Multieponential T2 Analyses in a Murine Model of Hepatic Fibrosis at 11.7T MRI

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Purpose: The purpose of this study was to characterize the multieponential T2 relaxation of liver using a murine model of hepatic fibrosis in a highly controlled setting using ex vivo imaging at 11.7T MRI.

Methods:

Imaging experiments were performed using 11.7T MRI. 17 male C57BL/6 mice were divided into a control group (n=2) fed normal diet and an experimental group (n=15) fed a diet containing 3, 5-dicarbethoxy-1, 4-dihydricollidine (DDC) to induce hepatic fibrosis. The experimental diet was continued for a total duration of 16 weeks and mice were sacrificed intermittently throughout this period for imaging and an experimental group dimensions = 150x150x700µm³ (reconstructed pixel size = 75x75x75μm³). Two methods of multieponential T2 analysis were utilized: a constrained regularization method (CONTIN) [1] and a regularized non-negative least squares method (AnalyzeNNLS) [2].

Subsequent to the imaging experiments, the liver specimens were embedded in paraffin and serial sections of 5µm were cut. Sections were stained with hematoxylin and eosin as well as Mason’s trichrome stains. A board certified pathologist reviewed the specimens to evaluate the extent of steatosis, inflammation, and fibrosis using commonly employed grading schemes. In addition to the subjective scoring, the trichrome stained specimens were digitized and digital image analysis (DIA) was used to determine the degrees of hepatic fibrosis, expressed as percentage area of fibrosis of the liver specimens.

The geometric mean T2 (GMT2) values and FWHM values for the CONTIN results were plotted against both subjective assessments of hepatic fibrosis, steatosis, and inflammation as well as digital image analysis derived percentage area of fibrosis. Geometric mean T2 (GMT2) values generated using the AnalyzeNNLS algorithm were similarly compared to histology. Pearson correlation coefficients (R) were derived using linear regression analyses.

Results: The DDC diet induced significant hepatic fibrosis in the experimental group of mice, none of which died prior to planned sacrifice. The degrees of fibrosis assessed by the pathologist ranged up to the maximum score of 4 and DIA based percentage area of fibrosis ranged up to 34%. Minimal steatosis was seen; 4 of 15 experimental mice demonstrated any degree of steatosis greater than a grade of 0. Inflammation ranged from mild to severe in all experimental mice.

When applying both CONTIN and AnalyzeNNLS algorithms, in all cases, two distinct peaks were identified, termed here short and long T2 components (Figure 1). Using the CONTIN algorithm, the dominant, short T2 component had a mean GMT2 of 30.2ms (range, 24.5-35.3ms) and mean area fraction of 97.4% (range 95.1-98.9%). Using the AnalyzeNNLS algorithm, the short T2 component had a mean GMT2 of 30.6ms (range, 24.8-35.8ms) and mean area fraction of 97.3% (range, 94.9-98.8%). Using the CONTIN algorithm, the minor, long T2 component had a mean GMT2 of 385.9ms (range, 321.5-431.3ms) and mean area fraction of 2.62% (range 1.13-4.94%). Using the AnalyzeNNLS algorithm, the minor, long T2 component had a mean GMT2 of 434.2ms (range, 332.4-482.0ms) and mean area fraction of 3.09% (range 1.22-9.12%).

Using both CONTIN and AnalyzeNNLS, poor correlation between geometric means of the short T2 components and subjective, pathologist scored and DIA derived degrees of hepatic fibrosis. Using CONTIN, moderate correlation between geometric means of the long T2 components and subjective, pathologist scored (R=0.50) and DIA derived (R=0.58) degrees of hepatic fibrosis were seen (Figure 2). Using AnalyzeNNLS, poor correlation between the geometric means of the short components degrees of fibrosis were seen. Fair correlation was seen using AnalyzeNNLS between long T2 components for subjective (R=0.34) and DIA (R=0.28) derived degrees of fibrosis. Increasing degrees of hepatic fibrosis were seen to result in an increase in FWHM values for the CONTIN algorithm. Based on scatterplot correlations, fair correlation between FWHM and the pathologist-determined fibrosis score (R=0.39) and the percentage area of fibrosis by DIA (R=0.44) were seen. Poor correlations between degrees of hepatic steatosis or inflammation and the multieponential T2 derived parameters from either algorithm were found.

Conclusion: Two distinct T2 components were seen in the murine liver samples; both geometric mean T2 values of the minor, long T2 component and the FWHM of the short T2 component correlated with hepatic fibrosis. Studying hepatic microenvironments using multieponential T2 analyses offer potential utility in the ongoing development of noninvasive assessments of hepatic fibrosis using MRI.