Evaluation of Intra-Renal Oxygenation During Water Diuresis: A Time Resolved Study Using BOLD MRI

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INTRODUCTION: The technique of blood oxygenation level-dependent (BOLD) MRI has been used in the past to non-invasively evaluate intra-renal oxygenation levels [*Kidney Int*. 1999; 55:294-8]. It was previously shown that renal BOLD MRI at 3.0T provides much higher sensitivity both in terms of R_2* and ΔR_2* in the medulla following administration of furosemide [*J Magn Reson Imaging*. 2004; 20:901-4]. Promising results have been reported recently using a newly implemented 3-D version of the multiple gradient-recalled echo (mGRE) sequence for BOLD MRI of the kidney [*Invest Rad*. 2005 (In Press)]. We sought to use the 3-D mGRE sequence at 3.0T to examine the temporal response of renal medullary oxygenation levels during water diuresis in a small set of selected young subjects. Based on the premise that this response is related to endogenous prostaglandin (PGE_2) stimulation, we also studied the effect of cyclooxygenase (COX) inhibition by naproxen.

METHODS: Five healthy young subjects (four female and one male, mean age = 22 ± 1.2 years) took part in this study. Each subject participated in two different data acquisitions separated by approximately two months. At each session, data was acquired pre- and post-waterload with the second study involving COX inhibition. For the COX inhibition study, 500 mg of naproxen was taken by mouth twice a day with meals for the four days preceding the study and also once on the morning of the study prior to the baseline scans. All of the participants gave informed consent according to the protocol approved by the Institutional Review Board prior to taking part in the study. All of the subjects were weighed and a sample of urine was collected prior to being placed in the magnet. Baseline BOLD MR images were then acquired in the supine position. To induce water diuresis, the subjects were asked to drink 20 ml of water per kg of body weight within a 15 minute time period. The first post-waterload scan lasted for 30 minutes at a rate of 1 scan every two minutes. Each subsequent scan was performed for 15 minutes at a rate of 1 scan every two minutes. Urine samples were collected between scans in order to monitor flow rates. Scans were performed after water loading until the following occurred: (i) the urine flow rate exceeded 5 ml per minute and (ii) the urine flow rate decreased from the previously measured flow rate.

All studies were performed on a short bore 3.0T Twin Speed scanner with Excite technology (General Electric Medical Systems, Milwaukee, WI). A 3-D mGRE sequence with 8 echoes (TR/TE/Flip Angle/BW/slice/Matrix = 25.5 ms/1.86- 22.9 ms/10º/83.3 kHz/5 mm/256 x 160 and 36 to 42 cm FOV with 80% phase FOV) was used to acquire data during a single breath-hold of 23 s. R_2* maps were constructed on an Advantage Workstation (General Electric Medical Systems, Milwaukee, WI) using FUNCTOOL by fitting a single exponential function to the signal intensity *vs.* echo time (TE) data. Approximately 40 regions of interest (ROIs) covering at least 10 pixels each were drawn on the anatomic templates and R_2* values were read off the corresponding R_2* maps. The ROIs were carefully placed in the cortex and medulla on all of the 6 slices that were acquired for both kidneys. The data from the ROIs were combined in order to obtain a single representative mean value for R_2* per subject per time point.

RESULTS: In all five subjects, BOLD MRI measurements (R_2*) showed an improvement in the oxygenation levels of the renal medulla post-waterload. In all subjects, the medullary R_2* values begin to approach those found in the cortex. However, the time to reach the maximum response was variable among the subjects. Figure 1 combines the temporal response data for the same subject from the waterload studies (with and without naproxen). Table 1 details the average R_2* values pre- and post-waterload for both the renal cortex and medulla in both waterload studies. Since the temporal responses were unique for each individual, the post-waterload R_2* values were calculated as the average of the time points when the response to waterload had reached an equilibrium plateau. Water diuresis significantly improved medullary oxygenation when comparing the post-waterload to pre-waterload R_2* values. However, the post-waterload R_2* values in the naproxen study were slightly higher than the baseline values. No significant difference was observed in the cortical R_2* values. To document the differences in response as shown in Figure 1 in a quantitative fashion, the slope of the R_2* *vs.* time curve was estimated (included in Table 1).

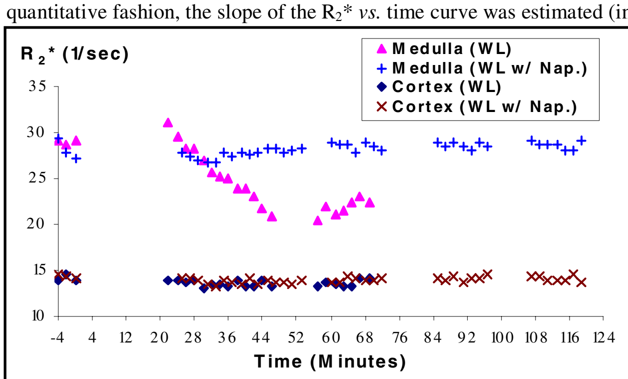

Figure 1 (Left): Time course of response to waterload (with and without naproxen) shown for one representative subject. The first three time points represent the baseline measurements. The presence of naproxen during water loading abolishes the temporal response associated with water loading. WL = Waterload; Nap. = Naproxen.

Table 1 (Below): Effect of waterload (with and without naproxen) on intra-renal oxygenation levels. Post-waterload values in the medulla were calculated as the average of the time points when the temporal response reached an equilibrium value. Also included are the average slope (rate of change in medullary R_2* over time) values of the temporal responses after water loading (with and without naproxen).

† implies $p<0.05$ by paired two tailed Student's *t*-test when compared to pre-waterload value. * implies $p<0.05$ by paired two tailed Student's *t*-test when compared to the waterload without naproxen study slope value.

	Cortex R_2* (s^{-1})		**Medulla R_2* (s^{-1})**		
	Pre-Waterload	Post-Waterload	Pre-Waterload	Post-Waterload	**Slope (1/s*min)**
Waterload without Naproxen	14.5 ± 0.6	13.5 ± 0.6	30.3 ± 1.1	22.8 ± 2.5 †	0.25 ± 0.096
Waterload with Naproxen	14.2 ± 0.2	13.9 ± 0.2	27.5 ± 1.2	28.5 ± 1.6 †	0.056 ± 0.031 *

DISCUSSION: The major outcome of this study is the reconfirmation of our previous observations with BOLD MRI on the effects of waterload and COX inhibition [*Kidney Int*. 1999; 55:294-8]. This is reassuring owing to the fact that a subsequent study had found that waterload produced a more variable response between subjects and in the same subject at different times [*J Magn Reson Imaging*. 2004; 19:610-16]. The present study was performed at 3.0T and utilized a newer implementation of the mGRE technique that allows for 3-D data to be acquired within a single breath-hold. Such fast acquisitions facilitated the monitoring of the temporal response during water diuresis without compromising spatial coverage. The overriding hypothesis for the interest in medullary hypoxia is that the kidneys have evolved to deal with it by developing a number of protective endogenous mechanisms. One of the well studied endogenous protective mechanisms is PGE_2 [*J Am Soc Nephrol*. 1990; 1:808-14]. Using BOLD MRI, we were able to observe improved oxygenation levels in the renal medulla during waterload. Pretreatment with naproxen resulted in a diminished BOLD MRI response to water diuresis. These results support the hypothesis that prostaglandins play a role in the maintenance of oxygenation status of the human renal medulla. A significant difference was observed when comparing the slope values of the temporal responses between the two studies. This observation helps support the ability of the technique to monitor acute drug induced changes in the regional hemodynamics within the kidney.

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