Dynamic hepatospecific contrast enhanced-MRI with Gd-EOB-DTPA: correlation between MR quantitative parameters and hepatocyte transporter expression

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Purpose: The hepatic function is important to assess in liver cirrhosis because it has both prognostic and therapeutic implications[1,2]. A decrease in hepatocyte uptake transporters is a cause of altered function in liver cirrhosis[3]. Gd-EOB-DTPA is a hepatospecific MRI contrast agent which is partially taken up by hepatocytes and excreted in the bile through the OATP1-MRP and NTCP transporters[4,5]. The purpose of this study was to determine the correlations between quantitative functional parameters measured with dynamic Gd-EOB-DTPA enhanced MRI and the expression of hepatocyte transporters in rats with liver cirrhosis.

Material and methods: Twenty-one rats underwent a liver injury program composed of two weekly intraperitoneal injections of CCl_4 for 8 or 12 weeks. Nine normal rats were used as controls. Four rats died during the protocol. All rats underwent dynamic contrast enhanced MRI with Gd-EOB-DTPA (Eovist™, 0.025mmol/kg). The relative concentration versus time curves were analyzed quantitatively through deconvolution analysis with the portal input to determine the hepatic extraction fraction and the input relative blood flow[6]. All rats were sacrificed, liver fibrosis was staged at histopathology according to METAVIR and reverse transcription-polymerase chain reaction (RT-PCR) expression of the hepatocyte transporters Oatp1a1, Oatp1a4, Oatp1b2, Mrp2, Ntcp, Mrp3, and Mrp4 was measured. The functional parameters determined at dynamic contrast enhanced MRI between cirrhotic and control rats were compared with the Mann–Whitney U test. The correlations between MRI and RT-PCR were assessed with Spearman's rank correlation coefficients and multiple regression analysis.

Results: According to the METAVIR classification, 9 rats had F0 fibrosis, 2 F3 and 15 F4. The hepatic extraction fraction and relative blood flow decreased significantly in the rats with liver cirrhosis relative to the control rats (Fig 1). RT-PCR showed a decrease of the uptake transporters Oatp1a1, Oatp1a4, Oatp1b2 and Ntcp, a decrease of the biliary transporter Mrp2 and an increase of the backflux Mrp3 transporter (Fig 2). Significant correlations were observed between the hepatic extraction fraction and relative blood flow on one hand and the expression of the hepatocyte transporters on the other (Table 1). At multiple regression analysis, the hepatic extraction fraction was correlated to the expression of uptake transporters Ntcp and Oatp1b2.

Conclusion: The hepatic functional parameters determined at Gd-EOB-DTPA enhanced MRI correlate with the changes of hepatocyte transporters of the OATP1-MRP and NTCP systems in liver cirrhosis. In particular, the hepatic extraction fraction of Gd-EOB-DTPA correlates strongly with the expression of the hepatocyte uptake transporters Ntcp and Oatp1b2. These results suggest that the extraction fraction of Gd-EOB-DTPA is a marker of the decreased hepatocyte uptake function in liver cirrhosis.

References:

[1] Belghiti, HPB 2005
[2] Zipprich, Gut 2010
[3] Tsuda, Radiology 2010
[4] Leonhardt, Drug Metab Dispos 2010
[5] Millet, JPharmacol Exp Ther 2011
[6] Nilsson, J Magn Reson Imaging. 2009

	Quantitative parameters			
	HEF		irBF	
	p	r	p	r
Oatp1a1	< 0.0001	0.8	0.0011	0.6
Oatp1a4	< 0.0001	0.8	0.0014	0.6
Oatp1b2	< 0.0001	0.9	< 0.0001	0.8
Mrp2	0.0002	0.7	0.0204	0.5
Ntcp	< 0.0001	0.9	< 0.0001	0.7
Mrp3	0.0036	-0.6	0.0020	-0.6
Mrp4	0.9534	0.0	0.3150	-0.2

Table 1 - Correlation between quantitative parameters and hepatocyte transporter expression

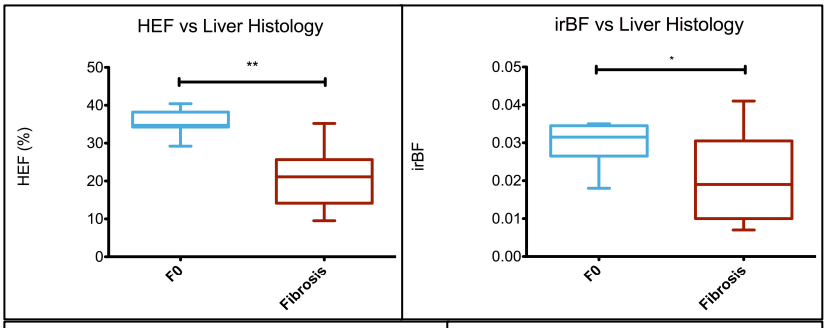

Figure 1 – Comparison of hepatic extraction fraction (HEF) and input relative blood flow (iRBF) in normal and cirrhotic rats

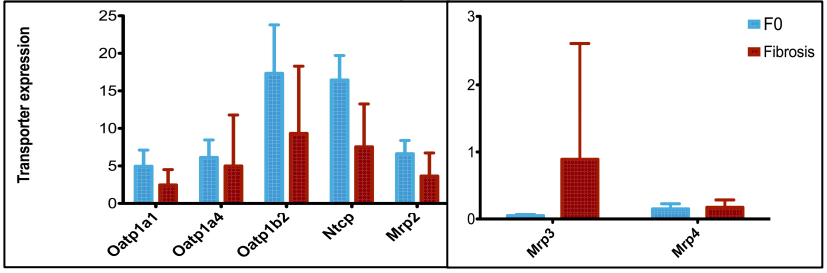

Figure 2 –Hepatocyte transporter expression