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Comparison of image sensitivity between conventional tensor-based and fast diffusion kurtosis imaging protocols in a rodent model of acute ischemic stroke

Yin Wu^{1,2}, Jinsuh Kim³, Suk-Tak Chan¹, Iris Yuwen Zhou¹, Yingkun Guo¹, Takahiro Igarashi¹, Hairong Zheng², Gang Guo⁴, and Phillip Zhe Sun^{1,3,*}

¹ Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA 02129, USA

² Paul C. Lauterbur Research Centre for Biomedical Imaging, Shenzhen Key Laboratory for MRI, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen, Guangdong 518055, China

³ Department of Radiology, University of Illinois at Chicago, IL 60612, USA

⁴ Department of Radiology, Xiamen 2nd Hospital, Xiamen, Fujian 361021, China

Abstract

Diffusion kurtosis imaging (DKI) can offer a useful complementary tool to routine diffusion MRI for improved stratification of heterogeneous tissue damage in acute ischemic stroke. However its relatively long imaging time has hampered its clinical applications in the emergency setting. Recently proposed fast DKI approach substantially shortens the imaging time, which may help overcome the scan time limitation. However, to date, the sensitivity of fast DKI protocol for imaging acute stroke has not yet been fully described. In this study, we performed routine and fast DKI scans in a rodent model of acute stroke, and compared sensitivity of diffusivity and kurtosis indices (i.e. axial, radial and mean) in depicting acute ischemic lesion. In addition, we analyzed the contrast-to-noise ratio (CNR) between the ipsilateral ischemic and contralateral normal regions using both conventional and fast DKI methods. We found that mean kurtosis shows a relative change of $47.1 \pm 7.3\%$ between the ischemic and contralateral normal regions, being the most sensitive parameter in revealing acute ischemic injury. The two DKI methods yielded highly correlated diffusivity and kurtosis measures and lesion volumes ($R^2 = 0.90$, $P < 0.01$). Importantly, the fast DKI method exhibited significantly higher CNR of mean kurtosis (1.6 ± 0.2) compared to the routine tensor protocol (1.3 ± 0.2 , $P < 0.05$), with its CNR per unit time (CNR efficiency) approximately doubled when the scan time is taken into account. In conclusion, the fast DKI method provides excellent sensitivity and efficiency to image acute ischemic tissue damage, which are essential for imaging-guided and individualized stroke treatment.

Keywords

acute stroke; contrast-to-noise ratio; diffusion kurtosis imaging; mean diffusion; mean kurtosis

INTRODUCTION

Diffusion kurtosis imaging (DKI) is a relatively new MRI technique that measures the degree of peakedness of a random walk distribution, providing unique information on non-Gaussian diffusion in complex biological tissues (1-14). Since previous studies have demonstrated that mean kurtosis (MK) (i.e. the average kurtosis along all uniformly distributed directions) is sensitive to subtle structural alterations following acute ischemia (15,16), DKI has gained tremendous interest as a complementary MRI technique to the widely-used diffusion-weighted imaging (DWI) in acute stroke (17). In animal stroke models, initially decreased mean diffusivity (MD) renormalizes typically in 1-2 days after ischemia and then becomes elevated afterwards, while MK elevation persists up to one week (15). The relative magnitude change of MK is generally twice larger than that of MD (16,18). Furthermore, ischemic tissue with decreased diffusivity without changes in kurtosis shows a propensity of restoration following early reperfusion whereas areas with concurrent abnormalities in diffusion and kurtosis show poor recovery (19). These findings strongly suggest that DKI is a promising diagnostic method that can unravel complex ischemic tissue injury and provide improved tissue stratification, which are essential for imaging-guided and individualized stroke management (20,21).

The commonly-used DKI protocol requires DWI images at multiple b-values along fifteen or more directions in order to resolve diffusion and kurtosis tensors; thereby significantly lengthens its scan time (1,22). As millions of neurons are lost each minute in acute stroke patients, it is important to minimize the scan time before any new imaging methods can be adopted to the emergency setting (23). Recently, Hansen et al. introduced a fast DKI protocol for mapping mean diffusivity and kurtosis (24,25). With acquisition of thirteen DWI images, followed by linear combination of log diffusion signals, they found that the obtained diffusion and kurtosis maps agree well with those estimated from conventional DKI. This approach has been further validated in applications such as tumor grading in glioma patients (26) and acute stroke imaging in rodent models (27). Our previous work revealed that MD/MK measurements from the conventional DTI tensor-model (6 directions) and the fast DKI method were in good agreement (27). However, it is not clear whether mean diffusion and kurtosis measurements are sufficient when compared to conventional DKI approach during acute stroke imaging. Herein we evaluated the sensitivity of tensor indices to detect acute ischemic injury, and the commonly used tensor-model DKI (conventional) and fast DKI methods were compared by means of the contrast-to-noise ratio (CNR) and CNR per unit time (efficiency) using an acute ischemic stroke model to elucidate its diagnostic value in the acute stroke setting.

METHODS

Animals

All experiments were approved by the institutional animal care and use committee. Adult male Wistar rats (n=12) were anesthetized with inhalation of 1.5-2.0% Isoflurane-air mixture throughout all procedures. Heart rate and oxygen content of the blood (SpO₂) were monitored continuously (Nonin Pulse Oximeter 8600, Plymouth, MN), and body temperature was maintained by a circulating warm water jacket positioned around the torso. Unilateral stroke was induced following a standard intraluminal middle cerebral artery occlusion (MCAO) procedure. Rats underwent MR experiments 60 minutes after the procedure. One rat was excluded from the analysis due to failed MCAO surgery, which displayed a very small ischemic lesion in the hypothalamus region.

MRI

MRI scans were performed at a 4.7-Tesla small-bore scanner (Bruker Biospec, Billerica, MA). Animals were immobilized with a tightly fitted MRI-compatible cradle with bite and ear bars and anesthetized throughout the study. Five slices, with slice thickness/gap = 1.8/0.2 mm, were acquired with a single-shot echo-planar imaging (EPI) sequence. Imaging parameters applied to both conventional and fast DKI protocols include: field of view = 20x20 mm², acquisition matrix = 48x48, the gradient pulse duration/diffusion time (δ/Δ) = 6/20 ms, repetition time (TR)/echo time (TE) = 2,500/36.6 ms, and number of signal average (NSA) = 4. For the conventional DKI protocol, two b-values of 1,000 and 2,500 s/mm² were applied in fifteen diffusion directions in addition to a single reference image of b = 0. The scan time was 5 min and 10 s. The fast DKI protocol consisted one reference image of b = 0, three images of b = 1,000 s/mm² along gradient directions of (1,0,0), (0,1,0) and (0,0,1), and nine images of b = 2,500 s/mm² along nine diffusion directions of $\hat{n}^{(i)}$, $\hat{n}^{(i+)}$ and $\hat{n}^{(i-)}$, which were defined as $\hat{n}^{(1)} = (1, 0, 0)^T$, $\hat{n}^{(1+)} = (0, 1, 1)^T$ and $\hat{n}^{(1-)} = (0, 1, -1)^T$, and similarly for i = 2 and 3. Note that the superscript i in $\hat{n}^{(i)}$ labels the position of the “1” while in $\hat{n}^{(i+)}$ and $\hat{n}^{(i-)}$ it labels the position of the “0” (24). The fast DKI scan time was 2 min and 10 s.

Image Analysis

The data acquired with conventional DKI scheme was analyzed using the Diffusion Kurtosis Estimator (DKE; <http://academicdepartments.musc.edu/cbi/dki/dke.html>). We chose linearly constrained algorithm for the tensor estimation in DKI model fitting, and fractional anisotropy (FA), axial ($D_{\parallel}$) and radial ($D_{\perp}$) diffusivity, axial ($K_{\parallel}$) and radial ($K_{\perp}$) kurtosis, and tensor-based MD and MK (denoted as MD_{tensor} and MK_{tensor}, respectively) were derived (28). Due to sufficient anesthesia and restricted motion using a rat cradle, we observed no head motion and hence, postprocessing motion correction was not necessary. For the fast DKI, images were analyzed in MATLAB (MathWorks, Natick, MA). Mean diffusion (denoted as MD_{fast}) was calculated as the mean of MD_{x,y,z} following the formula of Jensen et al. (29):

$$MD_{x, y, z} = \frac{(b_1 + b_3) D_{x, y, z}^{(12)} - (b_1 + b_2) D_{x, y, z}^{(13)}}{b_3 - b_2} \quad (1)$$

where $D_{x, y, z}^{(ij)} = \frac{\ln S(b_i)/S(0) - \ln S(b_j)/S(0)}{b_j - b_i}$, $i=1, j=2, 3$, and $b_1=0, b_2=1,000$, and $b_3 = 2,500$ s/mm². Furthermore, directional average kurtosis (denoted as MK_{fast}) was obtained using the method described by Hansen et al. (24):

$$MK_{fast} = \frac{\frac{6}{15} \left(\sum_{i=1}^3 \ln \frac{S(b_3, \hat{n}^{(i)})}{S(0)} + 2 \sum_{i=1}^3 \ln \frac{S(b_3, \hat{n}^{(i+)})}{S(0)} + 2 \sum_{i=1}^3 \ln \frac{S(b_3, \hat{n}^{(i-)})}{S(0)} \right) + 6 \cdot b_3 \cdot MD_{fast}}{b_3^2 \cdot MD_{fast}^2} \quad (2)$$

Note that MK_{tensor} is the mean kurtosis averaged over all directions, whereas MK_{fast} represents average of the kurtosis tensor (24,25). The conventional DKI acquisition scheme was denoted as the tensor approach because of its capability in measuring axial and radial diffusivity/kurtosis.

Image Segmentation

Baseline mean MD and its standard deviation (SD) were measured from the contralateral normal brain. The background and ventricles were selected and removed with empirical thresholding of DWI signal (with the b-value of 1000 s/mm²) > 1200 (a.u.) and $MD_{tensor} < 1.2$ $\mu m^2/ms$ (30). The contralateral normal region was determined from the manually drawn brain midline for each animal. The ischemic lesion was defined using an MD_{tensor} threshold criterion that was two SDs below the mean MD of the contralateral normal region (27,31). The reference region of interest (ROI) was designated by mirroring of the semiautomatically segmented lesion into the contralateral brain. The MK_{tensor} , MD_{fast} and MK_{fast} lesions were similarly defined by thresholding at two SDs outside their respective means. The semiautomatic segmentation results were reviewed by a board-certified neuroradiologist, whose visual assessments were in good agreement with computational method.

Data Analysis

The contrast-to-noise ratio (CNR) was calculated as:

$$CNR = (S_{ischemia} - S_{normal}) / \sqrt{(\sigma_{ischemia}^2 + \sigma_{normal}^2) / 2} \quad (3)$$

where S and σ represent the signal of the diffusion or kurtosis and their SDs from the ischemic and contralateral regions, respectively. Note that the CNR index calculated here includes not only image noise but also tissue heterogeneity. Additionally CNR per unit time (CNR efficiency), defined as $CNR / \sqrt{\text{scan time}}$, was calculated for each protocol (32).

Two-tailed Student's t-test was performed between paired measurements in ipsilateral ischemic and contralateral normal regions. Statistical significance of measurement differences across the ROIs was tested using one-way analysis of variance (ANOVA) with Bonferroni correction ($P < 0.05$).

Results

Fig. 1 shows representative multi-parametric maps of diffusion indices (MD_{tensor} , $D_{\parallel}$ and $D_{\perp}$), FA and kurtosis indices (MK_{tensor} , and $K_{\parallel}$ and $K_{\perp}$) from the conventional DKI scan on an acute stroke rat. Ischemic lesion showed diffusion decrease and FA and kurtosis increase when compared to the contralateral normal region, consistent with prior studies (15,33). Fig. 2 compares diffusion and kurtosis measurements of the contralateral normal and ipsilateral ischemic regions from the conventional DKI method. The ipsilateral ischemic region was defined by thresholding MD_{tensor} at two SDs below the mean value in the contralateral normal region, so that the paired measurements of the two DKI methods could be compared. There were significant decreases in diffusion indices (MD_{tensor} : $32.1 \pm 2.1\%$, $D_{\parallel}$: $28.4 \pm 2.1\%$, and $D_{\perp}$: $34.9 \pm 2.3\%$), and increase of FA ($22.5 \pm 4.5\%$) and kurtosis indices (MK_{tensor} : $47.1 \pm 7.3\%$, $K_{\parallel}$: $50.6 \pm 6.2\%$, and $K_{\perp}$: $37.4 \pm 7.6\%$) in the ischemic regions compared to those in the contralateral regions ($P < 0.05$). Notably, the magnitude of percentage changes were significantly higher in MK_{tensor} and $K_{\parallel}$ than other indices ($P < 0.05$). In addition, the difference between the percentage changes of MK_{tensor} and $K_{\parallel}$ was not statistically significant ($P > 0.05$). The results indicate that MK_{tensor} and/or $K_{\parallel}$ provide the most sensitive measurements to detect acute ischemia-induced structural changes. Notably, the percentage change of MK_{fast} was $50.9 \pm 4.7\%$ (not shown), slightly higher than that of the MK_{tensor} ($P = 0.05$), suggesting elevated sensitivity of MK_{fast} for revealing acute ischemic tissue damage than that of conventional approach.

Fig. 3 compares MD and MK maps between the conventional and fast DKI methods from a representative acute stroke animal. MD and MK lesions determined from the aforementioned threshold-based algorithm were overlaid on a diffusion-weighted image and were colored in red and green, respectively. Note that regions with concurrent mean diffusivity and mean kurtosis abnormalities were shown in deep green, and there were only a few pixels in the medial caudate-putamen showing kurtosis abnormality without diffusion deficit (light green). Importantly, there was noticeable mismatch between diffusion and kurtosis lesions. In comparison of relative CNR over the MK maps between the two methods, fast DKI method yielded significantly higher CNR between the reference and ischemic regions (1.6 ± 0.2), compared to that from the conventional DKI method (1.3 ± 0.2 , $P < 0.05$). The acquisition time of the fast DKI method was about 50% shorter than that of the conventional DKI protocol, leading to 1.9 times higher gain of CNR efficiency. For the representative rat in Fig. 3, its lateral striatum showed slightly higher MK_{tensor} in the ipsilateral ischemic lesion than that of the contralateral region, but was not detected using the threshold-based algorithm. This is likely due to the relatively low sensitivity of the routine DKI method, demonstrating the benefits of the fast DKI approach in capturing kurtosis abnormality. Despite that CNR of MD_{fast} (3.0 ± 0.4) is slightly lower than that of MD_{tensor} (3.4 ± 0.4 , $P < 0.05$), the CNR efficiency from fast DKI method was 1.4 times of that of conventional DKI, owing to its shortened scan time. These observations suggest that the fast DKI protocol is advantageous in circumstances where MK and MD need to be quickly mapped, which would be particularly useful in the acute stroke setting.

Fig. 4 shows that the lesion sizes between the two DKI methods are highly correlated (Pearson Correlation, $P < 0.01$). Specifically, average volumes of the MD abnormality from

the conventional and fast methods measured at $117.0 \pm 79.9 \text{ mm}^3$ and $110.0 \pm 77.8 \text{ mm}^3$, respectively ($R^2 = 0.99$). The volumes of the MK abnormality from the two methods were $64.9 \pm 44.8 \text{ mm}^3$ and $78.9 \pm 50.6 \text{ mm}^3$, respectively ($R^2 = 0.98$). In addition, values of MD and MK were in good agreement between the two DKI methods (Pearson Correlation, $P < 0.01$). Explicitly, the baseline MD from the conventional and fast methods were 0.84 ± 0.04 and $0.87 \pm 0.04 \text{ } \mu\text{m}^2/\text{ms}$ ($R^2 = 0.93$) in the contralateral region, and 0.57 ± 0.04 and $0.60 \pm 0.04 \text{ } \mu\text{m}^2/\text{ms}$ ($R^2 = 0.94$) in the ipsilateral ischemic region, respectively. In comparison, the baseline MK was 0.59 ± 0.05 and 0.66 ± 0.05 ($R^2 = 0.83$) in the contralateral region, and 0.87 ± 0.07 and 1.00 ± 0.09 ($R^2 = 0.90$) in the ischemic region, from the conventional and fast DKI protocols, respectively.

Fig. 5a illustrates representative multi-slice diffusion (MD_{fast}) and kurtosis (MK_{fast}) lesion mismatch from an acute stroke rat, and the corresponding 3D volume rendering of MD_{fast} and MK_{fast} lesions overlaid on a structural scan (Fig. 5b). Notably, there was lesion mismatch with MK_{fast} lesion significantly smaller than MD_{fast} lesion, with their normalized lesion area ratio being 0.75 ± 0.11 ($P < 0.05$). Fig. 6 compares MD_{fast} and MK_{fast} values in the contralateral normal area, ipsilateral MD_{fast} lesion and MK_{fast} lesion (defined as two SDs outside their respective means from the contralateral normal region) as well as their mismatch. Although MD_{fast} values were significantly reduced in ischemic lesions (MD_{fast} lesion, MK_{fast} lesion, and their mismatch area) from the contralateral normal area ($P < 0.05$), differences of MD_{fast} values across the three lesions were statistically insignificant. In comparison, MK_{fast} across the three lesion areas was significantly elevated from the normal area ($P < 0.05$), and more importantly, MK_{fast} shows significant difference across the three lesion areas ($P < 0.05$). This shows that the fast DKI method can indeed resolve the heterogeneity within the commonly used DWI approach.

Discussion

DKI is an emerging method complementary to the conventional diffusion MRI that enables refined characterization of ischemic tissue injury (15,18,34-37). Previous in vivo DKI studies mostly used the diffusion kurtosis tensor approach that models anisotropic properties of the brain structure. However, its scan time is relatively long, limiting its adoption in the acute stroke setting. MK, a composite parameter of non-Gaussian water diffusion free from tensor estimation, provides sensitive and fast characterization of acute ischemic tissue injury (29). Our study demonstrated concordant results with previously published data that indicated MK renders the highest sensitivity to detect early structural alterations in acute stroke (16,18). Moreover, we found significant difference in MK_{fast} values across three distinctive ischemic regions (e.g., MD_{fast} lesion, MK_{fast} lesion and their mismatch) but no differences in their MD_{fast} . Notably, MK difference between the ischemic and contralateral normal regions ($S_{\text{ischemia}} - S_{\text{contralateral}}$) was 0.28 ± 0.04 and 0.34 ± 0.04 for the routine and fast DKI MRI, respectively ($P < 0.05$), while their noise level was similar (0.22 ± 0.02 vs. 0.21 ± 0.02 , $P = 0.33$). The higher CNR in MK measurement observed in the fast DKI method is largely due to increased signal contrast between normal and ischemic regions, as shown in Fig. 3, which nearly doubles the CNR efficiency when the scan time is taken into account. This upholds our postulation that the fast DKI method is suitable for acute stroke imaging.

It is important to point out that MD lesions and part of MK lesions showed gradual transition from the normal brain tissue to the ischemic area. The threshold-based lesion segmentation algorithm performed reasonably well with less bias in the situation where manual determination of transitional regions would be otherwise extremely difficult. Although higher spatial resolution may better resolve ischemic lesions, our study chose to balance between SNR and scan time without significant penalty in lesion definition. It has been shown that MK_{fast} and MK_{tensor} convey similar diagnostic information on the underlying ischemic tissue damage (27). Indeed, MK can be accurately determined based on measures along nine directions without need of computationally expensive nonlinear regression fitting of diffusion signals (24,38,39). Notably, for in vivo applications, the fast DKI method tends to slightly overestimate both MD and MK indices compared to the conventional method. Apart from the differences in direction and number of diffusion measurements, this discordance may also be attributed partly to the different mathematical models assumed in equations for diffusion and kurtosis indices. Specifically, the fast DKI method approximates kurtosis equation using the Taylor expansion of the logarithm of the diffusion-weighted signal, assuming negligible high order diffusion (e.g., $O(b^3)$) and Rician noise terms (24), whereas such terms are treated as the residual fitting error in the conventional DKI approach (27). Nevertheless, pairwise statistical test of MD and MK measurements showed significant correlations between the two methods. MD_{fast} lesion volume was found to be slightly smaller than MD_{tensor} lesion volume with marginal significance ($P=0.04$), while MK_{fast} lesion was significantly larger than that of MK_{tensor} . This may be because that the sensitivity advantage in the fast DKI method allows more accurate lesion segmentation (Fig. 3). Besides, considering the increased risk of intracranial hemorrhage upon late recanalization, a slightly more conservative estimation of diffusion/kurtosis mismatch may be beneficial to minimize risk of unnecessary interventional rescue therapy (40-42). One pitfall of the fast DKI method is its inability to resolve the full diffusion and kurtosis tensors, which limits its general applicability (43-49). However, for the case of acute stroke imaging, MD and MK maps render superior sensitivity compared to the anisotropy maps as the anisotropic diffusion measurement may not consistently ascertain ischemic insult (50-52). Therefore, fast DKI could serve as a time-efficient imaging approach to quickly assess tissue salvageability, advancing imaging-guided triage for recanalization therapy.

CONCLUSION

In this study, we recapitulated that mean kurtosis is one of the most sensitive parameters to detect acute stroke injury, and demonstrated the enhanced sensitivity of the fast DKI method for stratification of graded ischemic tissue injury during acute stroke. The fast DKI method may provide critically important information for resolving heterogeneous DWI lesion, particularly translatable in the acute stroke setting.

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Abbreviations

CNR	contrast-to-noise ratio
DKI	diffusion kurtosis imaging
MD	mean diffusivity
MK	mean kurtosis

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Fig. 1. Multi-parametric maps of mean diffusivity (MD_{tensor}), axial diffusivity ($D_{\parallel}$), radial diffusivity ($D_{\perp}$), fractional anisotropy (FA), mean kurtosis (MK_{tensor}), axial kurtosis ($K_{\parallel}$), and radial kurtosis ($K_{\perp}$) obtained using the conventional DKI method from a representative acute ischemic stroke rat. Ipsilateral ischemic lesion was defined using a threshold-based algorithm and the lesion was mirrored into the contralateral normal region as the reference region of interest (ROI). The unit of diffusivity is $\mu\text{m}^2/\text{ms}$.

Fig. 2. Comparison of change of multiple indices between ischemic and contralateral regions obtained using the conventional DKI method. The unit of diffusivity is $\mu\text{m}^2/\text{ms}$.

Fig. 3.

Comparison of mean diffusivity and mean kurtosis maps obtained using the conventional and the fast DKI methods. Lesions of mean diffusivity and mean kurtosis were overlaid on a diffusion-weighted image and were colored in red and green, respectively. Note that regions with concurrent diffusivity and mean kurtosis abnormalities were shown in deep green, and there were only a few pixels in the medial caudate-putamen showing kurtosis abnormality without diffusion deficit (light green). The unit of diffusivity is $\mu\text{m}^2/\text{ms}$.

Fig. 4. Correlation of lesion volume size of (a) mean diffusion and (b) mean kurtosis determined from the conventional and fast DKI methods. The linear regression is shown as a solid line, and the identity line shown as a dash-dotted line.

Fig. 5. Demonstration of fast DKI in an acute stroke rat. (a) Multi-slice diffusion and kurtosis lesion mismatch from fast DKI. (b) 3D illustration of mean diffusion/mean kurtosis lesions and their mismatch in a representative acute stroke rat using the fast DKI method.

Fig. 6. Comparison of mean diffusion and kurtosis values in the contralateral normal area, ipsilateral ischemic diffusion lesion (MD_{fast} lesion), kurtosis lesion (MK_{fast} lesion), and MD_{fast}/MK_{fast} lesion mismatch obtained using the fast DKI method. The unit of diffusivity is $\mu\text{m}^2/\text{ms}$.