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

To the Editor:

We enjoyed reading the excellent and stimulating paper of Ørntoft *et al.*, describing the intrahepatic kinetics of a novel ^{11}C-labelled bile acid analogue, ^{11}C-CSar before and after food consumption.[1] They performed linear least squares computerised modelling to obtain K_1, defined as the unidirectional clearance of ^{11}C-CSar from sinusoidal blood into hepatocytes, and the rate constants that respectively govern tracer movement from hepatocytes back into blood (k_2), from hepatocytes into bile canaliculi (k_3) and from liver tissue to extrahepatic bile (k_5). Transport from the bile canaliculus to hepatocytes (k_4) is assumed not to take place.

Extraction efficiency of tracer from blood to hepatocyte (E_0) was almost 100%, so K_1 is equal to hepatic perfusion. K_1 was almost identical to total hepatic blood flow (derived from indocyanine green clearance) divided by total hepatic volume (Q). From its method of measurement, hepatic volume will include hepatic blood volume, which in a seminal paper by the same group[2] was determined to be 25% of total liver volume. In contrast, K_1 is obtained from modelling in units of ml/min per *hepatocyte* volume. Because the sinusoidal endothelium is highly permeable, interstitial volume, which this group estimated to comprise another 15% of total volume,[2] can be added to the blood volume to give a so-called extended blood volume of 40%. Q should, therefore, have been about 40% less than K_1, but they were found to be equal.

There are 3 further aspects of the study that we hope Ørntoft *et al.* would kindly comment on.

Firstly, based on histological measurements,[3] bile duct volume has been set as 3.2 ml/L liver tissue. This value is based on a limited dataset (n = 5) and showed substantial inter-subject variability, with the uncertainty on fractional duct volume being around 50%. It is questionable whether or not this is a reasonable term to fix in the model, without some validation of the robustness of the model in response to variation in this value of bile duct volume.

Secondly, a fasting k_3 value as high as 0.4 min^{-1} and a k_2 value of 0.1 min^{-1} give a k_3/k_2 ratio of 40, rising to 223 after fasting. From compartmental analysis,[4] we find in comparison a corresponding ratio for the ^{99m}Tc-labelled organic anion hepatobiliary iminodiacetate (^{99m}Tc-HIDA) of about unity. A high ratio such as 40 should give a mono-exponential blood clearance curve, but the arterial curves in Fig. 2 of the study of Ørntoft *et al.*, especially fasting, give a strong impression of being bi-exponential (ignoring the 1 min point), as they are with ^{99m}Tc-HIDA.[4,5] Indeed, estimation by eye of individual values in the upper panel of their Fig. 2 gives a second exponential rate constant of about 0.07 min^{-1}, not dissimilar to ^{99m}Tc-HIDA.[4]

Finally, k_5 should be the same for ^{11}C-CSar and ^{99m}Tc-HIDA. With a value as low as 0.07 min^{-1}, k_5 for ^{99m}Tc-HIDA would be expected to lower the rate constant (α_2^h) of the declining phase of the hepatic time-activity curve. Because it is disconnected

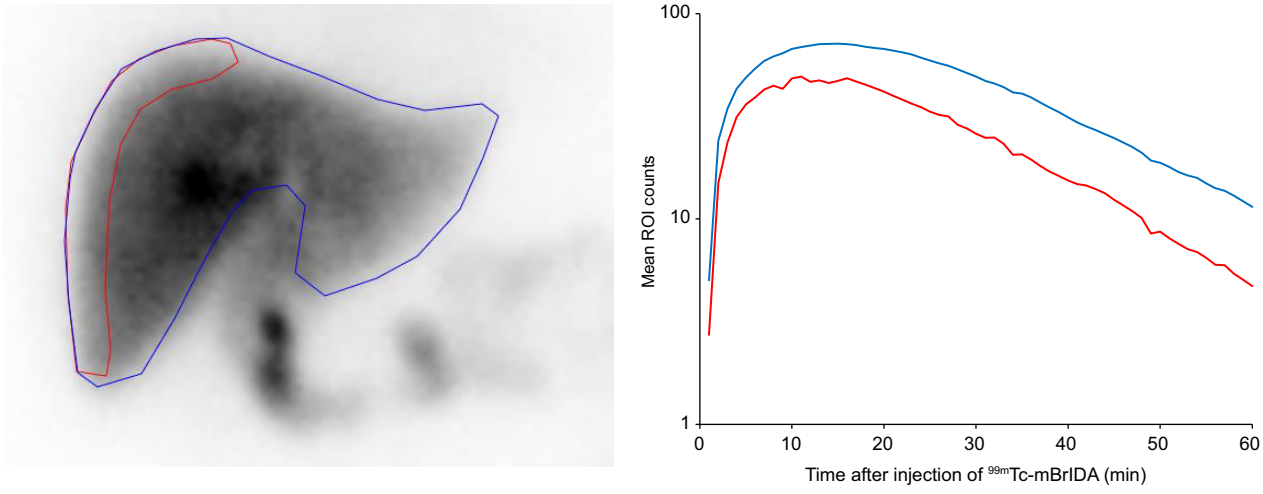

Fig. 1. Time activity curves recorded over the liver from a peripheral ROI (red) and a global ROI (blue) in a healthy liver after correction for background. Placement of ROIs is shown in left panel. ROI, region of interest.

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from the blood curve, a low but variable k_5 should abolish any correlation between α_2^h and the rate constant (α_2^b) of the second exponential of the corresponding blood time-activity curve. Yet α_2^h and α_2^b are not only similar but, more importantly, correlate with each other,[4] in keeping with a 2-compartment model with 'run-off' into bile, as previously proposed,[4,5] in which k_5 is high enough to have minimal influence on α_2^h. This correlation is not the result of basing α_2^h on a small peripheral 'parenchymal' region of interest (ROI) with a small bile volume because, at least in a healthy liver with no intrahepatic bile duct dilatation, small parenchymal and global hepatic ROIs give very similar values of α_2^h (Fig 1). Thus, it is difficult to see how k_5 could be so low. If k_5 is indeed higher, then bile flow rate will have been underestimated.

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Conflicts of interest
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Authors' contributions
NH analysed data and produced the figure. AMP wrote the submission.

Supplementary data
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