

# Renal Oxygen Bioavailability in Healthy Volunteers and Patients with Well-functioning and Diseased Renal Transplants

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## INTRODUCTION

Blood oxygen level dependent (BOLD) MRI sequences provide the ability to measure renal oxygen bioavailability on a regional basis, which allows for the cortical and medullary regions of the kidney to be assessed individually. This ability to evaluate the cortical and medullary regions separately is useful for investigating normal physiology as well as how oxygen bioavailability changes in diseased states. For example, previous studies have used BOLD MRI to assess oxygen bioavailability in subjects with normal functioning transplanted kidneys along with transplanted kidneys undergoing acute tubular necrosis (ATN) and acute rejection [1-4]. Other studies have compared oxygen bioavailability in patients with chronic allograft nephropathy (CAN) versus healthy volunteers [5]. However, to our knowledge, no study has directly compared the oxygen bioavailability of all of these patient populations. The purpose of this study was to measure and compare cortical and medullary oxygen bioavailability with BOLD MRI in healthy volunteers, patients with well-functioning transplanted kidneys, and transplant patients with CAN, ATN, and acute rejection.

## MATERIALS & METHODS

This HIPAA-compliant study was approved by our institutional human subjects review committee and written informed consent was obtained from all subjects. Seventeen healthy volunteers with native kidneys (20 - 62 years;  $40 \pm 14$  years; eGFR (MDRD):  $85 \pm 13$  ml/min/1.73 m<sup>2</sup>), eleven patients with well-functioning transplanted kidneys (21 - 61 years;  $42 \pm 13$  years; eGFR (MDRD):  $59 \pm 14$  ml/min/1.73 m<sup>2</sup>), five transplant patients with allografts undergoing ATN (35 - 70 years;  $48 \pm 13$  years; eGFR (MDRD):  $21 \pm 21$  ml/min/1.73 m<sup>2</sup>), twelve transplant patients with allografts undergoing acute rejection (21 - 63 years;  $49 \pm 12$  years; eGFR (MDRD):  $23 \pm 17$  ml/min/1.73 m<sup>2</sup>), and ten transplants patients undergoing CAN (31 - 70 years;  $49 \pm 12$  years; eGFR (MDRD):  $44 \pm 9$  ml/min/1.73 m<sup>2</sup>) were recruited for this study. Subjects were imaged with a 1.5 T MR scanner (Signa Excite HD, GE Healthcare, Waukesha, WI, USA) and an 8-channel body coil. Subjects fasted for twelve hours prior to the MR examination.

MR BOLD images were acquired with a TR/TE/flip angle = 87ms/7-42ms/40°, FOV = 32-34cm, 244 Hz/pixel, and a 256x128 matrix. Each of three slices was acquired in a separate 12-second breath hold.  $R_2^*$  (s<sup>-1</sup>) measurements of oxygen bioavailability were measured from BOLD images by placing 6-10 regions of interest (ROIs) in both the medullary and cortical regions of the kidney. Values within the cortex and medulla were averaged across all three slices. Averages were reported as mean  $\pm$  standard deviation. Values of oxygen bioavailability were compared between groups with a Welch's t-test.

## RESULTS

Bar graphs of medullary and cortical  $R_2^*$  values are shown in Figure 1. Medullary  $R_2^*$  values in transplant patients undergoing acute rejection ( $16.3 \pm 2.0$  s<sup>-1</sup>) were significantly less than transplant patients undergoing ATN ( $21.9 \pm 1.6$  s<sup>-1</sup>;  $p < 0.001$ ), transplant patients with CAN ( $20.6 \pm 2.6$  s<sup>-1</sup>;  $p < 0.001$ ), subjects with normal native kidneys ( $21.3 \pm 2.1$  s<sup>-1</sup>;  $p < 1 \times 10^{-6}$ ), and transplant patients with well-functioning allografts ( $21.9 \pm 3.7$  s<sup>-1</sup>;  $p < 0.001$ ). No other significant differences were found with medullary or cortical  $R_2^*$  values. p-values are summarized in Table 1.

## DISCUSSION & CONCLUSIONS

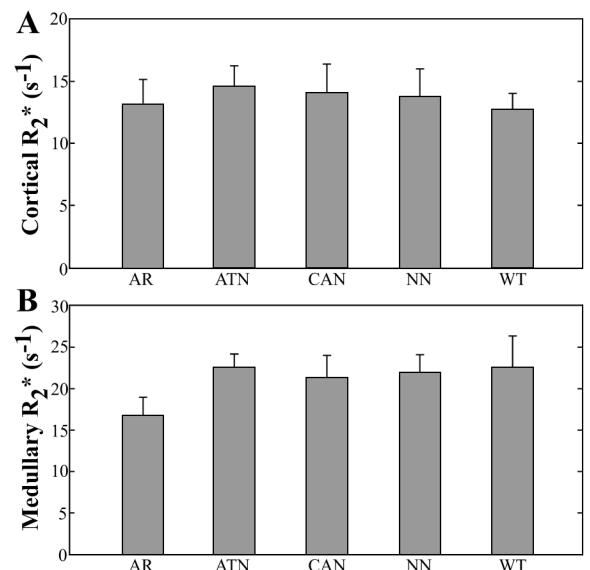
Our findings suggest that medullary oxygen bioavailability was higher (as seen by the lower  $R_2^*$  values) in transplant patients undergoing acute rejection than in patients undergoing ATN or CAN, normal native subjects, and well-functioning transplant patients. While there was a slight upward trend in medullary  $R_2^*$  values from subjects with CAN, normal native subjects, and well-functioning transplant subjects, no other significant differences were found.

The elevated medullary oxygen bioavailability in patients undergoing acute rejection was unexpected. Local inflammation and oxidative stress may lead to blood shunting toward the medulla in these patients [1]. Alternatively, there may be decreased tubular workload leading to elevated medullary oxygen bioavailability [6]. BOLD MRI essentially represents the oxyhemoglobin availability in blood vessels and tissues; BOLD therefore does not provide information on whether abnormal oxyhemoglobin levels are due to cell over- or underutilization or increased or decreased diffusivity of oxygen through blood vessel walls. The inclusion of an MR perfusion technique in future studies may elucidate the mechanisms behind these abnormal measurements in oxygen bioavailability.

While the number of subjects in each group is relatively small, we found significant differences between acute rejection subjects and the other four groups, as detailed above. However, given the number of comparisons with t-tests, it is likely that one or more p-values was found significant by random chance. While Bonferroni correction was considered, it was not employed. This was an exploratory study in a small number of subjects and thus Bonferroni correction was considered too conservative to detect potential differences.

## REFERENCES

[1] Sadowski et al. *Radiology*. 2005. 236(3):911-9. [2] Sadowski et al. *MRI*. 2010. 28:56-64. [3] Xiao et al. *Eur J Radiol*. 2011; [Epub ahead of print]. [4] Han et al. *Nephrol Dial Transplant*. 2008;23(8):2666-72. [5] Djamali et al. *Am J Physiol Renal Physiol*. 2007. 292:F513-22. [6] Jani et al. *J Am Soc Nephrol*. 2002. 13:773-8.



**Figure 1.** Bar graphs of cortical (A) and medullary (B)  $R_2^*$  values in patients undergoing acute rejection (AR), acute tubular necrosis (ATN), and chronic allograft nephropathy (CAN), as well as normal native (NN) subjects and well-functioning transplant (WT) subjects. Error bars are standard deviation.

**Table 1.** p-values from Welch's t-tests comparing  $R_2^*$  values in patients undergoing acute rejection (AR), acute tubular necrosis (ATN), and chronic allograft nephropathy (CAN), as well as normal native (NN) subjects and well-functioning transplant (WT) subjects. Comparisons with cortical  $R_2^*$  values are shaded in white; medullary values are shaded in grey. p-values were considered significant if less than 0.05.

	AR	ATN	CAN	NN	WT
AR		<0.001	<0.001	<1e10 <sup>-6</sup>	<0.001
ATN	0.20		0.29	0.49	0.99
CAN	0.35	0.64		0.51	0.39
NN	0.40	0.43	0.76		0.63
WT	0.54	0.11	0.14	0.08	

While there was a slight upward trend in medullary  $R_2^*$  values from subjects with CAN, normal native subjects, and well-functioning transplant subjects, no other significant differences were found.