Effect of Iodinated Contrast Medium in Diabetic Rat Kidney as Evaluated by BOLD MRI

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INTRODUCTION
Iodinated contrast induced acute kidney injury (CIAKI), is the leading cause of hospital-acquired AKI. The exact underlying mechanisms of CIAKI have yet to be fully elucidated but are likely to involve the interplay of decreased blood flow, renal medullary ischemia and hypoxia 1. Clinical studies have shown diabetes mellitus as an independent risk factor for CIAKI 2 due to enhanced renal medullary hypoxia and impaired endothelium-derived vasorelaxation. Previous studies have used a functional CIAKI model by simulating endothelial dysfunction by pre-treating animals with L-NAME (nitric oxide synthase inhibitor) and indomethacin (prostaglandin inhibitor). While the model has been shown to be useful in the evaluation of contrast media on intra-renal oxygenation using BOLD MRI 3, the relevance to humans has been questioned. We hypothesized that the use of a commonly used diabetes model by treating rats with streptozotocin (STZ) may prove to be a more translational model. A previous study has shown increased R2* values (implying increased hypoxia) as early as 48 hours following administration of STZ and continued to increase over a 4 week period 4. The purpose of this study was to test whether STZ-induced diabetic model is suitable to evaluate CIAKI.

MATERIALS AND METHODS
The study protocol was approved by our IACUC. Twelve Sprague-Dawley (SD) rats were divided into 2 groups, diabetes (n=6), and healthy control (n=6). Rats were induced with diabetes under light anesthesia (isoflurane). Streptozotocin (Sigma, 50–55 mg/kg body weight) was injected via the lateral tail vein. Animals with blood glucose levels of 15 mmol/L or less at 24 hours after STZ administration were excluded from the study. On the day of MRI (typically day 14 after STZ), rats were anesthetized using inactin (100 mg/kg i.p.) and femoral vein was catheterized. Imaging was performed on a 3.0 T scanner (Siemens Magnetom Verio) 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 were acquired every 3' continually. R2* data were acquired at baseline, following saline (1ml/kg), and after iodixanol (at dose of 1600 mg of organic iodine per kilogram body weight). R2* (=1/T2*, unit: s⁻¹, high value indicating higher level of hypoxia) maps were generated online on the scanner. ROIs were defined in four renal regions, but only data in inner stripe of outer medulla (ISOM) is shown based on previous experience indicating maximum response.

RESULTS
Figure 1 is the representative R2* map in a diabetes rats with typical ROI positions indicated as inner medulla (IM), inner and outer stripe of outer medulla (IOSM and OSOM) and cortex (CO). Arrows point to different renal tissue where ROIs were placed. The medulla is brighter than cortex suggesting more hypoxia in that area. Figures 2 is the summary of R2* (ISOM) time course in healthy and diabetes (a), and in the functional CIAKI model (c). (b) shows the same data as in (a) but normalized w.r.t. baseline. For comparison, we also provide data from our previous study in a functional CIAKI model 5. Note the higher baseline R2* in diabetic rats compared to healthy controls (see (a)). The increased baseline R2* in diabetes rats is comparable to values following the administration of L-NAME and indomethacin in the functional CIAKI rats (see (c)). Post-contrast administration, R2* values rise fast followed by a slow washout phase in healthy SD, and relatively faster washout that reaches the baseline values in diabetic rats (see (b)). This may be related to the known persistent hyperfiltration in this model leading to increased urine flow (up to 10 times higher than controls) 6. Such cortical diuretic may effectively emulate pretreatment with furosemide which has been shown to be protective based on correlative biomarker neutrophil gelatinase-associated lipocalin (NGAL) data in CIAKI rats (ISMRM 2014).

CONCLUSION AND DISCUSSION
Even though our preliminary experience support the feasibility of using STZ treated diabetic rats to study the effects of iodinated contrast media, contrary to our hypothesis that the diabetic animals show responses similar to the functional CIAKI model, the results actually show the response to be more similar to those pre-treated with furosemide in the CIAKI model. This is most probably related to the increased urine flow in STZ treated animals 6. Further studies are warranted to document whether this leads to an inherent protection against CIAKI by evaluating independent biomarkers such as NGAL. Future studies should also evaluate whether fluid restriction in STZ treated animals may make their response similar to the functional CIAKI rats. Future studies may also have to evaluate alternate diabetic models such as type II diabetic rats.

REFERENCE
3. Li LP, JMRI. 2012;36:1162-1167
5. Lu-Ping Li JT, ISMRM 21st annual meeting. 2013;21:4155
6. Palm F. Diabetes/metabolism research and reviews. 2004;20:452-459