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14. ABSTRACT

The etiology of blast-induced traumatic brain injury (bTBI) is largely undefined. Along with reducing mortality, in preliminary experiments Kevlar vests significantly protected against bTBI in rats. We postulate that: 1) blast-induced fiber degeneration in brain results from pressure surges transmitted through the vasculature that elicit intracranial disruptions, and 2) Kevlar vests are neuroprotective by uncoupling this pressure transmission following exposure to blast. Using a compression driven shock tube, we compare external, systemic (e.g. vascular), and central (e.g. intracranial pressure) BOP-induced pressure changes, and assess the impact of Kevlar vests on these changes. We seek to: 1) determine if measured pressure changes are blast severity-dependent and correspond with outcome measures, and 2) assess the impact of Kevlar vests on measured BOP-induced pressure changes and outcome measures and establish whether a protective vest encasing the thorax ameliorates blast-induced brain injury, pointing to a contribution of the effects of blast on the thorax to brain injury. These studies will provide insights into the etiology of blast-induced brain injury and will advance the development of mitigation strategies.

15. SUBJECT TERMS
Traumatic Brain Injury (TBI), Kevlar Vests, Neuroprotection

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INTRODUCTION:

Body armor has made blast injuries survivable; consequently, we speculate that to a large extent blast-induced head injuries have emerged among troops who without body armor would have simply been killed in action as a result of injury to more vulnerable organs such as the lung. Serendipitously, in a preliminary experiment we noted that along with reducing mortality, lung injury, and cardiovascular disruptions by blast overpressure (BOP), Kevlar vests protected against BOP-induced neuropathological changes in rats. These preliminary findings suggested that a protective vest encasing the thorax might ameliorate blast-induced brain injury, pointing to a significant contribution of the effects of blast on the thorax to brain injury pathophysiology. We hypothesize that much of the blast-induced fiber degeneration in brain results from pressure surges transmitted through the vasculature (venous as well as arterial) that elicit a series of intracranial disruptions, and that Kevlar vests are neuroprotective by uncoupling this pressure transmission following exposure to blast.

To address how BOP effects on the thorax contribute to brain injury and to evaluate how Kevlar vests protect the brain, we are attempting to measure, compare, and correlate external, systemic (e.g. vascular arterial and venous), and central (e.g. intracranial pressure) BOP-induced pressure changes, and assess the impact of Kevlar vests on these changes. In particular, we use a compression driven shock tube to: 1) determine if measured pressure changes are blast severity-dependent and correspond with neuropathological and neurobehavioral outcome measures, and 2) assess the impact of Kevlar vests on measured BOP-induced pressure changes and outcome measures. As detailed below, in addition to neuropathological and neurobehavioral evaluations, these outcome measures include assessments of blood-brain barrier integrity and cerebral blood flow measurements, since we postulate that the cerebrovasculature plays a pivotal role in blast-induced brain injury pathophysiology, and is likely to be disrupted by blast-induced perturbations.

BODY: Research accomplishments associated with each task outlined in the approved Statement of Work are described below.

Overview**:** An air-driven shock tube is used to simulate blast overpressure (BOP) and study how BOP effects on the thorax contribute to brain injury and to evaluate how Kevlar vests protect the brain. Progress toward this objective has been hampered during this reporting period by substantial personnel changes, prompting the need to request a no-cost extension (NCE) period to complete the project. Notably, two Ph.D. contractors departed and 5 federal government employees were lost as a result of a reduction in force (RIF) action. We have largely recovered from the turbulence associated with these sweeping, abrupt changes and now anticipate completing the project within the NCE period.

The biomechanical characteristics of our shock tube-induced BOP injury to rats have changed considerably due in large part to the substantial modifications in blast

exposure conditions that were implemented to improve the fidelity of our blast simulation. Previously, rats were positioned (but not secured) at the mouth of the shock tube in a rigid metal holder for BOP exposure which we subsequently learned in all likelihood caused extremely different loading and injury phenomena due to the conversion of flow energy to a collimated jet as it exits the tube. Working closely with a blast physicist, we modified both the holder and and the positioning of the rat in the tube (fig 1). Rats are now exposed to a shock wave when snuggly suspended in a tautly drawn course mesh netting 2.5 ft within the tube and are substantially less injured than were those exposed to the exit flow conditions at the mouth of the tube. Pressure wave characteristics are determined by Mylar membrane thickness and driver volume (figs 2 & 3). As a result of these "cleaner" improved BOP exposure conditions, TBI is much less severe and it has been difficult documenting persistent neurobehavioral deficits after BOP exposures, despite attempts to improve the sensitivities of these tests to distinguish mild TBI. In addition to the position of the rat in the tube (mouth vs 2.5 ft within the tube), we also discovered that the manner in which the rats are suspended appears to impact their sensitivities to BOP. In particular, high speed videography and accelerometers revealed displacement and large acceleration of rats impacted by BOP within the tube (fig 1) which is influenced by the tautness or play of the netting in which the rats are suspended. By more tightly securing the netting, we have reduced exposure variability (i.e. levels of acceleration and displacement) which has in turn further lessened the severity of the resultant injury.

Task 1: Using a compression-driven shock tube, measure, compare and correlate external (i.e. shock tube), systemic (i.e. vascular arterial and venous), and central (e.g. intracranial pressure) effects of BOP of varied intensities.

Using rupturable Mylar membranes of varied thicknesses, we mapped the shock tube and determined resultant pressure readings at varied points through the length of the shock tube. Tip and side-on gauges provided total and static pressure measurements. In addition to providing essential calibration guidelines, these data revealed that the positioning within the shock tube greatly influences the blast flow conditions to which the experimental subject is exposed (figs 4-6). When rats were positioned 2.5 ft within the mouth of the tube (12.5 ft from the membrane), we observed that vascular and intracranial pressures tracked closely with ambient pressures (fig 7 & 8). Experimental subjects positioned at the mouth of the tube, as was the case in the experiments yielding the observations upon which this project is based, are in all likelihood experiencing very different loading and injury phenomena than are produced within the tube, since we subsequently learned that dynamic pressure is greatly increased relative to static pressure as flow energy is converted to a collimated jet as it exits the tube. Impulse ratios are particularly affected (fig 6). Since the protective effect of vests upon which this proposal is based were originally observed at the mouth of the shock tube, we also made pressure recordings and evaluated rats exposed to blast at this position as well. As noted above, flow conditions (i.e. pressures) were very different at the mouth of the tube. Nevertheless, although for a given membrane thickness the

intracranial and intravascular pressures recorded in rats at the mouth of the tube differed substantially from those seen in rats positioned 2.5 ft within the tube, they again closely resembled the external pressures measured at this position.

Task 2: Determine if measured pressure changes in the experimental subject are blast severity-dependent and correspond with neuropathological and neurobehavioral outcome measures.

Intracranial and intravascular pressures closely paralleled ambient pressures in the tube and increased in parallel with increased membrane thicknesses (fig 7-9). Across all blast pressure exposure conditions, intracranial pressures closely corresponded to external side-on pressure recordings, revealing that the skull provides little protection against elevated pressures in rats. With increased membrane thicknesses, peak pressures and pressure impulses both increased for side-on and tip gauge recordings in the tube, and yielded correspondingly elevated and prolonged intracranial and intravascular pressure responses. Neuropathological and neurobehavioral disruptions of rats exposed to different BOP intensities are presented in figs 12-18. In general, the functional impairments observed using refined BOP exposure conditions in these experiments were limited and quite modest, in striking contrast to the behavioral impairments resulting from exposures to comparable pressures at the mouth of the shock tube (Long et al., 2009). The behavioral deficits are typically accompanied by scattered fiber degeneration that characteristically appears in cerebellum, optic tracts, and the internal capsule (fig 12).

Task 3: Assess the impact of Kevlar vests on measured BOP-induced pressure changes and neurobehavioral outcome measures.

Whether positioned 2.5 ft within or at the mouth of the shock tube, BOP-induced increases in intracranial and intravascular pressures closely resembled peak pressures and durations and were not appreciably altered by protective Kevlar vests (fig 10,11).

Task 4: Assess the impact of Kevlar vests on measured BOP-induced pressure changes and acute cerebrovascular measurements.

Extravasation of Evans blue dye into the brain was used to quantitate BOP-induced disruption of the blood-brain barrier. Experiments completed to date reveal appreciable cerebrovascular disruptions at 2 and 5 hr post-BOP that is diminished by protective vests (fig 19).

KEY RESEARCH ACCOMPLISHMENTS: Bulleted list of key research accomplishments emanating from this research.

- Shock tube BOP exposure conditions have been further characterized and refined to create a high fidelity simulation of blast TBI.

- Neurobehavioral, neuropathological, and neurochemical consequences of shock tube BOP exposures of varied intensities have been described and are ongoing.
- BOP-induced intracranial, vascular, and esophageal pressure changes in rats have been thoroughly compared to ambient pressure changes and reveal that they are very similar and unaffected by protective Kevlar vests.
- BOP-induced acceleration and displacement have been discovered to present potentially significant contributions to TBI injury mechanisms.

REPORTABLE OUTCOMES: Provide a list of reportable outcomes that have resulted from this research to include:

Based in part upon the work supported by this award, funding was sought through research preproposals and proposals submitted to the CDMRP and DMRP, which included:

- Imaging biomarkers for mild blast-induced traumatic brain injury
- Blast-induced acceleration in a shock tube: distinguishing primary and tertiary blast injury mechanisms in rat TBI
- Roles of polyunsaturated fatty acids in traumatic brain injury vulnerabilities and resilience: evaluation of salutary effects of DHA supplementation using neurolipidomics and functional outcome assessments
- Diagnostic and Therapeutic Targeting of Neuroinflammation in Blast TBI
- Novel nitroxide-based therapy to optimize 100% oxygen use in critical traumatic brain injury resuscitation and transport

ABSTRACTS/PRESENTATIONS

Shoge, R.O. Experimental evaluation of blast-induced traumatic brain injury in rats using a cylindrical shock tube. Poster presentation at the Advanced Technology Applications for Combat Casualty Care (ATACCC) Meeting, Ft Lauderdale, FL, Aug, 2011.

CONCLUSION: A high fidelity laboratory simulation of blast has been achieved using an air driven shock tube and a custom designed gauged rat holder that records the static and dynamic pressures specifically occurring in the immediate environment of the experimental subject for each airblast exposure. Intracranial and intravascular pressure recordings have been made and reveal that blast pressure responses in the rat closely resemble those recorded in the atmosphere adjacent to the rat with respect to both magnitude and timing. Protective vests have not altered these pressure responses, nor under these conditions have they substantially altered neurobehavioral disruptions resulting from blast exposures.

REFERENCES: Long, J.B., Bentley, T.L., Wessner, K.A., Cerone, C.Sweeney, S., and Bauman, R.A. Blast overpressure in rats: recreating a battlefield injury in the laboratory. J. Neurotrauma 26: 827-840, 2009

SUPPORTING DATA: Below.

SUPPORTING DATA:

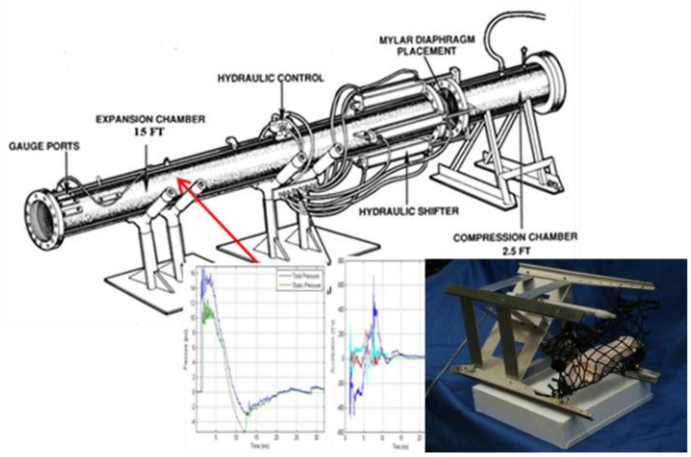


Fig 1. BOP exposure: The shock tube consists of a 2.5 ft long compression chamber that is separated from a 15 ft long expansion chamber by polyester Mylar membranes (DuPont, Wilmington, DE). Both chambers are 1 ft in diameter. The compression chamber is pressurized with room air, causing the Mylar membrane to rupture at a pressure that is linearly dependent upon its thickness. For whole body exposures, anesthetized rats were suspended in a transverse prone position in a tightly secured mesh pouch positioned 2.5 ft within the mouth of the shock tube. The critical biomechanical loading to the experimental subject is determined from both the static (Ps) and dynamic pressure (Pd) of the blast wave, which are fully recorded by the combination of side-on and head-on pressure gauges (left tracing). Accelerometers also reveal appreciable acceleration of the rat during BOP exposure (right tracing).

Fig 2.

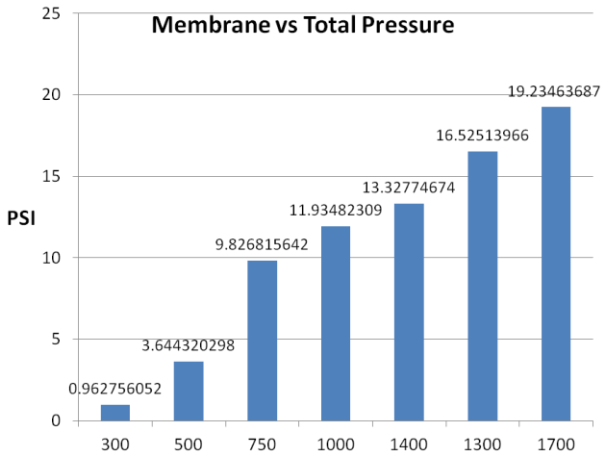


Fig 3.

Reducing Driver Volume Reduces Overpressure Duration

254 µ Thick Membrane						
	Max Tip Pressure (psi)	Max Side Pressure (psi)	Impulse Tip (Psi-s)	Impulse Side (Psi-s)	Tip Overpressure Width (ms)	Side Overpressure Width (ms)
Original Volume	21.1	16.3	97.9	71.9	8.4	6.7
50% of Original Volume	18.9	16.1	53.8	35.6	5.5	4
% Reduction	10	2	45	51	35	40

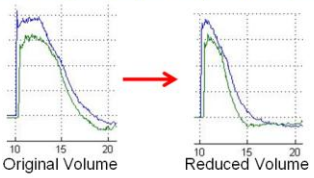


Fig 4. Flow conditions vary along the length of the shock tube, particularly at the mouth.

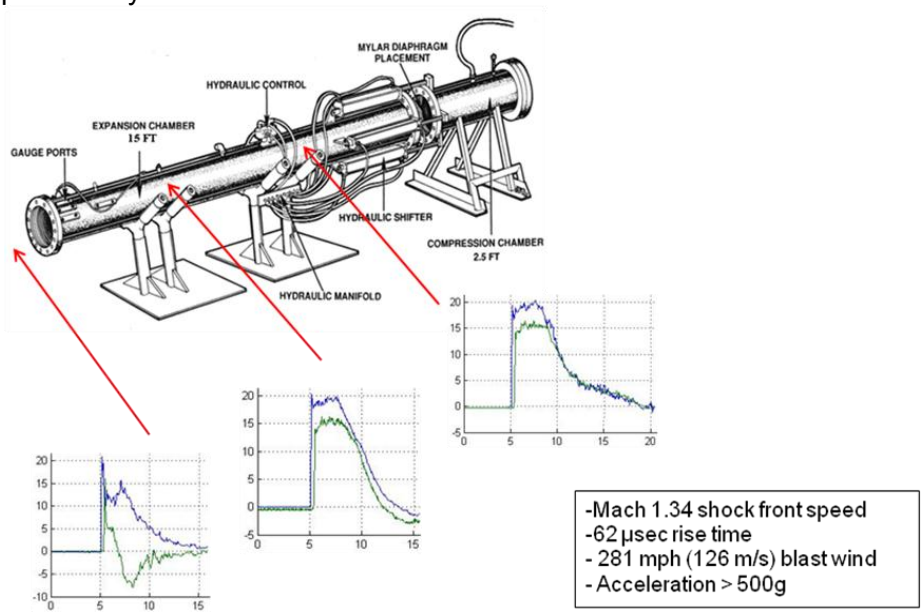


Fig 5.

Overpressure Parameters at Varied Positions within the Blast Tube

254 µ Thick Membrane N=3						
Feet from mouth of tube	Avg Peak Total Pressure (psi)	Avg Peak Static Pressure (psi)	Total Impulse (psi-ms)	Static Impulse (psi-ms)	Total Overpressure Duration (ms)	Static Overpressure Duration (ms)
10	20.87	16.73	118.26	100.48	13.42	13.32
2.5	21.05	16.30	97.92	71.90	8.42	6.70
-0.5	21.17	15.47	65.22	6.88	12.85	1.40

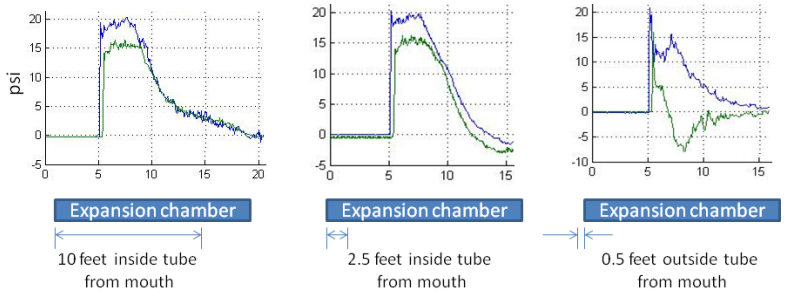


Fig 6.

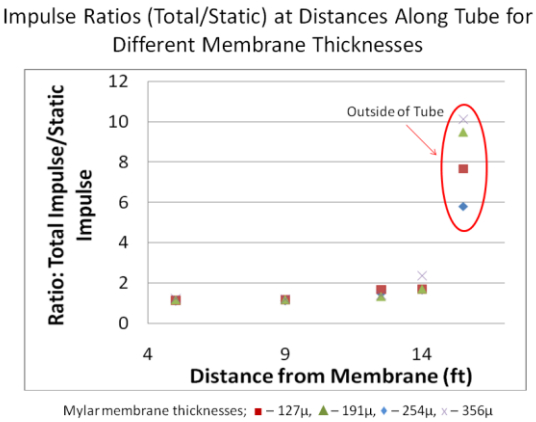


Fig 7. ICP (top), venous (middle), and esophageal (bottom) pressures track closely with ambient static pressures.

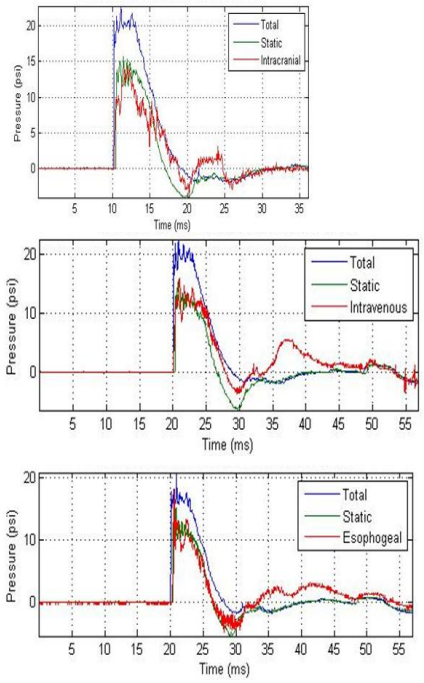


Fig 8. BOP-induced elevations in ICP increase with increased Mylar membrane thickness.

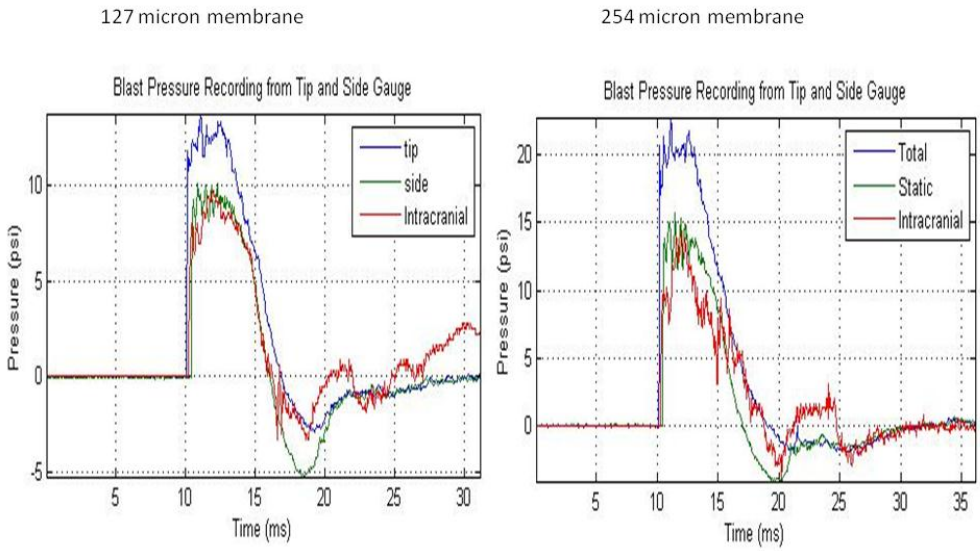
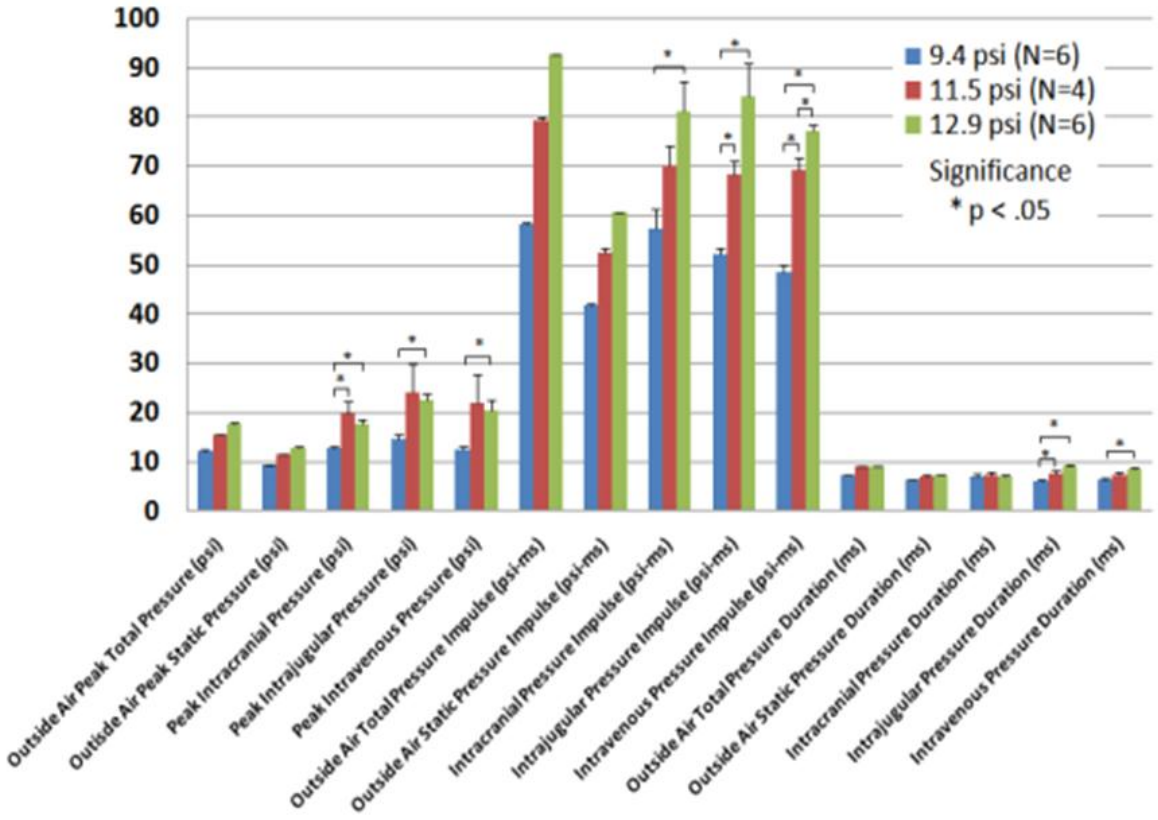


Fig 9.



BOP parameters (peak pressure, impulse, and duration) recorded in the intracranial space between the skull and in the jugular and femoral veins at different ambient static pressures.

Fig 10. Intracranial pressure response to blast was not reduced by the vest.

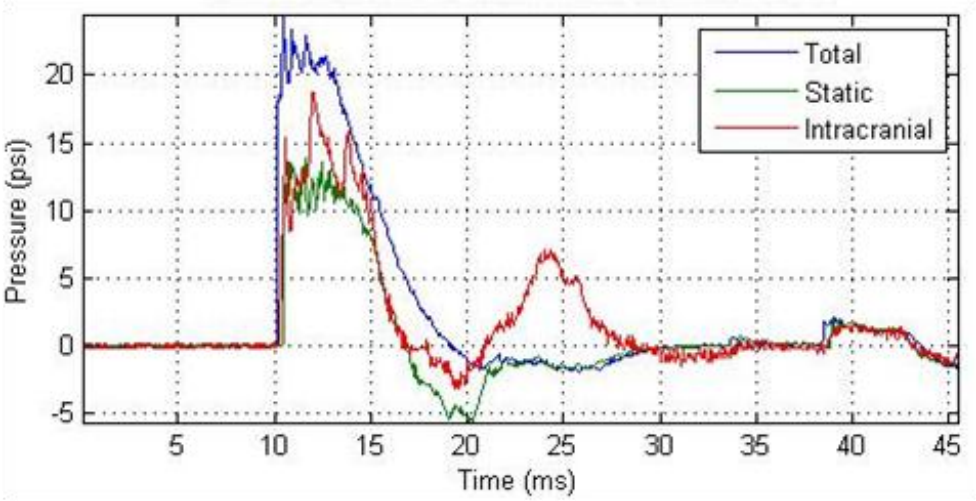


Fig 11. Protective vests did not alter rats' pressure responses to BOP

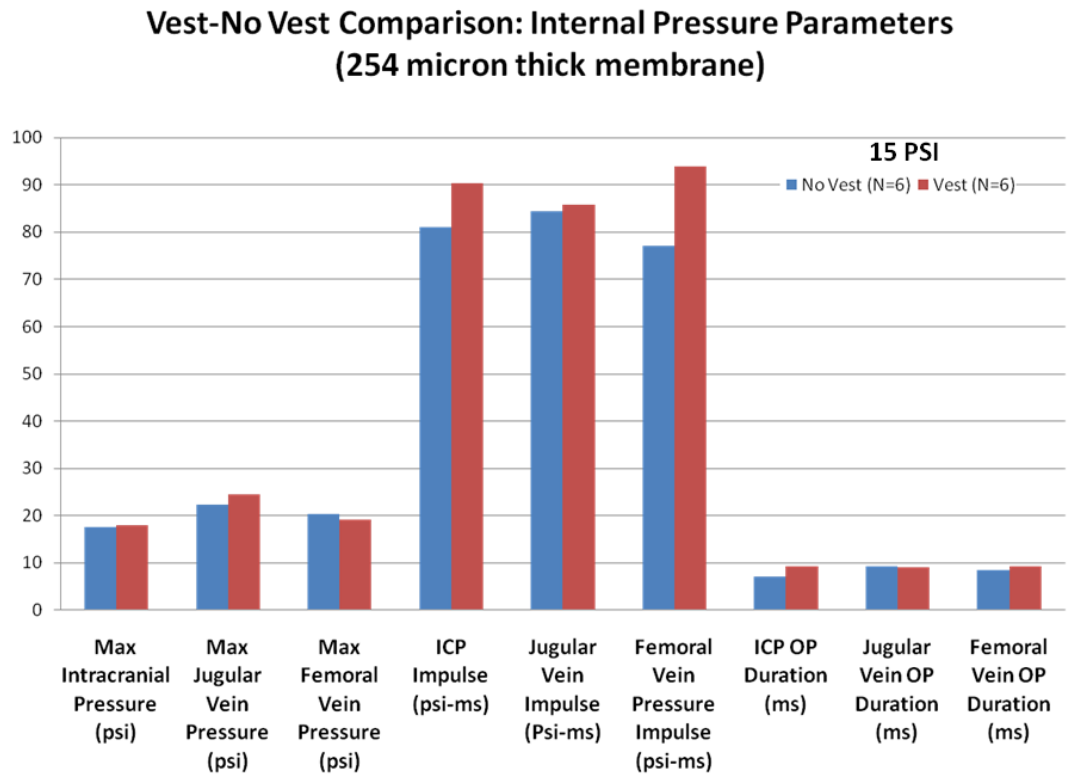


Fig 12. Characteristic BOP-induced fiber degeneration in optic tract and cerebellum

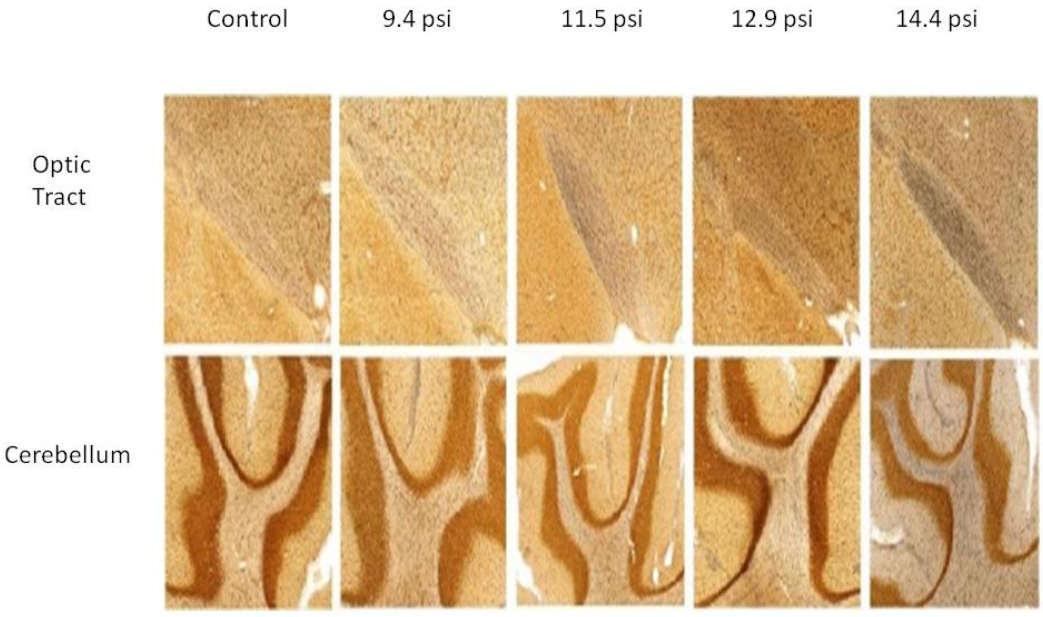


Fig 13. MWM latencies following 10 psi BOP

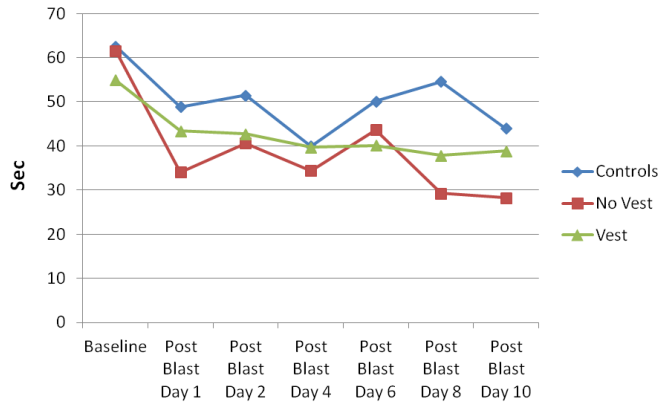


Fig 14. MWM latencies following 12 psi BOP

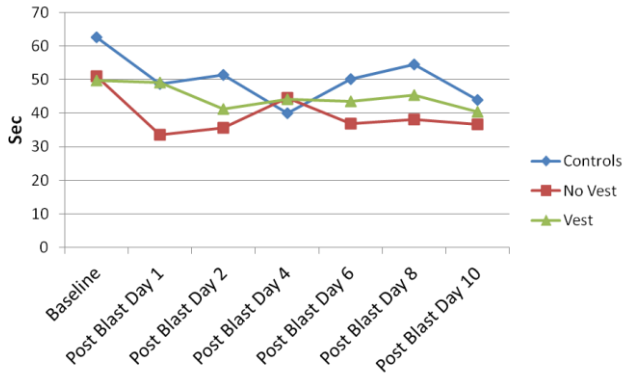


Fig 15. MWM latencies following 13 psi BOP

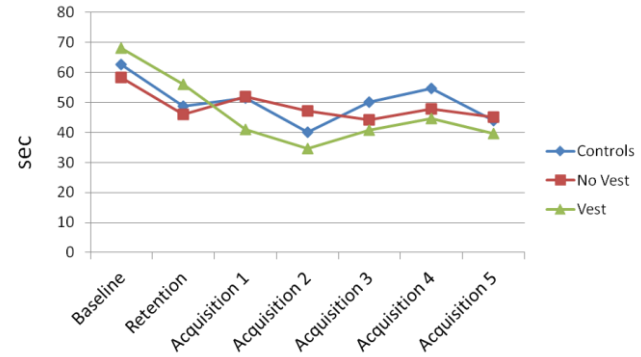


Fig 16. Rotating pole scores following BOP

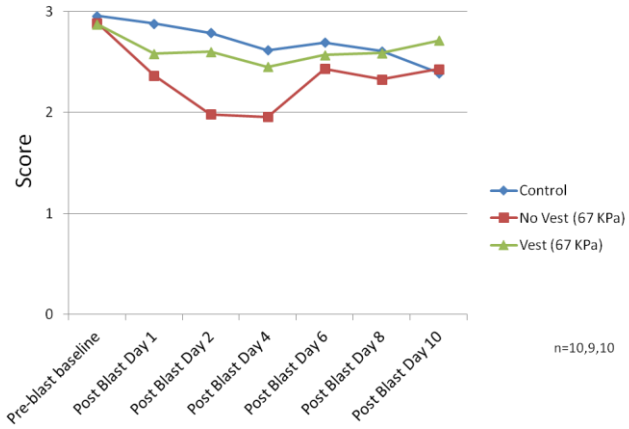


Fig 17. Rotating pole scores following BOP

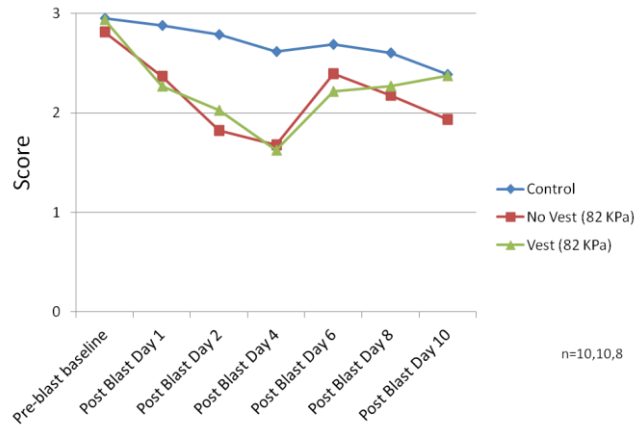


Fig 18. Rotating pole scores following BOP

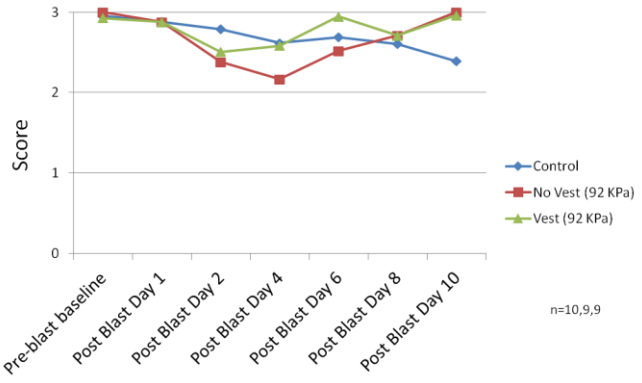


Fig 19. Evans blue dye extravasation 2hrs after 12 psi BOP exposure