Pericontusional and contalateral tissue show differential metabolism and perfusion changes after traumatic brain injury

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INTRODUCTION: Traumatic brain injury (TBI) is a common cause of death and disability in the United States and across the world. Substance abuse is a frequent comorbid condition among patients with TBI, but little is known about its potential additive or interactive effects on tissue injury or recovery from TBI. This study aims to evaluate regional metabolism, cerebral perfusion, and white matter integrity using MR spectroscopy, arterial spin labeled (ASL) MRI, and diffusion tensor imaging (DTI) in TBI patients with and without history of methamphetamine (METH) abuse.

METHODS: Twelve patients with TBI (6 had positive and 6 had negative urine toxicology for METH) were recruited from our neuro-intensive care unit (ICU), located at the only Trauma Center (Level II) in our State. Informed consent was obtained from a surrogate decision maker. All subjects were comatose and received mechanical ventilation with light sedation with benzodiazepines and opiods, and monitored by the ICU team during the scans (on a 3T Siemens TIM Trio). Structure MRI included high-resolution MP-RAGE and FLAIR sequences to identify the contusion. Localized ^{1}H MRS was performed in pericontusional and contralateral white matter using point-resolved spectroscopy (PRESS) (**Figure 1**) (TR/TE=3000/30ms, 64 averages, 3.5 min per location), using an absolute concentration protocol[1] and LCModel[2] to determine the NAA and lactate concentrations. An arterial spin labeling (ASL) sequence was used to measure perfusion (**Figure 2, top**), and regional cerebral blood flow (rCBF) was assessed using Image J[3]. DTI were obtained with 12 diffusion direction axial spin-echo echo-planar imaging (EPI) scans (**Figure 2, bottom**) (28 slices, 4.6mm slice, 0.46mm gap, TR/TE=3700/88ms, 128x128x28, b factor=([0,1000]s/mm^2). Mean diffusion trace and fractional anisotropy (FA) were calculated in the same brain regions where MRS were performed using the DTIStudio program[4].

RESULTS: *Methamphetamine status*: The subjects were 41 ± 13 years of age and had Glasgow Coma Scale (GCS) score of 6 ± 2 (range: 3-9). The subjects with or without positive METH toxicology had similar ages and GCS, as well as similar NAA and cerebral blood flow measurements. However, lactate was non-significantly higher in the pericontusional tissue of the METH-positive compared to the METH-negative subjects (0.86 vs 0.71 mM), but similar in the contralateral tissue in both groups (0.58 vs 0.63 mM). ***Pericontusional hemisphere:*** rCBF showed an inverse correlation with the duration of injury (r=-0.89, p=0.001, **Figure 3 top left**). rCBF also showed an inverse relationship with tensor trace (r=-0.67, p=0.05, data not shown). Furthermore, pericontusional tissue rCBF showed a trend to correlate with [NAA] (r=0.67, p=0.07, **Figure 3, top right**), but not with lactate levels. ***Contralateral hemisphere:*** Scans performed at later post-injury days showed lower NAA (r=0.76, p=0.004) and lactate levels (r=0.53, p=0.08), but higher tensor trace (r=0.62, p=0.03). Also, [NAA] correlated with [lactate] (p=0.03), but not with rCBF (**Figure 3 bottom left**).

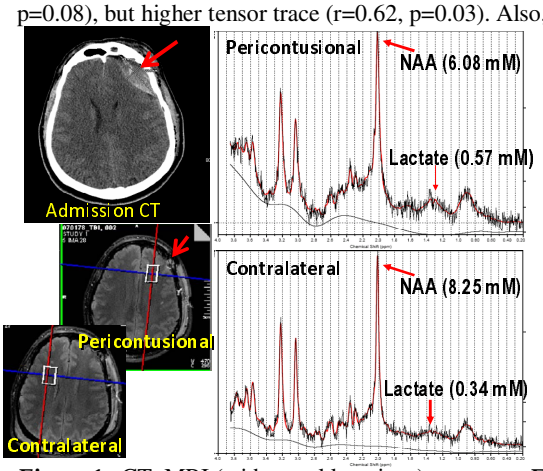

Figure 1. CT, MRI (with voxel locations) and corresponding spectra in a subject.

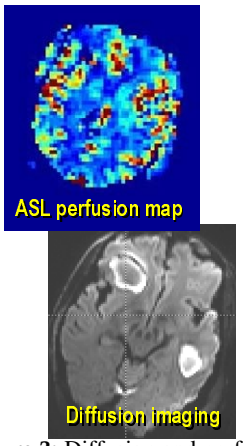

Figure 2: Diffusion and perfusion images for another subject showing the contusions and the blood flow in those regions.

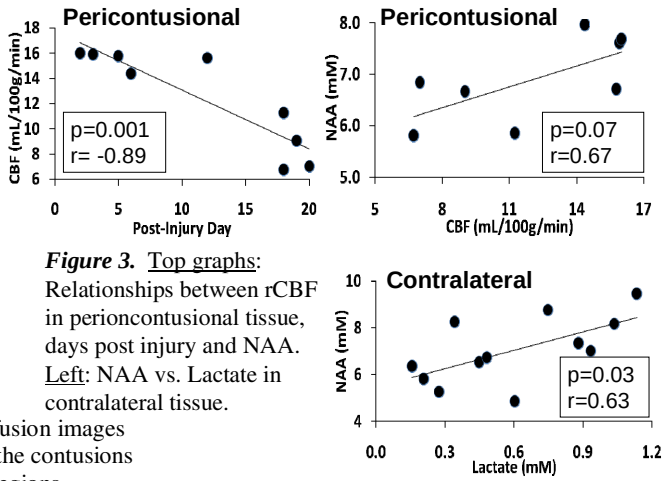

Figure 3. Top graphs: Relationships between rCBF in perioncontusional tissue, days post injury and NAA. Left: NAA vs. Lactate in contralateral tissue.

Age-related decline in FA was observed in the contralateral but not pericontusional tissue, but age had no effect on NAA values in either side. There were no significant differences in metabolite levels, rCBF or DTI measures between the pericontusional and contralateral regions. Likewise, none of the variables showed a significant correlation with Glasgow Coma Scores on admission.

DISCUSSION: Based on multi-dimensional MR measurements performed within 3 weeks of TBI, pericontusional and contralateral tissues behaved differently in response to the injury, and exhibited different patterns of recovery over time. Specifically, findings in the pericontusional hemisphere suggest cytotoxic edema, with lower rCBF, higher diffusion, but lower NAA, in those with >2 weeks post injury days. These findings suggest that the predominant risk for pericontusional tissue may be ischemia. Conversely, the contralateral white matter regions did not appear to have ongoing ischemia (with decreasing lactate over time), but show evidence of diffuse axonal injury (with lower NAA and higher diffusion).

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