Which physiological parameters determine outcome in the acute and the subacute phases of acute ischemic stroke?

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Introduction Patients presenting with acute ischemic stroke within 3 hours of symptom onset are routinely treated with rt-PA. The time window of thrombolytic treatment is currently being extended to 9-12 hours in patients with a perfusion-diffusion mismatch. Chronic tissue damage may, however, not be avoided by acute recanalization alone: Prolonged ischemia may trigger molecular and cellular processes that cause necrosis at a much longer time scale (days), even in tissue with seemingly benign perfusion levels. The optimal therapeutic therapy in later time-windows may therefore include neuroprotective agents. In this study we use predictive algorithms to characterize the temporal evolution of infarct risk in acute stroke, and assess the extent to which perfusion and diffusion MRI parameters alone predict subsequent infarct.

We used multiparametric statistical models to predict tissue infarction at 2 hours, 24 hours and 3 month after rtPA treatment at a voxel level ([1], [2]). In particular, we developed stroke progression models for the acute – 2 hour post treatment interval, where rtPA is effective, for the 2 – 24 hour interval, where a potential effect of late reperfusion competes with inflammatory damage, and the sub-acute interval from 24 hours – 3 month, where the infarct grows due to apoptosis, inflammation and new ischemic events.

The models predicting the sub-phases are compared to the classical model predicting the acute – 3 month interval. We also estimate the change in the risk of infarction in the diffusion-perfusion mismatch (DPM) at each time-point.

Materials and methods Standard perfusion, diffusion and structural images (MTT, Delay, CBF, CBV, iDWI, ADC and T2) were acquired acutely, at 2 hours and 24 hours after rt-PA treatment (3 h ± 20min after acute scan) for n=15 patients with acute stroke. A T2 follow-up scan was acquired after 3 months. We developed standard logistic regression models $M_{0h\text{-}2h}$, $M_{2h\text{-}24h}$ and $M_{24h\text{-}3month}$ to predict the DWI lesions at 2 hours and 24 hours, which serve as surrogates for the outcome in the acute phases, and the 3 month final outcome, using the acute, 2 hours and 24 hours scans, respectively. The training sets were balanced and consisted of voxels in the outcome lesion and healthy voxels from both the contra-lateral hemisphere and the DPM. A jack-knifing approach was used to evaluate each of the models [1]. The standardized estimates of the coefficients of the models and odds ratios (OR) (change in odds when increasing/decreasing diffusion/perfusion) were estimated to compare the relative influence of the physiological parameters in the different sub-phases.

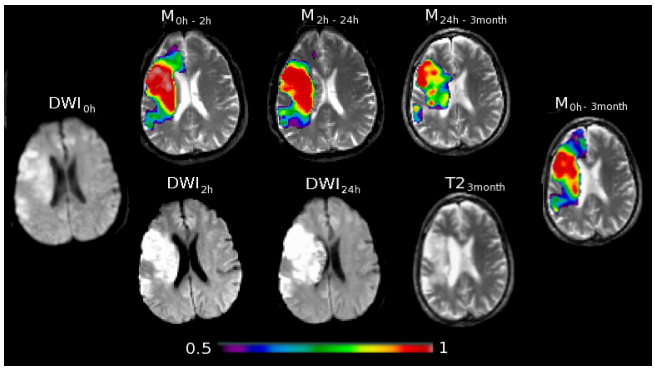
Results

Median AUC and inter-quartile range (IQR) for each of the models are shown in the table. AUC was calculated using voxels with prolonged MTT. The sub-models are all superior ($p < 0.05$) in predictive performance to the classical model $M_{0h\text{-}3month}$ predicting the final outcome using acute images, which had median AUC 0.73 and IQR [0.66; 0.77]. We speculate this is in part due to the heterogeneity of mechanisms causing subsequent neuronal damage mentioned above.

The odds ratio for DWI increased from 3.1 to 8.4 going from 0 hours to 24 hours. In contrast, the OR for the perfusion parameters CBF, MTT and Delay decreased gradually with time, e.g. MTT OR decreased from 1.4 to 1.1 going from the acute stage to 24 hours. CBV predicted the follow up outcome based on 24 hour scans together with DWI, but had OR of approximately 1 in the acute phases. This suggests that the role of perfusion in driving subsequent tissue damage is most dominant in the acute phases.

Model	AUC	Infarction risk in DPM
$M_{0h\text{-}2h}$	0.86 ; [0.80; 0.91]	0.18 ; [0.12; 0.25]
$M_{2h\text{-}24h}$	0.77 ; [0.75; 0.85]	0.39 ; [0.33; 0.50]
$M_{24h\text{-}3month}$	0.84 ; [0.75; 0.88]	0.70 ; [0.45; 0.83]

The median risk of infarction at a typical voxel in DPM was calculated at each time-point and is shown in the table together with IQRs. A significant increase in the risk of infarction was found ($p<0.05$) moving in the 0-2 hour interval relative to the 2-24 hour interval. We ascribe this in part to the beneficial effect of rtPA [3] and early reperfusion. Interestingly, the increasing risk of infarction in DPM beyond 2 hours after rtPA treatment, associated with a decreasing role of perfusion parameters parallels the known, increasing role of inflammation and apoptosis in subacute ischemia. The figure shows an example of risk maps for a specific subject overlaid on T2 structural maps and the corresponding DWI images as well as the follow up T2 image. Note the temporal evolution of risk of subsequent infarction.



Conclusions The predictive performance is increased when predicting the different phases of acute ischemic stroke separately, underlining the temporal, spatial and physiological heterogeneity of stroke progression. AUC based on all brain voxels (as typically reported in other studies) showed a similar trend, but with AUC values approximately 10% higher. We speculate, however, that this increase is less informative as it is mainly caused by the voxel risks in the contra-lateral hemisphere. The heterogeneity in the relative importance of the physiological parameters is reduced when studying the sub-models in comparison to the acute – 3 month prediction. We speculate that predictive algorithms may help elucidate the diagnostic significance of imaging findings at various time intervals after stroke onset. Furthermore, we believe the MRI and predictive algorithms may help target thrombolytic and neuroprotective therapy in the acute and subacute phases of acute stroke.

Reference List

[1]. Wu, O. et al. Stroke, 2001. [2]. Mouridsen, K. et al. ISMRM 12th international meeting and exhibition, 2004. [3] Wu, O et al., Brain 2006.