Magnetic Resonance Diffusion Tensor Imaging and Diffusion Compartmental Modeling in an Animal Model of Chronic Kidney Disease

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Purpose:

According to National Health and Nutrition Examination Survey (NHANES), Chronic Kidney Disease (CKD) affects 25% of the US population over age 60[1]. Renal fibrosis, a common pathological consequence of CKD, is a progressive process that ultimately leads to end-stage renal failure that requires dialysis or kidney transplantation[2]. There is a compelling need for non-invasive biomarkers that track changes in the tissue microenvironment associated with CKD. Several studies using magnetic resonance diffusion tensor imaging (DTI) have been proposed as imaging biomarkers for CKD[3]. In this study, in addition to DTI, we explored a diffusion-compartmental modeling technique[4] to study the microstructures of hypoxia induced animal models of CKD.

Method:

Preparation of the animal CKD model: Experiments were performed in 4 Wistar Rats using protocols approved by the Institutional Animal Care and Use Committee (IACUC). Two days prior to the first magnetic resonance imaging (MRI) scan; surgical intervention in right renal artery was performed in all the animals to create hypoxia induced renal fibrosis. The MRI scans were repeated at an interval of approximately one month. During the imaging session, the rats were sedated and kept in head-first supine position. **_MRI imaging:_** The MRI diffusion pulse sequence was a single-shot spin-echo echo-planar imaging (SS-SE-EPI) sequence with multiple diffusion-weighting b-values (i.e. 3 shells with b-values of 150, 300 and 450 s/mm^2) and multiple diffusion-weighting directions at each shell (i.e., 10, 19 and 30, respectively). Diffusion directions in each shell and in the projected sphere with all directions (i.e., total 59) were optimized for uniform diffusion sampling in the spherical space[5]. The repetition time (TR) is 2200 ms and echo time (TE) is 73.6 ms. A total of four signal averages was performed. The imaging parameters were field-of-view (FOV) = 128 x 64 mm, matrix size = 128 x 64, isotropic voxel size of 1 mm^3, and 20 oblique coronal slices. **_Image data processing:_** DTI derived parameters including axial diffusivity (D_a), radial diffusivity (D_r), mean diffusivity (MD), and fractional anisotropy (FA) were computed[6]. The diffusion compartmental model originally proposed for the brain called neurite orientation dispersion and density imaging (NODDI)[4] was modified to fit the water diffusivities of kidneys. The NODDI model with Watson stick framework produces the volume fraction of stick like diffusion compartment that may explain
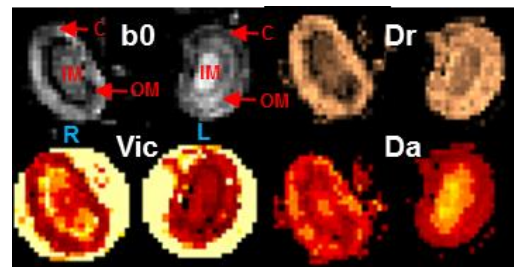

Figure 1: The DTI and Diffusion compartmental modeling parameter for RAT Kidney 2 days after surgical intervention. The Cortex (C), the Outer Medulla (OM) and Inner Medulla (IM) are shown in raw b0 maps. The orientation of the images follows radiology convention.

the active diffusion (transport) of water in the interstitial space between renal tubules, ellipsoid like diffusion compartment that may explain diffusion inside renal tubule, and a fast isotropic diffusion to account for the pseudo-diffusion term relating to bulk vascular flow. The normalized diffusion intensity was fit with a non-linear mathematical model given by A = $(1-V_{iso})$ $(V_{ic}A_{ic}+(1-V_{ic})$ $A_{ec})$ + $V_{iso}A_{iso}$; where V_{ic} and V_{iso} are the volume fraction of active water transport and free diffusion compartments in the kidney, respectively. A_{ic}, A_{ec} and A_{iso} are the normalized diffusion signal contribution from stick, tubule and free diffusion compartments, respectively. In the raw DW data, the b-value=0 volume clearly shows three distinct layers in the rat kidney representing the inner medulla, outer medulla and cortex (Figure1). Non-overlapping ROI's were constructed from the b-value =0 images.

Results:

On post-surgical day 2, the overall water diffusivity (i.e., mean diffusivity (MD)) decreased significantly in the outer medullae and inner medullae of the surgical kidneys (Figure 2 B green bars). In the compartmental model, the volume fraction of the stick (interstitial) diffusion compartment (V_{ic}) in right outer and inner medulla was significantly increased compared to the left (Figure 2A blue bars), whereas the volume fraction of water diffusion inside the tubules (V_{ec} = $(1-V_{ic})$) decreased significantly. In addition, isotropic free diffusion compartment (V_{iso}) was significantly lower in the inner medullae of the right kidneys. The axial diffusivity (D_a) that may describe the diffusion parallel to the tubules decreased significantly in outer and inter medullae of the right surgical kidneys (Figure 2 B blue bars). The radial diffusivity (D_r) that may describe the water diffusion perpendicularly to the renal tubules decreased significantly in only the outer medullae of the right kidneys (Figure 2B gray bars). While FA shows high value in the inner medullae for both left and right kidneys, no significant results were found between left and right kidneys and between two time points. Over the one-month period of time, right inner medullae continued the significant changes in the diffusivity measurements (Figure 2C and D, right groups), but the diffusivities remained similar in the outer medullae (Figure 2 C and D, middle groups). No significant findings were found in the renal cortices between the right and left kidneys on post-surgical day 2 (Figure 2 A and B). Interestingly, the right renal cortices did have significant increase in V_{ic} and decreases in D_a, D_r, and MD over the one-month time period (Figure 2C and D).
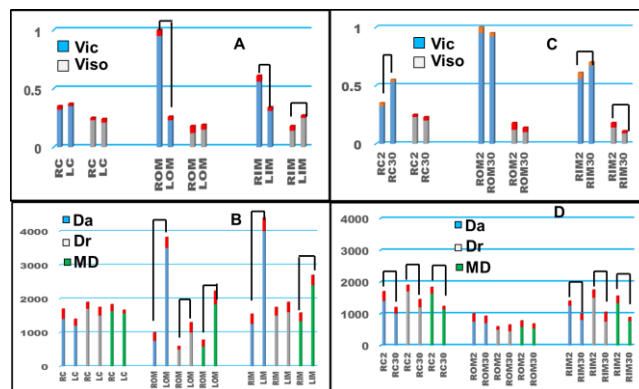

Figure 2: Diffusion Compartmental (Figure 2A) and DTI (Figure 2B) parameters for Right Cortex (RC) and Left Cortex (LC), Right Outer Medulla (ROM) and Left Outer Medulla (LOM) and Right Inner Medulla (RIM) and Left Inner Medulla (LIM) on post-surgical day 2. (Figure 2C) Is the time series study of diffusion compartmental parameters and (Figure 2D) for DTI parameters for the right kidneys at post-surgical day 2 and 30, respectively. The bars represent diffusion measurements of all four rats. The overhead connecting lines represent significant statistical student t-test with p-value < 0.01.

Discussions and Conclusion:

The DTI and NODDI analogous diffusion compartment derived parameters are sensitive to the micro-structural changes in kidneys after surgical hypoxia intervention. The outer and inner medullae appear most sensitive to the surgical hypoxia intervention as early as post-surgical day 2. The preliminary result suggests that water diffusion decreases due to renal fibrosis, and more so inside the Henle tubules. In post-surgical day 30, renal cortices start to show changes in water diffusivities while inner medullae continue pathological changes. The NODDI compartmental model shows promising preliminary results in revealing renal microenvironments under the influences of hypoxia induced renal fibrosis. Further study is required to optimize and validate the model.

References: 1. Tonella M., et al., Nephrol Dial Transplant 2014;29 (2):221-224. 2. Fukagawa M., et al., Nephrol Dial Transplant 1999;14(2):2793-2795. 3. Ries M. et al., J. Magn. Reson. Imaging. 2001;14(1):42-49. 4. Zhang et al., Neuroimage 2012; 1000-1016. 5. Caruyer, E., et al., Magnetic Resonance in Medicine 2013;69:(6)1534-1540. 6. Basser et al. J Magn Reson B 1994;103(3):247-54.