Background and Purpose—Ischemic tissue damage is heterogeneous, resulting in complex patterns in the widely used diffusion-weighted MRI. Our study examined the spatiotemporal characteristics of diffusion kurtosis imaging in an animal model of transient middle cerebral artery occlusion.

Methods—Adult male Wistar rats (N=18) were subjected to 90 minutes middle cerebral artery occlusion. Multiparametric MR images were obtained during middle cerebral artery occlusion and 20 minutes after reperfusion with diffusion-weighted MRI obtained using 8 b-values from 250 to 3000 s/mm² in 6 diffusion gradient directions. Diffusion and kurtosis lesions were outlined in shuffled images by 2 investigators independently. T₂ MRI was obtained 24 hours after middle cerebral artery occlusion to evaluate stroke outcome.

Results—Mean diffusion lesion (23.5% ± 8.1%, percentage of the brain slice) was significantly larger than mean kurtosis lesion (13.2% ± 2.0%) during middle cerebral artery occlusion. Mean diffusion lesion decreased significantly after reperfusion (13.8% ± 4.3%), whereas mean kurtosis lesion showed little change (13.0% ± 2.5%) with their lesion size difference being insignificant.

Conclusions—We demonstrated that mean diffusion/mean kurtosis mismatch recovered reasonably well on reperfusion, whereas regions with concurrent mean diffusion and mean kurtosis deficits showed poor recovery. Diffusion kurtosis imaging may help stratify heterogeneous diffusion-weighted MRI lesions for enhanced characterization of ischemic tissue injury. (Stroke. 2012;43:2252-2254.)

Key Words: acute ischemia ■ diffusion ■ kurtosis

Diffusion-weighted imaging (DWI) detects severely damaged ischemic tissue that is likely to infarct and has been widely used in stroke imaging.¹,² However, tissue damage within DWI deficit is heterogeneous, which may partially recover with prompt treatment. There have been no well-established techniques capable of stratifying heterogeneously damaged DWI lesion.³,⁴ Diffusion kurtosis imaging is an emerging MRI technique that measures the degree of the non-Gaussian water diffusion and is sensitive to microscopic structural changes.⁵ Indeed, diffusion kurtosis imaging has been shown capable of detecting microstructural cerebral tissue changes in aging brains, acute stroke, and tumor.⁶–⁸ We postulated that diffusion kurtosis imaging could stratify heterogeneous DWI lesions, improving characterization of tissue injury. Our study examined the spatiotemporal characteristics of mean diffusion (MD) and kurtosis (MK) MRI using a transient filament middle cerebral artery occlusion (MCAO) rodent model.

Materials and Methods

Animal Model

Transient MCAO was induced in 18 adult male Wistar rats (Charles River Laboratory, Wilmington, MA), anesthetized under 1.5% to 2.0% isoflurane with heart rate and saturation of peripheral oxygen monitored online, following institution-approved guidelines. Animals were reperfused by withdrawing filament 95 minutes post-MCAO. One rat died during MRI and was excluded from analysis.

Magnetic Resonance Imaging

MR imaging was obtained using a Bruker 4.7-T small-bore scanner (5 slices, 2 mm/slice, field of view=25×25 mm², matrix size=64×64). Multiparametric MR imaging was obtained during MCAO (20–90 minutes post-MCAO), after reperfusion (120–190 minutes post-MCAO). DWI was acquired with b-values of 250, 500,
calculated as the percentage of the brain. During MCAO, MD

time [TE]=2500/40.5 ms, number of average
/H11005

UTES). We also obtained follow-up T2 MRI 24 hours post-MCAO.

TE[2]

6500/14.8 ms, number of average
/H11005

images were obtained with 2 TEs (repetition time/TE[1]/
/H11005

14.8 ms, number of average=32, duration=7 minutes).

Figure 1. Multiparametric ADC, MD, and MK maps of a repre-
sentative MCAO rat during acute ischemia and immediately after
reperfusion. Tissue outcome was confirmed with follow-up T2 MRI and histology. ADC indicates apparent diffusion coefficient; MD, mean diffusion; MK, mean kurtosis; MCAO, middle cerebral artery occlusion.

Data Analysis
Images were analyzed in Matlab (MathWorks, Natick, MA). DWI signal (S(b)) was fitted per pixel using S(b)=S(0)*exp(−b*D_{app}^2+1/6b^2*D_{app}^4+K_{app}), MD and MK were obtained by averaging diffusion (D_{app}) and kurtosis coefficients (K_{app}) along 6 directions, respectively.5 Apparent diffusion coefficient (ADC) was derived from S(b)=S(0)*exp(−b*ADC) using b=250 and 1000 s/mm^2, and cerebral blood flow was obtained from amplitude modulated arterial spin labeling MRI as described previously.9 MD and MK lesions were independently outlined from shuffled images by 2 investigators in the central slice (2 mm behind the bregma) and averaged. Lesions were mirrored to the contralateral brain as reference region of interest. Results were reported as mean±SD, and we used repeated measures analysis of variance with Tukey multiple comparison test.

Results
Figure 1 shows that MD lesions were significantly larger than MK deficits during MCAO. After reperfusion, MD lesions decreased to approximately the size of MK lesions, which showed negligible change. Notably, MD and ADC maps showed very similar lesion, as expected. Stroke outcome was confirmed using follow-up T2 MRI and histology.

Figure 2 shows reperfusion-induced change in lesion size, calculated as the percentage of the brain. During MCAO, MD

lesion (23.5%±8.1%) was larger than MK (13.2%±2.0%, P<0.01). MD lesion decreased significantly after reperfu-
sion, and the difference between MD (13.8%±4.3%) and MK (13.0%±2.5%) lesion became insignificant. However, the follow-up T2 MRI showed infarction (28.1%±9.6%) significantly larger than acute MD and MK lesions (P<0.01), likely due to severe ischemia and reperfusion injury.

Figure 3 compares reperfusion-induced change in multipa-
rametric MRI values. During MCAO, MD in ischemic lesion decreased significantly from the contralateral normal region (0.55±0.03 versus 0.78±0.02 μm^2/ms, P<0.01), whereas MK was elevated (0.98±0.04 versus 0.69±0.03, P<0.01). Using the contralateral region of interest as reference, the percentage difference between nonischemic and ischemic tissues was −29.0%±3.6% and 42.6%±4.8% for MD and MK, respectively. After reperfusion, the ischemic lesion MD improved (0.60±0.04 μm^2/ms, P<0.01) but was still significantly less than the reference (P<0.01). Moreover, ischemic tissue MK decreased significantly, yet it was still elevated from the contralateral normal tissue (0.93±0.06 versus 0.70±0.03, P<0.01). The percentage differences between nonischemic and ischemic tissues were −22.7%±5.3% and 33.9%±10.9% for MD and MK, respectively.

Discussion
Our study found that the MD/MK mismatch recovered reason-
ably well on reperfusion, whereas areas with concurrent MD and

Figure 2. MD and MK lesion volumes, expressed as the per-
centage of the brain in the same section, during MCAO and
and after reperfusion. Error bars represent SEM. *P<0.01; **P<0.05;
NS indicates nonsignificant. MD indicates mean diffusion; MK, mean kurtosis; MCAO, middle cerebral artery occlusion.

Figure 3. Comparison of MD (A) and MK (B) of the contralateral normal (con.) and ipsilateral ischemic (ipsi.) regions before and
and after reperfusion. MD indicates mean diffusion; MK, mean kurtosis.
MK deficits showed little recovery. In comparison, T1 and T2 MRI are not sensitive to ischemic tissue injury during acute stroke. Our results suggest that MD/MK mismatch may represent mildly damaged and potentially salvageable ischemic lesion, whereas areas with simultaneous MD and MK deficits likely indicate aggravated cellular damage. However, the mechanisms of diffusion and kurtosis deficits in acute stroke are complex. MD decreases in the MD/MK mismatch is likely due to cytotoxic edema. In contrast, MK is sensitive to intracellular tortuosity and viscosity changes subsequent to breakdown of cytoskeletal structures and swelling of mitochondria, likely indicating more severe tissue damage. Nevertheless, the filament stroke model used in our study is subject to severe ischemia and reperfusion injury, and the DWI renormalization was transient. Indeed, we found that cerebral blood flow decreased significantly in the ipsilateral hemisphere from the contralateral region of interest both during MCAO (0.88 ± 0.27 versus 1.43 ± 0.33 mL/g/min) and after reperfusion (1.15 ± 0.23 versus 1.72 ± 0.25 mL/g/min). Importantly, reperfusion induced significant cerebral blood flow increase in both hemispheres (P < 0.01). Therefore, rodent embolic stroke models that more closely resemble human stroke may be more suitable to elucidate the mechanisms of stroke diffusion kurtosis imaging. Moreover, the study may be improved with remote reperfusion techniques to enable pixel-based analysis of MD and MK evolution. Furthermore, histology immediately after reperfusion may help characterize early tissue damage of MD and MK deficits, augmenting evaluation of stroke outcome currently assessed by follow-up MRI.

Conclusion

We showed that MD/MK lesion mismatch recovered reasonably well on reperfusion, whereas regions with concurrent MK and MD deficits responded poorly. Diffusion kurtosis imaging may augment DWI for improved characterization of ischemic tissue injury.

Sources of Funding

This study was partially supported by National Science Foundation of China-30900365, American Heart Association/Scientist Development Grant-0835384N, National Institutes of Health/National Institute of Biomedical Imaging and Bioengineering-1K01EB009771, and National Institutes of Health/National Center for Research Resources-P41RR14075.

Disclosures

None.

References

Stratification of Heterogeneous Diffusion MRI Ischemic Lesion With Kurtosis Imaging: Evaluation of Mean Diffusion and Kurtosis MRI Mismatch in an Animal Model of Transient Focal Ischemia
Jerry S. Cheung, Enfeng Wang, Eng H Lo and Phillip Zhe Sun

Stroke. 2012;43:2252-2254; originally published online July 5, 2012; doi: 10.1161/STROKEAHA.112.661926
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/43/8/2252

Data Supplement (unedited) at:
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SUPPLEMENTAL MATERIAL

MCAO

Reperfusion

-20 min: Loading animal into magnet + planning slices

~5 min: Withdrawing filament + ~20 min loading animal into magnet + planning slices

MRI

MRI

MRI

T₂ MRI

20-90 min post MCAO

95min post MCAO

120-190 min post MCAO

24 hr post MCAO

~20 min: Loading animal into magnet + planning slices