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14. ABSTRACT
Enter a brief (approximately 200 words) unclassified summary of the most significant findings during the research period.

The high incidence of mild TBI in Warfighters exposed to blast has triggered interest in injury mitigation and increased TBI resilience as well as concerns over safe return-to-duty and minimization of long-term and delayed TBI-related debilitations in returning veterans. These objectives require the utilization of high fidelity animal models to investigate the underlying neurobiological mechanisms of injury as a rational basis for defining risks and establishing effective countermeasures. The etiology of blast TBI (bTBI) is largely undefined, and several mechanisms, likely interactive, have been proposed. Using a well-validated blast model, we are exploring blast-induced acceleration of the head as one of the primary component of bTBI. Having successfully worked with a range of inanimate objects of varied areal densities to define relations of blast flow conditions to acceleration and displacement, we have begun examination of the effects of systematically varied conditions on anesthetized rats to isolate and distinguish the contributions of blast-induced head acceleration and displacement from other biomechanical components and effects of the shockwave.

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INTRODUCTION: The prevalence of blast-induced TBI (bTBI) has prompted an urgent need to develop improved mitigation strategies and advance medical care targeting casualties with bTBI. Despite considerable effort and a broadened interest in the study of mild TBI of all causes, the basic mechanisms of blast induced brain injury are for the most part still undefined. Based largely upon computational modeling and the parallel evolution of interest in athletic concussive head injuries, several candidate mechanisms of non-impact blast TBI have been identified and include head acceleration. Animal models are required to verify and validate these models, to identify the underlying biomechanical and neurobiological events resulting in injury, and to establish effective countermeasures. Examination of each of these proposed mechanisms requires shock wave exposure conditions and specimen targets that are appropriate for the question being asked. We believe that the rat can be employed in a laboratory simulation of blast in a manner that directly addresses the role of acceleration as a critical component of bTBI.

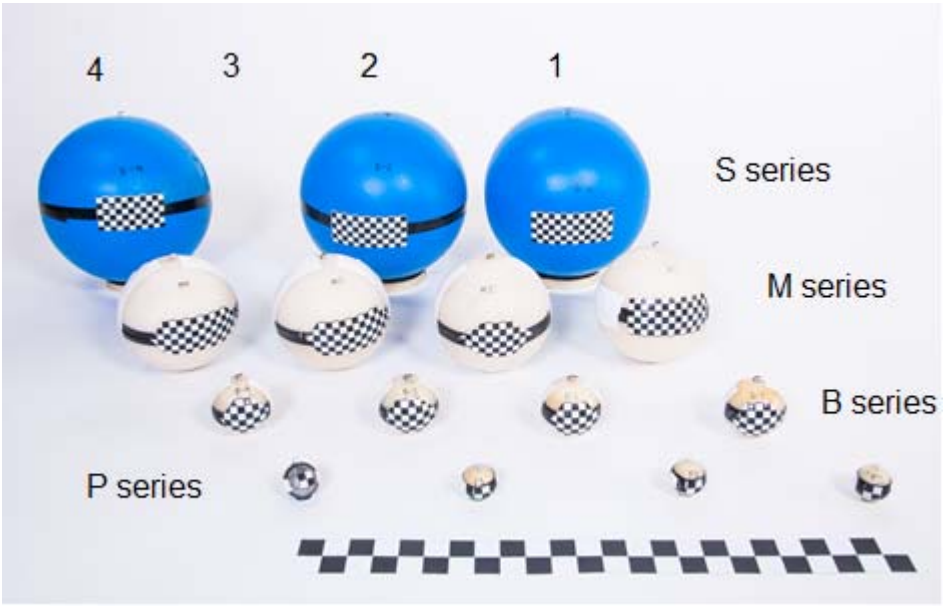
We hypothesize that explosion flow conditions can cause head acceleration sufficient to injure the brain, and that these inertial forces combine with other injury mechanisms to yield blast TBI. Based upon empirically defined relations between blast flow conditions (e.g. peak static and total pressure, positive phase duration, and impulse) and acceleration and displacement of a wide range of inanimate objects, we have continued examination of the effects of systematically varied conditions on surrogate rats, cadaveric rat specimens, and anesthetized rats to isolate and distinguish the contributions of blast-induced head acceleration and displacement from other biomechanical components and effects of the shockwave.
Using a highly characterized simulation of blast in an Advanced Blast Simulator (ABS) in the laboratory, rats are exposed to BOP with varied peak amplitudes and impulse in comparison with systematically matched and carefully controlled independent acceleration of head and torso. High speed video recordings of experimental subjects during blast exposure and independent acceleration are closely compared and the resultant pressure responses in varied compartments in concert with the neuropathological, neurochemical, and neurobehavioral consequences of exposures under these conditions provides a basis for determination and quantitation of the underpinnings of blast TBI.

BODY: A primary innovation of this project is the continued development, characterization, and utilization of high fidelity simulations of blast flow conditions in an Advanced Blast Simulator that are possible through close consultation with blast physics experts who are actively involved in this project. With this device it is possible to replicate all key features of blast flow wave conditions, including the negative phase and secondary shock. Analysis and tight control of these components (notably acceleration and displacement) in combination with functional outcome measures provides a means to understand the relation of the former to the latter. An explosive shockwave is unlike any other conventional mode of loading and imparts both an abrupt transient crushing action (i.e. static pressure) which envelops the head as well as some aerodynamic drag (i.e. dynamic pressure creating blast wind). The use of animal models to investigate blast-induced neurotrauma requires appreciation of the relative biomechanics and scaling; it is essential to replicate the proper incident blast conditions to assess relevant brain injury mechanisms. Ongoing controversies and confusion concerning the contributions of blast-induced head acceleration to blast-induced TBI have in great part resulted from laboratory studies in which blast was inappropriately simulated, and head acceleration was likely in many cases an experimental artefact uniquely associated with those particular exposure conditions. Experiments with an advanced blast simulator (ABS) yield a higher fidelity, ecologically valid simulation of blast and thereby provide critical insights into the etiology of bTBI that can serve to guide the rational development of mitigation measures and further elucidate pathophysiological mechanisms that can be therapeutically targeted.

The project has been approached in 3 stages. During the first stage, an adult-size and weight surrogate rat and rat cadaveric specimens have been used along with other appropriately scaled inanimate objects to record acceleration and displacement resulting from BOP and to establish the operational parameters required to evaluate relations between pressure conditions (i.e. peak pressure and impulse) and resultant acceleration and displacement. In the second stage, under these well-defined exposure conditions, anesthetized rats are used to simultaneously record intracranial pressure (ICP), intravascular pressure, and acceleration/displacement of the head and trunk. Tissue samples are used to investigate the neurobiological underpinnings of the brain injuries resulting from these blast-induced biomechanical conditions. In the third stage, rats subjected to each of these injury conditions (blast and acceleration vs acceleration alone) undergo neurobehavioral and histopathological assessments to comprehensively characterize and compare the resultant injuries and functional impairments.

Task 1. Using rat surrogates in a 24 in diameter advanced blast simulator (ABS), determine the exposure parameters required to optimally and independently manipulate pressure conditions (i.e. peak pressure and impulse) and acceleration and displacement. Establish 12 exposure conditions (including controls) that will be used to systematically pair BOP peak pressure/impulse (3 intensities) and acceleration/displacement (3 intensities).

Task 1 Progress: During this reporting period, work centered on completing blasts on the 16 weighted balls that were developed for this project (see below).



Weighted balls used in Task 1

The balls were weighted so that the areal densities (i.e., total mass divided by 'presented' cross-sectional area) were similar across the different diameters. So the lightest of each diameter ball had an areal density close to 1.25 grams/cc. The table below describes the characteristics of the balls. Note that ball S-3 is not pictured. It was damaged in the testing.

Sphere Designation	Diameter (cm)	Volume (cm)	Presented Area (cm^2)	Weight (grams)	Density ($grams/cm^3$)	Areal Density ($grams/cm^{2)}$
P-1	3.4	20.6	9.1	11	0.53	1.21
P-2	3.4	20.6	9.1	36	1.75	3.97
P-3	3.4	20.6	9.1	69	3.35	7.60
P-4	3.4	20.6	9.1	144	7.0	15.86
B-1	6.9	172.0	37.4	52	0.30	1.39
B-2	6.9	172.0	37.4	143	0.83	3.82
B-3	6.9	172.0	37.4	285	1.66	7.62
B-4	6.9	172.0	37.4	572	3.33	15.3
M-1	14.3	1531.1	160.6	192	0.13	1.20
M-2	14.3	1531.1	160.6	557	0.36	3.47
M-3	14.3	1531.1	160.6	1138	0.74	7.09
M-4	14.3	1531.1	160.6	2269	1.48	14.13
S-1	25.1	8279.8	494.8	756	0.09	1.53

S-2	25.1	8279.8	494.8	756	0.19	3.16
S-3	25.1	8279.8	494.8	756	0.38	6.44
S-4	25.1	8279.8	494.8	756	0.75	12.58

It is important to note how important the Advanced Blast Simulator (ABS) is for this study. The ABS is the first simulator to produce a high fidelity improvised explosive device (IED)-like blast wave, generating an entropy gradient through the flow with a true negative phase that has both under-pressure and flow reversal. To facilitate mid-air blasts, a release mechanism was devised. Balls were attached to the bail of the mechanism. The blast wave would cause the bail to pull out from under the balls just before the arrival of the shockwave without causing motion artefacts which might confuse the motion due to the shockwave.

Task 2. Using the systematic pairings of exposure conditions defined in task 1, record head and trunk acceleration and intravascular and ICP responses under each BOP exposure condition. Collect blood and brain tissue 24 h after exposures to establish neurochemical and biomarker correlates.

Task 2 Progress: A number of rats underwent pressure sensor catheterization in which Millar pressure sensors were inserted to record ICP (ventricle and epidural), femoral artery and carotid artery pressures during blast. 12 blasts were recorded with rats in a prone position facing the blast and 37 blasts were recorded with the animals in a free-flying vertical position. Prone animals were strapped to a table using cargo net and Velcro straps. Vertical animals were placed in 'cocoon' of cargo net with Velcro straps and, using a piece of fishing line, were hung from a hook in the ceiling of the ABS. These animals were free to move during the blast as the fishing line came off the hook.

Task 3. Using the systematic pairings of exposure conditions defined accelerations and identify the ensuing neurobehavioral disruptions consequences resulting from each of the 12 exposure conditions.

Task 3 Progress: The accelerator jig was delivered in the final quarter of FY16. Initial tests indicate that the acceleration profile are comparable to blast acceleration. The accelerator jig will be fully characterized in the first 2 quarters of FY17 (NCE).

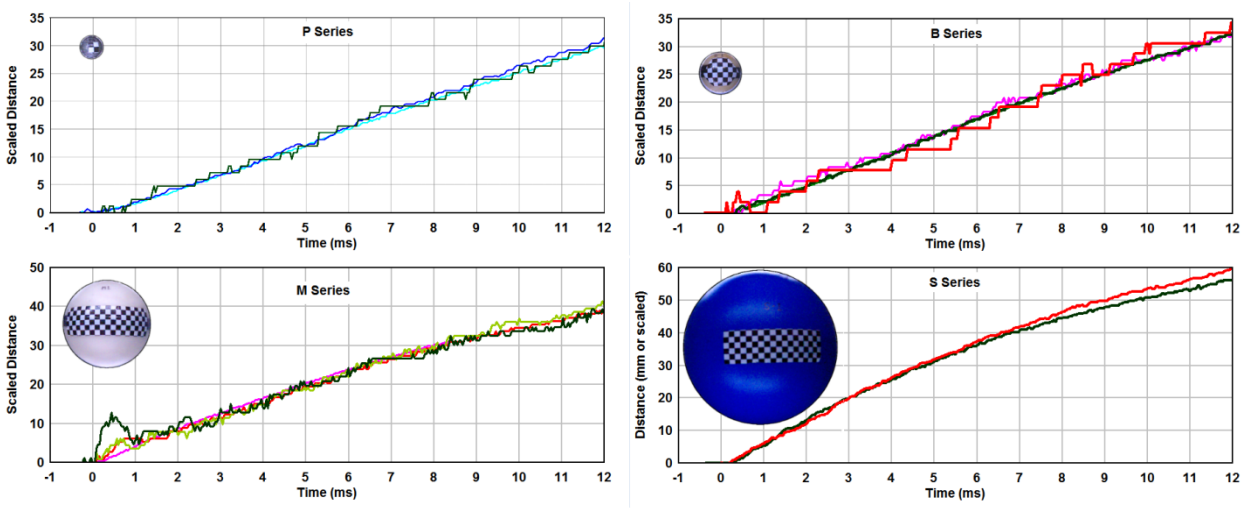
KEY RESEARCH ACCOMPLISHMENTS:

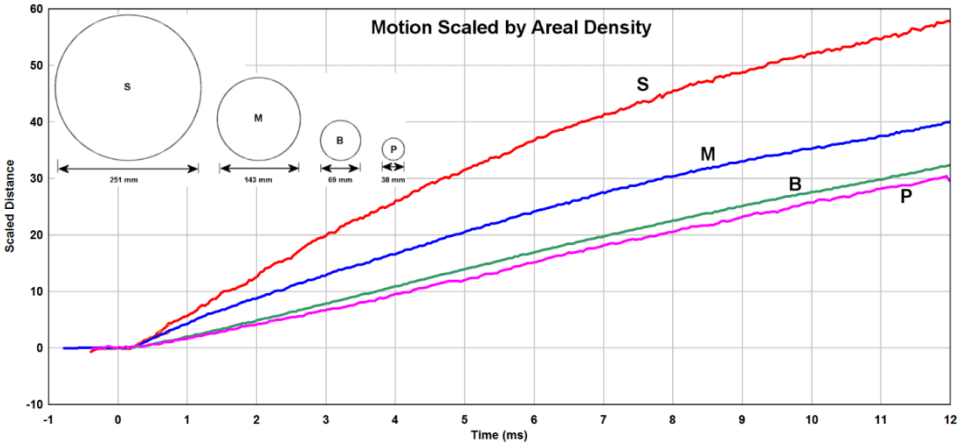
- Fully integrated test system to include:
    - Advanced Blast Simulator
    - Reliable membranes
    - Data recording system
    - High-speed video system
    - Unique release mechanism

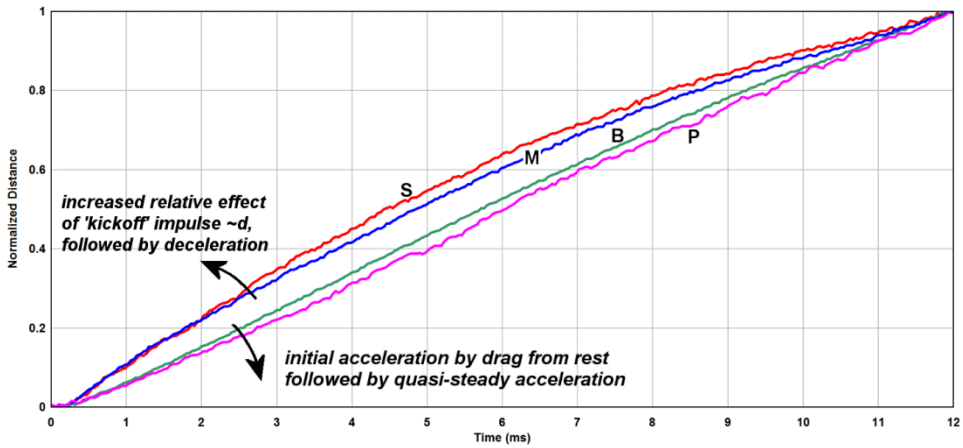
- First test of blast on mid-air objects
- First test of blast on free-flying pressure instrumented animals
- Development of accelerator jig with the capability to match blast-induced acceleration

REPORTABLE OUTCOMES:

The work using the weighted balls showed that if balls of similar diameter were scaled by areal density their trajectories would overlay as shown in the top 4 figures below.

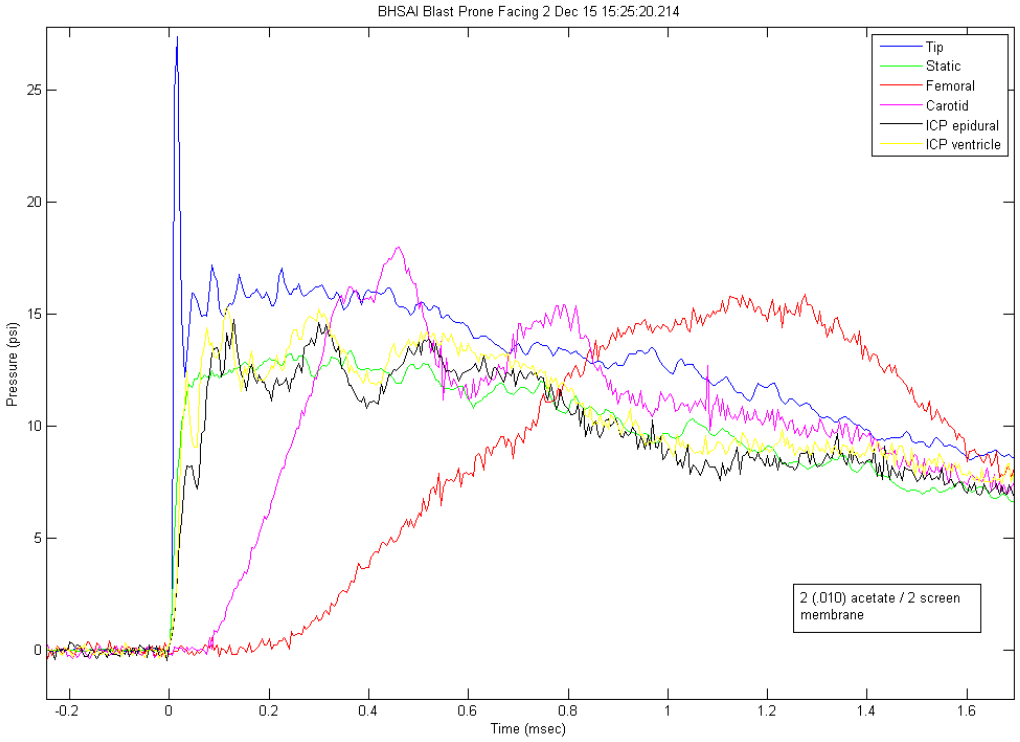






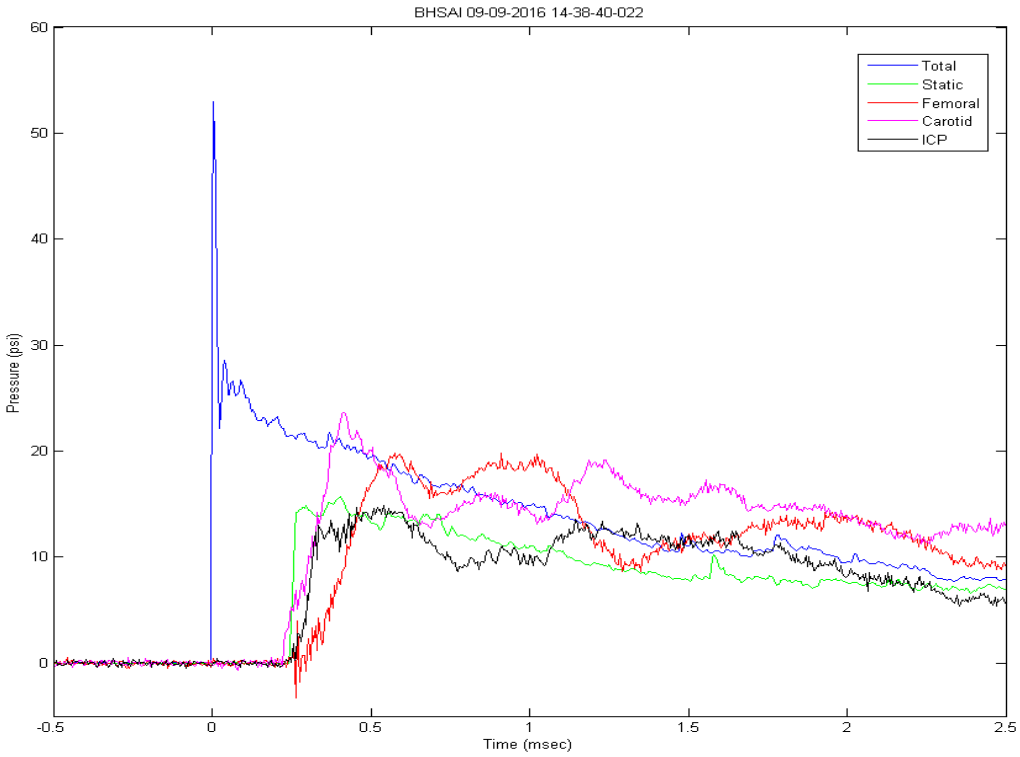
The figure in the middle shows that trajectories of the different diameter balls do not overlay each other however. In the lower figure, the trajectories are scaled to their displacement after 12 ms (i.e. the distance travelled in 12 ms represents 100% of the

travel). The lower two figures show a systematic shift in the nature of the response from drag (i.e. blast wind) -dominated for the smaller 2 sets of spheres to diffraction (i.e. leading edge)-dominated accelerative forces for the larger 2 sphere sets. Taken to the extreme it is clearer to imagine that a dust grain would be affected far more greatly by the drag (blast wind) phase of a blast wave then the diffraction (leading edge) phase. In contrast, a large boulder would be affected to a much greater extent by the diffraction phase. The range of weighted balls used in these experiments spans the cross-over (drag-dominated to diffraction-dominated). The size of a rat's head is similar to the P series of weighted balls, whereas the human head falls between the M and S series. The cross-over effect has great importance when trying to scale experimental effects from rats to humans. The human head will experience a distinct "kick-off" velocity imparted by the shock diffraction loading that cannot be duplicated using a rat. Further investigation is required to properly design and interpret blast-induced acceleration injury to personnel and the subsequent scaling of model experiments.
Experiments were also conducted in which pressure sensors were place in rats to measure ICP, carotid and femoral arterial pressure during the blast.



The chart above shows two simultaneous measures of ICP. One probe was placed in the lateral ventricle and one probe was placed epidurally. The pressure tracings in this graph, as with every other similar preparation, shows that the two ICP traces are identical, leading us to believe that the developed pressure inside the skull is equal and independent of where it is measured. The chart above shows traces from a rat in a prone position facing the blast wave. The physiological signals react in an appropriate fashion, ordered in the sequence in which the blast wave encounters them: ICP first followed by carotid and finally femoral. The rise time of these signals is likely related to

the compliance of the associated area coupled with the amount of compressible space and the depth from the surface of the pressure probes. The ICPs react the quickest as while the rat skull is fairly compliant compared to pig and human, it is far less compliant than thorax or abdomen. Since there are no compressible spaces in the brain, a slight compression will cause a fast rise time. The thorax/neck region provide less resistance to compression than the skull, but since the lungs can compress, it takes longer to build up pressure leading to the slower rise time The abdomen with gut and fat deposits is the most compliant but as with the lungs, gut compression causes the longest pressure build up.



The figure directly above is from a rat positioned vertically in the shock tube. The 3 physiological traces (note only one ICP sensor was placed) onset times are similar because they are vertically aligned; however, due to compliance factors and associated gas-filled compressible organs the slopes are similar to prone animals.

CONCLUSION: A thorough understanding of basic shock wave-target interactions is crucial in the development of models, interpretations of results and understanding of injury mechanisms in blast-induced TBI. Progress during this reporting period has led to the development of a complete high fidelity IED-like blast test system. Initial results using a series of weighted balls have shown that acceleration of objects similar in size to rodent heads are dominated by drag phase loading across the positive phase of the shock wave. Larger human-head sized objects are initially ‘kicked-off’ as the shock wave diffracts around the object. Basic findings will pave the way for more complicated modeling of shell/fill systems more representative of skull and brain of the human head.

REFERENCES: G Jourdan, L Houas, O Igra, J.-L Estivalezes, C Devals and E.E Meshkov, “Drag Coefficient of a Sphere in a Non-Stationary Flow: New Results”, Proc. R. Soc. A 2007 463.

APPENDICES: Paper submitted to the 2016 Military Aspects of Blast and Shock meeting.

SUPPORTING DATA: Available upon request.