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PSB-268

MODULATION OF NRF2/HO-1 ALTERS HEME PROCESSING AND IMPROVES FUNCTIONAL OUTCOME AFTER TRAUMATIC BRAIN INJURY

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Heme Oxygenase-1 (HO-1) is rapidly induced following traumatic brain injury (TBI), mediating breakdown of erythrocyte released heme and generating potentially cytotoxic molecules CO, Biliverdin/Bilirubin, and Fe. Since rise in HO-1 expression is time dependent relative to the extent of heme accumulation and is driven by oxidant induced transcription factor Nrf2 (known to upregulate cytotoxic buffering proteins) we hypothesized that acute postinjury activation of Nrf2 could preemptively drive HO-1 elevation for more rapid clearance of heme, add protective buffering and improve behavioral outcome post-TBI. Using the male rat central fluid percussion model of TBI, we delivered Nrf2 inducer sulforaphane or hemin (FDA approved compounds) activating Nrf2 gene transcription during early postinjury intervals, testing for effects on cortical HO-1 expression, heme processing and motor behavior. Results show both compounds elevate cortical Nrf2 in a dose dependent manner. Further, acute postinjury delivery of either sulforaphane or hemin reduces the time dependent HO-1 peak expression within the cortex of 3d survivors approximately 70% relative to untreated cases. Notably, histological analysis showed advanced loss of heme pigment within injured areas of treated animals, with evidence of fully processed heme (identified as pale yellow bilirubin) as early as 1 day post injury. This facilitated cortical heme processing and reduced accumulation correlated with significant improvement in rotarod motor behavioral performance 1–3d post-injury relative to untreated injured cases. Paired confocal analysis after sulforaphane/hemin treatment shows altered patterns of cellular HO-1 expression after TBI. HO-1 and LCN2 (an iron sequestering protein) expression within reactive glia was reduced surrounding identifiable hemorrhagic/necrotic sites, suggesting a narrowing of the injury penumbral field. Together, these results suggest Nrf2 manipulation of HO-1 and antioxidant gene transcription may provide a means to proactively clear heme-related toxins post-TBI and improve both structural and functional outcome. While current motor behavioral results are associated with brain regions known to experience hemorrhage in our TBI model, we propose that our parallel observations of HO-1 activation in the hippocampus indicate that post-injury Nrf2 gene transcription modulation may also improve recovery in a non-hemorrhagic tissue.

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Keywords: traumatic brain injury, heme oxygenase 1, Nrf2, hemin, sulforaphane

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EXAMINING ANIMAL SURVIVABILITY FOLLOWING STRESS, ACUTE LOW LEVEL BLAST EXPOSURE, AND HYPOBARIC CONDITIONS

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In combat, service members undergo stress and physical injury such as from blast overpressure. Therefore, service members are often medically evacuated via airplane to receive medical care. During medical evacuation, there is a risk of exposure to hypobaric conditions that may have a detrimental effect on cardiovascular physiology, which may also be impaired from battlefield stress and injuries from pressure blast exposure. Therefore, there is a need to assess which physiological measures are at greatest risk for impairment and survivability after a blast injury and during hypobaric conditions. To examine these effects, rats were exposure to 45-minutes of restraint stress and then a blood draw was taken from a femoral artery catheter to assess changes in cardiovascular (i.e., mean atrial pressure) and physiological parameters (i.e., electrolytes, coagulation factors). Then, using a shock tube, rats were exposed to a 75 KPa blast followed by a 35% blood volume hemorrhage. Fifteen minutes after hemorrhage, rats received saline as resuscitation fluid. Finally, animals underwent a simulated flight (within a hypobaric chamber) for 3 hours and were then euthanized. Blood draws from the femoral artery were again taken after blast exposure and after flight to assess changes in cardiovascular and physiological parameters. Pressure blast hemorrhagic shock injury and restraint stress were significant predictors of survival, whereas the hypobaric flight condition was not. Physiological parameters such as hematology cell counts (i.e., hematocrit), and the blood chemistry measures (i.e., creatin kinase) were all significantly associated with stress and injury. These results suggest that hypobaric conditions are not as much of concern for survival, but rather physiological impairments of injuries involving blood loss combined with stress may pose greater risk to warfighters.

Keywords: mild TBI, stress, hypobaric, survival

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DTI ABNORMALITIES IN THE CLOSED HEAD INJURY MODEL OF ENGINEERED ROTATIONAL ACCELERATION (CHIMERA) MOUSE MODEL

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Acceleration and rotation causing deformation and contusion of the brain within the skull accompanies most traumatic brain injury (TBI) incidents. These forces cause diffuse axonal injury (DAI), a hallmark TBI pathology. Recently, the Closed Head Injury Model of Engineered Rotational Acceleration (CHIMERA) was developed to provide an ecologically relevant injury that generates white matter damage closely resembling human DAI. Diffusion MRI has the capability to detect abnormalities that may be invisible to anatomical MRI. In particular, diffusion tensor imaging (DTI) can probe the microstructure of the brain by measuring the magnitude and shape of water diffusion. DTI metrics Trace and Fractional Anisotropy (FA) provide tools to identify axonal abnormalities. Further, non-Gaussian diffusion MRI approaches including mean apparent propagator (MAP)-MRI offer new parameters that may be more specific for DAI pathomechanisms such as axonal damage, demyelination and glial reactivity. Ex vivo imaging of CHIMERA mouse brains

were directly compared to histopathology, using silver stain to identify degenerating tracts, and immunohistochemistry with antibodies to glial fibrillary acid protein (GFAP), Iba-1, Beta-amyloid precursor protein (B-APP), myelin basic protein (MBP), and neurofilament (NF). Optic tract, anterior corpus callosum, and the brachium of the superior colliculus were among the regions that showed both DTI and histopathologic abnormalities. Regions of reduced FA showed abundant silver stain, increased Iba-1 and GFAP immunoreactivity, and accumulations of NF indicative of axonal damage. Regions positive for neurodegeneration and increased neuroinflammation were carefully investigated using MAP-MRI. This study elucidates metrics of DTI that correspond with regions of DAI pathophysiology.

Keywords: DTI, animal model, CHIMERA, diffuse axonal injury, diffusion MRI

PSB-271

MRI-CENTRIC ASSESSMENT AND MANAGEMENT IN ACUTE PEDIATRIC TBI: UTILITY AND RELIABILITY COMPARED TO CT

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Introduction: Increased experience with early MRI in pediatric TBI, advances in speed and sensitivity, and concerns about radiation exposure and decreased resolution in reduced-radiation CT protocols have led to shifts from CT to MRI for early assessment in our population. We report results comparing MRI to CT in acute Emergency Department (ED) assessment, as well as utility and reliability of early MRI in the management of patients with TBI cared for in the Pediatric Intensive Care Unit.

Methods: Three separate studies were performed. First, sensitivity of MRI compared to CT for different pathoanatomic entities in patients < / = age 6 years evaluated for TBI in the ED were compared. Next, interrater reliability of early MRI for pediatric patients treated in the PICU was measured, and utility of early MRI in decision-making in head injury management in the PICU was assessed.

Results: In the ED, in a series of 33 patients who underwent both studies, CT and MRI detected similar pathoanatomic entities, except that skull fracture was better seen on CT. In a consecutive PICU population of 78 children with acute TBI and early MRI (0–3 days post-injury), inter-rater reliability for specific pathoanatomic entities following Common Data Elements definitions was generally comparable to CT. Of interest, additional findings were seen on MRI compared to CT in 74% of patients, and in 13% of patients, the diagnosis was changed based on MRI compared to CT. Management decisions to target and/or escalate care, or to de-escalate care were made on the specific basis of MRI findings in 31% and 56% of patients, respectively, and additional prognostic information was obtained in 23% of patients.

Conclusions: MRI has increased sensitivity compared to CT, and provides useful information for clinical decision-making during acute care after TBI in children, without radiation. Rapid reduced-radiation skull-only CT scans can identify skull fractures when needed. MRI should be considered as a front-line early management tool in pediatric TBI.

Keywords: MRI, CT, neuroimaging, management, emergency department, intensive care unit

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SENSITIVITY COMPARISON BETWEEN GLUCOCEST, FDG-PET AND 2DG-AUTORADIOGRAPHY IN MEASURING GLUCOSE METABOLIC DISORDER IN MILD TBI

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Introduction: ^{18}F-fludeoxyglucose (FDG) PET is the major noninvasive molecular imaging modality to measure glucose metabolism in vivo. Recently, an alternative MRI-based chemical exchange saturation transfer (glucoCEST) imaging was introduced capable of detecting glucose levels without the need for a radioisotope. This study compared the sensitivity between glucoCEST and FDG-PET on a weight drop model of mild TBI in rat followed by post-mortem 2-deoxyglucose (2DG) autoradiography as the gold standard for comparison.

Methods: Diffusion MRI and glucoCEST were acquired on five TBI injured rats using a Bruker 9.4T at baseline, day 1, week 2 and week 4 post-injury. Fractional anisotropy (FA) and the asymmetry of magnetization transfer ratio were derived for mapping diffuse axonal injury and glucose levels. Another 5 rats underwent static brain FDG-PET using Inveon Multimodality PET/CT scanner at the same time point. Standardized uptake values were calculated from the volumes of interest. Additional three TBI injured rats were processed at each time point for 2DG autoradiography. Data acquired from the cerebral cortex were compared by one-way ANOVA.

Results: Comparing to baseline, DTI demonstrated the diffuse axonal injury pattern showing 18% ($p < 0.05$) decrease of FA in corpus callosum at day 1. FDG-PET detected a 30% ($p < 0.05$) increase of glucose uptake in cortex at day 1 and no significant difference afterward. Contrarily, glucoCEST demonstrated progressively decrease of glucose levels to 42% ($p < 0.05$) from day 1 to week 2 and returned towards baseline levels (63%, $p < 0.05$) at week 4. 2DG autoradiography substantiated the glucoCEST measurements demonstrating comparable results with the lowest glucose uptake at week 2 (81% of the baseline level, $p < 0.05$). 2DG data then normalized toward baseline levels at 30DPI (p = N.S.).

Conclusion: While FDG-PET revealed a different trend of glucose uptake than the gold-standard 2DG autoradiography data, the glucoCEST results paralleled the 2DG results demonstrating decreased glucose levels in brain after mild TBI. These results suggest that FDG-PET had limited role and was less sensitive than glucoCEST in measuring the changes of glucose levels following mild TBI.

Keywords: glucoCEST, FDG-PET, 2DG Autoradiography, diffuse axonal injury, diffusion tensor imaging

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ISCHEMIA AND LATE BLOOD BRAIN BARRIER DISRUPTION DURING EVOLUTION OF WHITE MATTER MICROVASCULAR INJURY

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