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Carbon Dioxide Inhalation Mitigates Functional Deficits Elicited by Blast-Induced Traumatic Brain Injury

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Abstract

Traumatic Brain Injury (TBI) is a significant public health burden affecting nearly 3 million individuals within the US alone annually. Large amounts of research dollars have been spent attempting to ameliorate the effects of TBI, however these efforts have failed to reduce injury rates or minimize the effects of primary injury incurred during activities such as contact sports or active military deployment. Preclinical and clinical work has revealed that mitigating brain SLOSH during cranial rotation or impact provides a profound protective effect against the effects of TBI. The biologic mechanism behind SLOSH mitigation is a filling of the compensatory reverse volume (CRV) of the skull, an effect that minimizes brain movement and the imparting of external forces on brain tissue. The most powerful biologically controllable determinant of CRV and intracranial pressure (ICP) is partial pressures of carbon dioxide (CO_2, pCO_2) within the bloodstream. We hypothesize that increased CO_2 inhalation acting to minimize the CRV acts to minimize SLOSH and is therefore protective in the context of TBI. To initiate testing this hypothesis, we have combined increased environmental CO_2 exposure with a murine model for blast-induced TBI. Murine subjects exposed to 5% CO_2 for a period of 10 min in an environmental exposure chamber prior to TBI or sham treatments exhibited an increase in freezing behavior, indicative of actual exposure to gas composition, as compared to their medical grade atmospheric air counterparts. TBI treatment resulted in a significant increase in righting reflex time (RRT) as compared to sham treatment, an effect mitigated by prior inhalation of 5% CO_2. Three hours post-injury, TBI results in a significant reduction in general exploratory locomotor activity as compared to sham treatment, an effect that is also mitigated by prior inhalation of 5% CO_2. Inhalation of CO_2 however was found to have no effect on TBI-elicited increases in cortical tnf-α mRNA expression indicative of a complex biologic mechanism behind observed physiologic effects. Future studies will seek to ascertain molecular adaptations associated with the ability of CO_2 to mitigate TBI-induced effects in vivo. These studies provide the first in vivo evidence identifying a targetable biologic mechanism to reduce the effects of primary injury and may lead to viable medical devices and methodologies for the prevention of mild TBI in contact sports and/or military operations.