Temporal Behavior of Peripheral Organ Distribution Volume in Mammillary Systems

TO THE EDITOR: We would like to draw attention to two problems encountered in the related papers recently published by Decostre and Salmon in *The Journal of Nuclear Medicine* (*1,2*). The first concerns the description of the peripheral organ distribution volume (PODV) as a monoexponential function of time. The PODV is the ratio of the organ (including its contained plasma, Vo) to plasma activity (P). It has been expressed by many previous authors as a function of the ratio, $\int P(t).\,dt:P(t)$, which also has units of time, and applied to the movement of ^{68}Ga-EDTA into focal cerebral lesions (*3*), ^{99m}Tc-sulphur colloid into the liver and spleen (*4*), ^{99m}Tc-DTPA into the kidney (*5–10*), and ^{99m}Tc-DTPA into the interstitial space (*11,12*).

It can be shown theoretically for bidirectional transport (Michel CC, *personal communication*) that the time course of the ratio organ to plasma activity is dependent on the time course of the plasma curve. It can be seen that over 20 min following injection of ^{99m}Tc-DTPA the plasma curve, based on a region of interest (ROI) over the cardiac blood pool, is clearly biexponential (Fig. 1), and so is the ratio of organ-to-plasma activity, the PODV curve (Fig. 2). Decostre and Salmon (*1*) are mainly concerned with the initial PODV (i.e., Vo), the determination of which is critically dependent on whether a monoexponential or biexponential fit is applied to the PODV curve. Thus, with respect to

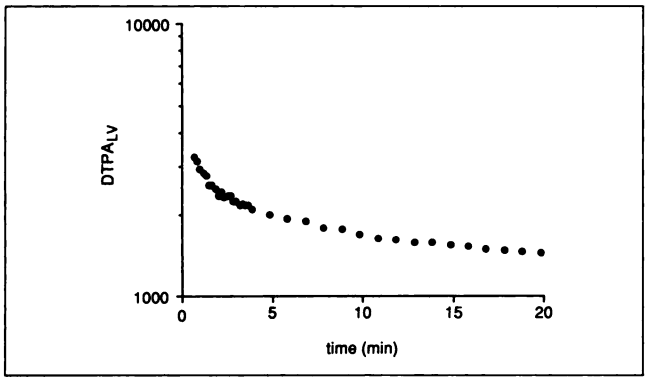

FIGURE 1. The time course of the activity signal recorded over the cardiac blood-pool ROI ($DTPA_{LV}$) is clearly biexponential up to 20 min after injection of ^{99m}Tc-DTPA. (Note logarithmic scale of y-axis.)

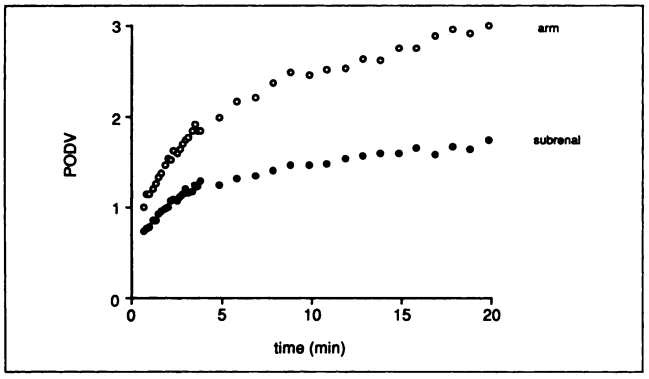

FIGURE 2. The time course of PODV (i.e., tissue-to-blood-pool ratio) also appears biexponential for both the forearm and subrenal ROI.

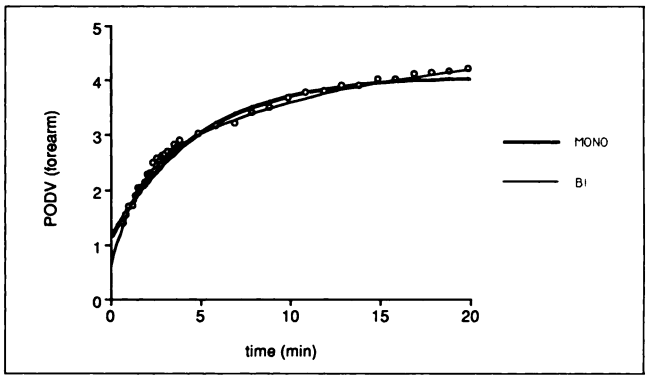

FIGURE 3. Comparison of monoexponential and biexponential fits to PODV curve recorded from a scintillation probe over the forearm and gamma camera over the chest. Vo from the monoexponential fit was twice that from the biexponential fit.

the interstitial space, for which the transport of ^{99m}Tc-DTPA from plasma is bidirectional, Vo obtained from a monoexponential fit in 15 samples taken at random from our own data base was 1.39 (s.e.m. 0.1) that for a biexponential fit when applied to a tissue region below the kidneys (n = 7) and 1.4 (0.11) when applied to the forearm (n = 8) (Fig. 3).

The second point concerns the application of the PODV curve to the measurement of single kidney glomerular filtration rate. Here, Decostre and Salmon (*2*) adopt a two-stage process of background subtraction: first, subtraction of the extravascular component using a sub-renal background ROI and then subtraction of the intravascular component using the PODV approach. The resulting background-corrected renogram is then subjected to the technique originally described by Piepsz et al. (*13*). It is well recognized that the algorithm described by Hawkins et al. (*3*), Rutland (*4,5*), and Rehling et al. (*6*) (based on an abscissa of the ratio of intergrated blood activity-to-blood activity) corrects for intravascular background. However, the principal problem facing correct background subtraction is identifying the extravascular signal [essentially as its GFR equivalent (*8*)] in the renal ROI. Decostre and Salmon (*2*) rather dismissed this and assumed at the outset that the GFR equivalent in the subrenal ROI is the same, per pixel, as in the renal ROI. This is highly unlikely to be the case when one considers that the renal ROI is occupied by a large "bag" (the kidney) containing essentially no extravascular GFR equivalent. In other words, a sub-renal background ROI probably requires scaling down for correct subtraction of the extravascular signal. The technique used by Decostre and Salmon (*2*) to validate their background subtraction procedure elegantly demonstrates the accuracy of the correction for the intravascular signal but in no way addresses the validity of the extravascular subtraction.

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REPLY: The peripheral organ distribution volume (PODV) is indeed an old concept whose temporal behavior was seldom studied in the past (*1,2*).

More recently, it has been studied, as a function of the integrated-plasma-to-plasma concentration ratio, in unidirectional phenomena (*3*), its main advantage being the easy correction for activity in vascular and exchangeable compartments in the region of interest (ROI). Its interest, in metabolic studies with PET, has recently been reviewed by Gjedde and Wong (*4*).

In our first paper (*5*), we mainly were concerned with the kinetic behavior of PODV as a function of the time itself (instead of the integrated-plasma-to-plasma ratio), not only for irreversible but also for reversible processes.

From the study of more than 460 patients, we conclude that, with [^{99m}Tc]pertechnetate or ^{99m}Tc-DTPA, only two simple functions, linear for irreversible transfer or uniexponential for reversible exchange, are actually necessary and sufficient to represent the PODV time behavior, at least in the time limits of our investigations. This may not be valid for other tracers or for longer time intervals.

The second paper (*6*) illustrates a simple application of the PODV approach in a largely used clinical test.

Peters and Bell's first concern is the temporal behavior of PODV for bidirectional tracer exchange.

After the first minute (Figure 3 of reference 5), our ^{99m}Tc-DTPA data clearly show two characteristics, not found in Peters and Bell's Figure 3, but are constant in our DTPA data base: an equilibrium is practically reached at 20 min and the monoexponential fit fully describes the observed data. Figure 4 of reference 5 confirms a similar pattern in 85 thyroid and 166 interstitial fluid studies with pertechnetate.

During the first minute, we agree that a monoexponential fit does not follow the data. A biexponential function fits the whole interval, even the first minute (Fig. 1 and Table 1): the slow exponential component of the biexponential fit in the whole interval is practically identical to the single exponential component of the monoexponential fit limited to the 2–20-min interval.

Unfortunately, in their letter, Peters and Bell give no description of the function they used to fit their data and an accurate comparison with ours is not straightforward.

The second exponential term is very rapid (25 times faster

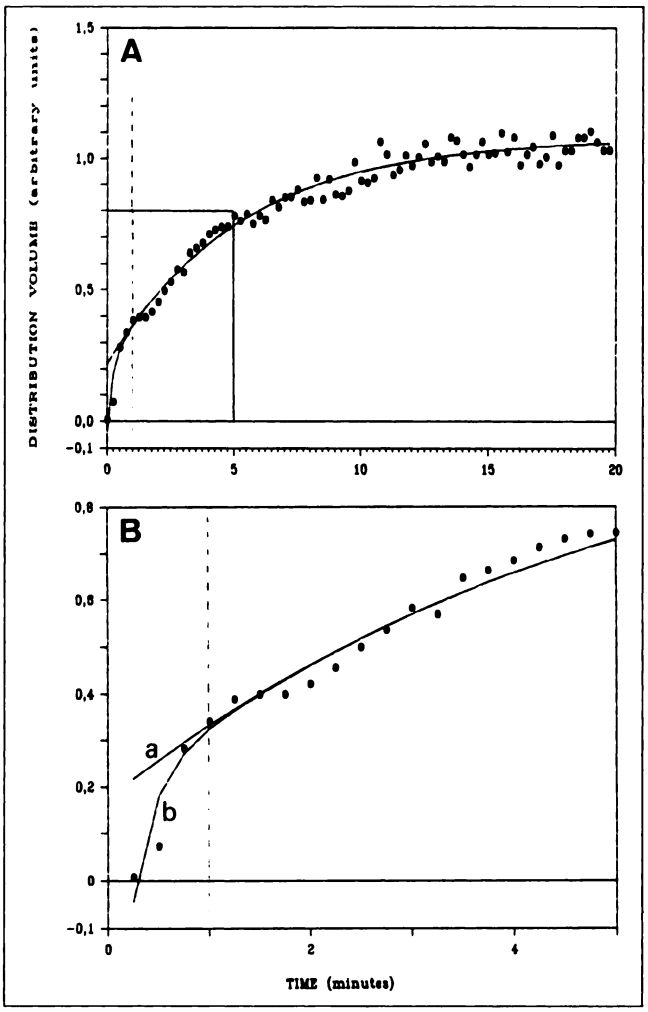

FIGURE 1. Mono-exponential versus bi-exponential fit of PODV in a subrenal ROI with ^{99m}Tc-DTPA. (A) Mono-exponential fit in the 2–20-min interval and bi-exponential fit in the whole interval. (B) Magnification of the first 5 min showing the difference between the fits to be no more significant after the 1st minute (a: mono- and b: bi-exponential).

TABLE 1
Comparison of PODV Monoexponential and Biexponential Fit for Reversible Bi-directional Exchange

Fit	Interval	Vo	V∞	k1	k2	r
Mono	5-80	0.1763	1.077	0.003169	—	0.981
Bi	1-80	−0.7327	1.076	0.003197	0.08354	0.987

Mono: $V(t) = V_o + (V_\infty - V_o)\cdot(1\text{-}e^{-k1t})$.
Bi: $V(t) = V_o + (V_\infty - V_o)\cdot(1 - \frac{1}{2}e^{-k1t} - \frac{1}{2}e^{-kt2})$.