**REPLY:** Dr. van den Hoff raises several issues regarding our article (*1*), which showed that myocardial perfusion at rest can be measured quantitatively with 1-$^{11}$C-acetate.

The first issue that Dr. van den Hoff raises pertains to the fact that we set the rate of tissue clearance to be equal to perfusion, *F* (Fig. 1 (*1*)). Despite Dr. van den Hoff's assertions to the contrary, the observation that tissue–tracer activity plateaus for 2–3 min after initial extraction does not invalidate the model structure. In fact, the model depicted in Figure 1 (*1*) ensures that, as the input tracer activity level falls toward zero, total tissue activity will remain nearly constant. This is a consequence of the fact that the tracer cannot leave the metabolically trapped pool even as tracer activity levels fall toward zero both in arterial blood and in the freely exchangeable pool.

The underlying question is whether modeling the egress from the system to be equal to blood flow, *F*, is justified. It should be noted that net tissue clearance after the plateau phase that is less than what would be expected, based on perfusion, does not address the question because egress is only from the freely exchangeable pool, which contains only a small fraction of the total tissue–tracer activity. The equivalence of the clearance rate with the rate constant exiting the system is only true for a 1-compartment model. One way to address the question of how reasonable it is to model the egress as being equal to *F* is by examining the influence of the exit rate constant on estimates of perfusion. This can be accomplished by decreasing the rate constant to a small fraction of *F* or even to zero. When the rate constant is set to zero, there is a mean underestimation of blood flow of 34% among the group of healthy volunteers (range, 19%–47%). This contrasts with no significant difference in blood flow estimates with 1-$^{11}$C-acetate and $H_2{}^{15}O$ using the published model structure (*1*).

The second issue Dr. van den Hoff raises regards our method for computing the recovery coefficient, $F_{MM}$. Unfortunately, Dr. van den Hoff has overlooked the basis of the jackknife procedure and the point that the model as configured produced accurate blood flow estimates. In essence, the jackknife procedure allows one to perform an independent experiment for each subject in which the data from all other subjects are used as calibration, including control subjects for whom the adjustment was unnecessary. Although it is theoretically possible that extraction, as well as $F_{MM}$ (which cannot be determined independently from each other), could be altered in hypertrophy, there is no experimental evidence that this in fact is the case. The fact that the methodology is empiric does not invalidate its accuracy. The incorporation of $F_{MM}$ into other models has been previously proposed and validated (*2–4*).

Dr. van den Hoff raises additional concerns including the use of fitting data beyond 3 min to improve statistical accuracy and the use of $F_{MM}$ from the $H_2{}^{15}O$ scans as an alternative to the jackknife procedure. Use of data beyond 3 min would require correction for egress of metabolites (predominantly $^{11}CO_2$), which would require additional analysis and, optimally, sampling from an arterial catheter. We wanted to develop a simpler approach obviating these steps. Using $F_{MM}$ from the $H_2{}^{15}O$ scans defeats the purpose of the study, which was to determine whether myocardial perfusion as well as myocardial oxygen consumption could be measured without resorting to additional tracers. It may be of interest, however, to note that the $F_{MM}$ from the jackknife procedure and from $H_2{}^{15}O$ scans correlated significantly ($P = 0.01$) and that the regression line had a slope of 0.86, which did not differ significantly from unity.

It should be remembered that all mathematic models are merely approximations that greatly simplify the system under study. In the context of PET, the primary objective of modeling is to find a structure that can be used to obtain parameter estimates that accurately reflect underlying biologic processes. The model that we proposed appears to be useful for allowing estimates of myocardial perfusion using 1-$^{11}$C-acetate.

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## Parenchymal Mean Transit Time Analysis

**TO THE EDITOR:** A recent interesting paper by Fine et al. (*1*) raises both conceptual and technical questions. Whether or not any test is necessary depends on one's point of view. The authors conclude that mean transit time (MTT) analysis is not necessary for $^{99m}$Tc-diethylenetriaminepentaacetic acid (DTPA) captopril renography. The authors acknowledge "the theoretic advantages" of parenchymal MTT compared with other renographically determined indices. As the authors state, the key issue is the attempt to move from what may be called "curveology" (i.e., taking 2 points on the time–activity curve with empirical evaluation) to measurements related to the underlying pathophysiology of renovascular disorder (RVD). In the study, the reduction in perfusion pressure was transduced into an MTT measurement that was prolonged in renovascular hypertension, because of the increased salt and water reabsorption in the proximal tubule and the increased water reabsorption in the collecting ducts in functionally significant RVD. To make this move, a robust technique of deconvolution was required. The authors appear to have deconvolved a 3-s frame rate for 8 min where counting rates per time interval are too low for good statistical analysis compared with 10-s intervals. Also, they used DTPA but only in a 185-MBq (5 mCi) dose instead of the 370-MBq (10 mCi) dose required for optional deconvolution and instead of the better-extracted mercaptoacetyltriglycine (MAG3). This may well explain the poor results in RVD obtained with both MTT and the empirical curveology methods they used. These results are all poor compared with the European multicenter trial of Fommei et al. (*2*) with $^{99m}$Tc-DTPA.

The main criticism is the authors' (*1*) lack of outcome data. The authors equate RVD with renal artery stenosis (RAS); yet, small vessel disease is the most common cause of RVD and, with such a high percentage of patients with poor overall renal function, small vessel disease is likely. Without evidence of correction of large vessel disease causing RVD with subsequent reduction of blood pressure, no certainty can be given that the RAS was

functionally significant. Furthermore, the age range is not given for group II. If they are elderly, essential hypertension is common, as is atheroma, including that of the renal artery. This association does not imply causation.

Before MTT is considered to be unnecessary, the results should be obtained with the original validated method with $^{99m}$Tc-MAG3 and a 10-s frame rate (*3*), which predicted a successful blood pressure lowering in 20 of 23 patients (87%) (*4*). It is this outcome that the pathophysiology measured by MTT predicts, not whether there is a narrowing of a renal artery. If a simpler index of MTT is required, then the corticopelvic transfer time—the time of the first appearance of activity at the kidney to the first appearance of activity in the pelvis—described by Makoba et al. (*5*), which has a respectable relation to MTT, is an objective alternative to empirical curveology.

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**REPLY:** We have reviewed Dr. Britton's comments regarding our investigation of diethylenetriaminepentaacetic acid (DTPA) mean transit time (MTT) in the evaluation of patients suspected of having renovascular hypertension (*1*). Several of Dr. Britton's assertions require a response.

1. Dr. Britton suggests that we concluded that "MTT analysis is not necessary for $^{99m}$Tc-DTPA captopril renography." In fact, our conclusion was limited to patients with reduced renal function. In these individuals the value of MTT analysis using DTPA was not supported by our data. We drew no conclusion about the general utility of MTT, but it may be inferred from Figure 1 of our study (*1*) that the diagnostic value of MTT decreases with declining renal function and improves with improving renal function, similar to other methods of assessing renography.
2. He indicates that our deconvolution 3-s frame rate was too short for optimal statistics. In fact, we did acquire data at 3-s framing intervals but regrouped 7 frames at a time in our analysis. The 21-s intervals and other technical aspects referenced in the original study (*1*) are described by our colleagues, Rottman and Zhang (*2*).
3. Dr. Britton criticizes the fact that we used only 185-MBq (5 mCi) doses of DTPA. However, we actually used both 185-MBq (5 mCi; precaptopril) and 370-MBq (10 mCi; postcaptopril) activities of DTPA. We did not report our results for 370-MBq injections of DTPA because they were no different from the results for 185 MBq.
4. He also states that our results were poor compared with those of the European multicenter trial. We are uncertain what Dr. Britton means here because the European multicenter trial (*3*) did not report on MTT. In any event, using other measures of abnormality, their results for patients with renal dysfunction showed reduced accuracy (67% for postcaptopril examination) compared with their subjects with normal renal function. Our results for subjects with renal dysfunction were comparable (54%–61% accuracy).
5. His main criticism is our lack of outcome data. We heartily agree, and we acknowledge this limitation of our study. We disagree, however, that convincing outcome data exist in the literature supporting the value of MTT in patients with renal dysfunction. The study by Gruenewald et al. (*4*) includes eleven 2-kidney patients with renal artery stenosis without renovascular hypertension, only 4 of whom had a glomerular filtration rate of <50 mL/min. Three of these subjects had false-positive MTT values.

Mercaptoacetyltriglycine (MAG3) MTT may be superior to DTPA in subjects with renal dysfunction, though there are no data yet to support this assertion. The reference by Dr. Britton to a validated method using MAG3 is in error, because the article by Al-Nahhas et al. (*5*) uses DTPA and a method very similar to ours.

The coexistence of renal dysfunction in many of the subjects in our study certainly reflects small vessel disease, as suggested by Dr. Britton. Small vessel disease is a common endpoint for many kinds of renal insufficiency. In fact, we showed decreased usefulness of MTT as renal function declined. The observation that an abnormal MTT may have lower specificity for renovascular hypertension in patients with abnormal renal function is not refuted by the very limited data of Gruenewald et al. (*4*) (3 false-positives in the whole group [$n = 11$], and 3 false-positives in subjects with renal dysfunction [$n = 4$], as indicated above). Renal dysfunction is an unfortunate fact of life for many hypertensive individuals. MTT may provide complementary information, but, as we concluded, existing data do not support a unique role for MTT in these individuals.


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