IMAGING OF HEPATIC STEATOSIS AND HYPERPOLARIZED CARBON METABOLISM AT 14T - APPLICATIONS TO A MURINE MODEL OF NON-ALCOHOLIC FATTY LIVER DISEASE

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INTRODUCTION: Non-Alcoholic Fatty Liver Disease (NAFLD) is the most common cause of chronic liver disease in North America, with a prevalence approaching 35% in some population groups. The disease is closely associated with obesity and the metabolic syndrome. Although the etiology is multifactorial, current understanding of the metabolic abnormalities of NAFLD, as well as of the factors that lead some patients to progress to hepatic inflammation and end-stage liver cirrhosis while others do not, is limited. Magnetic resonance imaging at high field allows the acquisition of anatomic images with exquisite spatial resolution and detail. Additionally, specialized pulse sequences can be used to determine the degree of adiposity of tissues in vivo, providing a method to visualize the severity of steatosis within the liver. Hyperpolarized [13C] MR continues to be a valuable tool for the investigation of metabolic and biochemical processes in a variety of organs and pathologic conditions. The goal of these studies was to utilize hyperpolarized [13C] MR to identify and quantify metabolic derangements in mice fed a diet deficient in methionine and choline (MCD diet), an animal model of Non-Alcoholic Fatty Liver Disease.

RESULTS AND DISCUSSION: Co-localized water- and fat-sensitive axial images acquired simultaneously through the livers of both normal and NAFLD mice demonstrate a marked increase in the degree of fat signal within the hepatic parenchyma after 14 days of feeding the MCD diet when compared to the livers of normal mice (Figure 1). Additionally, characterization of the pulse sequence using phantom lipid/water emulsions of varying concentrations demonstrated a linear relationship between signal intensity and fat percentage in lipid-sensitive images (data not shown), allowing quantification of the deposition of microscopic fat in the liver.

3D frequency-specific acquisition (Figure 2) following injection of hyperpolarized [13C]pyruvate generates metabolic maps with high spatial (1.25 mm3 voxel size) and temporal resolution (acquisition time 140ms per metabolite), with the previously described large increase in signal to noise over standard spectroscopy. This allows the use of respiratory gating during acquisition, minimizing motion artifact. Initial experiments comparing normal mice (n=3) with mice on the fatty liver diet (n=3) demonstrate no significant change in pyruvate metabolism of hyperpolarized [13C]-pyruvate substrate within the liver (Table 1). It has been reported previously that although mice on the MCD diet are hypermetabolic, this appears to be related to increased fatty acid flux through β-oxidation pathways. Thus, pyruvate metabolism via the action of pyruvate dehydrogenase and ALT may remain unchanged in this model of fatty liver disease.

CONCLUSION: Early studies from this project have demonstrated the feasibility of noninvasive monitoring of steatosis progression through the use of quantitative lipid:water imaging sequences. Hyperpolarized [13C] metabolic imaging of NAFLD using hyperpolarized [1,13C]pyruvate has been performed with high temporal and spatial resolution and with high signal-to-noise. These initial studies demonstrate no significant change in pyruvate metabolism as assessed by hyperpolarized lactate, pyruvate, and alanine levels following intravenous injection in the fasting state, a finding that appears consistent with previously published work in this model. Additional experiments to assess hepatic oxidative stress in MCD-NAFLD mice are ongoing.

REFERENCES:

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