Assessment of Chemical Exchange Saturation Transfer Effects in Liver Tissue at 7T

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INTRODUCTION

While liver disease is currently ranked as the seventh leading cause of adult death in the United States, the gold standard to diagnose and monitor the progress of patients afflicted with hepatic pathologies remains limited to liver biopsy. Liver biopsies can be associated with sampling variability, poor reproducibility and major complications, rendering it essential to develop non-invasive techniques able to diagnose different liver conditions. With the advent of high performance magnetic resonance (MR) systems and advanced sequences, MRI shows potential for improved and non-invasive assessment of liver disease. Fast spin echo or single shot techniques, often combined with fat suppression, are the most common T2 weighted sequences used in liver MRI procedures[1]. Liver MRI is highly dependent on the administration of contrast agents, especially when detection and characterization of focal lesions are the issues[2]. Currently, there is no single MRI technique that is optimal for detecting the different liver pathologies. The technique known as chemical exchange saturation transfer (CEST) enables one to image nuclear spins that exchange with bulk water in biological tissues[3]. This technique has been used earlier to map the pH changes in tissues[4], map the protein content in the brain[5], and measure the GAG concentration in collagen[6] as well as glycogen concentration changes in the liver[7]. The objective of the present study was to determine the CEST effects of water signal in normal and pathological liver samples on 7T MR clinical scanner *ex vivo*.

MATERIALS AND METHODS

The study was conducted under an approved Institutional Review Board protocol of the University of Pennsylvania. Liver samples that are normal as well as two pathologies were included in the current study. The two pathological samples were Primary sclerosing cholangitis stage V and hepatocellular carcinoma. MR spectroscopy experiments were performed on a 9.4 T vertical bore scanner (Inova; Varian, Palo Alto, CA) using a 5-mm radiofrequency probe. Z-spectra from all three samples were acquired over a saturation frequency range of ±7.5ppm relative to the bulk water resonance in steps of 0.125ppm with a 1 second pre-saturation pulse of amplitude, B_1=127 Hz. The CEST imaging experiments were performed on a 7.0T Siemens whole-body MR scanner (Siemens medical systems, Erlangen) using a custom built RF coil. The tissue samples were added to small test tubes, and immersed inside a large beaker containing PBS. For CEST imaging, we used 1.5-second duration and 75 Hz amplitude pre-saturation RF pulse with offset frequency set at +2.75ppm and -2.75ppm gradient echo acquisition (slice thickness=5mm, TR=7s, TE=3ms, field of view=40*40 mm, matrix size=128*128, and 32 echoes per TR). The total imaging time was around 1 minute. The CEST contrast was calculated using the equation, CEST contrast=100%*[M_{neg} – M_{pos}] / M_{neg}, where M_{pos} and M_{neg} are the acquired MR signals with saturation at +2.75 ppm and -2.75 ppm respectively.

RESULTS AND DISCUSSION

In all liver tissue samples, the z-spectra showed a dip around ~2.75ppm downfield to the bulk water resonance, suggestive of exchangeable proton at this frequency (Figure 1).Compared to the normal liver tissue, high CEST contrast was observed in the two pathological liver tissues. Earlier the liver glycogen has been detected by CEST methods using the labile –OH protons of glycogen[7]. In the current study, we also observed very little CEST effect due to –OH spins form all of the tissue samples. However, no differentiation between the normal and pathological tissue samples was possible based on the –OH CEST effect. The CEST images obtained by applying the saturation pulse at the frequency offset of ±2.75ppm showed a clear difference in the CEST contrast between the normal and pathological tissue samples as shown in Figure 2. The normal liver tissue showed around 6.0±3.6% CEST contrast while the two pathological tissues showed significantly higher CEST contrast (Primary sclerosing cholangitis stage V=16.9±5.3% and hepatocellular carcinoma=15.3±5.5%). PBS shows negligible CEST contrast (<1%). However, at this stage we haven't determined which metabolite is providing the CEST effect. We are hypothesizing that the formation of liver fibrosis in various disease conditions may be expressing metabolites with exchanging groups resonating at the observed CEST frequency. We are in the process of analyzing the biochemical content of the tissue to tease out the metabolite/s that are responsible for the observed CEST effect. Once validated, this CEST effect will allow for improved patient diagnostics by providing a reliable and non-invasive tool for the assessment of liver disease without exogenous contrast injection.

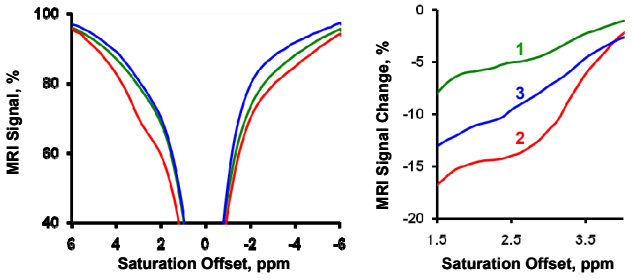

Figure 1. Z-spectra (Left) of three different tissues i.e. normal (1), Primary sclerosing cholangitis stage V (2), and hepatocellular carcinoma (3). Subtraction of the two sides of the Z-spectrum (Right) shows CEST effect at ~2.75 ppm downfield to bulk water resonance.

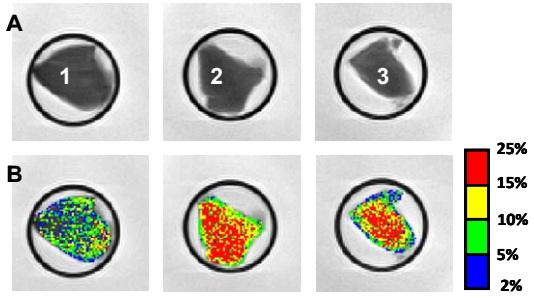

Figure 2. A two-chambered phantom containing liver tissue samples [normal (1), Primary sclerosing cholangitis stage V (2) and hepatocellular carcinoma (3)] in inner chamber and PBS in outer chamber (A). CEST contrast from liver tissues overlay on the image obtained with saturation at -2.75ppm (B).

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