l plasma equivalent). V′ and F′ are the volume (l plasma) and glomerular filtration rate (ml plasma/min), respectively, that are calculated from the two data points by assuming a one-compartment model, i.e.,

$$F' = \frac{D \ln(P_1/P_2)}{T_2 - T_1} \exp\left[\frac{T_1 \ln P_2 - T_2 \ln P_1}{T_2 - T_1}\right] \qquad (2)$$
$$V' = 0.001 \exp\left[\frac{T_1 \ln (P_2/D) - T_2 \ln (P_1/D)}{T_2 - T_1}\right],$$

where D = dose, counts/min; P_1 = plasma activity at time T_1, counts/min-ml; P_2 = plasma activity at time T_2, counts/min-ml. Equations (1) were obtained by linear regression of ECV on F′ and V′. Equation (2) is simply the algebraic counterpart of drawing a straight line between two points on semilog graph paper. Together, these represent a one-compartment model that has been modified by a three-parameter empirical correction.

TABLE 1
Compartment Parameters Giving Best Agreement between Two-Sample ECV (sampled at 1 and 3 hr) and Eight-Sample ECV*

	α/V_1 min^{-1}	α/V_2 min^{-1}
[^{99m}Tc]DTPA	0.032	0.024
[^{169}Yb]DTPA	0.028	0.023

* See Data Processing for definition of parameters.

TABLE 2
Error (l) Introduced by Estimating ECV from Two Samples Instead of Eight Samples*

	Computer model	Equation 1
[^{99m}Tc]DTPA	1.7 ± 0.5	1.4 ± 0.4
[^{169}Yb]DTPA	2.2 ± 0.6	2.1 ± 0.6

* Residual s.d. ± 90% confidence limits, 40 patients, confidence limits from χ^2 distribution with 38 (computer model) or 37 [Eq. (1)] degrees of freedom.

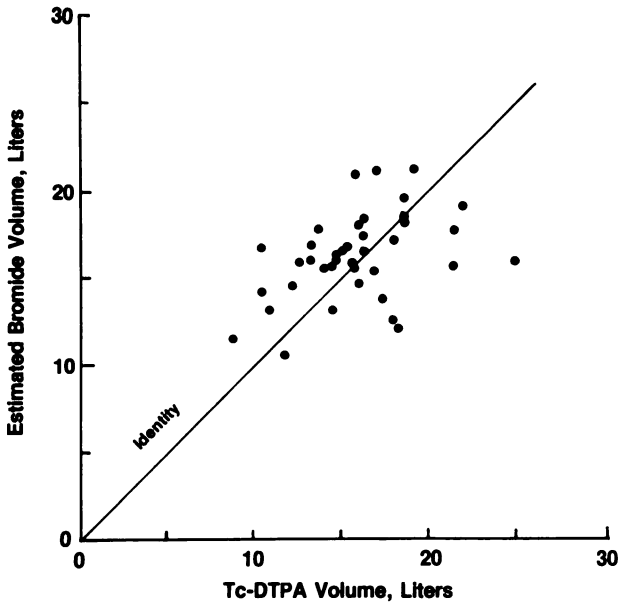

FIGURE 2
Bromide space estimated from patient weight and sex (*9*) versus [^{99m}Tc]DTPA space calculated from 8-point plasma clearance curve. Correlation coefficient = 0.44.

DISCUSSION

In principle, ECV can be measured by any tracer that fails to penetrate the cell wall. This includes some radiopharmaceuticals in routine clinical use, such as [^{99m}Tc]DTPA, as well as the more traditional research agents, such as sulfur-35 sulfate or bromine-82 bromide. Brøchner-Mortensen has employed [^{51}Cr]EDTA (*3*). Penetration of such fluid compartments as cerebrospinal fluid, gastrointestinal contents, cartilage, and so forth, varies from one agent to another so that the calculated volume will depend on the agent used. This corresponds to a conceptual problem. Which, if any, of these compartments should be included in the "true" extracellular space? Inulin appears to have a smaller volume of distribution than other agents so that the inulin space can be regarded either as "true" ECV or at least a lower limit of the "true" ECV. However, most investigators have been willing to expand their concept of ECV to include the space penetrated by agents with which it is easier to work. Radiobromide has been widely used. Figure 2 shows the correlation between the [^{99m}Tc]DTPA volume and the bromide volume estimated from the patient's weight and sex (*9*). As can be seen, the [^{99m}Tc]DTPA volume approximates the bromide volume.

The error in the volume estimates of Table 2 is about twice that reported by Brøchner-Mortensen, who used a formula based on the terminal slope of the clearance curve for [^{51}Cr]EDTA (*3*). We applied the Brøchner-Mortensen formula (with his constants for [^{51}Cr]EDTA) to the terminal slope of our [^{99m}Tc]DTPA clearance curves, but found a root mean square error of 2.4 l in the calculated ECV. With our data, therefore, Eq. (1) gives better results. The reason for this discrepancy is not clear, but it may reflect differences between [^{99m}Tc]DTPA and [^{51}Cr]EDTA. Our data covered almost the same time interval (10–240 min) used by Brøchner-Mortensen (5–240 min), and closely fit the two-compartment model (rms error 1.8% calculated from the pooled intra-run variance for 40 curves).

Two earlier single-injection methods have been used, one based on the terminal slope of the plasma clearance curve (*6*) and the other based on "equilibrium" with correction for excretion (*10*). These methods contain errors that are not widely recognized. The concentration difference between compartments at "equilibrium" leads to error in both methods. There is an additional error in the terminal slope method related to extrapolating to zero time. Application of first order perturbation theory (*11*) to the two-compartment model leads to correction factors for conventional formulas. To obtain true ECV, the ECV measured by the equilibrium method must be multiplied by $1\text{-}A_2\lambda_1/A_1\lambda_2$, where λ_1 and λ_2 are slowest and next slowest respectively of the decay constants in the plasma clearance curve. A_1 and A_2 are the coefficients of the corresponding exponential terms. (This correction is an approximation based on the assumption that λ_1 is much smaller than λ_2.) The error is twice as great for the terminal slope method, the correction factor being $1\text{-}2A_2\lambda_1/A_2\lambda_2$. These corrections do not pertain to the methods of Brøchner-Mortensen or of this paper, which already include an empirical correction.

In conclusion, when GFR is estimated from [^{99m}Tc]DTPA plasma clearance using two plasma samples at 1 and 3 hr, a reasonable estimate of ECV can be obtained from the same data by using Eq. (*1*).

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REFERENCES

1. Dubovsky EV. Comprehensive renal function studies with iodine-131-OIH. In: Tauxe WN, Dubovsky EV, eds. *Nuclear medicine in clinical urology and nephrology.* Norwalk, Connecticut: Appleton-Century-Crofts, 1985:157–169.
2. 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.
3. Brøchner-Mortensen J. A simple single injection method for determination of the extracellular fluid volume. *Scand J Clin Lab Invest* 1980; 40:567–573.
4. Sapirstein LA, Vidt DG, Mandel MJ, et al. Volumes of distribution and clearances of intravenously injected creatinine in the dog. *Am J Physiol* 1955; 181:330–336.
5. Russell CD, Crittenden RC, Cash AG. Determination of net ionic charge on Tc-99m-DTPA and Tc-99m-EDTA by a column ion exchange method. *J Nucl Med* 1980; 21:354–360.
6. Pitts RF. Physiology of the kidney and body fluids. 3rd ed. Chicago: Year Book Medical Publishers, 1974:23–24, 93.
7. Russell CD, Bischoff PG, Rowell KL, et al. Quality control of Tc-99m-DTPA for measurement of glomerular filtration. *J Nucl Med* 1983; 24:722–727.
8. Fogh-Andersen N. Binding of the chromium-ethylenediaminetetraacetic acid complex (Cr-EDTA) to human albumin. *Scand J Clin Lab Invest* 1980; 40:805–808.
9. Moore ED, Olesen KH, McMurrey JD, Parker HV, Ball MR, Boyden CM. The body cell mass and its supporting environment. Philadelphia: W. B. Saunders, 1963:85.
10. Bauer FK. Radioisotope dilution methods: Measurement of body composition. In: Blahd WN, ed. *Nuclear medicine, 2nd Ed.* New York: McGraw-Hill, 1971:574–592.
11. Wilkinson JH. The algebraic eigenvalue problem. Oxford: Clarendon Press, 1965:62–69.