Positron emission tomography (PET) with the radiolabeled conjugated bile acid [*N*-methyl-^{11}C]cholylsarcosine (^{11}C-CSar).

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- PET is a molecular imaging technique that yields 3-D images of radioactivity concentrations in tissue following administration of a radiolabeled tracer.

- ^{11}C-CSar (as well as unlabeled cholylsarcosine)
  - does not metabolize *in vivo*,
  - exerts no pharmacological effects,
  - uses same transporters as endogenous conjugated bile acids.

- ^{11}C-CSar therefore serves as a tracer for endogenous bile acids and is an ideal PET tracer for the study of bile acid kinetics in humans.

Les Diablerets September 2019

Biodistribution of ^{11}C-CSar in human

Hepatobiliary excretion of ^{11}C-CSar in human

Methodology

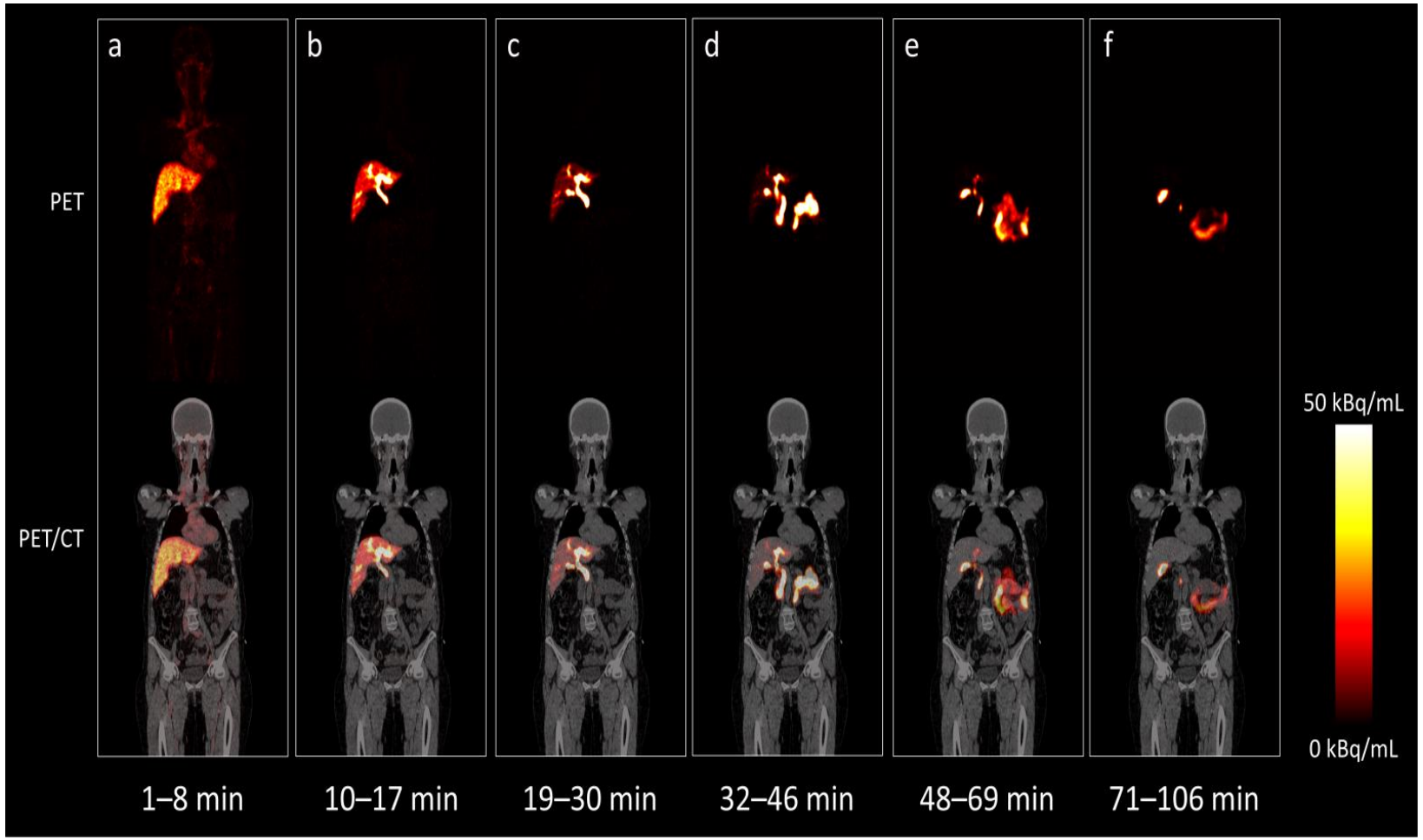
Two clinical examples:

i) Healthy vs. Cholestasis

ii) Drug-induced cholestasis

Perspectives

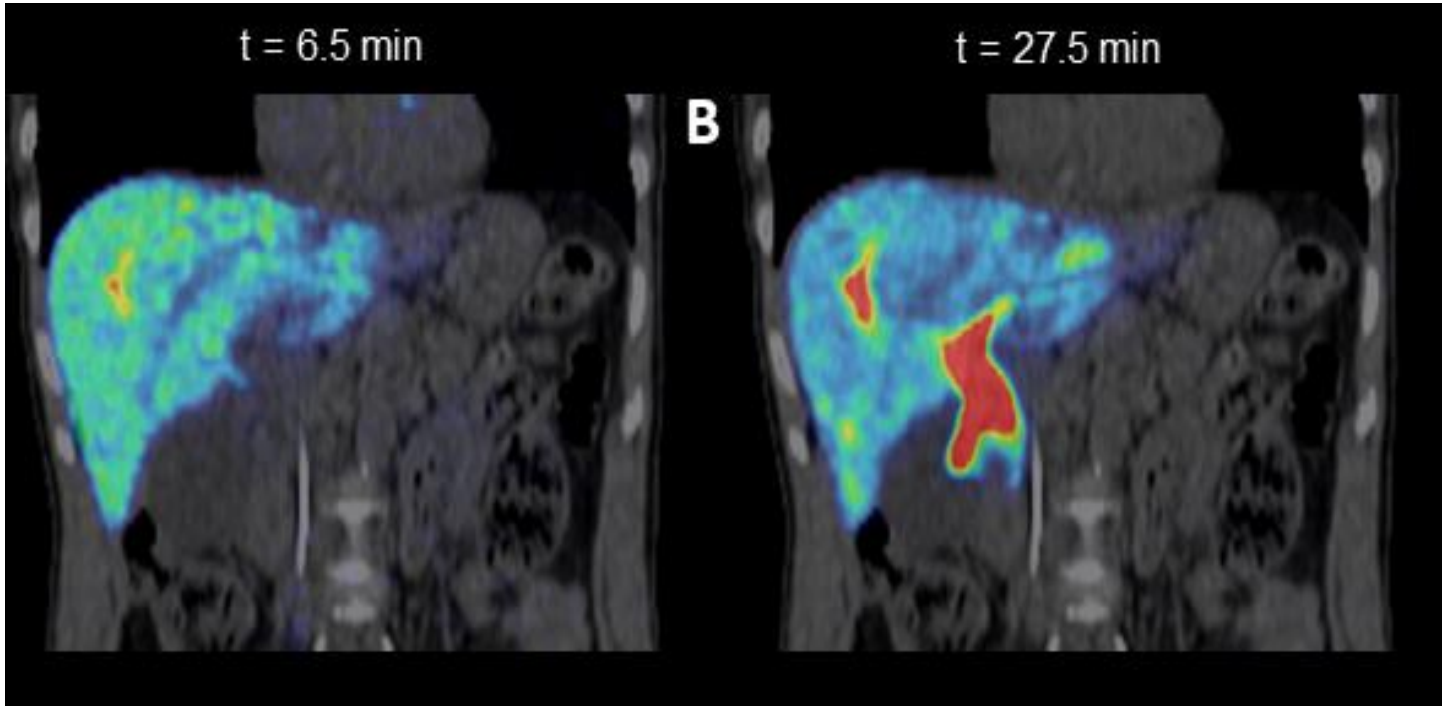
Biodistribution of ^{11}C-CSar



IV ^{11}C-CSar to a healthy human subject at time = 0.

Frisch K, Kjærgaard K, Horsager J, Schacht AC, Munk OL. *Nucl Med Biol*. 2019;72-73:55-61.

Biodistribution of ^{11}C-CSar



Coronal PET/CT Images of ^{11}C-CSar Concentrations from Dynamic ^{11}C-CSar Scans in a Human Subject.
Images of the upper abdomen (liver, bile ducts, and gallbladder) at time points as indicated after IV ^{11}C-CSar.

Frisch K, Kjærgaard K, Horsager J, Schacht AC, Munk OL. *Nucl Med Biol*. 2019;72-73:55-61.

Hepatobiliary excretion of ^{11}C-CSar

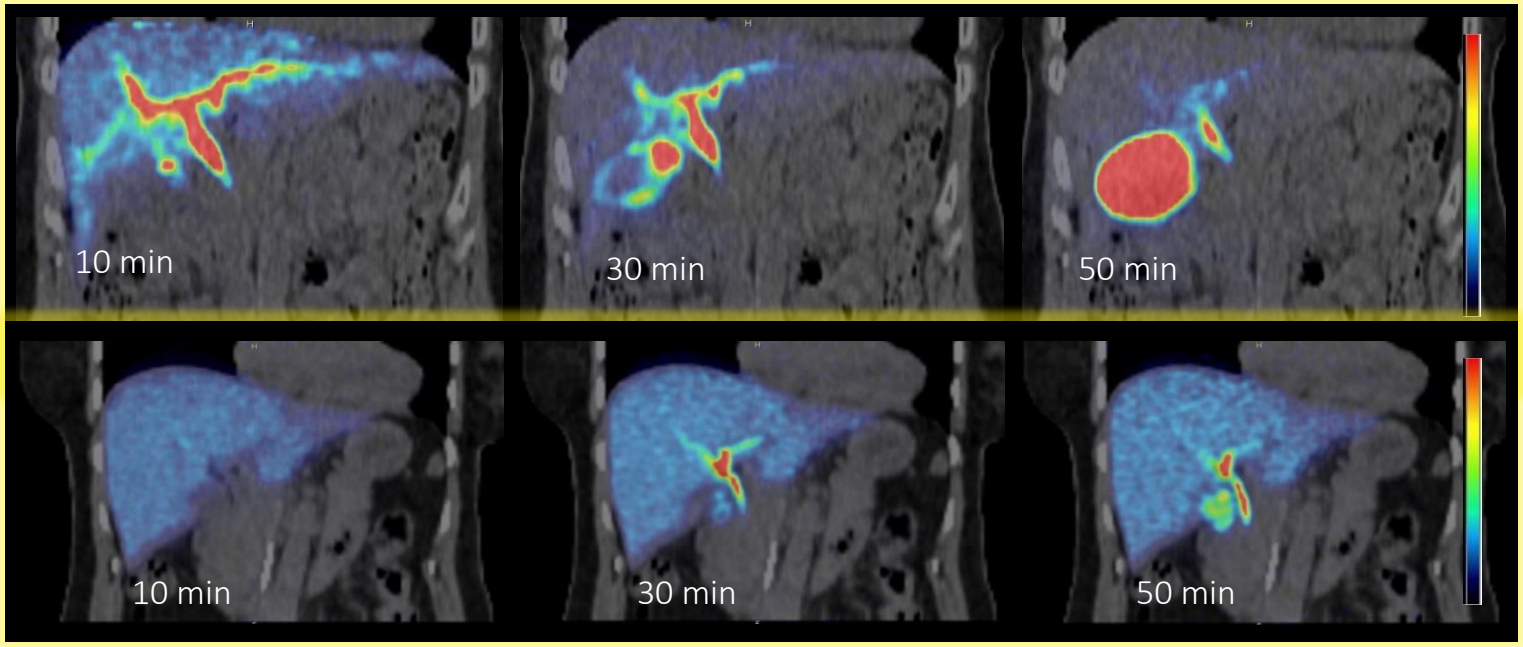
***In vivo* quantification of separate hepatic membrane transport processes of bile acids with ^{11}C-CSar PET**

Hepatobiliary excretion of ^{11}C-CSar

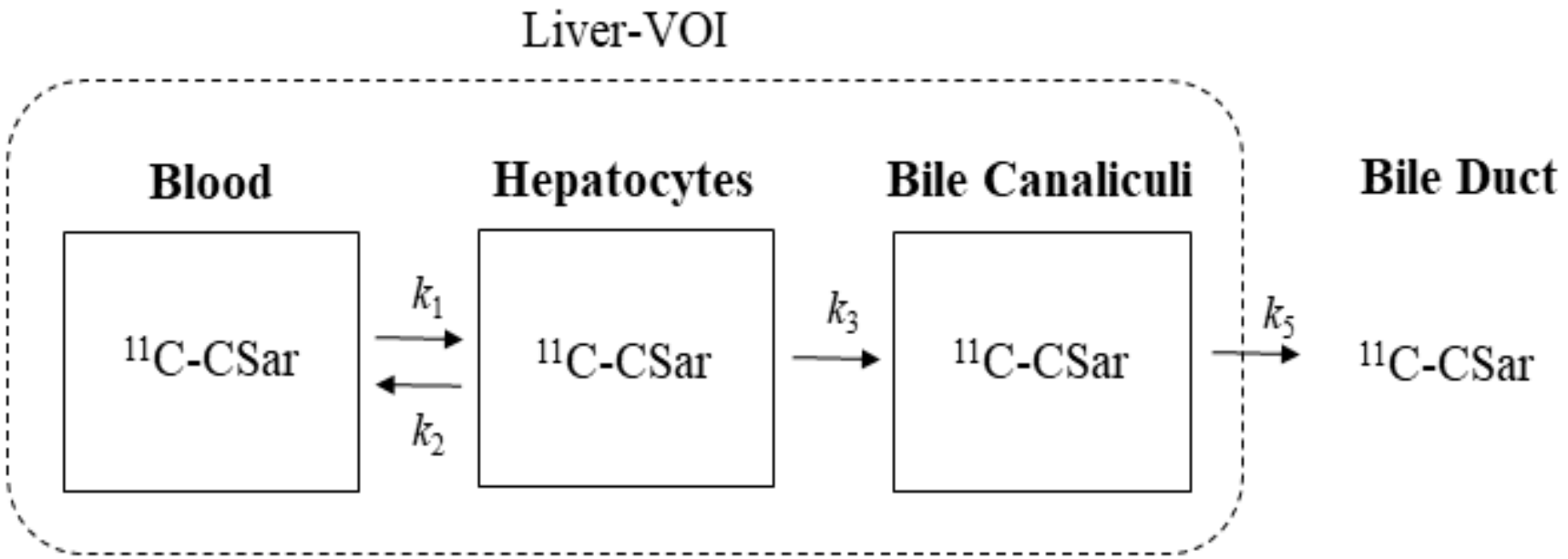
PET with ^{11}C-CSAR

HEALTHY SUBJECT

PATIENT WITH CHOLE-STASIS



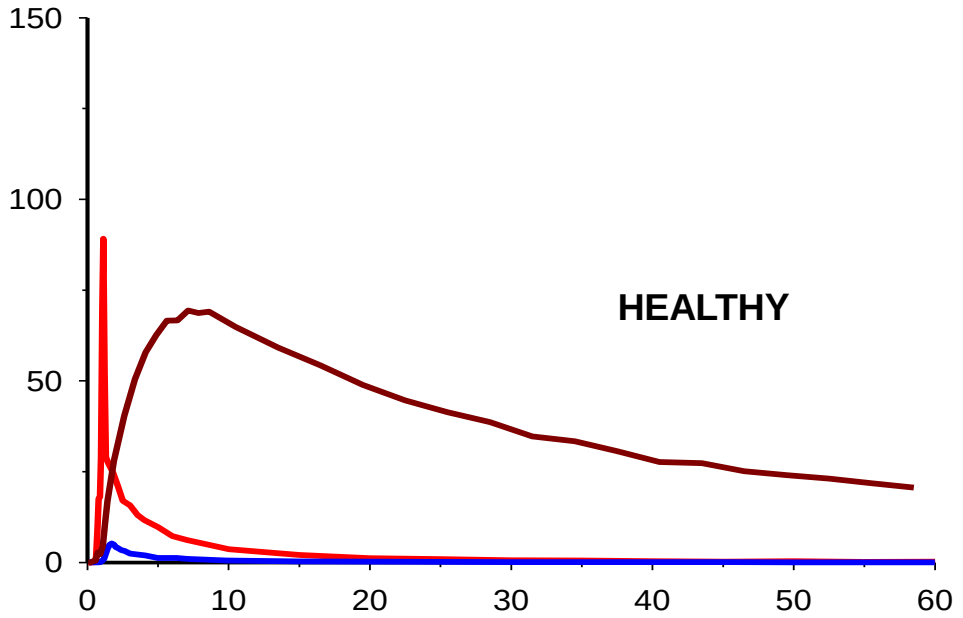
Hepatobiliary excretion of ^{11}C-Csar: Kinetic model

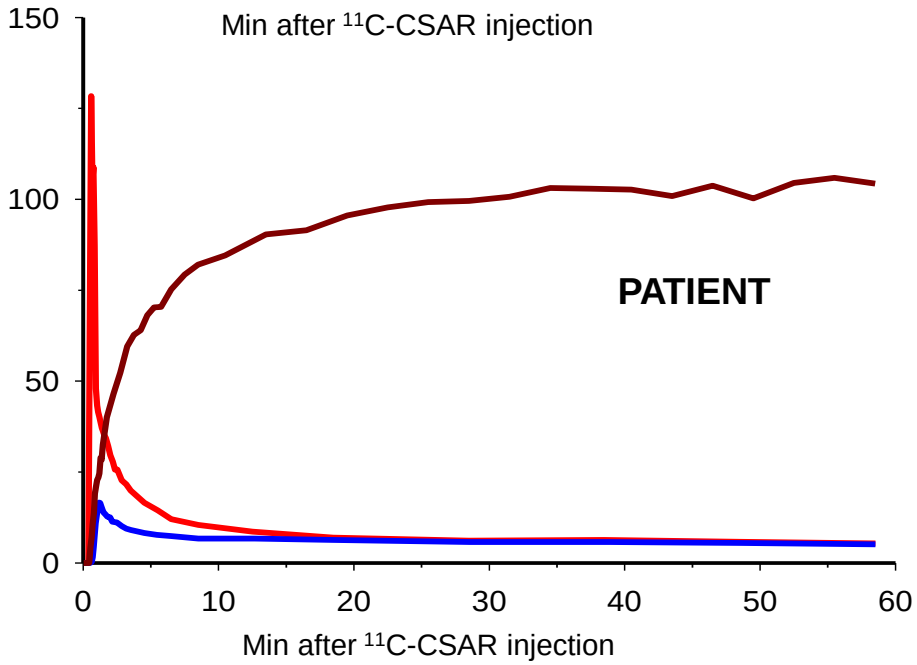


^{11}C-CSAR conc. kBq/mL:

Arterial blood
Hepatic vein blood

Liver tissue (PET)





Estimation of kinetic rate constants

The ^{11}C-CSar tracer supply to the liver comes from the hepatic artery and the portal vein that mix completely at entry to the sinusoids.

Accordingly, the flow-weighed dual input to the liver of ^{11}C-CSar, $C_{dual}(t)$ is

$$C_{dual}(t) = f_{HA}C_A(t) + (1\text{-}f_{HA})C_{PV}(t) \qquad \text{Eq. 1}$$

$C_A(t)$ is the time course of the measured concentration of ^{11}C-CSar in the arterial blood samples (kBq/mL blood/min),
$C_{PV}(t)$ the calculated time course of the concentration of ^{11}C-CSar in the portal vein (kBq/mL blood/min), and f_{HA} is the hepatic arterial flow fraction, 0.25.

The rate constants k_1, k_2, k_3, and k_5 are estimated by model-fits to the PET-measured $C_{liver}(t)$, using $C_{dual}(t)$ as input:

$$C_{liver}(t) = V_{blood}C_{dual}(t) + C_{hep}(t) + C_{bile}(t), \qquad \text{Eq. 2a}$$

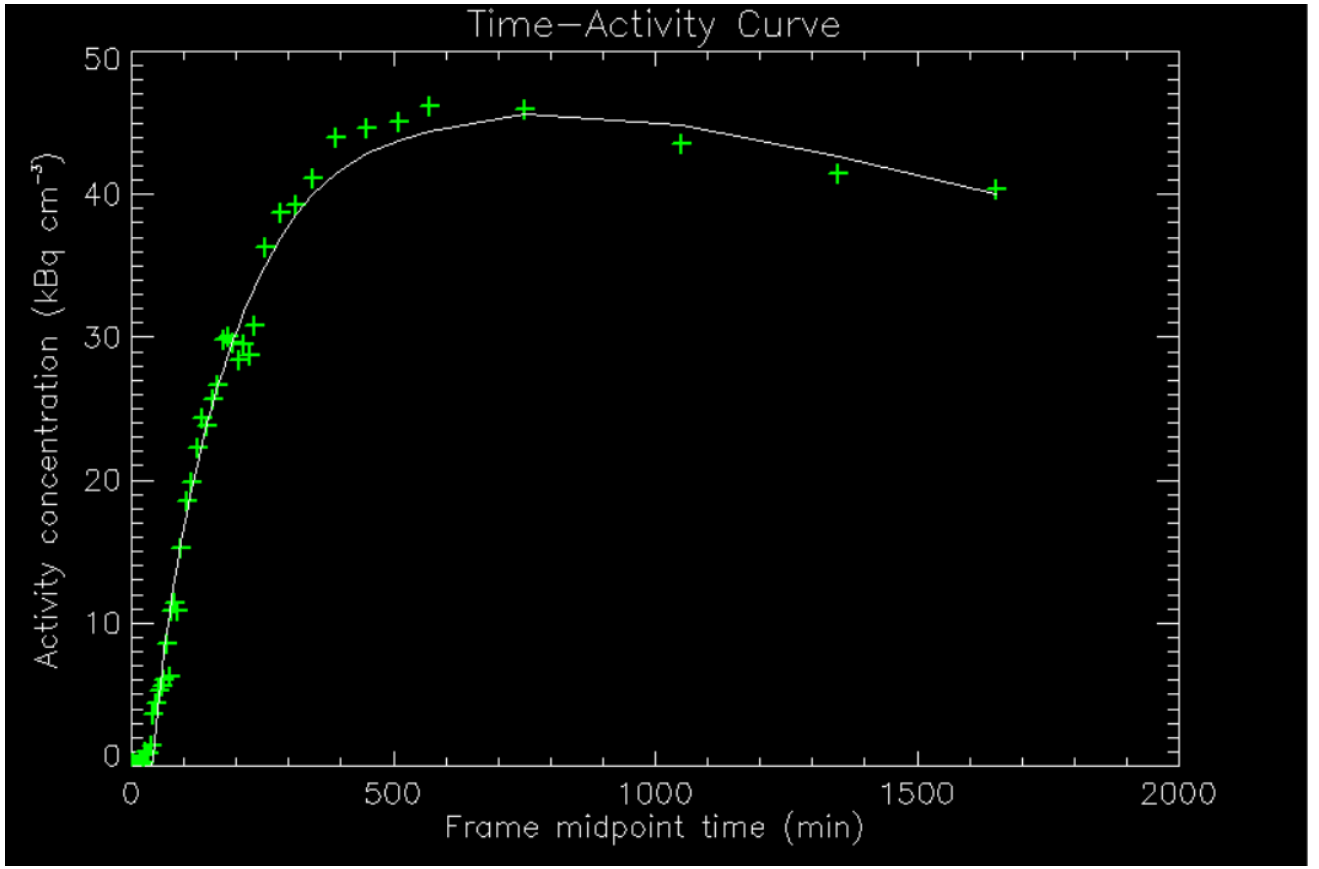
$$dC_{hep}(t)/dt = k_1C_{dual}(t) - (k_2 + k_3)C_{hep}(t) \qquad \text{Eq. 2b}$$

$$dC_{bile}(t)/dt = k_3C_{hep}(t) - k_5C_{bile}(t) \qquad \text{Eq. 2c}$$

V_{blood} intrahepatic blood volume, C_{hep} hepatocellular conc. of ^{11}C-CSar, C_{bile} conc. of ^{11}C-CSar in bile canaliculi.

Sørensen M, Munk OL, Ørntoft NW, Frisch K, …, Hofmann AF, Keiding S. *J Nucl Med* 2016 57:961-66.

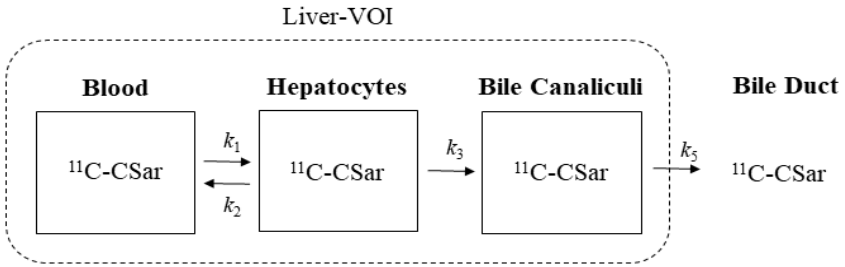
Hepatobiliary excretion of ^{11}C-CSar

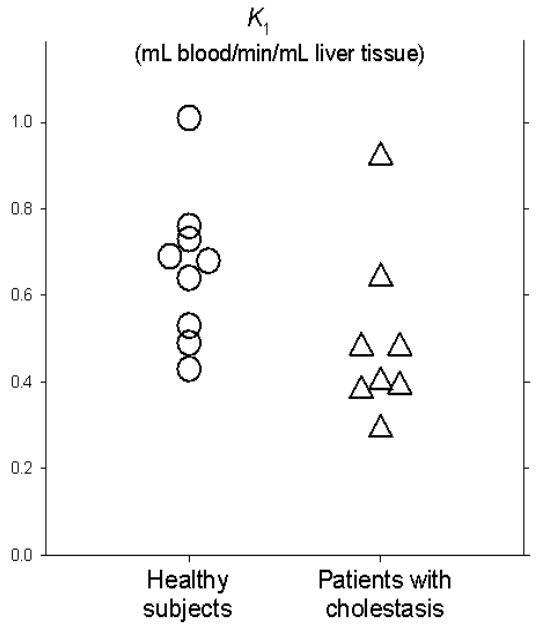


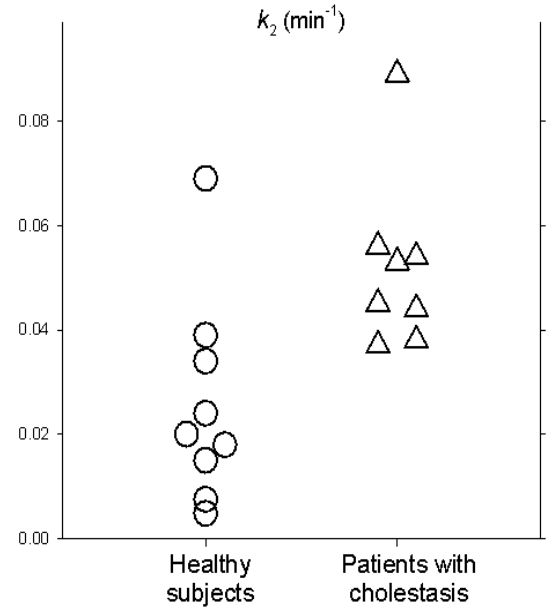
Time course of ^{11}C-CSar concentrations in liver tissue after start of ^{11}C-CSar administration (Time-Activity-Curve) (+) and the fitted curve of the model (white curve)

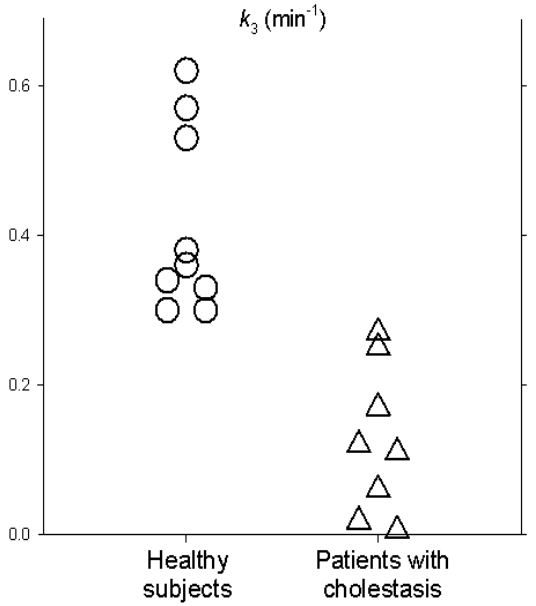
S. Keiding data

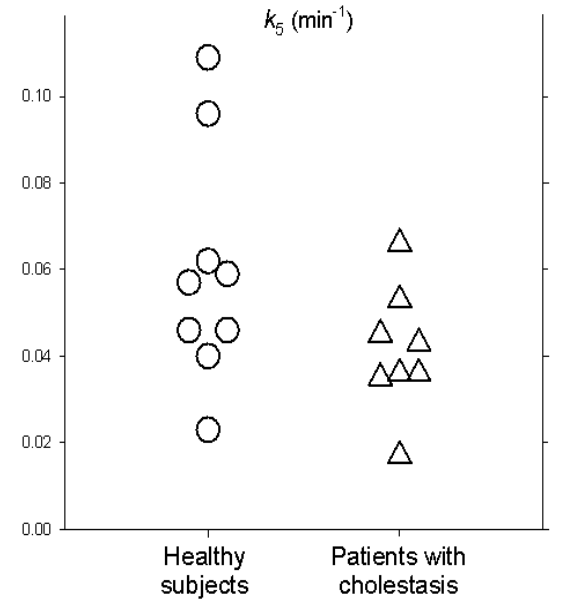
Hepatobiliary excretion of ^{11}C-Csar







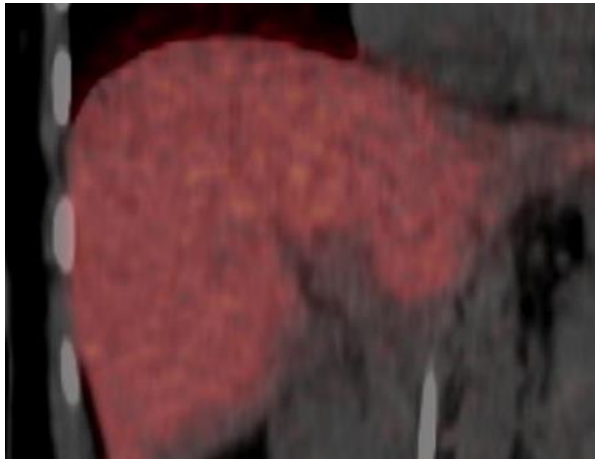




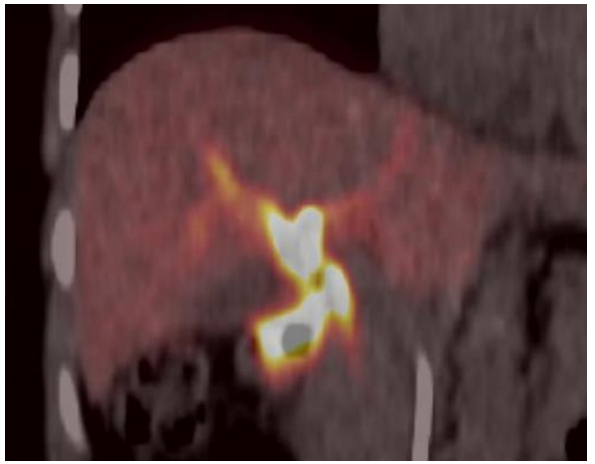
Ørntoft NW, Munk OL, Frisch K, Ott P, Keiding S, Sørensen M. *J Hepatol* 2017;67:321-7.

Hepatobiliary excretion of ^{11}C-CSar

During drug-induced cholestasis



After recovery



Ørntoft N, Frisch K, Ott P, Keiding S, Sørensen M. BBA - Molecular Basis of Disease; Special issue: Cholangiocytes. 2018;1864:1240-4.

Perspectives

- bile acid pathophysiology in patients with cholestasis
- effect of treatment of patients with cholestasis on hepatic bile acid kinetics
- prediction of cholestatic hepatotoxicity in humans during drug development
- effect of drugs, physiology, food intake
-

Original publications

Kjærgaard et al., AASLD 2019 Poster

Frisch et al., NMB 2019

Ørntoft et al., J Hepatol 2017

Sørensen et al., JNM 2016

Frisch et al., NMB 2012

Reviews

Keiding et al., AmJNMMI 2018

Ørntoft et al., BBA 2018

Frisch et al., Falk Symp 2013