

# Longitudinal intrarenal oxygenation estimated by BOLD MRI in a murine model of renal ischemia reperfusion injury

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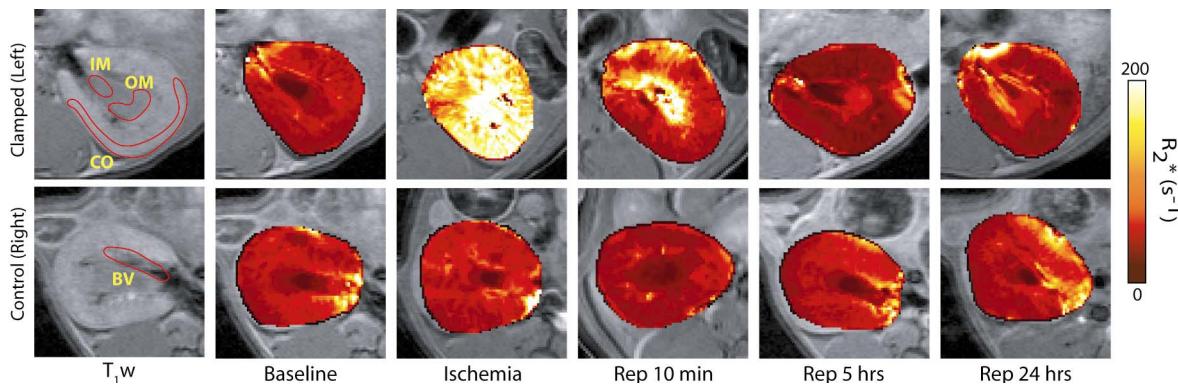
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## INTRODUCTION

Kidney transplantation results in superior life expectancy and quality of life compared to dialysis treatment for patients with end-stage renal disease[1]. After renal transplantation ischemia-reperfusion injury is an important cause of acute renal failure. In the physiological situation, blood flow to the hairpin loops of the renal medulla is low to preserve osmotic gradients and enhance urinary concentration. As a result the partial pressure of oxygen in the medulla is low, in contrast to the partial pressure of oxygen in the cortex. When oxygenation is further impaired during ischemia, the renal medulla is therefore most susceptible to injury[2]. Intrarenal oxygenation can be assessed using blood oxygen level dependent (BOLD) MRI, which reflects changes in the apparent transverse relaxation rate ( $R_2^*$ ). Due to the paramagnetic nature of deoxyhemoglobin, increasing  $R_2^*$  indicates a decreased oxygenation[3]. The purpose of this study was to investigate whether differences in renal oxygenation in the various regions of the kidney are detectable with BOLD MRI in a mouse model of renal ischemia-reperfusion injury.

## METHODS

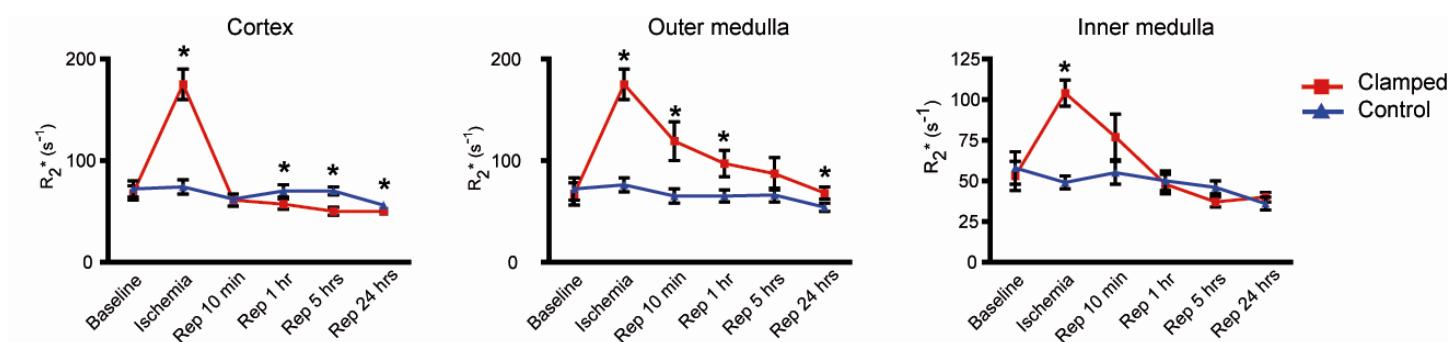
Eight male Swiss mice were anesthetized using 2% isoflurane. Mice were subjected to 45 minutes of unilateral ischemia by clamping of the left renal pedicle. Experiments were conducted on a 7.0 T Bruker Biospec 70/30 USR. BOLD measurements were performed using a standard multi-slice multi-gradient echo sequence using the following parameters: TR = 770 ms, TE = 4, 10, 16, 22, 28 and 34 ms, FA = 30°, 4 signal averages, matrix 256x256, FOV 4x4 cm<sup>2</sup>. On average, 18 1.0 mm thick axial slices were acquired covering both kidneys. Measurements were performed at baseline, during ischemia, immediately after reperfusion (mean 10 min), and 1, 5 and 24 hours after reperfusion. The signal intensity vs. echo time curves were fitted in Matlab to the gradient echo signal intensity function  $S=S_0 \exp(-TE R_2^*)$  to generate  $R_2^*$  maps on a voxel-by-voxel basis. Three slices in the center of the kidney were selected to draw regions of interest (ROIs) on the maps for cortex (CO), outer medulla (OM) and inner medulla (IM, fig 1). Blood vessels (BV) were excluded from the ROIs. Mean  $R_2^*$  and standard error of the mean were calculated for each 3 regions. Statistical testing between left and right kidneys was performed using paired Student's t-tests. P < 0.05 was considered statistically significant.



**Figure 1** Color-coded  $R_2^*$  maps from clamped kidney (upper panels) and its control kidney (lower panels).

## RESULTS

Figure 1 shows axial T<sub>1</sub>-weighted images with color-coded overlay of  $R_2^*$  maps. Figure 2 shows  $R_2^*$  values for the different regions for all time points. At baseline there were no differences between left and right kidney. During ischemia proof of principle is established by showing that  $R_2^*$  values were significantly higher in all regions than at baseline. Ten minutes after reperfusion cortical  $R_2^*$  values were normalized, while the inner and outer medulla  $R_2^*$  values were still elevated. After 1, 5 and 24 hours of reperfusion the outer medulla still had higher  $R_2^*$  values representing lower oxygenation than the control kidney. Remarkably, a slightly lower  $R_2^*$  (i.e. higher oxygenation) was found in the cortex of the injured kidney at 1, 5 and 24 hours after reperfusion compared with the control kidney.



**Figure 2.** Summary of  $R_2^*$  values in the different regions of the kidney. Presented are mean  $\pm$  SEM values. \* indicates P < 0.05.

## CONCLUSIONS

BOLD MRI is an adequate tool to distinguish ischemically damaged kidneys from kidneys without ischemia-reperfusion injury. For the first time it is demonstrated that even after 24 hours of reperfusion the outer medulla of an ischemically damaged kidney is still more hypoxic than that of the control kidney. This may cause ongoing ischemic tissue injury to the outer medulla, even after reperfusion. In addition it was observed that the cortex had a slightly higher oxygenation after reperfusion. This may be due to compensatory mechanisms or decreased oxygen consumption in the damaged kidney. MRI may be a useful tool to assess interventions protecting kidneys from ischemia-reperfusion injury, also in the clinical setting as BOLD MRI is a non-invasive tool based on endogenous contrast.

## REFERENCES

1. Wolfe RA et al. New Engl J Med 1999    2. Brezis M et al. New Engl J Med 1995    3. Prasad PV et al. Circulation 1996