

T2 relaxation time as a surrogate marker of liver fibrosis

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Introduction

Cirrhosis, the final common pathway for liver fibrosis, remains a major public health problem with disease-related complications leading to ~40K deaths and more than \$1.4 billion in medical costs in the US annually. [1] The progression of liver fibrosis to cirrhosis is dynamic, and has significant potential for resolution. Patients with hepatic fibrosis need quantitative assessment and staging of their risk for the development of cirrhosis, liver failure, or hepatocellular carcinoma. Currently, the diagnosis, quantification, and staging of liver fibrosis rely on liver biopsy, an invasive procedure with significant risks, which is limited by variability in pathologic interpretation and sampling errors approaching 25-45%.

Noninvasive, surrogate, quantitative measures of liver fibrosis, whether based on blood tests or imaging, could overcome these limitations. Recent studies have investigated prospectively in animal models the capability of differentiating degrees of liver fibrosis by surrogate markers using magnetic resonance imaging (MRI) in vivo in a rat bile duct ligation (BDL) model. Among the 66 MRI parameters tested, the highest correlation with the area of fibrosis was observed for relative T2 measurements ($r = 0.78$, $p < 0.001$) [2]. We chose to test this hypothesis retrospectively in patients with either Hepatitis B or Hepatitis C, undergoing random liver biopsy for fibrosis staging, all of whom had obtained a clinical MRI within 3 months of their biopsy.

Methods

This was a retrospective study approved by the Institutional Review Board. 83 patients who underwent both liver MRI and nonfocal liver biopsy for staging of hepatic fibrosis within a 6 month period, between January 2004 and December 2008 were enrolled. The average time between MRI and biopsy was -8days (range: -165 to 177). All biopsies were staged histologically (Ishak classification system (0-6)) and grouped into control (stage (0) n=0) mild (stage (1-2) n=20), moderate (stage (3-4), n=17), severe (stage (5-6), n=46). MR imaging was performed with a phased array body coil (8 channel) on either Siemens 1.5T Avanto/Allegra or GE Excite using RARE equivalent pulse sequences with dual TE values (46-99msec and 84-177msec.) and TR 2000-3500msec. T2 relaxation time of liver parenchyma in patients was calculated by measuring the signal intensity (SI) in the same representative area of right lobe of the liver on both echoes and fitting with a two-point fit (MS Excel, Seattle, WA). Statistical analysis included one way ANOVA and student's unpaired t-test between individual groups.

In order to answer potential criticism associated with putative high variance, and validity of quantifying T2 with a two point fit utilizing turbo spin echo (TSE) technology, we performed a phantom study comparing T2 fits from mono-exponential fits of Carr-Purcell-Meiboom-Gill (CPMG) type sequences as compared to double echo TSE in an iron oxide nanoparticle phantom with serial dilutions of saline. Our phantoms consisted of one cc of magnetic iron oxide nanoparticle (MION 48) ($R_2 - 49 \text{ sec}^{-1}$) (1 mg Fe/ml) diluted with the following fractionations (1:250, 1:500, 1:1000) and placed in 50cc Eppendorf tubes. MRI was performed in a 1.5T Siemens Avanto with TIM technology. Imaging was performed using a multi-channel array head coil (4 channels). All imaging was performed with an asymmetric FOV (16 x 14cm) and 512 x 409 matrix using a 4mm slice thickness, interleaved with no gap. The CPMG sequences were performed all with TR 5000msec. and TE (22 msec. in 22 msec. intervals). The TSE sequences were performed with effective TE of 22 and 86msec., with an echo train length of 7. T2 was fit by using a mono-exponential fit and ROI within each tube (Osirix®).

Results:

Table 1 demonstrates a comparison of the T2 values and variance for each subgroup in each of the three phantoms. There is close agreement with the mean T2 value in the CPMG sequences as compared with the TSE sequences. The SNR of the CPMG data was approximately 350:1, while that of the TSE sequences was approximately 325:1.

Figure 1 demonstrates the values of the absolute T2 measurements (control 65.4 +/- 2.9msec.; mild 66.7 +/- 1.9msec; moderate 71.6 +/- 1.7msec; severe 72.4 +/- 1.4msec), which demonstrated low standard error (~2.9msec). Furthermore, there was a monotonically increasing mean T2 value with increasing degree of histologic fibrosis. There was a statistically significant difference between degrees of mild vs. severe fibrosis ($p < 0.05$) with results approaching statistical significance amongst all groups by ANOVA ($p < 0.1$).

Conclusion:

Our phantom data demonstrate that there is close agreement in absolute T2 values comparing a 2 point fit from RARE/TSE data as compared to conventional T2 quantification with multi-echo CPMG data. In addition, our retrospective analysis demonstrates that there is a monotonically increasing T2 value with increasing fibrosis stage. This data corroborates a possible quantifiable inflammatory component from recent animal data to this important aspect of chronic liver disease. Furthermore, our data demonstrate that there was a statistically significant difference in absolute T2-relaxation time between mild degrees of fibrosis as compared to severe fibrosis, which imply that T2 may be a surrogate marker of liver fibrosis. We propose that this study warrants further examination of this biomarker in a prospective trial comparing T2 to other more established, robust surrogate markers of fibrosis.

References

1. Vong, S. and Bell, B. P. Chronic liver disease mortality in the United States, 1990-1998. (2004). *Hepatology* 39:476-483
2. Aube, C. et al. Diagnosis and measurement of liver fibrosis by

Table 1

	1:250	1:500	1:1000
16 echoes CPMG	63 +/- 4	102 +/- 2	191 +/- 2
12 echoes CPMG	52 +/- 3	102 +/- 2	192 +/- 2
8 echoes CPMG	52 +/- 5	103 +/- 1	194 +/- 2
4 echoes CPMG	54 +/- 1	110 +/- 2	218 +/- 7
2 echoes CPMG	56 +/- 3	116 +/- 3	242 +/- 10
2 echoes TSE	53 +/- 2	103 +/- 2	188 +/- 6

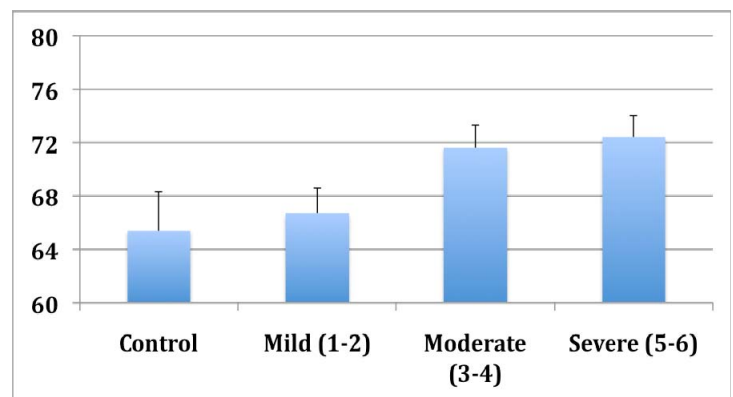


Figure 1 – Absolute T2 values expressed as mean +/- SEM for varying degrees of fibrosis in patients with chronic liver disease from Hepatitis B/C.