Effect of occlusion duration on risk of infarction in a rat embolic stroke model studied with serial MRI-based predictive algorithms

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Introduction*:* Diffusion-weighted MRI (DWI) and perfusion-weighted MRI (PWI) provide insight into extent of tissue injury and hemodynamic disturbance for acute cerebral ischemia. Algorithms have been developed that combine these modalities to predict tissue infarction on a voxel-wise basis in both human and experimental animal cerebral ischemia [1-4]. However, the duration of ischemia, an important parameter for assessing tissue viability, has so far not been taken into consideration in such algorithms. In clinical settings, onset times are often ill-defined and the ability to perform serial MRI examinations are hampered by ethical and logistical considerations. Experimental animal stroke models provide an ideal environment for evaluating the effect of occlusion time on risk of infarction. This study investigates the evolution of the apparent diffusion coefficient (ADC) and PWI-derived hemodynamic parameters and estimated risk of infarction over a 5 h period in an embolic stroke model. Furthermore, these voxel-wise analysis techniques that are sensitive to spatial variations are compared to volumetric analysis approaches.

Materials/Methods: Unilateral stroke was induced in Sprague-Dawley rats by embolic occlusion of the right middle cerebral artery [5]. DWI and PWI from the control arm of a trial of thrombolytic treatment with pamiteplase were retrospectively analyzed (n=8) [6]. MRI experiments were performed on a 2T spectrometer at 44±10, 76±5, 139±6, 199±6, 259±6, 318±5 min post-occlusion. The fourth time point (199±6 min) was omitted since DWI data was not available for all animals, leaving a total of 5 time points for 8 rats used in this study. Mean trace ADC maps were calculated from DWI. CBF, CBV and mean transit time (MTT) maps were derived from single-slice dynamic susceptibility-weighted contrast-enhanced gradient echo EPI [7]. Lesion volumes were defined as tissue with ADC < 2 SD from mean contralateral values. The lesion on the last ADC map at 5 h was used to represent final lesion regions [4].

All images for each animal were coregistered to one another using a semi-automated image registration software package (AIR 5.2.3, UCLA) [8]. Images were normalized with respect to mean values in the contralateral hemisphere and then used as covariates in predictive algorithms based on a generalized linear model (GLM) whose output values are the probability of infarction [1]. Coefficients were calculated using bootstrapping and jackknifing [9] (S-PLUS 6.1.2, Insightful). Separate models were generated for the first 4 time points. A model was not developed for the last time point since that study had been used to define the training lesion volume, which would heavily bias its results. Sensitivity and specificity of the GLMs in predicting infarction were calculated along with receiver operating characteristic curves. Area under these curves (AUC), representing the accuracy of the models in predicting infarction, was calculated and compared. One-tailed paired Wilcoxon signed-rank tests were used for statistical analysis across time points. Data are presented as mean ±standard deviation (SD).

Results: No significant change over time was found for ADC lesion volume in the single slice used for the PWI experiment. No significant change over time was noted for mean relative ADC and MTT values in the infarct volume. However, CBV was significantly greater at the second time point than the last 3 time points ($p<.04$) and CBF for the second time-point was significantly greater than the average CBF measured for the last time point ($p<.04$). At the last time point, CBF increases > 50% of the first time point values were detected in 2 animals, indicating some degree of spontaneous recanalization. The SD of ADC values within the lesion was significantly higher at the first time point than at the last 3 time points ($p<.01$). The SD of the ADC at the last time point was significantly lower than at earlier time points ($p<.01$) suggesting reduction in heterogeneity of ADC values over time. CBF also showed loss of heterogeneity over time in that the SD was significantly higher ($p<.03$) at the second time point as compared to the last 3 time points.

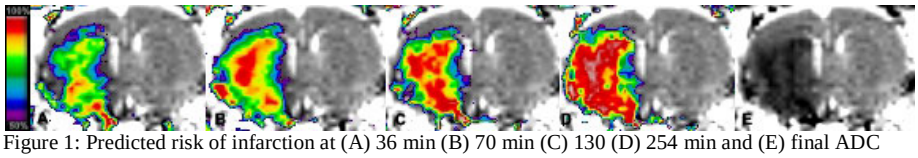

Figure 1: Predicted risk of infarction at (A) 36 min (B) 70 min (C) 130 (D) 254 min and (E) final ADC (310 min) used to delineate infarction volume. Only values at greater than 50% risk are shown.

Fig 1 shows example GLM risk maps calculated from MR data acquired at different time points along with the final ADC map used to delineate lesion volume. The estimated likelihood of infarction increases over time from moderate to very high risk of infarction. The AUC was .92±.05, .92±.06, .95±.07, .95±.07 for the 4 models examined in this study. The AUC of models developed from the two early time points was significantly less than the AUC of models trained on the latter two time points ($p<.05$). The GLM predicted risk of infarction in the lesion was .68±.09, .68±.1, .73±.2, .73±.3. For animals without spontaneous recanalization (n=6), GLM values at the latter two time points (> 2h) were significantly greater ($p\leq.03$) than at earlier time points (< 2h), reflecting an increased risk of infarction with occlusion duration.

Discussion: The results of this study demonstrate that the evolution of ADC and PWI-derived parameters are highly variable both spatially and temporally in the hyperacute stages. The loss of heterogeneity of ADC and CBF values over time may reflect the transition of tissue from threatened but still viable tissue to irreversibly damaged tissue as reflected in increased risk of infarction over time. Volumetric analysis would obscure these findings leading us therefore to conclude that voxel-wise analysis approaches may improve identification of salvageable tissue after stroke.

References 1. Wu O, et al. *Stroke*. 2001; 32, 933-42. 2. Jacobs MA, et al. *Stroke*. 2001; 32, 943-9. 3. Jacobs MA, et al. *Stroke*. 2001; 32, 950-7. 4. Shen Q, et al. *JCBFM*. 2004; 24, 887-97. 5. Asahi M, et al. *JCBFM*. 2000; 20, 452-7. 6. Dijkhuizen RM, et al. *JCBFM*. 2003; 23 (Suppl 1), 217. 7. Østergaard L, et al. *MRM*. 1996; 36, 715-25. 8. Woods RP, et al. *JCAT*. 1992; 16, 620-33. 9. Efron B. *The jackknife, the bootstrap and other resampling plans.* 1982.