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BOLD Quantified Renal pO₂ is Sensitive to Pharmacological Challenges in Rats

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Abstract

Purpose—Blood oxygen level dependent (BOLD) MRI has been effectively used to monitor changes in renal oxygenation. However, R2* (or T2*), is not specific to blood oxygenation and is dependent on other factors. This study investigates the use of a statistical model that takes these factors into account and maps BOLD MRI measurements to blood pO₂.

Methods—Spin echo and gradient echo images were obtained in six Sprague-Dawley rats and R2* and R2 maps were computed. Measurements were made at baseline, post-LNAME, and post-Furosemide administration. A simulation of each region was performed to map R2' (computed as R2* - R2) to blood pO₂.

Results—At baseline, blood pO₂ in the outer medulla was 30.5 ± 1.2 mmHg and 51.9 ± 5.2 mmHg in the cortex, in agreement with previous invasive studies. Blood pO₂ was found to decrease within the outer medulla following L-NAME ($p < 0.05$) and increase after furosemide ($p < 0.05$). Blood pO₂ in the cortex increased following furosemide ($p < 0.05$).

Conclusions—Model derived blood pO₂ is sensitive to pharmacological challenges and baseline pO₂ is comparable to literature values. Reporting pO₂ instead of R2* could lead to a greater clinical impact of renal BOLD MRI and facilitate the identification of hypoxic regions.

Keywords

Renal; BOLD; Oxygenation; Oxygen Saturation of Hemoglobin; pO₂

Introduction

Blood oxygen level dependent (BOLD) MRI is a non-invasive method that is sensitive to regional oxygen saturation of hemoglobin (SHb). It is currently the only non-invasive method available to evaluate relative renal oxygenation status, and it can be readily applied in humans (1). Previous studies have established BOLD MRI as an effective and sensitive method for monitoring changes in both pre-clinical models (2–4) and in humans (1,5,6). However, translation of BOLD MRI to the clinic remains challenging (7).

Two key limitations are suspected to play a role. One is the use of small region of interest (ROI) analysis. Small ROIs are subjective and may be limited by the available contrast between regions, which can be compromised under certain disease states (8). There have been recent developments to mitigate this issue by using methods that analyze the entire renal parenchyma (9–12). Another limitation of BOLD MRI is the inability to directly compare the measurements between regions due to the fact that the $R2^*$ (or $T2^*$) measurements, the transverse relaxation rate, depend on more parameters than just the magnetic susceptibility of deoxygenated hemoglobin. These parameters include the spin-spin relaxation rate ($R2$), regional blood volume, and hematocrit (Hct). Each of these may vary significantly between individuals, even regionally within a kidney, and with disease. These dependencies limit the ability to directly compare $R2^*$ measurements between kidney regions or measurements between groups. For example, the inner medulla in rodents consistently has a lower $R2^*$ than the cortex, and would be viewed as having a higher blood pO_2 level based on the usual BOLD interpretation. However invasive measurements show the inner medulla has the lowest pO_2 (13). This discrepancy is thought to be due to the lower blood volume and lower hematocrit of the inner medulla (14). Furthermore, $R2^*$ cannot directly indicate hypoxic regions. An increased $R2^*$ may show a region with decreased oxygen availability due to the measured decrease in SHb, but it does not indicate whether the tissue's oxygen demand is being met. It is known that certain regions of the kidney are operating on the verge of hypoxic conditions and the ability to convert $R2^*$ measurements to blood pO_2 could provide a means of comparing these regions to pO_2 levels that may be at risk of hypoxic damage.

Recent work has demonstrated the feasibility of mapping BOLD MRI measurements to blood pO_2 (15). The method is based on $R2'$ ($R2^* - R2$) as opposed to the conventional $R2^*$ parameter. Using Monte Carlo simulation, the model estimates $R2'$ for a given SHb value, resulting in a look-up table from $R2'$ to SHb, for each tissue type based on regional parameters. In this preliminary study, we apply this model to a small number of rats to find baseline blood pO_2 values, how they compare to invasive measurements in the literature, and further evaluating the sensitivity to changes in pO_2 following pharmacological maneuvers.

Methods

Animals

The Institutional Animal Care and Use Committee approved all procedures and protocols in this study. Six male Sprague-Dawley rats (Charles River, Chicago, IL), weighing 402 ± 20 g, were used in this study. Rats had free access to water and food prior to being anesthetized.

All procedures were conducted under anesthesia using Inactin (thiobutabarbital sodium, 100 mg/kg i.p., Sigma-Aldrich, St. Louis, MO). A catheter (PE-50 tubing) was placed in the femoral vein of each rat for administration of nitric oxide synthase inhibitor (L-NAME) and furosemide (Sigma- Aldrich, St. Louis, MO). These drugs were used to modulate renal perfusion and/or oxygenation. Each drug is administered at a concentration of 10 mg/kg body weight into the femoral vein as a bolus.

Each animal's tail was connected to a peripheral oximeter to monitor any systemic changes in global blood SHb (3150 MRI Patient Monitor, Invivo Research Inc). Measurements were recorded every five minutes.

MRI

All experiments were performed on a 3-T whole body scanner (Magnetom Verio, Siemens Healthcare, Erlangen, Germany), equipped with high-performance gradient coils (45 mT/m maximum gradient strength, 200 mT/m per milliseconds slew rate). Rats were placed in a right decubitus position, such that the kidneys were in the middle of a knee coil (8-channel Knee Coil, Siemens Healthcare, Erlangen, Germany). Each rat was then positioned within the MRI scanner such that the middle of the kidney being examined was at the isocenter of the magnet.

Imaging was performed in three stages: baseline, post-LNAME and post-furosemide administration. Figure 1 shows a schematic outline of the procedure. Each stage consisted of two sequences: a multiple gradient recalled echo sequence (mGRE, 12 Echoes: TE: 3.56 - 41.29 ms increments of 3.43 ms, TR: 69.0 ms, Matrix: 256*128, PhaseFOV: 50%, resolution: 0.47*0.47 mm, slice thickness: 2.0 mm), and a standard spin echo sequence (SE, 8 echoes: TE: 9.9 – 79.2 ms increments of 10ms, TR: 500ms, Matrix: 256*128, PhaseFOV: 50%, resolution: 0.47*0.47mm, slice thickness: 2.0 mm). Each set of mGRE and SE acquisitions were acquired three times, leading to a total study time of approximately 75 minutes per rat.

In two additional animals, data was obtained at baseline and repeated after administration of furosemide.

Analysis

Following MRI data acquisition, regions of interest (ROIs) were manually defined (Figure 4.b) in the cortex (region furthest from the renal pelvis, containing majority of glomeruli) and the outer medulla (OM) (outer portion of the closest region to renal pelvis, borders cortex) of each kidney. A suite of custom image-processing software written in Python was used for the analysis (Python 2.7, NumPy 1.10, SciPy 0.16.1). $R2^*$ maps were created from the 12 echoes acquired by the mGRE sequences using a linear least squares fitting method, with regions near large susceptibility artifacts removed using thresholding (9). $R2$ maps were created from the eight echoes acquired by the SE sequences using a linear least squares fitting method. As each MRI stage acquired 3 pairs of mGRE and SE acquisitions, the computed maps were averaged over these repetitions. ROIs representing the two regions were applied to the $R2^*$ and $R2$ maps, and the mean of each region was found. $R2'$ was calculated by subtracting the $R2$ mean from the $R2^*$ mean for each region.

A statistical model was used for estimating the oxygen saturation of hemoglobin (SHb) as well as the blood pO₂ of each region (15). The model simulates the BOLD signal by modeling blood vessels as randomly oriented cylinders within a voxel and red blood cells as spheres. At the start of the simulation protons diffuse through the voxel, accumulate different phases, leading to a signal decay that is sensitive to the oxygen saturation of hemoglobin. The model was used to establish a relationship between SHb and R2' (Figure 2.a). Blood pO₂ was estimated from SHb using the oxyhemoglobin dissociation curve (Figure 2.b). The following parameters were assumed for each region: cortex (vascular fraction: 0.27, hematocrit: 0.4, extravascular diffusion coefficient: 1.45, intra-vascular diffusion coefficient: 1, average vesicle radius: 10 (um)); outer medulla (vascular fraction: 0.18, hematocrit: 0.25, extravascular diffusion coefficient: 1.04, intra-vascular diffusion coefficient: 1, average vesicle radius: 10 (um)) (16–18).

Statistical Analysis

Statistically significant changes were assessed between each sequential stage within each region. Cohen's d was used to assess the magnitude of the change and Wilcoxon's signed-rank test was used to assess the statistical significance. While the range of d values depends on the experiment, a value of 0.8 or greater is generally considered a large effect (9,19). P-values are reported with each test as well, values below 0.05 are considered statistically significant.

Results

Our estimates for SHb and blood pO₂ showed regional responses to L-NAME and furosemide. Figures 3a-d show boxplots for each region at each of the three stages for estimated R2, R2*, SHb, and blood pO₂, respectively. At baseline, blood pO₂ in the outer medulla was found to be 30.5 ± 1.2 mmHg and 51.9 ± 5.2 mmHg in the cortex.

Statistically significant changes were observed in the outer medulla following L-NAME and furosemide. In the cortex, the change from L-NAME to furosemide was significant as well. Figures 3a-d show box and whisker plots. Each box extends from the lower quartile to the upper quartile, the horizontal line indicates the median. The whiskers show the range of the data to within 1.5 times the inter-quartile distance or the maximum data value. Values outside of the whisker's range are plotted as plus signs, indicating potential outliers.

Figure 4.a shows examples of R2 and R2* maps at each stage in one representative animal. Figure 4.b is the summary of the mean pO₂ values for all rats at each time point within the stages.

Figure 5 shows the relative values of R2, R2* and blood pO₂ in three spatial locations of the rat kidney. The differences observed in blood pO₂ are consistent with prior data based on invasive measurements.

No significant changes in peripheral SHb were found during the experiment in any of the rats (data not shown).

In the two additional rats given just furosemide, the mean pO₂ change in the outer medulla was from 29.1 to 31.3 mmHg and in the cortex from 48.1 to 53.1 mmHg.

Discussion

Our data supports the feasibility of applying this quantitative model to estimate renal blood pO₂ based on BOLD MRI data acquisitions in rat kidneys where there is a great amount of literature (20–22). At baseline, blood pO₂ in the outer medulla was found to be 30.5 ± 1.2 mmHg and 51.9 ± 5.2 mmHg in the cortex, which is in line with previously measured values using microelectrodes (20). However, as microelectrode studies are unable to differentiate between capillary blood pO₂ and tissue pO₂ the measurement is not entirely specific to the measurements reported here. Future studies that can differentiate between the two are necessary, *e.g.* using phosphometric measurements (23).

L-NAME acts as a vasoconstrictor in the renal circulatory system. Our results show that blood pO₂ decreases following administration of L-NAME as expected (24). The OM showed a significant decrease in pO₂ ($p=0.028$; $d=3.60$). While the cortex showed downward shifts as well in blood pO₂, it was not statistically significant.

Furosemide acts to increase renal pO₂ by inhibiting sodium reabsorption in the medullary thick ascending limb, and is generally confined to the medulla region (21). As L-NAME is known to act for up to 2 hours (25), the observed post-furosemide response is really a combined response to L-NAME and furosemide. In this preliminary study, our focus was to demonstrate sensitivity to hemodynamic changes and not to study the exact effects of each of the drugs in isolation, thus we consider this to be an acceptable compromise. From the results we see that a significant increase in pO₂ is observed in both regions, with the larger change resulting in the OM ($p=0.046$; $d=-1.40$). However, in two additional rats, given just furosemide, an increase in pO₂ was observed in outer medulla consistent with prior reports (21). The cortex also showed an increase, probably due to the fact that cortical portion of the nephrons are a part of Henle's loops at the cortico-medullary junction and is consistent with a previous study (26).

Changes in R2* are often discussed as being a measure of changes in oxygenation or degree of hypoxia. However, as shown in Figure 5, the relative values of R2* do not strictly indicate the relative oxygenation in different regions. For the same reason, it is also not possible to define a threshold value of R2* above which the tissue can be assumed to be hypoxic. However, by taking the differences in physiological parameters (HCT, blood volume, etc.) between the two regions into account, the estimated blood pO₂ shows the well accepted gradient between the cortex and outer medulla. Further pO₂ of the inner medulla (IM) is lower than the cortex, even though it is not lower than the outer medulla, as expected (22). This is probably due to the lack of data on relative values of blood volume and Hct, specifically for IM. For this preliminary study, we assumed the same values for the entire medulla.

The primary mechanism for transporting O₂ molecules in blood plasma to the mitochondria is diffusion (27). The difference in blood pO₂ and mitochondrial pO₂ is what establishes this

diffusion gradient and the maximum amount of O₂ that can be extracted from the blood in a given amount of time. While it is difficult to determine mitochondrial pO₂ (28), one study has estimated it to be in the range of 30-40 mm Hg (29). Thus, if blood pO₂ is at or below this range, the oxygen will not be transported to the cells by diffusion and the tissue will be at risk of hypoxic injury. Interestingly, the systemic venous pO₂ is also about 40 mmHg (30).

The relative pO₂ values in Figure 5 suggest that the cortex is normoxic while both the outer and inner medulla are in the middle or below the mitochondrial pO₂ range and could be classified as hypoxic. The estimates of inner medulla were based on blood volume and hematocrit estimates in outer medulla (due to lack of literature values). Whether that explains the relative higher values of pO₂ requires further investigations.

There are limitations to this approach. The method for converting from MRI measured parameters (R₂, R₂^{*}) to physiological ones (SHb and pO₂) requires a number of parameters that are regionally inhomogeneous and may not be readily available. This is especially true for changes in these parameters (e.g. regional hematocrit) in response to the pharmacological maneuvers. For example, following L-NAME administration, blood flow decreases and possibly a reduction in blood volume occurs as well. While a reduction in blood flow leads to a decrease in blood oxygenation, normally seen as increased R₂^{*}, the corresponding reduction in blood volume would serve to decrease R₂^{*}, possibly negating the former effect. Without an independent measure of blood volume, our model is unable to capture such a change, causing us to overestimate blood pO₂ following LNAME. Similarly changes in these parameters under certain disease states could make comparisons to healthy subjects challenging. The model makes assumptions about blood pH and the corresponding oxygen saturation curve that may not hold under certain disease conditions as well. Additionally, we did not control the water and salt intake of the animals in this preliminary study, which are known to influence R₂^{*} (31,32).

In conclusion, the model for estimating blood pO₂ based on BOLD MRI measurements shows promise in its ability to measure baseline pO₂ in cortex and outer medulla. The validity of the changes observed following pharmaceutical maneuvers requires further work to validate against an invasive blood pO₂ measurement. By taking into account the difference in hematocrit between the renal cortex and the outer medulla, the large difference in oxygenation between the two regions becomes readily apparent, this is not clear from the relative R₂^{*} values (in Figure 5). The conversion of R₂^{*} to pO₂ also allows for the possibility of classifying regional hypoxia. While there are several parameters that must be taken into account (blood pH, systemic hematocrit, etc.), it may be possible to calibrate these with a blood sample from each subject. By reporting physiological parameters, rather than conventional R₂^{*} measurements, renal BOLD MRI may find a greater acceptance amongst physicians and an increased clinical utility.

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Figure 1. MRI protocol. The MRI data acquisition was performed in three stages: baseline, LNAME and furosemide. Each MRI stage consisted of three repetitions of alternating mGRE and SE acquisitions.

Figure 2. Monte Carlo simulation results in cortex and outer medulla. (a) Plot shows the relationship between a measured $R2'$ and the expected hemoglobin saturation (SHb). (b) Plot showing the relationship between SHb and blood pO2. See the methods section for a list of parameters used in the model.

Figure 3.

Box-whisker plots for R2 (a), R2* (b), SHb (c), and blood pO2 (d). The two regions assessed are shown (cortex and outer medulla (OM)). Each region shows three time points at which MRI was assessed: baseline, post-LNAME, post-furosemide.

Figure 4.

(a) shows R2 and R2* maps at each stage in a representative animal. (b) is the summary of cortical and outer medullary pO₂ estimates from all animals at all individual time points for each stage. Typical ROIs are illustrated in (b) as well.

Figure 5.

The relative values of R2, R2* and blood pO2 between each region are illustrated here. At baseline, the mean and standard deviations of are shown for each region for R2* and blood pO2 measurements. The relative R2* values are hard to interpret because the low R2* in the inner medulla would indicate higher blood oxygenation. However, it is well known that inner medulla has the least pO2 (22). Using the same parameters as the outer medulla, the estimated pO2 appears to be closer to the outer medulla. The conversion to pO2 also facilitates identifying regions that are hypoxic, e.g. compared to systemic venous pO2.