Evaluation of the progression of obstructive nephropathy in a UUO mouse model using BOLD, hyperpolarized 13C, and DCE MRI

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Introduction: Congenital obstructive nephropathy is the most common cause of end-stage renal disease in children [1]. Currently we have a poor understanding of its pathogenesis, prognosis, and the best course of treatment. Development of non-invasive, non-radioactive approaches is needed to improve the diagnosis and outcomes of obstructive nephropathy. In this study we investigated whether functional MRI measurements can be used as diagnostic indicators of obstructive nephropathy using a 14-day unilateral ureteral obstruction (UUO) mouse model. Blood oxygen level-dependent (BOLD) MRI, dynamic contrast-enhanced (DCE) MRI, and hyperpolarized [1-^{13}C] pyruvate (^{13}C) MRI were used to assess renal oxygenation, perfusion, and pyruvate metabolism, respectively. The results show the potential of using functional MRI, particularly ^{13}C MRI, to track the progression of pathology.

Materials and Methods: ***Animal models:*** Complete obstruction of the left ureter was performed surgically on one male FVP mouse (31 g; 8 weeks of age). The contralateral kidney served as an internal control. MRI exams were performed prior to surgery and at 1, 3, 6 and 14 days post-surgery. Images were acquired with a 32 mm^2 coronal FOV using a 4.7T Agilent scanner with respiratory triggering. The mouse was fasted for at least 5 hours prior to MRI. MRI was performed under isoflurane anesthesia (1-2% in 100% O_2), and temperature was maintained above 36°C by a warm air blower. All experiments complied with IACUC policies. ***^{1}H MRI:*** For all ^{1}H images, matrix=128x128 and slice thickness=1 mm. For T_2-weighted FSE, TR/TE=3500/16.5 ms, flip=90°, ETL=8, TE_{eff}=66 ms. For BOLD fat-saturated multi-GRE, TR/TE/ΔTE= 350/2.04/2.35 ms, echoes=64, flip=30°. For DCE GRE, TR/TE=6.5/3.01 ms, flip=20°. ***^{13}C MRI:*** 400 ul of 100 mM [1-^{13}C] pyruvate was injected over ~5 seconds through a tail-vein catheter followed by a 100 µl saline flush. Pyruvate and lactate images were acquired sequentially 20 seconds after the start of injection. Each species was selectively excited using a spectral-spatial RF pulse. TR/TE=81/16 ms, slice thickness=10 mm, pyruvate flip=10°, lactate flip=30°, BW=1 kHz, matrix=16x16, centric phase encoding. ***Analysis.*** BOLD images were fitted with an exponential decay model to produce R_2* maps. ^{13}C images were zero-filled to 128x128. Cortex and medulla were identified by manual segmentation of the T_2-weighted images.

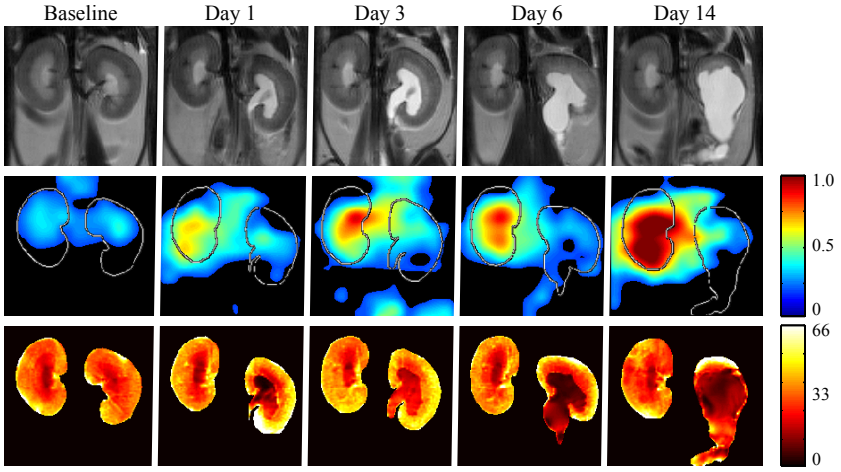

Figure 1. T_2-weighted images (**top row**) show the progression of fluid build-up and swelling of the renal pelvis in the obstructed kidney over 14 days. ^{13}C lactate (**center row**) images show progressively increasing lactate signal in the unobstructed kidney, suggesting compensatory increase in metabolism in this kidney. Kidney boundaries are overlaid and lactate data are scaled to arbitrary units. BOLD images (**bottom row**) show increased R_2* in the cortex of the obstructed kidney at days 6 and 14. BOLD data are expressed in seconds^{-1}.

Results and Discussion: Representative T_2-weighted images, ^{13}C lactate images, and BOLD R_2* maps are shown in **Fig. 1**. Lactate signal in the unobstructed contralateral kidney increased nearly three-fold at day 1 and more than six-fold by day 14 compared to baseline (**Fig. 2A**), while the lactate signal in the obstructed kidney increased only slightly over 14 days. This suggests upregulation of metabolism in the contralateral kidney to compensate for impaired function in the obstructed kidney. Cortical R_2* increased by day 6 in the obstructed kidney while no changes in R_2* occurred in the contralateral cortex or in the medulla of either kidney (**Fig. 2B**). This result supports prior results in swine [1] but differs from a more recent study in mice [2]. DCE MRI showed impaired glomerular filtration in the obstructed kidney compared to the contralateral kidney (**Fig. 2C-D**).

Conclusion: This study shows that the progression of the UUO model corresponds with functional changes in both the obstructed and unobstructed kidneys which can be detected by MRI. To our knowledge this is the first study of UUO using hyperpolarized ^{13}C imaging. Together the imaging results are consistent with impaired glomerular filtration and reduced metabolic work in the obstructed kidney and a compensatory increase in metabolism in the contralateral kidney. This study is necessarily a feasibility study in a single animal, but further studies with a larger cohort seem justified.

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References: 1. M.R. Benfield et al. Pediatr. Transplant. 2003; 2. M. Pedersen et al. Kidney Int. 2005; 3. M.E. Haque et al. ISMRM 2011.

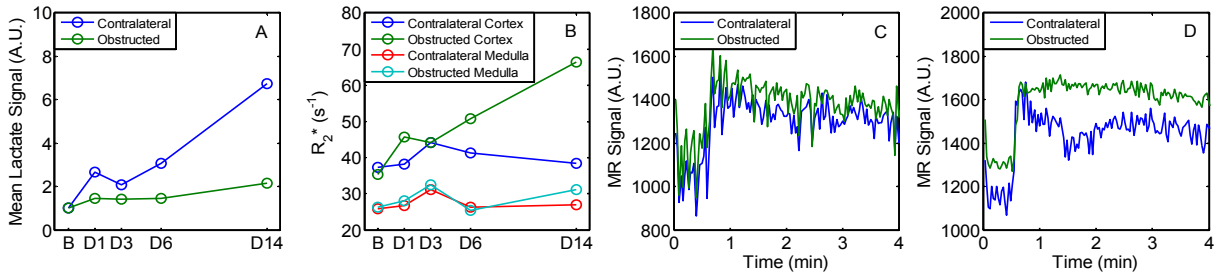

Figure 2. Whole-kidney lactate signal (**A**), showing progressive increase in the contralateral kidney over 14 days. Lactate data presented are normalized to the value of the left kidney at baseline. R_2* (**B**) showed an increase at days 6 and 14 in the cortex of the obstructed kidney. DCE signal in the cortex showed impaired glomerular filtration in the obstructed kidney beginning at day 1 (**D**) compared to pre-UUO baseline (**C**), as evidenced by the prolonged elevation of signal in D. Gadolinium injection (0.1 mmol/kg) occurred at approximately t = 30 seconds. B = baseline; D1 = day 1; D3 = day 3; D6 = day 6; D14 = day 14.