# Effect of Iodixanol, a Iso-osmolar Radio-Contrast Agent on Intra-Renal Oxygenation by BOLD MRI

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## INTRODUCTION

Since radio-contrast nephropathy (RCN) was recognized more than 50 years ago [Acta Med Scand. 1954; 150( 4): 297-302], there have been continuing efforts to chemically modify radio-contrast agents to be less nephrotoxic. Even though nonionic, low- and iso-osmolality radio-contrast agents are believed to be safer than ionic high-osmolality agents [N Engl J Med. 1992 Feb 13;326(7):482-4], RCN remains to be a major source of in-hospital and long-term morbidity and mortality in patients with preexisting kidney disease [J Hosp Med. 2009 0ct; 4(8): 500-6]. Studies have found that higher renal medullary hypoxia after radio-contrast is a key contributing factor to renal failure [Adv Exp Med Biol. 2009;645:213-8]. Commonly associated predisposing factors are associated with a propensity to enhance renal hypoxia [Clin J Am Soc Nephrol. 2008 Jan;3(1):288-96].

A previous study had demonstrated enhancing hypoxia as evaluated by blood-oxygen-level dependent (BOLD) MRI following administration of a first generation hyper-osmolal radiocontrast agent, iothalamate [J Magn Reson Imaging. 2001 May;13(5):744-7]. In the present study, the same model of radio-contrast nephropathy [J Clin Invest. 1994 Sep;94(3):1069-75], was used to study the effect of a nonionic iso-osmolal agent, iodixanol, a third generation agent. The progressive changes in renal medullary hypoxia were monitored by BOLD MRI.

## MATERIAL AND METHODS

The study protocol was approved by the Institutional Animal Care and Use Committee. Male Sprague-Dawley rats (Harlan Laboratories, Madison, WI US, weight: 355.7± 19.3 grams) were anesthetized using 100 mg/kg of Inactin (Sigma, St. Louis, MO) *i.p.*. The femoral vein was catheterized for administration chemicals. Imaging was performed on a 3.0T scanner (Magnetom Verio, Siemens, Germany) using a multiple gradient recalled echo sequence (TE=3.6-41.3ms; FOV=12x6cm; TR=69ms; BW=320Hz/pixel; FA=30$^{o}$; NEX=20; matrix=256x256) to acquire 12 T2* weighted images. The rat kidneys were positioned in the middle of the eight channel standard knee coil. One transverse slice was selected in the middle of the kidney. Six rats were pre-treated with both L-NAME (Sigma, St. Louis, MO, 10mg/kg) and indomethacin (Sigma, St. Louis, MO, 10mg/kg). After acquiring five baseline BOLD MRI scans at 3 min intervals, pre-treatment agents were administered as a bolus 15 min apart, followed by radiocontrast iodixanol (Visipaque, 320mgI/ml, GE Healthcare, Waukesha, WI) at dose of 2.45ml/kg. After each administration, BOLD images were obtained every 3 minutes for 15 min following L-NAME and indomethacin, and for 1 hour following iodixanol. ROIs were placed in renal medulla and cortex on T2* maps reconstructed inline on the scanner console. The statistical significance of the differences between pre- and post- administration R2* values was assessed using the two-tailed paired Student's t-test.

## RESULTS

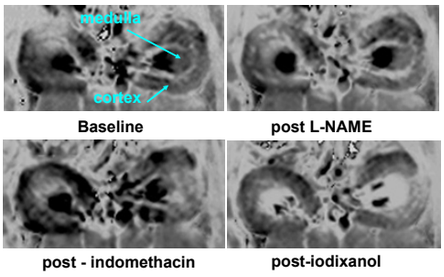


**Figure 1.** Representative inverted T2* maps with same display window setting generated on the scanner console. The brightness in tissue corresponds to lower oxygenation level or higher deoxyhemoglobin level. The arrows point to the outer medulla and cortex where the ROIs were defined. At baseline, renal cortex appears darker than renal medulla, implying better oxygenation. Note the progressive increase in medullary brightness signifying increased level of hypoxia.

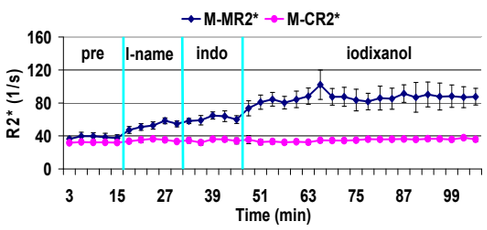


**Figure 2.** Averaged (mean ± SE) renal BOLD R2* time course from six rats. The medullary R2* increases steadily after each chemical. The cortical R2* did not show change over time.

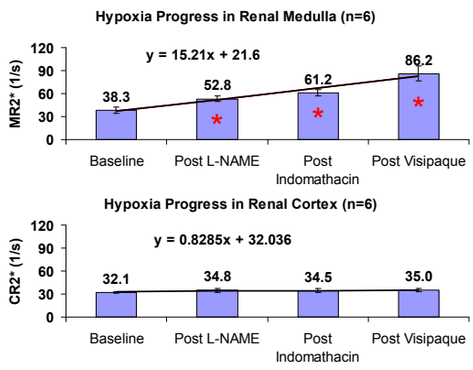


**Figure 3.** Summary of R2* in renal medulla and cortex after treatement with L-NAME, indomethacin and iodixanol. * implies statistical significance in R2* between every two treatment. Significant changes were found after each treatment compare to the previous phase in renal medulla but not in cortex. Data are the average of all animals in each group (mean±SE). The means were fitted to a liner equation to illustrate the progression of renal hypoxia.

## DISCUSSION AND CONCLUSION

The results presented here are consistent with the previous report [JMRI. 2001 May;13(5):744-7]. We see the R2* to increase progressively following the administration of L-NAME, indomethacin and radiocontrast. The magnitude of change in R2* with respect to baseline is almost twice (125% of baseline vs. 67% of baseline) compared to the previous report. However, the previous study was performed at 1.5 T while the present study utilized a 3T scanner. Because the BOLD response doubles at 3T compared to 1.5T [JMRI. 2004 Nov;20(5):901-4], our data would suggest a similar effect of iso-osmolal agent compared to high osmolal agent in terms of increased renal hypoxia. Also, the dose of radiocontrast used in the previous report was higher (6 ml/kg *vs.* 2.45 ml/kg). We did not observe a dip in meduallary R2* immediately following radiocontrast administration in this study as observed in the previous study. It is consistent with the biphasic hemodynamic response to hyper-osmolal radio-contrast, characterized by immediate transient vasodilatation followed by a prolonged vasoconstriction phase [Nephrol Dial Transplant 20(8):1542-1550, 2005].

In conclusion, our preliminary analysis suggests the effect of iodixanol on renal hypoxia is comparable to that associated with iothalamate. However, further studies are necessary to compare these two agents head to head. Also, additional conventional markers for RCN should be acquired.

## ACKNOWLEDGEMENT

This work was supported in part by a grant from the National Institutes of Health, NIDDK 53221.