T1ρ-based MR Imaging for the Non-Invasive Quantification of Extracellular Matrix Protein Concentration in Hepatic Fibrosis

D. Daye[1], C. Wang[2], E. Mellon[3], S. Gaddam[4], R. Wells[5], E. Furth[6], and R. Reddy[4]

[1]Department of Bioengineering, University of Pennsylvania, Philadelphia, Pennsylvania, United States, [2]Department of Bioengineering, University of Pennsylvania, [3]Department of Biophysics and Molecular Biochemistry, University of Pennsylvania, [4]Department of Radiology, University of Pennsylvania, [5]Department of Medicine, University of Pennsylvania, [6]Department of Pathology and Laboratory Medicine, University of Pennsylvania

Introduction: Cirrhosis of the liver is currently ranked as the fourth leading cause of death for individuals between the ages of 45 and 54 in the United States and as the ninth leading cause of death for all ages (1). Despite the prevalence of liver disease, the gold standard to diagnose and monitor the progress of patients afflicted with liver cirrhosis remains limited to liver biopsy (2). Yet, liver biopsies are invasive, associated with high complication rates, poor reproducibility and inter- as well as intra- observer variability and have been reported to misclassify up to one third of cirrhotic livers (3). All of these shortcomings mandate a new reliable and non-invasive clinical tool, able to objectively diagnose and quantify the stages of fibrosis leading to cirrhosis. T1ρ-based MR imaging is a technique that has been previously shown to be dependent on the exchange processes that are associated with water protons and other exchangeable protons on macromolecules (-OH and-NH) and residual static dipolar coupling between protons and macromolecules (4). Given that liver fibrosis manifests as a progressive deposition and re-organization of a number of extracellular matrix proteins, mainly Type I and Type III collagen, we hypothesize that the exchange between protons on –OH and -NH of collagen with bulk water of tissue as well as the presence of residual dipolar interactions might lead to concentration- and architecture-dependent T1ρ relaxation and T1ρ dispersion in the liver.

Materials and Methods: In a preliminary study to evaluate the diagnostic potential of this technique, T1ρ-weighted images of 10 human liver explants exhibiting either early or advanced degrees of fibrosis were collected using a 3T Siemens Magnetom Trio scanner. Spatial T1ρ relaxation maps were calculated. Fibrosis grading of samples from each of the imaged liver explants was performed by the collaborating pathologist, according to the Metavir scale. On the Metavir scale, F0 corresponds to no fibrosis, F1 to portal fibrosis, F2 to the presence of a few septae, F3 to the presence of numerous septae and F4 to the presence of bridging septae. Correlation between the Metavir grade as determined by the pathologist and the T1ρ MRI relaxation and dispersion parameters was done by calculating T1ρ mean of similar ROIs in each liver.

Results: Results demonstrate that consistent differences exist between the relaxation times and the dispersion response of samples with different degrees of fibrosis *in vitro*. T1ρ relaxation for normal liver samples were in the vicinity of 25 ms, while increasing fibrosis was associated with increasing T1ρ values reaching up to 70 ms in severe cirrhosis. Furthermore, for the samples imaged in this study, we saw a linear correlation between T1ρ relaxation times and the extent of fibrosis. Our technique did also demonstrate an ability to detect small changes in fibrosis within one histopathologic stage (F4).

Discussion: Correlation between mean T1ρ and pathological grading was excellent in all cases for both early and advanced degrees of fibrosis (F0 and F4) and thus could potentially provide for a clinically-valuable test to diagnose and stage fibrosis. The increasing T1ρ values associated with increased fibrosis are thought to be due to increased water trapping associated with increased matrix deposition in the space of Disse in the liver. In addition, since our technique was able to detect small changes within one histopathological stage of fibrosis, we project that T1ρ-based MR imaging of the liver might be sufficiently sensitive to measure early and small changes in hepatic ECM proteins and thus could be used to monitor the progress of patients through different disease stages over short periods.

Conclusion: In conclusion, the preliminary results presented here indicate that this technique has significant potential to provide for a quantitative and a non-invasive assessment of fibrosis in the liver. Once validated in a larger sample size and on human subjects, this technique can be useful both in the setting of improved patient care and in quantitative tracking of new treatments for liver disease.

References: (1)Wolf et al., eMedicine(2008). (2)Manning et al., Gatroenterol (2008). (3)Thampanitchawong et al., World J Gatroenterol (1999). (4)Duvvuri et al, PNAS (2001).

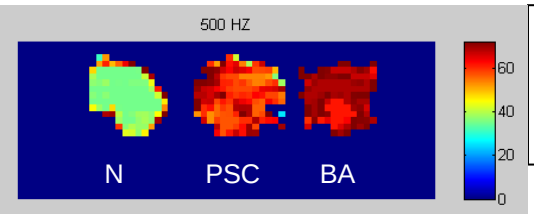

Figure 1: T1ρ map of normal and cirrhotic human liver explants. The correlations between T1ρ signal and the histopathologic stage of fibrosis is apparent. Normal liver (N) exhibits lower T1ρ relaxation time than cirrhotic livers (PSC and BA). N: Normal. PSC: Primary Sclerosing Cholangitis. BA: Biliary Atresia. The color map refers to T1ρ relaxation times in ms.

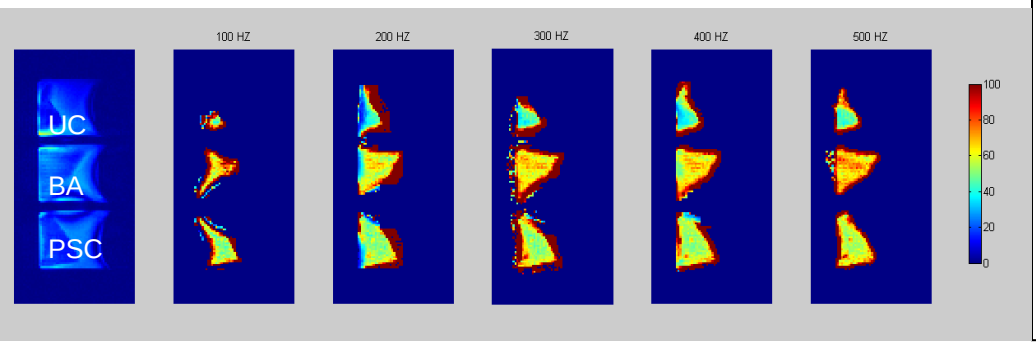

Figure2: T1ρ map of cirrhotic human liver explants at the same histopathologic stage of fibrosis at different spin-lock frequencies. Within the same stage of fibrosis (F4 on the Metavir scale), T1ρ MR imaging is able to distinguish smaller, more subtle changes with fibrosis. According to the collaborating pathologist, here, UC had the least fibrosis and BA had the most, with PSC being in the middle.