Characterizing Unilateral Ureter Obstruction of Mouse Kidney with Chemical Exchange Saturation Transfer and Magnetization Transfer Methods

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PURPOSE: Chemical exchange saturation transfer (CEST) and magnetization transfer (MT) imaging are sensitive to small molecules with exchangeable protons and macromolecules, respectively. Such methods could complement the physiological information obtained from conventional assays of kidney function and facilitate our understanding of pathological mechanisms in kidney disease. In this study, we used CEST and MT to assess mouse kidney following unilateral ureter obstruction (UUO) to determine if these methods are sensitive to the associated pathology.

METHODS: MRI protocols were optimized on Agilent 7T MRI system using a doty25 volume coil. During MRI scans, UUO mice (3 and 6 days after UUO surgery) were anesthetized and the body was stabilized in a MR compatible head/body frame. Rapid acquisition MRI methods and respiration gating were applied to minimize motion artifacts. T_1-weighted imaging was used to observed structural changes. The magnetization transfer ratio (MTR) was measured using a 2D RF-spoiled gradient echo sequence (TR=24ms, flip angle=7, TE=3.3ms, FOV=25.6×25.6 mm^2, matrix size=128×128, slice thickness (ST)=0.5 mm, 81 accumulations). Off-resonant RF irradiation was accomplished with use of Gaussian RF pulses (6000 Hz, 12ms). Additional images were acquired without MT pulses. CEST experiments were performed using a continuous wave (CW) CEST sequence with a 8.0 s irradiation pulse followed by a multishot spin-echo echo-planar-imaging (2 shots, TR=10s, TE=17.6 ms, matrix of 64×64, ST=1 mm and NEX=2). Z-spectra were acquired with RF offsets from -1500 Hz to 1500 Hz (61 images with RF offsets from -5 ppm to 5 ppm) with an interval of 50 Hz (~0.167 ppm at 7.0 T). B_{cw} was 1.6 μT. A control scan was performed by setting the RF offset to 20000 Hz. MTR_{asym} was computed using asymmetric analysis.

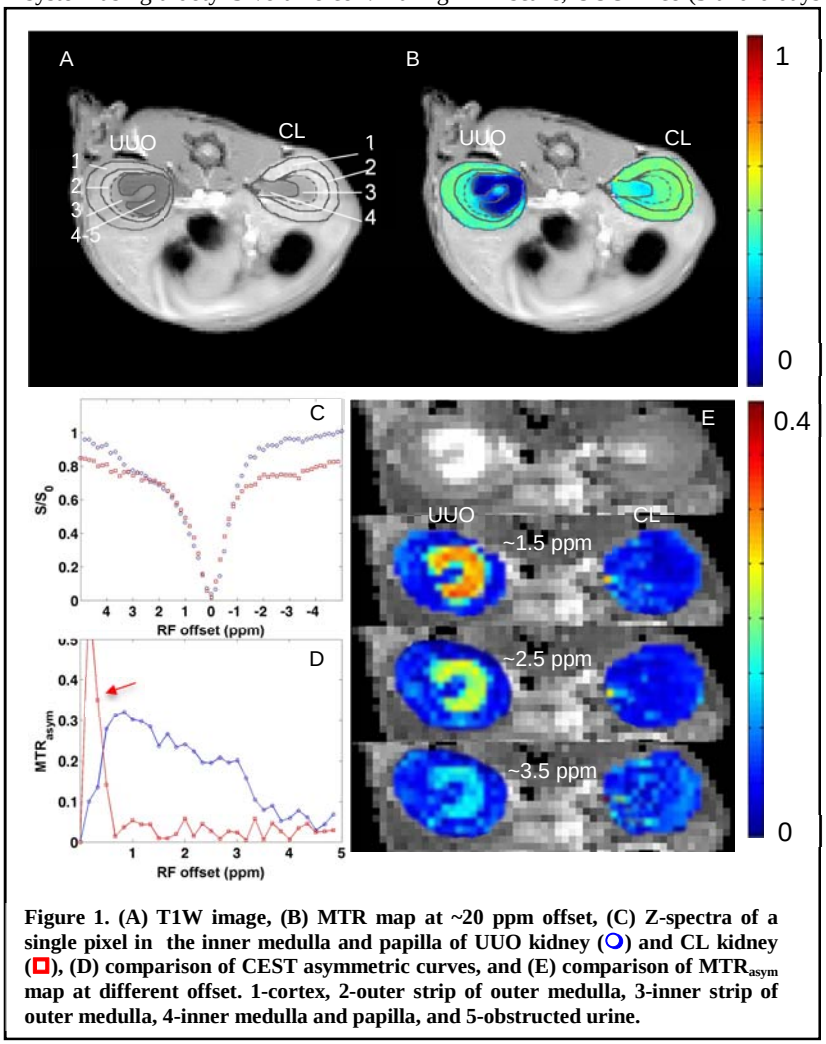

Figure 1. (A) T1W image, (B) MTR map at ~20 ppm offset, (C) Z-spectra of a single pixel in the inner medulla and papilla of UUO kidney (○) and CL kidney (□), (D) comparison of CEST asymmetric curves, and (E) comparison of MTR_{asym} map at different offset. 1-cortex, 2-outer strip of outer medulla, 3-inner strip of outer medulla, 4-inner medulla and papilla, and 5-obstructed urine.

RESULTS: Fine structural changes (size, shape, contrast and thickness) of renal compartments were detected in UUO kidney 3 days after the obstruction (**Fig.1A**). The overall MTR of the UUO kidney declined and its reduction was pronounced in renal medulla (**Fig.1B**). The obstructed urine showed very low MTR (**Fig.1B**) and very high MTR_{asym} (**Fig.1E**). UUO kidney showed asymmetric curve across the entire Z-spectrum (**Fig.1C**) while control lateral (CL) kidney did not. The MTR_{asym} curve of the UUO kidney exhibited positive CEST contrast while the CEST contrast in CL kidney was much lower by comparison (**Fig.1D**). The red peak around ~0.3ppm was due to B_0 inhomogeneity. **Figure 1E** shows MTR_{asym} maps at different RF offsets. The MTR_{asym} values in CL kidneys were very low (<0.1). The cortex in CL kidney showed higher positive MTR_{asym} values at 3.5 ppm than those at 2.5 and 1.5 ppm. In contrast, higher MTR_{asym} values were observed in medulla and cortex of UUO kidney than CL kidney at ~2.5 ppm, while lower MTR_{asym} values were observed in the cortex of UUO kidney than CL kidney at ~3.5 ppm. Based on the ROI (region of interest) analysis at ~2.5 ppm, outer medulla showed lowest MTR_{asym} among different compartments in the healthy kidney (**Table 1**). Even though the observed MTR_{asym} values were small, their changes were significant as early as UUO day 3. The change in MTR_{asym} (at 2.5ppm) and decline of MTR in the medulla of UUO kidney (day 3) could be related to the apoptosis and necrosis pronounced at that stage.

Table 1. Comparison of MTR_{asym} at ~2.5 ppm RF offset

MTR_{asym}	CL	UUO Day 3	UUO Day 6
IM+P(U)	0.042 ± 0.043	0.187 ± 0.044	0.236 ± 0.033
OM	0.022 ± 0.019	0.072 ± 0.043	0.078 ± 0.055
C	0.039 ± 0.027	0.054 ± 0.032	0.063 ± 0.028

Note: IM-inner medulla, P-papilla, U-urine, OM-outer medulla, and C-cortex. Standard deviations are across voxels.

DISCUSSION: The optimized MT and CEST imaging methods used herein are suited for evaluating mouse renal structural integrity. MTR is highly related to cell apoptosis and necrosis while CEST is sensitive to mobile molecules (mainly metabolites), and therefore they should have some special contrast in kidney disease. Such imaging methods could be used for the assessment of kidney diseases associated with the variation of the components of small molecules with exchangeable protons and macromolecules. Our next step is a longitudinal evaluation of the potential of MT and CEST to assess pathology in multiple models of kidney disease that mimic abnormalities in the basement membrane.

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