

Diffusion kurtosis is sensitive to hyperacute cerebral ischemia and increases with ischemic progression without renormalization

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Introduction

The outcome of stroke treatment relies in large part on reliable staging of ischemic tissue, and it remains a challenge to find the optimal MR techniques as such¹. Owing to the high sensitivity and specificity of conventional MR diffusion-weighted imaging in ischemic tissue delineation^{1,2}, additional clinically relevant information regarding ischemic tissue microstructure can be probed using higher order diffusion techniques. One of the potential candidates is the diffusion kurtosis imaging (DKI) model which measures non-Gaussianity of water diffusion (a major pitfall of conventional diffusion model is that it assumes Gaussian diffusion) as an indicator of tissue complexity, such as tissue heterogeneity and cell membrane permeability³. DKI application to stroke remains limited and only a few human studies have been reported⁴⁻⁶. The goal of this study was to further explore what additional DKI data could offer in ischemic stroke in an established transient middle cerebral artery occlusion (MCAO) rat model during the hyperacute and acute phases. Comparisons were made with perfusion, conventional diffusion, and T2-weighted (T2W) MRI.

Methods

Seven Male Sprague Dawley rats (250-300g) were subject to 45min MCAO⁷. MRI experiments were subsequently performed using a 7T/30cm magnet immediately (denoted as 0hr, N=7), 1.5hr (N=7), 24hr (N=3) and 48hr (N=4) after reperfusion. A surface coil (2.3cm ID) with active decoupling was used for brain imaging and a neck coil for perfusion labeling. Cerebral blood flow (CBF) map was obtained using continuous arterial spin labeling. Diffusion-weighted images (DWIs) with 2 non-zero b-values (1.2 and 2.5ms/μm²) along 30 diffusion encoding directions were acquired using single-shot SE-EPI with NEX=2. The entire imaging block took ~13min. Mean diffusivity (MD), fractional anisotropy (FA) and mean kurtosis (MK) maps were estimated by fitting DWIs to the DKI model³. Region-of-interests (ROIs) of infarct core within cortex and striatum of both hemispheres were defined using MD (<0.7μm²/ms) and FA (<0.25) maps at 0hr, and ROIs with similar location and size were applied on subsequent time points.

Results

Fig.1 shows the CBF, FA, MD, MK maps and T2W images of a representative rat obtained immediately (0), 1.5, 24 and 48 hrs after reperfusion. The infarct core consistently showed decreased MD and elevated MK across all time points. MK of the ICortex and IStriatum at 48hr after reperfusion increased to values higher than before reperfusion, while MD simply returned to a value closer to that of contra-lesion hemisphere (MD renormalization). Another interesting observation is that the FA of cortex and striatum gradually decreased with time after stroke. In addition, MK map clearly better delineates the infarct core as compared to T2W image. Fig.2 shows the percentage change (mean ± standard deviation) in ROI measurements of the infarct core in cortex and striatum in the ipsi-lesion (ICortex and IStriatum) with respect to contra-lesion hemispheres (CCortex and CStriatum). Both MD and MK are sensitive to ischemic changes in the hyperacute phase, and both transiently recovered, suggesting both indicating potential tissue salvageability. In contrast, MD renormalized at 24 hrs whereas MK continued to increase, indicating MK may offer better disease staging. FA decreased with time, but was not sensitive to ischemic changes during the hyperacute phase.

Discussions and Conclusions

MK is highly sensitive in hyperacute stage at 0hr, an increase of ~50% as compared to normal hemisphere. MK increased with time in the acute phase (1-48 hrs). A possible explanation is that during the acute phase, cells are in transition to necrosis¹, which likely increases tissue heterogeneity in the infarct core. This notion is further support by the gradual decrease in FA as infarct evolved suggesting that the coherences in cell packing have been compromised. FA however is not sensitive to ischemic injury in the hyperacute stage.

More importantly, MK increases with time, offering the potential to stage the infarct severity. The increasing diffusional kurtosis in ischemia suggests increased heterogeneity of tissue microstructures. By contrast, MD renormalizes in the late acute and chronic phase, which is less informative for disease staging. Finally, at 48 hrs, MK lesion matched T2W infarct delineation.

A disadvantage of DKI is its longer acquisition by 50-100%. However, with advances in MRI, this will be less limiting and DKI acquisition can also be optimized to reduce scan time⁸.

In conclusion, these results show that MK is a sensitive index of hyperacute ischemic injury and MK increases with time from the hyperacute to the acute phase, offering a valuable tool to better stage ischemic brain injury. This is in contrast to DWI and ADC changes which renormalize at 24-48 hrs after stroke. T2 has been shown to renormalize. DKI thus offers unique clinically relevant information, as well as complementary information to existing modality, to probe tissue microstructural changes in ischemic brain injury, ultimately improving clinical stroke diagnosis. Future studies will include MCAO of different durations, and histological analyses to correlate infarct severity with MK value.

References: 1. Baird, *et al. J Cereb Blood Flow Metab* **18** (1998). 2. Merino, *et al. Nat Rev Neurol* **6** (2010). 3. Jensen, *et al. Magn Reson Med* **53** (2005). 4. Jensen, *et al. ISMRM* (2010). 5. Peeters, *et al. ISMRM* (2010). 6. van Westen, *et al. ISMRM* (2010). 7. Shen, *et al. J Cereb Blood Flow Metab* **24** (2004). 8. Poot, *et al. IEEE Trans Med Imaging* **29** (2010).

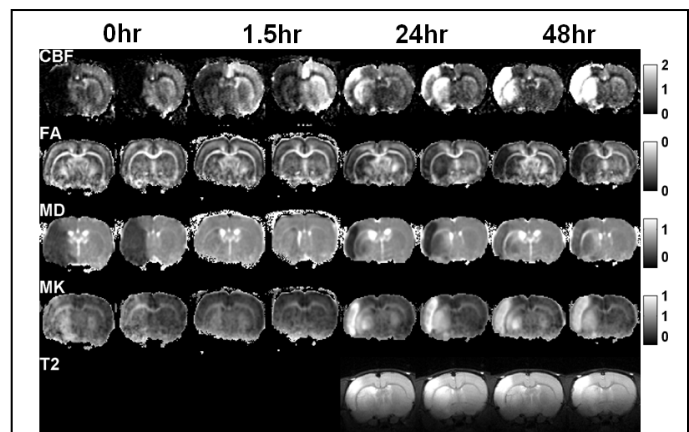


Fig.1 CBF, FA, MD, MK maps and T2W images (two brain slices) of a representative rat obtained immediately (0hr), and 1.5, 24hr and 48hr after reperfusion. The MCAO duration for this rat was 45 mins.

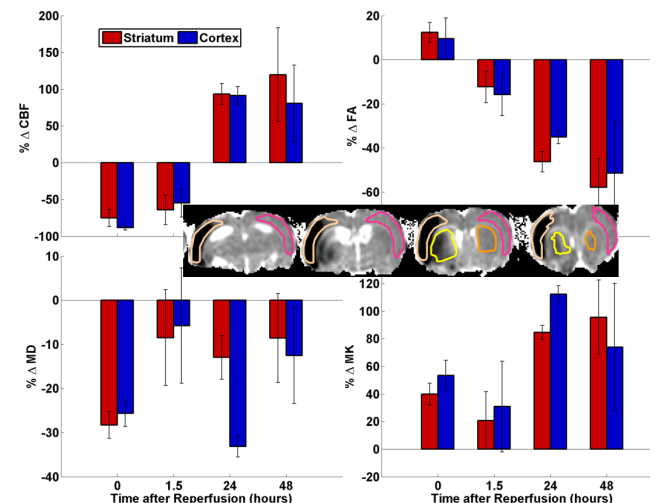


Fig.2 Percentage change (mean ± S) in ROI measurements of CBF, FA, MD and MK of the infarct core in cortex and striatum of the ipsi-lesion (ICortex and IStriatum) with respect to contra-lesion hemispheres (CCortex and CStriatum). ROI definitions on MD maps obtained at 24hr after reperfusion are shown. 0-1.5hr (N=7), 24hr (N=3), 48hr (N=4).