Editorial Focus: Functional MR Imaging of Kidney -- Novel Approaches to Monitoring Renal Physiology

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Running title: Editorial Focus: Functional Renal MRI
In this issue, Cornelius von Morze from the University of California (San Francisco, California, USA) reported the use of hyperpolarized $[^{13}\text{C}]$urea magnetic resonance imaging (MRI) to monitor urea transport in a rat kidney. The researchers applied a bolus infusion of hyperpolarized $[^{13}\text{C}]$urea under acute diuretic and antidiuresis conditions, and observed upregulation of the urea transporter UT-A1 at the renal inner medulla under antidiuresis. This research reflects progress within the MRI community, and the radiology community in general, from what once was a primarily anatomic discipline to one that provides in vivo dynamic imaging of biological processes that have traditionally been studied in vitro, or analyzed in a very invasive fashion.

With the advancement of instrumentation, pulse sequences, comprehension of MR biophysical mechanisms, and novel data analysis methods, MRI is able to provide a dynamic picture of tissue physiology, which includes tissue perfusion, tissue oxygenation and oxygen metabolism (5, 14), water/solute transportation across cell membranes (4), tissue energetics (6), and more. For instance, based on the sensitivity of the MR signal to the blood oxygenation level (BOLD), the renal BOLD technique can provide a semi-quantitative mapping of intra-renal oxygenation (10), thus opening new possibilities to study kidney diseases, particularly those related to tissue hypoxia (9). The quantitative BOLD (qBOLD) technique (5), originally developed for quantification of absolute blood oxygenation in neural applications, has the potential to obtain an absolute quantification of intra-renal oxygenation by separating the effect of blood oxygenation from the rest of hemodynamic parameters affecting renal BOLD signal (3). Since the major portion of kidney oxygen metabolism is used for active transportation of sodium, these BOLD based techniques enable researchers and clinicians to non-invasively investigate important pathways regulating urine concentration. The intra-renal sodium gradient can also be directly quantified with sodium-MRI in both animal models and human subjects (2, 8). The kinetics of sodium gradient change is site specific and related to the loop diuretic mechanism in both intact and diseased kidneys.
Other implementations of in vivo multinuclear magnetic resonance spectroscopy (MRS), including oxygen-17, fluorine-19, phosphorus-31, and carbon-13, have been utilized to measure oxygen consumption, phosphate content and energy reserves, substrate selection and rate of metabolic flux, respectively. However, compared to proton MRI, these multinuclear approaches usually suffer from extremely low intrinsic sensitivity, which results from low magnetogyric ratio, low natural abundance and low in vivo concentration. At biological temperatures and field strengths that are attainable in a clinical setting, only a very small fraction of nuclei of interest (in the order of $10^{-6}$) are visible by MRI. Hyperpolarization with the dynamic nuclear polarization (DNP) technique can yield $>$50,000-fold signal increase in MR-active nuclei. When used with MRI and/or MRS, hyperpolarized $^{13}$C-labeled metabolic tracers allow unprecedented real-time visualization of the biochemical pathways of normal and abnormal metabolism. For example, hyperpolarized $[1,2-^{13}$C$_2]$pyruvate enables simultaneous investigation of cardiac pyruvate dehydrogenase flux, Krebs cycle metabolism, and pH (1). In the study by Zierhut et al, hyperpolarized $^{[^{13}$C]$pyruvate has been used to investigate the metabolic exchange between $^{13}$C-labeled pyruvate, $^{13}$C-labeled lactate and $^{13}$C-labeled alanine in preclinical murine models (15). The metabolic parameters estimated with a kinetic model were able to differentiate anatomical structures based on metabolic activity, and may be useful for in vivo monitoring of tumor progression and treatment efficacy.

Metabolically inactive agents such as hyperpolarized $[^{13}$C]urea may hold great potential for angiography or perfusion imaging. In renal perfusion imaging, using $[^{13}$C]urea signal acquired over 30 s (12-s bolus injection), it is feasible to quantify kidney blood flow (12). Infused urea quickly diffuses into interstitial space in most tissues, and is rapidly taken up by cells through facilitated transport. With respect to the urinary concentration mechanism, while sodium chloride is the dominant solute in the outer medullary interstitium, urea is important in the inner medulla. In the inner medullary collecting duct (IMCD), facilitated transporters such as UT-A1 and UT-A3 allow specific reabsorption of urea from the luminal fluid, followed by reabsorption of water down
the resulting osmotic gradient via aquaporins. The novel technique described by von Morze et al.
investigated the difference in renal cortex and medulla $[^{13}\text{C}]$urea signal dynamics over the time
course of 45 s between an acute diuretic and antidiuretic state. The observed changes of the
medullary $[^{13}\text{C}]$urea signal after 30 s are attributed to the upregulation of UT-A1 by antidiuretic
hormone (ADH). The capability of monitoring dynamic changes of a urea transporter in vivo is
exciting and opens new possibilities for studying the role of the urea transporter in urinary
concentration to improve medical care. This technique enables the monitoring of novel diuretic
drugs that inhibit the urea transporter for the treatment of water and salt imbalance disorders.
Familial azotemia, an inherited disease characterized by impaired urea excretion despite normal
renal function, may be another potential target for this technique.

There are several limitations for the hyperpolarized $[^{13}\text{C}]$urea technique and caution should be
exercised when interpreting the observed result. First is the limitation imposed by the intrinsic
T1 decay of the $[^{13}\text{C}]$urea signal. Unlike MR imaging using Gd-DTPA based contrast, the decay
of hyperpolarization (T1 ~40 s) implies that experimental observation time would be less than 2
minutes when adequate signal can be observed. Although that may be adequate for a small
animal study, it may pose challenges for human use where the combined transit time for the
tubular and collecting duct is approximately 2 to 3 minutes (13). At the same time, new methods
in hyperpolarization are continually increasing the attainable level of polarization, which extends
the imaging window. And also, larger doses of urea than described in this study would likely be
safe, which could also extend the imaging window significantly. Second is the challenge for an
accurate quantitative analysis, which needs detailed modeling of $[^{13}\text{C}]$urea kinetics among
different tissue types such as blood vessel, renal cortex and renal medulla. Existing approaches
are not able to differentiate the distribution of $[^{13}\text{C}]$urea among renal tubules and interstitium
within renal cortex and medulla. Compartment-sensitive $^{12}\text{C}$ shift reagents may potentially be
utilized to distinguish $[^{13}\text{C}]$urea compartments in renal tissue, similar to TmDOTP$^{5−}$ as a $^{23}\text{Na}$
shift reagent to separate intracellular Na$^+$, vascular Na$^+$, and intraluminal Na$^+$ (11) in a rat kidney
study. Additionally, the potential role of UT-A2 at the descending thin limb, and UT-B at the
descending vasa recta should also be considered (7). It has been discovered that UT-B1 activity
is also regulated by antidiuretic hormone (ADH).

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