Can multiparametric MRI-based predictive algorithms assess efficacy of thrombolysis in hyperacute stroke patients?

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Introduction

Multiparametric algorithms that combine acute DWI and PWI parameters have been shown to accurately predict tissue infarction on follow-up imaging in patients receiving conservative, non-thrombolytic treatment [1]. It has been speculated that these maps may be useful in evaluating therapeutic efficacy of novel treatments in clinical trials by providing a baseline risk assessment. To determine if predictive algorithms can be used for assessing effects from novel therapies, we applied predictive algorithms to acute stroke patients treated with tissue plasminogen activator (tPA), a proven therapy for acute stroke,

Patients and Methods

Acute stroke patients that received either intravenous (IV) (n=28), intra-arterial (IA) (n=1) thrombolytic therapy or conservative treatment (no thrombolysis) (n=12) within 6 h of symptom onset were retrospectively analyzed. For both groups, median scan time was 3 h. Median age was 61 for Group 1 and 60 for Group 2. All patients underwent a protocol of acute DWI/PWI and a 7-day follow-up (F/U) MRI on a 1.5 T scanner (Siemens). Apparent diffusion coefficient maps were calculated from the DWI. The low b-value (b=0) and high b-value (b=1000) images were used as the T2-weighted image and isotropic DWI (iDWI) maps respectively. CBF, CBV and mean transit time (MTT) maps were calculated by deconvolution with an arterial input function selected from the ipsilateral hemisphere using singular value decomposition [2]. Delay maps were measured as the peak time of the residue function [3]. All acute images were coregistered to the F/U and to Talairach space (MNI Autoreg) [4]. These seven images were then normalized with respect to mean contralateral normal white matter values producing relative values and used to train a tissue risk model based on a generalized linear model (GLM) [1]. Coefficients of the GLM were calculated (S-PLUS 6.1.2) using jack-knifing [1] among the conservative treatment arm (Group 1) to avoid biasing from training and evaluating models on the same dataset. Infarcted tissue was delineated on the F/U by a neuroradiologist. Non-infarcted tissue was defined as all remaining tissue in the ipsilateral hemisphere. Coefficients were combined with a probabilistic atlas [5] to create anatomically-weighted risk maps [6].

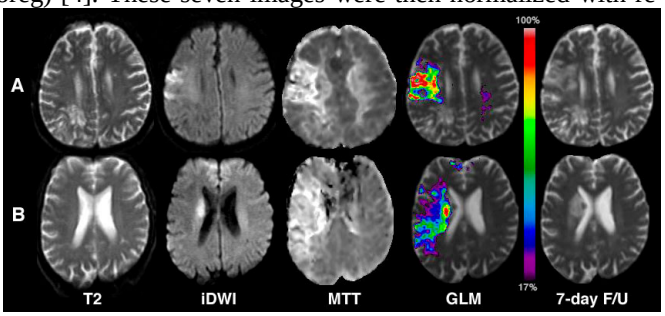

Fig 1: Example GLM maps for Group 1 (A) and Group 2 (B) patients.

A model trained on data from all Group 1 patients was applied to patients receiving IV or IA thrombolysis (Group 2). Sensitivity and specificity were calculated along with receiver operating characteristic curves. Area under the curves (AUC) was calculated and compared (paired Wilcoxon test). The probability value at the optimal operating point (OOP) [7] was measured from Group 1 and used as a threshold for identifying tissue at risk of infarction. Correlations between measured F/U lesion volume (MLV) and predicted lesion volume (PLV) were calculated (Pearson product-moment correlation coefficient) and compared (Z-test).

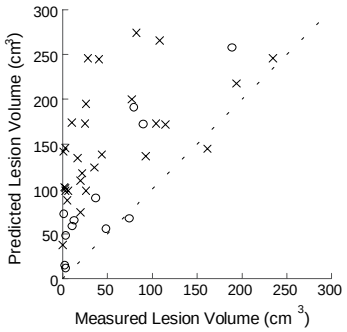

Fig 2: Correlation of PLV with MLV for Group 1 (o) and Group 2 (x) patients.

Results

Fig 1 shows examples of predicted maps for patients from Groups 1 and 2, as well as their F/U and acute MRI (3.4 and 3.5 h). OOP was found to be at 17%. Group 1's sensitivity was 78% with specificity of 88% while Group 2's sensitivity was 78% with specificity of 73%. Group 1 AUCs (.90±.08) were significantly greater than AUCs for Group 2 (.86±.08) (p=.05). PLV was significantly correlated with MLV for both groups (p≤.001) with Group 2 having a significantly smaller (p=.03) correlation coefficient (R=.57) than Group 1 (R=.90) (Fig 2). In tissue that was predicted to infarct (GLM risk>17%), a significant difference was found in the GLM values in tissue that infarcted (.68±.16) versus those that did not (.44±.10) (p<.001) in both groups. GLM values in tissue that infarcted in Group 1 (.59±.19) were significantly lower (p=.02) compared to Group 2 (.71±.13). In tissue that did not infarct, GLM values were significantly lower (p=.007) in Group 1 (.38±.06) than in Group 2 (.47±.11). This suggests that tissue that infarcted in the treatment group was originally at high risk, while tissue that did not infarct in treated patients had a higher baseline risk than in patients that were not given thrombolysis.

Discussion

We speculate that the reduced accuracy of the GLM in predicting outcome in Group 2 is due to thrombolytic therapy saving tissue that was at moderate risk infarction. This preliminary study demonstrates that by providing a baseline assessment of tissue's risk of infarction on an individual voxel-by-voxel basis, therapeutic effects of treatments can be objectively evaluated even with a limited number of patients. This suggests that perhaps instead of using a mismatch between DWI/PWI for guiding therapeutic intervention, an alternate metric may be using a mismatch between tissue at high and intermediate risk.

References 1. Wu O; *Stroke.* 2001; 32, 933-42. 2. Østergaard L; *MRM.* 1996; 36, 715-25. 3. Wu O; *MRM.* 2003; 50, 164-74. 4. Collins DL; *JCAT.* 1994; 18, 192-205. 5. Mazziotta J; *Philos Trans R Soc Lond B Biol Sci.* 2001; 356, 1293-322. 6. Wu O; ISMRM 12th Meeting; Submitted. 7. Halpern EJ; *Acad Radiol.* 1996; 3, 245-53.