Identifying stroke patients most likely to benefit from reperfusion therapy using acute MRI

O. Wu[1,2], S. Christensen[2], N. Hjort[2], A. Neumann[2], A. G. Sorensen[1], G. Thomalla[3], J. Fiehler[4], T. Kucinski[4], J. Rother[3], and L. Østergaard[2]

[1]Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA, United States, [2]Center for Functionally Integrative Neuroscience, Aarhus University Hospital, Aarhus, Denmark, [3]Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [4]Neuroradiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Introduction: Early reperfusion has been shown by several prospective studies to be a good indicator of favorable clinical outcome after acute ischemic stroke 1, 2. It has been hypothesized that patients presenting with greater than 20% mismatches in lesion volumes on acute diffusion-weighted (DWI) and perfusion-weighted imaging (PWI) were candidates likely to benefit from thrombolytic therapy. However, by relying on the PWI/DWI mismatch as a surrogate for the ischemic penumbra, one is presupposing that the DWI lesion is an immutable core of infarcted tissue while the PWI lesion reflects tissue that will die without treatment, which has been demonstrated to be not the case in all circumstances.[3, 4] Algorithms that combine multiple acute MR modalities have been shown to more accurately predict tissue infarction than any single individual imaging modality[5, 6]. We hypothesize that using these risk maps of tissue infarction may provide insight into which patients may respond favorably to reperfusion therapy.

Patients and Methods: Acute stroke patients imaged within 6 h of symptom onset with a 5 to 8 day follow-up (F/U) MRI were retrospectively analyzed [4]. Patients either received standard medical treatment (non-rt-PA; n=17), or intravenous recombinant tissue plasminogen activator (rt-PA) thrombolytic therapy (rt-PA; n=80). Patients receiving rt-PA were imaged prior to drug administration. Reperfusion was assessed from the 1-day follow-up PWI and MRA studies (N=77) according to the modified Thrombolysis in Myocardial Infarction (TIMI) criteria [7]. Patients exhibiting no, minimal, incomplete reperfusion (TIMI=0,1,2) were classified as Non-Reperfusers. Patients with complete reperfusion (TIMI=3) were classified as Reperfusers. Apparent diffusion coefficient (ADC) maps were calculated from the DWI. The low b-value (b=0 s/mm2) and high b-value (b=1000 s/mm2) 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 as previously described[8]. Tmax maps were measured as the peak time of the residue function[9]. All acute images were coregistered (MNI Autoreg)[10], normalized with respect to contralateral normal white matter values and then used to train a generalized linear model (GLM) whose output is the risk of infarction on a voxel-wise basis[6]. GLM coefficients were calculated using bootstrapping and jackknifing (R)[11]. Training regions consisted of infarcted tissue delineated by a neuroradiologist as the measured lesion volume (MLV), defined here as the union of hyperintensities on the F/U T2 and iDWI, and non-infarcted tissue defined as all remaining ipsilateral hemisphere tissue excluding regions of CSF.

The model trained on data from all non-rt-PA treated patients was applied to patients receiving rt-PA. Using the calculated coefficients, the risk of tissue infarction was calculated on an individual voxel-wise basis along with upper and lower 95% prediction intervals (PI)[6]. We speculate that the 95% prediction intervals (PI) may provide supplemental information regarding tissue viability since they reflect the variability of infarction outcome found among other tissue presenting with the same acute MRI parameters. Predicted lesion volumes (PLV) were defined as all tissue with > 50% risk of infarction. An index of tissue salvage potential (TSP) was calculated as $(PLV_{GLM}-PLV_{LowerPI})/PLV_{GLM}$ (see Figure 1). The PLV for the Upper PI was not examined since it consistently overestimates tissue infarction[6]. Acute iDWI lesions were manually delineated as hyperintense regions on the initial MRI. Abnormal Tmax was determined as tissue > 2 s on normalized maps. DWI and PWI mismatch was defined as (Tmax – iDWI)/iDWI lesions.

Results: All results are provided as median [interquartile range] or mean±SD. 70 patients were assessed for reperfusion status and of these 21 were found to have complete reperfusion (TIMI=3). 4 out of 10 non-rtPA treated patients reperfused compared to 17 out of 60 in the rt-PA group. There was no significant difference (Wilcoxon rank sum test) in terms of age (61±12 vs 61±14 y), onset-time to MRI (146±60 vs 171±67 min), admission NIHSS scores (12 [7-15]) vs 14 [9-17]), gender 52% male vs 67% male), and days to follow-up (7±1 vs 9±7) between the reperfusers and non-reperfusers. Reperfusers had significantly (P=0.002) smaller MLV (33±49 cm^3) compared to non-reperfusers (72±59 cm^3). Of these patients, 55 had 3 month mRS evaluations. Reperfusers (N=15) had better (P=0.06) outcomes (1 [0-1]) compared to non-early-reperfusers (2 [1-3]). The site of the arterial occlusion was found to significantly differ (Pearson Chi-square test: P=0.03) between reperfusers and non-reperfusers overall. The reperfusers involved ICA/MCA (5%), MCA-trunk (24%), MCA trifurcation (14%) and MCA-branch (57%) while the non-reperfusers involved ICA/MCA (14%), carotid T-occlusion (CTO) (27%), MCA/ACA (2%), MCA-trunk (20%), MCA trifurcation (14%) and MCA-branch (22%).

The Figure shows an example of predicted infarction risk for patients given rt-PA who (A) did not reperfuse and (B) did reperfuse. PLV was larger (P=0.05) in patients who did not reperfuse (116±77 cm^3) compared to patients who did (77±47 cm^3). No statistically significant differences were found for either acute iDWI or percent mismatch between patients with and without reperfusion. Tmax however was larger in the non-reperfusion group (122±76 cm^3) compared to the TIMI=3 group (84±64 cm^3). However, correlation with actual lesion volume was significantly greater for PLV than Tmax in cases of reperfusion (R=0.69 vs R=0.3, P=0.03) but not in cases of non-reperfusion (R=0.70 vs R=0.62, P=0.15). For Tmax, volumes significantly differed by occlusion site for both non-reperfusers (P=0.01, one way ANOVA) and reperfusers (P=0.0002). For PLV, there was a significant dependency for non-reperfusers (P=0.01) and an association for reperfusers (P=0.07) on occlusion site.

TSP was found to be greater (P=0.08) in TIMI=3 group (0.86±0.14) compared to the others (0.80±0.15). The difference between the PLV using the Lower PI and MLV was found to be significantly lower in patients with reperfusion (P=0.005). However the GLM point predictions showed no such dependency. $PLV_{LowerPI}$ showed no dependency on occlusion site for cases with and with reperfusion.

Discussion: Our results show that for patients given thrombolytic therapy, the likelihood of reperfusion depends on the degree and extent of the ischemic injury at the time of treatment, which we measure using multiparametric predictive algorithms. Our findings reinforce the idea that large perfusion deficits and low recanalisation rates have a common source – namely a large proximal clot. Similar findings have been reported for patients given rt-PA where patients with large acute DWI lesion volumes have poor outcome despite reperfusion therapy. Our study also demonstrates the potential utility of calculating 95% PI in addition to each point prediction. We speculate that the improved performance of the Lower PI with reperfusion is due to the Lower PI representing the best case scenario for recovery while the GLM-point prediction represents expected outcome under "natural-history conditions." We speculate the differences between the point-prediction and Lower PI may provide insight into which tissue is potentially salvageable. A limitation of this study is its retrospective nature, which involved many patients in the training data who spontaneously reperfused. Future studies predicting tissue outcome for condition of reperfusion and no reperfusion separately may provide additional insight for identifying which patients are likely to benefit from reperfusion therapy.

References: 1. Albers GW, et al. Ann. Neurol. 2006; 60, 508-17. 2. Davis SM, et al. Lancet Neurol. 2008; 7, 299-309. 3. Kidwell CS, et al. Ann. Neurol. 2000; 47, 462-9. 4. Fiehler J, et al. Stroke. 2002; 33, 79-86. 5. Wu O, et al. Stroke. 2001; 32, 933-42. 6. Wu O, et al. Brain. 2006; 129, 2384-93. 7. Fiehler J, et al. Stroke. 2004; 35, 514-9. 8. Østergaard L, et al. Magn. Reson. Med. 1996; 36, 715-25. 9. Wu O, et al. Magn Reson Med. 2003; 50, 164-74. 10. Collins DL, et al. JCAT. 1994; 18, 192-205. 11. Efron B. The jackknife, the bootstrap and other resampling plans. 1982.

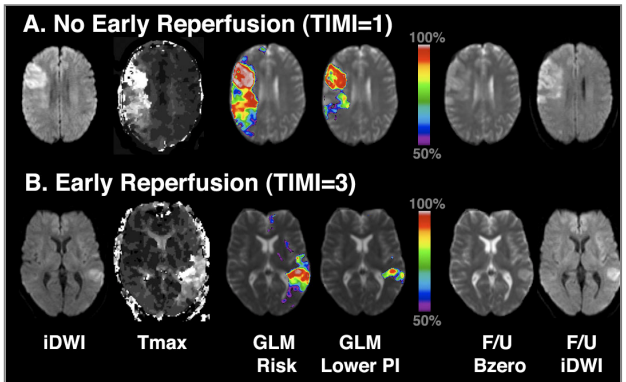

Fig 1: Example input and output GLM maps for patients receiving rt-PA who did not reperfuse (A) and who did reperfuse (B). Note the much larger PLV for (A) who did not reperfuse compared to (B) despite having a larger PWI and DWI mismatch. A larger lesion volume on the lower 95% PI can also be observed in (A) compared to (B), suggesting presence of more severely injured tissue.