Significant Changes in Diffusion Anisotropy are Associated with Time of Onset After Stroke

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Introduction: Many attempts have been made at using Diffusion Tensor Imaging (DTI), in particular indices of diffusion anisotropy, to characterize the progression of acute (<24 hours) ischemic lesions, and to predict the severity of the ischemic insult and outcome after stroke [1-8]. However, studies reporting changes in fractional anisotropy (FA) have been variable with some groups suggesting that FA may be reduced acutely [2, 3], whereas others have proposed an elevation [4], or a mixture of changes [5-8]. Although reductions in FA are likely due to the loss of structural integrity of cells and membranes [1, 3], the determinants of elevated FA are not well established. Controversies surrounding FA trends following stroke onset may be analytical in nature arising from the practice of sampling larger regions-of-interest (ROIs) that encompass different types of white matter (WM) tracts or both WM and gray matter (GM) areas within the ROI in the ischemic core [2, 4-5, 7-8]. Due to the variability of anisotropy in WM tracts throughout the brain, diffusion parameters evaluated for individual WM tracts would enable a more robust quantification of tissue-specific FA changes in acute stroke. The purpose of this study was to determine the changes of diffusion anisotropy in anatomically distinct ischemic WM relative to normal contralateral WM per slice in stroke patients within 36 hours of onset with an emphasis on less than 14 hours. Further insights into changes of anisotropy were obtained by evaluating the eigenvalues, λ_1, λ_2, and λ_3 of the diffusion tensor within ischemic WM.

Methods: Sixteen patients (11M, 5F; age range= 46-91 years) were scanned on a Siemens 1.5T Sonata scanner within 36 hours of presenting with a non-hemorrhagic ischemic stroke (mean time of first MR= 14 ± 9 hours, range= 2-34 h). DTI was performed with: TR / TE / NEX = 3.2 s / 88 ms / 8, 96x128 matrix zero filled to 256x256, 22 cm FOV and twenty 5 mm-thick contiguous axial slices aligned with the AC-PC, b = 0 s/mm^2 and six sets with b = 1000 s/mm^2. Additionally an EPI based sequence (EPI GMWM) with good gray-white matter contrast was used to aid ROI placement (TR / TE / TI / NEX = 5.5 s / 57 ms / 200 ms / 4, with identical matrix, FOV and slice coverage as DTI). The acquisition time was 3 min for DTI and 57 secs for EPI GMWM. Unique WM regions within the acute ischemic lesion (defined by 30-50% drop in trace ADC relative to the contralateral side) were traced separately using a free hand ROI with the aid of the EPI GMWM images and FA maps. Measurements of FA, ADC// (λ_1), ADC⊥ ((λ_2+λ_3)/2), and T2-weighted signal intensity (b=0 images) of the corresponding WM tract in the normal contralateral hemisphere were used as a reference. Relative (ipsi/contra) means and standard deviations were calculated for each specific tract and were then grouped into either major WM or subcortical WM (in the gyri). The percentage of total ROIs showing changes in rFA were calculated per patient, where significant increases or decreases were considered to be ±10% of contralateral values. Paired t-tests were used to analyze differences between the ipsilateral and contralateral trace ADC, FA, ADC//, ADC⊥, and T2-weighted signal intensity ($p \leq 0.05$).

Results and Discussion: Nine patients had involvement of both major and subcortical (in the gyri) WM tracts (e.g. **Fig. 1**), and out of the remaining 7, 4 had only major WM tracts and 3 had only subcortical gyral WM areas that were involved within the trace ADC-defined infarct.

Major WM Tracts – Lesions with mean decreases of ~40% in relative (r) trace ADC demonstrated an average rFA of 1.17 ± 0.15 (p=0.0002) during the hyperacute (2-3 h) phase (**Fig. 2**). In the acute (7-14 h) and subacute (28-34 h) phases, rFA declined to 0.84 ± 0.13 (p<0.01) and 0.88 ± 0.09 (p=0.0007). It is interesting to note that 74% of the evaluated WM ROIs in the hyperacute phase showed an increase in rFA as opposed to only 3% or 0% of the ROIs evaluated at the acute and subacute phases, respectively (**Fig. 3**). Furthermore, 66% and 62% of the ROIs demonstrated reductions in rFA at the acute (7-14 h) and subacute (28-34 h) phases, whereas there were none at the hyperacute (2-3 h) time point. Relative ADC// for major WM tracts declined by 33% during the hyperacute phase, further decreasing to 45% and 47% in the acute and subacute phases (p<0.01). Significant reductions of 39%, 36%, and 41% were noted in rADC⊥ (p<0.01) from the hyperacute to the subacute phase. The steeper decline of rADC⊥ relative to rADC// (p=0.002) in the hyperacute phase accounts for the increased FA, whereas in the acute and subacute phases, greater reductions in rADC// relative to rADC⊥ (p<0.01) account for the reduction in FA within major WM tracts. Our findings also revealed that rT2-wt signal intensity increased by 8%, 19%, and 24% from the hyperacute to the subacute phase (p<0.01), with an inverse correlation between mean rFA and rT2 (R=-0.41, p=0.0008).

Subcortical WM (in the gyri) demonstrated changes in rFA similar to major WM tracts with increases in mean rFA hyperacutely (1.15 ± 0.23, p<0.01), and reductions acutely (0.92 ± 0.19 p=0.01), and subacutely (19-34 h; 0.90 ± 0.26, p=0.01), although the results were more variable. Findings of elevated FA in the hyperacute phase in animal [1] and human [4-7] stroke studies have been attributed to cell swelling during cytotoxic edema, that could decrease myelin fiber bundle spacing in WM and increase extracellular tortuosity, leading to a restriction of water movement perpendicular to the fiber direction.

Conclusion- Although ischemic areas demonstrated consistently low trace ADC (~40% decrease) with time of onset, diffusion anisotropy of the major central and subcortical WM tracts was significantly elevated in the hyperacute phase, and reduced in the acute and subacute phases. Variable reductions in ADC// and ADC⊥ provide complementary information to interpret these changes in FA. The transition zone from high FA to lower FA appears to lie between 3 and 7 hours post symptom onset after stroke.

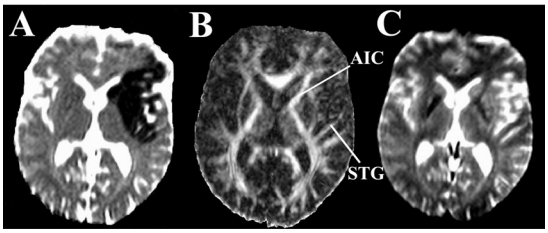

Figure 1: Trace ADC (A), FA (B), and T2-weighted (C) images from a 51 year-old patient 2 hours post stroke onset. On the FA map (B), elevations in anisotropy were measured in several WM tracts such as the anterior limb of the internal capsule (AIC, 36% increase), and the superior temporal gyrus (STG, 12% increase) in areas of low trace ADC (39% decline) within the left MCA distribution.

References: [1] Sotak NMR Biomed, 15:561 (2002). [2] Zelaya *et al* MRI, 17:331(1999). [3] Sorenson *et al* Radiology, 212:785 (1999). [4] Schaefer *et al* AJNR, 24:436 (2003). [5] Green *et al* Stroke, 33:1517 (2002). [6] Yang *et al* Stroke, 30:2382 (1999). [7] Ozunar *et al* AJNR, 25:669 (2004) [8] Harris *et al* JMRI, 20:193 (2004).

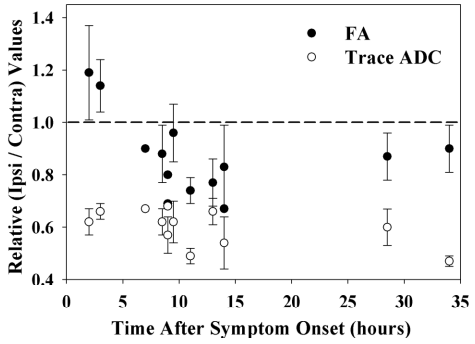

Figure 2: Comparisons of relative FA and trace ADC values in ischemic major WM tracts within 2-34 hours of symptom onset in 13 patients. Values are mean ± SD over the ROIs and slices per patient.

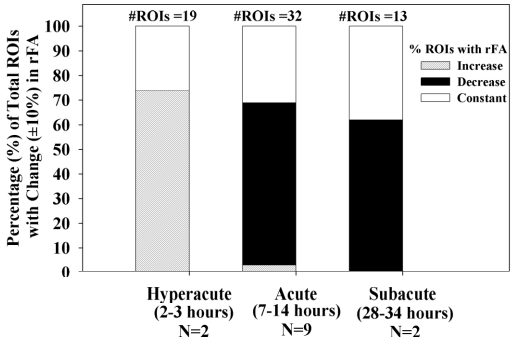

Figure 3: Percentage of major WM ROIs in lesion with either increase, decrease, or no change of rFA in 13 patients.