ADDENDUM

Since the preparation of this manuscript, a patient at our Veteran's Hospital with no prior neurological history (similar to our previous patient) unexpectedly suffered amaurosis fugax following dipyridamole administration despite the above precautions. This brings our overall incidence to 2 of 735 studies. Our recognition and response to the incident was facilitated by the concepts discussed above. This second event may suggest that the actual incidence of CVA or TIA is higher than previously suspected and that physician recognition and reporting of such may increase with education and closer patient monitoring.

REFERENCES

1. Whiting JH JR, Datz FL, Gabor FV, Jones SR, Morton KA. Cerebrovascular accident associated with dipyridamole thallium-201 myocardial imaging: case report. *J Nucl Med* 1993;34:128–130.
2. Pounds BK, Moore WH, Ladwig EJ, et al. Dipyridamole thallium imaging. *J Nucl Med Technol* 1990;18:165–175.
3. Depuey EG, Rozanski A. Pharmacological and other nonexercise alternatives to exercise testing to evaluate myocardial perfusion and left ventricular function with radionuclides. *Semin Nucl Med* 1991;21:92–102.
4. Verani MS. Pharmacological stress with adenosine for myocardial perfusion imaging. *Semin Nucl Med* 1991;21:266–272.
5. van Rugge FP, van der Wall EE, Bruschke AVG. New developments in pharmacological stress imaging. *Am Heart J* 1992;124:468–485.

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The Technetium-99m-DTPA Renal Uptake-Plasma Volume Product: A Quantitative Estimation of Glomerular Filtration Rate

TO THE EDITOR: In their recent description of the renal uptake-plasma volume product (RUPV) as a measurement of individual kidney glomerular filtration rate (IKGFR), Zubal and Caride (*1*) assumed that the plasma concentration of ^{99m}Tc-DTPA remained constant for the first 3 min after injection, so that the activity accumulated by the kidneys in this time could be compared with the injected dose, thereby giving IKGFR as a fraction per unit time of the plasma volume. They quoted a paper by Peters et al. (*2*) in support of this assumption. On the contrary, in their paper, Peters et al. (*2*) emphasized the marked fall in the plasma concentration that occurs during this time and quantified its effect, as a background signal, in terms of its "GFR equivalent." This group has also emphasized the high extraction efficiency of small hydrophilic solutes such as ^{99m}Tc-DTPA (MW 492 Daltons) in the capillaries of skin and muscle (*3,4*), which results in the rapidly declining early plasma concentration of ^{99m}Tc-DTPA.

It is very easy to appreciate the substantial early loss of ^{99m}Tc-DTPA from the plasma compartment from any routine multiple sample ^{99m}Tc-DTPA or ^{51}Cr EDTA plasma clearance study by dividing the sum of the zero-time intercepts, A + B, of the conventional bi-exponential clearance curve with the injected dose, which should give the plasma volume. In fact, it gives a value of almost 6 liters, twice the expected value, implying the presence of a fast early exponential which is completed shortly after about 5 min, and which has a zero-time intercept approximately equal to A + B. This early exponential can also be inferred by careful inspection of the relationship of a 5-min sample, in such a multiple sample clearance curve, to the conventional first exponential based on samples from 10 min, which always passes under the 5 min point. By simultaneously measuring plasma volume with radio-iodinated albumin, Neilsen (*5*) was able to identify and quantify an early rapid exponential for the plasma clearance of polyfructosan (a larger molecule than ^{99m}Tc-DTPA), which had an intercept of about 25% of the total zero-time plasma concentration and a rate constant of about 0.5 min^{-1}.

From data derived as part of a previously published study (*6*), I have measured the decrease in left ventricular count rate of ^{99m}Tc-DTPA in comparison with an intravascular reference marker, ^{99m}Tc human serum albumin (HSA). Data were available in nine patients who had relatively normal renal function and who were undergoing routine ^{99m}Tc-DTPA renography for suspected outflow tract obstruction. About 40 MBq of HSA were given 5 min before the DTPA (300 MBq) and dynamic data recorded at a frame rate of 20 sec for HSA and 10 sec for DTPA. The count rate from HSA at 5 min was subtracted from the subsequent count rate to generate the DTPA count rate. Examples of the time-activity curves recorded over the left ventricle are shown in Figure 1. The zero-time count rates were determined by fitting exponential functions to the data recorded between 0 and 4 min. HSA and DTPA count rates both fell between injection and 3 min, the HSA to 0.86 (s.d. 0.037) and the DTPA to 0.63 (s.d. 0.054) of their corresponding zero time values. The mean ratio of these two values at 3 min was 0.74 (s.d. 0.054; range 0.65–0.81), implying a loss of DTPA from the vascular compartment of 26%. This is an underestimation of DTPA lost since, first, a small amount of ^{99m}Tc-HSA may also be lost, and second, even at 3 min, as much as 20% of the count rate over the left ventricle after DTPA may arise from extravascular tracer in the overlying chest wall (*6*). On average, at least 30% of DTPA will have left the vascular compartment by 3 min. This would effectively result in an overestimation of 30% of the dose in Equation 7 of Zubal and Caride's paper (*1*), and a corresponding underestimation of RUPV.

This would explain the regression slopes recorded by Zubal and Caride (*1*) of about 0.7 in their correlations against blood clearance GFR of RUPV based on two of the three conversion equations used for estimating plasma volume from height and weight. Their third conversion equation, which gave a slope close to unity for the regression of RUPV on blood sample GFR, gives estimates of plasma volume some 30% higher than the other two, and clearly higher than the 3 liters for standard man that would be expected from the literature.

The error in RUPV resulting from intravascular loss of DTPA may be systematic, since, unless there is an abnormality of microvascular permeability which might affect the rate of transfer of ^{99m}Tc-DTPA between the intravascular and extravascular compartments in the first few minutes, the early rate of decrease of plasma concentration should be relatively constant (note the range in the nine patients above). Brochner-Mortensen (*7*), when describing the first equation for correcting GFR measurements based on the terminal exponential of the clearance curve (in reality the *third*), pointed out that the area under the *conventional first* exponential (in reality, the *second*) was relatively constant from patient to patient and could therefore be assumed.

Precisely what physiological processes these exponentials represent is by no means clearly understood. Bell et al. (*3*) have shown that the net extraction efficiency of ^{99m}Tc-DTPA from

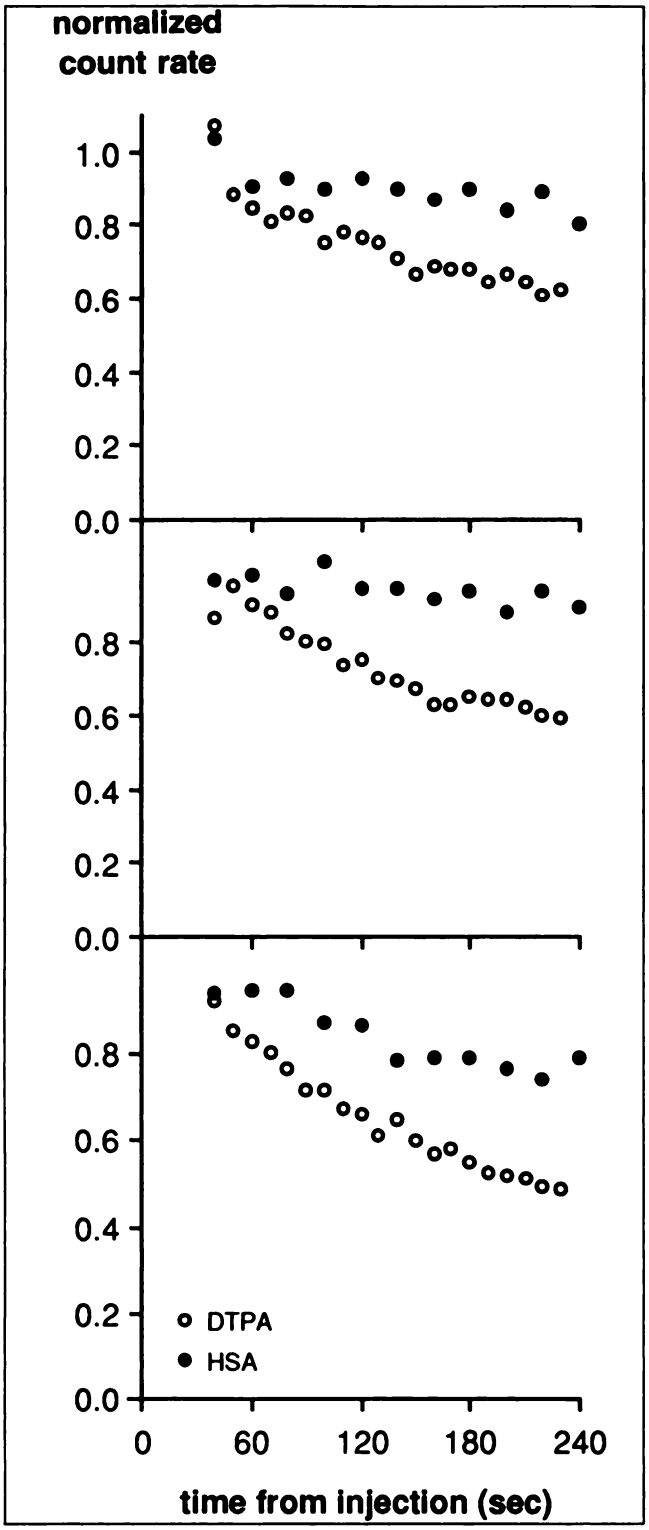

FIGURE 1. Time-activity curves from a region of interest over the left ventricle following injection of ^{99m}Tc-labeled human serum albumin (HSA) and, ^{99m}Tc-DTPA 5 min later. The DTPA count rate has been corrected for the preceeding HSA counts. Both curves have been normalized to their respective extrapolated zero-time count rates. Data from three patients are illustrated.

intravascular to extravascular compartments in the human forearm becomes negative by 15 min. Since skin and muscle must represent a substantial majority of the body tissues equilibrated by the tracer, it seems unlikely that the various exponentials represent different anatomical regions with different rates of equilibration.

Zubal and Caride (*1*) are to be supported in their expression of GFR in terms of a body fluid volume, plasma in their case, in contrast to body weight or surface area. Expressing GFR in terms of a body fluid volume is not only physiological but technically easier when compared with body size. For instance, expressing GFR in terms of extracellular fluid volume requires only the rate constant of the terminal exponential (*8*) and this can even be obtained without blood sampling (*9*). Having obtained their GFR as the RUPV, Zubal and Caride (*1*) left it unscaled for body size. For intersubject comparisons, one wonders how they scale it. Do they use the same height and weight measurements to *renormalize* it in terms of body surface area, the conventional approach, or do they leave it as the GFR per unit of plasma volume?

REFERENCES

1. Zubal IG, Caride VJ. The technetium-99m-DTPA renal uptake-plasma volume product: a quantitative estimation of glomerular filtration rate. *J Nucl Med* 1992;33:1712–1716.
2. Peters AM, Gordon I, Evans K, Todd-Pokropek A. Background in Tc-99m DTPA renography evaluated by the impact of its components on individual kidney glomerular filtration rate. *Nucl Med Commun* 1988;9:545–552.
3. Bell SD, Myers MJ, Peters AM. Noninvasive techniques for the measurement of extraction fraction and permeability surface area product of Tc-99m DTPA in the human forearm. *Phys Med Biol* 1992;37:1759–1771.
4. Peters AM. Measurement of microvascular permeability to small solutes in man: limitations of the technique. *Cardiovasc Res* 1990;24:504–509.
5. Neilsen OM. Extracellular volume, renal clearance and whole body permeability-surface area product in man measured after a single injection of polyfructosan. *Scand J Clin Lab Invest* 1985;45:217–222.
6. Bell SD, Peters AM. Extravascular chest wall technetium-99m diethylene triamine penta-acetic acid: implications for the measurement of renal function during renography. *Eur J Nucl Med* 1991;18:87–90.
7. Brochner-Mortensen J. A simple method for the determination of glomerular filtration rate. *Scand J Clin Lab Invest* 1972;30:271–274.
8. Peters AM. Expressing glomerular filtration rate in terms of extracellular fluid volume. *Nephrol Dial Transplant* 1992;7:205–210.
9. Rossing N, Bojsen J, Frederiksen PL. The glomerular filtration rate determined with Tc-99m DTPA and a portable cadmium telluride detector. *Scand J Clin Lab Invest* 1978;38:23–28.

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REPLY: We agree with Peters that the plasma concentration falls during the first few minutes after injection of ^{99m}Tc-DTPA. As we pointed out in our article (*1*): "It is important to note that the renal uptake of DTPA is calculated when the tracer is not evenly distributed within the intravascular and extravascular spaces while the plasma concentration is continuously changing. While the volume of DTPA distribution at equilibrium is larger than the plasma volume, the volume of distribution in the first 3 min is necessarily much smaller, possibly within the range of the intravascular plasma space. Similar assumptions were used by Peters et al. [. . .] in their analysis of background corrections for the estimation of renal uptake."

We believe that the early drop in radiotracer concentration in the plasma is due to three primary causes: (1) ongoing mixing of the tracer in the plasma; (2) extravascular leakage; and (3) renal filtration. We know from our measurements of normals that just under 10% of the tracer leaves the plasma through filtration by the kidneys over the first 3 min. It should be realized that during the initial seconds we are dealing with a nonequilibrium state where