Research Article

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Regional metabolic liver function measured in patients with cirrhosis by 2-[^{18}F]fluoro-2-deoxy-D-galactose PET/CT

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Background & Aims: There is a clinical need for methods that can quantify regional hepatic function non-invasively in patients with cirrhosis. Here we validate the use of 2-[^{18}F]fluoro-2-deoxy-D-galactose (FDGal) PET/CT for measuring regional metabolic function to this purpose, and apply the method to test the hypothesis of increased intrahepatic metabolic heterogeneity in cirrhosis.

Methods: Nine cirrhotic patients underwent dynamic liver FDGal PET/CT with blood samples from a radial artery and a liver vein. Hepatic blood flow was measured by indocyanine green infusion/Fick's principle. From blood measurements, hepatic systemic clearance (K_{syst}, L blood/min) and hepatic intrinsic clearance (V_{max}/K_m, L blood/min) of FDGal were calculated. From PET data, hepatic systemic clearance of FDGal in liver parenchyma (K_{met}, mL blood/mL liver tissue/min) was calculated. Intrahepatic metabolic heterogeneity was evaluated in terms of coefficient-of-variation (CoV, %) using parametric images of K_{met}.

Results: Mean approximation of K_{syst} to V_{max}/K_m was 86% which validates the use of FDGal as PET tracer of hepatic metabolic function. Mean K_{met} was 0.157 mL blood/mL liver tissue/min, which was lower than 0.274 mL blood/mL liver tissue/min, previously found in healthy subjects (p <0.001), in accordance with decreased metabolic function in cirrhotic livers. Mean CoV for K_{met} in liver tissue was 24.4% in patients and 14.4% in healthy subjects (p <0.0001). The degree of intrahepatic metabolic heterogeneity correlated positively with HVPG (p <0.05).

Conclusions: A 20-min dynamic FDGal PET/CT with arterial sampling provides an accurate measure of regional hepatic metabolic function in patients with cirrhosis. This is likely to have clinical implications for the assessment of patients with liver disease as well as treatment planning and monitoring.

Keywords: Liver metabolism; Galactose; Positron emission tomography; Molecular imaging; Clearance.

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Introduction

It has become increasingly evident that liver cirrhosis is not necessarily a static end point of parenchymal liver disease, but can indeed be dynamic and potentially reversible. This has, together with the increasing use of local treatments, for e.g., liver tumours in patients with cirrhosis, led to an increased clinical demand for non-invasive methods that can quantify stiffness and metabolic functions of the liver [1]. It is also of clinical interest to be able to predict remnant liver function following e.g., partial liver resection, by estimating regional-to-global liver function, especially in patients with parenchymal liver disease [2]. In Japan, hepatic scintigraphy with measurements of the asialoglycoprotein receptor density with ^{99m}Tc-galactosylneoalbumin (^{99m}Tc-GSA) is used for assessment of liver function, but the method is not approved in Europe or the USA [2]. Another method is hepatobiliary scintigraphy (and more recently single photon emission computer tomography, SPECT) with ^{99m}Tc-mebrofenin, a substrate that is taken up from blood by hepatocytes and excreted unmetabolized into bile [2]. Hepatic uptake and excretion of ^{99m}Tc-mebrofenin are, however, impaired by hypoalbuminemia and high levels of plasma bilirubin, as well as impaired bile flow [2]. Furthermore, scintigraphy suffers from poor spatial and temporal resolutions compared to e.g. positron emission tomography (PET).

We recently developed a molecular imaging method for *in vivo* quantification of hepatic galactokinase capacity using dynamic PET/CT and the galactose analogue 2-[^{18}F]fluoro-2-deoxy-D-galactose (FDGal) [3–5]; the galactokinase enzyme metabolizes galactose and analogues hereof and is almost exclusively found in the liver. The capacity of the liver to remove intravenously injected galactose is measured with the galactose elimination capacity (GEC) test [6,7]. The GEC test yields a measure of global metabolic liver function and provides prognostic information for patients with acute [8,9] and chronic [10,11] liver disease, as well as for patients undergoing hepatic resection [12]. However, the GEC test does not provide any information on potential intrahepatic metabolic heterogeneity. FDGal PET/CT offers a unique possibility to study regional variations in metabolic function in terms of hepatic galactokinase activity [5]. In our study in healthy subjects, the FDGal PET/CT measurements were validated against direct measurements of hepatic removal kinetics of galactose and FDGal by blood measurements from

an artery and a liver vein [5]. The aim of the present study was to validate the use of FDGal PET/CT for non-invasive 3D quantification of regional hepatic galactokinase capacity in patients with liver cirrhosis, and to apply the method to test the hypothesis of an increased heterogeneity of galactokinase capacity in liver cirrhosis.

Patients and methods

Study design

A 60-min dynamic liver FDGal PET/CT with blood sampling from a radial artery and a liver vein was performed with simultaneous determination of hepatic blood flow by indocyanine green infusion/Fick's principle. Blood concentration measurements of FDGal in arterial and liver venous blood and hepatic blood flow measurements were used to validate FDGal as a PET/CT tracer for galactokinase capacity. The FDGal PET/CT scan and arterial blood samples were used to measure galactokinase capacity in liver parenchyma as well as metabolic heterogeneity.

Patients

Ten patients with liver cirrhosis were included in the study; one patient was excluded due to technical problems with the PET/CT scanner causing the experiment to be cancelled. The patients were included from the outpatient clinic at the Department of Medicine V (Hepatology/Gastroenterology), Aarhus University Hospital. Patients referred to the department for hepatic venous pressure gradient (HVPG) measurement, by liver vein catheterization, were offered to participate in the study. Patients were instructed not to take any food or drugs for 8 hours before the study, but were allowed to drink water. None of the patients received medical treatment for portal hypertension at the time of the study. Patient characteristics are given in Table 1. No patients with hepatocellular carcinoma (HCC) were included as we know that HCC nodules may have increased accumulation of FDGal [13].

Ethics

The study was approved by The Central Denmark Region Committees on Biomedical Research Ethics and conducted in accordance with the 1975 Declaration of Helsinki. Written informed consent was obtained from all patients. The mean radiation dose received by each subject was 4 mSv. No complications to the procedures were observed.

Galactose elimination capacity test

As part of the standard clinical work-up, a GEC test was performed in all patients. The GEC provides an estimate of the maximum removal rate of galactose (mmol/min) for the whole liver, i.e., global galactokinase capacity [6,7]. The result is normalized to provide an index of the metabolic function of the liver as a fraction of the expected value for a healthy individual of the same sex, age, and body weight (normalized GEC; Table 1).

Catheterizations

Catheters were placed in a cubital vein in both arms and in a radial artery. For blood sampling and HVPG measurement, a 6F catheter (Cook Catheter, Bjaeverskov, Denmark) was placed in a liver vein in the right liver lobe, via an introducer catheter in the right femoral vein. The HVPG was calculated as the difference between pressures measured in the wedged and free position in the liver vein.

Hepatic blood flow

An intravenous infusion of indocyanine green (Hyson, Wescott and Dunning, Baltimore, MD, USA) was started 90 min before the PET study. During the PET study, four pairs of blood samples (5 mL each) were collected from the radial artery and the liver vein for spectrophotometric determination of plasma concentrations of indocyanine green [15,16]. Good approximation to steady state concentrations was obtained in each subject and individual mean concentrations from the artery and liver vein were used to calculate an individual mean hepatic blood flow (F, L blood/min) according to Fick's principle with adjustment for individual hematocrit values [17].

FDGal PET/CT and blood measurements

The subjects were placed on their back in a 64-slice Siemens Biograph TruePoint PET/CT camera (Siemens AG, Erlangen, Germany). A topogram of the abdomen was performed for optimal positioning of the liver within the 21.6 cm transaxial field-of-view of the PET camera followed by low-dose CT scan (50 effective mAs with CAREDose4D, 120 kV, pitch 0.8, slice thickness 5 mm) for definition of anatomical structures and attenuation correction of PET data. A bolus of 100 MBq FDGal in 10 mL saline was administered intravenously during the initial 15 sec of a 60-min dynamic PET recording. FDGal was produced in our own radiochemistry laboratory (radiochemical purity $\geqslant$97%) [18]. PET data were reconstructed using iterative processing and a time-frame structure of 18×5, 15×10, 4×30, 4×60, and 10×300 s (total 60 min) and corrected for radioactive decay back to start of the recording.

Table 1. Patient characteristics.

Subject	Sex/age (yr)	Body weight (kg)	Etiology	Albumin (g/L plasma)	Bilirubin (μmol/L plasma)	ALT (U/L plasma)	ALP (U/L plasma)	Child-Pugh class	MELD score	Normalized GEC	HVPG (mmHg)
1	Male/61	70	Alcohol	43	14	43	n.a.	A	6	0.62	12.0
2	Male/66	86	Alcohol	37	11	28	80	B	8	0.60	18.5
3	Female/60	82	Cryptogenic	40	12	39	96	A	8	0.48	19.9
4	Male/57	79	Alcohol + HCV	35	18	121	155	B	8	0.45	30.5
5	Female/71	83	Cryptogenic	41	17	n.a.	n.a.	A	8	0.65	23.5
6	Male/50	93	Alcohol	36	11	23	98	B	8	0.51	22.0
7	Male/62	90	Alcohol	35	10	14	91	B	10	0.55	22.7
8	Male/65	62	Alcohol	33	20	21	104	B	13	0.49	24.0
9	Male/43	70	Alcohol	40	4	13	91	A	8	0.81	18.0

Albumin (reference interval 36–45 g/L plasma); bilirubin (reference interval 5–25 μmol/L plasma); ALT, alanine aminotransferase (reference interval 10–70 units/L plasma); ALP, alkaline phosphatase (reference interval 35–105 units/L plasma); n.a., not available; Child-Pugh class, patients were scored according to the Child-Pugh classification [14]; normalized GEC, galactose elimination capacity (GEC) normalized to the expected value from a healthy subject of same body weight, age, and sex; HVPG, hepatic venous pressure gradient; HCV, hepatitis C virus.