Comparison of Proton Diffusion in Regenerative Nodules and Fibrosis in Explanted Human Liver

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Object or Purpose of Study:

The apparent diffusion coefficient (ADC) of liver is reduced in patients with fibrotic liver disease [1-5]. This reduction is generally assumed to be caused by the fibrosis itself. This assumption may be too simplistic, as it overlooks the potential contribution of non-fibrotic regenerative liver tissue, which usually constitutes the dominant fraction of total liver content in liver diseases associated with fibrosis. In clinical practice, diffusion weighted (DW) imaging of the liver is performed at low spatial resolution, and liver voxels contain a mixture of regenerative and fibrotic tissues. Calculated ADC values in clinical subjects are composite measurements of proton diffusion in both tissue types and it is difficult or impossible to directly assess each tissue separately. The purpose of this study was to assess and compare proton diffusion in regenerative nodules and fibrosis in cirrhosis. The study was performed prospectively on freshly explanted cirrhotic liver specimens, utilizing higher-resolution DW images than used in the clinical setting, and with pathology as the reference standard for tissue classification.

Materials, Methods and Procedures:

Freshly explanted, cirrhotic liver specimens obtained from 17 human transplant patients were placed in saline and imaged at room temperature on a 1.5T Siemens system with 30mT/m gradient strength. Conventional spin echo DW images were obtained with b-values of 0 and 250-1700 sec/mm^2, TR1000-2500 msec, TE 30-60 msec, slice thickness 2-5mm, image matrix 256x256, and field of view 135-180 mm. Voxel size ranged from 0.5 mm^3 to 2.5 mm^3, about 25-125 times smaller than those obtained with routine clinical DW sequences. ADC maps were generated using scanner software. T2w (TR 2000 msec, TE 80 msec, slice thickness 1-5mm, image matrix 512x512) conventional SE images were obtained for comparison. Source images and maps were transferred to PACS. Specimens were photographed, trimmed around the edges, fixed in formalin, and submitted to histology for H&E, reticulin, iron and trichrome staining.

MR images were reviewed in conjunction with specimen photographs and histology slides. Using pathology as the reference, liver parenchyma in each specimen was classified as fibrosis or regenerative nodule. The appearance of the two tissues on MR images was assessed qualitatively. On ADC maps, regions of interest (ROIs) were placed on fibrosis and regenerative nodules and the mean ADC value of each ROI was recorded. Ten to 25 paired ROIs were manually selected in different portions of each specimen so as to be representative of the whole specimen. Fibrosis and regenerative nodule ADC values were averaged by specimen and compared using a conservatively adjusted, unpaired, two-tailed t-test.

Results:

Histology revealed characteristic changes of cirrhosis including bridging fibrosis and regenerative nodules (**Fig 1**). The fibrosis was up to 3 mm thick and contained collagen, large extracellular spaces, and fluid-filled bile ducts and blood vessels. Regenerative nodules were up to 10 mm in diameter and contained tightly packed cords of hepatocytes. Central veins were absent within the nodules, and sinusoidal and other extracellular spaces were small. On spin echo images obtained with a b value of 0 sec/mm^2, fibrosis was clearly visible in all specimens as high-signal reticulations surrounding the nodules, which were of low signal (**Fig 2**). On DW images obtained with b-values of 250-1500 sec/mm^2, fibrosis was not clearly visible and was of only minimally higher signal than regenerative nodules (**Fig 2**). Subjectively, regenerative nodules lost less signal than fibrosis at all tested b-values in all specimens, suggesting more restricted proton diffusion in regenerative nodules than fibrosis.

Quantitative ADC measurements were consistent with the subjective observations. In every specimen, the measured ADC was smaller in regenerative nodules than in fibrosis by a factor of 1.3 to 6.0. Pooling data from all specimens, mean ADC of regenerative nodules was 2.3 times smaller than mean ADC of fibrosis ($P<0.03$).

Conclusions:

In this prospective study on explanted cirrhotic liver tissue, proton diffusion was more restricted in regenerative nodules than in fibrosis. This observation suggests that regenerative tissue contributes significantly to the reduced liver ADC value observed in cirrhosis. The greater restriction of diffusion in regenerative nodules compared to fibrosis may be explained by differences in extracellular volume between the two tissues. Future work will include animal studies to assess proton diffusion in regenerative and fibrotic tissue at several stages of disease progression from normal to cirrhosis.

References:

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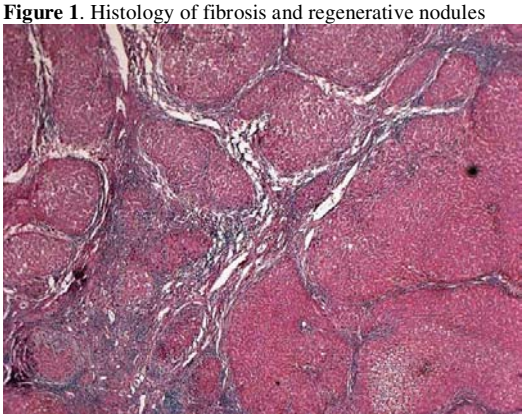
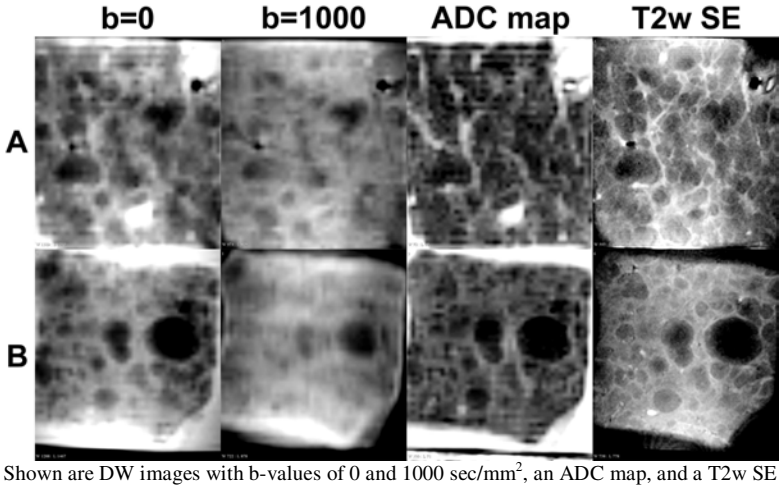
Figure 1. Histology of fibrosis and regenerative nodules



Nodules have tighly packed hepatocytes with small extracellular spaces and a paucity of vessels. Fibrosis has large extracellular spaces and scattered vessels. H&E slide, 200x.

Figure 2. Diffusion weighted and T2-weighted spin echo imaging of fibrosis and nodules



Shown are DW images with b-values of 0 and 1000 sec/mm^2, an ADC map, and a T2w SE image from two different specimens (A and B). On b=0 image, fibrosis is visible as high-signal reticulation surrounding low-signal regenerative nodules. Image contrast between fibrosis and nodules is high. On b=1000 image, contrast between fibrosis and nodules is reduced due to preferential signal loss in fibrosis. ADC map confirms higher ADC values in fibrosis than in regenerative nodules. Despite artifacts, ADC map shows fibrosis with higher clarity than source DW images. Notice close correspondence between ADC map and T2w SE image.