High Resolution Hyperpolarized ^{13}C Urea MRI Renography

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Target Audience: Nephrologists, Hyperpolarized MRI researchers.

Purpose: Urea is a key osmolyte that plays a crucial role in the urine concentrating function of the kidney. Dynamic Nuclear Polarization enhanced MRI[1] of urea[2] has been shown to be sensitive to changes in urea transport[3]. In this study we show a method for obtaining high resolution (1.2 mm isotropic) images of urea within the renal tubules and collecting system. This method utilizes the increased urea ^{13}C T_2 from ^{15}N labeling[4,5] combined with specialized 3D SSFP sequence and the exceptionally long (4s–20s) location-dependent T_2 values observed within the kidney. *In vivo* ^{13}C relaxometry experiments were used to understand the vascular and tissue dependence of the renal ^{13}C urea T_2 values.

Methods: The first set of experiments studied the *in vivo* ^{13}C urea polarizaton loss from T_1 relaxation induced by the infusion of a vascular contrast agent consisting of bovine serum albumin labeled with GdDTPA (BSA-GdDTPA)[6]. This compound is too large (mw~85,000) to be filtered by a normally-functioning glomerulus. Dynamic ^{13}C SSFP(θ =180°) urea images were acquired 28 s after a 12 second intravenous infusion of hyperpolarized [^{13}C,^{15}N$_2$]urea. Next, an identical hyperpolarized image acquisition was performed, but 1 mL of 50 mg/mL BSA-GdDTPA was injected 20 s post hyperpolarized ^{13}C urea injection and 8 s prior to ^{13}C imaging. In a second set of experiments, hyperpolarized [^{13}C,^{15}N$_2$]urea T_2 mapping[5] was performed on 3 rats in both the antidiuresis and diuresis states to selectively activate and deactivate the urea transporter UT-A1[3]. Finally, in the third experiment, a 3D encoded SSFP pulse sequence was developed similar those presented previuosly[2,5,7] but with the addition of Z phase encoding gradients. A flip angle θ =120° was determined to be SNR-optimal for renograpy based on the T_2 values observed from T_2 mapping experiments, the number of phase encoding steps used (800), and the repetition time (11.5ms). 1.2 mm isotropic ^{13}C images were acquired in 8 s starting at 20 s, 25 s, and 30 s after the beginning of 3 different injections of hyperpolarized [^{13}C,^{15}N$_2$]urea. Data were undersampled in the A/P and R/L dimensions; the sequence used a long effective echo time (5s) to filter out the short-T_2 signal from blood to enable this undersampling. All experiments were conducted using male Sprague Dawley rats imaged on a 3T GE clincal scanner. DNP experiments used a Hypersense polarizer, and 3mL of 110mM [^{13}C,^{15}N$_2$]urea was injected via tail vein catherters.

Results: The 3D renographic images at 3 different delay times are shown in Figure 1. The image resolution was sufficient to directly visualize the inner and outer medulla and renal pelvis margins, and collection to the inner kidney regions was observed. Images from the BSA-GdDTPA relaxation experiments are shown in Figure 2. ^{13}C urea signal intensity in the renal pelvis in both images was nearly identical (*SNR*=120); the post Gd ^{13}C urea signal relative to the no-Gd ^{13}C urea signal was .31 in the aorta, .75 in the renal cortex, .and .78 in the renal medulla. T_2 mapping experiments are shown in Figure 3. Faster urea collection to the inner medulla and renal pelvis was detected in the antidiuretic rats which in turn yielded a much larger apparent T_2 (Figure 3, left) in the renal pelvis.

Discussion: The selective attenuation of the aorta versus the medulla and renal pelvis of the BSA-GdDTPA indicates that the ^{13}C urea signal is primarily tubular, and this corresponds spatially to regions of long ^{13}C T_2. Some signal attenuation in the cortex and medulla (Figure 2, right) likely arises from the intrarenal vascular urea pool which is accessible to the BSA-GdDTPA. This is demonstrated by strong attenuation of the intralobolar arteries on the post- BSA-GdDTPA image (Figure 2, right). The short T_2 observed in the vascular supply and long T_2 observed in the kidney (Figure 3) likely report on the erythrocyte residence time of the hyperpolarized probe. The urea which has passed through the glomerulus no longer experiences the erythrocyte relaxation effects; the latter effect is likely very strong due to urea's high erythrocyte permeability.

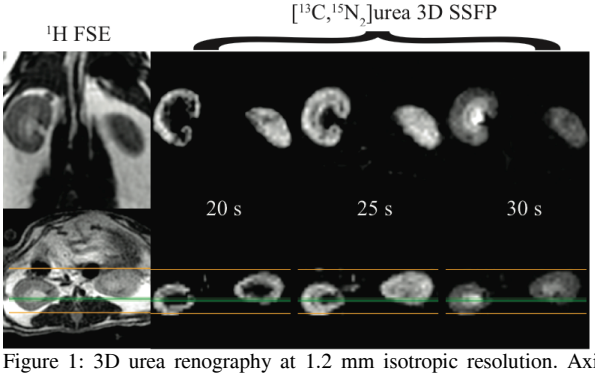

Figure 1: 3D urea renography at 1.2 mm isotropic resolution. Axial reformats (bottom) show residual signal from aorta and vena cava. The inner medulla and renal pelvis are hyperintense due to a large inward T_2 gradient and strong T_2 weighting of the sequence.

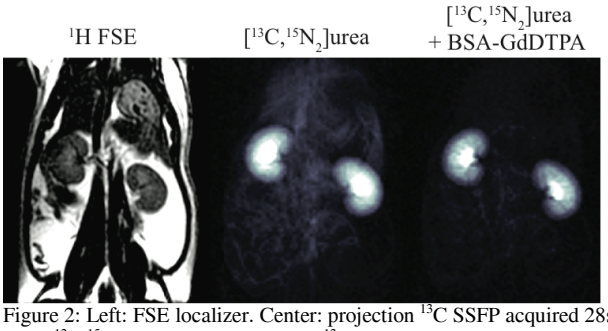

Figure 2: Left: FSE localizer. Center: projection ^{13}C SSFP acquired 28s post [^{13}C,^{15}N$_2$]urea injection. Right: ^{13}C SSFP acquired 28s post urea injection and 8s post BSA-GdDTPA injection. The macromolecular Gd complex attenuates vascular signal but not the renal urea signal.

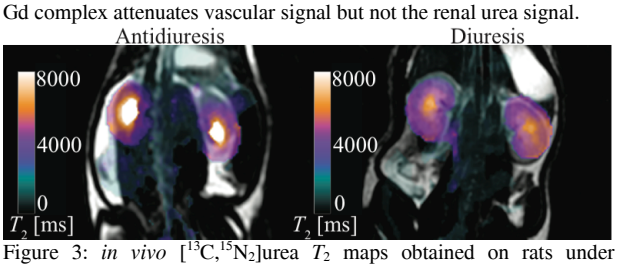

Figure 3: *in vivo* [^{13}C,^{15}N$_2$]urea T_2 maps obtained on rats under antidiuresis (T_2, medulla = 4.9±.9s, T_2, pelvis = 10.3±4.9s) and diuresis (T_2, medulla = 4.3±.5s, T_2, pelvis = 5.9±.4s). The antidiuresis state activates the UT-A1 transporter thereby increasing the urea concentration in the renal pelvis. Due to the large inward T_2 gradient of the kidney, T_2 mapping shows large contrast between the two states.

Conclusion: Relaxometry experiments were used to isolate the vascular and tissue dependence of a long T_2 signals observed with hyperpolarized [^{13}C,^{15}N$_2$]urea in the kidney. The exceptionally long ^{13}C T_2 of the intrarenal urea and the very large T_2 difference between tubular, vascular, and renal pelvis urea enabled a novel image contrast source, and direct visualization of the tubular urea component at 1.2 mm isotropic resolution. This work presents a method for separation of vascular and filtered urea using a non-invasive imaging approach.

References 1) Ardenkjaer-Larsen JH et al. Proc Natl Acad Sci USA. 2003; 100: 10158–10163. 2) Golman K et al. Proc Natl Acad Sci USA. 2003; 100: 10435-10439 3) von Morze C et al. Am J Physiol Renal Phsyiol. 2012; 302(12): 1658-1662. 4) Chiavazza E et al. J Magn Reson. 2013; 227: 35-38. 5) Reed G et al. IEEE TMI, in press. 6) Dafni H et al, Cancer Res. 2010: 70(19): 7400-741 7) Svensson J et al. Magn Reson Med. 2003; 50(2): 256-262