Predicting Tissue Infarction Using Acute MR Imaging in Stroke Patients Treated with Thrombolytic Therapy

O. Wu[1,2], S. Christensen[2], N. Hjort[2], K. Mouridsen[2], A. Rodell[2], R. M. Dijkhuizen[1], T. Kucinski[3], J. Fiehler[3], J. Röther[4], L. Østergaard[2]

[1]Image Sciences Institute, University Medical Center Utrecht, Utrecht, Netherlands, [2]Center for Functionally Integrative Neuroscience, Århus University Hospital, Århus, Denmark, [3]Dept Neuroradiology, University Hospital Hamburg-Eppendorf, Hamburg, Germany, [4]Dept Neurology, University Hospital Hamburg-Eppendorf, Hamburg, Germany

Introduction: Assessing potential benefits of treatment strategies for stroke patients at the hyperacute stage on an individual basis may aid the therapeutic decision making process and thereby improve patient outcome[1-3]. Algorithms that combine multiple acute MR modalities have been shown to accurately predict tissue infarction [4]. However, these studies were limited to patients imaged relatively late outside the therapeutic time window (<12 h) and to patients who were not treated with thrombolytic therapy. This study investigates the feasibility of the application of these algorithms to patients imaged at the hyperacute stage (< 6h) treated with thrombolytic therapy to predict outcome under different treatment options.

Patients and Methods: Acute stroke patients imaged within 6 h of symptom onset were retrospectively analyzed [5]. Patients either received standard medical treatment (Group 1; n=12), or thrombolytic therapy (Group 2; n=29) via intravenous (n=28) or intra-arterial (n=1) administration of recombinant tissue plasminogen activator (rt-PA) For both groups, median scan time was 3 h. Median age was 61 for Group 1 and 60 for Group 2. All patients underwent acute diffusion-weighted (DWI) and perfusion-weighted (PWI) imaging and a 5 to 8 day follow-up (F/U) MRI on a 1.5 T NMR scanner (Siemens). All patients receiving rt-PA were imaged prior to drug administration. Apparent diffusion coefficient (ADC) maps were calculated from the DWI. The low b-value (b=0 s/mm^2) and high b-value (b=1000 s/mm^2) images were used as the T2-weighted image (T2WI) 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 [6]. Delay maps were measured as the peak time of the residue function [7]. All acute images were coregistered (MNI Autoreg) [8]. These seven images were then normalized with respect to contralateral normal white matter values and used to train a generalized linear model (GLM) [4] whose output is the risk of infarction on a voxel-wise basis. GLM coefficients were calculated using bootstrapping and jackknifing (S-PLUS 6.1.2) [9]. Training regions consisted of infarcted tissue delineated by a neuroradiologist as the union of hyperintensities on the F/U T2 and iDWI and non-infarcted tissue defined as all remaining ipsilateral hemisphere tissue.

The model trained on data from all Group 1 patients (Model 1) was applied to patients receiving rt-PA (Group 2). To evaluate the effects of thrombolytic therapy on likelihood of infarction on a voxel-wise basis, a second model was developed using MR data from rt-PA treated patients (Model 2). Predicted lesion volumes (PLV) were then defined as all tissue with > 50% risk of infarction on the GLM maps. The PLV was compared with the measured lesion volume (MLV) that had been used for training. In addition, the root mean square error, RMSE=$1/N \sum(y_i-\pi_i)^2$, where y_i is the true outcome for the tissue (0 or 1), π_i is the predicted risk and N the total number of voxels, were calculated for both models. One-tailed paired Wilcoxon signed-rank tests were used for statistical analysis. Data are presented as mean ±standard deviation (SD).

Results: Table 1 shows the coefficients for Model 1 (assuming no rt-PA) and Model 2 (assuming rt-PA therapy). The PLV for Model 1 (163±69 mm^3) and Model 2 (135±68 mm^3) were significantly greater (p<.001) than the final measured lesion volume, MLV (67±75 mm^3) for the Group 2 patients receiving rt-PA. However, the absolute difference between PLV and MLV was significantly larger for Model 1 than Model 2 (p<.001), suggesting improved prediction in models taking into consideration treatment effect. This is further reflected in the RMSE being significantly larger (p<.001) for Model 1 than Model 2. The average GLM calculated risk of infarction in tissue that infarcts was significantly higher (p<.001) for Model 1 (.73±.13) than Model 2 (.65±.12), indicating that thrombolytic therapy is effective since the probability of infarction is reduced if rt-PA is administered. An example is shown in Figure 1. Using the same input parameters, significantly lower risk of infarction is predicted if the patient were to receive rt-PA. Model 2 predicted infarct volume correlates better with the actual infarct seen on the 8-day F/U.

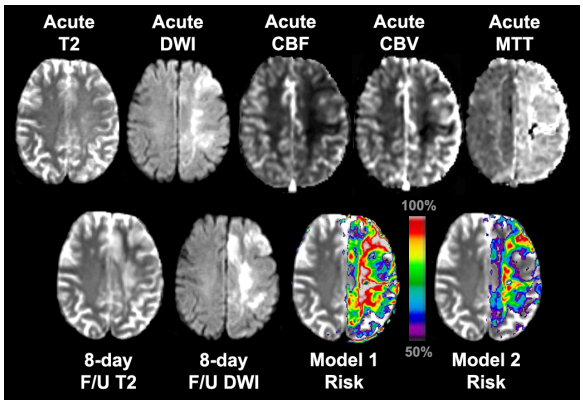

Fig 1: Example input and output GLM maps for a patient imaged 4.5 h after symptom onset. The PLV is clearly greater for Model 1 than Model 2. Only GLM values >50% are shown.

Table 1: Bootstrapped GLM coefficients for models trained only on non-rt-PA treated patients (Model 1) and trained only on rt-PA treated patients (Model 2)

Model	Bias	T2WI	ADC	iDWI	CBF	CBV	MTT	Delay
Model 1	-9.6±.28	-.37±.19	.94±.21	6.3±.24	.25±.03	-.19±.03	1.3±.07	.25±.01
Model 2	-5.9±.18	-.28±.09	1.0±.10	3.4±.15	-.04±.04	-.17±.03	.99±.03	.05±.00

Discussion: Our results show that the risk of infarction on a voxel-wise basis is predicted to be reduced by thrombolytic therapy, demonstrating the potential of these algorithms for retrospectively assessing efficacy of novel therapeutic interventions. Furthermore, although, on a volumetric basis, the PLV over estimates the MLV, noteworthy is the spatial heterogeneity of GLM predicted risk values within the PLV that likely reflects the varying degrees of existing tissue injury at a particular time point.

References: 1. Warach S. *Stroke.* 2001; 32, 2460-1. 2. Fisher M. *Stroke.* 2003; 34, 1539-46. 3. Levine SR. *J Neurol Sci.* 2004; 225, 1-2. 4. Wu O, et al. *Stroke.* 2001; 32, 933-42. 5. Fiehler J, et al. *Stroke.* 2002; 33, 79-86. 6. Østergaard L, et al. *MRM.* 1996; 36, 715-25. 7. Wu O, et al. *Magn Reson Med.* 2003; 50, 164-74. 8. Collins DL, et al. *JCAT.* 1994; 18, 192-205. 9. Efron B. *The jackknife, the bootstrap and other resampling plans.* 1982.