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 CO2 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]. T2 was also acquired. CBF % changes due to 5% CO2 was analyzed using ROI in the S1 region. T2 lesion volumes were determined.

Results Figure 1 shows representative images of CBF, T2 and CO2 responses by CBF fMRI at different time points after TBI. At 3 hrs, abnormal perfusion and CO2 reactivity were markedly larger in area than T2 abnormality. Hyperperfusion was observed on day 2 in the impact region. Mild hypoperfusion was evident on day 7 and 14. CO2 reactivity normalized by day 7 and 14. T2 lesion peaked on day 2.

Figure 2 shows the group-averaged CO2 reactivity by CBF changes across time. In the contralesional cortex, CO2 reactivity was attenuated at 3hrs and day 2, and recovered by day 7 and 14. In the ipsilesional cortex, CBF actually decreased with CO2 inhalation, suggesting a hemodynamic stealing effect. There were statistical differences in CO2 reactivity between the ipsi- and contralesional cortex at 3 hrs and on day 2. CO2 reactivity in the ipsilesional cortex largely normalized by day 7 and 14, although remained slightly depressed. For comparison, T2 lesion volumes were analyzed for all time points. T2 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 T2 lesion volumes (data not shown).

Discussion and Conclusions Extensive and severe CO2 reactivity disruptions within and beyond the impacted area were observed in hyperacute phase of mild TBI. The area of CO2 response abnormality appeared much larger than CBF, T2, and ADC abnormality. T2 and CO2 reactivity mostly normalized by day 14, but mild hypoperfusion and reduced CO2 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.