Endogenous Urea CEST (urCEST) for MRI monitoring of kidney function

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INTRODUCTION: The prevalence of Chronic Kidney Disease (CKD) is approaching critical levels worldwide. Many of these diseases alter normal intrarenal pH and urea distribution. These changes often precede detectable reduction in glomerular filtration rate (GFR), the current clinical "gold standard" to detect and quantify renal dysfunction. However, the pathological derangements may affect one kidney while sparing the other, or some regions of both kidneys but with functional compensation from other regions, thus not altering overall renal function and the composition of the final urine. Thus, pathological processes may be underway, while the clinical tests remain normal. Imaging remains the only way to assess any regional changes *in-vivo*. Generally used imaging modalities for anatomic renal evaluation are CT[1], ultrasound[2] and MRI[3]. However, commonly used clinical protocols do not provide accurate information about the renal function. Moreover, the Gd agents, which are the go-to means for MRI image enhancement, have limited applicability in patients with compromised kidney function. Thus, there is a considerable clinical need for new MRI approaches, including novel contrast agents and non-contrast methods that provide regional information about renal function *in vivo*.

In this abstract we assess the application of CEST to monitor kidney function using endogenous urea (urCEST). Urea is a natural CEST agent: it possesses two amine groups with exchanging protons. Indeed, urea was the first endogenous CEST agent reported *in vivo,* but after the first study in early 2000[9], no further exploration was reported. We believe that the challenge was largely technological: amine resonates only 1ppm away from water, thus direct saturation is a challenge. Here we report a successful implementation of urCEST on a 3T whole-body clinical MRI scanner. We present normal volunteer images as well as urCEST modulation following an intervention.

METHODS: All experiments were performed on dual-transmit 3T Philips Achieva scanner, using the torso array coil. The sequence was respiratory triggered and employed parallel, alternating RF transmission[4] allowing generation of very long saturation pulses. The saturation employed 40 sync shaped RF units, each of 50msec, for total saturation time of 2sec. Images at 22 offsets (±500Hz) were acquired with B0 homogeneities corrected using WASSR on the pixel-by-pixel basis. The average saturation B_1 was optimized to achieve maximum urCEST and was found to be 1.1±0.3uT. The imaging parameters were: single-shot TSE acquisition, FOV 40x40cm,slice thickness 10mm, TR_{eff}/TE_{eff}=11sec/6msec, matrix size 200x200, with total acquisition time of 4min for urCEST and 2.5min for WASSR. All the human studies were performed in accordance with the UTSW IRB Three healthy volunteers were scanned, two of them multiple times.

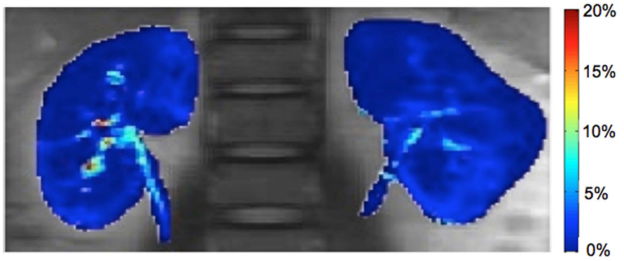

Figure 1. urCEST map of kidneys overlaid on the reference image

In addition, phantom experiments were performed, with the identical imaging parameters. Aqueous urea solution of 30mM and 75mM were prepared and titrated to pH values of 4,5,6 and 7.

RESULTS AND DISCUSSION: Fig. 1 shows *in-vivo* urCEST maps of the kidneys measured in a healthy male volunteer, using the protocol described above. There is an increased urCEST (up to 15%) in the renal medullas as well as in the renal pelvis. The urCEST in the bladder (not shown here) is up to ~30%. This is in agreement with expected high concentration of urea in these structures. The left kidney in the Fig. 1 exhibits slightly lower CEST because the structures are not captured equally in the image plane.

The urCEST effect is very high. So far, we have scanned 3 healthy volunteers multiple times, and the lowest urCEST in medulla was ~6%, while ~16% in the bladder. These data indicates the feasibility of urCEST *in-vivo*. To compare with other endogenous DIACEST: the CEST effect observed at 3T in a brain cancer is up to about 3%[5], in articular cartilage is up to 2%[6] and in vertebral discs up to 10%[7]. The high effect observed in urCEST suggests high sensitivity to changes, i.e. even minor change in urea concentration or pH would lead to observable changes in urCEST.

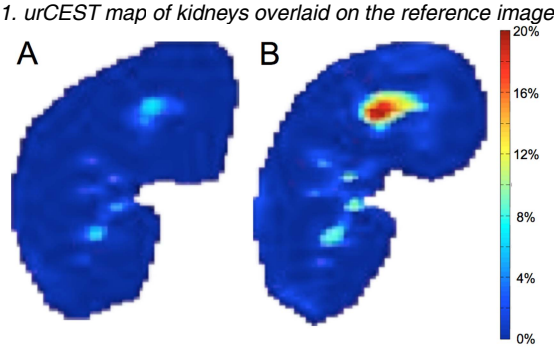

Figure 2. urCEST map of the right kidney of a male volunteer: (A) "dehydrated" and (B) "hydrated"

As the first preliminary step to utilize the ability of urCEST to monitor physiological changes, we have compared the urCEST maps acquired under two conditions: (i) in the absence of fluid and food intake for over 8 hrs ("dehydrated") vs (ii) the regular fluid and food intake ("hydrated") (Fig. 2). In the "dehydrated" state the urCEST effect in medulla was 4±1% while in hydrated 11±5%. While the exact physiological changes behind this observation require further clarification, the increase in urCEST may reflect either the increased urea concentration following liquid and food intake and/or decreased pH of the produced urine. Additional studies will be conducted to explore changes in urCEST under different interventions.

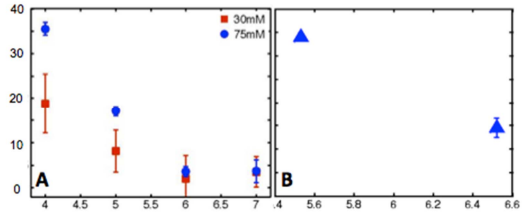

Figure 3. UrCEST vs pH in-vitro (A) and in-vivo (B).

To further study the urCEST dependence on pH and concentration we have conducted a preliminary study *in vitro* and *in vivo* comparing urCEST in bladder with pH in voided urine. The results (Fig.3) indicate that urCEST increases with the decreasing pH, as could be expected from the acid-catalyzed exchange. In-vitro the threshold for exchange slow enough to observe CEST is about pH=5.5, while *in-vivo* it is estimated around 7. This increase may occur with increase of protolysis rate *in-vivo*. In overall, the data indicate sensitivity of urCEST to pH in the physiologically relevant ranges.

CONCLUSION: We have demonstrated the successful implementation of urCEST on a clinical whole-body 3T scanner, utilizing alternating RF transmission. We anticipate that the urCEST combined with other non-contrast methods, such as ASL and diffusion, may become a powerful tool in the non-invasive evaluation of kidney disease. The urCEST effect is inherently sensitive to tissue pH. We are investigating recent advances in CEST quantification, e.g. Omega-plots corrected for direct water saturation[8], to create MRI mapping of pH and urea gradients in kidneys.

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