Distinction between non-advanced and advanced liver fibrosis: Comparison between MR DCE imaging and T2-corrected IVIM at 3.0T.

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Introduction

Liver fibrosis is an important cause of mortality and morbidity in patients with chronic liver diseases and cirrhosis, end-stage of fibrosis, involve 15,000 and 40,000 deaths per year in France and in USA respectively (1,2). Reversible aspect of liver fibrosis has been recognized, and more effective treatment strategies have emerged. Nevertheless these latter require an early detection and a clinical follow-up of liver fibrosis. While liver biopsy is the gold standard for the diagnosis of chronic liver diseases, inherent risk, interobserver variability and sampling errors makes liver biopsy unusable for the clinical follow up. Thus, there is a real clinical need in the development of non-invasive methods for liver fibrosis assessment. At 1.5 T, human *in-vivo* studies have demonstrated that liver perfusion imaging using a MR dynamic contrast enhanced method (MR-DCE) has the potential to detect and assess vascular modifications associated to liver fibrosis (3,4). On another hand, intra-voxel incoherent motion imaging (IVIM) has been proposed to asses liver fibrosis (5). This technique was able to separate two kind of diffusion: the pure molecular diffusion and the perfusion-related diffusion. Our objective was to combine IVIM with perfusion imaging using a MR-DCE technique at 3.0 T and evaluate this protocol for fibrosis severity assessment on a prospective study including patients with chronic liver diseases. Through this study, perfusion-related diffusion parameters given by IVIM and quantitative perfusion parameters given by MR-DCE imaging were compared.

Materials and Methods

Subjects: Twenty two subjects (10 W, 12 M; mean age: 43.8 ± 14.6 years; mean weight: 74.3 ± 15.9 Kg) with chronic liver diseases were prospectively enrolled. Liver fibrosis was histologicaly quantified with METAVIR and Brunt or CRN quantification in patients with viral hepatitis and NAFLD respectively. ***MR acquisition:*** Acquisitions were performed on a 3.0 T Discovery MR 750 *(GEHC, Milwaukee, WI, USA).* Dynamic acquisition was performed with a 3D LAVA sequence employing the autocalibrating reconstruction for cartesian imaging with an accelerating factor of 3. Acquisition parameters were: TR/TE, 1.9/0.8 ms; 9° flip angle; 128 × 160 acquisition matrix (256² rebuilding); 480² mm² FOV; 2/3 partial K-space filling, 24 cm slab thickness including 48 coronal slices of 5 mm thickness rebuilt with a ZIP 2 interpolation algorithm. Temporal resolution was 1.8 s. Dynamic acquisition started simultaneously with contrast medium injection *(Multihance, Bracco s.p.a, Milano, Italy*) and lasted 180 s in free-breathing. Injection rate was 6.0 mL.sec^{-1} and posology was 0.2 mL.Kg^{-1}. IVIM was performed using a single-shot SE-EPI sequence, in free breathing, with 12 b-values (0-10-20-40-60-80-100-200-300-400-600-800 s.mm^{-2}) and a weighted signal averaging procedure (2 to 9 signal accumulations according to b-values). Three orthogonal diffusion gradients were sequentially applied. A 2000 ms TR, 54 ms minimum TE; 21 axial slices of 8 mm thick; 400 × 300 mm² FOV; 128 × 96 acquisition matrix (256² rebuilding) were used. Scan duration was 5'12". ***Images processing:*** First, a dedicated algorithm was used to quantify perfusion parameters. It included an image registration procedure based on affine transformation. signal intensity was converted into relative concentration using $C(t) = (S(t) - S_0) / S_0$. Quantitative perfusion parameters were quantified using a non-linear least square fit on a dual-input one compartment model. This model includes two delays (arterial and portal) and gives three main perfusion parameters: arterial and portal perfusion and Mean Transit Time (MTT). Hepatic Perfusion Index (HPI) was calculated as the arterial perfusion to total perfusion ratio. Regional Blood Volume (RBV) was calculated as RBV = MTT × Total perfusion. IVIM parameters (pure molecular diffusion coefficient, D_{Slow}; perfusion fraction, f; and perfusion-related diffusion coefficient, D_{Fast}) were calculated from the diffusion-weighted set of images using a non-linear least-square fit to a modified bi-exponential IVIM model with the Levenberg-Marquardt algorithm. This model was based on Le Bihan's model (6) and including a T_2 correction to compensate T_2 relaxation difference between blood and hepatic tissue. This correction used *a-priori* T_2-values (34 and 255 ms for liver and blood respectively). To reduce local minima problems, all optimization algorithms started with a grid of pseudo-random initial coefficients generated between two threshold values. Each fit procedure was done with 1000 different initializations.

Tab.1: *Mean perfusion and IVIM parameters stratified according to fibrosis severity and p-values calculated using the Wilcoxon test.*

Fibrosis severity	**Non-advanced fibrosis**	**Advanced fibrosis**	**p-value**
Arterial perfusion *(ml.min^{-1}.100g^{-1})*	36.3 ± 14.7	27.3 ± 19.0	0.21
Portal perfusion *(ml.min^{-1}.100g^{-1})*	**84.2 ± 25.7**	**28.3 ± 11.0**	**0.00008**
Total perfusion *(ml.min^{-1}.100g^{-1})*	**120.5 ± 28.4**	**55.6 ± 24.9**	**0.0003**
HPI *(%)*	**30.1 ± 10.8**	**45.5 ± 16.0**	**0.03**
MTT *(s)*	**5.06 ± 1.25**	**11.2 ± 4.41**	**0.0003**
RBV *(ml.100g-1)*	10.4 ± 4.18	9.43 ± 3.74	0.64
D_{Slow} *(×10^{-3} mm.s^{-2})*	**1.06 ± 0.11**	**0.87 ± 0.06**	**0.0009**
f *(%)*	3.90 ± 1.56	5.04 ± 2.50	0.4
D_{Fast} *(×10^{-3} mm.s^{-2})*	**89.5 ± 15.1**	**66.8 ± 6.59**	**0.0005**

Results

Histological results were: 5 NASH (2 scored Brunt 2 and 2 scored Brunt 3), 2 NAFLD (scored Brunt 0), 13 viral hepatitis (2 scored F0, 5 scored F1, 3 scored F2 2 scored F3 and 1 scored F4) and 2 cholangiopathies without fibrosis. Using these results, two groups were constituted: non-advanced fibrosis for subjects with METAVIR < F2, Brunt < 2 or CRN < F2; advanced fibrosis, for subjects with METAVIR ≥ F2, Brunt ≥ 2, or CRN ≥ F2 advanced fibrosis. Statistical relevance of IVIM and perfusion parameters to distinguish between these two groups was evaluated using the Wilcoxon test. IVIM and perfusion parameters stratified according to each group then p-values are summarized in Tab.1. Portal and total perfusion, D_{Slow} and D_{Fast} significantly decreased between non-advanced and advanced fibrosis. Portal perfusion diminution induced a significant increase of HPI between these two groups. MTT was significantly longer in advanced fibrosis. In patients without fibrosis, mean D_{Slow}-values were smaller for patients with NAFLD than in patients with chronic hepatitis (9,61 ± 0.02 vs. 1,16 ± 0.06 *×10^{-3} mm.s^{-2}).* Between IVIM and perfusion parameters, a strong correlation was found between D_{Fast} and portal perfusion or total perfusion (Spearman's rho = 0.77 and 0.69 respectively, p <0.001).

Discussion

Perfusion parameter variations confirm the existence of hemodynamic changes associated with fibrous damage. Parameter modifications are consistent with previous results obtained at 1.5 T (4). The deposition of extracellular matrix components in liver fibrosis restricts the pure molecular diffusion as illustrated by D_{Slow} decrease with fibrosis severity. As suggested by the correlations between D_{Fast} and total perfusion or portal perfusion, D_{Fast} reflects the hemodynamic changes, in particularly the decrease of portal perfusion induced by fibrosis. As showed by D_{Slow}-values differences between NAFLD and chronic hepatitis for the group with no fibrosis, fat vesicles in NAFLD also restrict pure molecular diffusion. Even if this double contribution to molecular diffusion restriction did not affect the relevance of this parameter to evaluate fibrosis severity in this study, fat overload has to be taking into account with IVIM since it may constitute a confounding factor for fibrosis evaluation. In the present case, histology-confirmed fat overload did not modified perfusion parameters-values. All these issues suggest that the combination of IVIM with MR DCE imaging do not bring additiona information to assess liver fibrosis. Indeed, perfusion parameters given by MR-DCE imaging alone are already relevant to evaluate fibrosis severity. Nevertheless, T_2-corrected IVIM could be a useful injection-free alternative to distinguish between non-advanced and advanced fibrosis.

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