Published in final edited form as:

Acad Radiol. 2008 November ; 15(11): 1467–1473. doi:10.1016/j.acra.2008.04.013.

Urinary Oxygen Tension Measurement in Humans Using MR Imaging

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Abstract

Rationale and Objectives—Renal medullary hypoxia is frequently implicated in renal dysfunction; and urinary oxygen tension (pO_2) in the renal pelvis can be used as a surrogate for the adjacent renal medullary oxygenation. We aim to assess the feasibility of MR quantification of urinary pO_2 in humans.

Materials and Methods—The longitudinal relaxivity (R_1) of fluids is linearly related to pO_2 , allowing MR quantification of urinary pO_2 . We imaged urine phantoms with a range of pO_2 using a real time saturation recovery T2-prepped SSFSE sequence to calibrate urine R_1 values to pO_2 . Following IRB approval, we imaged the urinary bladders of 7 healthy subjects while breathing room air, and the renal pelvis of 9 healthy subjects breathing room air or 100% O_2 via facemask. The renal pelvic urine pO_2 was compared before, during and after 100% O_2 breathing.

Results—Our phantom study confirmed that urine R_1 is linearly related to pO_2 : pO_2 (mmHg) = $(R_1 - 0.2253 \text{ s}^{-1}) / (2.61 \times 10^{-4} \text{ s}^{-1} / \text{mmHg})$. The mean bladder urine pO_2 ranged from 23 to 45 mm Hg among the 7 subjects. Successful MR measurements of renal pelvic urine pO_2 were obtained in 7 of 9 healthy subjects. Following 100% O_2 breathing, the renal pelvic urine pO_2 showed a significant mean increase of 29 mmHg ($p < 0.05$).

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Conclusions—We show that MR quantification of urinary pO_2 is feasible. Noninvasive renal pelvic urine pO_2 determinations could serve as a valuable indirect measure for renal medullary oxygenation, allowing for clinical investigations of the role of renal medullary hypoxia in renal disease.

Keywords

Magnetic resonance imaging; oxygen; T1; kidneys

Introduction

The oxygen tension in the renal medulla is amongst the lowest in the human body due to low medullary perfusion and the large amount of oxygen required for sodium reabsorption and urinary concentration (1,2). This low oxygen environment places the medulla at risk for ischemic injury, which is associated with numerous common renal diseases including acute tubular necrosis, diabetic nephropathy, and drug or contrast-induced nephropathy (2,3). Previous studies have shown that measurements of urine oxygen tension (pO_2) in the renal pelvis is a sensitive surrogate measure of the oxygenation of the immediately adjacent renal medulla (4–6). As urine flows through the tubules of medullary thick ascending limb into the renal pelvis, the urine pO_2 equilibrates with the medullary pO_2 , which in turn reflects medullary perfusion and oxygen consumption (4,7,8).

Urine pO_2 can change in response to a variety of physiological and pathological stimuli. For example, when healthy subjects breathe supplemental oxygen, their urine pO_2 increases, likely due to the increased dissolved oxygen in the blood supplying the medulla (9). In patients with renal failure and loss of urine concentrating ability, the urine pO_2 increases and this change is thought to reflect the reduced medullary metabolic function in such patients (10). Urine pO_2 has also been shown to decrease progressively down the ureter into the bladder due to equilibration with ureteral wall (5). Therefore, the renal pelvic urine pO_2 most accurately reflects the renal medullary pO_2 (5).

Traditionally, measurement of urine pO_2 is obtained by use of oxygen probes. However, oxygen probes are invasive, cumbersome, and not practical for routine clinical use (4,7,11, 12). A noninvasive means to monitor urine pO_2 under physiologic conditions or in the setting of disease is therefore desirable and may become a useful tool for monitoring several common renal diseases and their associated medullary hypoxia.

It is possible to measure fluid pO_2 by MR imaging because of the paramagnetic property of oxygen. The longitudinal relaxivity ($R1 = 1/T1$) is directly proportional to oxygen content in most low-protein ($< 1\text{--}2$ g/L) fluids (13–15), allowing the quantification of pO_2 based on $R1$ measurements. Recently, Zaharchuk et al have validated the first oxygen tension measurements *in vivo* in human cerebrospinal fluid (CSF) with a novel MR technique (16). Quantitative pO_2 measurements were obtained and were noted to increase along the cortical sulci and basilar cisterns upon inspiration of 100% oxygen by facemask. We postulate that this technique can be extended to the measurement of urine pO_2 , another low-protein body fluid. In this study, we present our preliminary experience in measuring urine pO_2 in humans using MR imaging.

Materials and Methods

MR imaging

All MR imaging was performed using an 8-channel body coil on a 1.5-Tesla scanner (Signa, General Electric Healthcare, Madison, Wisconsin). A real-time modified single-shot fast spin-echo (SSFSE) pulse sequence that minimizes artifacts from partial volume and fluid flow was

used to measure the fluid longitudinal relaxivity (R_1), as previously described (16). Briefly, a pair of images at each location was acquired in succession (Fig. 1). The longitudinal magnetization is nearly completely recovered prior to the first acquisition (S_1), and only partially recovered prior to the second acquisition (S_2). The variation in signal intensity of the two acquisitions will be due only to R_1 . The ratio of S_1 and S_2 (as well as the saturation recovery times, T_{R1} and T_{R2} of the two acquisitions) is used to calculate the R_1 of the urine. In order to minimize partial volume averaging of the voxels that contain both fluid and soft tissue, a T2 preparatory segment was used prior to excitation to suppress non-fluid signal (17). In addition, nonselective T2 preparation and refocusing pulses were used during image acquisition to equally saturate both stationary and flowing fluid, therefore minimizing the artifacts from fluid flow.

Phantom Studies

The purpose of the phantom study was to calibrate measured urine R_1 values to pO_2 . Freshly voided urine sample was collected from one healthy subject and distributed into 7 glass flasks. Mixtures of nitrogen (N_2) and oxygen (O_2) gas were bubbled through the urine in the flasks to achieve a range of oxygen tensions. The pO_2 of each urine phantom was measured with a polarographic electrode (Licor; GMS, Kiel-Mielkendorf, Germany), and the flask was then immediately sealed with a ground glass stopper. MR imaging of the urine phantoms (pO_2 ranging from 10 to 210 mm Hg) was performed in a 37°C water bath at 1.5T. The following MR parameters were used: T_{R1} = 10 seconds, T_{R2} = 3 seconds, nonselective T2-preparatory segment = 900 msec, TE = 60 msec, field of view = 20 cm, matrix = 320×256 , slice thickness = 10 mm, bandwidth = 31.25 kHz, and echo train length = 136. The pO_2 of each urine phantom was then re-confirmed by electrode measurement immediately following imaging.

Human Studies

The human study was approved by our institution's Committee on Human Research. Written informed consent was obtained from each study participant. All study participants ($n = 11$) were healthy volunteers (4 men and 7 women; mean age, 37-years-old; range, 29- to 40-years-old) without a history of renal disease. The imaging sequence used for the human studies was the same as for the phantom study, with the exception of changes of field of view (30–36 cm) and matrix (256×256). A single 10 mm thick slice centering on either the bladder or the renal pelvis was selected for imaging. As in the phantom study, heavy T2-weighting was applied by using a 900 ms nonselective T2-preparatory segment followed by a short TE (60 ms) in order to minimize partial volume errors. These values were chosen based on previous simulations of partial volume errors (16). The acquisition time (with readout time) for a pair of images in succession was approximately 15 seconds. Signal averaging with number of excitation (NEX) of 10 was used, resulting in imaging time of 150 seconds (2.5 minutes) for each pO_2 measurement (i.e. a set of images consisting of 10 image pairs acquired over 2.5 minutes was used to obtain each pO_2 measurement).

Bladder Urine—Seven of the 11 healthy subjects underwent MR imaging of the urinary bladder while breathing room air. The subjects were neither fluid-restricted nor hydrated with water prior to the MR scans. Bladder urine pO_2 was continuously measured over 10 minutes, with each pO_2 measurement acquired in 2.5 minutes, and a total of four pO_2 measurements over 10 minutes for each subject. In 4 of the 7 subjects, freshly voided urine samples were collected immediately after the MR scan, the pO_2 of their urine samples was measured using the oxygen probe within 2 minutes of sample collection, and compared to that measured by MR imaging.

Renal Pelvic Urine—Nine of the 11 healthy subjects underwent MR imaging of the renal pelvis (including the 5 subjects who also had imaging of the urinary bladder on the same day).

All subjects drank approximately 250 cc water 30 minutes prior to imaging to improve renal pelvis distension and visualization. Prior to being placed on the MR scanner, all subjects were fitted with a non-rebreather facemask (Model 1060; Hudson RCI, Temecula, CA) that covered the nose and mouth. Previous study using similar non-rebreather facemask has shown a reliable increase in arterial oxygenation by four fold, achieving arterial oxygenation > 350 mm Hg (18). Two baseline MR measurements of renal pelvic urine pO_2 were obtained while the subjects breathed room air (21% O_2), using the same MR imaging parameters described above and centering on a renal pelvis. Because a single 10 mm image slice was selected to center on a renal pelvis, the image slice only allowed for optimal visualization of either the right or the left renal pelvis, but not both. The subjects were then administered 100% oxygen (10L per minute) via the facemask. Three additional urine pO_2 measurements were obtained at time points 5, 10, and 15 minutes after the initiation of oxygen breathing. Because each pO_2 value was measured over 2.5 minutes, the total time of 100% oxygen breathing for each subject was 17.5 minutes. Two final renal pelvic urine pO_2 measurements were obtained at 5 and 10 minutes after the subjects resumed breathing room air. In order to reduce motion artifact of the kidneys, the subjects were instructed to hold their breath in expiration during each of the approximately 5 second intervals that encompass the actual acquisition of the image pairs (i.e. the breathhold period extended from immediately before the acquisition of the first image of the pair to immediately after the acquisition of the second image of the pair, see Fig. 1), and to otherwise breathe freely.

Image Analysis

The images were transferred to a desktop computer (Dell Dimension 4700, Round Rock, TX) for data analysis using a commercially available image analysis software program (MISar, Apollo Medical Imaging, Melbourne, Australia). Regions-of-interest (ROIs) were placed in the urine phantom (approximately 20 mm^2), urinary bladder (approximately 70 mm^2) or renal pelvis (approximately 10 mm^2) with care to avoid the edge of the structure that was being measured or areas of artifact. The typical standard deviation of the voxels placed centrally in the area of interest was on the order of 15–20% of the mean, depending on the voxel size (unpublished data). The ROIs for the renal pelvis were corrected for spatial misregistration due to respiratory motion if necessary using a built-in motion-correction tool in the MISar software program. The R1 of the urine was calculated from signal intensities of the ROIs via an iterative process with five iterations, as described previously (16). In order to increase the signal-to-noise ratio for the urine pO_2 quantification (16), the R1 values of 10 image pairs acquired over 2.5 minutes were averaged to obtain a mean R1 value for each image set. The R1 values were then converted to pO_2 using the relationship established in the phantom experiment.

Statistical Analysis

Statistical analysis was performed using Stata software package version 8.0 (Stata Corporation, College Station, TX). For the phantom study, the slope and the intercept of the line describing the relationship between R1 and pO_2 were determined by least-squares fittings. Analysis of variance (ANOVA) with Tukey's HSD correction for multiple comparisons was used to evaluate changes of renal pelvic urine pO_2 in response to oxygen breathing. P-values less than 0.05 were considered statistically significant.

Results

The phantom study showed a highly linear relationship between urine R1 as measured by MR imaging and pO_2 of the urine phantom as measured by the oxygen probe (Fig. 2). The equation, $pO_2 \text{ (mmHg)} = (R1 - 0.2253 \text{ s}^{-1}) / (2.61 \times 10^{-4} \text{ s}^{-1}/\text{mmHg})$, derived from the phantom study was then used to convert subsequent measured urine R1 values to pO_2 .

The bladder urine pO_2 measured by MR imaging in the 7 healthy subjects is shown in Fig. 3. The mean bladder urine pO_2 over 10 minutes ranged from 23 to 45 mm Hg among the subjects. For the 4 subjects whose bladder urine pO_2 was measured by both MR imaging and the oxygen probe, there was good correlation between the measurements (Fig. 4).

Successful *in vivo* MR measurements of renal pelvic urine pO_2 were obtained in 7 of 9 healthy subjects; pO_2 measurements could not be obtained in 2 others due to excessive motion and poor visualization of the renal pelvis. The temporal change of renal pelvic urine pO_2 with breathing 100% oxygen for each of the 7 subjects is shown in Fig. 5. The renal pelvic urine pO_2 increased significantly with oxygen breathing at 10 and 15 minutes (mean increase of 29 mmHg), and decreased when the subjects resumed room air breathing. An example of renal pelvic urine pO_2 map for a subject before and after oxygen breathing is shown in Fig 6. The mean renal pelvic urine pO_2 increased from 47 mmHg to 78 mmHg for that subject.

Discussion

Our initial experience demonstrated that noninvasive urine pO_2 measurement using MR imaging is feasible. The urine phantom study confirmed a highly linear relationship between urine R1 and pO_2 , as predicted by theory (13), allowing conversion of *in vivo* R1 measurements to the physiological parameter of pO_2 . The *in vivo* bladder urine pO_2 values obtained by MR imaging in our study are in agreement with those previously reported in the literature (4,10, 19). In the 4 subjects where both the MR and oxygen probe measurements were obtained, the bladder urine pO_2 values as measured by MR imaging correlated well with those measured by oxygen probes in voided urine samples. The slightly higher pO_2 values obtained by oxygen probes compared to MR imaging likely reflect atmospheric oxygen contamination of the voided urine samples. The variation in bladder urine pO_2 among the study subjects may have been due to differences in their hydration status (4). The renal pelvic urine pO_2 measurements obtained by MR imaging are also in agreement with those reported in the literature in humans using invasive methods (11). Although the sample size was small ($n = 7$), we found a consistent and significant change in renal pelvic urine pO_2 with oxygen breathing, demonstrating the ability of our MR technique to monitor temporal changes in urine pO_2 in response to physiological stimulus. The increase in renal pelvic urine pO_2 with oxygen breathing can be interpreted as a result of increased arterial pO_2 (i.e. the amount of dissolved oxygen) in the blood. The additional oxygen may increase the available interstitial oxygen of the medulla in proportion to its blood flow, which in turn is reflected in the urine excreted into the adjacent renal pelvis.

Prior experiments using invasive oxygen probes have already shown a close relationship between urine pO_2 and renal medullary pO_2 (6), suggesting that urine pO_2 may be used as a surrogate for medullary oxygenation, which in turn reflects medullary perfusion and metabolic function. In patients undergoing cardiopulmonary bypass, the bladder urine pO_2 was shown to decrease during bypass, and a failure to return to normal after bypass was predictive of subsequent postoperative increase in serum creatinine concentration (20). The authors of that study suggested that the decrease in urine pO_2 may be a result of abnormal changes in medullary oxygen metabolism associated with bypass (20). In another study, the selective dopamine agonist, Fenoldopam, was shown to result in a dose-dependent increase in the bladder urine pO_2 in critically ill patients (19). The observed change may be attributed to both an increase of renal medullary perfusion and a reduction of tubular sodium reabsorption (19). In yet another study, the renal pelvic urine pO_2 was shown to be different at baseline and responded to oxygen challenge differently in patients with various renal parenchymal and vascular diseases (11). The techniques used in those prior studies, however, all involved invasive bladder or ureteral catheterization with placement of oxygen probes, and such invasive monitoring has prevented its wide clinical use. The MR imaging method in this study, on the other hand, is noninvasive

and has the potential for providing both improved spatial and temporal evaluation of urine pO_2 as a marker for renal medullary pO_2 in both physiological conditions and in diseases.

Blood-oxygen-level-dependent (BOLD) MR imaging is another technique that has been used to study renal medullary oxygenation (21–23). BOLD MR imaging measures tissue oxygenation by using deoxyhemoglobin as an endogenous contrast agent. The measurements obtained by BOLD MR imaging, however, may be affected by factors such as macroscopic field heterogeneity, vascular volume and hematocrit level. In addition, the nonlinear relationship between the apparent relaxation rate ($R2^*$) and the oxygen partial pressure limits the ability of BOLD MR imaging to give absolute quantification of tissue oxygen level. Our MR technique, on the other hand, has the capability to quantify pO_2 from R1 measurements because of the known linear relationship between the two in low-protein fluid such as urine. At the present, the technique is limited to the pO_2 measurement in fluids. However, since renal pelvic urine pO_2 closely reflects the renal medullary pO_2 (6), our MR technique may provide a novel means to measure medullary oxygenation.

Several technical challenges remain for imaging urine pO_2 . First, despite the application of nonselective refocusing pulses, flow related artifacts still likely occurred in our study and contributed to measurement errors, especially in the bladder where ureteral jets are known to cause turbulence of the urine. This may partly explain the fluctuations observed in the bladder urine pO_2 over the 10 minutes imaging time in this study. Second, in order to increase the signal-to-noise ratios for the urine pO_2 quantification, each pO_2 measurement was acquired over 2.5 minutes, with signal averaging of 10 pairs of images. The relatively long imaging time may lead to more misregistration artifacts, especially in the renal pelvis which can move with respiration. Coaching with appropriate breath-holding during image acquisition can potentially reduce such misregistration, however it would require patient cooperation. Third, the renal pelvis may not be distended well enough and visualized consistently to obtain reliable urine pO_2 measurements. In our study, renal pelvic urine pO_2 could not be measured in two of the nine subjects because of poor visualization of the renal pelvis. Clearly, additional modifications of the MR sequence to further reduce the flow related artifact and to increase signal-to-noise ratios are needed to make this a more robust technique.

In addition to the technical challenges, there are other limitations to our study. First, the sample size of our study is small. However, as a proof of concept, we have demonstrated the feasibility of measuring urine pO_2 using MR imaging. Our urine pO_2 measurements by MR imaging were in good agreement with those obtained from invasive studies reported in the literature (4,10, 19). We also showed a consistent rise of renal pelvic urine pO_2 in response to oxygen breathing in the 7 healthy subjects. With each subject served as his/her own control in the dynamic oxygen breathing study, we believe the observed changes in renal pelvic urine pO_2 reflected the physiologic changes in the kidneys, despite the relatively small number of subjects. Future larger scale studies, however, are needed to further assess the utility of this MR techniques in measuring urinary oxygenation in subjects with renal diseases and following other physiological stimuli. Second, because of the invasive nature of bladder and renal pelvis catheterization, we did not compare the urine pO_2 measured by MR imaging to that measured by direct placement of oxygen probes in the bladder or the renal pelvis. Oxygen probe measurement of pO_2 in voided urine sample serves as an imperfect reference standard because of the likely atmospheric oxygen contamination of the samples. Nonetheless, the bladder urine pO_2 as measured by MR imaging correlated reasonably well with that measured by the oxygen probe in the 4 subjects in our study. Third, we did not test for urine protein in our subjects. It has been shown that there is a weak dependence of R1 on protein level in the fluid (16). The R1 increase due to protein content at body temperature corresponds to an overestimation in pO_2 of 11 mm Hg for every 1 gm/L increase of protein (16). The subjects in our study, however, were healthy volunteers without a history of renal disease, and therefore were unlikely to have

large amounts of urinary protein that may potentially alter the pO_2 measurements. In patients with significant proteinuria, however, the R1 measurements should be adjusted for the urine protein content.

Despite the technical challenges, our current study serves as proof-of-concept and demonstrates the feasibility of *in vivo* MR measurement of urine pO_2 , which can be used as a surrogate for renal medullary pO_2 . With further optimization of the techniques, this method may become a useful noninvasive tool for the evaluation of renal medullary hypoxia which is implicated in the pathogenesis of several common renal diseases.

Acknowledgements

This study was supported in part by the following sources: NIBIB T32 Training Grant 1 T32 EB001631-01A1, Society of Uroradiology Seed Grant, and the RSNA Fellow Award

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Figure 1.

Schematic diagram of the MR sequence used for fluid oxygen tension (pO_2) imaging. The ratio of the signal intensity in any voxel (S_1/S_2) is solely a function of R_1 . T_{R1} and T_{R2} : saturation recovery time for two successive acquisitions.

Figure 2.

Plot of $R1$ (1/sec) for urine samples at body temperature (37°) and 1.5T. The slope ($\Delta R1 / \Delta pO_2$) and intercept [$R1(pO_2 = 0)$] were used to calibrate the *in vivo* urine measurements.

Figure 3. Bladder urine pO₂ measured by MR imaging over 10 minutes in 7 healthy subjects. The mean bladder urine pO₂ (filled circles) ranged from 23 to 45 mmHg among the 7 subjects. The open circles represent individual pO₂ measurements over 10 minutes for each subject. Error bars represent standard deviation.

Figure 4. Bladder urine pO₂ measured by MR imaging versus that measured by oxygen probe in 4 healthy subjects. Error bars represent standard deviation of the MR imaging measurement over 10 minutes.

Figure 5.

Temporal measurements of renal pelvic urine pO₂ by MR imaging in 7 healthy subjects with 100% oxygen breathing (A. Temporal urine pO₂ measurements for individual subjects; B. Mean temporal urine pO₂ measurements for all 7 subjects). Gray background indicates the time period of 100% oxygen breathing (17.5 minutes). BL, average of the two baseline renal pelvic urine pO₂ values while the subjects breathed room air. Asterisks (*) represent significant changes in urine pO₂ values when compared to those obtained at room air ($p < 0.05$). Error bars represent standard deviation of the mean renal pelvic urine pO₂ in the 7 subjects.

Figure 6. Color maps of renal pelvic urine pO₂ (a) before and (b) after 17.5 minutes of 100% oxygen breathing in a 36-year-old healthy male subject. The mean renal pelvic urine pO₂ increased from 47 mmHg to 78 mmHg.