

Comprehensive Assessment of Diffuse Liver Disease with Quantitative MRI Biomarkers of Steatosis, Fibrosis and Portal Flow: A Biopsy Correlation Study.

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Target audience: Those with an interest in chronic liver disease and portal venous hemodynamics

Purpose: Non-alcoholic fatty liver disease (NAFLD) is an emerging condition increasingly recognized as the most common type of chronic liver disease [1]. A large and increasing number of NAFLD patients develop cirrhosis and liver failure. Currently it is diagnosed based on a combination of clinical history and lack of alcohol consumption, however definitive diagnosis requires liver biopsy. Therefore, *the purpose of this study* is to evaluate non-invasive MRI biomarkers of liver disease (fat, stiffness, and portal flow) in patients with diffuse liver disease undergoing non-targeted biopsy.

Methods: In this IRB-approved, and HIPAA-compliant study 31 patients referred for non-targeted liver biopsy for diffuse liver disease [all causes] (50.5±12.6years, 83.5±18.1kg) were included after written informed consent.

MR-Imaging. Studies were conducted within one month of a non-targeted liver biopsy performed to evaluate for diffuse liver disease. Imaging was performed either on clinical 1.5 or 3T scanner (GE Discovery MR450w and MR750, Waukesha, WI) with a 12-channel (1.5T) or 32-channel (3T) body coil (NeoCoil, Pewaukee, WI). Image acquisition was performed with: 1) 3D multi-echo chemical shift encoded MRI (investigational version of IDEAL IQ) to quantify liver proton density fat-fraction (PDFF)[2], 4D-flow MRI to quantify arterial and venous flow to/from the liver comprehensively [3,4], and magnetic resonance elastography (MRE) to quantify liver stiffness [5] (Figure 1).

Liver Biopsy. All histological slides were stained with H&E and/or Masson's trichrome stain, and were re-evaluated in a blinded manner for this study.

Biomarkers: PDFF (%), blood flow in the supraceliac aorta (Q_{SCA0}), portal vein (Q_{PV}) and hepatic artery (Q_{HA}) and liver stiffness (kPa) were measured with MRI. Q_{PV} was also normalized to Q_{SCA0} to evaluate portal venous blood flow relative to the total abdominal flow. Steatosis, fibrosis and inflammation were evaluated per NASH CRN criteria [6].

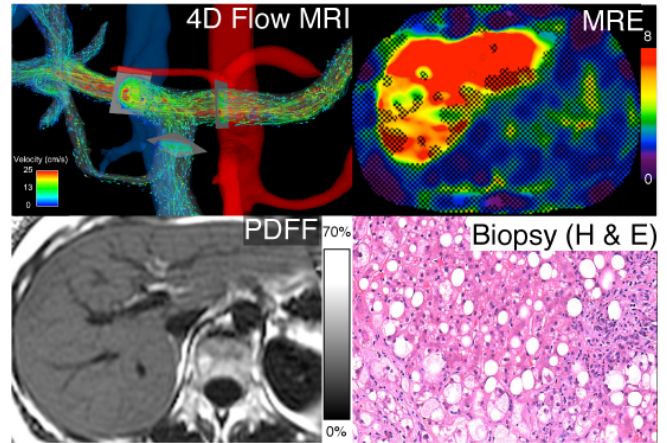


Figure 1. 4D flow MRI was used to quantify blood flow in different vessels. MRE provided information about liver stiffness. Fat content in the liver was quantified both using MRI and liver biopsy

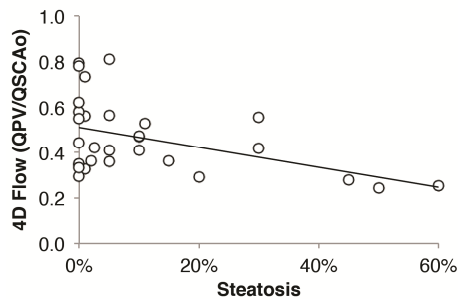


Figure 2. Negative linear correlation between normalized portal venous blood flow (Q_{PV}/Q_{SCA0}) and liver steatosis ($r^2=-0.36$, $p=0.05$).

results previously reported [2] and supports the use of quantitative MRI methods for non-invasive assessment of hepatic fat content. The positive correlation between normalized portal flow and liver stiffness agrees with the known hyperdynamic state that can occur in patients with portal hypertension [6], although the correlation did not show statistical significance. Negative correlation of normalized blood flow and liver steatosis (evaluated by liver biopsy) was an interesting and unexpected finding, raising questions about the relationship between hepatocyte dysfunction and blood flow [5].

Conclusion: The combination of quantitative MRI biomarkers for fat content, stiffness and normalized portal blood flow provides a valuable combination of biomarkers for the diagnosis and potential treatment monitoring of diffuse liver disease.

References: [1] Browning, Hepatology 2007; [2] Meisamy Radiology 2011; [3] Gu AJNR 2007; [4] Johnson MRM 2010; [5] Yin Clin Gastro & Hepatol 2007; [6] Kleiner Hepatology 2005.

Statistics: A multivariate analysis was performed. Specifically, we computed Spearman rank correlations for each pair of variables, and tested against the null of zero correlation. Variables with $P < 0.1$ (two-sided) were included in a multivariable model. Computations and graphics were obtained in R 2.12.2 (R Development Core Team 2009).

Results: MRI measurements of blood flow and liver PDFF and stiffness were successfully acquired for all 31 patients. PDFF and steatosis grading from biopsy were highly correlated ($r^2=0.71$, $p<0.001$ – data not shown). Q_{PV} and Q_{PV}/Q_{SCA0} both showed negative correlation with steatosis ($r^2=-0.45$, $p<0.012$), ($r^2=-0.36$, $p=0.05$, see figure 2), respectively. Further, there was no correlation between flow and either PDFF or stiffness ($r^2=0.12$, $p=0.5$). Figure 3 shows a positive (but not statistically significant) linear correlation between Q_{PV}/Q_{SCA0} and stiffness ($r^2=0.12$, $p=0.5$). A positive correlation was found between stiffness and ballooning ($r^2=0.36$, $p=0.047$), inflammation ($r^2=0.31$, $p=0.099$), fibrosis ($r^2=0.31$, $p=0.092$) and NASH CRN score ($r^2=0.37$, $p=0.041$). There was no correlation between stiffness and PDFF ($r^2=-0.23$, $p=0.2$).

Discussion: The strong correlation with PDFF and steatosis grading agrees with

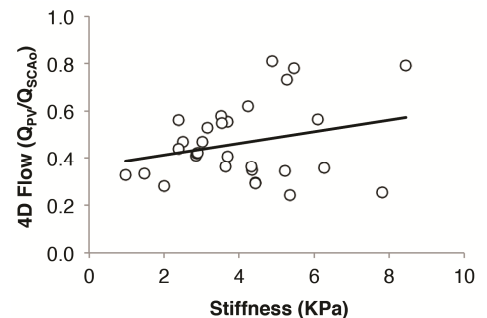


Figure 3. Positive linear correlation between normalized portal venous blood flow (Q_{PV}/Q_{SCA0}) and liver stiffness did not show statistical significance ($r^2=0.12$, $p=0.5$).