



More promising results of liver intravoxel incoherent motion imaging analysis for the assessment of nonalcoholic steatohepatitis and fibrosis

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Diffusion-weighted imaging (DWI) has many advantages. It is widely available among MRI scanners, and has the ability to provide both tissue diffusion and perfusion information without an intravenous contrast agent or additional hardware. Le Bihan *et al.* (1) proposed the intravoxel incoherent motion (IVIM) principle of DWI, which provides the estimation of quantitative parameters reflecting tissue diffusivity [slow diffusion (D_{slow})] and tissue microcapillary perfusion [PF (perfusion fraction) and fast diffusion (D_{fast})]. We proposed that the relationship between liver DWI signal and b -values can be separated into two parts: part-1 is the signal difference between the $b=0$ s/mm² image and the first very low b -value image; the rest is part-2 and fitted with a bi-exponential decay model starting from the first non-zero very low b -value data (2,3). On DWI, blood vessels show a high signal when there is no diffusion gradient ($b=0$ s/mm²) and a low signal even when very low diffusion gradient values (e.g., $b=1$ s/mm²) are applied. Therefore, for part-1, the signal difference between images when the diffusion gradient is off and images when the diffusion gradient is on, reflects the extent of tissue vessel density [referred to as diffusion-derived vessel density (DDVD)] (2,4). For part-2, starting from a nonzero very

low b -value, the relationship between DWI signal and b -value follows a bi-exponential decay (2,3). It has been shown that DDVD is correlated with the IVIM parameters and is a useful biomarker for the separation of livers with and without fibrosis, and livers with severe fibrosis tend to have even lower DDVD measurement than those with milder liver fibrosis (4). Recently, we demonstrated that liver parenchyma in healthy subjects has an aging-dependent decrease of DDVD and D_{slow} (5,6). As the magnitude of aging-related liver diffusion metrics changes is expected to be small compared with pathology induced changes, our results suggest the relative precision of liver diffusion metrics quantification.

We also published results which strongly support the clinical usefulness of liver IVIM analysis. The report of Wáng *et al.* (7) had 16 healthy volunteers and 33 hepatitis B liver fibrosis patients, among them 15 patients had stage 1 liver fibrosis; the report of Huang *et al.* (8) had 26 healthy volunteers and 12 hepatitis B liver fibrosis patients, among them four patients had stage 1 liver fibrosis; the report of Li *et al.* (9) had 20 healthy volunteers and 28 hepatitis B liver fibrosis patients, among them 11 patients had stage 1 liver fibrosis. All patients and healthy volunteers in these

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three studies can be separated by IVIM analysis, except for one case of stage 2 fibrosis in the study of Li *et al.* (9). Interestingly, the studies of Huang *et al.* and Li *et al.* each had four patients with biopsies showing no fibrosis, and these eight subjects' diffusing MRI measurements resembled those of healthy volunteers (8,9). Moreover, we recently completed an animal-based study using the biliary duct ligation (BDL) model (10). Liver diffusion MRI was conducted with male Sprague-Dawley rats (weight: 300 ± 20 g), and included control rats ($n=6$), and experimental rats of 7 days ($n=5$), 14 days ($n=5$), 21 days ($n=5$) and 28 days ($n=3$) after BDL surgery. In addition, 12 rats had BDL for 7 days and then under partial biliary duct recanalization status for a mean of additional 14 days. Of the rats with surgery, 4, 12, 7, and 6 rats had stage 1, 2, 3, 4 liver fibrosis respectively (one BDL day-21 rat missed histology). Our results show IVIM and DDVD analysis allowed total separation of healthy rat livers and fibrotic rat livers (10).

While our liver diffusion MRI was conducted with three clinical studies on liver fibrosis due to viral hepatitis B and one animal study with biliary blockage induced liver fibrosis, recently Troelstra *et al.* (11) reported a liver diffusion MRI study on nonalcoholic fatty liver disease (NAFLD) with very promising results. The Amsterdam NAFLD-NASH cohort (ANCHOR) study is an observational prospective study aiming to identify and validate noninvasive diagnostic methods, both imaging and molecular markers, for the assessment of NAFLD disease spectrum. The first 37 individuals (23 men, 14 women) with hepatic steatosis on ultrasonograph were included in this report. The imaging modalities included ultrasonographic elastography, MR elastography (MRE), IVIM, and three MR approaches to quantify liver fat (MR spectroscopy, magnitude-based MRI proton density fat fraction, and three-point Dixon). MRI was conducted at 3.T scanner. MRE was performed using a gravitational transducer at 50 Hz and a generalized multishot gradient-recalled echo. Stiffness based on the shear modulus (G') and loss modulus (G'') were determined. The IVIM sequence consisted of a free breathing multislice diffusion weighted single-shot echo-planar imaging sequence with 18 b -values (0, 1, 2, 5, 10, 20, 30, 40, 50, 75, 100, 150, 200, 300, 400, 500, 600, 700 s/mm^2). PF, D_{slow} and D_{fast} parameters were computed using a Bayesian-probability based fit. The histology analysis included the steatosis, activity, and fibrosis (SAF) score, classifying non-NAFLD, simple steatosis, or NASH. Fibrosis was scored according to the NASH Clinical Research Network (CRN) criteria. According to the SAF-score, NASH was present in 22 of

the 37 participants. According to the NASH-CRN criteria, two individuals exhibited no fibrosis (F0), seven patients had F1 fibrosis, 20 patients had F2 fibrosis, seven patients had F3 fibrosis, and one had cirrhosis (F4). MRE data were not available for two individuals (one F2 case and one F4 case) due to technical issues with the MRE hardware. One IVIM scan (a F2 case) was not included in the analysis due to low image signal-to-noise ratio.

As expected, the results of Troelstra *et al.* show, the diagnostic performance of MRI based methods generally outperformed ultrasonographic method (11). For liver steatosis evaluation, ROC (receiver operating characteristic) analysis showed similar performance for all three MR methods (MR spectroscopy, magnitude-based MRI proton density fat fraction, and three-point Dixon). Fibrosis grade correlated significantly with disease activity score ($r_{spearman}=0.65$). Steatosis grade did not correlate with either disease activity grade or fibrosis stage.

MRE G' showed a significantly positive correlation with activity grade ($r_{spearman}=0.55$), and comparison of stiffness results for individual activity grades showed a significant difference in medians between the groups. For both PF ($r_{spearman}=0.37$) and D_{slow} ($r_{spearman}=0.40$), a significant negative correlation with histological activity grade was noted. MRE ($r_{spearman}=0.55$), PF ($r_{spearman}=0.35$), D_{slow} ($r_{spearman}=0.37$) correlated significantly with ballooning (11).

There was a significant positive association between MRE G' and fibrosis stage ($r_{spearman}=0.55$), and a significant difference between MRE G' and fibrosis stages. For distinguishing individuals with no/mild (F0–F2) *vs.* advanced fibrosis stages (F3–F4), the AUROC (area under receiver operating characteristic curve) for MRE G' was 0.92 [95% confidence interval (CI), 0.83–1], with a sensitivity of 100% and a specificity of 78.6%. G'' showed an AUROC of 0.74 (95% CI, 0.48–1), with a sensitivity of 71.4% and specificity of 92.9%. There were significant correlations between PF ($r_{spearman}=0.53$) and D_{slow} ($r_{spearman}=0.46$) and fibrosis grades. Significant difference in medians was noted between PF and fibrosis stages. Among IVIM parameters, PF performed best out of the IVIM parameters for distinguishing between no/mild and advanced fibrosis with an AUROC of 0.88 (95% CI: 0.72–1), sensitivity of 75.0% and specificity of 100%. Distinction between no/mild and advanced fibrosis for D_{slow} had an AUROC of 0.79 (95% CI, 0.63–0.95), with a sensitivity of 75.0% and specificity of 78.6%; while D_{fast} had an AUROC of 0.70 (95% CI, 0.47–0.93), with a sensitivity of 62.5% and specificity of 75.0% (11).

For MRE G' and D_{slow} , medians of the NASH group

were all significantly different compared to the simple steatosis group. For distinguishing individuals with NASH from those with simple steatosis, MRE G' and D_{slow} showed an AUROC of 0.79 and 0.73, respectively. The specificity was highest for MRE at 86.7%, while D_{slow} showed the highest sensitivity at 85.7% (11). The diagnostic performance of MRE for NASH in this study broadly agree with a recent meta-analysis (12).

The limitations of the study of Troelstra *et al.* include its relatively small sample size, particularly there were only two patients with no fibrosis (F0). Some aspects of correlations may be strengthened if a larger sample was included. Histology was read by a single pathologist, rather than with consensus reading by more than one pathologist (12).

Our overall interpretation of the results of Troelstra *et al.* is that MRE and IVIM performed at an approximately similar level in fibrosis assessment as well as the differentiation of simple steatosis and NASH, though MRE might have had marginally better performance. In practice when both methods are implemented, their roles would be more complementary.

Along with the global increase in obesity and diabetes mellitus type 2, the prevalence of NAFLD is rising (13). In adults, NAFLD is typically classified into two categories: nonalcoholic steatohepatitis (NASH), a progressive liver disease characterized by a particular pattern of steatosis, inflammatory changes and hepatocellular injury, and simple steatosis which is also called nonalcoholic fatty liver (NAFL). NASH is strongly associated with coronary artery disease and metabolic syndrome (diabetes mellitus type 2, insulin resistance, central obesity, dyslipidemia, and hypertension). NASH can progress to cirrhosis in 21–26% of the subjects (14). To determine treatment and monitoring plans, distinction between simple steatosis and NASH, and detection and staging of fibrosis are essential. Some degree of fibrosis is often present in livers with NASH (15). Although not a requirement for the NASH diagnosis (16), the presence of fibrosis may help to identify patients with NASH. Fibrosis is a key marker of disease progression in subjects with NASH (15). The stage of fibrosis is the most essential determinant of liver-related progression and mortality, and a key indicator for the development of other comorbidities like type 2 diabetes and cardiovascular disease (17–21). In a longitudinal study of patients with NAFLD, Angulo *et al.* (22) noted that, fibrosis stage, but no other histologic features of steatohepatitis, was associated independently with long-term overall mortality, liver transplantation, and liver-related events.

The IVIM analyses of our studies and the study of Troelstra *et al.* have a number of similarities and differences. Both of us sampled relatively large number of b -values, with we aimed to sample 16 b -values and Troelstra *et al.* sampled 18 b -values (3,11,23). Several very low b -values (those <10 s/mm²) were sampled but no b -value higher than 700 s/mm² was acquired (2,11). Subjects or slices with artifacts were excluded which resulted in one subject was excluded from IVIM analysis in the study of Troelstra *et al.* (11); and with our results of poor curve fitting were also excluded so that till now we had a higher exclusion rate of approximate 15% (5,7–9,24). This exclusion rate difference between that of Troelstra *et al.* and ours could be due to different exclusion standards were applied. In addition, Troelstra *et al.* adopted the Bayesian probability analysis. Bayesian analysis allows reasonable estimates at lower signal-to-noise ratio under certain circumstances (25). In this aspect, our laboratory is currently working to reduce our relative high exclusion rate with better image post-processing. While we used METAVIR score for viral hepatitis induced fibrosis and Troelstra *et al.* used fibrosis score according to the NASH-CRN and all their study participants had hepatic steatosis, our results demonstrated very good results in separating control healthy livers and fibrotic livers with AUROC close to 1 (7–9). Till now, reported data on non-invasive imaging for diagnosis of any NASH fibrosis (F0 *vs.* F1–4) has been sub-optimal. One recent review suggested MRE had a summary AUC, sensitivity and specificity for diagnosing stage \geq F1 of 0.87, 71%, 85%, respectively (12). It is possible that additional approaches such as a combination all of all diffusion metrics and removal of b -value=0 s/mm² data from IVIM modeling can further improve the results of Troelstra *et al.* As starting from $b=0$ image, the relationship between liver DWI signal and b -value does not follow bi-exponential decay (2,26), in our experience, removal of b -value=0 s/mm² data from IVIM modeling greatly improves the diagnostic performance of resulted IVIM parameters (2,9). The fact that slow diffusion measure and fast slow diffusion measures are mutually constrained further increases the necessity of checking all IVIM parameters together (instead of evaluating these parameters individually) (7,27).

Finally, the knowledge of the 'coupling' between slow diffusion measure and fast diffusion measures further highlights the challenges in interpreting IVIM data (5,27,28). According to the currently prevalent IVIM modeling, IVIM parameters are likely affected by biochemical composition of the target tissue as well as diffusion and perfusion of

this tissue (29,30). Till now, we consider this problem is not easily solvable by a better fitting or a better image post-processing approach. Before improved solutions are available, a practical approach would be that, we standardise the image data acquisition methodology (critically the *b*-value distribution) and image data post-processing/IVIM parameter computing methodology, so to build the database of ‘normal’ reference distribution of diffusion metrics (the distribution of a reference cluster in 3-dimensional space), then deviation from the reference distribution could be considered an abnormality with fibrosis shown to induce a reduction of all diffusion metrics (23).

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