Diffusivity/Kurtosis Mismatch in Acute Ischemic Stroke: Potential Indicator of Reversible Ischemic Injury

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Introduction Diffusion-weighted imaging (DWI) detects ischemic lesion within minutes after stroke onset, significantly earlier than conventional relaxation MRI [1]. Ischemic lesion with mean diffusivity (MD) abnormality has often been considered as ischemic core in which tissue is proceeding to infarction. However, MD lesion, if reperfused promptly, is reversible yet its long term outcome is rather variable [2]. As such, complementary imaging markers are needed to better characterize heterogeneous ischemic tissue damage for prediction of final outcome. By providing detailed properties on water diffusion and therefore more specific information on microstructural environment, diffusional kurtosis imaging (DKI) may stratify heterogeneous ischemic cerebral tissue [3]. In this study, we hypothesized that measurement of mean kurtosis (MK) by means of DKI may complement conventional DWI in assessing acute cerebral ischemic injury by providing additional information. The aim of this study was to examine and compare MD and MK lesions during middle cerebral artery occlusion (MCAO) and after reperfusion in a rat model of transient ischemic stroke.

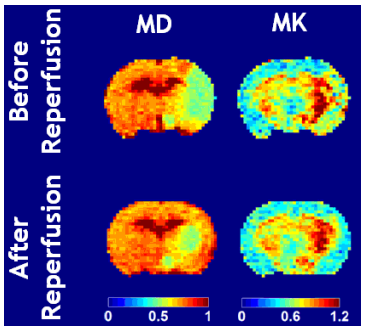

Fig. 1. MD (in 10^{-3} mm^2/s) and MK maps of a representative rat brain during MCAO and after reperfusion.

Materials and Methods Animal Model: Transient middle cerebral artery occlusion (MCAO) was induced in adult male Wistar rats (260-300 g; *N* = 18). After approximately 90 min of cerebral ischemia, reperfusion was established by withdrawal of the suture in animals outside the magnet. The animals were scanned at approximately 30 min after onset of MCAO and again 30 min after reperfusion. Only 17 animals (*N* = 17) were included in data analysis as one animal did not survive during the MRI scan. MRI and Data Analysis: MRI experiments were performed on a 4.7T Bruker MRI scanner. Multi-slice single-shot spin-echo DW EPI was obtained with 8 b-values of 250, 500, 750, 1000, 1500, 2000, 2500 and 3000 s/mm^2 in 6 diffusion gradient directions (FOV = 25×25 mm^2, imaging matrix = 64×64, slice thickness/gap = 1.8/0.2 mm, number of slices = 5, TR/TE = 2500/40.5 ms, and NA = 4). Apparent diffusion coefficient (ADC) and apparent kurtosis coefficient (AKC) maps along each diffusion gradient direction were estimated simultaneously by least-square fitting the DW signals non-linearly to $S(b) = S(0) \exp(-bD_{app} + 1/6\, b^2 D_{app}^2 K_{app})$, where S(b) is the DW signal at a particular b-value and S(0) is the signal without diffusion weighting. MD and MK maps were then calculated as the average of the ADC and AKC maps along all applied diffusion gradient directions, respectively [4]. Region of interest (ROI) analysis was performed manually in one slice with substantial MD and MK lesions in each animal. Specifically, MD and MK lesions were defined as regions of abnormality in MD and MK maps, respectively, as compared with the contralateral side. Repeated measures analysis of variance (ANOVA) with Tukey's multiple comparison test was performed to compare the MD and MK lesion volumes and values before and after reperfusion.

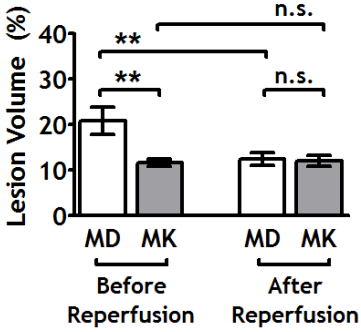

Fig. 2. MD and MK lesion volumes, expressed as percentage of the brain in the same section, before (during MCAO) and after reperfusion (*N* = 17). Error bars represent SEM. ** for *p*-value < 0.01, * for *p*-value < 0.05, and n.s. for insignificance.

Results Fig. 1 shows the MD and MK maps of a representative animal before and after reperfusion. Prior to reperfusion (i.e., during MCAO), obvious mismatch between MD and MK lesions could be observed. Specifically, MD lesion was remarkably larger than MK lesion during hyperacute phase of cerebral ischemia. It is worthwhile to note that, subsequent to reperfusion, volume of MD lesion reduced to that similar to MK lesion. In contrast, MK lesion after reperfusion exhibited only negligible change in lesion volume, as compared with that during MCAO. Fig. 2 shows the comparisons of MD and MK lesion volumes before and after reperfusion, expressed as percentage of the brain in the same section. Briefly, during MCAO (before reperfusion), lesion volume depicted by MD (22.3 ± 7.7 %) was found to be significantly larger ($p < 0.01$) than that by MK (12.0 ± 1.8 %). Following 30 min of reperfusion, lesion volume between MD (14.3 ± 4.4 %) and MK (13.0 ± 3.6 %) showed no significant difference. It is important to note that, after reperfusion, MD lesion volume significantly decreased ($p < 0.01$) while MK lesion volume revealed no significant change, as compared with those during MCAO. MK lesion volumes expressed as a percentage of the MD lesion volumes were 59.5 ± 19.2 % and 93.3 ± 13.2 % before and after reperfusion, respectively. Fig. 3 shows the MD and MK values of the contralateral non-ischemic tissues and ipsilateral ischemic lesions before and after reperfusion. During MCAO, MD of the ischemic lesions (0.55 ± 0.03 x 10^{-3} mm^2/s) was significantly lower ($p < 0.01$) than that of the non-ischemic tissues (0.78 ± 0.02 x 10^{-3} mm^2/s). On the other hand, MK of the ischemic regions (1.00 ± 0.05) was found to be significantly higher ($p < 0.01$) than that of the contralateral control areas (0.70 ± 0.04). Similarly, following reperfusion, MD of the ischemic lesions (0.61 ± 0.04 x 10^{-3} mm^2/s) was significantly less ($p < 0.01$) than that of the non-ischemic regions (0.77 ± 0.02 x 10^{-3} mm^2/s), while MK of the ischemic tissues (0.94 ± 0.06) was significantly higher ($p < 0.01$) than that of the contralateral normal tissues (0.69 ± 0.03). In addition, MD of ischemic lesions after reperfusion was noted to be significantly higher ($p < 0.01$) than that during MCAO. Such percentage rise in MD was 10.3 ± 6.0 %. MK of ischemic tissues after reperfusion was significantly lower ($p < 0.01$) than that before reperfusion, with percentage drop of 5.9 ± 6.6 %.

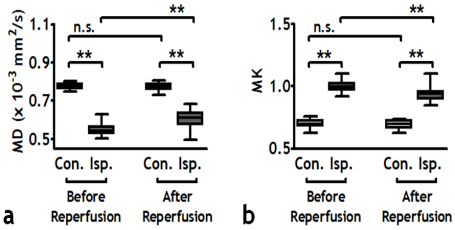

Fig. 3. MD (**a**) and MK (**b**) values of the contralateral (con.) non-ischemic and ipsilateral (isp.) ischemic tissues before and after reperfusion.

Discussions The experimental results in this study demonstrate that substantial mismatch between MD and MK lesions existed during MCAO, yet largely vanished following reperfusion, in a transient ischemic stroke model. These initial findings suggest that diffusional kurtosis in addition to water diffusivity may improve understanding of the diffusion changes related to microstructural disturbances following acute cerebral ischemic injury. Furthermore, DKI may assist the prediction of irreversible ischemic injury and susceptible infarction, and hold great promise on evaluation and management of patients with acute ischemic stroke.

References [1] Moseley ME et al. MRM 1990;14:330-346. [2] Fiehler J et al. Stroke 2002;33:79-86. [3] Jensen JH et al. NMR Biomed 2011;24:452-457. [4] Jensen JH et al. MRM 2005;53:1432-1440.