Predicting tissue outcome using multiparametric algorithms and the four Ps of acute stroke imaging: parenchyma, pipes, perfusion and penumbra

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Introduction: The four Ps of stroke imaging – parenchyma, pipes, perfusion and penumbra – can provide a framework for diagnosis, prognosis and management of acute stroke patients [1]. Parenchymal injury can be assessed through diffusion-weighted MRI (DWI) while perfusion-weighted MRI can assess perfusion status. The mismatch between the DWI and PWI lesion has often been hypothesized to be a neuroimaging correlated of the ischemic penumbra, dysfunctional but still viable tissue [2], and hence is the focus of treatment. The "pipes" or the vessels can be imaged using angiography to provide information regarding the location of the occlusion. Extent of lesion growth [3] and chances of favorable clinical outcome in acute stroke patients receiving thrombolytic therapy [4] have been linked to vascular occlusion site and extent of collateral supply. Multiparametric MRI-based algorithms combining acute DWI and PWI have been shown to more accurately predict tissue outcome in patients receiving standard medical therapy than using the modalities separately [5]. These models, however, did not include the "pipes" in the algorithms. The degree of tissue injury and hence salvageability likely depends not only on the duration and degree of ischemia, but the presence of collaterals, which in turn will also be a function of the location of the occlusion. We hypothesize that extending these models to incorporate vascular territory will improve the predictive performance of these algorithms as well as provide insight into the pathophysiology of lesion evolution.

Subjects and Methods: DWI and PWI data from patients imaged <12 h from stroke onset who received a >= 5 days follow-up imaging study were retrospectively analyzed (n=74). Generalized linear models (GLM) combining acute DWI and PWI were developed using techniques previously described [6]. Vascular territory affected by the occlusion was determined by a neurologist using acute MR angiography (MRA) or CT angiography (CTA) and acute PWI and MRI. Territories were classified as being M1 (n=26), M2 (n=14), M3 (n=12), ACA (n=4), PCA (n=4), ICA (n=4), or small vessel (SV) (n=10). Maps of acute cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), tracer-arrival delay (DELAY), apparent diffusion coefficient (ADC), T2-weighted image (T2WI) and isotropic DWI (iDWI) were combined to produce maps of infarction risk on a voxel-wise basis [5]. GLMs were trained and evaluated using the patients' follow-up imaging studies (F/U). Models were trained for each vascular occlusion type as well as for all 74 patients using bootstrapping and jackknifing [7] and the coefficients compared (Z-test). Sensitivity and specificity of the GLM in predicting infarction were calculated along with receiver operating characteristic curves. Area under these curves (AUC) were calculated and compared (paired one-sided Wilcoxon signed rank tests). AUC=0 means incorrect classification for all thresholds while AUC=1 means perfect prediction of infarction regardless of risk threshold used for classifying infarcted tissue. The predicted lesion volumes (PLV) using 50% threshold were calculated and compared with the actual measured lesion volume on follow-up imaging (MLV). 50% was used since all models were designed to have an optimal operating point at this risk threshold.

Results: Follow-up infarction volumes (Table 1) as well as GLM model coefficients (Table 2) varied considerably as a function of vessel territory. The model built using all 74 patients (ALL) most closely resembles the M1/M2 models, likely because the majority of the cases consisted of M1/M2 regions (54%). However, the differences in the MTT and DELAY coefficients were enough to make the M1 model perform significantly better (P<.05) than the territory independent model. The differences between PLV and MLV were also significantly (P<.001) smaller for the M1-model (35±59 cm^3) than the non-specific (ALL) model (47±60 cm^3). Furthermore, the models appear to perform better for occlusions involving large lesions. We also note that for M3 regions, DWI plays a greater role than perfusion parameters.

Table 1: Lesion Volumes in median (IQR) cm^3 and accuracy of models as a function of occlusion location. *P<.05 AUC ALL vs AUC occlusion-site-specific model.

Territory	MLV	AUC ALL (%)	AUC Site (%)
M1*	59 (19-121)	90 (83-92)	91 (84-92)
M2	55 (20-88)	92 (82-94)	92 (83-95)
M3	6 (3-14)	87 (75-93)	86 (78-95)
ICA	36 (28-57)	88 (86-90)	86 (84-87)
ACA	10 (3-24)	84 (68-97)	81 (68-93)
PCA	14 (5-26)	80 (74-87)	77 (73-83)
SV	2 (1-3)	84 (80-93)	85 (76-91)

Discussion: Our results demonstrate that the vascular terriory provides additional information that is useful for improving prediction of tissue outcome. We also found that combining DWI and PWI can produce accurate estimates in the majority of cases. Where vessel occlusion information plays a role may be in specific regions, e.g. penumbral tissue versus infarcted core. Fiehler et al [3] speculated that the occlusion site affects the degree of lesion growth by influencing the degree of collateral circulation that is available for sustaining oligemic tissue. We speculate that this variability translates to poorer prediction in our models when occlusion site and vascular territory is not taken into consideration since slight flow reductions in tissue with sufficient collateral flow will have better chances of survival. Further studies are necessary since our findings here are limited by the small sample size in vascular territories not fed by the MCA. The ACA/PCA/ICA models were developed using only 3 patients and therefore varied greatly across subjects. For example, the ACA group performed poorly since one patient's ACA infarct evolved into involving the MCA territory over the course of her hospital stay. Excluding this patient led to significant changes in the model characteristics, leading to significant coefficients for all parameters, including MTT (see Table 2). Another contributing factor to poor performance is the overall smaller lesion volumes involved in certain territories, e.g. M3 and SV. This can be overcome by increased number of patients in each occlusion category. Despite these limitations, the improved performance of the models for M1/M2 suggest that taking the vascular territories and hence location of the vessel occlusion into consideration can improve prediction of tissue outcome and ultimately may play an even more important role in predicting individual patient responses to therapeutic intervention.

References: 1. Rowley HA. *AJNR. Am. J. Neuroradiol.* 2001; 22, 599-601. 2. Astrup J, et al. *Stroke.* 1981; 12, 723-5. 3. Fiehler J, et al. *AJNR. Am. J. Neuroradiol.* 2005; 26, 1056-61. 4. Kucinski T, et al. *Neuroradiology.* 2003; 45, 11-8. 5. Wu O, et al. *Stroke.* 2001; 32, 933-42. 6. Wu O, et al. *Brain.* 2006; 129, 2375-93. 7. Efron B. *The jackknife, the bootstrap and other resampling plans.* 1982.

Table 2: GLM coefficients for models. *Non-significant coefficient; †P<.05 Site-specific model vs Generic model (ALL).

Model	Bias	T2WI	ADC	iDWI	CBF	CBV	MTT	DELAY
ALL	-5.2±.2	0.4±.1	0.02±.1*	3.3±.1	-0.4±.05	0.08±.03	1.0±.05	0.08±.003
M1	-4.9±.1	0.4±.1	0.09±.1*	3.3±.1	-0.4±.05	0.08±.03	0.8±.04†	0.07±.003†
M2	-5.9±.2†	0.3±.1	0.3±.1	3.7±.1	-0.3±.06	0.02±.04*	1.1±.06	0.07±.003†
M3	-8.0±.2†	1.2±.2†	-1.2±.2†	5.6±.2†	0.2±.04†	-0.2±.03†	1.4±.05†	0.1±.005†
ICA	-6.3±.2†	0.2±.1*	0.5±.1†	4.4±.2†	-0.5±.05†	0.3±.03†	0.5±.05†	0.1±.003†
ACA	-3.3±.2†	0.9±.1†	-0.7±.1†	3.5±.2	0.1±.03†	-0.4±.03†	-.05±.05*†	0.06±.004†
PCA	-3.8±.2†	-0.4±.1†	0.8±.1†	3.9±.1†	-1.6±.05†	0.7±.04†	0.5±.05†	0.01±.002†
SV	-4.5±.2†	-0.4±.1†	0.4±.1†	3.6±.1†	-0.9±.07†	0.3±.05†	1.2±.07†	0.1±.006†