Comprehensive Assessment of Renal BOLD MRI using Multiple Moment Analysis: Application to Subjects with CKD

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PURPOSE

Renal hypoxia is thought to play a key role in the progression of chronic kidney disease (CKD) (1,2), which has lead to an increased interest in non-invasive techniques for the assessment of renal oxygenation. Renal blood oxygenation level-dependent (BOLD) magnetic resonance imaging is currently the only known non-invasive method that can be used to evaluate renal oxygenation in humans (3). However, experience to-date has led to conflicting reports regarding this method's ability to detect differences between controls and subjects with CKD. Non-uniform hydration status, varied oxygenation due to multiple etiologies and a variation in medication amongst the subjects may have led to some of the discrepancies (4). Recent studies have indicated the inherent subjective nature of traditional small-region of interest (ROI) techniques (5), which may also have contributed in part to the conflicting results. Here, we have tested the hypothesis that a method for analyzing the R2* distribution over the entire renal parenchyma will be able to detect quantitative changes in subjects following interventions and between groups of subjects with impaired kidney function.

METHODS

Subjects: All procedures were performed with approval from the institutional review board and written subject consent. A total of 47 subjects participated: controls (n=17; age: 41.6±12.9 yr; eGFR=97.1±15.0 ml/min/1.73m^2; 9 male/8 female), CKD (age: 61.9±10.4 yr; eGFR in the range of 30-90 ml/min/1.73m^2 (n=20) and < 30 ml/min/1.73m^2 (n=10); proteinuria: 0.83 ± 0.9; systolic BP: 130.7±25.6 mm Hg; diastolic BP: 70.7±15.5 mm Hg; avg. duration: 7.6 ± 5.2 yr; 15 male/15 female).

MRI Protocol: All experiments were performed on a 3T whole-body scanner (MAGNETOM Verio, Siemens Healthcare, Erlangen, Germany). BOLD Parameters: mGRE, breath-hold, FOV: 360x245mm, slices: 5, thickness: 5.0mm, Matrix: 256x176, TR: 62ms, 8 equally spaced echoes (3.09–32.3ms). Measurements were made at baseline and 15 minutes after iv-administration of 20 mg of furosemide.

R2*: R2* was calculated on a voxel-by-voxel basis, using a log-linear least squares regression method. On the magnitude images, a threshold of 20 (a.u.) was used to mask any voxels that decay to the noise floor. A single observer defined ROIs in the cortex and medulla and segmented the entire renal parenchyma.

Moments: Following manual segmentation of the entire renal parenchyma, the R2* distributions were analyzed using four sample moments. The first moment is simply the sample mean, μ_1, and the next three are central moments, which are computed around the mean. Given the mean μ_1, the n$^{\text{th}}$ central moment is $\mu_n = \frac{1}{N}\sum_{i=1}^{N}(I_i - \mu_1)^n$ for $N > 1$. We also estimated the mode, m, or the R2* value corresponding to the peak, of each parenchymal R2* distribution. A kernel density estimate with Gaussian kernels and automatic bandwidth calculation was used to estimate the continuous probability distribution function and the mode was then calculated from this distribution.

Statistics: A Wilcoxon non-parametric test was used to assess changes between baseline and post-furosemide R2* measurements, separately in control and CKD groups, for each region. Control and CKD groups were compared in each region and at each stage for statistically significant differences with a Mann-Whitney U test. To help estimate the effect size for each comparison, we report Cohen's d. We report values as being significant when both a substantive effect size, (i.e. $|d| \geq 0.5$) and statistical significance (i.e. $p<0.05$) are satisfied. Multiple comparisons were corrected for by applying the Holm-Bonferroni method to limit the family wise error rate in reporting false rejections of the null hypothesis.

RESULTS

Furosemide: A significant change was observed in the medullary region of the control group (30.2 ± 5.0 to 22.5 ± 5.0, p<0.01; d=1.28). No significant changes were observed in the cortex for either group. In the moment analysis, significant changes were observed in m (p<0.01; d=0.56), μ_1 (p<0.01; d=0.8) and μ_2 (p<0.01; d=0.7). No significant changes were observed in the CKD group with moment analysis.

Group Comparison: A significant difference was observed between controls ($19.8 \pm 3.5\ s^{-1}$), and CKD ($24.1 \pm 7.0\ s^{-1}$) in the renal cortex (p<0.05; d=-0.71). Moment analysis showed a significant difference in two of the moments, μ_2 and μ_3 (p<0.05; d>0.83) at baseline and four parameters, m, μ_1, μ_2, μ_3 (p<0.05; d>0.67) following furosemide.

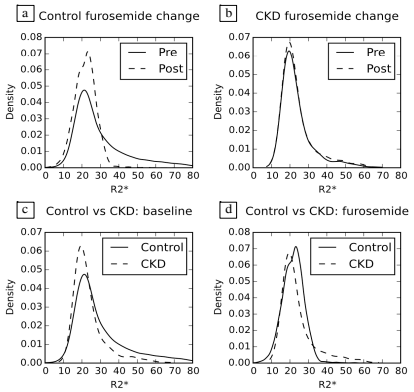

Figure 1: Example kernel density plots of typical cases for each of the comparisons performed. (a) shows pre vs. post-furosemide in a control subject. This is a distribution where the contribution from the medulla to the slice is typically more than the cortex. (b) depicts pre vs. post-furosemide in a representative CKD subject. (c) shows data from control subject (in a) vs. CKD subject (in b) at baseline. (d) shows control vs. CKD data following furosemide.

DISCUSSION

Conventional ROI Analysis: Significant changes in the renal medulla following furosemide were observed in control subjects, which is consistent with several previous reports (6–9). When comparing the subject groups using conventional ROI analysis, only the cortex showed a significant difference, with CKD subjects showing a higher cortical R2* than the controls.

Moment Analysis: Figure 1 shows an example of the kernel density plots for a control and CKD subject.
In control subjects, we found significant differences in several of the parameters following furosemide. Differences between controls and CKD were also apparent. These observations were in general agreement with the conventional ROI analysis.

CONCLUSION

Moment analysis provides a method for performing inter- and intra-subject comparisons without having to place regional ROIs, which becomes challenging in advanced CKD when cortico-medullary contrast is reduced. For the first time, we have observed that analysis based on the entire renal parenchyma without any *a priori* assumptions about regional distributions is able to demonstrate differences following furosemide administration and between control and CKD groups. Further studies maybe necessary to investigate how to interpret the changes observed with moment analysis in terms of changes in intra-renal oxygenation.

REFERENCES (1) pmid:16291837, (2) pmid:9551436, (3) pmid:8989140, (4) pmid:22419042, (5) pmid:22183077, (6) pmid:2914562, (7) pmid:10792627, (8) pmid:24760031, (9) pmid:15503343