Distinction between pure steatosis and NASH using a fat quantification method in combination with liver intravoxel incoherent motion imaging in MRI at 3.0 T.

Benjamin Leporq[1], Frank Pilleul[1,2], Jerome Dumortier[3], Olivier Guillaud[3], Thibaud Lefort[3], and Olivier Beuf[1]

[1]CREATIS; CNRS UMR 5220; INSERM U1044; INSA-Lyon; UCBL, Université de Lyon, Villeurbanne, Rhône-Alpes, France, [2]CHU Edouard Herriot; Department of digestive imaging, Hospices Civils de Lyon, Lyon, Rhône-Alpes, France, [3]CHU Edouard Herriot; Department of Hepatology, Hospices Civils de Lyon, Lyon, Rhône-Alpes, France

Introduction

In the past decade, the incidence rise of obesity, particularly of childhood obesity (1), diabetes and lipid metabolism disorders involved an epidemic increase of Non-Alcoholic Fatty Liver Diseases (NAFLD) prevalence which was estimated at 33.6 % in the USA (2) and between 20 and 30 % in Europe (3). In about 20 % of cases, NAFLD evolves to its aggressive form known as Non-Alcoholic SteatoHepatitis (NASH) and characterized by inflammation and fibrosis in addition to steatosis. Many of these patients may lead to cirrhosis, the end-stage of liver fibrosis. Complications such as hepatic decompensation, portal hypertension and hepatocellular carcinoma (HCC) are becoming a growing public health concern. Fat content quantification and distinction between pure steatosis and NASH is clinically important and drive the therapeutic strategy. While histology after liver biopsy is the gold standard for liver steatosis diagnosis to distinguish between NASH and pure steatosis, inherent risk with a recognized morbidity and mortality renders this method unsuitable and problematic for longitudinal clinical monitoring, particularly on children (4). Furthermore, liver biopsies have other limitations such as cost, inter-observer variability and sampling errors (5). For these reasons, non-invasive and cost effective quantification methods have been developed to quantify liver fat content (6,7). These latter allow an accurate quantification of fat content but are inadequate to separate between pure steatosis and NASH. On another hand, intra-voxel incoherent motion imaging (IVIM) has been proposed to asses liver fibrosis (8). Thus, the aim of this study was to evaluate the combination of liver IVIM and a MRI fat quantification method at 3.0 T to make the distinction between NASH and pure steatosis.

Materials and Methods

Subjects: 33 healthy volunteers constituted the control group and 20 subjects with NAFLD the patients group (16 with pure steatosis (Brunt = 0) and 4 with NASH (2 scored Brunt 2 and 2 scored Brunt 3)). Pure steatosis group was subdivided into 2 groups: mild steatosis (grade 1) and moderate steatosis (grade 2). ***MR acquisition:*** Acquisitions were performed on a 3.0 T GE Discovery MR 750 (*GEHC, Milwaukee, WI, USA*) system. For fat quantification, a 2D SPGR sequence with the ASSET procedure for parallel imaging was used. SPGR sequence was repeated 4 times on the liver with 4 different flip angles: 5°, 15°, 30° and 45°. Fifteen slices of 10 mm thickness in the axial plane were acquired using 4 echoes: 1.10, 2.33, 3.55 and 4.78 ms; a 100 ms TR; a 256² matrix; a 410 mm^2 FOV; a 976 $Hz.pixel^{-1}$ receiver bandwidth and 1 signal accumulation. Signal was collected using a 32-channel body coil. Acquisitions were realized in apnea and scan duration was 14 s per acquisition. 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 using the multiple-echo multiple angle set of images, correcting for relaxation time effects using a disjointed estimation of T_1 and T_2^*-values of fat and water, accounting for the NMR spectrum of fat and solving the component dominant ambiguity leaded to seven parametric-maps: a fat volume fraction (FVF) map, relaxation times (T_1 and T_2*) and proton density maps of fat and water respectively. IVIM parameters (pure molecular diffusion coefficient, D_{Slow}; perfusion fraction, f; and perfusion-related diffusion coefficient, D_{Fast}) were mapped from the diffusion-weighted set of images using a non-linear least-square fit to the bi-exponential IVIM model (8), with the Levenberg-Marquardt algorithm. ADC was also computed using a mono-exponential approach and two b-values (b = 0 and 800 $s.mm^{-2}$). To reduce local minima problems, optimization algorithm was started with a grid of pseudo-random starting coefficients generated between two threshold values. Each fit procedure was done with 50 different initializations.

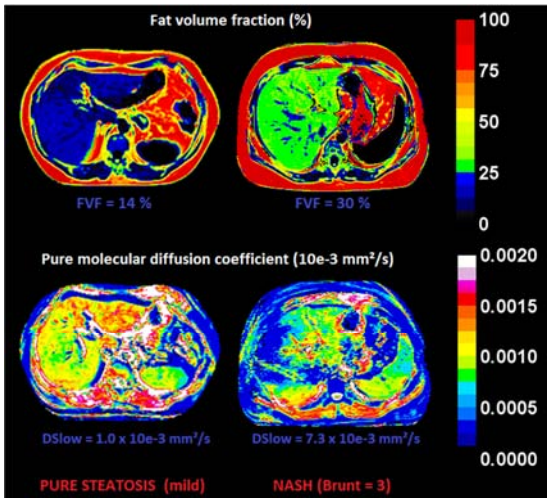
Tab.1: *Mean fat and water relaxation times, FVF, IVIM parameters and $ADC_{0/800}$ in the control group, in pure steatosis subgroups and in the NASH group.*

	Control	Pure steatosis (mild)	Pure steatosis (moderate)	NASH
Water T_1 *(ms)*	732 ± 65	676 ± 85	738 ± 77	794 ± 287
Fat T_1 *(ms)*	/	276 ± 37	300 ± 57	284 ± 87
Water T_2* *(ms)*	20.5 ± 3.8	21.2 ± 2.5	18.1 ± 3.6	18.2 ± 1.1
Fat T_2* *(ms)*	/	20.3 ± 7.0	21.7 ± 6.2	28.0 ± 8.2
FVF *(%)*	2.9 ± 0.9	7.6 ± 2.5	25.6 ± 7.3	23.8 ± 4.5
D_{Slow} *($\times 10^{-3}$ mm.s^{-2})*	1.11 ± 0.08	1.06 ± 0.08	1.03 ± 0.10	0.83 ± 0.07
f *(%)*	19.7 ± 6.0	18.6 ± 5.1	22.7 ± 6.6	18.0 ± 4.4
D_{Fast} *($\times 10^{-3}$ mm.s^{-2})*	104 ± 27.3	112 ± 51.7	105 ± 48.1	68.7 ± 10.6
$ADC_{0/800}$ *($\times 10^{-3}$ mm.s^{-2})*	1.37 ± 0.15	1.30 ± 0.12	1.34 ± 0.12	1.11 ± 0.14

Results

In-vivo results were summarized in Tab.1. Wilcoxon tests showed that D_{Slow} was significantly lower in mild and moderate pure steatosis compared to the control group ($p<0.05$). No significant differences were observed between mild and moderate steatosis. In NASH group, D_{Slow} decreased significantly compared to control group, mild and moderate steatosis group individually taken ($p<0.01$). D_{Fast} did not varied between control group and pure steatosis groups (mild and moderate) but decreased significantly in the NASH group ($p<0.01$).

Fig.1: *Example of FVF and D_{Slow} parametric maps computed in a patient with a grade 1 pure steatosis (left) and in a patient with a NASH scored Brunt = 3 (right).*



Discussion

Fat vesicles in patients with pure steatosis restrict molecular diffusion without modification of micro-perfusion as illustrated by the significant decrease of the pure molecular diffusion in patients with pure steatosis compared to the control group. In patients with NASH, fibrosis still increase the restriction of molecular diffusion compared to patients with pure steatosis and decrease the micro-perfusion as illustrated by the significant decrease of both molecular and perfusion-related diffusion coefficients in the NASH group compare to others. Diminution of pure molecular diffusion between NASH and pure steatosis was not found related to fat content. Indeed, despite high fat content difference between mild and moderate pure steatosis (7.6 % vs. 25.6 %), no D_{Slow} variations were found significant between these subgroups. These preliminary results indicate that the combination of a fat quantification method correcting for confounding factors such as relaxation times and fat spectrum complexity with IVIM could be a non-invasive mean to evaluate steatosis severity and to distinguish between pure steatosis and NASH. Significant difference about D_{Slow}-values observed between the control group and pure steatosis patients suggest that fat overload may constitute a confounding factor when IVIM is use alone to assess liver fibrosis. These results need to be confirmed with larger groups.

References

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