# Intra-Renal Oxygenation in Radio-contrast Nephropathy Model by BOLD MRI: Effect of the Dose and Viscosity

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## INTRODUCTION

Since radio-contrast induced nephropathy (CIN) was recognized more than 50 years ago [Acta Med Scand. 1954; 150( 4): 297-302], there have been continuing efforts to chemically modify radiocontrast agents to be less nephrotoxic. Even though nonionic, low- and iso-osmolar radiocontrast agents are believed to be safer than ionic high-osmolality agents [N Engl J Med. 1992 Feb 13; 326(7):482-4], CIN remains to be the third major source of in-hospital acquired acute renal failure and is associated with long-term morbidity and mortality in elderly patients and those with preexisting kidney insufficiency and diabetes [J Hosp Med. 2009; 4(8): 500-6]. The role of renal medullary hypoxia in the pathophysiology CIN is well accepted [Nephrol Dial Transplant 2005; 20 [Suppl 1]: i6–i11]. A number of previous studies show that increased viscosity compromises blood flow and oxygen supply to kidney [J Am Soc Nephrol. 2007; 18:2912-20] and a dose dependent response has been observed [J. Appl. Toxicol. 19, 341–346 (1999)].

Inhibition of endogenous prostaglandin and nitric oxide production predisposed rats to severe renal injury following radio contrast administration in studies employing invasive Doppler flow probe measurements of regional blood flow [J Clin Invest 1994; 94:1069–1075]. Using this model, a previous study has shown that blood oxygen level-dependent (BOLD) MRI technique can be used to monitor progressive changes in intra-renal oxygenation following administration of a 1st generation radio-contrast, iothalamate [JMRI 2001; 13:744–747]. In this study, we have compared a 3rd generation radiocontrast, viz. Iodixanol against iothalamate. Iodixanol is an iso-osmolal agent with significantly higher viscosity compared to iothalamate [Radiol 1997; 204: 297-312] and has been shown to be associated with hemodynamic consequences [J Am Soc Nephrol. 2007 18:2912-20].

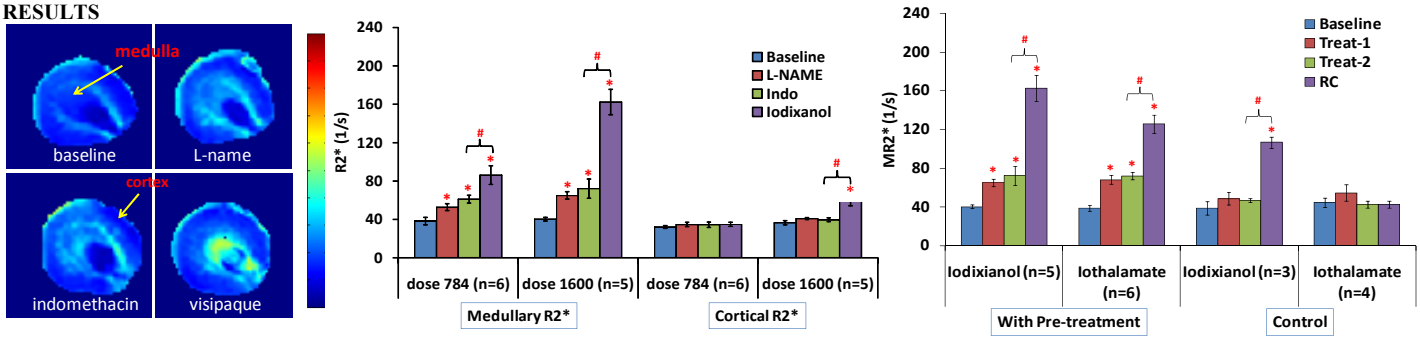
## METHODS

The study protocol was approved by our IACUC. Twenty four male Sprague-Dawley rats (Harlan Laboratories , Madison, WI USA) were anesthetized using Inactin (100 mg/kg i.p., St. Louis, MO, USA) and divided into 5 goups (iodixanol with low, high dose and control; iothalamate high dose and control). The femoral vein was catheterized. Nitric oxide synthase inhibitor, N-nitro-L-arginine methyl ester (L-NAME, 10mg/kg), and prostaglandin inhibitor, indomethacin (10 mg/kg) were administered *iv* to pre-condition the rats. Saline, instead of L-NAME and Indomethacin, was administrated in control group. Either iso-osmolar radio-contrast, Iodixanol (Visipaque, 320 mg/ml, GE Healthcare, USA, viscosity at 37°C of 11.8) or high osmolarity radio-contrast, iothalamate (Conray, 282 mg/ml , Mallinckrodt, St. Louis, MO, USA, viscosity at 37°C of 4) was administered based on the amount of iodine content.

Imaging was performed on a 3.0 T scanner (Magnetom Verio, Siemens, Germany) using a multiple gradient recalled echo sequence (TE=3.6-41.3ms; FOV=12x6cm; TR=69ms; bandwidth=320Hz/pixel; FA=30°; NEX=20; matrix: 256x256; slice thickness=2mm) to acquire 12 T2* weighted images. The rat kidneys were positioned in the middle of the standard knee coil. One transverse slice was selected in the middle of the kidney. Five sets of baseline BOLD images (each 3 minutes) were acquired. L-NAME, Indomethacin, or saline were administered as pretreatment. Following each pretreatment, five sets of BOLD images were acquired. Radio-contrast agents were administered and followed with scanning for one hour.

T2* maps were generated inline on the scanner. ROIs were chosen on the maps to obtain T2* measurements and then converted into R2* in Microsoft Excel. The average of all R2* measurements in each stage was used to represent the mean R2* value of that stage. The statistical significance of the differences between pre- and post- R2* values was assessed using the two-tailed paired Student's t-test. Differences were considered significant if $p < 0.05$.

## RESULTS




* stands for $p<0.05$ in Student t-test compare to baseline. # indicates a significant difference ($p<0.05$) from the previous phase. n = Number of animals in each group.

**Figure 1(left):** R2* maps were generated using MRImapper (Beth Israel Deaconess and MIT, MA) in one representative animal. The relative brightness in renal medulla suggests lower oxygenation level compared to cortex. The windows and settings are the same in all maps. The brightness in renal medulla increases gradually after each chemical suggesting the progressive decreasing of oxygenation.

**Figure 2 (middle):** Summary of dose dependence of BOLD R2* response in renal medulla and cortex with iodixanol. Data shown as mean ± SE. The unit for "dose 784" and "dose 1600" is mg of iodine per kilogram body weight. There is no significant difference in baseline values between low and high dose groups. Medullary R2*(MR2*) shows a dose dependent response to Iodixanol. L-NAME, Indomethacin and Iodixanol each induced a significant increase of MR2* compared to their own baseline in both groups. In addition, MR2* after iodixanol is significantly increased compared to post-indomethacin in both groups. However, the magnitude of the increase in MR2* after Iodixanol in high dose group is more than doubled compared to low dose group (303% *vs* 133%). Low dose iodixanol did not change cortical R2* (CR2*). However, CR2* increased significantly compared to baseline and post-indomethacin in high dose indixanol group.

**Figure 3(right):** Comparison of BOLD MR2* response to iodixanol and iothalamate with and without pre-treatment. With treatment, Treat1 is L-NAME; Treat2 is Indomethacin. In control group, both Treat1 and Treat 2 were saline. Both radio contrasts induced significant R2* response compared to baseline. However, the magnitude of the change is higher with iodixanol than with iothalalmate in pre-treated group (303% vs 225.6% ). In addition, in control group, iodixanol induced significant MR2*increase, but not iothalamate.

## DISCUSSION AND CONCLUSION

In conclusion, our data demonstrates that the physico-chemical properties do influence the renal hemodynamics differently and in a dose dependent manner. These may be useful in better understanding the risk of developing CIN and more importantly how to mitigate them. Future studies should include other biomarkers to document CIN or renal injury such as 24 hour serum creatinine, histology or kidney injury molecule [Invest Radiol 2009; 44: 114–123].

**ACKNOWLEDGEMENTS:** Work was supported in part by a grant from the National Institutes of Health, DK-53221.