

Elevations of Diffusion Anisotropy are Associated with Hyper-Acute Stroke: A Serial Imaging Study

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Introduction: Diffusion tensor imaging (DTI) studies of stroke patients have consistently demonstrated marked reductions of fractional anisotropy (FA) within the lesion (~29-70% FA decreases) or regions remote (upstream or downstream) from the infarct (~8-40% FA reductions) over a time course of 2 days to 1 year [1,2]. However, DTI studies of acute stroke are more variable. Increased FA within the first day of stroke has been observed, but this is not as consistent as several others report reductions, or no change in FA over the same time frame [3,4]. A recent cross-sectional DTI study of ischemic white matter (WM) regions showed that FA was only significantly elevated (up to 25%) ≤ 7 h of symptom onset, but consistently reduced (~15% declines) from 8-34h after stroke [5]. Serial DTI scans after ischemic stroke in individual patients may help clarify the discrepancies in some of those previous reports. Previous longitudinal DTI studies of human ischemic stroke that include time points of less than 24h have primarily focused on demonstrating the subsequent reductions of FA that occur at 1 week and several months post symptom onset [4,6]. Serial DTI reports of human stroke that characterize changes in diffusion anisotropy within 24h of stroke onset are non-existent. Mean diffusivity (MD) is consistently low during the first day of stroke; on the other hand, FA may yield discriminating data on the microstructural status of tissue within that time frame. We aimed to characterize serial FA changes during the hyperacute (≤ 7 h) and acute (21.5-29h) phases of human stroke. Deep and subcortical WM and deep and cortical GM regions within the infarcts were analyzed individually due to the known variability in normal FA values within these regions as well as to assess whether there are different evolution patterns for the anisotropic water diffusion.

Methods: Thirteen patients (6M, 7F; age range= 45-80 years) presenting with an ischemic stroke were initially scanned on a Siemens 1.5T Sonata scanner equipped with an 8-element head RF coil within 2.5-7h of symptom onset (median of 5h), and then subsequently scanned within 21.5-29h for a follow-up session (median of 26h). Modified SENSE based DTI (R=2 and 24 reference lines) was performed with: TR / TE / NEX = 2.5s / 81ms / 8, 96x128 matrix, 195x260 mm rectangular FOV with R-L phase-encode direction, and 20 3-mm thick contiguous axial slices aligned with the AC-PC, b=0 s/mm² and six sets with b=1000 s/mm². The 20 3-mm thick contiguous slices for DTI were centered on the lesion identified on conventional diffusion-weighted images. The acquisition time was 2 min 37 s for DTI. Raw data were post-processed off-line to yield maps of the eigenvalues λ_1 , λ_2 , and λ_3 , MD and FA. Discrete WM and GM regions within the ischemic lesion (defined by $\geq 30\%$ drop in MD relative (r) to the contralateral side) were traced using a free-hand Region-of-interest (ROI) method with the aid of the FA and MD maps, as well as the isotropic DW (b=1000) images separately for individual patient scans from the hyperacute and acute periods. A semi-automated method was employed to threshold the MD maps and all ROI traces were cross-checked with b=1000 images to avoid inclusion of any visible sulcal spaces. This was particularly important in cases where ROIs adjacent to cerebrospinal fluid filled sulcal spaces such as subcortical WM and cortical GM were part of the ischemic core. Measurements of FA, λ_1 , λ_2 , λ_3 , and T2-weighted signal intensity (measured on b=0 images) of the corresponding WM and GM regions in the contralateral hemisphere were used as a reference to yield relative parameters. Data were separated into categories of deep WM, subcortical WM, deep GM and cortical GM. Relative (ipsilateral/contralateral) values for each ROI measurement per patient were averaged over all patients within a distinct scanning period, with respect to the 4 tissues. Paired t-tests were used to examine differences between the ipsilateral and contralateral MD, FA, λ_1 , λ_2 , λ_3 and T2-wt signal intensity (p<0.05).

Results and Discussion: MD values were consistently low (~40% decline) for all 4 tissues over time; however rFA values differed in time for all 4 tissues in that FA was increased (above unity) in the hyperacute phase and subsequently reduced in the acute phase in most patients after stroke (e.g. Fig. 1). Overall, 9/13 patients within 7h post symptom onset showed elevated FA in at least one of the four tissues, and within the same cohort, 11/13 patients showed reduced FA in at least one of the ischemic WM and GM regions at 21.5-29h after stroke. Steady increases in rT2-wt signal intensity were seen in all 4 tissues from the hyperacute to the acute period of stroke onset.

WM lesions- Of the 10 patients that had deep WM lesions (Fig. 2), FA was elevated in 4 patients (7-21% higher than contralateral regions; mean rFA= 1.10 \pm 0.11, p<0.01) hyperacutely (2.5-7h), and reduced in the same 4 patients during the acute phase (21.5-29h) of stroke onset (0.96 \pm 0.12, p=0.02). On average, in the 4 patients showing elevated rFA in deep WM tracts hyperacutely (2.5-7h), the r λ_1 , r λ_2 and r λ_3 values declined by 39%, 43% and 47%, respectively. The greater reduction of r λ_3 relative to r λ_1 and r λ_2 provides a rationalization for the increased FA. In this same group of 4 patients, the slightly greater reduction of r λ_1 (50% decrease) relative to r λ_2 (44% decrease) and r λ_3 (49%) accounts for the small decrease observed in rFA values in the acute period. In all 10 patients with deep WM lesions, the mean rT2-wt signal intensity was 1.03 \pm 0.11 (p=0.07) hyperacutely and 1.19 \pm 0.13 (p<0.01) acutely, with an inverse correlation between mean rFA and rT2-wt signal intensity (R= -0.29, p=0.03) observed during the hyperacute phase only. Patients with subcortical WM lesions (N=10) demonstrated a similar FA trend, where FA was elevated in 4 patients (8-27% increases; mean rFA= 1.13 \pm 0.14, p<0.01) hyperacutely and reduced in the same group of 4 patients acutely (0.89 \pm 0.14, p<0.01). In WM, the restricted water diffusion perpendicular to the fiber direction and the concurrent increases in FA hyperacutely are suggestive of cellular swelling from cytotoxic edema that results in a) additional water restriction in the axoplasm and b) a more tortuous extracellular environment due to a decrease in myelin fiber bundle spacing [2]. The acute phase (21.5-29h) reductions in FA linked to greater decreases in λ_1 , compared to λ_2 and λ_3 , are suggestive of early axonal injury after stroke [3].

GM lesions- Of the 4 patients with deep GM lesions, only one showed elevated rFA values hyperacutely (1.07 \pm 0.06, p=0.02) and subsequent decreases in the acute period (0.76 \pm 0.09, p=0.01) after stroke. In the group of 8 patients with cortical GM lesions, 5 showed significantly elevated FA values hyperacutely (mean rFA= 1.22 \pm 0.13, p<0.01) and decreases in the acute phase (0.84 \pm 0.11, p<0.01).

Conclusion: The phenomenon of elevated diffusion anisotropy is mainly associated with the hyperacute phase (≤ 7 h) of stroke, with reduced FA primarily noted in the acute (~24h) phase. These findings suggest that diffusion restriction is directionally confined in the hyperacute phase, although this varies with tissue type and location but by ~24 hours after stroke onset, directional restriction decreases as cellular and axonal structures lose integrity.

References: 1-Pierpaoli *et al* Neuroimage, 13:1174 (2001). 2-Sotak NMR Biomed, 15:561 (2002). 3-Sorensen *et al* Radiology, 212:785 (1999). 4-Munoz-Maniega *et al* JNNP, 75:1714 (2004). 5-Bhagat *et al* JCBFM, 26:1442 (2006). 6-Yang *et al* Stroke, 30:2382 (1999).

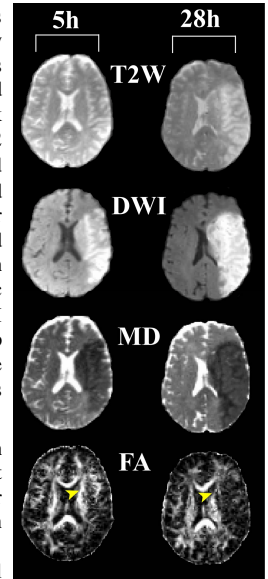


Figure 1: Images of one representative slice from the initial (5h) and follow-up (28h) scanning periods of a 68 year old male patient with a left MCA infarction. The contrast of the FA maps for both time periods was made extreme to better visualize deep WM regions such as the anterior limb of the internal capsule (arrowheads) within the ischemic core where FA was elevated (up to 28%) relative to the contralateral side in the hyperacute phase and declined (11% decrease) acutely post stroke onset.

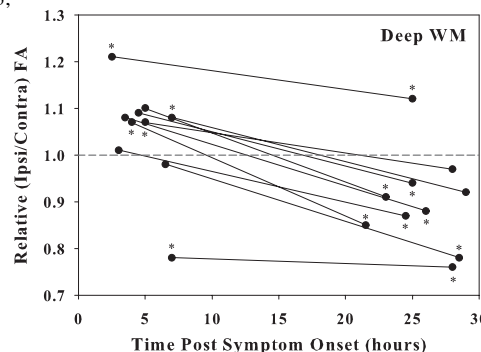


Figure 2: Time course of relative FA in deep WM (N=10) following stroke onset. The solid lines connect the mean rFA serial data points of each patient between the hyperacute (≤ 7 h) and acute (21.5-29h) phases post symptom onset. * indicates significant difference from unity.