Prediction of Ischemic Tissue Fate----Comparison Among 30-min, 60-min and Permanent Occlusion Groups

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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 sub-acute 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 reported 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 this statistical algorithm [3] to predict ischemic tissue fate after acute stroke in transient (30-min and 60-min) MCAO models. Quantitative perfusion, diffusion and T2 imaging were obtained. A modified ISODATA (iterative self-organizing data analysis) 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 using CBF and ADC data were compared and correlated with endpoint imaging and histology. The resultant prediction maps were not used to identify tissue infarction but were probability maps used to predict of the *risk of future infarction*. Sensitivity, specificity, receiver operating characteristic and other performance measures of the prediction algorithm were also evaluated. The results of the 30-min, 60-min MCAO model were compared with previous results of the permanent MCAO.

Methods Three stroke models (n = 12 for each model) on male SD rats (300-350g) were performed: 30-min, 60-min and permanent MCAO as described elsewhere [3,4]. Reperfusion was performed remotely while the animals were in the magnet. MRI data at 4.7T were acquired at 30, 60, 90, 120, 180 mins, at ~24 hrs post-occlusion and followed by TTC staining. ADC_{ave} was measured using spin-echo EPI with matrix = 64x64, FOV = 2.56x2.56cm, 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 similar parameters 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_{av}, 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 the ISODATA method [4] based on both ADC and T2 maps. Six of the 12 animals in each stroke model 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. Prediction of infarct volume was made for **Group B** using the 30-min data (a representative time point) for the 30-min MCAO stroke model and using the 60-min data for the 60 min MCAO data by looking up the P_I contour plots of **Group A** on a pixel by pixel basis. Performance measures to evaluate the algorithm's accuracy in predicting tissue fate included sensitivity, specificity, receiver operating characteristic (ROC).

Results & Discussion Figure 1 shows the probability of infarct contour plot at just before reperfusion (30-min or 60-min post occlusion) for 30-min, 60-min transient occlusion and earliest acquisition time point (30-min) for permanent occlusion groups. Transient occlusion groups showed much lower P_I in the ischemia core relative to permanent occlusion group. In the perfusion-diffusion mismatch zone (normal or close normal ADC and low CBF), P_I was essentially 0% for 30-min MCAO, ~40% for 60-min MCAO and ~60% for permanent MCAO, as expected. These results indicated that some core pixels and most mismatch pixels were salvaged by reperfusion.

The probability of each pixel becoming "infarcted" at 24 hrs was computed for a separate group of animals (Group B) based on the 30-min or 60-min ADC and CBF data for 30-min or 60-min MCAO groups. **Figure 2**(A) and (B) show the results from one representative animal of each group. For comparison, ADC and CBF maps at 30-min or 60-min post-occlusion for 30-min or 60-min MCAO groups 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.

Figure 3 shows a comparison of ROC performance measures among 30-min, 60-min and permanent MCAO. Prediction performance was the best for permanent MCAO, followed by 60-min MCAO and 30 -min MCAO, as indicated by the area under the ROC curves (0.93 ± 0.03, 0.88 ± 0.04 and 0.87 ± 0.03, respectively). This is expected to the 30-min MCAO had higher variability than the 60-min MCAO which in turn had higher variability than permanent MCAO. Sensitivity, specificity, area under the ROC curves and partial area index which is the normalized area under the curve with false positive ratio lower than 20%), showed more improved prediction for permanent MCAO, followed by 60-min MCAO and 30-min MCAO.

Conclusion: This study demonstrated an algorithm to statistically predict ischemic tissue fate based on early perfusion and diffusion data. This algorithm is computation inexpensive. Future studies will involve means to statistically determine which prediction algorithms should be applied to a specific patient that could best predict stroke outcome. This approach is expected to have significant clinical value.

REFERENCES [1] Welch et al., Stroke 1995, 26:1983. [2] Wu et al., Stroke 2001, 32:933. [3] Shen et al, JCBFM, 2005, 25:1336. [4] Shen et. al., JCBFM 2004, 24: 887.

Fig. 1

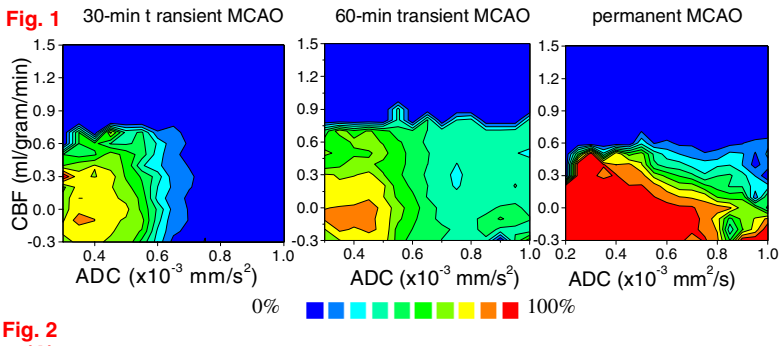

Fig. 2

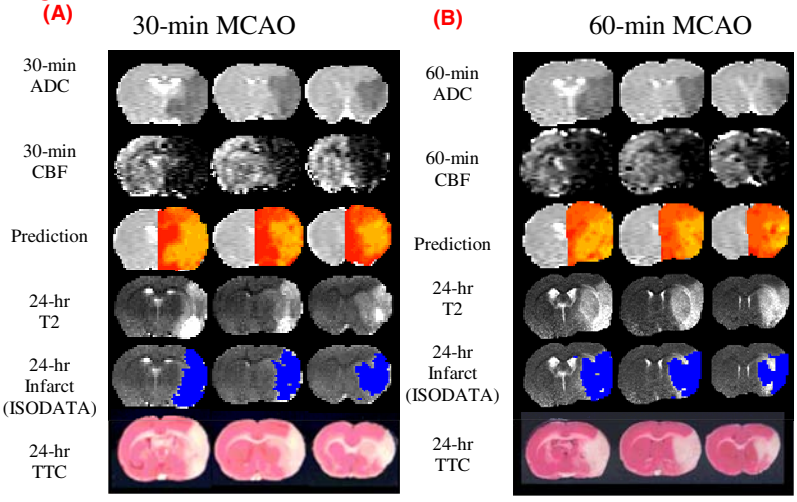

Fig. 3