Intra-Renal Oxygenation in Contrast Induced Nephropathy Model by BOLD MRI: Comparison of Four Radio-Contrast Agents

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INTRODUCTION

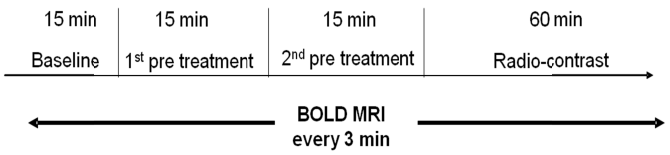
Since radio-contrast induced nephropathy (CIN) was recognized more than 50 years ago [*Acta Med Scand.* 1954; 150(4): 297-302], there have been continuing efforts to chemically modify radio-contrast agents to be less nephrotoxic. However, CIN remains as the third major source of in-hospital acquired 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]. Radio-contrast agents can be classified into three generations based on their osmolality (high, low and iso-osmolar). However, changes in the formulation have resulted in increasing viscosity which in turn leads to hemodynamic consequences. Epidemiological data are ambivalent probably because of the complex interplay of several factors involved (*e.g.* pre-existing conditions, pre-treatment management based on perceived risk etc.).

While pathophysiology of CIN is not yet fully understood, it is now well accepted that renal medullary hypoxia [*Invest Radiol.* 1999;34(11):685-91] plays an important role. Blood oxygenation level-dependent (BOLD) MRI is gaining acceptance as a non-invasive method for monitoring intra-renal oxygenation [Magn Reson Im Clin N Am 16 (2008) 613–25]. In a previous study, it was shown that administration of a 1st generation contrast agent (iothalamate) resulted in severe renal injury ***only*** when the kidneys were pretreated with agents inhibiting endogenous prostaglandins and nitric oxide [*J Clin Invest* 1994; 94:1069–75]. In another study, with the same model, it was shown that BOLD MRI technique can be used to monitor progressive changes in intra-renal oxygenation following administration of iothalamate [*JMRI* 2001; 13:744–7]. In the present study, we have compared four different radio-contrast agents with different osmolality, ionicity and viscosity as evaluated by BOLD MRI.

METHODS

The study protocol was approved by our IACUC. Male Sprague-Dawley rats were anesthetized by inactin (100 mg/kg i.p.) and femoral vein was catheterized. For the BOLD MRI study, four groups (total n=48) based on the contrast agent were further subdivided into pre-treatment group: receiving nitric oxide synthase inhibitor, N-nitro-L-arginine methyl ester (L-NAME, 10mg/kg) and prostaglandin inhibitor, indomethacin (10 mg/kg) prior to radio-contrast, and control group: receiving two times saline instead. One of the four radio-contrast agents (Table-1) was administered at 1600 mgI. Group assignments were made in a random order and blinded fashion. 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;

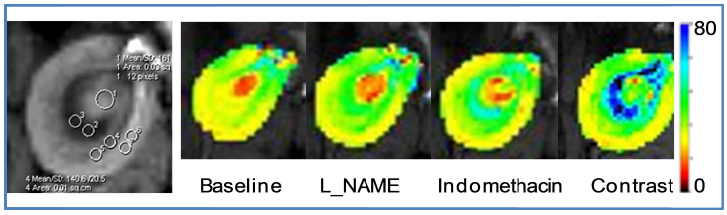
	Iodixanol	Iothalamate	Iohexol	Ioxaglate
Brand name	Visipaque	Conray	Omnipaque	Xexabrix
Ionicity	nonionic	ionic	nonionic	ionic
Osmolality (mOsmol/L)	isosmolar	1000	672	600
Iodine concentration	320 mg/ml	282 mg/ml	300	320
Viscosity at 37° C	11.8	4	6.3	7.5

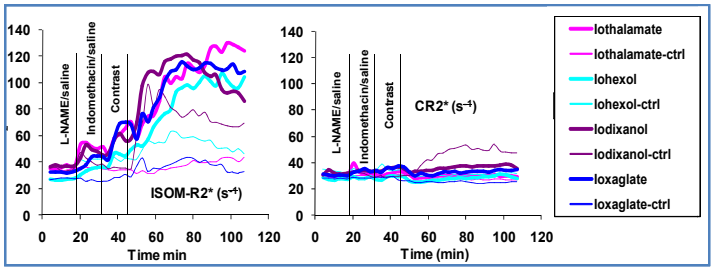


TR=69ms; bandwidth=320Hz/pixel; FA=30°; NEX=20; matrix: 256x256; slice thickness=2mm) to acquire 12 T2* weighted images. The rat kidneys were positioned in the middle of the standard knee coil. One transverse slice was selected in the middle of the kidney. BOLD MR images (3' each) were acquired in sequence as described in the above timing diagram.

R2* maps were generated inline on the scanner. ROIs were defined to represent inner- and outer-stripes of outer medulla (ISOM, OSOM), inner medulla (IM) and cortex (CO). R2* values, indicating relative level of hypoxia, was assessed by a linear mixed-effects growth curve model with first-order autoregressive variance-covariance for over time (a total of 35 time points) within each group and between-group difference. Differences were considered significant if $p < 0.05$.

RESULTS





Shown on the left are representative anatomical image of rat kidney with typical ROI positions (1 IM, 2,3 IOSM, 4,5 OSOM, and 6,7 CO). Also shown are representative R2* maps displayed with the same window settings. Note the progressively increasing R2* values in the medulla. Figure on the right summarizes the temporal change in R2* in ISOM and CO from all rats in all different groups. Renal IOSM generally demonstrated the largest changes in R2* post-contrast. The vertical lines show the time of administration of pre-treatment (or saline). Note, while R2* in ISOM increased significantly with all four agents in the pre-treated group, ***only*** iodixanol induced significant R2* increase in the control group.

The linear mixed-effects growth curve model showed that all agents increased the hypoxia level post-contrast administration in ISOM and IM in the pre-treatment group ($p<<0.01$) and the response was not different between the four agents with respect to baseline and change over time, all $p>0.05$. All contrast agents, except iothalamate, showed significant R2* increase in renal IM in the control group. Only iodixanol ($p=0.004$) and iohexol ($p=0.012$) showed a significant increase in the control group in renal ISOM. Cortex and OSOM showed the least response to any of the contrast agents in either groups ($p>0.05$), but demonstrated a statistically significant increase ***only*** with iodixanol in CO and only in the control group.

DISCUSSION AND CONCLUSION

The major findings of this study include:

- In the pre-treatment group, the degree of increase in hypoxia of ISOM with any of the contrast agents was comparable.
- In the control group, only iodixanol showed a similar increase in ISOM. Significant increase in R2* was observed in IM with all agents, except iothalamate.
- CO and OSOM generally showed the least change in both pre-treated and control groups.

These observations suggest that viscosity may play a more significant role in determining the renal hemodynamics. Whether the acute hemodynamic changes observed in this study lead to consequential deficits in renal function are not yet clear and currently under investigation. These observations may explain the ambivalence reported on the safety of iodixanol [*N Engl J Med* 2003; 348:491-9, *Kid Intl* (2006) 70, 1811–1817], probably related to population differences. Animal models may provide a more consistent platform to study the effects of radio-contrast media, as demonstrated in the present study.

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