Intravoxel Incoherent Motion MR Imaging shows lower pure molecular diffusion, lower diffusion fraction linked to microcirculation, and lower perfusion-related diffusion in fibrotic livers with a severity correlated manner

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Introduction: Prior studies suggested that liver fibrosis may be associated with progressive restriction of diffusion motion because of the increase in connective tissue associated with liver fibrosis. It is also well accepted that liver fibrosis/cirrhosis is associated with reduced liver perfusion [1-3]. Le Bihan et al [4] demonstrated that both pure molecular diffusion and microcirculation, or blood perfusion, can be distinguished by using intravoxel incoherent motion (IVIM)-based DW imaging, provided that multiple *b* values to encompass both low *b* values (<200 sec/mm^2) and high *b* values (>200 sec/ mm^2) are used. In biologic tissues, IVIM includes microcirculation of blood in the capillary network, which is also called perfusion. The signal attenuation is according to the Equation (1) $SI=SI_0[(1-f)\cdot\exp^{-b\cdot D} + f\cdot\exp^{-b\cdot D^*}]$, where *S* is the mean signal intensity, *f* is the fraction of the diffusion linked to microcirculation, *D* is the diffusion parameter representing pure molecular diffusion (slow component of diffusion), and *D** is the diffusion parameter representing incoherent microcirculation within the voxel (perfusion-related diffusion, or fast component of diffusion). This current study report the results of liver IVIM evaluation of 17 healthy volunteers and 34 liver fibrosis subjects.

Material and Methods: The study was approved by the local research and ethics committee and informed consent was obtained before commencement of the study. 17 healthy volunteers (10 males, 7 females, mean age: 36.4-yrs old; range 21-79-yrs old) and 34 patients (23 males, 11 females; mean age: 37.3yrs old; range 22-57-yrs old) with histopathologically proved liver fibrosis were included. Stage 1 of liver fibrosis is mild fibrosis only seen at the portal area; Stage 2 indicates fibrosis extending out from the portal areas with rare bridges between portal areas, but without the destruction of the lobular structure; stage 3 of liver fibrosis is severe fibrosis, there is fibrostic bridging between portal areas and between portal areas and center veins; In stage 4 there are pseudo-lobules formed and this stage is the final stage of cirrhosis. The IVIM DW imaging sequence was applied with a 1.5-T MR imaging system (Philips Healthcare). The sequence was based on standard single-shot DW spin echo-planar imaging, with 10 *b* values of 10, 20, 40, 60, 80, 100, 150, 200, 400, 800 sec/mm2 respectively. The IVIM DW imaging sequence was respiratory gated, which resulted in an average repetition time of 1500 msec, and TE was 63 msec. Slice thickness =7mm. NEX=2. With the *D* value determined by fitting the data points at b>200 sec/mm^2 to a monoexponential function[4], and *f* by the intersection of the fitted curve at b=0, *D** values were then calculated by using a nonlinear regression algorithm based on Equation 1. All regression algorithms were implemented with software (MatLab; Mathworks, Natick, Mass), which allowed the extraction of parametric maps representing *f*, *D*, and *D** parameters. Avoiding artifacts and blood vessel, one ROI was manually placed on the b=0 sec/mm^2 DWI image (see Fig.1) and then pixel-wise or ROI-averaged IVIM parameters values could be obtained with software (Matlab)[5]. Stage 3 and stage 4 patients are grouped together for analysis, due to the limited patient number of these two stages.

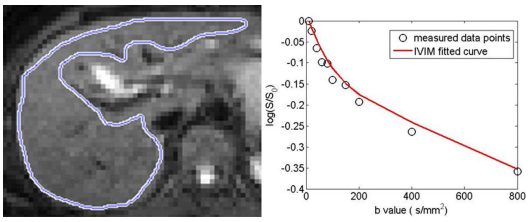
Table 1	**D(×10^{-3}mm^2/s)**	**f**	**D*(×10^{-3}mm^2/s)**
Volunteer (n=17)	1.096±0.155	0.164±0.021	13.085±2.943
Patients (n=34)	0.917±0.152	0.123±0.029	9.423±1.737
p value #	0.0015	<0.0001	<0.0001

#: by Mann Whitney U test

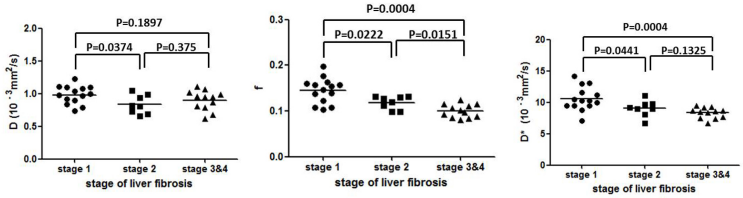
Results: All curves of signal-intensity decrease demonstrated biexponential type decay as expected, regardless of the measurements were obtained in the healthy liver group or in the liver fibrosis group (Fig 1). The mean *D, D*,* and *f* parameters measured in healthy volunteers and patients liver were listed in Table 1, Table 2, and Fig 2. The *D, f,* and *D** in liver fibrosis subjects were all significantly lower than those in healthy subjects. As the fibrosis severity progressed, all *D, f,* and *D** value decreased.

Table 2	**D(×10^{-3}mm^2/s)**	**f**	**D*(×10^{-3}mm^2/s)**
Patients-stage 1 (n=14)	0.981±0.137	0.145±0.028	10.583±1.872
Patients-stage 2 (n=8)	0.828±0.146	0.116±0.014	8.923±1.291
Patients-stage 3&4 (n=12)	0.898±0.152	0.100±0.014	8.332±0.851
significant linear trend#	ns	yes	yes

#: by One-way analysis of variance (ANOVA) & linear trend test.



Above: *Fig 1. The placement of ROI on the b=0 DWI image (left) and the corresponding IVIM fitted curve of measured signal decay (right).The ROI was placed over the whole liver, avoided the artifact and blood vessel.*



Left: Fig 2. *Relationship between stages of liver fibrosis and D, f and D*.*

Discussion: Recently there are great interests of using IVIM technique to study diffused liver diseases [6-9]. On the basis of the IVIM theory, Luciani et al [9] studied patients with documented liver cirrhosis (METAVIR score F4 liver fibrosis, n=12) and healthy liver group (n=25). They reported there was no difference in *D* value and *f* between the healthy livers and the cirrhotic livers. Our results demonstrated all *D* value *D** and *f* were lower in the cirrhotic livers compared with the healthy livers, and progressively so as the severity of liver fibrosis increased. These can be explained by that liver fibrosis is associated with progressive restriction of diffusion motion because of the increase in connective tissue, and liver fibrosis is associated with reduced liver perfusion. To our knowledge, this is the first study such effects are demonstrated in biopsy confirmed human subjects.

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