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14. ABSTRACT It is likely that the mild TBI and cognitive impairments observed among many of the troops returning from OIF and OEF result from repeated exposures to blast overpressure. Although the clinical symptoms of concussion are typically transient, there is both a cumulative risk for persistent damage due to repeated concussions, and a post-concussion period of greatest vulnerability to a second impact. Specific risk assessments and guidelines should be established for exposure to blast overpressure. We are using a preclinical model of blast overpressure in rats to investigate the cumulative effects of multiple blast exposures on neurologic status, neurobehavioral function, and brain histopathological endpoints. Repeated exposures to blast overpressure with varied inter-blast intervals are used to characterize and define the temporal window of brain vulnerability to repeated blast overpressure. We anticipate that these data will provide a critical first step in establishing rational risk guidelines and developing mitigation strategies.					
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INTRODUCTION:

It is likely that the mild TBI and cognitive impairments observed among many of the troops returning from OIF and OEF result from repeated exposures to blast overpressure. Although the clinical symptoms of concussion are typically transient, mild concussive brain injury can also result in persistent alterations in cognitive and emotional status. Based upon observations among athletes in contact sports, there is both a cumulative risk for persistent damage due to repeated concussions, and a post-concussion period of greatest vulnerability to a second impact, which may elicit subdural hematoma, vasospasm, brain swelling, elevated intracranial pressure, and occasionally death. Specific guidelines have been developed and periodically revised to establish when an athlete can resume their sport, based upon concussion severity and number. Similar risk assessments and guidelines should be established for exposure to blast overpressure. We are using a preclinical model of blast overpressure in rats to investigate the cumulative effects of multiple blast exposures on neurologic status, neurobehavioral function, and brain histopathological endpoints. Repeated exposures to blast overpressure with varied inter-blast intervals are used to characterize and define the temporal window of brain vulnerability to repeated blast overpressure. Spatial learning is assessed using the Morris water maze on days 8-12 post-BOP. Latencies to find the submerged platform are recorded along with swim patterns while doing so. Brains are then prepared for histopathological analysis to establish the extent of brain injury and to determine whether the brain injury severity increases with repeated exposure to blast, and diminishes with increased inter-BOP intervals. We anticipate that these data will provide a critical first step in establishing rational risk guidelines and developing mitigation strategies.

BODY:

Overview A preclinical model of air blast injury in rats is being used to investigate the cumulative effects of repeated blast exposures on neurological status, neurobehavioral function, visual acuity, and brain histopathological endpoints. Varied inter-BOP intervals are used to identify the temporal window of brain vulnerability to repeated BOP. We anticipate that these data will provide a critical first step in establishing rational risk guidelines and developing mitigation strategies.

KEY RESEARCH ACCOMPLISHMENTS:

During this initial reporting period, we have not yet achieved any project milestones due to technical challenges detailed below. Nevertheless, groundwork accomplishments essential to the success of the project were achieved and include:

- Comparison of telemetric physiological data collection systems from competing vendors, selection and purchase of a system from Data Sciences International,

and establishment of an EEG recording capability that is in place for data collection after airblast exposure.

- Determination of the best experimental means to perform required visual assessments in rats and purchase of visual discrimination equipment from Med Associates, Inc. to collect the postinjury visual data requested by proposal reviewers.
- Collection of brains for histopathological evaluations from rats subjected to single and repeated airblast exposures while positioned within the shock tube as well as at the mouth of the shock tube.

During this initial reporting period, we also recognized several significant technical challenges for our proposed research, and responded with design and experimental solutions. Notably:

- After gaining a better appreciation of blast physics, we recognized that it is critical to be able to vary the positioning of rats within the shock tube using a holder that is minimally intrusive regarding exposure of the rat to the shock wave and associated air movement (blast wind) that are created upon rupture of the Mylar membrane. Each of these physical factors can contribute to injury and vary in intensity at different positions within the shock tube. Realizing that our existing rat holders are inadequate (one is restricted to positioning at the mouth of the shock tube and the other whose position can be varied within the tube is limited by a heavy metal construction that likely shields the experimental subject), we designed a new rat holder that is under production. Through incorporation of piezoresistive gauges into the holder itself, the new holder will enable us to record both the static and dynamic pressures (i.e. shock wave and blast wind intensities) that each rat is exposed to in a non-rigid restraint device that neither shields the experimental subject nor contributes to the injury. The new holder will also better physically accommodate instrumentation required for physiological recordings (e.g. EEG and cardiovascular recordings). Although this unforeseen requirement has appreciably delayed our data collection from our original schedule projections, we are confident that we can complete the study within the overall time schedule with vastly improved, artefact-free data. In particular, recording of static and dynamic pressure changes in the shock tube and potential discrimination of their relative contributions to blast-induced TBI will represent a first and significant contribution to the scientific literature.

Despite these significant challenges that interrupted our planned schedule to expose rats to single and repeated airblasts, we did nevertheless initiate work to establish that rats exposed to a single airblast within the tube show the characteristic neuropathological changes we have previously described following exposures at the mouth of the tube. Notably, as previously characterized, the brains from rats exposed to a moderate (126-kPa) airblast typically were devoid of any obvious cell loss or injury, and instead most typically showed widespread fiber degeneration that was clearly prominent in silver-stained sections throughout all levels of the brain (Fig. 1). Fiber

degeneration was observed bilaterally and did not appear to be more prominent in either hemisphere. Axonopathy was strikingly evident in commissural fibers and other fiber tracts, and was also evident at higher magnification in small-caliber fibers as well. As previously reported following exposures at the mouth of the shock tube, neuropathological changes were not evident following exposure to a mild (114-kPa) airblast in a holder positioned within the tube. These neuropathological characterizations will necessarily be repeated with rats exposed to blast while positioned within the shock tube in the newly designed and gauged holder, when it becomes available.

REPORTABLE OUTCOMES:

Presentation

Long, J.B. Blast Overpressure in Rats: Recreating a Battlefield Injury in the Laboratory. Presentation at the International State-of-the-Science Meeting on Non-Impact, blast-induced mild traumatic brain injury in Herndon, VA, May 12-14, 2009.

CONCLUSION:

Conclusions concerning the stated objectives of the proposed research are not yet possible due to the technical issues and delays described above. Nevertheless, we can confidently conclude that through our recognition of these technical issues and the resultant modifications of our experimental recreation of blast, we now have a greatly improved experimental capability which will yield unambiguous, interpretable results.

REFERENCES: NONE

APPENDICES:

SUPPORTING DATA:

Figure 1. Exposure to a single air blast of approximately 126 kPa results in extensive axonopathy reflected by the prominent darkened fibers in the silver stained photomicrograph on the left). Despite widespread fiber degeneration, injured brains are typically devoid of any obvious cell loss in the cresyl violet stained section on the right.

