Perturbed CO2 reactivity within and beyond the impact area following hyperacute mild TBI

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Target Audience Neuroscientists in traumatic brain injury

Purpose The initial direct mechanical damage in traumatic brain injury (TBI) is followed by secondary damage that includes impaired cerebral blood flow, autoregulation, and metabolic function. The goal of this study was to longitudinally examine vascular reactivity to CO_2 in mild TBI during hyperacute and chronic phase up to 14 days.

Methods Male SD rats (250-350g, n=5) were studied. A 6mm craniotomy was created over the left forelimb somatosensory cortex (S1: +0.25mm anterior and 3.5mm lateral to bregma). The intact dura matter was impacted with a Ø3mm tip (5.0m/s, 250μs dwell time, 1mm depth). The cranial opening was sealed with bone wax following the impact. Multislice MRI was performed 3hrs, 2, 7 and 14 days after TBI on a 7T Bruker Biospec scanner under 1.5% isoflurane. Basal CBF and CBF fMRI was acquired with cASL using seven 1-mm thick coronal images, FOV=2.56x2.56cm, matrix=96x96 [1]. T_2 was also acquired. CBF % changes due to 5% CO_2 was analyzed using ROI in the S1 region. T_2 lesion volumes were determined.

Results **Figure 1** shows representative images of CBF, T_2 and CO_2 responses by CBF fMRI at different time points after TBI. At 3 hrs, abnormal perfusion and CO_2 reactivity were markedly larger in area than T_2 abnormality. Hyperperfusion was observed on day 2 in the impact region. Mild hypoperufsion was evident on day 7 and 14. CO_2 reactivity normalized by day 7 and 14. T_2 lesion peaked on day 2.

Figure 2 shows the group-averaged CO_2 reactivity by CBF changes across time. In the contralesional cortex, CO_2 reactivity was attenuated at 3hrs and day 2, and recovered by day 7 and 14. In the ipsilesional cortex, CBF actually decreased with CO_2 inhalation, suggesting a hemodynamic stealing effect. There were statistical differences in CO_2 reactivity between the ipsi- and contralesional cortex at 3 hrs and on day 2. CO_2 reactivity in the ipsilesional cortex largely normalized by day 7 and 14, although remained slightly depressed. For comparison, T_2 lesion volumes were analyzed for all time points. T_2 lesion volume peaked on day 2 and was largely reduced by day 7 and 14 (**Figure 3**). Functional outcomes by forelimb asymmetry and foot fault closely correlated with T_2 lesion volumes (data not shown).

Discussion and Conclusions Extensive and severe CO_2 reactivity disruptions within and beyond the impacted area were observed in hyperacute phase of mild TBI. The area of CO_2 response abnormality appeared much larger than CBF, T_2, and ADC abnormality. T_2 and CO_2 reactivity mostly normalized by day 14, but mild hypoperfusion and reduced CO_2 reactivity remained on day 14. fMRI of CO2 reactivity offers a means to probe the ability of vessels to react to a vasodilator in a non-invasive manner. Future studies will examine the underlying molecular mechanisms of widespread disruption of CBF and vascular reactivity as well as fMRI responses to forepaw stimulation. These multi-parametric MRI offers complementary, clinically relevant information.

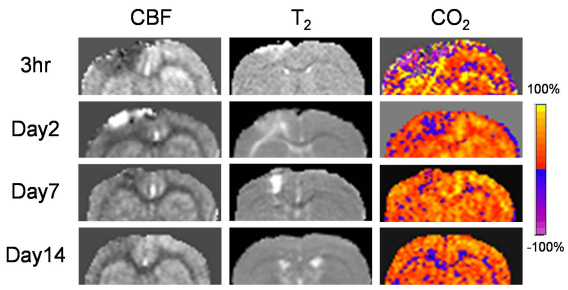

Figure 1. CBF, T_2 and CO_2 CBF responses at different time points after TBI.

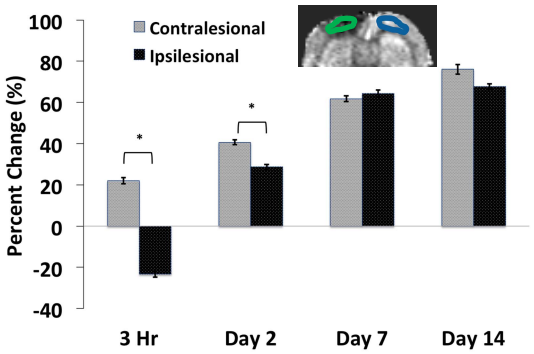

Figure 2. ROI CBF % changes due to CO_2 challenge.

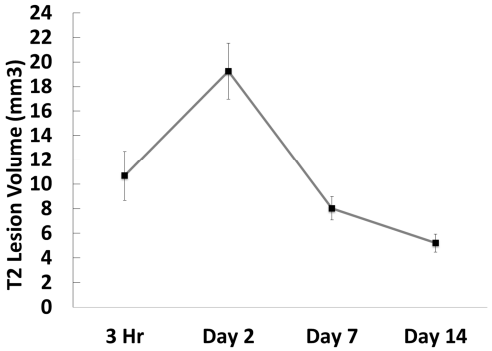

Figure 3. Lesion volume defined by T_2 at different time points

REFERENCE: 1) Shen Q, et al., J Cereb Blood Flow Metab, 2011; 31, 2076.