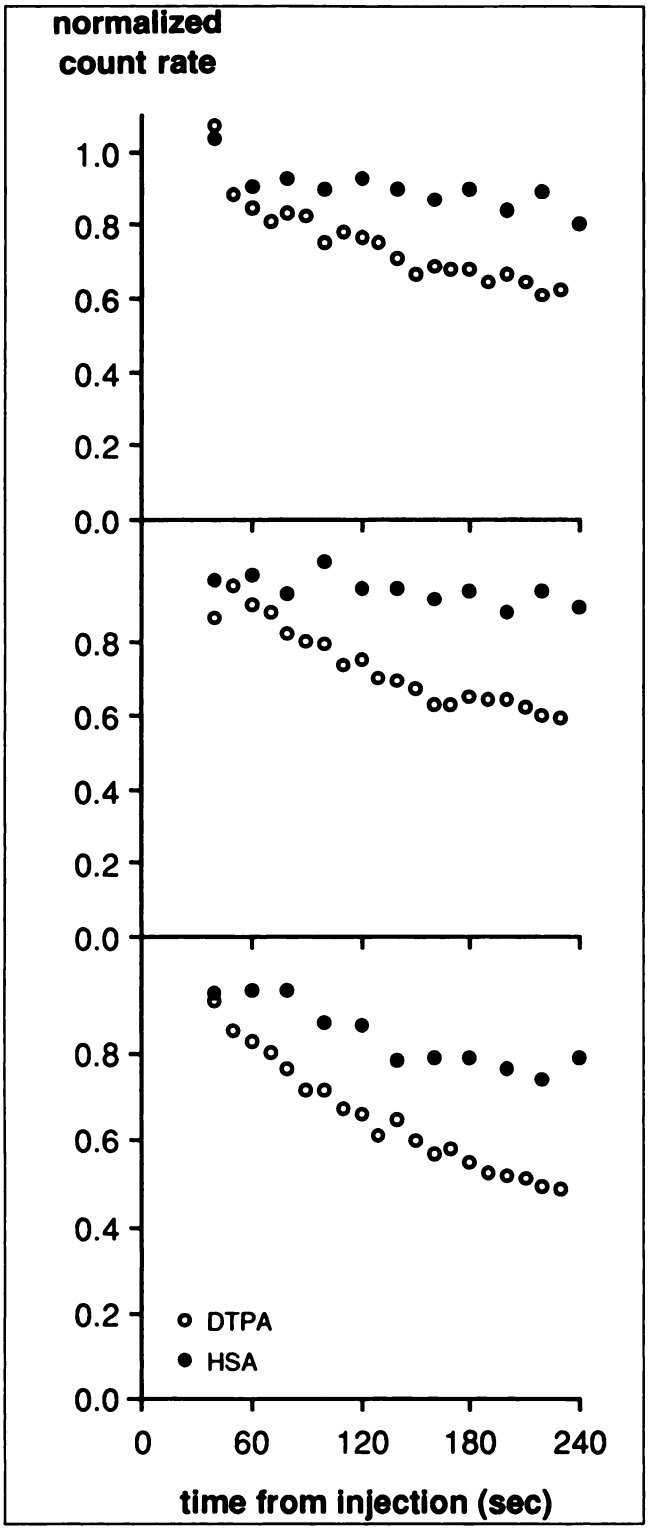

FIGURE 1. Time-activity curves from a region of interest over the left ventricle following injection of ^{99m}Tc-labeled human serum albumin (HSA) and, ^{99m}Tc-DTPA 5 min later. The DTPA count rate has been corrected for the preceeding HSA counts. Both curves have been normalized to their respective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

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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

the kidneys are filtering plasma carrying high specific activities (bolus) of the tracer.

When we take a mathematical viewpoint of the equation:

$$\int Q(t)\,dt = GFR \int c(t)\,dt,$$

the quantity "$\int Q(t)\,dt$" (evaluated from 0 to 3 min) can be estimated by placing a ROI over the kidneys at time = 3 min. "$\int c(t)\,dt$" (also evaluated from 0 to 3 min) can be expressed as an average value of c(t) over the same time; we do this by dividing the injected dose by the patient's estimated plasma volume. The concentration computed this way should represent the *average* concentration of the tracer during the first 3 min. Even if up to 30% of the radiopharmaceutical disappears from the blood (by time = 3 min, assuming exponential clearance of 0.1189 min^{-1}), the *average* concentration over 3 min is approximately 16% less than the concentration at time = 0. That is, when using our simplified linear relationship $Q = GFR \cdot C \cdot t$, a 30% loss of tracer by time = 3 min introduces approximately a 16% underestimation of GFR. Hence, we would expect a regression slope of 0.84 (not 0.7) when correlating blood clearance and our RUPV method. Since we do not attempt to directly measure each patient's individual change in tracer concentration during the first 3 min, we do not try to correct for this effect.

In reference to Peters' data showing differential rate of "disappearance" of HSA and DTPA from the plasma, it appears that Peters' interpretation is to attribute the DTPA loss (in excess to that expected from GFR) to transfer to an extravascular space. We think that in addition to the loss of approximately 10% of DTPA due to GFR during the first 3 min, the physical characteristics of the tracers (e.g., DTPA = 492 Dalton and HSA = approximately 69,000 Dalton) can result in a larger volume of distribution and faster rate of mixing for DTPA therefore resulting in lower concentrations at time = 3 min. Obviously, the clearance of the tracer is far from ideal and is affected by these and other factors. Initial mixing, protein binding, extravasation to extravascular extrarenal spaces and radiopharmaceutical impurities with separate pharmacokinetics, all complicate the simplifying models we try to apply.

Peters' comment on the effect of the "overestimation of 30% of the dose in Equation 7" in our paper is not clear to us, since we in fact measure the injected dose in a dose calibrator and convert MBq to camera counts. We are sorry if our explanation in the original text was unclear.

With regard to the shortcomings of the RUPV model assumptions, the method provides a simple noninvasive estimation of GFR that is relatively accurate. The introduction of an estimate of patient plasma volume resulted in an improvement in precision (the R value improved from 0.82 to 0.9), supporting the feasibility of using an average tracer concentration to solve the RUPV equation.

The goal of our study was to estimate the absolute GFR in units of ml/min without any further normalization. Normalizing this absolute measure is nontrivial and ultimately could include other factors like age and body build. When needed, we used the currently accepted normalization to a surface area of 1.73 m^2 (which can easily be calculated from each patients' height and weight). We did not investigate the possibility of using a plasma volume or extracellular volume as a normalization parameter.

We appreciate Dr. Peters' insightful comments on our work; it stimulated us to further define and clarify the rationale behind our RUPV estimation of GFR.

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Cardiac Uptake of MIBG in Patients With Aortic Stenosis

TO THE EDITOR: The recent paper by Fagret, et al. (*1*) described MIBG uptake in patients with left ventricular hypertrophy secondary to aortic stenosis. They concluded from their study that: (1) patients with left ventricular hypertrophy and aortic stenosis have lower cardiac MIBG activity and a more rapid washout than normal controls; (2) amiodarone and digoxin partially inhibit myocardial MIBG uptake; and (3) the extraneuronal uptake of MIBG in human hearts accounts for 13% of total cardiac activity. Because of methodologic flaws and incorrect interpretation of the data, all of these conclusions are questionable.

The authors state that their patients "were receiving treatment drugs known to affect myocardial uptake of tritiated norepinephrine or [^{123}I] MIBG." None of the drugs their patients were receiving have ever been reported to decrease myocardial uptake of ^{123}I-MIBG.

Study groups consisted of seven controls (age 30 ± 15 yr, mean ± s.d.), six patients (age 70.5 ± 9 yr) who were receiving amiodarone or digoxin and seven patients (age 62 ± 16 yr) who were not taking these medications. There is a large and highly significant ($p \leq 0.002$) difference between the ages in the patient and the control study groups. It has been shown in many studies that there is a correlation between age and plasma norepinephrine levels. Healthy 70-yr-old subjects have plasma norepinephrine levels that are approximately twice those of healthy 20-yr-olds (*2*). This difference is due to increased appearance rates of plasma norepinephrine with aging (*3*). Direct measurement of sympathetic nerve activity in dogs shows a marked increased in activity with age (*4*). Thus, the decreased uptake and the increased washout of MIBG in patients with aortic stenosis may be due in part to age-related differences. Since there is no data on the affects of aging on cardiac MIBG uptake, it is impossible to know to what extent the changes seen in patients with aortic stenosis are due to age versus cardiac disease.

The authors claim that there is a significant difference in MIBG uptake between patients treated with amiodarone and untreated