Quantification of the hepatobiliary uptake of Gd-EOB-DTPA can separate advanced from mild fibrosis

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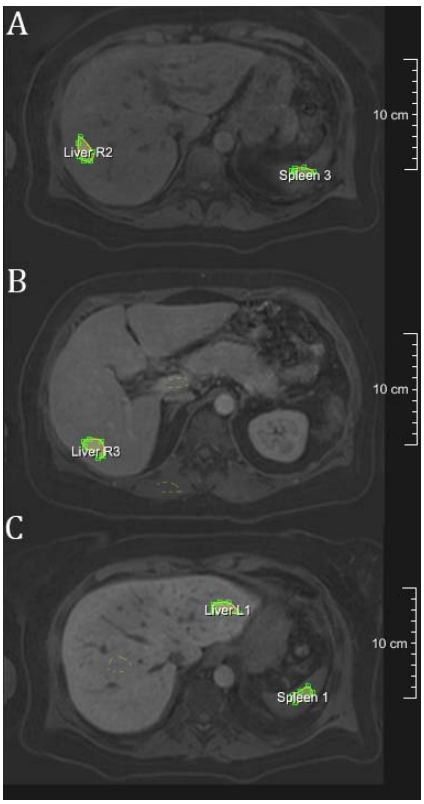

Fig. 1 *Representative ROI placement in the liver and spleen, in the same patient at varying time points, following a bolus injection of Gd-EOB-DTPA. The images were taken at pre-contrast (**Panel A**), portal venous phase (**Panel B**) and 30minuts post contrast (**Panel C**) respectively. ROIs were placed in both the left and right lobes of the liver, spread into several slices. Care was taken so that each ROI was in the same anatomical region throughout the time series.*

Introduction: In patients presenting with elevated liver enzymes without clinical signs of hepatic decompensation liver biopsy is often performed in order to assess fibrosis stage, which is a strong predictor of prognosis in many liver diseases. A wide range of non-invasive procedures, such as transient elastography (*FibroScan*), arrays of blood tests and various applications of Magnetic Resonance (elastography (MRE), spectroscopy (MRS) and diffusion (DWI)), have been proposed to replace liver biopsy, the current gold standard. The purpose of this study was to quantitatively measure the hepatocyte-specific uptake of Gd-EOB-DTPA using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and compare it with histopathological fibrosis stage.

Materials and Methods: In this prospective study, 38 asymptomatic patients were studied between 2008 and 2010. The patient group consisted of 21 men (median age: 45, range: 20-65 years) and 17 females (median age: 55, range: 27-77 years). They were referred to our hospital for evaluation of elevated serum alanine aminotransferase (ALT) and/or alkaline phosphatase (ALP) levels. Physical examination revealed no signs of liver disease, and none of the subjects reported weekly alcohol consumption exceeding 140 g.

Liver biopsy was performed on an outpatient basis using a 1.6 mm Biopince needle (Medical Device Technologies Inc., FL, USA). Biopsies were graded and classified according to the Batts and Ludwig system [1], i.e. fibrosis was staged as: no fibrosis (F0), portal fibrosis (F1), periportal fibrosis (F2), septal fibrosis (F3) and probable or obvious cirrhosis (F4). All biopsies were read by the same liver pathologist, who was blinded to patient details and the MR examination results. The biopsy scores were grouped into no/mild fibrosis (F0-2, *n*=27) and advanced fibrosis (F3-4, *n*=11).

A 1.5 T magnetic resonance system (Achieva, Philips Medical Systems, Best, The Netherlands) was used together with a phased-array body coil. Data were acquired from region of interests (ROIs) placed in the liver (*n*=7) and the spleen (*n*=3) in a T1-weighted 3D GRE MR imaging time-series (native, arterial and venous portal phase; 3, 10, 20 and 30 minutes) following a bolus injection of Gd-EOB-DTPA (0.025 mmol/kg) administered intravenously at a rate of 1 mL/s using a power injector (Medrad Spectris Solaris, Pittsburgh, PA, USA). The 20 minutes post-contrast acquisition was missing in two patients. ROIs were placed by an experienced radiologist avoiding focal lesions, large vessels and bile ducts (**Fig. 1**). ROI signal intensities (SI) were normalized and recalculated to relaxation rate values, *R1*, according to [2]. The *R1* values were used to determine contrast uptake rate (K_{Hep}) and the quantitative Normalized Liver Spleen Contrast (LSC_*N*) ratios LSC_*N*10 and LSC_*N*20, corresponding to 10 and 20 min post-contrast respectively, as described in [2]. For comparison, the Liver Spleen Contrast (LSC) ratio was determined according to [3], at 10 and 20 min post-contrast (LSC10 and LSC20, respectively). Groups were compared with an unpaired Wilcoxon test, and logistic regression including ROC analysis was performed.

Table 1 *Mean and standard deviation for the estimated rate and ratios grouped by their fibrosis grade (F0-F2 and F3-F4). The reported AUROC values indicate the variables' ability to discriminate between F3-4 and F0-2. In the last column, the p values for group differences are shown.*
[a] n = 27, [b] n = 26, [c] n = 11, [d] n = 10, † based on unpaired Wilcoxon test

	F0-2	F3-4	AUROC	p-value†
K_{Hep}	0.436±0.255[a]	0.293±0.254[c]	0.71	0.050*
LSC_*N*10	1.405±0.120[a]	1.243±0.138[c]	0.80	0.004**
LSC_*N*20	1.555±0.160[b]	1.382±0.161[d]	0.78	0.010*
LSC10	1.652±0.196[a]	1.504±0.252[c]	0.68	0.090
LSC20	1.823±0.265[b]	1.663±0.291[d]	0.64	0.223

Results: The determined hepatocyte-specific rate and ratios are shown in **Table** 1. AUROC values of 0.71, 0.80 and 0.78, respectively, were found for K_{Hep}, LSC_*N*10 and LSC_*N*20 with regard to fibrosis F3-4 versus F0-2. The non-normalised liver-spleen ratios yielded an AUROC value of 0.68 and 0.64 for 10 and 20 minutes post-contrast respectively (**Table 1**). Significant group differences were found for K_{Hep}, LSC_*N*10 and LSC_*N*20.

Discussion and Conclusions: A recently published study [7] showed a moderate inverse correlation between a hepatocyte-specific contrast enhancement index and fibrosis stage. Applying a new quantification procedure for calculation of the hepatocyte specific contrast uptake [2], this study can confirm that impaired hepatobiliary function severely influences the hepatocyte-specific uptake of Gd-EOB-DTPA and shows promising results for a non-invasive approach to separate mild/moderate liver fibrosis from advanced. The normalized LSC ratios show a significant group difference, which the SI-based LSC ratios fail to distinguish. Our results show, in agreement with a previous study [2], that the normalization procedure is an important step for removing patient and likely system bias. Potentially, the conversion of the normalized SI to *R1*, used for K_{Hep} determination, will further reduce patient and system bias yielding a robust approach for liver function determination. In comparison to MRE, which measures the mechanical properties of the liver, the proposed quantitative DCE-MRI analysis is a measure of liver function. These two techniques could probably be used together as complementary measures, possibly with the addition MRS, as replacement for invasive diagnostics. Further DCE-MRI studies are needed to evaluate the technique as a non-invasive tool to evaluate fibrosis stage, which could possibly even be employed on a segmental or voxel level.

References: [**1**] Batts KP, Ludwig J, Am J Surg Pathol 1995;19(12):1409-17. [**2**] Dahlqvist Leinhard O *et al*, Eur Radiol 2011 Oct 9. [Epub ahead of print]. [**3**] Motosugi U *et al*, Eur Radiol 2009;19(11):2623-29. [**4**] Bonekamp *et al*, J Hepatol 2009;509(1):17-35. [**5**] Nguyen D *et al*, Hepatology 2011;53(6):2107-10. [**6**] Nilsson H *et al*, HPB 2010;12(8):567-76. [**7**] Watanabe H *et al* Radiology 2011;259(1):142-50.