Applying MRI-based multiparametric algorithms to a randomized placebo-controlled pilot study of normobaric oxygen therapy in acute ischemic stroke

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Introduction: Early and accurate identification of tissue at risk of infarction that is still salvageable with therapeutic intervention is a major goal of acute stroke neuroimaging [1]. Using only acute baseline MRI data from patients with ischemic stroke, MRI-based predictive algorithms have been developed that accurately predict chronic tissue outcomes in patients not receiving novel treatment [2]. Theoretically, once a global model has been calculated, it can be used to predict tissue outcome in a separate cohort of patients. In this study, we evaluate the predictive performance of MRI-based predictive algorithms developed on a large cohort of patients (N=70) not receiving novel treatments on the placebo and treatment arms of a pilot study of normobaric oxygen (NBO) therapy in acute ischemic stroke which used MRI as an inclusion criteria [3]. We compare the performance of the generic model with a model trained on just the placebo group. Since techniques that are less sensitive to tracer arrival delays may be better suited for distinguishing truly ischemic tissue from benign oligemia, we will therefore also evaluate the performances of these algorithms in predicting tissue outcome as a function of different perfusion algorithms.

Subjects and Methods: MRIs from a randomized, placebo-controlled study of NBO treatment in acute stroke patients were retrospectively analyzed. Patients were included if they presented with a DWI and PWI mismatch of at least 20%. Patients were randomized to control (room air) (n=6) or NBO treatment (n=9) for 8 h. All patients received MRIs upon admission (<12 h after symptom onset), at 4 h (during treatment), & at 24 h (post-treatment). There was no significant difference in baseline NIH stroke scale score between the two groups. Admission DWI & PWI maps were coregistered, normalized and used to train generalized linear models (GLM) to predict infarction risk at follow-up imaging >=5 days (F/U). Control-NBO models (Control) were trained on data from all non-NBO patients using bootstrapping and jackknifing [4]. The generic GLM model (Generic) was calculated from retrospectively analyzed DWI and PWI data acquired from patients imaged <12 h from stroke onset who received a >= 5 days follow-up imaging study (n=70). Combinations of cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT) and tracer-arrival delay (DELAY), with apparent diffusion coefficient (ADC), T2-weighted image (T2WI) and isotropic DWI (iDWI) maps has been shown to produce the best prediction of tissue outcome [2] and therefore these 7 parameters were used for all models. PWI parameters were calculated using either standard singular value decomposition techniques (sSVD) [5] or using oscillation-index regularized SVD (oSVD) [6]. oSVD-based perfusion metrics have been previously demonstrated to be insensitive to tracer arrival delays and therefore a potentially more specific identifier of ischemic tissue. Predicted lesion volumes (PLV) were defined as tissue with > 50% infarction risk and compared with the measured lesion volumes (MLV) on F/U imaging (paired one-sided Wilcoxon signed rank tests). 50% was used since all models were designed to have an optimal operating point at this risk threshold. Correlation between MLV and PLV were also examined for the different models (Pearson product-moment correlation coefficient).

Table 1: Measured lesion volumes in median (interquartile range) cm^3 and differences with respect to predicted outcome. *P=.05 sSVD model vs oSVD model; †P<.05 Generic vs Control Model

Models	MLV	sSVD PLV-MLV	oSVD PLV-MLV
Placebo patients			
Control Arm	14 (11-36)	53 (35-80) †	44 (24-81)
Generic Model *		64 (46-86)	34 (8-65)
NBO-treated patients			
Control Arm	41 (36-73)	35 (33-52) †	46 (28-50)
Generic Model*		57 (42-70)	22 (-3-30) †

Table 2: Correlation (R) between MLV and PLV

Models	sSVD PLV-MLV	oSVD PLV-MLV
Placebo patients		
Control Arm	.84 (P=0.04)	.96 (P=0.002)
Generic Model *	.73 (P=0.10)	.87 (P=0.02)
NBO-treated patients		
Control Arm	.55 (P=0.12)	.70 (P=.04)
Generic Model†	.36 (P=0.35)	.63 (P=.07)

Results: Differences between MLV and oSVD-based PLV were significantly smaller than differences between MLV and sSVD-based PLV, an indication of better predictive perfomance (Table 1). An example of more accurate performance using oSVD-base models is shown in Figure 1 where the PLV on the oSVD-based maps clearly corresponds better with the actual infarct volume on follow-up. As expected, the PLV for the Control model was significantly correlated with the MLV for patients in the placebo group (Table 2). Due to the use of jackknifing, where the models that were applied to each patient were trained without the use of that patient's data, the correlation is not perfect. The Generic sSVD-based models performed more poorly than the Control models for both placebo and treatment arms as reflected by greater overestimation of the MLV (Table 1). There was no significant difference in the placebo arm for oSVD-based models. However, for the treatment arm, the difference between MLV and PLV was smaller for the Generic model than the Control model. oSVD-based models produced PLV that were significantly correlated with MLV for both placebo and treatment arms (Table 2). The correlations of PLV with the MLV were reduced for all models, possibly as a result of the expected tissue outcome having been altered as a result of NBO-treatment.

Discussion: Our results suggest that models developed from one cohort of patients can be applied to an independent cohort of patients to accurately predict tissue outcome. Models based on perfusion metrics that were independent of tracer arrival delays, e.g. oSVD, were found to perform more accurately and robustly across patient cohorts while sSVD based Generic models did not perform as well as models trained on the placebo arm. This is likely due to the inherent differences in the training data, where the Generic model included patients with variable patterns of DWI and PWI mismatch while the inclusion criteria for the NBO study required a mismatch >20%. This suggests that when evaluating therapeutic efficacy one should ideally use the placebo arm of a randomized, placebo-controlled trial with balanced control and treatment arms. However, by using a more robust perfusion metric, the effects of variations in training data are mitigated. Indeed, in terms of differences between MLV and PLV, the Generic oSVD-based model performed better than the equivalent Control-model (Table 1). This is likely due to the small number of patients used to develop the Control-model (n=6). Our study has also shown reduced correlation between the MLV and PLV in the treated arm. We speculate that this may be an indication that the expected ischemic cascade of events that proceeds in ischemia was interrupted by the NBO treatment, resulting in poorer correlation between the predicted outcome and the actual outcome. Further studies involving larger number of patients will be necessary to properly address this question.

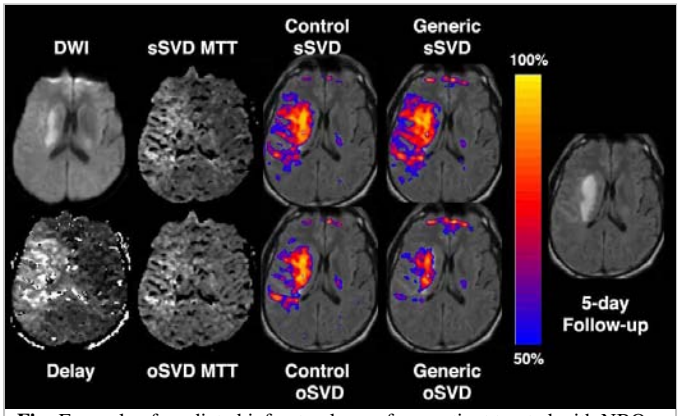

Fig: Example of predicted infarct volumes for a patient treated with NBO using models developed from the control arm of the trial and using a separate cohort of 70 patients (Generic) and different PWI parameters. Using oSVD-based models appear to produce the best estimate of infarct volume on follow-up imaging.

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