Stroke Assessment With Diffusional Kurtosis Imaging

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Background and Purpose—Despite being the gold standard technique for stroke assessment, conventional diffusion MRI provides only partial information about tissue microstructure. Diffusional kurtosis imaging is an advanced diffusion MRI method that yields, in addition to conventional diffusion information, the diffusional kurtosis, which may help improve characterization of tissue microstructure. In particular, this additional information permits the description of white matter (WM) in terms of WM-specific diffusion metrics. The goal of this study is to elucidate possible biophysical mechanisms underlying ischemia using these new WM metrics.

Methods—We performed a retrospective review of clinical and diffusional kurtosis imaging data of 44 patients with acute/subacute ischemic stroke. Patients with a history of brain neoplasm or intracranial hemorrhages were excluded from this study. Region of interest analysis was performed to measure percent change of diffusion metrics in ischemic WM lesions compared with the contralateral hemisphere.

Results—Kurtosis maps exhibit distinct ischemic lesion heterogeneity that is not apparent on apparent diffusion coefficient maps. Kurtosis metrics also have significantly higher absolute percent change than complementary conventional diffusion metrics. Our WM metrics reveal an increase in axonal density and a larger decrease in the intra-axonal (D_a) compared with extra-axonal diffusion microenvironment of the ischemic WM lesion.

Conclusions—The well-known decrease in the apparent diffusion coefficient of WM after ischemia is found to be mainly driven by a significant drop in the intra-axonal diffusion microenvironment. Our results suggest that ischemia preferentially alters intra-axonal environment, consistent with a proposed mechanism of focal enlargement of axons known as axonal swelling or beading. (Stroke. 2012;43:00-00.)

Key Words: axonal beading ■ diffusional kurtosis imaging ■ stroke ■ white matter modeling

Diffusion MRI (dMRI) is the most reliable neuroimaging technique for acute/subacute ischemic stroke assessment.1,2 The ischemic core manifests as a region of hyperintensity on diffusion-weighted images and is associated with a reduction in the apparent diffusion coefficient (ADC or D) that characterizes the rate of water molecules’ random movement.1,2 ADC generally remains low for 4 days after stroke onset and gradually pseudonormalizes thereafter, becoming normal or high in the subacute and chronic stages.2 The exact biophysical events that could result in the observed diffusion changes during acute stroke have remained elusive despite decades of research and are still under debate.4,5

A fundamental limitation of ADC obtained from conventional dMRI techniques such as diffusion-weighted (DWI) or diffusion tensor imaging is that the data analysis approximates biological water diffusion as being Gaussian, although substantial non-Gaussian diffusion is observed throughout the brain.6 Thus, information obtained using conventional dMRI may be incomplete. Since the introduction of DWI for stroke assessment in the 1990s,7,8 numerous alternative methods have been proposed to improve its clinical value. For example, delineation of the ischemic lesion may be improved by using higher diffusion-weighting factors (b-values),9,10 suggesting that more advanced dMRI techniques that use high b-values should prevail.11 One such technique is diffusional kurtosis imaging (DKI).5 Diffusional kurtosis (K) is a quantitative measure of the non-Gaussianity of the diffusion process in both white (WM) and gray matter (GM).6,12 unhindered, homogeneous diffusion gives rise to zero K, whereas water diffusion in biological tissue comprised of multiple barriers such as cellular/axonal membranes, organelles, and/or compartments results in positive K. In other words, K is an in vivo measure of the complexity or heterogeneity of the microenvironment in WM and GM, which offers information complimentary to conventional diffusion metrics and may potentially be a more sensitive biomarker for probing pathophysiological changes.6,12 Several studies have already shown the promise of DKI in...
contributing to a better understanding of diseases such as attention deficit hyperactivity disorder,\textsuperscript{13} glioma,\textsuperscript{14} and mild traumatic brain injury.\textsuperscript{15} Interestingly, preliminary human\textsuperscript{16–19} and animal\textsuperscript{20} stroke DKI studies have demonstrated that abnormalities apparent on images of the K metric were not as distinct and/or apparent on DWI or ADC images\textsuperscript{16} and that the K metric pseudonormalized at a later time point than ADC.\textsuperscript{20}

Recently, it has been shown by Fieremans et al that WM-specific diffusion metrics (WMM), namely axonal water fraction, intra-axonal (D_{\text{ax}}), extra-axonal axial (D_{\text{ea},\parallel}), and radial (D_{\text{ea},\perp}) diffusivity, can be obtained from K metrics using a WM model that describes the microstructural characteristics in the extra- and intra-axonal environments of WM.\textsuperscript{21,22} Figure 1A illustrates a schematic of water diffusion occurring inside (blue) and outside (red) axonal fibers. We hypothesize that WMM may serve as biomarkers that are more specific and/or sensitive to certain microstructural changes associated with pathological processes in WM. As a consequence, WMM may potentially provide clues on the plausible biophysical mechanism underlying ischemia in WM.

Given the fact that the sensitivity of K metrics and WMM toward ischemic stroke has not been comprehensively investigated, the current study serves as a pilot study focusing on the acute/subacute stroke phase where microstructural alterations in neural tissues are certain and well documented.\textsuperscript{1} Therefore, the goal of this study is to investigate the potential of K metrics and the new WMM for clinical stroke evaluation. Particularly, this study aims at elucidating the plausible biophysical events that affect water diffusion in WM after ischemia.

**Methods**

**Patient Recruitment**

This study was approved by the Institutional Review Board of the Medical University of South Carolina with waiver of informed consent. We performed a retrospective review of clinical and imaging data on consecutive patients who were admitted due to acute onset of neurological symptoms and were subsequently diagnosed with acute/subacute stroke in the middle cerebral artery territory as the cause for neurological impairments. A total of 44 patients admitted to our institution between August 2011 and February 2012 were included. Of these patients, 9 received tissue-type plasminogen activator before they were examined by MRI. Patients with a history of brain neoplasm or intracranial hemorrhages were excluded from study. Furthermore, patients with transient ischemic attacks, diffusion abnormalities due to nonvascular etiology (for example, posterior reversible encephalopathy syndrome or global hypoxic ischemic encephalopathy), or otherwise unexplained symptoms were also excluded. All patients who underwent MRI 6 hours to 2 weeks after symptom onset were analyzed. For 10 patients whose symptom onset was not well defined (for example, waking up with a focal neurological deficit after a night of sleep), the time of onset was defined as the time the patient was last seen without a neurological impairment. Patient characteristics are summarized in Table 1. In addition, based on Trial of ORG 10172 in Acute Stroke Treatment classification of subtypes of ischemic stroke,\textsuperscript{23} the number of patients with subtype of large-artery atherosclerosis, cardioembolism, and other causes are 9, 10, and 25, respectively.

**Magnetic Resonance Imaging**

All subjects were scanned on a 1.5-T Siemens Avanto MRI scanner (Siemens Healthcare, Erlangen, Germany). Axial T1-weighted magnetization-prepared rapid gradient echo, fluid-attenuated inversion recovery, and T2- and T2*-weighted images were acquired. Diffusion-weighted images, which are part of the standard of clinical care at our institution, were acquired with 3 b-values (0, 1000, and 2000 s/mm\textsuperscript{2}) along 30 diffusion encoding directions using a vendor-supplied single-shot twice-refocused spin-echo echoplanar imaging sequence with number of excitations = 1 (number of excitations = 10 for b = 0). Other imaging parameters were: slice thickness = 3 mm (no gap), number of slices = 40, TR/TE = 5500/99 ms, field-of-view = 222 × 222 mm\textsuperscript{2}, acquisition matrix = 74 × 74, image resolution = 3 × 3 mm\textsuperscript{2}, BW/pixel = 1325 Hz, acceleration factor = 2, acquisition time approximately 7 minutes.

**Data Processing**

Diffusion-weighted images were processed using in-house software Diffusional Kurtosis Estimator\textsuperscript{24} implemented in MATLAB (Math-Works, Natick, MA), and the diffusion and kurtosis tensors were calculated on a voxel-by-voxel basis. Parametric maps for fractional anisotropy (FA), mean (MD), axial (λ_{x}), radial diffusivity (λ_{r}), mean (MK), axial (K_{x}), and radial kurtosis (K_{r}) were subsequently obtained. Note that “axial” and “radial” refer to, respectively, diffusion along and perpendicular to the principal diffusion tensor eigenvector, whereas mean diffusion refers to diffusion averaged along all diffusion encoding directions.\textsuperscript{12} In WM, the principal eigenvector is typically aligned parallel to the axes of axonal fiber bundles, except in regions with substantial fiber crossing. Also calculated from the DKI data set were the WMM\textsuperscript{21} in WM voxels consisting largely of aligned fiber bundles (ie, FA > 0.3). All MRI images were normalized to a T1-weighted template obtained from elderly volunteers and subsequently segmented into WM and GM.

**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Acute/Subacute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>44</td>
</tr>
<tr>
<td>No. of WM/GM lesions</td>
<td>40/42</td>
</tr>
<tr>
<td>Age, y, mean±SD</td>
<td>63.5±17.1</td>
</tr>
<tr>
<td>Male/female, %</td>
<td>50/50</td>
</tr>
<tr>
<td>Time between symptom onset and MRI, h, mean±SD</td>
<td>41.6±28.9</td>
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</table>

WM indicates white matter; GM, gray matter.
Multislice regions-of-interest (ROIs) were manually identified by the hyperintensity on the mean of all diffusion-weighted images with b-value of 2000 s/mm² (mDWI2000). ROIs encompassed the ischemic lesion with pixel values distinctly higher than the contralateral hemisphere, and any ambiguous pixels (for example, lightly increased signal intensity around the periphery of the ischemic core) were not included. Because ischemia changed the contrast of T1-weighted images (reference image for brain normalization and segmentation), WM/GM masks of the ischemic lesion for individual patients were extracted from those of the contralateral hemisphere at a cutoff probability of 0.7. Because of the fact that WMM are only valid in regions consisting of aligned WM fiber bundles, an additional FA threshold of 0.3 was also applied to WM masks. ROIs covering normal WM/GM on the contralateral hemisphere were also obtained. Measurements were then performed by averaging all pixels within the ROIs. Percent change of diffusion metrics from normal to ischemic tissue was computed: \((\mu_i - \mu_c) / \mu_c\), where \(\mu_i\) and \(\mu_c\) denote the mean measurement of the ROI in lesional and contralateral hemispheres, respectively.

Statistical Analysis

We tested for differences between the ROI average values of all absolute diffusion metrics in lesional and contralateral hemispheres using paired t tests. Two-tailed probability value <0.05 was considered statistically significant.

Results

ROI Analysis

Figure 2 shows the FA, mDWI1000, MD, and MK maps of an acute/subacute patient. WM (red, without FA ≥ 0.3 threshold) and GM (green) ROIs in the ischemic lesion are also overlaid on the FA maps. Notice the distinct ischemic lesion signal heterogeneity on MK that is not apparent on MD maps (red arrowheads). For example, there is a clear gradation in MK contrast from prefrontal subcortical to cortical WM lesion but rather isoointense MD contrast (left slice). It is important to note that a small number of hypointense voxels (as compared with normal tissue values) appearing on the MK maps are likely attributable to poor model fitting as a result of noise and misregistration between raw DKI images rather than actual microstructural features. Percent changes of diffusion metrics from normal (contralateral hemisphere) to acute/subacute ischemic tissues are also shown. The error bars indicate SDs. FA indicates fractional anisotropy; WM, white matter; GM, gray matter; ROIs, regions of interest; MD, mean diffusivity; \(\lambda_m\), axial diffusivity; \(\lambda_r\), radial diffusivity; MK, mean kurtosis; K\(_{ax}\), axial kurtosis; K\(_{rad}\), radial kurtosis; AWF, axonal water fraction; D\(_{e,ax}\), axial extra-axonal diffusivity; D\(_{e,rad}\), radial extra-axonal diffusivity; P, probability value; DTI, diffusion tensor imaging; DKI, diffusion kurtosis imaging; WMM, white matter metrics.

Estimates of the diffusion metrics are tabulated in Table 2. Percent change of diffusion metrics and statistical results are also shown. Only measurements of MD and MK for ischemic GM are shown because this is where isotropic diffusion generally occurs, and therefore analysis using directional diffusion metrics (ie, axial and radial diffusion metrics) is deemed redundant. Generally, all conventional diffusion coefficients (FA, MD, \(\lambda_m\), \(\lambda_r\)) and the diffusion coefficients from WMM (D\(_{e,ax}\), D\(_{e,rad}\), D\(_{c,ax}\), D\(_{c,rad}\)) significantly decrease, whereas K metrics (MK, K\(_{ax}\), and K\(_{rad}\)) and axonal water fraction significantly increase in the ischemic lesion. K metrics (MK, K\(_{ax}\), and K\(_{rad}\)) have significantly (P<0.05) higher absolute percent change compared with complementary conventional diffusion metrics (MD, \(\lambda_m\), and \(\lambda_r\)). Note that absolute percent change along the axial direction is significantly (P<0.05) larger than the radial direction of WM: \(\lambda_g\) (-32%) versus \(\lambda_r\) (-19%); K\(_{ax}\) (58%) versus K\(_{rad}\) (22%); and D\(_{e,ax}\) (-26%) versus D\(_{e,rad}\) (-15%). Among all WMM studied, the absolute percent change in D\(_{e,ax}\) is the largest compared with D\(_{e,ax}\), D\(_{e,rad}\), and axonal water fraction: -46% versus -26%, -15%, and 10%.

Region of Interest Analysis

Multislice regions-of-interest (ROIs) were manually identified by the hyperintensity on the mean of all diffusion-weighted images with b-value of 2000 s/mm² (mDWI2000). ROIs encompassed the ischemic lesion with pixel values distinctly higher than the contralateral hemisphere, and any ambiguous pixels (for example, lightly increased signal intensity around the periphery of the ischemic core) were not included. Because ischemia changed the contrast of T1-weighted images (reference image for brain normalization and segmentation), WM/GM masks of the ischemic lesion for individual patients were extracted from those of the contralateral hemisphere at a cutoff probability of 0.7. Because of the fact that WMM are only valid in regions consisting of aligned WM fiber bundles, an additional FA threshold of 0.3 was also applied to WM masks.

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reactive astrogliosis,25 thus corroborating the notion that $K$ is increased amid pseudonormalization of MD and FA.25 Such observations are consistent with focal enlargement of axons and dendrites as a result of osmotic imbalance, known as axonal swelling or beading,26 which leads to local diffusion dead zones (as shown in Figure 1B). Indeed, our results are similar to those of a recent study27 based on in vitro diffusion measurements of axons under tensile stress and simulations that beading reduces the overall diffusivity along the fiber.

The relatively slight increase in the axonal water fraction is also in concordance with the axonal beading hypothesis.28 Despite the fact that conventional dMRI is deemed to be the most reliable method for stroke imaging, the specificity of conventional diffusion metrics is compromised by partial volume contamination from free fluid as a result of, for example, vasogenic edema during the subacute phase.29 Using inversion recovery dMRI to suppress cerebrospinal fluid, Hu et al30 found MD of GM to decrease by $>30\%$, which could potentially lead to quantification errors (eg, higher MD values). DKI, on the other hand, may help provide specific tissue microstructural information underlying the disease process despite the higher sensitivity as compared with conventional diffusion metrics (as reflected by the significantly larger absolute percent change in $K$ metrics).

Using the newly proposed WMM as derived from the same DKI data set,21 stroke etiology may be clarified. In particular, we find that the decrease in ADC observed in ischemic WM injury is mainly due to a drop in the intra-axonal diffusivity (reflected by the largest absolute percent change in $D_{a}$) and that ischemia has a larger effect on the intra- than the extra-axonal environments (ie, larger absolute percent change in $D_{a}$ than in the extra-axonal diffusivities). These observations are consistent with focal enlargement of axons and dendrites as a result of osmotic imbalance, known as axonal swelling or beading,26 which leads to local diffusion dead zones (as shown in Figure 1B). Indeed, our results are similar to those of a recent study27 based on in vitro diffusion measurements of axons under tensile stress and simulations that beading reduces the overall diffusivity along the fiber.

Discussion

The current study demonstrates that $K$ is consistently elevated and has higher percent change than conventional ADC in ischemic WM and GM in all 44 patients. Changes in the axial metrics were consistently larger than for the radial metrics, in consistency with prior work.18 Our results from WMM indicate that ischemia causes a small increase in axonal density, and the well-known decrease in ADC appears to be dominated by the change in the intra-axonal microenvironment of WM, because $D_{a}$ has a substantially larger absolute percent change in the ischemic core as compared with either $D_{e//}$ or $D_{e,\perp}$.

The increase in $K$ observed in the ischemic lesion likely indicates an increase in the complexity or heterogeneity of the water microenvironment in WM and GM.6,12 It was shown in an experimental model of traumatic brain injury that MF of neural tissues subjected to impact at a subacute stage was elevated amid pseudonormalization of MD and FA.25 Such increase in MK was shown to be associated with higher reactive astrogliosis,29 thus corroborating the notion that $K$ is a biomarker of tissue heterogeneity. Similar results were also previously observed in preliminary patient17 and animal20 stroke DKI studies. However, other than teasing out the direction in which structural change occurs, $K$ metrics cannot provide specific tissue microstructural information underlying the disease process despite the higher sensitivity as compared with conventional diffusion metrics (as reflected by the significantly larger absolute percent change in $K$ metrics).

| Table 2. Mean and SD of ROI Measurements in Acute and Subacute Ischemic Lesion and Percent Change of ROI Measurements From the Contralateral Hemisphere to the Ischemic Lesion |
|---------------------------------|-----------------|-----------------|-----------------|
|                                | L               | C               | Percent Change  |
| Fa                             | 0.29±0.06       | 0.39±0.04       | −0.27±0.12*     |
| MD, $\mu m^{2}$/ms              | 0.70±0.11       | 0.94±0.07       | −0.25±0.11†     |
| $\lambda_{a}$, $\mu m^{2}$/ms   | 0.92±0.14       | 1.35±0.12       | −0.32±0.11††    |
| $\lambda_{r}$, $\mu m^{2}$/ms   | 0.59±0.11       | 0.73±0.07       | −0.19±0.13†     |
| MK                             | 1.43±0.28       | 1.04±0.10       | 0.38±0.25†      |
| $K_{a}$                        | 1.30±0.25       | 0.83±0.07       | 0.57±0.32††     |
| $K_{r}$                        | 1.57±0.33       | 1.29±0.18       | 0.22±0.23†      |
| AWF                            | 0.40±0.05       | 0.36±0.03       | 0.10±0.12§      |
| $D_{a}$, $\mu m^{2}$/ms         | 0.35±0.07       | 0.66±0.07       | −0.46±0.12§     |
| $D_{e//}$, $\mu m^{2}$/ms        | 1.39±0.17       | 1.88±0.15       | −0.26±0.08§     |
| $D_{e,\perp}$, $\mu m^{2}$/ms    | 0.92±0.11       | 1.08±0.08       | −0.15±0.10§     |

ROI indicates region of interest; WM, white matter; GM, gray matter; L, lesional; C, contralateral; FA, fractional anisotropy; MD, mean diffusivity; $\lambda_{a}$, axial diffusivity; $\lambda_{r}$, radial diffusivity; MK, mean kurtosis; $K_{a}$, axial kurtosis; $K_{r}$, radial kurtosis. AWF, axonal water fraction; $D_{a}$, intra-axonal diffusivity; $D_{e//}$, axial extra-axonal diffusivity; $D_{e,\perp}$, radial extra-axonal diffusivity.

*Significant difference between the diffusion metrics in L and C.
††‡‡§Significant difference between the absolute percent change of conventional diffusion and kurtosis metrics (MD versus MK, $\lambda_{a}$ versus $K_{a}$, $\lambda_{r}$ versus $K_{r}$) of axial and radial diffusion metrics ($\lambda_{a}$ versus $\lambda_{r}$ and $K_{a}$ versus $K_{r}$) and among all WMM WM metrics (AWF, $D_{a}$, $D_{e//}$, $D_{e,\perp}$), respectively. $P<0.05$ is considered statistically significant.

The current study only investigates acute/subacute patients with time between symptom onset and MRI from 6 hours to 2 weeks. Despite the importance of studying patients with
hyperacute stroke, it is also critical to develop useful techniques for studying patients during the subacute phase. It is well documented in the literature that recovery of motor function is likely mediated by the neuroplasticity of remaining intact tissue, and measurement of this neuroplasticity could potentially assist in the planning of rehabilitative intervention. We believe that in vivo monitoring of this neuroplastic event in ischemic brain may be aided by using DKI together with WMM.

In our analysis, patients with acute and subacute stroke (using the definition from Kim et al[29]) were treated as a single group, because the diffusion metrics were not significantly different. This contrasts with some prior reports[33,34] in which differences between diffusion metrics measured from acute and subacute ischemic tissue were observed. However, it is worth noting that the distinction of ischemic tissue between the acute and subacute phase is largely determined by the extent of vasogenic edema, manifested as hyperintensity in fluid-attenuated inversion recovery images and pseudonormalization of ADC,[29,34] which varies among patients. It is also well documented in the literature that ADC pseudonormalization occurs at least 4 days after symptom onset.[1,3] The fact that the majority of our subacute patients were scanned at <4 days after stroke may explain why no significant differences were seen in our data.

For any new imaging technique, scan time is often a key consideration relevant to clinical use. Fortunately, DKI can easily be implemented on most up-to-date clinical scanners, and its acquisition time (approximately 7 minutes) is consistent with clinical constraints. Moreover, conventional diffusion metrics can also be calculated from a DKI data set, thus rendering acquisition of additional conventional DWIs unnecessary. Because it additionally yields metrics of diffusional non-Gaussianity and the WMM, DKI provides for a consideration relevant to clinical use.

Conclusions

The current study demonstrates the potential for K metrics and WMM to be useful for stroke assessment. Ischemia is found to preferentially exert a larger effect on the intra-axonal microenvironment of WM, consistent with a proposed mechanism of axonal beading.

Acknowledgments

We thank the MRI technologists of the Medical University of South Carolina for their help with data acquisition.

Table 3. Properties of DTI and DKI

<table>
<thead>
<tr>
<th>Property</th>
<th>DTI</th>
<th>DKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical scan time</td>
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<td>7</td>
</tr>
<tr>
<td>b-value, s/mm²</td>
<td>0, 1000</td>
<td>0, 1000, 2000</td>
</tr>
<tr>
<td>Diffusion metrics</td>
<td>FA, MD, λω, λ1, λ2</td>
<td>FA, MD, λω, λ1, λ2, MK, Kω, K1, K2</td>
</tr>
</tbody>
</table>

DTI indicates diffusion tensor imaging; DKI, diffusional kurtosis imaging; FA, fractional anisotropy; MD, mean diffusivity; λω, axial diffusivity; λ1, radial diffusivity; Kω, axial kurtosis; K1, radial kurtosis.

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Disclosures

None.

References

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