Probabilistic Prediction of Tissue Fates in Acute Ischemic Brain Injury: Permanent Occlusion

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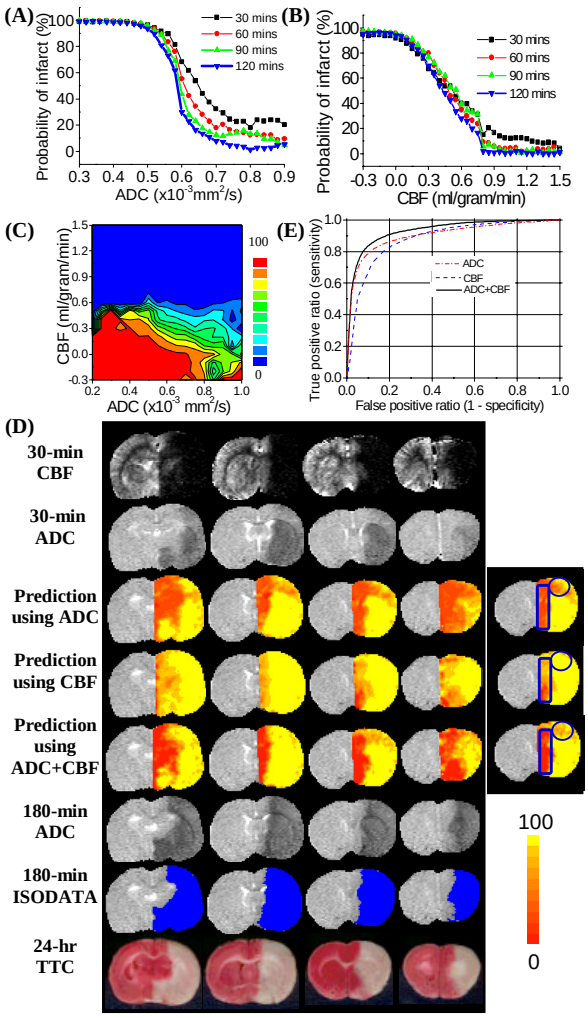
INTRODUCTION Perfusion and diffusion imaging has been widely used to ***characterize*** ischemic brain injury. Its use to ***predict*** tissue fates however is sparse. Wu et al. [1] recently used a general linear model to combine DWI and PWI and predicted 66% sensitivity and 84% specificity that proceeded to infarct in stroke patients.

In this study, we proposed a different and simplified pixel-by-pixel statistical algorithm to predict ischemic tissue fates during the acute phase. We developed and tested the algorithm in a well-established permanent MCAO stroke model in rats. Quantitative high-resolution (200x200μm) perfusion and diffusion imaging was performed. A modified ISODATA cluster analysis was used to classify tissue types. Probability profiles were derived and prediction using ADC data alone, CBF data alone and CBF+ADC data 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 evaluated. In addition to the prediction of overall tissue fates, probability of infarct (P_I) for different ISODATA-derived ischemic tissue types were also computed.

METHODS Permanent focal brain ischemia was induced on 12 male SD rats (300-350g) (**Group I**: 6 rats in training set, and **Group II**: 6 rats used for prediction). Imaging at 4.7T was performed on rats under 1% isoflurane at 30, 60, 90, 120, 180 mins, and followed by TTC staining at ~ 24 hrs. Blood pressure, heart rate, respiration rate, rectal temperature, blood gases were monitored and maintained within physiological ranges.

ADC_{ave} was measured using spin-echo EPI with matrix = 128x128, 4 segments, FOV = 2.56x2.56cm^2, eight 1.5-mm slices, TE = 37ms, TR = 2s, 16 averages, b = 10, 1270s/mm^2. CBF was measured using the continuous arterial spin-labeling technique with gradient-echo EPI and identical parameters except TE = 15ms.

ADC_{ave} and CBF maps were calculated. Lesion volumes were resolved using an improved unsupervised ISODATA (iterative self-organizing data analysis technique [2]) clustering method based on both ADC and CBF maps [3]. Profiles of the probability of infarct (P_I) were determined by calculating the percentage of pixels within each grid that migrated to the ischemic core of infracted tissue at 180 mins 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. P_I contour plots of ADC+CBF data were calculated and displayed with color coding ranging from 0 to 100% in steps of 10%. Prediction was made (Group II) and compared with ADC- and ISODATA-defined lesion volume at 3 hrs and correlated with TTC at 24 hrs [3, 4]..Accuracy of prediction (sensitivity, specificity and receiver operating characteristic) was compared for the three algorithms.



RESULTS & DISCUSSIONS **Panel A** and **B** show the profiles of the P_I vs ADC and P_I vs CBF, respectively, at different time points post ischemia. P_I rose rapidly when ADC or CBF dropped below normal value (ADC: 0.75 ± 0.01 x 10^{-3} mm^2/s, CBF: 1.2 ± 0.2 mL/g/min). In contrast to the ADC data, P_I was essentially zero for normal CBF at all time points. **Panel C** shows the contour plots of P_I at 30mins computed based on the ADC and CBF maps (Group I). The probability was determined with reference to the 180min time point. P_I of pixels with high ADC and CBF was essentially zero whereas P_I with very low ADC and CBF (ADC < 0.52x10^{-3}mm^2/s, CBF < 0.3ml/g/min) was very high (>90%). The "mismatch" zone where the ADC was normal or close to normal but the CBF was reduced [4] showed a non-zero P_I (>20%). In short, lower ADC and/or CBF generally showed a higher P_I, as expected.

Probability of pixels becoming "infarcted" at 3 hrs was computed on a separate group of animals (Group II) based on only the 30 mins data. **Panel D** shows the results from one representative animal. For comparison, ADC and CBF maps at 30 and 180 mins, ISODATA analysis of the 180-min data, and 24-hr TTC are also displayed. Prediction made with ADC alone underestimated infarct volume whereas predictions made with CBF alone overestimated infarct volume. With combined ADC+CBF data, the mismatch region (circular ROI in the inset) was predicted correctly to go into infarct (i.e., correlated with TTC), whereas with ADC data alone, the mismatch was incorrectly predicted not to go into infarct. Furthermore, with the combined ADC+CBF information, the "normal" tissue (rectangular ROI in the inset) was predicted to remain normal with significantly higher certainty (P_I ~ 0), whereas with CBF data alone, the "normal" tissues in the right hemisphere were predicted to have substantial non-zero P_I. Predicted infract volumes based on ADC+CBF showed the best correspondence with the ISODATA maps, and the 24-hr TTC infarct volumes.

Receiver-operating-characteristic (ROC) curves analysis (**Panel E**) shows predictions made using ADC+CBF data outperformed than using ADC or CBF data alone. It was reflected by higher sensitivity (86% *vs* 84% and 82%), specificity (89% *vs* 89% and 80%), and area under the ROC curves (0.93 *vs* 0.91 and 0.87).

In addition to predictions of *overall* tissue fate, predictions were also made for individual tissue types. ISODATA was used to classify normal, mismatch and core pixels at 30 mins. Prediction of infarct for each tissue type was made and the results were as follows: 1) For the P_I of the right-hemisphere normal cluster, combined ADC+CBF data correctly showed low P_I (18±4%), whereas ADC data alone and CBF data alone showed substantial probability of infarct of 30±5% and 71±6%, respectively. 2) For the mismatch cluster, combined ADC+CBF data correctly predicted P_I (73±5%) whereas ADC underestimated the P_I (44±12%) and CBF overestimated P_I (90±5%). 3) For the core cluster, P_I for ADC data alone, CBF data alone and ADC+CBF data were high and similar, namely, 93±5%, 90±5%, and 93±1%.

CONCLUSION A statistical algorithm was developed to predict tissue fates. By combining cluster analysis and probability analysis, prediction could be made for individual tissue types. Prediction based on ADC+CBF showed remarkable correlation with endpoint imaging and infarct volumes, and outperformed algorithms using ADC or CBF alone. This approach provides a novel means to analyze stroke data and could have potential clinical applications.

REFERENCES [1] Wu et al., Stroke 2001, 32:933. [2] Jacobs et al. JMRI, 2000; 11: 425. Theiler et al., Proc SPIE, 1997; 3159:108. [3] Shen et al., JCBFM 2004, 24: 887. [4] Shen et al, JCBFM 2003, 23:1479.