Quantification of ^{18}F-FDG Uptake in the Liver Using Dynamic PET

TO THE EDITOR: Recently, Brix and coworkers (*1*) described the quantification of liver metabolism by dynamic PET in dogs. Before that, we performed similar studies in pigs (*2*). Both studies address the important question of which input function to use for liver modeling. There are, however, some notable differences between the studies with regard to the selection of kinetic model, which we believe require special attention for correctly quantifying liver metabolism by dynamic PET. In particular, a physiologically based model is a prerequisite for obtaining physiologically meaningful parameters.

Initially, Brix and coworkers (*1*) used a 2-tissue-compartment model including a vascular volume for analyzing their data. However, their procedure provided an estimate of the vascular volume close to zero. This is clearly incorrect compared with the more reasonable blood volume of 28% that they derived from literature. Nevertheless, data were reanalyzed using the 2-tissue-compartment model without a vascular volume, and their conclusions were based on these results. In contrast, our data analysis (*2*) clearly supported the use of the model including a vascular volume. Our estimates of both the vascular volume and the clearance (K_1) were in agreement with independent measurements of the liver blood volume and flow in the same animals. Therefore, we wish to discuss why Brix and coworkers were unable to estimate a nonzero vascular volume, and to question the physiological relevance of the liver model without a vascular volume.

First, the unreasonably low vascular volume estimated by Brix and coworkers may have been due to an inaccurate input function. This raises the question of whether their blood sampling systems dispersed the arterial (and portal) blood time–activity curve (TAC) so much that their dual-input TAC did not resemble the true input to the liver. Their finding that the arterial blood sampling TACs were considerably dispersed compared with the internal aorta TACs from the PET scan supports this concern. Problems may also have arisen from their calculation of the flow-weighted dual-input function, which was based on mean values of arterial and portal flows (obtained from a different study) instead of the individual flows. After all, flows can vary markedly between animals (*3*) and during an experiment. If their input function does not describe the true input to the liver, this explains their unphysiologically low value for the vascular volume and gives rise to doubts concerning the validity of their comparison of different dual-input models.

Second, we question whether the choice of kinetic model configuration should be based solely on statistical criteria rather than including physiological considerations. We know that model parameters such as K_1 and the vascular volume parameter are correlated (*2*) and that the large hepatic vascular space will contain a large amount of nonextracted FDG activity after an FDG bolus injection. Accordingly, the use of a model without a vascular volume parameter will introduce systematic errors in the estimated parameters, which precludes a clear-cut physiological interpretation of the findings.

Third, Brix and coworkers suggest that arterial sampling may be used for clinical patients with liver lesions that are supplied mainly by the hepatic artery. We would like to comment that the validity of such an approach depends on the degree of arterialization and makes quantitative comparisons with the surrounding liver tissue difficult. Instead, we recommend analyzing such data by the more robust Gjedde-Patlak representation, perhaps with a correction for k_4 (*4*). Using this approach, we obtained similar values for the forward metabolic clearance, K, using either dual-input or arterial input function (*2*).

In summary, the unreasonably low estimates for the vascular volume of the liver give rise to questions as to whether the blood sampling procedures used by Brix and coworkers are capable of measuring the true input to the liver. In addition, we question the interpretation and physiological relevance of a liver model without a vascular volume.

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REPLY: We appreciate the comments of Munk et al. regarding our article (*1*), which give us the opportunity (a) to discuss central aspects of our investigation in more detail, and (b) to relate our results to those reported by Munk et al. (*2*). Please note that our manuscript had been accepted for publication about 1 month before the paper of Munk and coworkers appeared in *The Journal of Nuclear Medicine.*

The main challenge in the quantification of ^{18}F-FDG uptake in the normal liver using dynamic PET is the determination of the dual hepatic blood supply. It was therefore the aim of our experimental study to assess in foxhounds the effect of different input models on the rate constants of the standard 3-compartment FDG model. Each experiment comprised a dynamic PET scan together with the continuous detection of counting rates in arterial and venous blood feeding the liver using 2 independent coincidence-based detector systems. These measurements yielded 3 different blood curves (SUV^{PET}_{aorta}, $SUV^{detector}_{arterial}$, and $SUV^{detector}_{venous}$), which were used to define 5 different hepatic input functions, as described in our paper.

For quantification of rate constants characterizing FDG transport and metabolization in the liver, we used the conventional 3-compartment FDG model with a "vascular volume" characterized by a volume fraction f_B and a lag time to correct for the time delay of ^{18}F-FDG activity arrival in the liver. Although we started the nonlinear least-squares fitting procedure with an initial value for the "vascular vol-

ume" fraction of f_B = 0.28 mL/mL (mL blood/mL liver tissue) derived from the literature (*3*), this parameter was fitted to zero in the majority of the liver curves examined. In 3 cases, the analysis yielded a nonzero but very low value of f_B <0.057 mL/mL. The reason for this observation is that, in accordance with the results reported in Munk et al., the sharp initial peak of the arterial input functions $SUV_{arterial}^{detector}$ and SUV_{aorta}^{PET} was not reflected in the PET activity–time curves observed in the liver. Therefore, Munk et al. "raise the question of whether our blood sampling system dispersed the arterial (and portal) blood time–activity curves so much that the dual input curve did not resemble the true input to the liver". The relevance of dispersion effects on the estimation of the "vascular volume" of liver tissue and on the rate constants can, however, be ruled out due to 3 reasons:

1. The arterial blood curve SUV_{aorta}^{PET} was determined from a region of interest (ROI) defined over the central part of the aorta visualized on the PET scans of the foxhounds, and thus a substantial dispersion of this input on its way from the aorta to the liver can be neglected. As mentioned above, the fast initial increase of this arterial curve—which also contributes to the dual hepatic input function (see below)—is not compatible with the identification of a large vascular blood compartment in liver tissue.
2. Since tubing and flow rate were identical for both extracorporeal loops, it is reasonable to assume that the dispersion of the inputs $SUV_{arterial}^{detector}$ and $SUV_{venous}^{detector}$ caused by the monitor systems is nearly identical, and thus a notional system function S can be estimated based on the equation $S_{venous}^{detector} = S \otimes SUV_{arterial}^{detector}$, which describes only the "physiological" dispersion of the arterial input on its way through the GI tract. Using this function, a dual hepatic input was approximated from the arterial input SUV_{aorta}^{PET} determined from the PET scans according to

$$SUV_{in}^{PET} = w_{arterial} \cdot SUV_{aorta}^{PET} + w_{venous} \cdot S \otimes SUV_{aorta}^{PET}, \quad \text{Eq. 1}$$

   where the factors $w_{arterial}$ and w_{venous} determine the relative weights of the arterial and portal venous blood supply, respectively. It is important to note that the dual hepatic input function defined by Eq. 1 is not considerably affected by disturbing dispersion effects, since both SUV_{aorta}^{PET} and S are nearly free of them. Nevertheless, this dual input function also resulted in a very low "vascular volume" fraction.
3. Differences in the rate constants estimated for the "nondispersed" hepatic input function defined by Eq. 1 and those computed for the potentially "dispersed" input function

$$SUV_{in}^{detector} = w_{arterial} \cdot SUV_{arterial}^{detector} + w_{venous} \cdot SUV_{venous}^{detector} \quad \text{Eq. 2}$$

   were statistically not significant (*1*; Fig. 7).

The relative weights $w_{arterial}$ and w_{venous} were determined from perfusion measurements performed in the same animals by dynamic PET scanning using ^{15}O-water as well as by a standard microsphere technique as described in a previous paper (*4*). Since the correlation between the perfusion values determined by both techniques was poor, we used mean values of $w_{arterial}$ = 0.35 and w_{venous} = 0.65 averaged over 5 foxhounds for the computation of the input functions according to Eqs. 1 and 2 instead of the individual values. Munk and colleagues, on the other hand, measured the total organ blood flows in the hepatic artery and the portal vein continuously throughout the PET procedure by means of 2 sonographic transit-time flowmeter probes. Therefore, Munk et al. maintain in their letter that their procedure is more accurate since individual perfusion values are used instead of mean values. It should be noted, however, that they also use spatially averaged values, since regional perfusion in an ROI defined on the PET scans to evaluate FDG uptake in liver tissue is by no means identical with the average liver perfusion estimated from the total blood flows measured in the hepatic artery and the portal vein.

In consequence, the estimates obtained in our study for the "vascular volume" of liver tissue for different hepatic input models are fully based on the measured data and are caused neither by uncontrolled dispersion effects nor by the use of inaccurate weighting factors describing the relative fraction of the arterial and portal venous blood supply to the liver. Moreover, a small "vascular volume" does not result in an "unphysiological" model configuration, as stated by Munk et al. It is well known that the "vascular volume" in the standard 3-compartment FDG model does not represent a true physical volume, which can be identified with tissue blood (or plasma) volume. The reason is that the tracer in the capillaries has 2 states, 1 equal to the input concentration in a virtual "vascular volume" characterized by f_B, and 1 present at a "plasma equivalent" tissue concentration (*5*). In tissues with very high endothelial permeability, the "vascular volume" can approach zero (*5*). Therefore, the results of our study are not only based on reliable activity–time curves but are also in accordance with basic principles of compartmental analysis and tissue physiology.

We agree with the conclusion of Munk et al. (*2*) that dual-input models are superior to single-input models with respect to both the approximation of the acquired liver data and the estimation of physiologically reasonable rate constants. In relation to our foxhound PET data, however, differences between the rate constants estimated for different input models are smaller than the parameter variations among the animals. This is strongly supported by a comparison of our data with the results reported by Munk et al. for 6 pigs. Please note that the authors computed an unphysiologically high "vascular volume" of f_B = 0.40 mL/mL, in strong contrast to their own experimental result of f_B = 0.25 mL/mL obtained via the ^{15}O-carbon monoxide steady-state PET technique. However, their value of 1.07 ± 0.19 mL/min/g (mean ± SEM) obtained for the rate constant K_1 (FDG transport into the liver cells) fits very well into the range of the individual values ($0.5 < K_1 < 1.5$ mL/min/g) determined in our study for the dual-input models defined by Eqs. 1 and 2. Unfortunately, Munk et al. presented neither a plot of the individual rate constants estimated for the 6 pigs nor an appropriate (nonparametric) statistical test to prove that the reported differences in the mean values obtained for the examined single and dual hepatic input model are significant. On the basis of the data reported (mean ± SEM), it is not possible for the reader to assess whether the differences in the rate constants introduced by differences in the input models exceed the range of the interindividual variations.

Finally, we cannot agree with Munk et al. concerning the application of the Gjedde-Patlak technique in the quantitative analysis of dynamic FDG liver data. This graphical (in other circumstances very useful) approach simply neglects the dephosphorylation of FDG-6-phosphate via the enzyme glucose-6-phosphatase, which is present at a high level in normal liver cells. A Gjedde-Patlak analysis even "perhaps with a correction for k_4," as suggested by Munk et al., is not applicable since k_3 (the FDG phosphorylation rate constant) and k_4 (the dephosphorylation rate constant) are of the same order of magnitude, as is clearly seen in

their data (*2*; Table 1). This observation is further substantiated when the interested reader recalculates the Patlak parameters K (forward clearance of FDG) and V (virtual volume) directly from the compartmental parameters K_1, k_2, k_3, and V_0 using Eq. 7 in Munk et al. (*2*). The reanalysis of the data reveals that the FDG forward clearance K is underestimated in the Gjedde-Patlak approach by a factor of 2 to 3.

This discrepancy may also be a consequence of the fact that "data from the first few minutes were not included in the analysis," as stated in the paper of Munk and coworkers. So it is by no means astonishing that the "robust" Gjedde-Patlak analysis produces the same parameter estimates for the arterial input and the dual-input function, since the 2 input functions are virtually identical 1–2 min after tracer injection (*2*; Fig. 1). Moreover, the conclusion of Munk et al. that the use of the dual-input function is supported by better statistical scores is only valid for their compartmental analysis (*2*; Table 1). To the contrary, the single arterial input is clearly favored by the statistical criteria in their Gjedde-Patlak modeling approach (*2*; Table 2).

At the end of this controversial but stimulating discussion on a complex topic, we would like to emphasize that consensus exists between our groups that the dual hepatic input cannot be measured directly in humans and that it is thus necessary to evaluate alternative procedures for future noninvasive patient studies of liver metabolism. This very fact prompted us to initiate our PET investigation—namely, to provide the clinician with a practicable yet physiologically appropriate modeling approach. For normal liver tissue, the only practical alternative is to approximate the dual hepatic input by using the arterial input function and to estimate the blood supply through the portal vein by a notional system function that describes the dispersion of the arterial input in the GI tract. For humans, this function may be estimated from dynamic MRI studies using a suitable paramagnetic contrast agent. This approach is supported by our observation that the estimation of rate constants as defined by the standard 3-compartment FDG model is a relatively robust procedure in relation to uncertainties in the hepatic input function. With regard to FDG PET examinations of patients with liver diseases, there is a large body of evidence that both malignant and benign lesions of the liver are mainly supplied with blood by the hepatic artery. Taking this fact into account, it seems to be a valid approach for clinical FDG PET studies on patients with liver lesions to approximate the hepatic input by using the arterial input function.

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A Tabulated Summary of the FDG PET Literature

TO THE EDITOR: We read and re-read your outstanding supplement titled "A Tabulated Summary of the FDG PET Literature" (*1*). It helps take the world literature and put it in perspective. This has already helped us discuss the pros and cons of PET imaging in pancreatic carcinoma with a gastroenterologist.

Today we were trying to evaluate the literature on nuclear imaging on Parkinson's and related diseases and how we can help differentiate them for neurologists. We have a difficult time evaluating the literature from all over the world with multiple non–FDA-approved agents. We would appreciate additional *Journal of Nuclear Medicine* supplements to deal with other aspects of PET, and for that matter, other classical areas of nuclear medicine. It is very helpful to have the experts review the literature and put it all in one place. Is there a way to purchase additional supplements for distribution to some of our high-volume referring physicians? If there is not a method in place, please consider establishing it.

Keep up the good work—and hopefully more of it!

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REPLY: We are pleased to hear that the PET supplement is so valuable a resource. Copies of the supplement are available for purchase from the Society of Nuclear Medicine office. Cost is $15 per copy plus shipping and handling. Large-quantity bulk copy pricing is also available. Please contact the Society fulfillment office at 800-513-6853 or 703-326-1186 outside the United States, or by fax at 703-708-9015.

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