

Evaluation of Renal Metabolic Response to Partial Ureteral Obstruction with Hyperpolarized ^{13}C MRI

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Target Audience: Physicists and clinicians who are interested in hyperpolarized ^{13}C MRI or its potential applications with renal disorders.

Purpose: Congenital obstructive nephropathy is a major cause of end-stage renal disease in children [1], and improved approaches for its diagnosis and monitoring are needed. A recent pilot study demonstrated changes in ^{13}C MRI-derived lactate signal after complete unilateral ureteral obstruction in a mouse [2]; however, partial unilateral ureteral obstruction (PUUO) models more closely resemble human disorders, as most cases of congenital obstruction are partial. The purpose of this work is to longitudinally and non-invasively assess changes in renal metabolism with hyperpolarized ^{13}C MRI in a PUUO mouse model.

Methods: *Animals:* Partial obstruction of the left ureter was performed surgically on five female mice (25-29 g; 15 weeks of age). Mice were imaged on a 4.7T system (Agilent, Palo Alto, CA) after 12 hours of fasting and under isoflurane anesthesia (1.5%) at 4 time points: two days prior to surgery (Baseline) and 3, 7 and 14 days post-surgery. All experiments complied with IACUC policies. *^{13}C MRI:* Hyperpolarized [$1\text{-}^{13}\text{C}$]pyruvate (100 mM; volume, 10 $\mu\text{l/g}$) was injected over 3 s via the tail-vein. Single-shot spiral data were acquired with 4 s temporal resolution at 32 time points, beginning just before injection (5 echoes; TE=0.3 ms; ΔTE =1.19 ms; flip=10°; slice thickness=10 mm; FOV=64 mm; matrix=32x32). Pyruvate and lactate images were reconstructed from the multi-echo data using an iterative least squares estimation technique [3]. *Image analysis:* Whole-kidney ROIs were placed using anatomic ^1H images, and area under the curve across all 32 time points was calculated within each ROI for pyruvate (AUC_{PYR}) and lactate (AUC_{LAC}). The ratio of the AUC_{LAC} to the AUC_{PYR} ($\text{AUC}_{\text{ratio}}$) was used to quantitatively assess relative metabolic signal [4].

Results and Discussion: Three of the 5 mice were imaged at all time points. The remaining 2 mice died prior to Day 7. Statistical tests were precluded by the low sample size, but several qualitative trends were observed. Left and right kidneys showed similar pyruvate and lactate signal at baseline (Fig. 1B,C) and reduced pyruvate signal post-surgery (Fig. 1E; Fig. 2A). Pyruvate signal reduction was more pronounced in the left kidney, suggesting greater reduction of renal perfusion with obstruction. Lactate signal remained steady in the unobstructed right kidney but showed a negative trend in the obstructed left kidney (Fig. 1F, Fig. 2B). $\text{AUC}_{\text{ratio}}$ increased after Baseline in both kidneys, but with a slightly greater increase in the obstructed kidney (Fig. 2C). Together these results suggest a shift toward glycolytic rather than oxidative metabolism in both kidneys, but lower total metabolism in the obstructed kidney. These changes may result from reduced oxygen delivery and metabolic demand in the left kidney after obstruction.

Conclusions: We have used hyperpolarized ^{13}C MRI to non-invasively investigate longitudinal hemodynamic and metabolic changes following PUUO. Our results suggest reduced blood flow and lactate production in the obstructed kidney and a shift toward glycolysis in both kidneys. Further investigation into the metabolic changes related to ureteral obstruction is warranted. These results may contribute to our understanding of the pathogenesis of obstructive nephropathy and to the development of improved clinical diagnostic approaches.

Acknowledgments:

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References:

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- [4] D.K. Hill et al. *ISMRM* 2012.

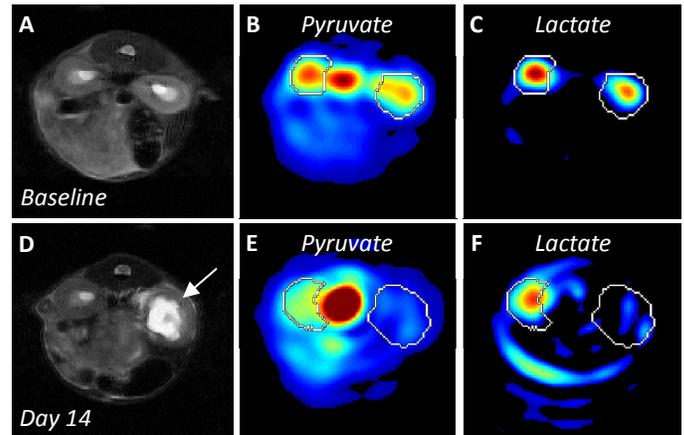


Figure 1. T_2 -weighted (A, D), pyruvate (B, E) and lactate (C, F) images at Baseline (top row) and Day 14 (bottom row). At Baseline signal in left and right kidneys is similar for both pyruvate and lactate (B,C), while at Day 14 the left kidney has markedly reduced metabolite signal compared to the left (E,F). The arrow indicates hydronephrosis caused by obstruction of the left ureter (D). Kidney ROIs are overlaid in white. Metabolite images are windowed to a common scale between days.

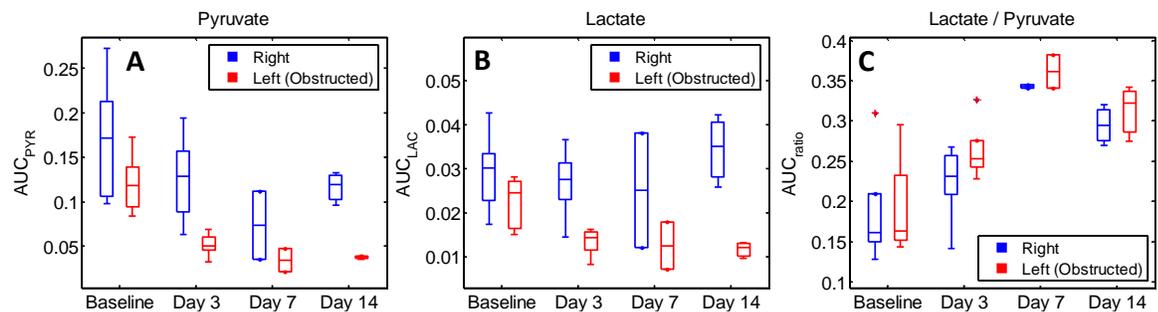


Figure 2. Box plots of AUC_{PYR} (A), AUC_{LAC} (B), and $\text{AUC}_{\text{ratio}}$ (C) for each kidney vs. time. The horizontal line indicates the median. $N=5$ for Baseline and Day 3. $N=3$ for Days 7 and 14.