# Functional renal imaging with BOLD: validation of a model for R2* in kidney cortex and medulla

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## Introduction

In spite of high perfusion, tissue oxygenation in the kidney, in particular in the renal medulla, is low. This is presumed to be the consequence of low oxygen delivery efficiency to medullary tissue (arterio-venous shunting, low medullary perfusion) and high metabolic activity in the medulla secondary to active transport of solutes (1). The resulting low level of $O_2$ in the medulla makes it particularly vulnerable to hypoxic injury. Techniques such as blood oxygenation level dependent (BOLD) imaging to measure renal oxygenation noninvasively show promise for functional assessment of the kidneys (2).

The kidney has unique features that affect its BOLD contrast. First, because of its filtration function, each kidney typically receives 300-500 ml/min of blood, but overall, only a small fraction of oxygen carried by the blood (~8%) is consumed. Second, the renal cortex and medulla have very different perfusion rates and different oxygen extraction fraction. The renal medulla is less perfused than cortex, but its oxygen extraction is high (~80%) secondary to active solute transport, particularly in the ascending limb of Loop of Henle. Third, in renal medulla the blood vessels are oriented radially, following the configuration of loops of Henle, unlike a more random vascular orientation in the cortex. Fourth, both passive and active types of water transit occur in the kidney to enable fluid homeostasis.

With BOLD imaging, the partial pressure of oxygen ($pO_2$) measured by microprobes has been shown to correlate with transverse relaxation rate $R_2$* (2). Clinically detected changes in renal $R_2$* have been reported in renal artery stenosis, diabetic nephropathy, transplant rejection, and other diseases. However, the mechanism of renal $R_2$* contrast is complex and not well understood. In addition to tissue oxygenation, $R_2$* is influenced by vascular density, vessel diameter, blood flow, water diffusion rate, field strength, acquisition parameters, and possibly tubular flow in the kidneys. While factors that may contribute to brain $R_2$* have been studied extensively (3, 4), the applicability of existing $R_2$* models to renal cortex and medullary tissue has never been established. We investigated the BOLD mechanism in the kidney and compared predictions made by the simulation technique of Martindale et al (4) with experimental results obtained in human kidney and with experimental results in rat kidney reported by Santos et al (5).

## Methods

We used a Monte Carlo technique to simulate blood vessels, red blood cells and diffusing protons in a voxel to examine the relationship between the oxygen saturation and the resulted BOLD signal or $R_2$*. A cubic voxel is modeled as the combination of intra-vascular (IV) and extra-vascular (EV) spaces. **EV**: The blood vessels (containing deoxyhemoglobins) are simulated as randomly oriented cylinders with magnetic susceptibility different from surrounding EV space. The magnetic field inhomogeneity $\Delta B_Z$, induced by such a cylinder, has been derived as (4),

$$\Delta B_Z(\vec{r}) = B_0 \frac{\Delta\chi}{2}\left(\frac{R}{r}\right)^2 \cos(2\varphi)\sin^2(\theta)$$

where $B_0$ is the main magnetic field (along Z axis), $\Delta\chi$ is the susceptibility difference between EV and IV, R is the radius of blood vessel, r is the distance from the cylinder axis to the location of interest, φ is the angle between $\vec{r}$ and the projection of $B_0$ onto the plane orthogonal to the cylinder axis, and θ is the angle between $B_0$ and the cylinder axis. At each location of EV, the overall $\Delta B_Z$ is obtained by summing up the inhomogeneity induced by all vessels. At time 0, $N_P$ protons are randomly distributed in EV space, and during time TE (echo time in gradient recalled echo imaging) diffuse randomly with coefficient $D_{EV}$, experiencing variable precession frequencies and thus phase shifts. The magnitude of the collective signal ($S_{EV}$) decays due to the combination of the static and dynamic dephasing effect. **IV**: Red blood cells (RBC) were simulated as random spheres whose number is determined from assigned volume fraction, Hct. A RBC of radius R and susceptibility difference $\Delta\chi$ produces $B_0$ shift (4),

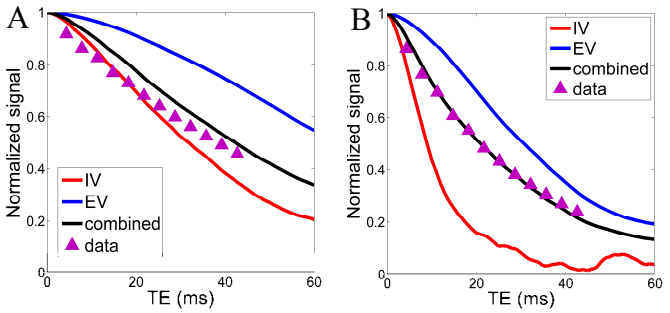


**Fig. 1** Signals from Monte Carlo simulation from (A) cortex ($pO_2$ 60 mmHg), and (B) medulla ($pO_2$ 32 mmHg), compared with signals from a healthy volunteer.

$$\Delta B_Z = B_0 \frac{\Delta\chi}{3}\left(\frac{R}{r}\right)^3 [3\cos^2(\theta) - 1]$$

where $r$ is the distance from the center of the sphere to the location of interest, and θ is the angle between $\vec{r}$ and $B_0$. As in EV, we simulate random diffusion process of $N_Q$ protons located in IV space and compute the overall signal decay ($S_{IV}$) during time TE. **EV + IV**: The overall signal from the entire voxel, following Obata et al (6), is the sum of that from EV and IV, $S = (1\text{-}v)\cdot S_{EV} + v\cdot\varepsilon\cdot S_{EV}\cdot S_{IV}$, where $v$ is vascular fraction, and $\varepsilon$ is the ratio of intrinsic signals, including effect of relaxation weighting. The $S_{EV}$ weighting in the second term reflects the contribution of all other vessels to signal decay of IV protons. Exponential fitting of the S vs. TE curve results in $R_2$* estimate. Simulation parameters were: *v*: 0.40 (cortex), and 0.25 (medulla); *Hct*: 0.40 (cortex), 0.20 (medulla); *R*: 10 μm (50%) and 4 μm (50%) (cortex), 10 μm (medulla); *D*: $1.5\times10^{-3}$ mm$^2$/sec (EV), and $1.0\times10^{-3}$ mm$^2$/sec (IV). $R_2$* value predicted with the above model were computed for variable blood $pO_2$ values.

For a healthy volunteer, BOLD imaging was performed at 3T using a gradient-echo sequence with 12 echoes (echo times from 4 ms to 43 ms). $R_2$* values were estimated for a cortical and a medullary region of interest (ROI), and with the above Monte Carlo approach $pO_2$ values were predicted. In the study of Santos et al (5), BOLD and $pO_2$ measurement (by microprobe) were performed in rat kidneys after induction of diabetes. Based on their $R_2$*, we predicted blood $pO_2$ values and compared with the measured $pO_2$.

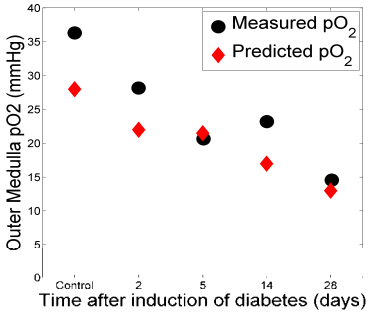


**Fig. 2** Medulla $pO_2$ measured by microprobe (from Ref. (5)), compared with predicted $pO_2$ by simulation.

## Results and Discussion

**Fig. 1** shows BOLD signals of volunteer data and the simulated signals of the same $R_2$* values. Predicted $pO_2$ values were 60 mmHg for cortex and 32 mmHg for medulla. For diabetic rats in Santos et al (5), the predicted and measured $pO_2$ values differ by less than 8 mmHg, and both decreased after induction of diabetes (**Fig. 2**).

Predicted $pO_2$ values from healthy volunteer were ~10 mmHg higher than literature values (~50 mmHg for cortex, 10-20 mmHg for medulla (7)). Predicted $pO_2$ was also in good agreement with microprobe measurements in diabetic rats. This modeling tool may help us better understand the different physiological contributions to renal BOLD signal and model them in disease states. Since the model contains multiple parameters (perfusion, vascular volume/geometry, diffusion coefficients), it appears suitable for situations where $pO_2$ change is the only dynamic variable, such as in lasix stimulus studies.

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