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Reply to: "Hepatic bile acid transport increases in the postprandial state: A functional ^{11}C-CSar PET/CT study in healthy humans"

To the Editor:

We thank Dr Heraghty and Dr Peters for their interest[1] in our work on fasting and postprandial hepatobiliary excretion kinetics of bile acids measured using positron emission tomography (PET) and the specific conjugated bile acid tracer [*N*-methyl-^{11}C]cholylsarcosine (^{11}C-CSar)[2]. They raise some important points regarding kinetic modelling and choice of tracer.

With regards to the question of K_1 and perfusion being similar, this gives us an opportunity to elaborate on the compartmental model shown in Fig. 1 in our paper, where the second compartment is denoted 'Hepatocytes'. In fact, the compartment model, using the dual-input function, is fitted to the radioactivity concentration curve in liver tissue, *i.e.* the volume of interest drawn in the dynamic PET series. Thus, as noted in the legend to Fig. 1, K_1 is the clearance of tracer from blood to liver tissue with the unit ml blood/min/ml liver tissue. K_1 is thus related to 'liver tissue volume' (not hepatocyte volume), and for extraction fractions close to 100%, K_1 estimates should be comparable to the independent perfusion measured Q. On that note, we would like to emphasize that the hepatic blood flow was measured using indocyanine green infusion and the Fick principle, not clearance as stated by Dr Heraghty and Dr Peters.

We illustrated the compartmental model with three boxes indicating three compartments (as it is often done in studies on tracer kinetics), but the vascular component is not a real compartment, and the same model configuration is often described as a 2-tissue compartmental model.

Compartmental models are based on several assumptions. The vascular tracer is accounted for by a separate term which is the vascular volume parameter multiplied by the input function. However, in reality and during the early phase following bolus injection of tracer, *i.e.* when K_1 and k_2 mainly affects the model solution, there are complex sinusoidal tracer concentration gradients that are not adequately accounted for in traditional compartmental models.[3] The transport for [^{11}C]CSar from blood through the hepatocyte and into bile is strongly polarized toward secretion, also obvious from the high steady state extraction fraction. This means that the impact of k_2 on the modelling is relatively weak compared to k_3 and therefore subject to more uncertainty. Additionally, the model does not account for reuptake further down the sinusoid.

With regards to the fixed value of bile duct volume, we agree that there probably is some biological variability. The fractional bile volume in liver tissue was set to 3.2 ml bile/l liver tissue using literature values[4,5] as explained in the supplementary material associated with Ørntoft *et al.* in *Journal of Hepatology*.[2] The main purpose of the present paper was to compare fasting and postprandial values and we do not think that there is reason to believe that the individual bile duct volume changes significantly before and after a meal. The relative individual changes should thus be robust. The observed k_5 translates to a median fasting intrahepatic bile flow of 0.30 ml bile/min and we find that to be in fair agreement with a fasting bile flow of 0.43 ml bile/min sampled in patients using a bile duct catheter.[6]

With regards to the comparison between [^{11}C]CSar and ^{99m}Tc-HIDA excretion kinetics, it is important to keep in mind that [^{11}C]CSar is a specific conjugated bile acid tracer which is handled by specific transport proteins whereas ^{99m}Tc-HIDA, not being a bile acid, is handled by other and far less specific hepatic transporter proteins.[7] Accordingly, values from the two tracers reflect different transporter systems and even if there is some overlap between transporter proteins, there are most likely differences in substrate affinity, maximum transport capacity etc. Based on this, we do not find it meaningful to compare the kinetic values from the two tracers. Moreover, as stated above, the main purpose of this paper was to compare individual secretion kinetics before and after a meal.

We hope this answers the authors' questions and we invite them to continue the discussion by personal communication.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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Authors' contributions

All three authors contributed in writing the text and approved the final version.

Supplementary data

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Nikolaj W. Ørntoft[1]
Ole L. Munk[2]
Michael Sørensen[1,3,*]

[1]*Department of Hepatology & Gastroenterology, Aarhus University Hospital, Aarhus, Denmark;*
[2]*Department of Nuclear Medicine & PET Centre, Aarhus University Hospital, Aarhus, Denmark;*
[3]*Department of Internal Medicine, Viborg Regional Hospital, Viborg, Denmark*

[*] Corresponding author. Address: Department of Internal Medicine, Viborg Regional Hospital, Viborg, Denmark.
E-mail address: michsoer@rm.dk (M. Sørensen).