# Dynamic Contrast-enhanced MRI Perfusion in a Unilateral Ureteral Obstruction (UUO) Mouse Model

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**Target audience:** Physicists, clinicians, and researchers who are interested in renal perfusion.

**Purpose:** The unilateral ureteral obstruction (UUO) model is widely used to study the pathogenesis of renal fibrosis. However, perfusion measurements with MRI in this model have not been previously reported. The purpose of this study is to assess longitudinal perfusion changes in a UUO mouse model with DCE-MRI.

**Methods: Animal subjects:** Complete obstruction of the left ureter was performed surgically on 6 male mice (mean weight 23.3g, 10 weeks of age) including 3 wild-type (WT) and 3 NADPH oxidase isoform2 (NOX2) knock out (KO) mice. NOX2 is highly expressed in phagocytes and may play a key inflammatory role in kidney disease[1]. Compiled with IACUC policies, Mice were imaged on a 4.7T small animal system (Agilent, Palo Alto, CA) after 12 hours of fasting and under isoflurane anesthesia (1.5%) at 3 time points: prior to surgery (Baseline) and 3 and 7 days post-surgery. **Imaging:** DCE images were acquired in two 2-mm-thick slices positioned obliquely on each kidney following a bolus injection of 0.15 mmol/kg Omniscan (TR/TE/FA = 7.6/1.9 ms/30°; spatial/temporal resolution = 0.25 mm/1s; scan time = 342s). 3D T1 maps were acquired immediately before and after DCE scanning using variable-flip-angle SPGR sequence[2] (TR/TE = 5.9/1.7 ms; FA = 4°/20°; RF phase/NEX = 169°/6; spatial resolution = 0.25×0.25×1 mm). To improve T1 mapping accuracy, a B1 field map was collected with the same volume and spatial resolution (TR/TE = 6.1/1.2 ms; FA/RF phase/NEX = 55°/35°/6). **Image Analysis:** The bookend method was used to estimate T1 and convert DCE images concentration time curves. Tissue ROIs were drawn on an average of 5 images after contrast arrival without image registration. The arterial input function was determined by averaging voxel-wise candidates in the abdominal aortic ROI to avoid inflow effects and to minimize partial volume effects. The 3-compartment model with gamma-variate fitting[3] was modified to fit the tissue concentration curves assuming the contrast arrival in the proximal tubule is delayed relative to the vascular compartment. The cortical concentration time data were fitted with a curve-fitting algorithm, which assumes a tricompartmental (vascular, proximal and distal tubular) distribution, $C(t) = c \cdot t^a \cdot \exp(-t/b) + d \cdot t^a \cdot \exp(-t/h) + i \cdot t^j \cdot \exp(-t/k)$, where a, b, and c describe vascular transit of the bolus, d and h describe accumulation and transit in the proximal tubule, and i, j, and k describe distal tubular fluid flow. Similarly, the aortic concentration time data were fitted by $C(t) = c \cdot t^a \cdot \exp(-t/b)$ where a, b, and c describe contrast kinetics in aortic vasculature. Mean transit time (MTT; s) was calculated as MTT = (a+1) •b. The tissue vascular area is defined as the area under the fitted vascular gamma-variate function. The blood volume fraction (BVF) is computed as tissue vascular area over the aortic vascular area. Tissue perfusion = 60•BVF/MTT/(1-BVF) •100 in ml/100g/min.

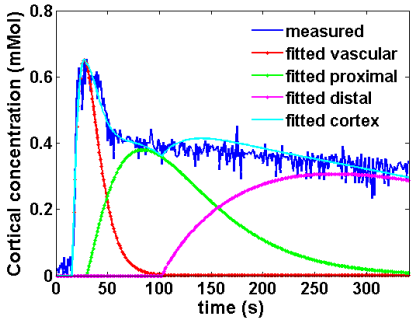


**Fig. 1** The fitted cortex (cyan) as a summation of 3 fitted compartmental (vascular in red, proximal and distal tubule in green and magenta) curves well approximated a measured (blue) cortical concentration time curve.

**Results:** The measured cortical concentration curve can be well fitted with 3 compartments (**Fig.1**). Statistical tests were not conducted due to the limited sample size, but quantitative trends were observed. Perfusion progressed to lower values in the obstructed kidney in both mouse strains by Day 7, but perfusion at baseline was greater in WT vs KO (**Fig.2**). Interestingly, the obstructed kidney in the KO mice showed gradually declining perfusion while the contralateral kidney in the same KO mice maintained baseline levels of perfusion at Day 7. For WT mice, both obstructed and contralateral kidneys showed markedly decreased perfusion relative to baseline.

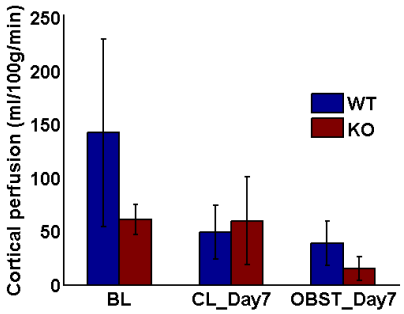


**Fig. 2** The cortical perfusion was greater in WT than KO at baseline (BL), and reduced in the obstructed kidney in both WT and KO mice. The contralateral (CL) kidney in KO mice had similar perfusion to its baseline level.

**Discussion:** Oxygen balance in the kidney is a complex physiologic process affected by oxygen delivery via perfusion, and utilization via metabolism and work to perform filtration and reabsorption. The role of phagocytic cells in mediating inflammatory response in kidneys under stress is an active area of study, particularly with respect to the role of reactive oxygen species and their role in kidney injury. In this preliminary study the KO and WT mice appear to respond differently physiologically and in terms of outcome with respect to histopathology markers of fibrosis (**Fig.3**). Further work needs to be completed to confirm a role for non-invasive perfusion MRI as a predictive measure of disease progression in this model of progressive kidney injury.

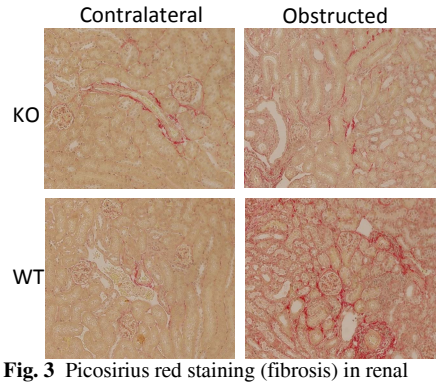


**Fig. 3** Picosirius red staining (fibrosis) in renal cortex showing the typical observed pattern of less fibrosis in KO vs WT mice.

**Conclusion:** The modified fitting model can effectively quantify the cortical perfusion. The measured perfusion alterations were consistent with expected physiological responses to UUO and histological findings. The tissue perfusion changes may precede irreversible renal fibrosis and therefore provide a sensitive indicator for early detection and monitoring of injury progression.

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**References:** 1. You YH, Okada S, Ly S, et al. Role of Nox2 in diabetic kidney disease. Am J Physiol Renal Physiol 2013; 304(7):F840-8 2.Hurley SA, Yarnykh VL, Johnson KM, et al. Simultaneous variable flip angle-actual flip angle imaging method for improved accuracy and precision of three-dimensional T1 and B1 measurements. MRM 2012; 68(1):54-64 3. Krier JD, Ritman EL, Bajzer Z, et al. Noninvasive measurement of concurrent single-kidney perfusion, glomerular filtration, and tubular function. Am J Physiol Renal Physiol 2001; 281(4):F630-8.