Research Article

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Hepatobiliary transport kinetics of the conjugated bile acid tracer ^{11}C-CSar quantified in healthy humans and patients by positron emission tomography

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Background & Aims: Hepatobiliary secretion of bile acids is an important liver function. Here, we quantified the hepatic transport kinetics of conjugated bile acids using the bile acid tracer [*N*-methyl-^{11}C]cholylsarcosine (^{11}C-CSar) and positron emission tomography (PET).

Methods: Nine healthy participants and eight patients with varying degrees of cholestasis were examined with ^{11}C-CSar PET and measurement of arterial and hepatic venous blood concentrations of ^{11}C-CSar.

Results: Results are presented as median (range). The hepatic intrinsic clearance was 1.50 (1.20–1.76) ml blood/min/ml liver tissue in healthy participants and 0.46 (0.13–0.91) in patients. In healthy participants, the rate constant for secretion of ^{11}C-CSar from hepatocytes to bile was 0.36 (0.30–0.62) min^{-1}, 20 times higher than the rate constant for backflux from hepatocytes to blood (0.02, 0.005–0.07 min^{-1}). In the patients, rate constant for transport from hepatocyte to bile was reduced to 0.12 (0.006–0.27) min^{-1}, 2.3 times higher than the rate constant for backflux to blood (0.05, 0.04–0.09). The increased backflux did not fully normalize exposure of the hepatocyte to bile acids as mean hepatocyte residence time of ^{11}C-CSar was 2.5 (1.6–3.1) min in healthy participants and 6.4 (3.1–23.7) min in patients. The rate constant for transport of ^{11}C-CSar from intrahepatic to extrahepatic bile was 0.057 (0.023–0.11) min^{-1} in healthy participants and only slightly reduced in patients 0.039 (0.017–0.066).

Conclusions: This first *in vivo* quantification of individual steps involved in the hepatobiliary secretion of a conjugated bile acid in humans provided new insight into cholestatic disease.

Lay summary: Positron emission tomography (PET) using the radiolabelled bile acid (^{11}C-CSar) enabled quantification of the individual steps of the hepatic transport of bile acids from blood to bile in man. Cholestasis reduced uptake and secretion and increased backflux to blood. These findings improve our understanding of cholestatic liver diseases and may support therapeutic decisions.

Clinical trial registration number: The trial is registered at ClinicalTrials.gov (NCT01879735).

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Introduction

Bile acids are important for intestinal uptake of lipophilic compounds and regulation of metabolism.[1–5] Since the major pool of bile acids undergoes enterohepatic circulation and *de novo* synthesis only plays a minor role, efficient hepatocellular uptake from blood and subsequent secretion into bile is essential to prevent hepatic and systemic accumulation of these potentially cytotoxic compounds.[3,4] This becomes particularly evident in liver diseases associated with varying degrees of cholestasis. Uptake from blood to hepatocytes is mediated primarily via the Na^+-taurocholate co-transporting polypeptide (NTCP/*SLC10A1*),[1] secretion from hepatocytes to bile by the bile salt export pump (BSEP/*ABCB11*)[6] and backflux from hepatocytes to blood by the multidrug resistance proteins 3 and 4 (MRP3/*ABCC3*, MRP4/*ABCC4*) as well as the heteromeric organic solute transporter (OSTα/β/*SLC51A/SLC51B*)[7]. These transport steps have been studied *in vitro* but *in vivo* quantification has not been possible in humans until now. Such functional assessment is pivotal for understanding the hepatic transport of bile acids in health and disease.

We recently developed a positron emission tomography (PET) method using intravenous administration of the radiolabelled conjugated bile acid tracer [*N*-methyl-^{11}C]cholylsarcosine (^{11}C-CSar) for quantification of hepatobiliary secretion kinetics in pigs.[8,9] The aim of the present study was to use this method for quantification of the *in vivo* hepatobiliary secretion kinetics of ^{11}C-CSar in healthy human participants and patients with cholestasis of different aetiologies.

Keywords: Functional molecular imaging of the liver; Cholestasis; Hepatic transport kinetics; Bile acid transporter; Hepatocytes; Bile acids and salts; Kinetics; Positron-emission tomography.

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Patients and methods

Human participants

Nine healthy human participants with no history of liver disease were included after responding to an advertisement in a local newspaper. Routine blood tests measured on the day of the experiment were normal. Eight patients with liver disease of various aetiologies and varying degrees of cholestasis, as judged by fasting plasma bile acid concentration, were recruited from our department (Table 1). All diagnoses were confirmed by liver tissue biopsies, except in patients IDs 13 and 15 with alcoholic cirrhosis. The patients were divided into two subgroups: patients with alcoholic liver disease (alcoholic cirrhosis and alcoholic hepatitis) and patients with inflammatory cholestatic diseases (primary sclerosing cholangitis (PSC), primary biliary cholangitis (PBC), and autoimmune hepatitis with cholestasis (AIH)).

Ethics

The study was approved by the Central Denmark Region Committees on Health Research Ethics and the Danish Medicines Agency, conducted in accordance with the Helsinki II Declaration, and monitored by the Good Clinical Trial Unit at Aarhus University Hospital. Written informed consent was obtained from all participants. The average radiation dose received by the participants was 4.1 mSv (maximum radiation dose was 5.2 mSv). No complications to the procedures were observed.

Study design

The tracer ^{11}C-CSar was prepared at Dept. of Nuclear Medicine & PET Centre, Aarhus University Hospital using a method similar to what has previously been described.[9] Since the radioactive half-life of carbon-11 (^{11}C) is 20.3 min, it was possible to perform two successive ^{11}C-CSar PET scans of an individual in one day using an interval between the ^{11}C-CSar administrations of 150 min. In the first three healthy participants, we showed that indocyanine green (ICG), used for measurement of hepatic blood flow, did not affect hepatobiliary secretion kinetics of ^{11}C-CSar by paired measurements with ^{11}C-CSar administered as two bolus injections (Table S1). In ten other participants (five healthy participants and five patients), we compared bolus injection and constant infusion of ^{11}C-CSar (Fig. S3). In subject with ID 13, however, blood sampling from the initial 30 min of the infusion experiment failed due to technical issues. In the final study design, as described in detail below, nine healthy participants and eight patients with cholestasis were examined with a dynamic PET scan of the liver with ^{11}C-CSar administered as a bolus injection and hepatic blood flow estimated by constant infusion of ICG. During the PET scan, blood samples were collected as described below for measurements of blood concentrations of ^{11}C-CSar in arterial and hepatic venous blood, and for measurements of hepatic blood flow using ICG.

Catheterizations

Catheters (Venflon, Becton Dickinson, USA) were placed percutaneously in both cubital veins for intravenous administrations of ^{11}C-CSar and ICG. For blood sampling, a catheter (Artflon, Becton Dickinson, USA) was placed percutaneously in a radial artery and a catheter (Torcon Advantage, Cook Inc., USA) was placed in a hepatic vein via the right femoral vein.

Hepatic blood flow and perfusion

ICG (Hyson, Westcott and Dunning, Maryland, USA) was administered as a constant intravenous infusion and during each PET scan, plasma concentrations of ICG were measured in five sets of blood samples from the radial artery and hepatic vein. Plasma concentrations were corrected for individually measured arterial haematocrit values and used to calculate hepatic blood flow (F, L blood/min) by Fick's principle.[10,11] Median hepatic blood flow in the bolus experiments was 0.93 (range 0.76–1.18) L blood/min in the healthy participants and 1.30 (range 0.77–4.48) L blood/min in the patients (Mann-Whitney U test, $p = 0.25$). The hepatic blood perfusion, Q (ml blood/min/ml liver tissue, Table S2) was calculated as F/V_{liver} where V_{liver} (ml liver tissue) is the total liver volume determined from PET data (median 1.38 (range 1.30–1.95) L liver tissue in healthy participants and median 1.55 (range 1.10–3.27) L liver tissue in patients with cholestasis).

^{11}C-CSar measurements

The PET examinations were performed after an overnight fast and the participants were instructed not to take any drugs on the day of the examination. The subject was placed in supine position in a Siemens Biograph™ 64 TruePoint™ PET/computed tomography (CT) camera. A low-dose CT scan was performed before each PET scan for attenuation correction of emission data and anatomical co-registration of PET data. ^{11}C-CSar was administered as an intravenous bolus during the initial 25 s of a 60 min dynamic PET scan. The median dose of ^{11}C-CSar per PET examination was 150 (range, 66–240) MBq. PET data were recorded in list-mode and reconstructed using attenuation weighted ordered subset expectation maximization with resolution recovery (TrueX 3D) with four iterations, 21 subsets, a 336 × 336 × 109 matrix and a 2 mm Gauss filter. Final PET image voxel size was 2 × 2 × 2 mm^3, time frame structure was 9 × 10 s, 10 × 45 s, and 17 × 3 min. PET measurements were corrected for radioactive decay back to start of the PET scan.

During the PET scan, blood concentrations of ^{11}C-CSar were measured in blood samples from the radial artery, $C_A(t)$ (kBq/ml blood *vs.* min), and hepatic vein, $C_{out}(t)$ (kBq/ml blood *vs.* min), using a well counter (Packard) cross-calibrated with the PET-camera and corrected for radioactive decay back to start of the PET scan. The time course of the flow-weighted mixed input of ^{11}C-CSar to the liver from the hepatic artery and the portal vein, $C_{in}(t)$ (kBq/ml blood *vs.* min), was calculated from $C_A(t)$ (Supplementary materials and methods).

PET images were analysed using the PMOD software (PMOD Technologies Ltd, Zürich, Switzerland). Regions-of-interest (ROIs) in liver tissue were drawn in adjacent planes using the combined PET/CT images with a minimum distance of two centimetres to the border of the liver and excluding large blood vessels and visible intrahepatic bile ducts. The ROIs were combined to a volume-of-interest (liver volume of interest [VOI], mean volume 44 ml liver tissue) used to generate the time course of the liver tissue concentration of ^{11}C-CSar, $C_{liver}(t)$ (kBq/ml liver tissue *vs.* time), which was used in the kinetic analysis. The time course of the concentration of ^{11}C-CSar in the common hepatic duct, $C_{CHD}(t)$ (kBq/ml liver tissue *vs.* min), was derived from the PET images as described in Supplementary materials and methods. The total liver volume, V_{liver} (ml liver tissue), was estimated using the isocontour tool within the first 3 min of the PET scan, *viz.* before ^{11}C-CSar appeared in the extrahepatic bile ducts.

Hepatic extraction fraction

The time course of the hepatic extraction fraction of ^{11}C-CSar from blood, $E(t)$, was calculated as:

$$E(t) = \frac{C_{in}(t) - C_{out}(t+T)}{C_{in}(t)} \quad (1)$$

where the concentration of ^{11}C-CSar in $C_{out}(t)$ was corrected for non-steady state using individual estimates of mean hepatic blood transit time, T (mean 21 s, range 11–36). T was calculated as (V_{blood}/Q), where V_{blood} is the fractional blood volume in human liver (0.25 ml blood/ml liver tissue).[12,13]

The unidirectional hepatic extraction fraction of ^{11}C-CSar (E_0) was calculated from Eq. (1) using blood concentrations of ^{11}C-CSar from the first minute when potential backflux of tracer from hepatocytes to blood can be ignored.[14]

The time course of the hepatic extraction fraction was also calculated using the areas under the curves (AUC) of the time courses of $C_{in}(t)$ and $C_{out}(t+T)$ as

$$E_{AUC}(t) = \frac{\int_0^t C_{in}dt - \int_0^{t+T} C_{out}dt}{\int_0^t C_{in}dt} \quad (2)$$

When comparing the infusion and bolus experiments, we found that E_{AUC} at t = 50 min (E_{AUC}) in the bolus experiments approximated steady state hepatic extraction fraction of ^{11}C-CSar (E_{ss}) in the infusion experiments (Fig. S3). We therefore used E_{AUC} at 50 min to substitute E_{ss} in the calculations of hepatic intrinsic and systemic clearances (Eqs. (4) and (5), respectively).

Hepatobiliary transport kinetics

The flow-independent permeability surface area product of the hepatocyte plasma membrane for ^{11}C-CSar, PS_{mem} (ml blood/min/ml liver tissue) was calculated as[15]:

$$PS_{mem} = -Q\ln(1-E_0) \quad (3)$$

The flow-independent hepatic intrinsic clearance of ^{11}C-CSar from blood to bile, Cl_{int} (ml blood/min/ml liver tissue), was calculated as[16,17]:

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