Statistical Prediction of Ischemic Tissue Fate in Acute Ischemic Brain Injury: Transient MCAO

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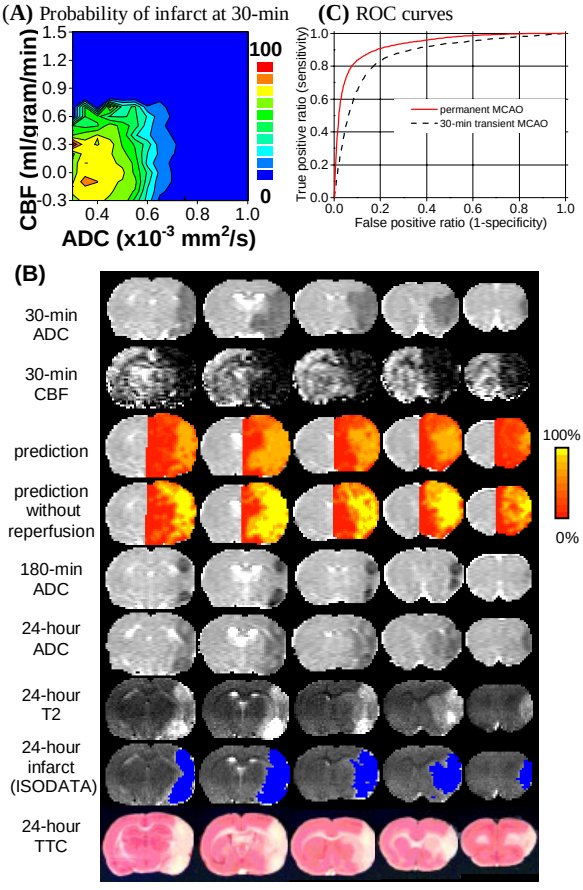
Introduction The ability to readily and reliably *identify* and *predict* ischemic tissue fate during the acute phase would be helpful in clinical decision making to maximize benefit and minimize side effects of therapeutic interventions. MRI data obtained early after stroke onset offers the unique opportunity to statistically predict ischemic tissue fate. Welch and colleagues [1] used a threshold-based analysis method and demonstrated that the combination of T_2 and ADC data provided improved prediction of infarction relative to either parameter alone in subacute stroke in humans. A generalized linear model has been proposed to predict stroke outcomes based on DWI, PWI and T_2 data in humans [2]. Lesions were defined using a threshold-based method to generate the training set. Our lab recently developed a simple statistical algorithm [3] for predicting ischemic tissue fate during acute stroke in a well-established *permanent* MCAO in rats.

The goal of this study was to extend the statistical algorithm [3] for predicting ischemic tissue fate after acute stroke in a *reperfusion* model. The reperfusion model is significantly more variable and challenging but is more closely mimic the human conditions. Quantitative perfusion, diffusion and T2 imaging were obtained. A modified ISODATA cluster analysis [4] (as opposed to a threshold-based analysis) was used to classify tissue types and determine final infarct. Probability profiles were derived and prediction were compared and correlated with endpoint imaging and histology. The resultant prediction maps were not used to identify tissue infarction but to predict of the *risk of future infarction*. Sensitivity, specificity, receiver operating characteristic and other performance measures of the prediction algorithm were also evaluated.

Methods Twelve male SD rats (300-350g,) were subjected to 30-min MCAO followed by reperfusion while the animals were in the magnet. MRI data (4.7T) were acquired at 30, 60, 90, 120, 180 mins, ~24 hrs post-occlusion and followed by TTC staining. ADC_{ave} was measured using spin-echo EPI with matrix = 64x64, FOV = 2.56x2.56cm^2, eight 1.5-mm slices, TE = 37ms, TR = 2s, 16 averages, b = 10, 1270 s/mm^2 along each of the 3 principle axes. CBF was measured using the continuous arterial spin-labeling technique with single-shot, gradient-echo EPI and parameters similar to the ADC measurement except TE = 15ms. At ~24 hrs post-occlusion, T2 was measured using RARE imaging with two echo times ($TE_{effective}$ = 53 and 106 ms). ADC_{ave}, CBF and T2 maps were calculated. Maps at 24 hrs were co-registered to 3-hr maps for each animal with a custom-designed co-registration software.

Lesion volumes at 24-hr were resolved using an improved unsupervised ISODATA (iterative self-organizing data analysis technique [2]) clustering method based on both ADC and T2 maps. Six of the 12 animals were randomly selected for generating the probability profiles (training **Group A**) and the prediction of tissue fate was then performed on the remaining 6 animals (experimental **Group B**). Probability of infarct (P_I) contour plots of the CBF and ADC scatterplots were determined by calculating the percentage of pixels within each grid that migrated to the ischemic core of infracted tissue at 24-hrs post-ischemia. A grid size of 0.05 x 10^{-3} mm^2/s for ADC and 0.1 mL/g/min for CBF was used. Prediction of infarct volume was made for **Group B** using only the pre-reperfusion (30-min) ADC and CBF data by looking up the P_I contour plots of **Group A** on a pixel by pixel basis. In addition, prediction was also made using the training data set of a previously acquired permanent occlusion group [3] to determine the probability of infarct if the animals were hypothetically not reperfused. Performance measures including sensitivity, specificity and receiver operating characteristic (ROC) were determined to evaluate the algorithm's accuracy in predicting tissue fate.



Results & Discussion Panel A shows the probability of infarct contour plot at 30-min post occlusion. At high ADC and CBF, P_I is close to 0%. In the ischemic core with low ADC and CBF, P_I was ~40%-90%. In the mismatch zone with normal or close normal ADC and low CBF, P_I was essentially 0%. These are in marked contrast to the permanent occlusion data where the P_I of "ischemic core" was ~100% and P_I of the mismatch zone was >20% (data not shown). These results indicated that some core pixels and essentially all mismatch pixels were salvaged by reperfusion.

The probability of pixels becoming "infarcted" was computed on a separate group of animals (Group B) based on the ADC and CBF maps at 30 mins only. **Panel B** shows the results from one representative animal. For comparison, ADC and CBF maps at 30 min post-occlusion are also displayed. The predicted tissue fates (3rd row) showed excellent spatial correspondence to the lesion volumes defined by ISODATA analysis, T2 and TTC at 24hrs. In addition, prediction was also made using the training data set of a previously acquired permanent occlusion group (data not shown) to determine the probability of infarct if the animals were hypothetically not reperfused. The results (4th row) showed that the infarct probability and infarct volume were overestimated as expected.

Panel C shows a comparison of ROC performance measures between the permanent and 30-min MCAO. The area under the ROC curve was larger in the permanent occlusion model compared to the 30-min occlusion model, which is expected because of the larger variability of reperfusion model. At the optimal operating points, the sensitivity and specificity, respectively, were 86±4% and 89±6% for the permanent MCAO, and 82±6% and 83±5% for the 30-min MCAO. Area under the ROC curves is 93±3 and 87±3, respectively.

Conclusion: This study demonstrated a pixel-by-pixel probability-based algorithm to statistically predict ischemic tissue fate based on pre-intervention perfusion and diffusion data. Accuracy of the prediction was quantitatively evaluated. Predicted tissue fate showed remarkable correlation with infarct volumes defined by ISODATA, T_2 and TTC data at 24 hrs on a pixel-by-pixel basis. The clinical implication is that prediction of tissue infarct could potentially be achieved by establishing catalogs of training data to guide therapeutic intervention of acute stroke patients in a computationally inexpensive manner.

REFERENCES [1] Welch et al., Stroke 1995, 26:1983. [2] Wu et al., Stroke 2001, 32:933. [3] Shen et al, ISMRM 2005. [4] Shen et al., JCBFM 2004, 24(8): 887.