Effect of Octreotide on Intra-Renal Oxygenation as Estimated by BOLD MRI in Rats

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INTRODUCTION

Hyperglycemia is common in critically ill patients, even in those without diabetes mellitus [JAMA. 2003 Oct 15;290(15):2041-7]. Acute hyperglycemia induces an oxidative stress [J Clin Invest. 2001 Aug;108(4):635-6] and there is a strong association between hyperglycemia and mortality in critically ill elderly patients [J Am Geriatr Soc. 2008 Jun;56(6):1106-10]. Blood oxygenation level dependent (BOLD) MRI measurements in type I diabetic rats (following administration of streptozotocin (STZ)) had documented increased levels of R2* as early as two days following STZ [Invest Radio 2007 (42):157-162]. While these observations are in general consistent with renal tissue pO2 measurements by invasive probes [Diabetologia. 2003;46:1153–1160], the observed changes as early as 2 days post-STZ raises the possibility that hyperglycemia may have a direct effect on renal hypoxia. It is known that sustained hyperglycemia induce a pronounced reduction preferentially in renal medullary pO2 [Curr Diabetes Rev. 2007 Feb;3(1):53-65] and acute hyperglycemia by infusion glucose results in a reduction in meduallary pO2 as measured by BOLD MRI [Proc. ISMRM. 16 (2008): 2692].

Acute hyperglycemia preparation necessitates use of insulin inhibitors such as octeotride to produce sustained and sufficiently high levels of blood glucose levels [Proc. ISMRM. 17 (2009): 4140]. With the use of octeotride, both blood glucose levels and BOLD MRI R2* showed a significant and comparable increase to those in diabetic rats [Proc. ISMRM. 17 (2009): 4140]. Because octeotride is associated with vasoconstriction [Surg Endosc 2003; 17(10):1570-1572], it is necessary to know the magnitude of any direct effect of octeotride on renal oxygenation. The purpose of this study is to investigate the orctreotide effect on intra-renal oxygenation using BOLD MRI technique.

MATERIAL AND METHODS

The study protocol was approved by the Institutional Animal Care and Use Committee. Six male Sprague-Dawley rats (Harlan Laboratories, Madison, WI US, weight: 323 ± 15 gram) were anesthetized using inactin (100 mg/kg i.p., St. Louis, MO, USA). The femoral vein was catheterized for administration of chemicals. Imaging was performed on a 3.0T scanner (Magnetom Verio, Siemens, Germany) using a multiple gradient recalled echo sequence (TE=3.6-41.3ms; FOV=12x6cm; TR=69ms; BW=320Hz/pixel; FA=30°; NEX=20; matrix=256x256) to acquire 12 T2* weighted images. The rats' kidney was positioned in the middle of the eight channel standard knee coil. One transverse slice was selected in the middle of the kidney. Five sets of T2*-weighted images were acquired as baseline. Then octreotide (Sigma, Louis, MO, USA) 400 µg was administered as a bolus [J.of Gastroenterology and Hepatology, 22 (2007): 1872-1876]. Further sets of T2*-weighted images were obtained every 3 minutes for one hour. ROIs were chosen on T2* maps reconstructed inline on the scanner console in renal medulla and cortex, then were inverted in excel for R2*. The averaged readings of medullary R2* (MR2*) and cortical R2*(CR2*) were used as post data. The statistical significance of the differences between pre- and post-glucose R2* values was assessed using the two-tailed paired Student's t-test.

RESULTS
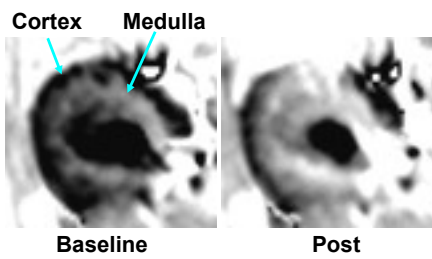
Figure 1: A inverted T2* maps from one representative rat with same display window setting generated on the scanner console. The arrows point to the outer medulla and cortex where the ROIs were defined. At baseline, renal cortex appears darker than renal medulla, implying better oxygenation. The relatively brighter medulla in the post-octreotide R2* map as compared to pre-octreotide map, signifies a decrease in medullary oxygenation.
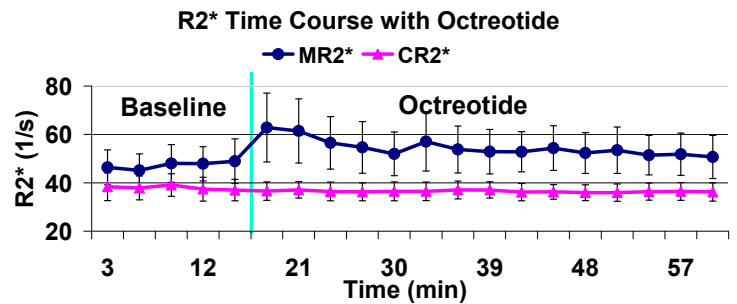
Figure 2. Averaged renal BOLD R2* time course before and after octreotide administration (mean ± SE) in six rats. The medullary R2* increases right after giving octreotide and slowly reverted back towards baseline. The cortical R2* did not show change over time.

	Glu (n=6)		Oct (n=6)		Oct+Glu (n=8)	
	MR2*	CR2*	MR2*	CR2*	MR2*	CR2*
Baseline	39.8 ± 3.8	34.8 ± 3.6	47.2 ± 7.6	37.9 ± 4.9	31.6 ± 2.1	26.9±1.6
Post	45.3 ± 3.8	38.1 ± 3.8	54.1 ± 9.9	36.4 ± 3.7	40.9 ± 3.5	30.9±2.7
% change	**14.2 ± 2.3**	9.7 ± 1.6	**13.8 ± 6.8**	2.0 ± 4.5	**30.1 ± 9.0**	14.0 ± 4.5

Table: Combining with the data from two previous reports, a summary of the averaged effect in R2* in different groups (mean ± SE): glucose only (Glu) [Proc. ISMRM. 16 (2008): 2692], octeotide only (Oct) [present study] and glucose infusion with pre-octeotide treatment (Oct + Glu) [Proc. ISMRM. 17 (2009): 4140]. A statistically significant increase in post MR2*, CR2* were observed in all three groups. The post is the average of all measurements when BGL reaches a plateau in glucose studies, and the post is the average of all points following octreotide administration in octeotide study. The change in Oct+Glu group (30.1%) is consistent with the additive effects from Glu (14.2%) and Oct (13.8%) groups.

DISCUSSION AND CONCLUSION

Our data clearly demonstrate increased R2* immediately following administration of octreotide and a trend towards normalization over the next hour. This may explain the earlier increase in R2* even before BGL increased in the previous study following infusion of glucose [Proc. ISMRM. 17 (2009): 4140]. The total R2* increase following glucose infusion with octreotide pretreatment is about twice as glucose or octreotide alone, suggesting an additive effect. The result shows for the first time that both insulin inhibition by octreotide and glucose contributed to the observed hypoxia status in this acute hyperglycemia model.

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