Effects of treatment on brain tissue classification with serial MRI-based ISODATA cluster analysis in an experimental subarachnoid hemorrhage model

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Introduction: Multiparametric MRI of different aspects of cerebral ischemic lesions may improve diagnosis of patients with cerebrovascular injury [1]. Nevertheless, spatial and temporal variations in the extent of various pathophysiological processes, complicates straightforward characterization of brain tissue status. In recent years, unsupervised algorithms have been developed to voxel-wise classify ischemic lesion areas in distinct categories based on multiparametric MRI data [1]. However, most of these analysis strategies have not incorporated dynamics of lesion changes into tissue classification. We have previously introduced a lesion classification approach that includes the temporal evolution of diffusion and T_2 changes in an experimental stroke model [2]. In the current study we extend this approach in an experimental subarachnoid hemorrhage (SAH) model, where we evaluate lesion characteristics in a treatment and control group based on the progression of diffusion, T_2 and perfusion parameters.

Material and methods: A total of eleven adult male Wistar rats were included from an ongoing study on treatment effects of Interferon-β (Inf-β) after experimental SAH. All procedures were approved by our institution's animal care committee. SAH was induced by perforating the vessel wall near the right internal carotid artery and middle cerebral artery bifurcation. After surgery, animals were allowed to recover and received daily subcutaneous injections of either 1.5 x 10^6 I.U./kg Inf-β (n=6) or placebo (n=5). MRI was conducted at 2 and 7 days after vessel wall perforation. T_2-weighted (TR=3600 ms; TE=15-180ms; FOV=32x32x19mm^3; 256x128x19 data matrix), diffusion-weighted (spin echo eight-shot EPI; TR=3000ms; TE=38.5ms; b=0 and 1430 s/mm^2; FOV=32x32x19mm^3; 128x128x19 data matrix), and dynamic susceptibility contrast-enhanced MRI (gradient echo EPI; α=35°; TR=330 ms; TE=25 ms; FOV=32x32x9mm^3; 64x64x5 data matrix) were acquired on a 4.7T horizontal bore MR spectrometer (Varian, Palo Alto, CA, USA). Subsequently, maps of the T_2, trace of the apparent diffusion coefficient (ADC_{trace}), cerebral blood flow index (CBF_i), and cerebral blood volume (CBV) were calculated from the acquired data [3]. Parametric maps were normalized (and expressed as relative) to the mean value in an invariably unaffected left striatal area derived from a lesion incidence map. Datasets were spatially aligned to a brain template created from six control animals. For each rat, T_2, diffusion and perfusion parameters over time were simultaneously analyzed using iterative self-organizing data analysis (ISODATA) [4], with pre-spatial contiguity constraint [2]. Resultant cluster maps were normalized according to a normalizing scale with values between 0 (white matter tissue) and 100 (CSF) [4]. Abnormal tissue was identified as voxel clusters with values between 15 and 95. Abnormal tissue clusters of all animals were pooled and evaluated based on their mean and standard deviation. Clusters which mean and standard deviation differed less than 1% were merged into one distinct global signature. In this way the number of global signatures was determined without user bias. Manual outlines of lesions on T_2 maps were used for correlation with the total volume of clusters with abnormal tissue (Pearson product-moment correlation). One-way ANOVA with Bonferroni post-hoc testing was used to compare volumes of the detected signatures between treatment groups.

Results: Figure 1 shows T_2 (a.1), ADC_{trace} (a.2), CBF_i (a.3) and CBV (a.4) maps of a coronal rat brain slice 2 days after SAH induction. Regions with prolonged T_2, reduced and increased ADC_{trace}, and hypo- and hyperperfusion were identified inside lesion areas. Parametric maps were combined and analyzed over two time-points resulting in a cluster map displaying areas with abnormal tissue status (b). On average 3 (±2) clusters per animal were identified as abnormal tissue. The total volume of abnormal voxel clusters correlated significantly with the manually outlined lesions (R^2=0.756). Over all animals a total of 31 clusters was identified. Pooling of these clusters resulted in five distinct global signatures. All signatures, except for D, were characterized by relatively increased perfusion. Signatures A, B had continuously normal ADC and elevated CBF_i and CBV at day 2, which was lowered after 7 days. Signature C was characterized by an ADC drop at day 2 followed by an increase at day 7, and continuously prolonged T_2. Signatures D and E were marked by normalizing T_2 from day 2 to 7. Signature E, but not D, had initially lowered ADC. Table 1 shows the percent distribution of the signatures in Inf-β- and placebo-treated animals. There was no significant difference in total volume of abnormal tissue between these two groups (p=0.128). However the distribution of signatures among animals was different. Signatures A and E had a higher distribution in the Inf-β group, while signatures B and D were more prevalent in the placebo group.

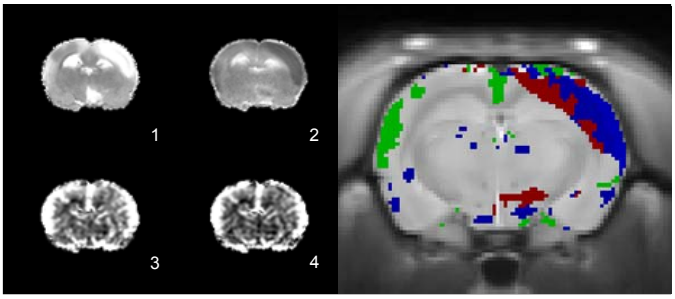

Figure 1 T_2 (1), ADC_{trace} (2), CBF_i (3), and CBV (4) maps of a coronal rat brain slice 2 days after SAH induction. b. ISODATA-based cluster map from multiparametric MRI maps at 2 and 7 days post-SAH. Differently colored voxel clusters indicate different abnormal tissue status (color-coding depicted in table 1)

Signature	*# animals*	*Inf-β*		*Placebo*	
		%	Volume (mm^3)	%	Volume (mm^3)
A	6	67	36.8 (±5.0)	33	33.6 (±12.5)
B	5	40	47.5 (±34.6)	60	45.3 (±36.2)
C	4	50	27.6 (±20.5)	50	23.9 (±14.3)
D	3	33	15.4 (±2.5)	67	26.9
E	4	75	17.4 (±0.2)	25	27.1 (±5.7)

Table 1 Distribution of abnormal tissue signatures in Inf-β- and placebo-treated animals. For each signature the animal incidence sum, distribution (%), and signature volume (mean ± SD) among animals treated with Inf-β or placebo are shown.

Discussion: Two treatment groups in a rat SAH model were analyzed for treatment effects on lesion development using multiparametric MRI-based ISODATA cluster analysis over time. Our analysis revealed five distinct clusters with different characteristics of cerebrovascular injury, which had a different prevalence in Inf-β-treated animals as compared to controls. The higher prevalence of signature E and lower prevalence of signature D following Inf-β therapy might point toward a treatment-specific effect on tissue ADC progression, even though we found no effect on total lesion size. Our study demonstrates that inclusion of temporal information in ISODATA cluster analysis may have added value in MRI studies on treatment effects after cerebrovascular injury. However, further analysis is required for accurate correlation of identified signatures with tissue outcome.

Refereneces: [1] Østergaard L, et al. *Curr. Opin. Neurol.* 22:54-9 (2009). [2] Bouts MJ, et al. *Proceedings of the 17th ISMRM meeting.* 943 (2009). [3] Dijkhuizen RM, et al. *J Cereb Blood Flow Metab.* 21: 964-71 (2001). [4] Soltanian-Zadeh H, et al. *J Magn Reson Imaging* 17:398-409 (2003).