Early Changes in Renal Hypoxia Following Iodinated Contrast: Need for Real-time Monitoring

Lu-Ping Li[1,2], Jing Lu[2,3], Tammy Franklin[1], Ying Zhou[4], Richard Solomon[5], and Pottumarthi V. Prasad[1,2]

[1]Department of Radiology / Center for Advanced Imaging, Northshore University Healthsystem, Evanston, IL, United States, [2]Pritzker School of Medicine, University of Chicago, Chicago, IL, United States, [3]Department of Obstetrics and Gynecology, Northshore University Healthsystem, Evanston, IL, United States, [4]Center for Clinical & Research Informatics, Northshore University Healthsystem, Evanston, IL, United States, [5]Nephrology, University of Vermont, VT, United States

INTRODUCTION

Iodinated contrast induced acute kidney injury (CIAKI) is one of the leading causes of hospital-acquired acute kidney injury (AKI) which is likely related to renal medullary ischemia and hypoxia [Angio. 2013;64:576-582]. The optimal treatment window is within 24 hours after patient exposure to iodinated contrast to avoid developing AKI. However, the clinical AKI marker, serum creatinine takes 48 to 72 hours to indicate renal injury [Rad. 2013; 267(1):106-18]. Recent studies have shown urinary neutrophil gelatinase-associated lipocalin (uNGAL) can detect changes as early as 8 hours in human [Rad. 2013;267:86-93] and 4 hours in rats post-contrast [Inv. Rad. 2014;49:403-410]. Blood oxygenation level dependent (BOLD) MRI demonstrated near-real-time changes following contrast administration in a functional CIAKI rat model by simulating endothelial dysfunction via pre-treating animals with L-NAME (nitric oxide synthase inhibitor) and indomethacin (prostaglandin inhibitor) [Inv. Rad. 2014 49: 403-410].

Here we have extended the observations to an alternate model. Diabetes mellitus is an independent risk factor for CIAKI due to enhanced renal medullary hypoxia and impaired endothelium-derived vasorelaxation. Streptozotocin (STZ)-induced diabetes in rat is the most common animal model used in research, and mimics many complications observed in the diabetic human including nephropathy [Diabetes Metab Res Rev. 2004;20(6):452-9]. In this study, we tested whether STZ induced diabetic rats develop CIAKI using uNGAL and monitored renal hypoxia using BOLD MRI.

MATERIALS AND METHODS

Study protocol was approved by our IACUC. Six rats were treated with STZ (50–55 mg/kg body weight, Group 1). For comparison, data from 12 rats from a previous study [Inv. Rad. 2014 49: 647-52] were used and re-analyzed using different parameters for BOLD MRI response. Six rats had received saline (10ml/kg, Group 2) and the other six rats had received furosemide (10mg/kg, Group 3) following L-NAME (10mg/kg) and indomethacin (10 mg/kg) as pre-treatments. Diabetic rats were scanned two weeks after STZ administration with a significant high blood glucose level (549.8 ± 22.3 mg/dL). On the scan day, rats were anesthetized using inactin (100 mg/kg i.p.). The femoral vein was catheterized for contrast administration. All rats were received iodinated contrast iodixanol (1600 mg of organic iodine / kg). Urine (200 µl) was collected prior to the MRI, and 4 hours after contrast administration. uNGAL was analyzed using rat NGAL ELISA Kit. Urinary creatinine levels were also measured in order to minimize any confounding effects of urine flow rate.

Group	Group Name	BOLD R2* Scan Timeline				Iodinated Contrast	Peak R2* (s^{-1})	R2* initial up-slope	uNGAL 4 hr post from baseline
1	Diabetes			baseline	saline	iodixanol	126.0 ± 10.1	8.1 ± 1.1	2.1 ± 0.3
2	pre-treatment	baseline	L-NAME	indomethacin	saline	iodixanol	159.7 ± 9.4	6.4 ± 0.7	1.8 ± 0.5
3	pre-treatment + Fur	baseline	L-NAME	indomethacin	Furosemide	iodixanol	78.5 ± 17.0	0.8 ± 0.3	0.0 ± 0.3

Imaging was performed on a 3.0T scanner (Siemens Magnetom Verio) using a multiple gradient recalled echo sequence (TE = 3.6-41.3 ms; FOV = 12 x 6 cm; TR = 69 ms; bandwidth = 320Hz / pixel; FA = 30°; NEX = 20; matrix: 256 x 256; slice thickness = 2 mm) 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 were acquired every 3' continually. R2* maps were generated inline on the scanner. ROIs were placed in the inner stripe of the outer medulla (ISOM) on R2* map, the most sensitive region for CIAKI [Inv. Rad. 2014;49:403-410]. Higher R2* values indicate higher hypoxia. The time sequence of the image acquisition and group information is illustrated in Table above.

Peak R2* and the initial up-slope (from one time-point before contrast, Time "0" in Figure, to the time-point of inflection when R2* stopped to increase) were calculated. A mixed effect regression model was used to assess R2* changes over time. Fixed effects in the model include group, time (continuous) and group by time interactions. uNGAL at 4 hours from baseline in the different groups and peak R2* values were compared using repeated measure ANOVA and $p<0.05$ was regarded as statistically significant.

RESULTS

Figure is the summary of R2* in ISOM. Phase-1: baseline for groups 2&3; Phase-2: L-NAME for groups 2&3; Phase-3: indomethacin for groups 2&3 / baseline for group 1; Fur: furosemide. R2* increased quickly followed by a "washout" phase after contrast administration in the diabetic rats (Group 1). The R2* values during phase-3 in diabetic rats was similar to pre-treatment rats with L-NAME and indomethacin, suggesting a similar renal hypoxia level before intervention (furosemide / saline). The R2* at the time "0" immediately before contrast administration in Group 3 is significantly lower than the other two groups, suggesting the reduced hypoxia by furosemide. The quick "washout" in Group 1 may be related to the polyuria in diabetic rats [Diabetes Metab Res Rev. 2004; 20(6):452-9.].

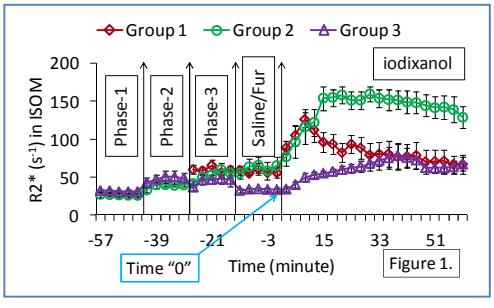

Figure 1.

Peak R2*, R2* initial up-slope and uNGAL (normalized to creatinine) are summarized in Table. Rats receiving furosemide showed significantly lower peak R2* and R2* initial up-slope in ISOM compared to other two groups, and also no significant change in uNGAL (suggesting no renal injury). There were no differences between the two groups susceptible to CIAKI (Group 1 and 2) in any of the three measurements.

DISCUSSION and CONCLUSION

The key and novel finding in this study is that even the temporary increase in renal medullary hypoxia may result in AKI. This strongly indicates the need for continuous monitoring of changes in renal hypoxia during contrast administration. This is consistent with a recent consensus report from Acute Dialysis Quality Initiative on the use of physiological biomarkers [*Contributions to nephrology*. 2013;182:65-81]. This will have important consequences to human translation. Alternate methods to evaluate renal medullary hypoxia during contrast administration may be necessary such as continuous monitoring of urine pO2 [*Journal of cardiothoracic and vascular anesthesia*. 1996;10:603-608].