Diffusional kurtosis imaging: Towards optimal subacute assessment of the microenvironment of ischemic tissue

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Introduction MRI is a robust technique for clinical assessment of stroke. Particularly, conventional diffusion-weighted imaging (DWI) has been extensively used for ischemic tissue staging due to its superior sensitivity to ischemic injury (1,2). However, the diagnostic value of apparent diffusion coefficient (D_{app}) obtained from conventional DWI is often dwarfed by pseudonormalization of D_{app} as a result of the presence of vasogenic edema during subacute stroke (3). It is therefore necessary to find an alternative technique that is less susceptible to free fluid contamination, and more sensitive and specific to the underlying structural changes occurring along the course of ischemic infarction. One of the potential techniques is diffusional kurtosis imaging (DKI) which measures non-Gaussianity of water diffusion (4). Apparent diffusional kurtosis (K_{app}) reflects tissue complexity due to the presence of cell membranes and organelles, and water compartments with differing diffusion properties (4). The goal of this study was therefore to explore what additional value DKI could offer to ischemic stroke diagnosis, especially during the subacute phase, in an established transient middle cerebral artery occlusion (MCAO) rat model (5). Monte Carlo simulations were also performed to understand the effect of changes in cell volume fraction, membrane permeability and radius on DKI contrast, all of which could occur during subacute phase. Comparisons were made with conventional diffusion metric.

Methods *In vivo experiments:* N=6 male Sprague Dawley rats (250-300g) were subject to 45 mins MCAO as described previously in ref (5). MRI experiments were subsequently performed using a 7T magnet at 30, 145 mins, 24, 48 hrs (N=3) and 7 days (N=3) after occlusion. In 2 animals, MRI was also acquired from 145 to 380 mins post-occlusion every 30 mins. Cerebral blood flow map was obtained using continuous arterial spin labeling to confirm the occlusion. Diffusion-weighted images (DWIs) with 2 b-values (1.2 and 2.5 ms/μm^2) along 30 diffusion encoding directions were acquired using single-shot SE-EPI with NEX=4. Other imaging parameters were: δ/Δ = 4/16 ms, acquisition matrix = 96 x 96, FOV = 2.56 x 2.56 cm^2, TR/TE = 3 s/35 ms. Mean diffusivity (MD), and mean kurtosis (MK) maps were estimated by fitting all DWIs to the DKI model (4). Region-of-interests (ROIs) of infarct core within striatum were defined using MD (<0.7μm^2/ms) maps at 30 mins post-occlusion. Contralateral ROIs were also obtained. ROIs with similar location and size were applied on subsequent time points.

Simulation: We implemented a random walk model and simulated a PGSE DWI experiment in C using the same imaging parameters as in vivo experiments. 60,000 spins were randomly placed in a 2D space, assuming an isotropic diffusion, with randomly packed intra- and extracellular compartments. The cell sizes were statistically distributed to simulate the tissue heterogeneity (standard deviation/mean of cell radius was 0.7). The intra- and extra-cellular diffusivity were 1.0/2.5 μm^2/ms, respectively, and the membrane permeability was defined in Szafer et al (6). Other simulation parameters were: cell membrane permeability (κ): 0.01, 0.1, 0.2 mm/s; cell radius (r): 2.5, 3.5, 5 μm; cell volume fraction (f): 0.5, 0.575, 0.65, 0.725, 0.79. The DKI model was fitted to the data using the Levenberg-Marquardt algorithm.

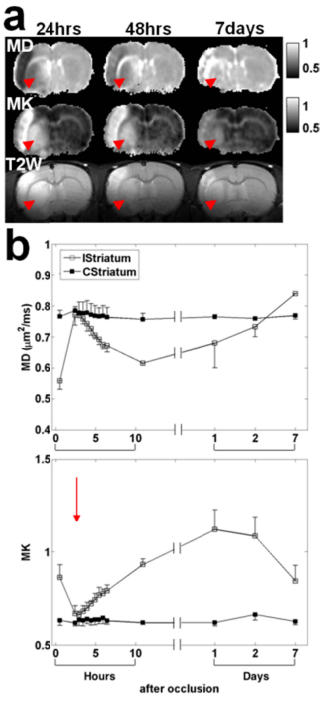

Fig.1 (a) MD, MK maps and T2W images of a rat obtained at 24, 48 hrs and 7 days after occlusion. The MCAO duration was 45 mins. Red arrow heads indicate where MD and T2W started pseudonormalizing. **(b)** ROI measurements (mean ± SD) of MD and MK of striatum of all animals subjected to transient MCAO. Red arrow indicates the time after reperfusion.

Results and Discussions **Fig.1a** shows MD, MK maps and T2W images of a representative rat obtained at 24, 48 hrs and 7 days after occlusion. The infarct core consistently showed elevated MK across all time points. It is evident that both MD and T2W pseudonormalized in these time points (indicated by red arrow heads) as a result of vasogenic edema (3). **Fig.1b** shows ROI measurement of MD and MK in the striatum. MD of ischemic tissue started to pseudonormalize from 11 hrs and reverted to normal value at 2 days post-occlusion, while MK remained elevated up to 7 days post-occlusion. The fact that MK did not pseudonormalize amid the presence of vasogenic edema suggested that diffusional kurtosis is much less susceptible to partial volume contamination from free fluid. Such claim is corroborated by the results by Hu et al (7) showing the minimal effect of CSF (7.6%) on MK but significant change in MD (-31.3%) after CSF suppression using inversion recovery. **Fig.2** shows the change in D_{app} and K_{app} with respect to **(a)** κ and f while keeping r at 2.5 μm, and **(b)** r and f while keeping κ at 0.1 mm/s obtained from 2D Monte Carlo simulations. f had apparently more effect on D_{app} than K_{app}. The percent change of D_{app} from highest to lowest f ranged from 53 to 85 %, and 45 to 63 % in **Fig.2a** and **b** respectively. But K_{app} ranged only from 28 to -4 %, and 19 to 11 % in **Fig.2a** and **b** respectively. Results from simulations further supported the notion that D_{app} is heavily contaminated by biological event that causes change in cell volume fraction (such as vasogenic edema or partial volume effect from free fluid) rather than change in structural integrity as compared to K_{app}. In other words, diffusional kurtosis is a more sensitive and specific biomarker for changes in structural heterogeneity, especially cell membrane permeability (see **Fig2a**). More comprehensive simulations will be performed in future study by using a wide variety of cell structural parameters.

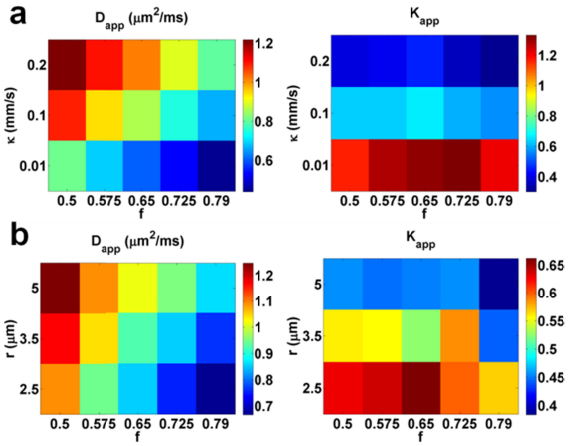

Fig.2 Variation of apparent diffusion coefficient (D_{app}, left column) and apparent diffusional kurtosis (K_{app}, right column) with **(a)** membrane permeability (κ) and cell volume fraction (f) while keeping cell radius (r) at 2.5 μm, and **(b)** r and f while keeping κ at 0.1 mm/s obtained from 2D Monte Carlo simulations.

Conclusions The current study showed that MK is a sensitive biomarker for ischemic injury, especially subacute stroke where MD and T2W pseudonormalize as a result of vasogenic edema. DKI could potentially complement conventional DWI for improving stroke diagnosis, particularly during subacute phase.

References 1. Baird, A.E. & Warach, S. *J Cereb Blood Flow Metab* **18**, (1998). 2. Merino, J.G. & Warach, S. *Nat Rev Neurol* **6**, (2010). 3. Knight, R.A., *et al. Stroke* **25**, (1994). 4. Jensen, J.H., *et al. Magn Reson Med* **53**, (2005). 5. Shen, Q., *et al. J Cereb Blood Flow Metab* **24**, (2004). 6. Szafer, A., *et al. Magn Reson Med* **33**, (1995). 7. Hu, C., *et al.* ISMRM (2008).