Quantitative T2 and Proton Density Mapping of a Murine Model of Hepatic Fibrosis Progression: An Application of Adaptive Iterative PD and T2 qMRI Algorithms

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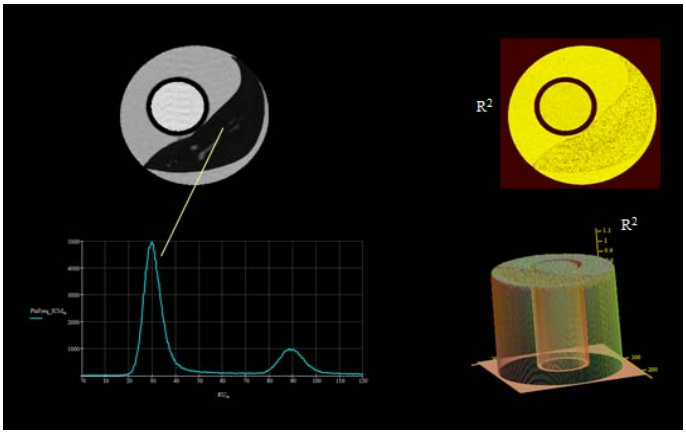
Purpose: The purpose of this work was to monitor the progression of hepatic fibrosis in a murine model *via* the proton density (PD) and the transverse magnetization relaxation time (T2) at 11.7T, using highly accurate adaptive iterative qMRI processing algorithms and whole-sample histogram analysis.

Methods: ***Animal model***: The experimental protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of our institution. Seventeen male, 6-week-old C57BL/6 mice were divided into a control group (n = 2) fed normal chow, and an experimental group (n =13) fed a 0.1% (w/w) 3, 5-diethoxycarbonyl-1, 4-dihydrocollidine (DDC)-supplemented diet (TestDiet, Richmond, IN) for the induction of hepatic fibrosis. This DDC-fed mouse model has been demonstrated to produce sclerosing cholangitis and marked biliary fibrosis (1), with minimum steatosis (2). The two control mice were sacrificed immediately before the initiation of the experimental diet. The experimental diet continued for a total duration of 16 weeks and mice were sacrificed approximately one mouse per week throughout this period for subsequent liver excision and ex vivo MR imaging. ***MR Imaging:*** All samples were scanned with a CPMG multi spin echo sequence (32 echoes, ES=6.4ms, 16 slices) using an 11.7T (Bruker Biospin, Billerica, MA) vertical bore MRI scanner. The multi-echo CPMG images were PD- and T2-qMRI processed with an algorithm that auto-detects the optimum number of echoes to be used in the semi-logarithmic linear regression on a pixel by pixel basis. In addition, T2 datasets were processed using a conventional algorithm which included all 32 echoes as input. The multislice PD and T2 qMRI volumetric datasets were further processed to generate whole sample histograms (see **Fig.** 1). ***Histologic Digital Imaging Analysis (DIA):*** Whole trichrome stained histologic slides were digitized using a digital scanner (ScanScope CS, Aperio Technologies, Inc., Vista, CA) to generate an additional, digital image analysis derived reference standard for subsequent comparison to the MRI data. Using automated software (Image-Pro Plus, Media Cybernetics, Inc., Bethesda, MD), a color-based segmentation was used to convert the histology image into a binary mask of the image. Colorimetric criteria were used to segment the blue staining fibrosis, the total area of which was expressed as a percentage of the total area of liver tissue on the slide.

Results: The histogram T2-peak value was negatively and linearly correlated with the histological measure of hepatic fibrosis as derived with DIA (r = -0.609) (see **Fig.** 2). The histogram PD-peak value was also negatively and linearly correlated with the histological measure of hepatic fibrosis as derived with DIA (r = -0.652) (not shown). In the case of T2 values derived using a conventional algorithm incorporating all 32 echoes as input, a positive correlation was found (r = 0.588) (see **Fig.** 2)



Whole sample T2 histogram (bottom left) and image of the T2 map (top left) as well as fit (displayed as R^2) of multi-echo data used as input via an iterative adaptive algorithm (top right) and its surface plot (bottom right).l as fit

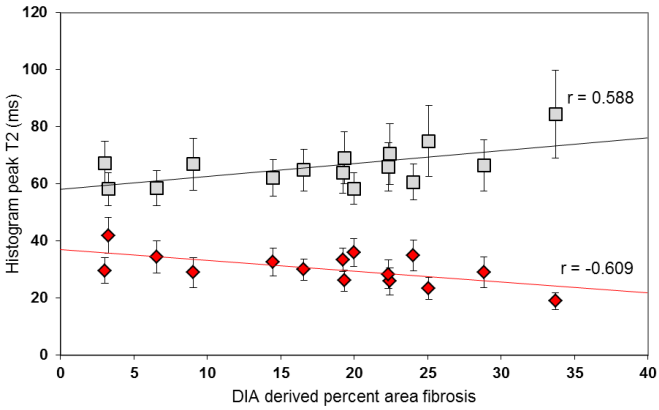


Figure 2. T2 versus DIA derived measure of hepatic fibrosis. Positive correlation seen with conventional algorithm and negative correlation seen with adaptive iterative algorithm.

Conclusion: This work demonstrates that when accurately calculated and in the absence of steatosis, both PD and T2 can be reliable correlates of hepatic fibrosis. Further work is necessary in order to assess the degrees of independence and complementarity of these two fundamentally different qMRI parameters. The use of the adaptive iterative algorithm reveals that, when compared to a conventional T2 qMRI algorithm which generally overestimates T2 values, in part due to image noise, there are marked differences in calculated T2 values, an observation which should be considered in future works deriving T2 values.

References

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2. Anderson SW, Jara H, Ozonoff A, O'Brien M, Hamilton JA, Soto JA. Effect of disease progression on liver apparent diffusion coefficient and T2 values in a murine model of hepatic fibrosis at 11.7 Tesla MRI. Journal of Magnetic Resonance Imaging 2012;35(1):140.