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The Bentil Group
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PANTHER

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Expanding the Range of TBI Studies: Histopathological Changes in the Brain following Repetitive Blast Wave Exposure

Introduction

Blast-induced traumatic brain injury (bTBI) can be caused by explosives from the battlefield, in regions of conflict, and even civilian areas due to acts of terrorism[1],[2],[3]. Advancing precision diagnostics and therapeutics, for service members and veterans with bTBI requires an understanding of the long-term changes in the brain after blast exposure. Human subjects cannot be used in blast injury research, due to ethical reasons. So, a pig model and an oxyacetylene-driven advanced blast simulator (ABS; **Fig. 1**) is used to advance preclinical bTBI research since the brain anatomy and vasculature is similar to a human.

Objective of Pilot Study: ***Examine the histopathological changes in the brain immediately and two-weeks following nonlethal repetitive blast wave exposure to capture the long-term effects and outcomes after bTBI.***

Outcomes of Pilot Study: *Set the stage for future preclinical bTBI research with current and future collaborators to (i) detect bTBI both on-site and in a quantitative manner, which will influence the development of precision diagnostics and therapeutics for service members and veterans, (ii) identify blast parameters that could be correlated with injury risk to predict the long-term effects and outcomes after bTBI, (iii) develop scaling laws that can translate blast injury results from animals to humans, and (iv) yield experimental data for validating digital twin models that can predict the mechanisms of bTBI.*

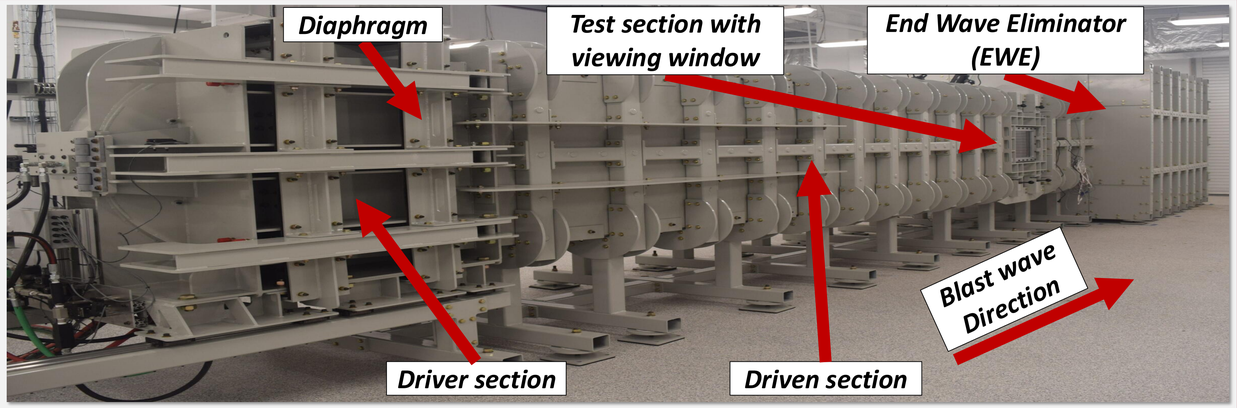

Fig. 1: *Oxyacetylene-driven advanced blast simulator (ABS) at Iowa State University. Length: 43-ft (13.11 m), Cross-section of Test Section: 4-ft x 4-ft (1.22 m x 1.22 m), EWE: 8-ft x 8-ft (2.44 m x 2.44 m).*

Results

ABS Pressures

Pressure sensors (in ABS floor) were 46 cm (18-in.) apart. Mach number was 1.5 (**Fig. 2**).

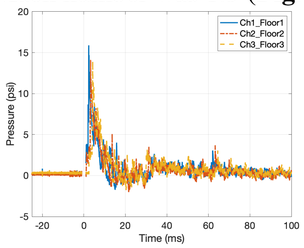

Fig. 2: *ABS floor pressure histories.*

DIC

Deformation quantified for blast wave interaction with the samples (**Fig. 3**).

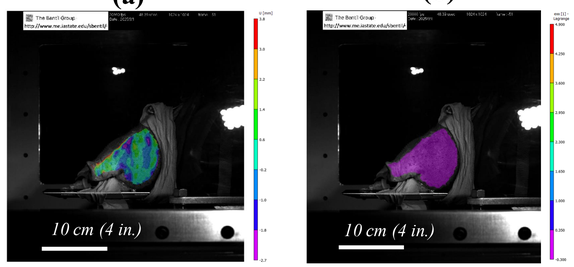

Fig. 3: *DIC results for horizontal (a) displacement [U] and (b) strain [exx].*

H&E Staining

- **Sample 1**: Multifocal vascular necrosis and vascular wall infiltration by neutrophils, as well as focal rarefication of neuropil with neuronal necrosis and hemorrhage[4] (**Fig. 4**).
- **Sample 2**: Vascular necrosis only, which may indicate that acute neuronal damage may be partially resolved over time.

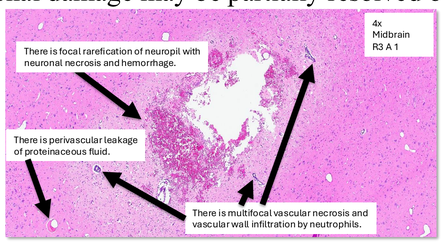

Fig. 4: *H&E stain for Sample 1.*

RNAscope Analysis

- Difference in glial fibrillary acidic protein (GFAP) content between Samples 1 and 2 (**Fig. 5**).
- Results suggest rapid astrocyte activation in response to initial tissue damage, with remodeling processes associated with tissue repair or chronic neuroinflammatory responses during later stages of bTBI[5].

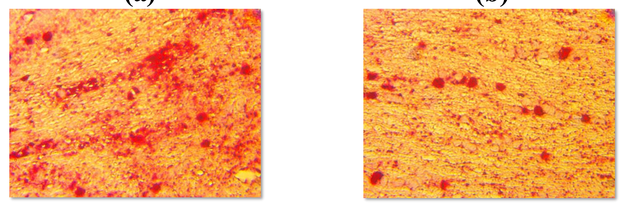

Fig. 5: *GFAP from RNAscope for (a) Sample 1 and (b) Sample 2.*

Material and Methods

Iowa State University's Institutional Animal Care and Use Committee (IACUC) and the U.S. Navy Bureau of Medicine and Surgery (BUMED) approved all protocols. An ABS (**Fig. 1**) exposed two anesthetized Yucatan minipigs (male, intact, six-months-old) to repetitive blast waves in the test section.

- **Sample 1:** Sacrificed within 24 hours, after receiving five blast exposures (103 kPa [15 psi] incident pressure), to understand the onset of bTBI.
- **Sample 2:** Sacrificed two-weeks, after receiving six blast exposures (103 kPa [15 psi] incident pressure), to assess recovery after bTBI.

Histopathological Analysis of Brain Tissue: Hematoxylin and eosin (H&E) stain to examine structural changes (i.e., damage). Ribosomal nucleic acid-scope (RNAscope) analysis to characterize the damaged types of neurons or glia, observed in H&E stain, by evaluating the changes in full-length messenger ribonucleic acid (mRNA) transcripts.

Digital image correlation (DIC) Analysis: Quantify (i) skin deformation for the minipigs and (ii) rigid body motion due to blast wave exposure, using images recorded at 20,000 frames per second from two high-speed cameras (Photron SA-Z) calibrated for stereovision.

Discussion and Conclusion

Protocol using an ABS and animal model developed for:

1. **Standardizing bTBI Experiments:** anesthesia cocktails since they influence outcomes, choice of implantable sensors (e.g., intracranial pressure), animal fixture inside the ABS, harvesting and storing organs (e.g., brain, eyes, lungs,) and biofluids (e.g., blood, saliva, urine, cerebrospinal fluid).
2. **Productive Collaborations:** facilitate the development of precision diagnostics and therapeutics for victims of bTBI (e.g., service members, veterans, and civilians).

References

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