Assessment of treatment effects with multiparametric MRI-based predictive algorithms in a rat embolic stroke model

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Introduction:

Multiparametric algorithms combining acute diffusion-weighted MRI (DWI) and perfusion-weighted MRI (PWI) have been shown to accurately predict tissue infarction in acute human cerebral ischemia [1]. However, a limitation of human acute stroke studies is the reliance on follow-up imaging to provide an indirect measurement of tissue infarction. Follow-up imaging can be confounded by numerous factors such as varying follow-up times, mass effect and/or encephalomalacia. Extending predictive algorithms to experimental animal models of stroke allows the extent of infarction to be histologically evaluated. This study examines the application of risk maps for identifying effects due to novel therapeutic interventions.

Materials/Methods:

Unilateral stroke was induced in halothane-anesthetized male Sprague-Dawley rats by embolic occlusion of the right middle cerebral artery. Acute DWI and PWI from the control arm of a trial of thrombolytic treatment with pamiteplase, a modified tissue plasminogen activator, (n=8) [2] were used to train a tissue risk model based on a generalized linear model (GLM). Coefficients were calculated (S-PLUS 6.1.2, Insightful) and applied to MR data acquired from control (n=6) (Group 2) and treatment (n=7) (Group 3) arms of a delayed recombinant tissue plasminogen agent (rt-PA) treatment study in spontaneously hypertensive rats [3]. Group 1 was imaged 1 h post-occlusion prior to saline injection. Groups 2 & 3 were imaged 4 h post-stroke prior to saline or rt-PA injection.

All animals were scanned with DWI and PWI on a 2T NMR spectrometer (Varian). Mean trace apparent diffusion coefficient maps were calculated from DWI. CBF, CBV and mean transit time (MTT) maps were calculated from dynamic susceptibility-weighted contrast-enhanced gradient echo EPI using singular value decomposition [4]. All images were normalized with respect to mean measured values in the contralateral hemisphere and the relative values used as predictors in a GLM. Groups 2 & 3 acute MRI and GLM risk maps were coregistered to triphenyletetrazolium chloride (TTC) stained brain sections (10 h post-stroke) using a semi-automated image registration sofware package (AIR 5.2.3, UCLA) [5].

Sensitivity and specificity of the GLM in predicting infarction were calculated along with receiver operating characteristic curves. Area under these curves (AUC) was calculated and compared (Wilcoxon rank-sum test). Correlation between hemispheric lesion volume percentage (HLV) on TTC-stained sections and predicted HLV percentage (PLV) were tested (Pearson product-moment correlation coefficient). Rats were categorized as having no reperfusion (rCBF<25%), partial reperfusion (25%≤rCBF<75%) or complete reperfusion (rCBF≥75%) compared to contralateral values base on final MR CBF values (10 h post-stroke).

Results:

Table 1 shows the GLM parameters derived from Group 1 training data. Fig 1 shows example GLM risk maps along with corresponding histology for a control (A,B), and a treated rat with complete reperfusion (C,D). A good assessment is seen for the non-treated rat (A) while overprediction is clearly evident in the treated rat (C). The optimal operating point (OOP) [6] was found to be 23%. At this OOP, sensitivity was 94% with specificity of 84% in Group 2 and was 84% with specificity of 77% for Group 3. Group 2 AUCs (.95±.03) were significantly greater (P=.03) than AUCs for Group 3 (.86±.11). Fig 2 shows PLV versus measured TTC-stained hemispheric lesion volume at the OOP. Group 2 PLV was significantly correlated with infarct volume (R^2=.6, p=.04). However, Group 3 PLV showed no correlation with infarct volume (R^2=.01, p=.6). This is likely due to two animals with complete reperfusion in Group 3 that had PLV greatly larger than measured HLV (77±6% and 12±12 % respectively).

Table 1: GLM coefficients derived from Group 1

Offset	ADC	CBF	CBV	MTT
-2.2	-.3	-.3	-.02	-.004

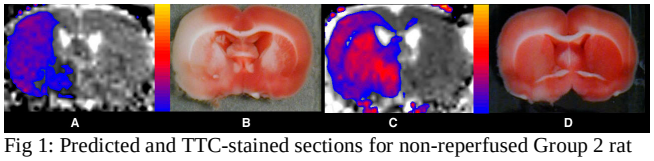

Fig 1: Predicted and TTC-stained sections for non-reperfused Group 2 rat (A,B), and completely reperfused Group 3 rat (C,D). Risk maps show risk of infraction from 23 (blue) to 100% (yellow).

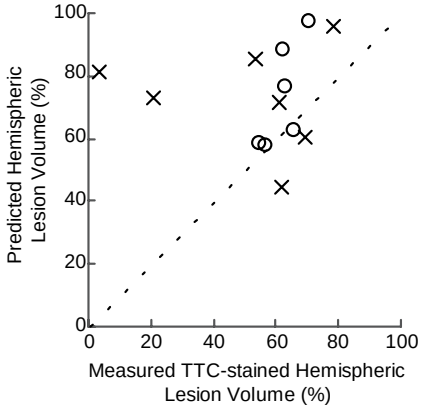

Fig 2: Predicted lesion volume vs measured lesion volume for Group 2(o) and Group 3 (x).

Discussion:

Our results indicate that delayed rt-PA treatment in a rat embolic stroke model changed the amount of tissue expected to infarct. This suggests that tissue signatures, by providing a baseline risk of infarction without treatment, can be used to assess effects of stroke therapies. Multiparametric MRI-based algorithms may therefore be useful for assessing efficacy of intervention in experimental stroke models, and furthermore, provide a metric that could translate readily into clinical settings.

References

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