Oscillating Gradient Spin-Echo (OGSE) DTI Yields Mechanistic Insights in Human Stroke

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Purpose. Diffusion MRI using pulsed gradient spin-echo (PGSE) diffusion encoding measures a marked decrease in the mean apparent diffusion coefficient (MD) of water after acute ischemic stroke. Insight into the microscopic environment can be gained by varying the "diffusion time", Δ_{eff}. The oscillating gradient spin-echo (OGSE) method enables greatly reduced Δ_{eff} compared to PGSE (Fig 1), which grants sensitivity to diffusion restriction/hindrance over smaller length scales [1]. In a rat model of global ischemia, larger differences between OGSE and PGSE were observed in ischemic grey matter relative to healthy tissue [1]. Also, recent ex-vivo and simulation work has suggested that cellular beading may cause the MD reductions in stroke [2]. While OGSE has been applied to healthy human brain [3-4], it has not yet been applied to human stroke. This work aims to determine the dependencies of MD and eigenvalues on Δ_{eff} in human stroke, and test whether any changes are consistent with cellular beading using simulations.

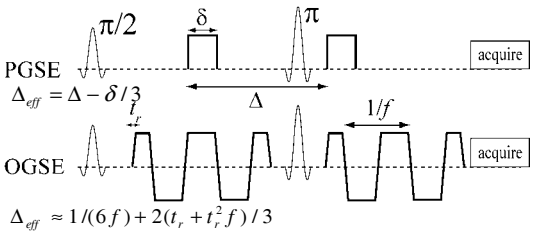

FIG 1: The gradient timing of OGSE (Δ_{eff}=4 ms) yields shorter diffusion times than PGSE (Δ_{eff}=40 ms).

Methods. *In vivo.* DWI was acquired in 5 acute stroke patients (age 40-65; onset 24-72 hr; NIHSSS 1-6) on a Varian Inova 4.7T using OGSE 50 Hz (Δ_{eff} = 4 ms) and PGSE (Δ_{eff} = 40 ms). Two patients each had 2 distinct lesions while the others had 1 lesion each; lesions were partially within white matter in 4 patients. The lesions were outlined on the PGSE DWI and then applied to the OGSE DWI to measure MD in all the lesions (N=7), as well as parallel ($\lambda_{||}$) and perpendicular ($\lambda_{\perp}$) eigenvalues in white matter lesions (N=4). Statistical significance was evaluated using paired t-tests for OGSE relative to PGSE. In a water phantom, consistent MD was measured for OGSE (MD 2.17±0.02 x 10^{-3} mm^2/s) and PGSE (MD 2.18±0.03 x 10^{-3} mm^2/s) (N=4). Both protocols used 2D single-shot EPI with: TR = 12.5 s; TE = 110 ms; FOV = 24 cm; 2x2x2.5 mm^3; 20 slices; 6 averages; R=2 GRAPPA; b = 300 s/mm^2; 6 gradient directions. *Simulation.* Random walk Monte Carlo simulations were performed with Camino [5]. Cylinders with an initial diameter of 4 μm and an intracellular volume fraction (IVF) of 0.7 were modeled as undergoing ischemia-induced beading of amplitude 0.6 [3] and an increase in IVF to 0.78. Simulated OGSE and PGSE diffusion encoding was the same as used in vivo, with a "free" diffusivity of 1.7x10^{-3} mm^2/s (= $\lambda_{||}$ measured in healthy white matter using OGSE).

Results. MD was reduced in the lesions compared to contralateral tissue for PGSE (-44 ± 10%), which is typical, but notably, MD did not reduce nearly as much for OGSE (-14 ± 23%) (Fig 2, 3). In the white matter, $\lambda_{||}$ had a similar trend as MD, with decreases in the lesion of (-44 ± 15%) for PGSE and (-23 ± 21%) for OGSE. Interestingly, while $\lambda_{\perp}$ decreased by (-26 ± 20%) in the lesion for PGSE, it increased by (23 ± 35%) for OGSE. The Monte Carlo simulations exhibited strikingly similar trends for changes of these three diffusion parameters with diffusion time (PGSE 40 ms vs OGSE 4 ms) in healthy tissue and ischemia-induced beading (Fig 3).

Discussion. The differential MD reductions agree with findings in a rat global ischemia model [1]. Only a small difference between OGSE and PGSE is observed in the healthy tissue since cells are not edematous and hence smaller. The increase of $\lambda_{||}$ in the lesion for OGSE vs PGSE suggests the introduction of parallel barriers upon ischemia (i.e. greater reductions at long diffusion times), which the simulations suggest could be due to axonal beading. The results for $\lambda_{\perp}$ are consistent with perpendicular swelling that occurs along with the beading. Notably, the OGSE-PGSE differences observed in the simulations diminished for axon sizes smaller than 4 μm (data not shown), suggesting that the in vivo findings are dominated by large axons; however, smaller diffusion times would increase the sensitivity to smaller axons. In grey matter, the results are consistent with cell swelling.

Conclusion. OGSE has demonstrated diffusion time dependencies of mean, parallel, and perpendicular diffusivities for the first time in human acute ischemic stroke. These results support the hypothesis that MD reductions during stroke are due to cellular beading.

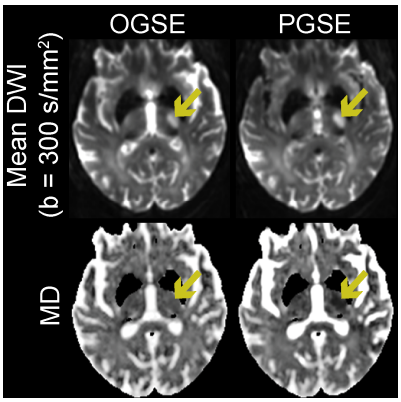

FIG 2: 36 hours post-onset, the lesion has greater MD reduction on PGSE vs OGSE.

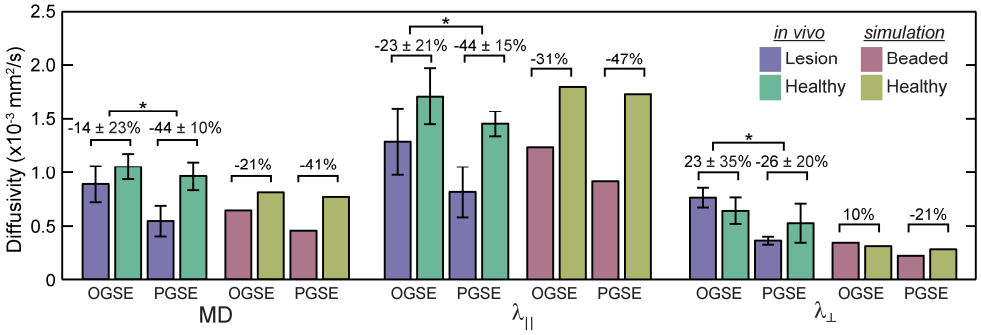

FIG 3: In the patients, MD decreases were observed in lesions compared to healthy tissue (N=7) for OGSE and PGSE; however, decreases were much smaller for OGSE. In the white matter (N=4), a smaller decrease (lesion vs healthy) in $\lambda_{||}$ was observed for OGSE compared to PGSE, while the change of $\lambda_{\perp}$ was opposite for OGSE compared to PGSE. The means of the individual percent changes are shown (* $p < 0.05$). Simulation results show close agreement to the trends observed in vivo.

References. [1] Does MD et al. MRM 49:206 (2003); [2] Budde et al. PNAS 107:14472 (2010); [3] Van et al. MRM doi: 10.1002/mrm.24632 (2013); [4] Baron et al. MRM doi: 10.1002/mrm.24987 (2013); [5] Hall et al. IEEE Trans Med Imag 28:1354 (2009)