Intra-Renal Oxygenation Measurement by BOLD MRI in Contrast Induced Nephropathy Model: Effect of Interventions

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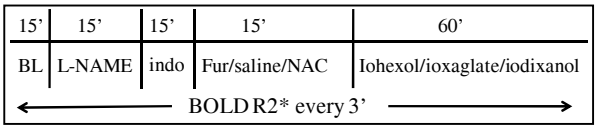
INTRODUCTION

Radio-contrast induced nephropathy (CIN) was first reported almost 60 years ago. As the number of interventional cardiac procedures has steadily increased over time, CIN has become the third leading cause for hospital acquired acute kidney injury. Introduction of the newer generation radio-contrast (RC) agents has not changed this statistic [*J Hosp Med* 2009;4(8):500-506] in patients with preexisting renal insufficiency and diabetes mellitus. A variety of therapeutic interventions have been proposed to mitigate the risk of developing CIN [*Ann Intern Med* 2008;148(4):284-294, *Radiol Clin North Am* 2009;47(5):801-811]. However, the results remain controversial, at least in part due to the natural heterogeneity within patient populations. Studies in animal models could alleviate the heterogeneity and could be useful in the evaluation of different contrast media and potential preventive strategies.

A rodent model of CIN involving pre-treatment with L-NAME (nitric oxide synthase inhibitor) and indomethacin (prostaglandin inhibitor) resulted in severe renal injury by histology [*J Clin Invest* 1994;94(3):1069-1075]. Since renal hypoxia is known to play a key role in the pathophysiology of CIN, blood-oxygen-level-dependent (BOLD) MRI technique was shown to be useful in monitoring the progressive changes in intra-renal oxygenation following administration of radio-contrast media [*J Magn Reson Imaging* 2001;13(5):744-747] in this model. The purpose of this study was to illustrate the effects of potential renoprotective interventions such as administration of N-acetylcysteine (NAC, antioxidant) and furosemide (Fur, diuretic) on intrarenal oxygenation as evaluated by BOLD MRI.

MATERICAL AND 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. All animals were pre-treated with L-NAME (10mg/kg) and indomethacin (10mg/kg) to induce risk of developing CIN prior to one of the protective agents (furosemide, NAC or saline (as control)). Animals were grouped based on radio-contrast and then further sub-divided based on the preventive agent received. One of three radio-contrasts ioxaglate (ionic, low-osmolal), iohexol (nonionic, low-osmolal) or iodixanol (nonionic, iso-osmolal and high viscosity) at dose of 1600 mg of organic iodine per kilogram body weight was administered 15' after prevention agent (furosemide at 10mg/kg, or NAC at 60mg/kg, or saline at 1ml/kg). Six rats in each sub-group led to a total of 54 rats in this study. To-date, we acquired data in 40 rats. A randomization chart was used to determine the contrast agent and intervention for each animal. The persons responsible for data acquisition and analysis remained blinded to the preventive intervention and type of contrast media.



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. BOLD MR images (3' each) were acquired in a sequence as described in the above timing diagram. R2* (=1/T2*, unit: s^{-1}, high value indicating higher level of hypoxia) maps were generated inline on the scanner. ROIs were defined to represent inner- stripe of outer medulla (ISOM), the region with most response to radio-contrasts based on a previous report [*Proc. ISMRM* 2012, 4073]. Mean R2* value, the average of all readings in each step (at baseline; following L-NAME, indomethacin, protective agent, and radio-contrast agent) was calculated based on group. Group differences were assessed by two–tailed Students t-test; $p<0.05$ considered as significant.

RESULTS

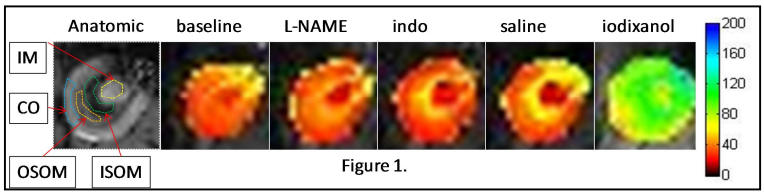
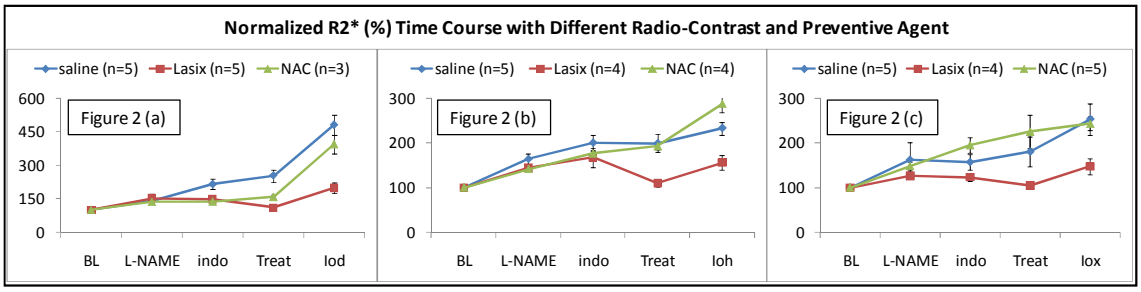


Figure 1.

Figure 1 is a representative anatomical image of rat kidney with typical ROI positions indicated as inner medulla (IM), inner and outer stripe of outer medulla (IOSM and OSOM) and cortex (CO). Also shown are representative R2* maps displayed with the same window settings. Note the progressively increasing R2* values following each chemical in the medulla suggesting increasing levels of hypoxia, especially in ISOM.

Figure 2 is a summary of R2* values in ISOM (mean ± SD) from 9 groups.



BL: baseline; indo: indomethacin; RC: radio-contrast; Iod: iodixanol; Ioh: iohexol; Iox: ioxaglate. L-NAME and indomethacin created similar increase in R2* in all groups. R2* increased the least with furosemide in all three radio-contrast groups compare to baseline and significant difference were reached compared to saline group. NAC group did not show protective to CIN in terms of reducing hypoxia level compared to saline group ($p>0.05$ for all radio-contrasts except for ioxaglate). The difference between furosemide and NAC treatment is significant. This suggests that radio-contrast induced decrease of renal pO2 was largely mitigated by furosemide compared to NAC regardless of which contrast agents rats received. The R2* with iodixanol increased the most in the control group, which is consistent with the previous observation [*Proc. ISMRM* 2012, 4073] implicating the role of high viscosity on renal hemodynamics [*J Am Soc Nephrol* 2007;18(11):2912-2920].

CONCLUSION AND DISCUSSION

The preliminary data from this study shows that diuretic furosemide can mitigate the effects of contrast media in terms of increased hypoxia. These results are consistent with previous report that showed reduced acute renal failure in rats when pre-treated with furosemide [*Kidney International,* 2001, 60: 1407–1414]. Earlier human trials of CIN with furosemide have failed to demonstrate efficacy [*N Engl J Med* 1994; 331: 1416–1420], however it is thought to be due to lack of compensation of fluid loss. A recent trial using furosemide with matched hydration showed reduced incidence of CIN in patients with chronic renal insufficiency who were undergoing coronary procedures [*JACC Cardiovasc Interv* 2012;5(1):90-97]. While our study did not include matched hydration by design, the animals did receive fluids *via.* administration of the different agents. The potential effects of NAC may have been compromised by the pre-treatment with L-NAME. Further studies are necessary to determine whether the reduced hypoxia actually results in reduced renal injury.