

Quantitative MR Microscopy of the Liver and Kidneys in a Mouse Model of Polycystic Kidney Disease (PKD)

C.-H. Lee^{1,2}, J. J. Flint^{2,3}, L. Guay-Woodford⁴, and S. J. Blackband^{3,5}

¹Electrical and Computer Engineering, University of Florida, Gainesville, Florida, United States, ²McKnight Brain Institute, University of Florida, Gainesville, Florida, United States, ³Neuroscience, University of Florida, Gainesville, Florida, United States, ⁴Genetics, University of Alabama, Birmingham, Alabama, United States, ⁵National High Magnetic Field Laboratory, Tallahassee, Florida, United States

Introduction

Polycystic kidney disease (PKD) is a major cause of end-stage renal disease (ESRD) in both children and adults, affecting 12.5 million people worldwide (~600,000 in the US). While current clinical trials are promising, there is no proven therapy for slowing disease progression and PKD patients continue to receive primarily supportive care (1). In an effort to understand disease progression and treatment, a variety of animal models have been developed (2). In this study, we examine the potential of MR microscopy (MRM) for evaluating the structural abnormalities involving ductal structures in the kidney and liver of the *cpk* mouse model of recessive PKD. In addition, we compare MR images and volumetrics of normal wild type and mutant isolated mouse kidney and liver.

Methods

Images were acquired with a Bruker 14.1 T vertical magnet equipped with 3000 mT/m gradients and interfaced with a 10 mm bird cage coil. In order to accommodate the liver samples into the inner diameter of a 10 mm NMR tube, the largest lobe of each liver sample was separated with a scalpel and fine surgical scissors. Images were acquired at ambient temperature ($22\text{ }^{\circ}\text{C} \pm 0.5\text{ }^{\circ}\text{C}$). For volume measurement and 3D rendering, 2D, multislice, multiecho images provided a clear contrast difference between the bile duct filled with PBS and liver tissues. After pilot images to check the correct positioning of the sample, the 2D MSME images both in coronal and sagittal view were acquired with TE = 50 ms, TR = 2.5 s, number of averages = 10, FOV = 2mm x 1mm, sampling matrix = 256 x 128, slice thickness = 200 μm , and in-plane resolution of 78 μm . Wild type (n=8) and mutant kidneys (n=12) as well as mutant (n=6) and wild type (n=6) livers were scanned. Image segmentation with the biliary trees and the entire volume of livers was performed by using AMIRA software version 3.1.1 (Template Graphics Software, CA, USA) in a semi-automatic way. In the kidneys, the total volume was determined. In the livers, the biliary tree volume was estimated semi-automatically by automatic threshold segmentation followed by manual refinement. Wild type and mutant livers were analyzed to yield the comparative differences in their volume. The total volume of the isolated kidneys was also estimated using water displacement as a check for the image volumetrics.

Results

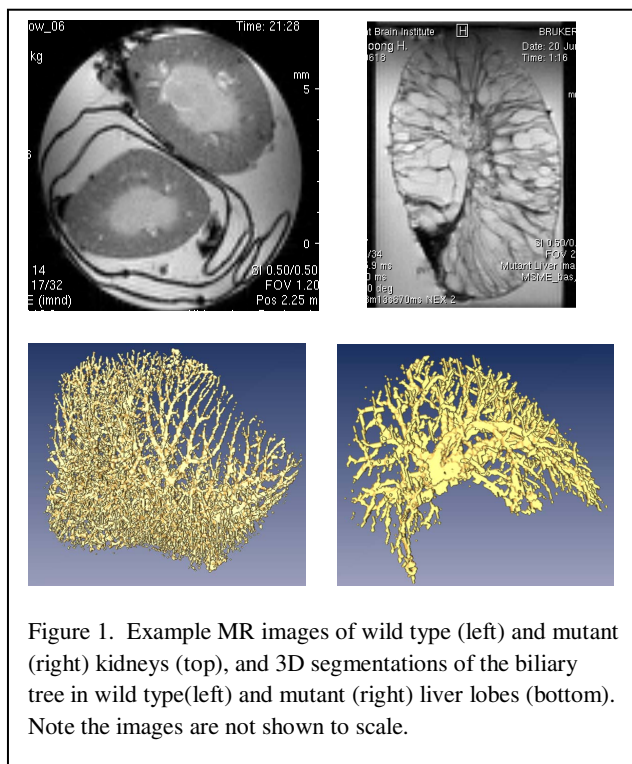


Figure 1. Example MR images of wild type (left) and mutant (right) kidneys (top), and 3D segmentations of the biliary tree in wild type(left) and mutant (right) liver lobes (bottom). Note the images are not shown to scale.

Figure 1 shows an example data set from a wild type and mutant PKD mouse model, and example data sets from the livers that have been segmented to isolate the biliary tree. The mutant kidney exhibits gross cystic formation and is several times larger than the wild type kidney ($1307 \pm 181\text{ mm}^3$ versus $93 \pm 10\text{ mm}^3$) and showed good agreement with water displacement volume measurements confirming the accuracy of the imaging and segmentation. The total wild type liver volumes were larger than the mutant counterparts by a factor of 1.7 ($519 \pm 72\text{ mm}^3$ versus $292 \pm 119\text{ mm}^3$), with the mutant livers exhibiting a much greater variability in volume. After segmentation, the total biliary tree volumes were similarly differentiated (wild type = $87.3 \pm 8.5\text{ mm}^3$, mutant = $35.0 \pm 22.4\text{ mm}^3$). The volume fraction of the biliary tree to the total liver volume was 0.17 ± 0.3 in the wild type and 0.11 ± 0.3 in the mutant, and are significantly different ($p=0.015$). This volume fraction difference is visualized in the images where the wild type biliary tree exhibits more extensive and finer branching, indicating developmental abnormality in the mutant livers.

Conclusions

MR microscopy of the excised tissues is able to detect statistically significant differences between wild type and mutant mouse kidney and liver in a murine model of PKD. The quantitative MRM volumetric studies illustrate not only a clear difference in the normal and PDK liver volumes, but also a significant difference in the volume fraction of the biliary ducts to total liver volume. These results suggest that MRM may play a role in evaluating genetic models of PKD, quantitating variance for genetic modifier studies and monitoring of potential

therapies. Future studies will include an investigation of the feasibility of similar studies *in vivo* so that time course studies may be enabled.

References and Acknowledgements

1. Cowley BD. *Drugs*. 64(12):1285-94 (2004); 2. Guay-Woodford LM. *Am J Physiol Renal Physiol*. 285(6):F1034-49 (2003). Funding provided by the National High Magnetic Field Laboratory and the NIH (P41 RR16105) and the Burroughs Wellcome Clinical Scientist Award in Translational Research (LGW). Thanks to Joshua Tate for technical support.