Widespread hemodynamic disturbance following experimental TBI

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Target Audience Researchers in traumatic brain injury.

Purpose The goal of this study was to investigate spatiotemporal dynamics of CBF and cerebrovascular reactivity (CR) in an established open-skull, controlled cortical impact (CCI) model of TBI in rats and how these hemodynamic disruptions affect T_2, ADC, FA, and lesion volume. The impact was applied over the left primary forelimb somatosensory cortex (S1FL). Multimodal MRI measurements were made longitudinally from 1 hour and up to 14 days post TBI. Comparisons were also made with behavioral assessments.

Methods TBI was induced on male rats (250-350g, n=12) on the left S1FL cortex through a cranial window using a Ø3mm tip (5.0m/s, 250μs dwell time, 1mm depth).[1] Multislice T_2, ADC, CBF MRI at 7T was acquired 1 and 3 hrs, 2, 7 and 14 days after TBI under 1.5% isoflurane. The spatial resolution was 267x267x1000microns[1-3]. Images were co-registered. T_2, ADC and fractional anisotropy (FA) were tabulated for different ROIs. Normalization (except CBF response) was made against homologous regions in the contralesional hemisphere. Foot fault and forelimb asymmetry scores were measured longitudinally.

Results Sham operated rats showed no abnormality in CBF, CBF % changes in response to 5% CO_2, FA, T_2 and ADC over the same time courses (n=6, data not shown).

In the contralesional hemisphere, CBF, T_2, ADC and FA did not differ from sham animals and did not change with time after TBI.

In the ipsilesional hemisphere, at 1 and 3 hrs after TBI, the area of CBF deficit was markedly larger than T_2 and ADC abnormalities, spreading over a large area of the cortex (**Figure 1**). Both diffusion and T_2 lesions grew larger with time and peaked on day 2, suggesting the presence of ischemic injury. On day 2 after TBI, hyperperfusion was observed in the impacted area that showed T_2 hyperintensity on day 0. By contrast, hypoperfusion was widespread in areas surrounding and beyond the impacted region.

The CBF responses to 5% CO_2 in air were also abnormal. At 1 and 3 hrs, surprising negative CBF % changes (blue to purple pixels) were detected in the core of the impact. The negative CR is a result of a vascular stealing effect, commonly observed 1-2 days after cerebral ischemia [2]. The area and the magnitude of abnormal CR were markedly larger than those of T_2 abnormality. CR returned toward normal values by day 7 and 14. Reduced CBF % changes were also detected in areas surrounding the impact core.

Group ROI analysis are shown in **Figure 2** and **3**. Of note, in the contralesional cortex, CR was attenuated at 3 hrs and on day 2, and recovered by day 7 and 14, suggesting there were systemic effects to evoked vascular response.

Foot fault and forelimb asymmetry scores were statistically different from pre-TBI and worse on day 2 and returned toward normal by day 14 (data not shown), consistent with our previous study.[3]

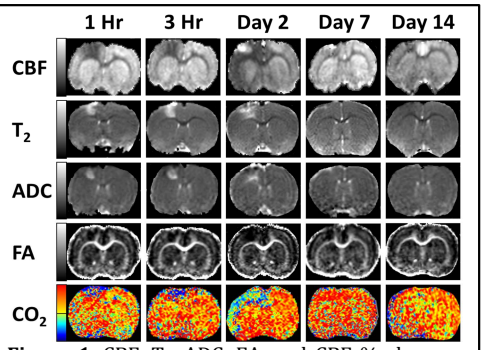

Figure 1. CBF, T_2, ADC, FA, and CBF % changes responding to 5% CO_2 at 150x150x1000 μm of one slice (out 7 slices acquired) at 1hr, 3 hr, 2, 7 and 14 days after TBI from one rat. CBF: 0-2.5 mL/g/min, T_2: 30-100 ms, ADC: 0.4-1.3 x10^{-3} mm^2/s, FA: 0.1-0.6; CO_2 % changes: -100% (blue-purple) to 100% (yellow-red).

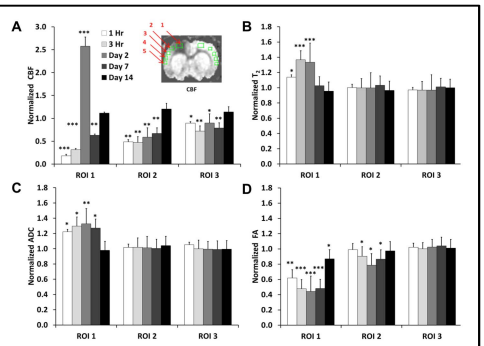

Figure 2. Normalized CBF, T_2, ADC and FA of the different ROIs at 1hr, 3hr, 2, 7 and 14 days after TBI. Mean±SEM, n=8, *p<0.05, **p<0.01, ***p<0.001 between ipsi- and contra-lesional ROIs. ROI 4 and 5 are similar to ROI 3 and their data are not shown for clarity.

Discussion & Conclusion: Quantitative multi-parametric MRI was used to systematically characterize spatiotemporal changes in an open-skull, controlled cortical impact (CCI) TBI model in rats. The major findings were: i) in the contralesional cortex, the CBF, T_2, ADC and FA were not affected at all time points studied, but the CBF response to 5% CO_2 was reduced followed by a gradual recovery, ii) in the ipsilesional cortex, the abnormal areas of the CBF and CBF responses on day 0 and 2 were larger than those of the T_2, ADC and FA which were localized to the area of impact, iii) within the area of impact, CBF reduced on day 0, increased to 2.5 times of normal on day 2, and returned towards normal by day 14, whereas in the tissue surrounding the impact, only hypoperfusion was observed on day 0 and 2, iv) CBF response in the ipsilesional hemisphere was negative in the ipsilesional cortex, most severe on day 2 but gradually returned toward normal, v) T_2, ADC, and FA abnormalities in the impact core were observed on day 0, peaked on day 2, and gradually returned towards normal by day 14, whereas these parameters in the tissue surrounding the core were only mildly affected, vii) lesion volumes, peaked on day 2, were correlated with behavioral scores by forelimb placement and forelimb foot fault tests.

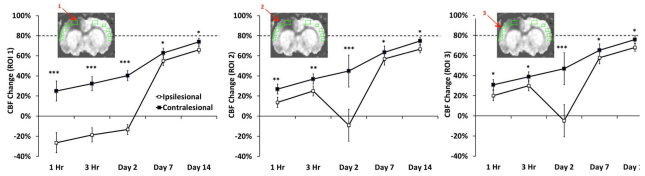

Figure 3. CBF percent changes in response to 5% CO_2 in ipsi- and contralesional ROI 1, 2 and 3 (see Figure 3 for ROI definition) after TBI (mean±SEM, n=8, *p<0.05, **p<0.01, ***p<0.001 between ipsi- and contra-lesional ROIs). The horizontal dotted lines indicated the average CBF % changes from the sham group (n=6).

In conclusion, there are widespread hemodynamic disturbances in basal CBF and CR following TBI, extending over a few days. Future studies will study impacts to different brain regions (i.e., the hippocampus) and repeated closed skull TBI, and incorporate rsfMRI to further characterize TBI.

References: 1) Watts J Neurotrauma 2014, 2) Shen JCBFM 2005. 3) Long J Neurotrauma 2014.