Establishment of a renal oxygen transit model based on BOLD MRI

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INTRODUCTION

BOLD provides a promising non-invasive approach to measure tissue oxygenation (1). Pioneering work by Prasad et al (2) demonstrated the ability of renal functional BOLD imaging to identify diuretic-induced change in oxygen level in renal medulla. The apparent spin-spin relaxation R_2* has been used as the sole surrogate marker of tissue oxygenation where larger R_2* or increased levels of deoxyhemoglobin are assumed to be associated with higher oxygen consumption. However it has been shown that in addition to R_2*, multiple factors influence tissue O_2 level (3). For example, blood perfusion determines the inflow rate of oxyhemoglobin into the tissue of interest and more importantly the washout rate of deoxyhemoglobin. Permeability of blood vessels to oxygen affects the rate of oxygen transfer from vascular space to interstitial space.

This study focuses on a tracer kinetic model to determine the transit of oxygen in renal tissue. Using BOLD measurements to derive estimates of blood pO_2, tissue pO_2 is derived using a kinetic model, in which oxygen is treated as a tracer. With our model, oxygen permeability and regional hematocrit are variables we first fit using a subset of experimental BOLD and O_2 probe measurements from pig kidneys. Using these fitted values, we then tested the performance of the model to predict cortical and medullary pO_2 based on BOLD MRI measurements using a different set of experimental data which included direct probe measurements of tissue pO_2.

METHODS AND MATERIALS

Animal experiment: All animal experiments were performed with the approval of the local Animal Care and Use Committee. The following measurements were performed at baseline, and repeated after a bolus of either furosemide (0.05 mg/kg, 12 pigs) or saline vehicle (8 pigs). BOLD scan: After anesthesia, the pig was positioned in scanner (Signa TwinSpeed EXCITE 1.5T system, GE Healthcare, Waukesha, WI). A gradient multi-echo sequence was used to acquire 16 echoes with parameters: TR/TE/flip angle/FOV/BW/matrix/thickness/NEX = 85ms/2.3-37.2ms/40°/32cm/63.95kHz/256x256/5-7mm/1. Each TE yielded 5-6 axial-oblique slices. R_2* was estimated for cortex and medulla. Tissue oxygen measurement: 5-7 days later, the animal was prepared similarly to the MRI study. Through a catheter positioned in the left carotid artery, arterial pO_2 was sampled and mean arterial pressure (MAP) was measured. The left ureter was exposed and cannulated through a small flank incision. The right kidney and ureter were exposed through a flank incision. The right kidney, surrounded by cotton wool soaked in saline and mineral oil, was placed in a lexan holder. An ultrasound flow probe (T206 Flowmeter, Transonic) was placed around the renal artery to measure renal blood flow. Ventilation rate and tidal volume were adjusted to maintain arterial pO_2, pCO_2 and pH between 90-110mmHg, 35-50mmHg and 7.3-7.5 respectively. Tissue pO_2 was collected every sec with Clark electrodes (Unisense, Aarhus, Denmark) that, after calibration, were inserted into the cortex and medulla of the right kidney by penetrating the kidney capsule to depth 0.7 cm for cortex and 1.1 cm for outer medulla.

Oxygen transit model: Oxygen in blood exists in two forms: as a gas dissolved in plasma, and as oxyhemoglobin. As blood goes through a capillary, a fraction of oxygen diffuses into the extravascular space, and is consumed. We describe the oxygen transit by a mass-conservation multi-compartment kinetic model where oxygen is considered as a tracer (Fig 1). The key parameters of this model are: perfusion F, concentration of oxygen in vascular space C_1, blood pO_2 P_1, oxygen permeability constant PS, oxygen solubility in the two sub-spaces α_1 and α_2, tissue pO_2 P_2 and oxygen metabolic rate M. With continuous and constant arterial oxygen input, one set of mass-conservation equations can be written for each compartment of renal tissue. Hill's equation was used to relate C_1 and P_1 (i.e. a non-linear O_2 saturation curve), because of the wide range of blood pO_2 in the kidney.

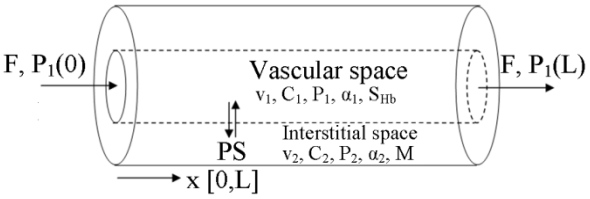

Fig 1. Oxygen transit model for renal tissue

Model tuning and testing: In the first part of this project, a tuning process was aimed to determine the two key variables in the model: capillary Hct, and PS. The pig data provided measurements of R_2*, arterial pO_2, blood flow (F) and tissue pO_2 (P_2). A Monte Carlo simulation approach (3,4) was used to convert R_2* to capillary blood pO_2 (P_1). Values for other parameters were: $\alpha_1 = 1.3\times10^{-6}$ mmol/ml/mmHg, $\alpha_2 = 1.25\times10^{-6}$ mmol/ml/mmHg, Hill's coefficient 2.55, half-saturation pO_2 26 mmHg. For each of the 8 pigs with saline vehicle, we fitted capillary Hct and PS, by adjusting their values to minimize the difference between model-predicted P_2 and measured P_2. We then tested the performance of the optimized Hct and PS values in predicting P_2 for the 12 pigs subject to the furosemide experiment.

RESULTS AND DISCUSSION

To convert R_2* to capillary blood pO_2 (P_1) we obtained by Monte Carlo simulation an approximately linear relationship between saturation rate (SHb) and R_2' (=R_2* - R_2): for cortex, SHb = -0.0115*R_2' + 0.925; for medulla: SHb = -0.0295*R_2' + 0.857. R_2 values were assumed based on a previous study (2). With SHb, P_1 can be readily computed by Hill's equation.

Table 1. Capillary Hct and PS optimized from experimental data on 8 pigs.

	Hct	PS (ml/s/ml)
Cortex	0.32±0.09	4.5±0.8
Medulla	0.19±0.05	18.9±3.5

The reduced Hct in medulla (Table 1) agreed with previous studies, and might be due to Fåhræus effect (5). PS was lower in cortex than that in medulla, probably because cortex contains a higher fraction of non-permeable blood vessels. As expected, renal PS values were small compared to PS for heart, reported as 50 ml/s/ml (6). The coefficient of variation of Hct across the individual animals was 26%~28%, and for PS 18%~19%, most likely due to individual difference and measurement error in R_2* and pO_2.

The pO_2 errors (Table 2) for baseline data averaged 2.3 mmHg for cortex, and -0.4 mmHg for medulla, indicating accurate prediction by the tuned model. The pO_2 errors for furosemide data were higher, especially that of cortex (6.9±3.9 mmHg). Fig. 2 displays the correlation between predicted and measured pO_2. Although the model was tuned with baseline data only, it successfully reflected the furosemide-induced change in medulla pO_2. In addition, our results seem indicate that furosemide does not alter capillary Hct and PS in the kidney.

We conclude that a tracer kinetic model has the potential to enable accurate quantification of tissue pO_2 based on BOLD MRI.

Table 2. Tissue pO_2 prediction for 12 pigs with the tuned model

	Baseline pO_2 (mmHg)			Furosemide pO_2 (mmHg)		
	Measured	Predicted	pO_2 error	Measured	Predicted	pO_2 error
Cortex	45.9±3.6	48.2±3.4	2.3±5.2	49.2±2.8	56.1±3.1	6.9±3.9
Medulla	25.0±3.5	24.9±2.1	-0.4±4.5	39.0±3.7	41.6±1.3	2.6±4.0

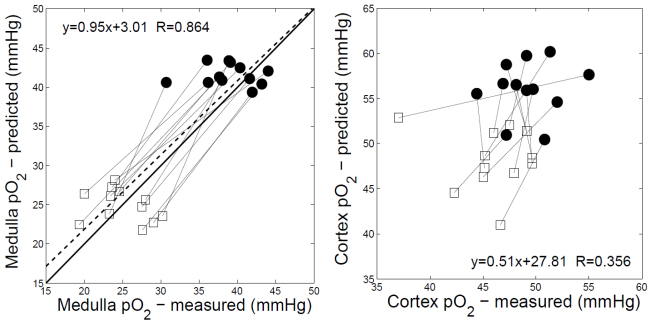

Fig 2. Renal tissue (medulla and cortex) pO_2 in 12 pigs: predicted versus measured values. Squares: baseline; circles: after furosemide

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