MR-liver fat volume fraction quantification using a magnitude-based technique with independent fat and water T2* estimations, T1-related bias correction and accounting for fat multiple resonances

Benjamin Leporq1, Helene Ratiney1, Herve Saint-Jalines2,3, Frank Pilleul1,2, and Olivier Beut1
1CREATIS, CNRS UMR 5220; INSERM U1044; INSA-Lyon; UCBL Lyon 1, Villeurbanne, Rhône-Alpes, France; 2LTSI, INSERM U642; Université Rennes 1, Rennes, Bretagne, 3CRLCC, Centre Eugène Marquis, Rennes, Bretagne, France; 4Hospices civils de Lyon; CHU Edouard Herriot, Lyon, Rhône-Alpes, France

INTRODUCTION
In Western countries, Non Alcoholic Fatty Liver Disease (NAFLD) is the most common cause of chronic liver disease. In about 20% of cases, NAFLD leads to steatohepatitis with liver fibrosis then to cirrhosis whose complications are an important cause of morbidity and mortality. While the histology after liver biopsy is the gold standard for liver steatosis assessment, inherent risk, interobserver variability and sampling errors of this method are inappropriate for clinical follow-up. Several accurate and non-invasive MR quantification methods have been proposed for liver fat fraction quantification including 1H MRS, low flip angle and single T1*, IDEAL, or low flip angle multiple gradient echoes. The aims of this work were to validate a magnitude-based technique for liver fat volume fraction (FVF) quantification with independent fat and water T2* estimations, a T1-related bias correction and accounting for the fat multiple resonances using a two-angles multiple gradient-echo acquisition. Validations were performed on an in-vivo prospective study at 1.5T, an in-vivo study on healthy volunteers at 3.0T and a fat-water emulsion phantom study at 3.0T where the presented method is compared with MRS FVF quantification.

MATERIAL AND METHOD
Subjects: At 1.5T: Fifteen subjects (4 women and 11 men; mean age: 55.0 ± 11.4 years; mean weight: 79 ± 11.7 kg) with biopsy-confirmed chronic liver diseases with NAFLD or at risk for NAFLD were enrolled prospectively. Steatosis was quantified as the proportion of hepatocytes containing intracellular vacuoles of fat, then stratified as follows: grade 0 (normal); < 5% of cells affected; grade 1 (mild); 5-33%; grade 2 (moderate): 34-66% and grade 3 (severe) > 66%. At 3.0T: Eight healthy volunteers (2 women and 6 men; mean age: 25.7 ± 1.8 years; mean weight: 68.2 ± 8.0 kg) with no risk for liver steatosis were enrolled.

MR acquisition: At 1.5T: Acquisitions were performed on a Magnetom Symphony (Siemens Medical Solutions, Erlangen, Germany). FLASH 2D sequence was repeated twice on the liver with two flip angles: 15° and 70°. Acquisition parameters were: 6 first Out-of-Phase (OP) echoes and 6 first In-Phase (IP) echoes; TR/TE, 219/2 ± 2.8 ms with n = 1,…,12; 208 ± 256 matrix; 244 × 400 mm FOV; 500 Hz/pixel bandwidth and 8 mm slice thickness in the axial plane. At 3.0T: Acquisitions were performed on a GE Discovery MR 750 (GEHC, Milwaukee, WI, USA) using a 8-channels torso coil. FSPGR with a two-angles multiple gradient-echo acquisition was repeated twice on the liver with two flip angles: 5° and 45°. Acquisition parameters were: 2 first Out-of-Phase (OP) echoes and 2 first In-Phase (IP) echoes; TR/TE, 100/1 × 1.2 ms with n = 4,…,8; 256 matrix; 410 × 410 mm FOV; 976 Hz/pixel bandwidth, 2 NEX and 8 mm slice thickness in the axial plane. All acquisitions were performed in breath-holding.

Phantom study: Nine lipid individual emulsions with increasing fat concentration with Gd-doped water (between 1.6 to 3.2 mL), oil surfactant and agar gel (between 0.25 to 0.5 %) were scanned at 3.0T by MRI and MRS acquisition parameters were: PROBE STEAM sequence with TR/TE, 3000/14 ms; (1.5) cm² voxel, 2048 readout points and 8 NEX. MRI parameters were the same as in vivo.

Post-processing was performed using an in-house application on Matlab R2010a (The MathWorks, Natick, MA, USA). Separation of fat and water signal was performed using a 2-parameters interference bi-exponential model. Then, apparent T1 (T1app) assuming a mono-exponential signal (single component) was estimated from the first IP images acquired with the two angles because T1 of fat (T1fat) is almost invariant, it was fixed at 340 and 390 ms at 1.5T and 3T respectively and then T1 of water (T1water) was calculated as: T1water = (T1app + (Mfat/Mwater) × T1fat) / (1 - (Mfat/Mwater + Mwater)). This relation was verified from fat and doped water mixture phantoms with measurement of pure water T1-values, pure fat T1-values and equally-mixed fat-water T1-values. Finally, quantification of proton density fat fraction (PDDF) was performed using a 4-parameters dual-T1* bi-exponential model including a T1 correction from previous estimated T1-values and a five resonance fat modeling (at 0.9-1.2-2.1-4.2 and 5.3 ppm) as described by Hamilton et al (6). Fat volume fraction (FVF) was then computed with: FVF = PDfat / (k × PDfat + PDwater) (k = a scaling coefficient (k = 0.95) correcting for the relative difference between proton density of fat (PDf) and water (PDw) as described by Reeder et al (7). All results were measured on 4 regions of interest (12.7 cm²) each and all fits were realized using the Levenberg-Marquardt algorithm and multi-start technique to improve fit robustness. Based on a pixel-by-pixel computing, 5 parametric maps (T1, T2* recombed, PDf, PDw and fat volume fraction) were generated. MRI post-processing consisted in generating spectra for each coil for the zero order phase and in combining them using a sum of squares weighting function. Combined spectra were quantified using a nonlinear least-squares algorithm that fits the time-domain signal to a Voigt model function and uses multiple random starting values and bounds (8). Ten Voigt components were selected from 0.9ppm to 4.7ppm. The total fat signal was calculated by summing the amplitude from peaks located at identical locations as the multi-peak fat spectrum used for MRI. The water and fat amplitudes were then corrected for T2 decay using a priori knowledge of the emulsions T2 values. As MRI, PDDF was calculated as PDDF = PDf / (PDw + PDf).

RESULTS
Histological results were as follows: 7 subjects scored grade 0; 4 scored grade 1 (mean: 27.5 ± 5%); 3 scored grade 2 (mean: 46.5 ± 5.8%) and 1 scored grade 3 (90%).

Phantom study: Regression coefficient (r) between MRI and MRS was r = 0.99; p<0.001 (Fig. 1).

In-vivo study: MR results were strongly correlated with histology (Pearson’s coefficient = 0.99, p<0.001) (Fig. 1). 1.5T: FVF stratified according to the grade of steatosis were: 0.67 ± 0.3%; 12.0 ± 1.54%; 18.4 ± 2.90% and 33.3% for grade 0 to 3 respectively when T1 correction was considered. With any T1 correction, FVF was systematically higher: 3.61 ± 4.09%; 17.9 ± 3.1%; 27.3 ± 3.4% and 46.5% for grade 0 to 3 respectively. Mann-Whitney test showed a significant difference between grade 0 vs. grade 1-3, between grade 1 vs. grade 2 and between grade 1 vs. grade 2-3 (p<0.001). 3.0T: FVF MR results were 2.2 ± 1.1% and 5.5 ± 0.9% with and without T1 correction respectively. Mean water T1*were: 21.9 ± 3.7 ms and 23.1 ± 5.7 ms at 1.5T and 3.0T respectively. Mean fat T1* were: 20.5 ± 5.6 ms and 5.07 ± 1.1 ms at 1.5T and 3.0T respectively. Mean T1 of water was 587 ± 105 ms and 793 ± 131 ms at 1.5T and 3.0T respectively.

DISCUSSION
Phantom study showed a very good agreement between the MRI method and MRS. 1.5T in-vivo results showed that MR-estimated FVF and histological results were strongly correlated and FVF estimates allowed a good separation between steatosis stages. Nevertheless, these results were correlated but not in agreement because FVF and histological analyses do not measure the same parameter. Liver water T1-values at 3.0T and 1.5T estimates were close to be literature in the condition (9). In-vivo results obtained at 3.0T were in accordance with results expected on healthy subjects. All these features demonstrate the good accuracy of this method and its ability in being used on different MR platform. Results obtained without any T1 correction were an overestimation of fat fraction compared to results obtained with T1 correction. Hence, at 3.0T and without T1 correction, grade 0 of steatosis could be erroneously scored as grade 1. This observation demonstrates the need to avoid T1 effect or to correct for it especially at 3.0T. Due to magnitude correction, the amplitude of FVF quantifiable with this method is limited to 0-50%. This is a minor limitation since FVF greater than 50% are uncommon in liver. Moreover, post-processing step was simplified especially since noise and eddy-current bias encountered with complex-based method were avoided. In conclusion, this method allows FVF quantification, corrected for the different confounding factors of fat and water respectively. The estimated FVF could be a suitable biomarker for the clinical follow-up of patients with NAFLD or at risk. Nevertheless, this latter is not dependent on acquisition parameters and could be transposable on any clinical systems and fields. Nevertheless, this results need to be confirmed with further large scale prospective study.

REFERENCE
[6] Reeder et al. ISMRM 2009 proceedings
[10] CRLCC; Centre Eugène Marquis, Rennes, Bretagne, France; 4Hospices civils de Lyon; CHU Edouard Herriot, Lyon, Rhône-Alpes, France