Increased Anisotropy in Acute Stroke
A Possible Explanation

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Background and Purpose—The increase in fractional anisotropy (FA) in acute stroke has yet to be explained. Using an engineering methodology known as pq diagrams, we sought to explain the increase in FA by describing changes in the total magnitude of the diffusion tensor (L) as well as the isotropic (p) and anisotropic (q) components.

Methods—Diffusion tensor imaging was performed in 10 patients with stroke <27 hours old. The diffusion tensor was decomposed into the p and q components and plotted to describe the diffusion trajectories. FA was also calculated and compared.

Results—There was significant and consistent reduction in p, q, and L (p: mean, −50.0%; range, −36.6% to −64.5%; q: mean, −50.8%; range, −30.8% to −72.8%; L: mean, −50.3%; range, −37.0% to −65.1%). There were inconsistent changes in FA (mean, −0.5%; range, −44.9% to +45.0%). Five patients had elevated FA due to proportionately higher loss of L than q.

Conclusions—Changes in FA only occur when there is a change in the ratio of q/L. Acute elevation of FA occurred in the context of a larger reduction in L than q. The elevation in FA occurs in the context of a reduction in the anisotropic tensor and therefore is a consequence of ratio-metric measurement. This appears to clarify the reported increase in FA in terms of alterations in the shape of the apparent diffusion tensor. pq diagrams appear to offer improved resolution of acute diffusion changes in ischemia. (Stroke. 2002;33:1517-1521.)

Key Words: diffusion ■ magnetic resonance imaging ■ stroke

The diffusion tensor is derived from diffusion-weighted images, characterizing the magnitude of tissue water diffusion in each voxel as a rotationally invariant ellipsoid.1, 2 Acute cerebral ischemia is characterized by an acute reduction in the apparent diffusion coefficient over 4 to 6 hours that may be reversible if perfusion is reestablished within a critical period of ischemia.3 An acute increase in fractional anisotropy (FA) of almost 20% is seen immediately after the onset of ischemia4 and is followed by a significant reduction in FA into the chronic phase.5–6

Anisotropic diffusion is most prominent in white matter within the brain, where water preferentially diffuses along axons.7 The measured apparent diffusion anisotropy is reduced in normal brain regions such as the pons, where structures promoting anisotropic diffusion are not coherently arranged.8 The acute increase in FA has been linked to cytotoxic edema9 that does not entail a significant change in structural coherence. Measurements of diffusion anisotropy relate the longitudinal diffusivity to the transverse diffusivities. The relative magnitudes of diffusion along these axes (the eigenvalues) may be different, giving rise to different shapes of diffusion ellipsoids. For instance, a “cigar”-shaped diffusion ellipsoid has transverse diffusivities that are equal but are shorter than the major axis. Expression of this anisotropy must reflect changes in all axes of diffusion. In the case of a “disc”-shaped diffusion ellipsoid, there are different magnitudes of diffusion in all 3 axes. If a reduction in the smallest transverse diffusivity is offset by an increase in the larger of the transverse diffusivities, there will be no change in the mean transverse diffusivity of the diffusion ellipsoid, but there will be an increase in anisotropy as measured with the use of indices such as FA.

Furthermore, detection of this acute elevation in FA is problematic because the increase is not large, has a short time course, and relies on comparison with a control region of interest (ROI) that may not be a direct anatomic comparison. In the absence of a control ROI, identification of an elevated FA is not possible because FA varies continuously throughout the normal brain.

The aim of the study was to explore the diffusion tensor and find possible reasons for this apparent increase in tissue diffusion anisotropy.
Subjects and Methods

Ten patients (2 female) with a mean age of 70 years presenting with acute stroke were imaged with diffusion tensor imaging. The mean time to imaging was 16 hours (range, 4 to 27 hours) from the known onset of symptoms. Informed patient consent was obtained. The local research ethics committee approved the study.

All patients were imaged on a 3.0-T clinical whole body magnet (Bruker Medspec x300; Bruker Medical). Sequences included a dual proton-density and T2-weighted fast spin-echo sequence; spin-echo, echo-planar diffusion-weighted imaging; and dynamic susceptibility contrast perfusion imaging. Only the diffusion-weighted imaging results are reported in this study.

Diffusion tensor imaging was performed with the use of a single-shot spin-echo, echo-planar imaging technique, with Stejskal-Tanner diffusion-sensitizing pulses. The diffusion-weighted imaging parameters were as follows: 250 x 250-mm field of view, 128 x 128 matrix size, 8 to 10 axial slices, 5-mm slice thickness, repetition time = 5070 ms, echo time = 107 ms; diffusion-sensitizing pulse duration (Δ) = 21 ms with separation; leading edge to leading edge (ΔL) = 66 ms.

Diffusion tensor data sets were calculated from the ADC measurements in 12 noncollinear gradient directions from 5 b values distributed equidistantly in the interval of b(min) = 318 s/mm², b(max) = 1541 s/mm².11

Analysis of the Diffusion Tensor

The diffusion in tissue can be mathematically represented as a symmetrical second-order Cartesian tensor such that D = dᵢⱼ as follows:

\[
D = \begin{bmatrix}
d_{11} & d_{12} & d_{13} \\
d_{21} & d_{22} & d_{23} \\
d_{31} & d_{32} & d_{33}
\end{bmatrix}
\]

From this mean diffusion tensor, the eigenvalues (λᵢ) are calculated with the use of a standard decomposition12 as λ₁, λ₂, and λ₃, with no particular order attached to the subindices.

Analysis of tensor matrices originated in continuum mechanics to describe the stress tensor. The diffusion tensor is mathematically analogous to this and can be decomposed as follows: D = λ₁D₁ + λ₂D₂ + λ₃D₃, where D₁ represents mean diffusivity and I the identity tensor.

The magnitude of the first term on the right-hand side of the equation represents the scalar invariant isotropic component of the tensor (represented hereafter as p), while the magnitude of the second term describes the anisotropic component of the tensor (represented as q). If these 2 variables are then taken as the axis of the xy plane, we are able to visualize simultaneously the values of the p and q components for the tensor. This plane is known as the pq plane.

On the basis of the eigenvalues of the diffusion tensor, a series of scalar indices13,14 can be derived on the basis of the invariants of the tensor. The 3 most commonly used in diffusion tensor imaging are as follows: the mean diffusion (D or p), FA, and relative anisotropy (RA). These can be mathematically related to the eigenvalues of the diffusion tensor, as follows:

\[
p = \frac{1}{3} \text{trace}(D) = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}
\]

with the deviatory component of diffusion (q) defined as

\[
q = \sqrt{(\lambda_1 - D)^2 + (\lambda_2 - D)^2 + (\lambda_3 - D)^2}
\]

and the Euclidean magnitude of the tensor (L) defined as

\[
L = \sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}
\]

This yields the RA, as follows:

\[
RA = \frac{\sqrt{3}}{3} q
\]

and the FA, as follows:

\[
FA = \frac{\sqrt{2}}{2} \frac{q}{L}
\]

From these equations, maps of FA, p, and q were produced from the diffusion tensor data sets for each patient. Then 3 x 3-voxel ROIs were selected in a representative slice through the epicenter of the lesion. These included the lesion and a control ROI situated contralateral to the lesion. Then p, q, RA, and FA were computed.

Results

The p and q components of diffusion were consistently reduced (Table). The mean change in p was -50.0%, with a range of -36.6% to -64.5%. q was similarly reduced by a mean of -50.8% and a range of -30.8% to -72.8%. This resulted in a consistent reduction in the Euclidean magnitude of the tensor (L) (mean, -50.3%; range, -37.0% to -65.1%). The trajectories described by the control and lesion ROIs resulted in inconsistent changes in FA (mean, -0.5%; range, -44.9% to +45.0%) (Figure 1). In 5 patients the lesion ROI had an increase in FA

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time to Imaging, h</th>
<th>p</th>
<th>q</th>
<th>L</th>
<th>FA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Lesion</td>
<td>Difference</td>
<td>Control</td>
<td>Lesion</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>0.66</td>
<td>0.30</td>
<td>-54.7%</td>
<td>0.45</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>0.54</td>
<td>0.24</td>
<td>-55.0%</td>
<td>0.67</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>0.62</td>
<td>0.22</td>
<td>-64.5%</td>
<td>0.66</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>0.61</td>
<td>0.28</td>
<td>-54.5%</td>
<td>0.34</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>0.55</td>
<td>0.34</td>
<td>-39.2%</td>
<td>0.78</td>
</tr>
<tr>
<td>6</td>
<td>21</td>
<td>0.57</td>
<td>0.27</td>
<td>-52.4%</td>
<td>0.31</td>
</tr>
<tr>
<td>7</td>
<td>24</td>
<td>0.64</td>
<td>0.31</td>
<td>-52.4%</td>
<td>0.64</td>
</tr>
<tr>
<td>8</td>
<td>24</td>
<td>0.74</td>
<td>0.47</td>
<td>-36.6%</td>
<td>0.40</td>
</tr>
<tr>
<td>9</td>
<td>24</td>
<td>0.57</td>
<td>0.32</td>
<td>-44.7%</td>
<td>0.74</td>
</tr>
<tr>
<td>10</td>
<td>27</td>
<td>0.60</td>
<td>0.32</td>
<td>-46.0%</td>
<td>0.71</td>
</tr>
<tr>
<td>Mean</td>
<td>16</td>
<td>0.60</td>
<td>0.32</td>
<td>-50.0%</td>
<td>0.45</td>
</tr>
</tbody>
</table>

FA values are 0 to 1, where 0 = no anisotropy (isotropic) and 1 = perfect anisotropy.
compared with the normal contralateral hemisphere. In this patient cohort there was no apparent relationship between changes in indices and the time between the onset of symptoms and diffusion tensor imaging.

**Discussion**

The diffusion tensor matrix contains information about the magnitude of water diffusion in 3 dimensions in an invariant frame of reference and the relationship of this axis to the laboratory frame of reference. Images derived from the diffusion tensor are free from T1, T2, and proton-density weightings, in contrast to diffusion-weighted imaging.

FA is related to both the presence of structures promoting anisotropic diffusion, such as myelinated axons, and the degree of structural coherence in cerebral structure at the voxel. Highly coherent white matter tracts such as the cerebral peduncles are associated with high FA. Gray matter or areas of white matter decussation result in much lower levels of FA. However, equal proportionate changes in q and L of the diffusion ellipsoid will not change FA because this is a ratio of the two. The FA of any tissue type is not unique because 2 different values of q and L will result in the same ratio of q and L and hence the value of FA. pq diagrams can resolve these diffusion tensor changes, showing that the observation of raised FA in acute ischemia is a consequence of the ratio-metric measure FA.

In pq space, p and q represent the x and y components, respectively, of the Euclidean magnitude of the measured diffusion tensor (L). FA and RA are both related to the angle (α) subtended by L (Figure 2a). With reference to equations 3 and 4 shown above, a line passing from the origin represents an isocontour of RA and FA. Thus, it is possible for a lesion and control ROI to have similar values of FA despite different values of p, q, and L (Figure 2b). A proportionately larger loss of q than p would result in the new tensor subtending a smaller angle (β), resulting in a reduction in FA (Figure 2c), and vice versa (Figure 2d). FA is already limited as a measure in that it is continuously variable across the cerebral parenchyma and hence has no normal range of values. Changes are currently resolved by comparison with a contralateral control ROI, with consequent introduction of registration errors.

Significant limitations remain in statistical testing of the diffusion properties of ROIs. Large ROIs necessarily introduce increases in measures of spread due to anatomic
variation across the ROI, the distribution of which cannot be assumed to be symmetrical. If only a small number of voxels are included in an ROI, then measurement uncertainty exists because of the presence of noise and the small sample size. Differences in the starting point and direction of the tissue trajectory prevent the use of multiple patients to minimize noise and achieve statistical significance. Standardization of diffusion changes by calculation of a ratio of the diffusion properties of the lesion to a contralateral control presumes that diffusion changes occur linearly across all values of p and q. In light of this, standard measures of spread are not meaningful and may even be misleading.

An acute increase in FA was seen with variable magnitude in only 5 of 10 patients in this study. This is in contrast to p, q, and L, which showed a consistent reduction in all 10 patients.

For some voxels within the ROI, there has been a disproportionate loss of isotropic over anisotropic diffusion, resulting in a small increase in FA, as observed by others. Yang et al discussed possible explanations for the increase in apparent anisotropy in acute ischemia. Increased tortuosity of the extracellular space and movement of water into the more restricted environment of the intracellular space may both occur with cytotoxic edema. Both of these models result in increased directionality of diffusion along the axon and hence increased apparent anisotropy. Carano et al demonstrated an increase in FA in an animal model of cerebral ischemia. FA increased in cortical and subcortical regions, to nearly 120% relative to the contralateral side, after only 15 minutes. This was followed by a steady decrease in FA such that lesion and control FA were normal between 1 and 2 hours after ictus and continued to decline even after reperfusion had been established after 1 hour. In the 10 patients presented here, there was no apparent relationship between the duration of symptoms at the time of the scan and FA, p, or q, although this possibly reflects the heterogeneity in the ischemic lesions and the small sample size. Of interest, it was possible to demonstrate an increase in FA of 8% in 1 patient as long as 24 hours after the onset of symptoms.

It is likely that the exact values of measured p and q are technique dependent because water distribution is broadly compartmentalized into intracellular and extracellular compartments. The strength of the MR signal used to measure the apparent diffusion of water in tissue is determined by the relaxation of protons in each compartment, the restrictions to diffusion in each compartment, and the ability for water protons to exchange between compartments through cellular membranes. Changes in the measured diffusion ellipsoid, and hence p and q, can potentially arise from changes in proton relaxation, diffusion, and compartmental volumes, which are known to occur in pathological conditions such as stroke. Different technical factors will also affect the proportion of the signal arising from each water compartment. For example, increasing the echo time will increase the signal contribution from the extracellular space, which has slower T2 relaxation. The use of very high b factors in diffusion tensor imaging results in markedly different maps of the diffusion tensor because of increased weighting toward more slowly diffusing water. The measured diffusion tensor will reflect the interplay between imaging parameters and pathological variation in the compartmentation of water.

Conclusions

The information contained in the whole diffusion tensor cannot be displayed on a single image, necessitating the use of indices. Changes in FA only occur when there is a change in the ratio of q/L. In acute stroke, there is a large reduction in q, p, and L. Acute elevation of FA appears to occur when there is a larger reduction in L than q. The elevation in FA occurs in the context of a reduction in the anisotropic tensor and therefore is a consequence of ratio-metric measurement. As a result, q and p appear to be more informative measures of diffusion changes in acute stroke.

Acknowledgments

This study was supported by the Cambridge Commonwealth Trust and Christ’s College Cambridge (to Dr Green). Dr Peñia is in receipt of a Wellcome Trust fellowship in mathematical biology, and Dr Warburton is in receipt of a PPP fellowship. This study was also supported in part by the Medical Research Council and Technology Foresight. We gratefully acknowledge the help of Arash Mostofi, Tim Donovan, Victoria Lupson, and Ruth Bisbrow-Chippendale.

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Stroke. 2002;33:1517-1521
doi: 10.1161/01.STR.0000016973.80180.7B
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/33/6/1517

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