Multi-modality 4D Stroke Template for the Characterization of Arterial Ischemic Stroke Evolution Over Time

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Target Audience: Stroke physicians, clinician research scientists, and neuroimaging researchers

Purpose: In addition to the notion of "time is brain," there has been great interest in characterizing the underlying pathophysiology during the evolution of ischemic injury[1]. The emergence of thrombolytic and recanalization therapy has shown promise in improving patient outcomes[2], but the benefit of these treatments is still unproven[3, 4, 5]. Considering cerebral ischemia is now understood to be a complex and dynamic process, serial neuroimaging that includes both pre- and post-therapy time points provides insight on the dynamics of reperfusion and may be useful in the guidance of further interventions. Here we demonstrate that a multi-modal four-dimensional ischemic stroke template of middle cerebral artery (MCA) stroke can be used to characterize the effects of thrombolytic intervention over time as ischemic brain tissue makes the transition from injury into repair.

Methods: The 4D MCA stroke template was built from data collected from May 2010 to September 2013 in an ongoing prospective registry of MCA stroke patients evaluated with diffusion-perfusion MRI at our academic medical center. A total of 360 MRI studies, of which 244 studies were from patients who received thrombolytic and/or recanalization therapy, were used. For each patient, a routine clinical MRI protocol was performed at various time points following stroke onset and included diffusion weighted imaging (DWI), gradient recalled echo (GRE), fluid attenuated inversion recovery (FLAIR), and 3D GRASE pseudo-continuous arterial spin labeling (pCASL) perfusion imaging sequences. ASL images were corrected for motion, subtracted pairwise between label and control images, averaged to generate the mean difference image, and converted to quantitative cerebral blood flow (CBF) maps[6]. CBF maps, GRE, and FLAIR images were co-registered with DWI for each time point in each subject and normalized into the MNI template using SPM8. All normalized imaging modalities were displayed on the same axial slices and, if necessary, flipped such that all ischemic regions were on the left before processing with Matlab programs developed in-house. To construct a continuous template of 3D volumes, a moving average was calculated based on the ASL time from the last known well time (LKWT) for each modality. Logarithmically increasing window sizes were used to account for higher scan density in the first few hours after stroke, with each window containing 10-33 scans. Statistical testing was performed using SAS 9.4 to determine if there was a relationship between treatment and measurements of the injured leptomeningeal MCA territory for each modality over time. Since many subjects had more than one scan, a quadratic mixed model with a subject random effect and time (in log [hours]), treatment (yes/no), and time*time*treatment fixed effects was used. Statistical significance was considered at $P<0.05$.

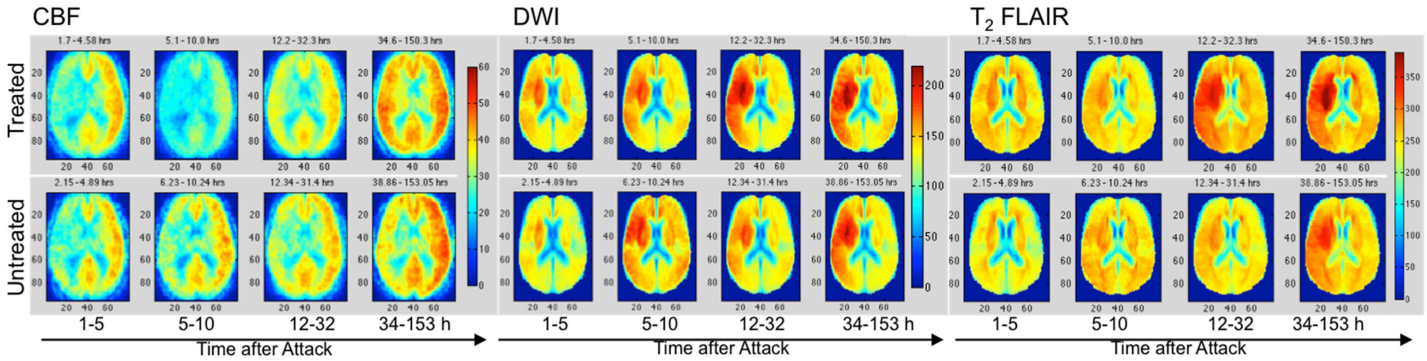

Figure 1. Representative moving average center-slice maps from the 4D stroke template of CBF, DWI, and FLAIR for treated (top row) and untreated (bottom row) patients over a time span of 153 hours from LKWT.

Results: Figure 1 shows center-slice snapshots of CBF, DWI (b=1000), and FLAIR maps during 4 representative time windows from the treated and untreated 4D stroke templates. The image series for CBF are most remarkable, since it is evident that the injured brain tissue does not reperfuse completely when left untreated. By contrast, treated patients exhibit a global decrease in perfusion before or around treatment administration followed by a hyperemic response. In DWI and FLAIR, the typical progression of the injury core formation is seen over time. Figure 2 shows the mean time courses of CBF, DWI, and FLAIR signals as measured in the ischemic leptomeningeal MCA territory. For CBF, there is a significant difference between the treated and untreated trajectories over time. When evaluating the quadratic behavior of the time course, the interaction between time^2 and treatment is significant ($P<0.04$), indicating that the CBF time course follows a different quadratic trajectory when treatment is administered. No significant difference was found between treated and untreated group trajectories in DWI and FLAIR.

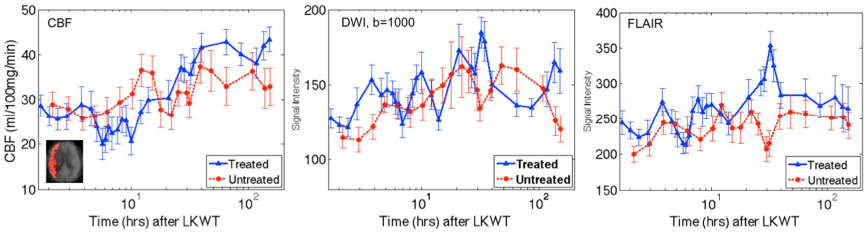

Figure 2. Mean time courses of CBF, DWI (b=1000), and FLAIR measurements within ischemic leptomeningeal MCA territory for treated (blue) and untreated (red) groups are shown in log scale. Error bars indicate standard error of the mean (SEM). A center-slice map of the ROI used to measure the ischemic region is inlaid in the CBF plot.

Discussion and Conclusion: The multi-modal 4D stroke template sheds light on the dynamic pathophysiological changes of ischemic brain tissue as it undergoes repair either with the aid of thrombolytic and/or recanalization therapy or on its own. Although the ischemic core of injury still forms over time as seen in DWI and FLAIR, there is clear evidence of hypoperfusion followed by a significant hyperemic response upon treatment that may indicate penumbral tissue transitioning to repair. Future work will expand the patient population base to better represent individual time courses and assist in the early identification of patients who may differentially benefit from intervention, and we aim to make the template publicly available.

References: [1] Ip HL and Liebeskind DS. *Interv Neurol*. 2014; 2: 105–117. [2] Liu R, et al. *Neurol Res.* 2012; 34: 331-7. [3] Kidwell CS, et al. *N Engl J Med*. 2013; 368: 914-23. [4] Chimowitz MI. *N Engl J Med*. 2013; 368: 952-5. [5] Hacke W, et al. *Lancet Neurol*. 2009; 8: 141-50. [6] Wang DJ, et al. *Stroke*. 2012; 43: 1018-24.