Effects of MR perfusion parameters selection on the prediction of tissue infarction in acute human stroke

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Introduction: There is increasing interest towards using mismatches in diffusion (DWI) and perfusion MRI (PWI) lesions for guiding clinical decisions in acute stroke patients [1]. However, although PWI has been shown to be a sensitive marker of tissue likely to die without therapeutic intervention, it is not very specific [2], leading to the possibility of overestimating lesion growth without therapy. Moreover, the amount of tissue identified as abnormal depends heavily on which of the many perfusion metrics is used to evaluate ischemic damage, e.g. cerebral blood flow (CBF), cerebral blood volume (CBV), tissue mean transit time (MTT) or tracer arrival time (DELAY) [3]. These parameters, in turn, may vary depending on where the arterial input function (AIF) is selected [4] and which algorithm is used for deconvolution. Tissue risk maps have objectively shown that combinations of DWI and PWI can more accurately predict tissue outcome than either PWI or DWI alone [5]. We therefore extended the risk map framework to evaluate which perfusion metrics provide the best prediction of tissue infarction.

Subjects and Methods: DWI and PWI data from patients imaged <12 h from stroke onset who received a follow-up imaging study > 5 days later were retrospectively analyzed (n=80). Generalized linear models (GLM) to evaluate the predictive performance of the different PWI metrics and deconvolution techniques were developed. It has been previously shown that combinations of CBF, CBV and MTT with apparent diffusion coefficient (ADC), T2-weighted image (T2WI) and isotropic DWI (iDWI) maps produced the best prediction of tissue outcome [5]. Therefore, in this study we limited our comparisons to models using these three DWI parameters and three PWI parameters with models using these six parameters along with DELAY as a covariate. The PWI parameters were calculated using either standard singular value decomposition techniques (sSVD) or using a block-circulant deconvolution matrix with minimization of oscillation index (oSVD) [3]. Models were created using deconvolution with an AIF selected from either the ipsilateral or contralateral hemisphere resulting in a total of 8 models – sSVD using an ipsilateral AIF (ipssSVD), ipssSVD with DELAY covariate (ipsSVD-DELAY), sSVD with contralateral AIF (cnlsSVD), cnlsSVD with DELAY (cnlsSVD-DELAY), oSVD with ipsilateral AIF (ipsoSVD), ipsoSVD with DELAY (ipsoSVD-DELAY), contralateral oSVD (cnloSVD), and cnloSVD with DELAY (cnloSVD-DELAY). Images were coregistered, normalized with respect to mean contralateral values and then used as covariates in predictive algorithms based on a GLM whose output values are the probability of infarction on a voxel-wise basis [5]. Coefficients were calculated using bootstrapping and jackknifing [6] and compared across models (one-tailed Z-tests). GLMs were trained and evaluated using the patients' follow-up imaging studies (F/U) for determining infarct volume. 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 two-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 Youden's J index [7], defined as sensitivity+specificity-1, was also calculated and compared across groups (paired two-sided Wilcoxon signed rank tests) to assess the overall performance of the algorithms at a single decision threshold of 50% for classifying infarcted tissue. Youden's J index=0 indicates no diagnostic value while J=1, indicates perfect diagnosis. 50% was used since all models were designed to have an optimal operating point at this risk threshold.

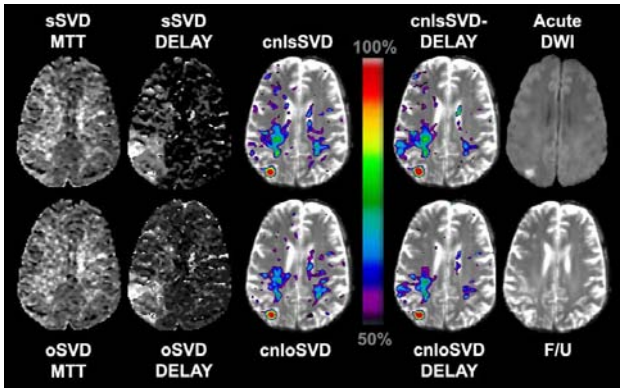

Fig 1. Example acute DWI and PWI maps calculated using an AIF from the contralateral hemisphere and deconvolution with sSVD and oSVD and their corresponding predicted infarction. A clear PWI/DWI mismatch is present. Note that adding DELAY as an additional covariate improves the specificity of the predictions resulting in risk maps which match better with the 5 day F/U. Relying on only DWI would have underestimated the lesion, and only on DELAY would have overestimated it.

Results: Coefficients for the eight models are shown in Table 1. There was no significant difference between ipsilateral and contralateral model coefficients not including DELAY. However, for models that included DELAY as a covariate, there was a significant difference ($p<.05$) in the DELAY coefficients for sSVD models. For the oSVD models, CBF, CBV and DELAY parameters had significantly different coefficients ($p<.05$). There was also a significant difference in perfusion coefficients between sSVD and oSVD models. Inclusion of an explicit DELAY parameter led to the reduction of weighting given to CBF for all models. Due to possibility of co-registration errors confounding results, analysis of performance accuracy was limited to patients with measured final lesion volumes at least 1 cc (n=74). No significant difference was found between AUC and Youden's J index for models using perfusion maps created with an AIF from the ipsilateral or contralateral hemisphere. There was also no significant difference between the AUC and Youden's J-index for sSVD and oSVD models. For both sSVD and oSVD based models using an AIF from the ipsilateral or contralateral hemisphere, incorporating DELAY as a covariate significantly improved the AUC ($p<.01$) (from .85±.1 to .86±.1) as demonstrated in the example shown in Fig 1. For sSVD, the Youden's J-index did not significantly change (.53±.2) whereas for oSVD, significant improvement was found for both ipsoSVD ($p=.02$) (.52±.2 to .53±.2) and cnloSVD ($p<.05$) (.52±.2 to .53±.2). Subset analysis of patients imaged <6h (n=32) showed cnlsSVD-DELAY Youden's J index (.52±.2) was significantly less ($p=.02$) than that of ipsoSVD-DELAY (.55±.2) and cnloSVD-DELAY (.55±.2) while there was no difference with respect to ipsSVD-DELAY (.55±.2).

Discussion: Our results suggest that tracer arrival delay may be a useful additional acute marker for identifying tissue at risk of infarction if no therapeutic intervention occurs. Its inclusion benefits oSVD based models more so than sSVD models, as noted by improved J-index, which is consistent with the fact that sSVD perfusion metrics are already weighted by tracer arrival times. No statistically significant difference was found between models developed using an ipsilateral or contralateral AIF in terms of performance, but that is likely due to differences in coefficients weighting the perfusion parameters. The same holds true for the similar performance for oSVD and sSVD models. However, in the hyperacute stage (< 6 h), we found that oSVD provides better assessment of tissue likely to infarct than sSVD based models, probably due to the underestimation of flow in sSVD models due to tracer arrival. Finally, we have shown that these tissue risk maps can be used to objectively assess promising new markers for the acute prediction of tissue outcome. This framework can be used not only for comparing different perfusion parameters, but also for evaluating non-perfusion-based MRI parameters, such as pH-weighted MRI [8], for detection of salvageable tissue.

References: 1. Hjort N, et al. *Stroke.* 2005; 36, 388-97. 2. Baird AE and Warach S. *J. Cereb. Blood Flow Metab.* 1998; 18, 583-609. 3. Wu O, et al. *Magn. Reson. Med.* 2003; 50, 164-74. 4. Yamada K, et al. *Stroke.* 2002; 33, 87-94. 5. Wu O, et al. *Stroke.* 2001; 32, 933-42. 6. Efron B. *The jackknife, the bootstrap and other resampling plans.* 1982. 7. Youden WJ. *Cancer.* 1950; 3, 32–5. 8. Zhou J, et al. *Nat. Med.* 2003; 9, 1085-90.

Table 1: GLM coefficients for models. *p<.05 Ipsilateral vs Contralateral; †p<.05 sSVD vs oSVD; §p<.05 with and without DELAY

Model	Bias	T2WI	ADC	iDWI	CBF	CBV	MTT	DELAY
cnlsSVD	-4.6±.1	.41±.08	-.04±.08	3.1±.1	-.59±.05§	.10±.04†	1.0±.05†	–
cnlsSVD-DELAY	-4.7±.1	.31±.09	-.04±.08	3.0±.1	-.34±.05§	.04±.03	.92±.05	.08±.003*†
cnloSVD	-4.4±.1	.45±.08	-.05±.08	3.2±.1	-.65±.05§	.21±.04†	.82±.05†	–
cnloSVD-DELAY	-4.6±.1	.33±.09	-.06±.09	3.1±.1	-.37±05*§	.09±.04*§	.82±.05	.11±.004*†
ipssSVD	-4.7±.1†	.40±.08	-.02±.08	3.2±.1	-.53±.05†§	.09±.04†	1.1±.05†	–
ipssSVD-DELAY	-4.8±.1†	.34±.09	-.03±.09	3.1±.1	-.37±.05†§	.06±.03†	1.0±.05†	.07±.003*†
ipsoSVD	-4.3±.1†	.52±.08	-.10±.08	3.2±.1	-.77±.05†§	.30±.04†	.78±.05†	–
ipsoSVD-DELAY	-4.4±.1†	.40±.09	-.08±.08	3.1±.1	-.56±.05*†§	.22±.04*†	.76±.05†	.08±.003*†