A liver function test based on measurement of liver-specific contrast agent uptake

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Introduction:
An important goal in grading liver disease is to assess the level of remaining liver function and to estimate regional liver function. New surgical and image-guided techniques lead to a growing need for non-invasive imaging methods for morphological and functional assessment of the liver and biliary system, ideally providing quantitative measures.

We have developed a liver function test based on quantitative analysis of the hepatic extraction of liver-specific MRI contrast agents. The test compensates for differences in renal extraction rate as well as differences in blood plasma volume and administered dose. Gd-EOB-DTPA (Primovist®, Bayer Schering Pharma AG, Berlin, Germany) and Gd-BOPTA (Multihance®, Bracco Imaging, Milan, Italy), eliminated via the hepatobiliary route by 50% and less than 5% respectively, were compared and evaluated in a group of healthy volunteers. A pilot study in patients with elevated bilirubin was also performed.

Materials and Methods: After approval by the local ethics committee, eight healthy volunteers were examined, five using Gd-EOB-DTPA (0.025 mmol/kg) and three using Gd-BOPTA (0.05 mmol/kg). Four patients with elevated bilirubin level were also included and examined using Gd-EOB-DTPA.

Imaging was performed in an Achieva 1.5T (Philips Medical, Best, the Nether_lands). A single breath hold fat saturated T1W 3DFFE sequence (THRIVE), TR 5.2 ms, α 10°, scan time 23 s, was acquired prior to, in the arterial and venous phase, and 5 (patients only), 10, 20, 30 and 40 minutes after the bolus injection.

Signal intensity (SI) curves were averaged from four different ROI's in the liver and two ROI's in the spleen. The SI time series were recalculated into *R1* time series for each organ using the sequence-specific signal equation, assuming equal initial *T1* in the different organs for all subjects. The contrast agent concentrations, C_{liver} and C_{spleen} were then estimated as

$C = (R1 - R1(t=0))/R$, where R is the relaxivity of the contrast agent.

The dynamics of the contrast agent liver uptake were analyzed using a simplified model assuming two compartments in the liver – blood and hepatobiliary – and two in the spleen – blood and splenic tissue, the latter inaccessible by contrast agent. The hepatobiliary compartment comprises hepatocyte intracellular water, bile canaliculi and ductules. The model attempts to estimate the contrast concentration in the hepatobiliary compartment, $C_{hepatobiliary}$, without influence from C_{blood}, the latter determined by measurements in the spleen:

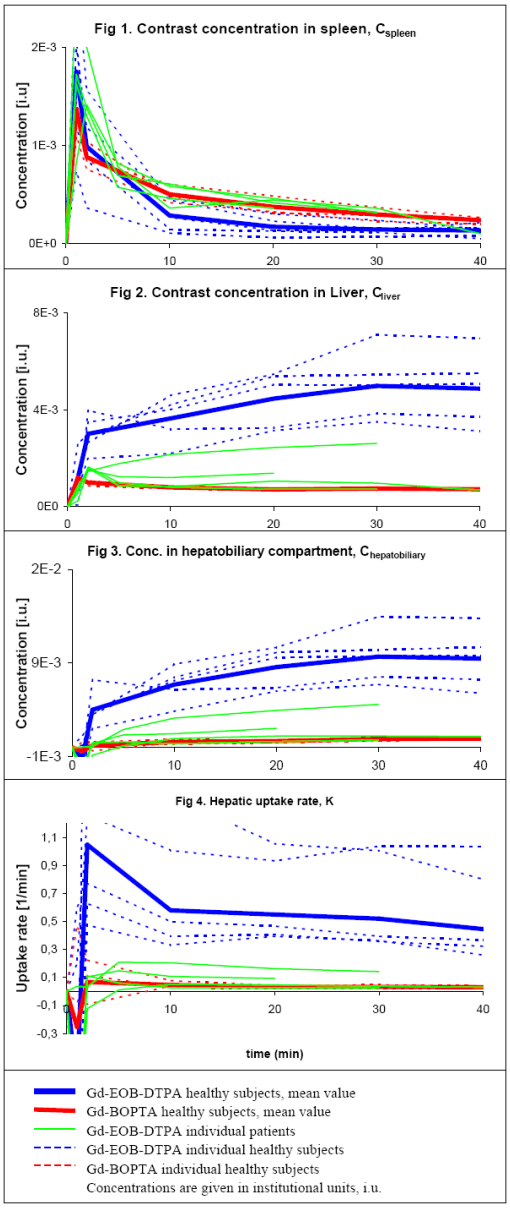
$C_{hepatobiliary} = (C_{liver} - C_{spleen})/\varphi_{blood}$, where φ_{blood} denotes the volume fraction of blood, assumed to be 0.5 in both spleen and liver.

In addition, an uptake rate was computed by relating $C_{hepatobiliary}$ to the total exposure of contrast during the time series:

$K = C_{hepatobiliary} / \int C_{blood}\, dt$.

If the hepatobiliary uptake of contrast is proportional to the blood plasma concentration, a constant value of K should be obtained regardless of variations in renal clearance, blood volume and contrast agent relaxivity. K is also expected to decrease in late time phases due to biliary contrast extraction.

Results: In late time phases, healthy Gd-EOB-DTPA subjects showed lower C_{spleen} than patients and Gd-BOPTA subjects, indicating higher clearance (Fig 1). Estimated C_{liver} differed clearly between the groups (Fig 2). Twenty min after contrast injection, the healthy Gd-EOB-DTPA subjects had 6.2 times higher contrast concentration than the Gd-BOPTA subjects. In patients, C_{liver} varied between the levels of the two groups of healthy subjects, indicating decreased hepatic uptake of Gd-EOB-DTPA. The apparent negative rate of contrast uptake in the patient and the Gd-BOPTA group in Fig 2 was after the correction of the influence from blood contrast agent positive, reflecting the active uptake of the contrast agent (Fig 3-4). At 20 minutes, $C_{hepatobiliary}$ is 12.6 times higher in the healthy Gd-EOB-DTPA subjects than in the Gd-BOPTA subjects (Fig 3).



Discussion: The results indicate that by using a simplified model describing the contrast agent dynamics we were able to estimate the active hepatic uptake of contrast agent. The obtained values are in good agreement with the known difference in hepatic uptake between Gd-EOB-DTPA and Gd-BOPTA (1, 2). The results in the patient pilot group indicate that impaired liver function is reflected in the lower hepatic uptake of Gd-EOB-DTPA. The method used has several limitations. For more reliable results, quantitative measurement of relaxivity should be used. In the current setup, the measurements are sensitive to patient motion, and the *T1* values are calculated based on assumed starting values neglecting differences in *T2** during the time series. The values of the volume fractions of the compartments should be identified and the methodology to measure the blood concentration based on relaxivity in the spleen should be validated. Despite these limitations, the results are promising and show that MR imaging with quantitative measurement of contrast uptake gives information about hepatobiliary function.

References: 1. (Gd-BOPTA) Kirchin MA. Invest Radiol 1998;33:798-809. 2. (Gd-EOB-DTPA) Schuhmann-Giampieri G. J Clin Pharmacol 1997;37:587-96.

Acknowledgement: This work was funded by the Linköping University Hospital Research Funds, and the Medical Research Council of Southeast Sweden.