

Changes in Intra-Renal Oxygenation by BOLD MRI as an Early Marker of Iodinated Contrast Induced Acute Kidney Injury

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INTRODUCTION

Iodinated contrast induced acute kidney injury (CIAKI) is the third leading cause for hospital acquired AKI¹. However, some recent reports have questioned the causality, *i.e.* is the AKI necessarily related to contrast administration². This is most probably related to the clinical definition of CIAKI which is based on serum creatinine measurements 48-72 hours post-contrast. Novel markers that can detect changes more acutely are being sought and a recent report indicated urinary neutrophil gelatinase-associated lipocalin (NGAL) can detect changes as early as 8 hours post-contrast³. Previous reports using BOLD MRI have shown near real-time responses to iodinated contrast⁴, especially in CIAKI susceptible rats⁵.

The purpose of this study was to evaluate whether increased R2* values observed post-contrast administration in CIAKI susceptible animals do lead to AKI as determined by urinary NGAL. Further, whether interventions that can abolish the increase observed in R2* post-contrast administration are protective from developing AKI as determined by urine NGAL.

MATERIALS AND METHODS

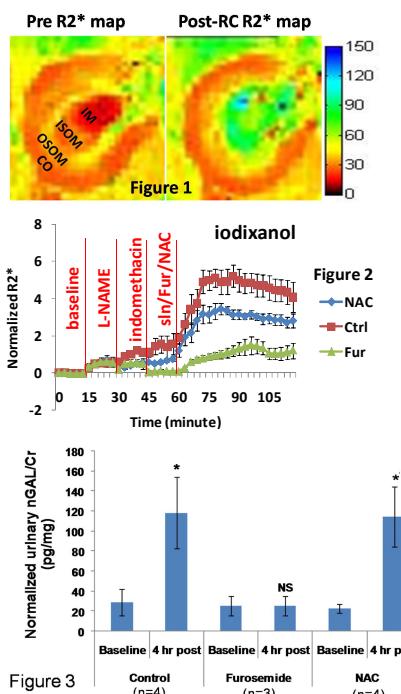
group #	baseline	Chemicals			
		pre-treat 1	pre-treat 2	intervention	contrast
1	L-NAME			saline	
2		iodomethacin		furosemide	
3			NAC	iodixanol	
scan time	15'	15'	15'	15'	60'

The study protocol was approved by 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 (nitric oxide synthase inhibitor, 10mg/kg) and indomethacin (prostaglandins inhibitor, 10mg/kg) to induce risk of developing CIAKI⁶. Animals were grouped based on the preventive agent received (see Table on the left), six animal in each group. Group 1: saline (1mL/kg) as control; Group 2: furosemide (10mg/kg); Group 3: NAC (60mg/kg). Iodinated contrast iodixanol (nonionic, iso-osmolal and high viscosity) at dose of 1600 mg of organic iodine per kilogram body weight was administered 15' after interventional agent. Group assignments were

performed in a random order and the person acquiring data was blinded to the assignment. BOLD imaging was performed on a 3.0 T scanner (Magnetom Verio, Siemens) 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 every 3 minutes. The rat kidneys were positioned in the middle of the standard knee coil. One transverse slice was selected in the middle of the kidney. 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 four regions as shown in Figure 1, but only data from inner-stripe of outer medulla (ISOM), the region with most response to contrasts based on a previous report⁴, is shown. The reader was blinded to the assignment.

Urine was collected before BOLD MRI scan (bl) and 4 hours (4 hr) after administration of iodixanol. Urinary NGAL concentrations were measured using NGAL ELISA kit (046, BioPorto Diagnostics, Denmark) according to manufacturer's instruction and were normalized to urine creatinine concentrations to minimize any confounding effects of urine flow rate⁷.

Mixed effect regression model was used to assess BOLD R2* and NGAL measurements in terms of changes over time (slope).



RESULTS

Figure 1 shows representative R2* maps from one rat. Different renal regions where ROIs were defined is indicated on the pre R2* map: inner medulla (IM), inner and outer stripe of outer medulla (IOSM and OSOM) and cortex (CO). Also shown is post R2* map displayed with the same window settings. Note the increasing R2* values following contrast iodixanol suggesting increasing levels of hypoxia, especially in ISOM.

Figure 2 is the summary of BOLD R2* readings from the three groups of rats. Each point is the mean±SE over the 6 rats in each group. Note the progressively increasing R2* after each pre-treatments and following contrast in the control group. While NAC did show reduced R2* post-contrast compared to control group, furosemide close to completely abolished the increase in R2* post-contrast.

Figure 3 summarizes the urine NGAL measurements obtained at baseline and 4 hour post-contrast. Note that there is a significant (*) increase at 4 hrs in both control and rats treated with NAC suggesting AKI, while there is no change in those treated with furosemide.

Table 1

	IM	ISOM	NGAL
Iodixanol_ctrl	0.82*	0.99*	19.19*
Iodixanol_fur	0.20*#†	0.33*#†	-1.93#†
Iodixanol_NAC	0.56*#	0.94*	19.97*

.indicates slope is significantly different from zero ($p < 0.05$)

#indicates significant change in slope compared to corresponding control group ($p < 0.05$)

†indicates significant change in slope compared to corresponding NAC group ($p < 0.05$)

Table 1 summarizes the statistical analysis of BOLD R2* and corresponding NGAL data. The temporal data were fit to linear function and shown are the slope estimates. It is clear that the slopes of R2* in IM and ISOM are significantly higher in the control and NAC groups compared to the furosemide group. Similarly, NGAL showed a large increase in both control and NAC groups with no change in the furosemide group.

CONCLUSION AND DISCUSSION

These data reconfirm that acute changes in kidneys can be monitored following iodinated contrast

administration using BOLD MRI. Further, for the first time BOLD MRI data have been compared with NGAL measurements as a direct marker for AKI. These suggest that large increase in R2* following contrast administration is associated with renal injury. Our data suggest protective nature with furosemide, while NAC was not. However, it should be noted that the dose of furosemide used in this study is much larger than clinically viable

dose. It is not clear whether the dose of NAC is optimal. Future studies are necessary to determine the optimal dose for efficacy for each of the interventional agents. It would also be interesting to determine whether the initial lowering of R2* towards baseline values following administration of interventional agents are indicative of optimal dose for efficacy. If so, these observations can be readily translated to humans. Future studies with larger number of contrast media and interventions could provide an opportunity to determine threshold values for R2* changes that lead to AKI as determined by NGAL.

REFERENCE

1. European heart journal. 2012;33:2007-15. 2. Radiology. 2013;267:106-18. 3. Radiology. 2013;267:86-93. 4. JMRI. 2012;36:1162-7. 5. ISMRM 2012 proceeding, p. 4073. 6. The Journal of clinical investigation. 1994;94:1069-75. 7. Renal failure. 2008;30:904-13.