Increased Corticospinal Tract Fractional Anisotropy Can Discern Stroke Onset Within the First 4.5 Hours

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Background and Purpose—The role of diffusion tensor imaging in determining stroke age remains unclear. We tested the ability of diffusion tensor imaging metrics to discriminate ischemic stroke <4.5 hours of onset.

Methods—We enrolled 60 consecutive patients for multimodal 1.5 T MRI within 12 hours of middle cerebral artery ischemic stroke onset. We measured fractional anisotropy (FA), mean diffusivity (MD), apparent diffusion coefficient (ADC), and T2-weighted signal intensity in affected ipsilateral and unaffected contralateral deep gray matter, cortical gray matter, deep white matter in the corticospinal tract (CST), and subcortical white matter and calculated ipsilateral-to-contralateral ratios (r). Hyperintensity in infarcted tissue was considered fluid-attenuated inversion recovery-positive.

Results—We analyzed the 48 patients (17 women; mean age, 68±14 years) with known onset. In 25 (52.1%) patients, onset was ≤4.5 hours (mean, 182.3±65.6 minutes). Variables differing significantly between infarcts <4.5 hours and >4.5 hours were rFA CST (P=0.001), rMD cortical gray matter (P=0.036), rADC cortical gray matter (P=0.009), rT2 CST (P=0.006), and fluid-attenuated inversion recovery (P<0.001). rFA at CST was the most reliable to discriminate infarcts <4.5 hours (Goodman-Kruskal=0.76). The sensitivity, specificity, and positive and negative predictive values for infarct <4.5 hours of onset by rFA at CST >0.970 were 93.8%, 84.6%, 88.2%, and 91.7%, respectively.

Conclusions—These preliminary results suggest rFA at CST may be a surrogate marker of acute stroke age. (Stroke. 2013;44:1162-1165.)

Key Words: cerebral ischemia ■ diffusion tensor imaging ■ fractional anisotropy

Knowing the onset of acute stroke is a prerequisite for intravenous tissue plasminogen activator, because this treatment is approved only within 4.5 hours of onset.1 Reliable MRI (MRI) surrogate markers of lesion age are needed, because 14% to 28% of patients discover stroke on waking up.2 Fluid-attenuated inversion recovery (FLAIR) can identify patients within 4.5 hours of onset with moderate accuracy.3 Diffusion tensor imaging (DTI) measures anisotropic water diffusion as fractional anisotropy (FA).4 FA can detect microstructural changes attributable to ischemia, but the value of DTI-metrics as a biological tissue clock remains unclear. We tested the utility of DTI-metrics for differentiating ischemic strokes with onset of ≤4.5 hours.

Methods
Sixty consecutive patients with first-ever middle cerebral artery territory infarction underwent multimodal MRI on a 1.5 T scanner (Gyroscan Intera; Philips Medical Systems, Best, the Netherlands) within 12 hours of symptom onset. Forty-eight patients with known onset were analyzed (17 women; mean age, 68±14 years). Our ethics committee approved the study, and all patients provided written informed consent.

DTI were acquired by using single-shot echo-planar imaging sequences with the sensitivity encoding parallel-imaging scheme. Diffusion-sensitized gradients were applied along 15 noncollinear directions with a b-value of 1000 s/mm². Other DTI acquisition parameters were TR/TE, 6795/72 ms; 23×23-cm FOV; 112×112 matrix size; and 2.05×2.05×3 mm voxel size. DTI acquisition took about 3 minutes.

Diffusion tensor images were coregistered; 2 neuroradiologists used NeuroScape 2.0 MR Stroke Edition (Olea Medical, La Ciotat, France) to place free-hand regions of interest (ROIs) on deep and cortical gray matter, deep white matter at the level of the corticospinal tract (CST), and subcortical white matter in the slice, where the infarct had the largest diameters on diffusion-weighted sequences. We measured FA, mean diffusivity (MD), apparent diffusion coefficient (ADC), and T2-weighted signal intensity in the ipsilateral affected side and in the homologous contralateral regions, and then calculated the ipsilateral-to-contralateral ratios (r). Mean ROI area

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Hyperintensity in infarcted tissue was considered FLAIR-positive; discordant FLAIR ratings were resolved by consensus. Interobserver agreements were calculated. The two measurements were averaged for statistical analysis by paired t tests (Minitab version 15.1.0.0; Minitab Inc, State College, Pennsylvania).

### Results

Onset was <4.5 hours in 25 patients (52.1%; 182.3±65.6 minutes). CST was affected in 35 patients (72.9%). Significant differences between infarcts <4.5 and >4.5 hours were found for rFA at CST (P=0.001; Figure in the online-only Data Supplement), rMD cortical gray matter (P=0.036), rADC cortical gray matter (P=0.009), rT2 at CST (P=0.006), and FLAIR (P<0.001; Table). Logistic binary regression models and receiver-operating characteristic curves demonstrated rFA at CST most reliably discriminated infarcts <4.5 hours (Goodman-Kruskal=0.76; Kendall=0.39; Figure 1), with sensitivity, specificity, and positive and negative predictive values for an rFA at CST cutoff of >0.970 being 93.8%, 84.6%, 88.2%, and 91.7%, respectively. Interobserver reliability for ROI measurements and FLAIR rating were good (interclass correlation coefficient 0.89 and 0.75, respectively).

### Discussion

This prospective study in patients with territorial middle cerebral artery stroke found rFA at CST increased in the first 4.5 hours, and rFA>0.970 reliably predicted whether <4.5 hours had elapsed since onset.

FA is a DTI-metric of the relative difference in water diffusivities along multiple axes expressed by 3 eigenvalues: lambda 1 (principal axis or axial diffusivity), representing water motion along the length of axons, and lambda 2 and lambda 3 (shorter perpendicular axes or radial diffusivity), indicating perpendicular water diffusion across the axon.5 Oligodendrocyte swelling from cytotoxic edema, one of the earliest morphological changes after stroke, results in extraxonal water and compression of the axoplasm by swollen myelin sheaths, which translates to greater decline in radial than axial water diffusivity in infarcted white matter and increased rFA.5,6 Although the cellular basis of this phenomenon is not completely clear, it could explain the increase in rFA in the first 4.5 hours (Figure 2A). Our findings of elevated FA in hyperacute stroke are consistent with previous studies.4,6–11 As the infarct evolves over time, the breakdown of the axons eventually results in massive water accumulation in axon tracts that translates to hyperintensity in FLAIR and T2-weighted images.10 In the hyperacute stage, large decreases in FA suggest loss of cellular integrity with irreversible axonal injury not reflected on conventional MRI (Figure 2B). We detected significant FA alterations only in the CST, probably attributable to the greater anisotropy of the tightly packed single-directed fibers.

### Table. Diffusion Metrics and Signal Characteristics According to Stroke Evolution

<table>
<thead>
<tr>
<th></th>
<th>&lt;4.5 h (n=25)</th>
<th>&gt;4.5 h (n=23)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), mean±SD</td>
<td>66.7±16.0</td>
<td>69.7±13.0</td>
<td>0.485</td>
</tr>
<tr>
<td>Sex (Men/Women)</td>
<td>16/9</td>
<td>15/8</td>
<td>0.930</td>
</tr>
<tr>
<td>Stroke onset to MRI (min), mean±SD (n)</td>
<td>182.3±65.6 (25)</td>
<td>485±152 (23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NIHSS score, mean±SD</td>
<td>10.6±6.36</td>
<td>12.3±6.3</td>
<td>0.315</td>
</tr>
<tr>
<td>Stroke mechanism</td>
<td></td>
<td></td>
<td>0.105</td>
</tr>
<tr>
<td>Large artery, n (%)</td>
<td>8 (32)</td>
<td>10 (43.5)</td>
<td></td>
</tr>
<tr>
<td>Cardioembolic, n (%)</td>
<td>7 (28)</td>
<td>7 (30.3)</td>
<td></td>
</tr>
<tr>
<td>Indeterminate/other, n (%)</td>
<td>10 (40)</td>
<td>6 (26.1)</td>
<td></td>
</tr>
<tr>
<td>FLAIR (normal/hyperintensity; n)</td>
<td>19/6</td>
<td>5/18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>rFA cortical GM, mean±SD (n)</td>
<td>1.209±0.295 (18)</td>
<td>1.064±0.278 (17)</td>
<td>0.146</td>
</tr>
<tr>
<td>rFA subcortical WM, mean±SD (n)</td>
<td>1.189±0.392 (13)</td>
<td>1.416±0.522 (10)</td>
<td>0.247</td>
</tr>
<tr>
<td>rFA deep GM, mean±SD (n)</td>
<td>1.175±0.184 (13)</td>
<td>1.030±0.296 (9)</td>
<td>0.170</td>
</tr>
<tr>
<td>rFA CST, mean±SD (n)</td>
<td>1.178±0.287 (18)</td>
<td>0.826±0.209 (17)</td>
<td>0.001</td>
</tr>
<tr>
<td>rMD cortical GM, mean±SD (n)</td>
<td>0.682±0.122 (13)</td>
<td>0.529±0.212 (11)</td>
<td>0.036</td>
</tr>
<tr>
<td>rMD subcortical WM, mean±SD (n)</td>
<td>0.632±0.148 (13)</td>
<td>0.607±0.180 (8)</td>
<td>0.733</td>
</tr>
<tr>
<td>rMD deep GM, mean±SD (n)</td>
<td>0.695±0.166 (16)</td>
<td>0.728±0.255 (13)</td>
<td>0.679</td>
</tr>
<tr>
<td>rMD CST, mean±SD (n)</td>
<td>0.703±0.235 (18)</td>
<td>0.622±0.248 (17)</td>
<td>0.339</td>
</tr>
<tr>
<td>rADC cortical GM, mean±SD (n)</td>
<td>0.670±0.139 (13)</td>
<td>0.506±0.132 (10)</td>
<td>0.009</td>
</tr>
<tr>
<td>rADC subcortical WM, mean±SD (n)</td>
<td>0.670±0.214 (13)</td>
<td>0.581±0.119 (9)</td>
<td>0.273</td>
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<tr>
<td>rADC deep GM, mean±SD (n)</td>
<td>0.680±0.185 (16)</td>
<td>0.756±0.206 (12)</td>
<td>0.311</td>
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<tr>
<td>rADC CST, mean±SD (n)</td>
<td>0.707±0.178 (18)</td>
<td>0.574±0.132 (17)</td>
<td>0.018</td>
</tr>
<tr>
<td>rT2WI SI cortical GM, mean±SD (n)</td>
<td>1.172±0.297 (13)</td>
<td>1.158±0.139 (10)</td>
<td>0.889</td>
</tr>
<tr>
<td>rT2WI SI subcortical WM, mean±SD (n)</td>
<td>1.076±0.218 (13)</td>
<td>1.295±0.397 (8)</td>
<td>0.117</td>
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<tr>
<td>rT2WI SI deep GM, mean±SD (n)</td>
<td>1.113±0.255 (18)</td>
<td>1.168±0.242 (17)</td>
<td>0.537</td>
</tr>
<tr>
<td>rT2WI SI CST, mean±SD (n)</td>
<td>1.036±0.143 (18)</td>
<td>1.221±0.192 (17)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

ADC indicates apparent diffusion coefficient; FA, fractional anisotropy; FLAIR, fluid-attenuated inversion recovery; GM, gray matter; MD, mean diffusivity; NIHSS, National Institutes of Health Stroke Scale; r, ratio; T2WI SI, signal intensity on T2-weighted imaging; and WM, white matter.
Certain limitations merit comment. Manual ROI placement is subject to operator bias; automated ROI analysis or voxel-based analysis may resolve this issue. Our small sample limits the power of our findings. The rFA cutoff value was not applicable to other regions of territorial infarction, although most patients (72.91%) had CST damage. The expected rate of CST involvement in real-world practice is, therefore, critical to the applicability of the technique, and an independent validation cohort would be necessary. Finally, analyzing radial diffusivities might provide additional information about stroke time.4

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**Figure 1.** Predicting stroke evolution <4.5 hours using receiver operating characteristic analysis. ADC indicates apparent diffusion coefficient; CST, corticospinal tract; FA, fractional anisotropy; FLAIR, fluid-attenuated inversion recovery; GM, gray matter; and r, ratio.

**Figure 2.** Hyperacute and acute infarcts in the right deep middle cerebral artery territory. A, Slightly increased signal intensity (SI) on fractional anisotropy (FA) maps at corticospinal tract (CST; arrows) with normal fluid-attenuated inversion recovery (FLAIR)/T2-weighted imaging (T2WI). B, Markedly decreased FA on the CST (arrows) reflects the loss of axonal integrity. Lower anisotropy predicts stroke onset better than T2/FLAIR images, in which marked SI would have been expected (11 hours from onset). ADC indicates apparent diffusion coefficient; and r, ratio.
In conclusion, our preliminary results suggest that FA at CST can reliably discriminate ischemic strokes with onset <4.5 hours.

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Disclosures
None.

References
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Online Figure. rFA between the affected and unaffected sides at the CST according to time from stroke onset. The line parallel to the x-axis represents the prespecified cutoff point that discriminates patients <4.5 hours and > 4.5 hours on the basis of rFA. The graph shows medians and quartiles. rFA indicates fractional anisotropy ratio; CST= corticospinal tract.