Molecular and Cellular Fingerprints of Brain Overpressure Load: Potential Biomarkers of Blast Brain Injury

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Abstract

A comprehensive experimental model for studies of controlled blast wave impact in rats is presented. Repeatable blast signatures of controlled duration, peak pressure and transmitted impulse enable to reproduce blast impact in laboratory animals in accurate fashion. Animal survival, brain pathomorphology and the levels of putative biomarkers of brain injury GFAP, NSE and UCH-L1 was examined in CSF and blood after head-directed non-penetrating blast of 358 kPa magnitude at surface for 10 msec. The high speed imaging demonstrated strong head acceleration/jolting accompanied by typical intracranial hematomas and brain swelling. The microscopic injury was revealed by prominent silver staining in the deep brain areas including nucleus subthalamicus zone suggesting both diffused and focal neurodegeneration. GFAP and CNPase, markers of astroglia and oligodendroglia, accumulated substantially in hippocampus and, to a lesser extent, in the cortex 24 h after blast and persisted for 30 days post-blast. In blood however, GFAP content significantly increased 24 h after injury, followed by a decline thereafter and subsequent accumulation in CSF in a time-dependent fashion. A similar profile is shown for neuronal marker UCH-L1 increase in blood, while increased CSF levels of UCH-L1 persisted throughout 14 days after blast exposure and varied significantly in individual rats. NSE levels in blood were significantly elevated within 24 and 48 hours post-blast. The proposed model of controlled non-penetrating blast in rats, demonstrates the critical pathological and biochemical signatures of blast brain injury that may be triggered by cerebrovascular responses, including blood brain barrier disruption, glia responses and neuro-glial alterations.

Objectives/Methodology

Task 1: Design and construct of a universal blast-wave generator that enables replication of blast events of peak overpressure and duration; high speed imaging and measurement of relevant wave parameters.

Task 2: Study the characteristic parameters of the blast waves generated by the shock tube, injury mechanisms, and relevant molecular biomarkers of blast brain injury. Evaluate rat mortality, gross anatomy and microscopic brain features via silver staining

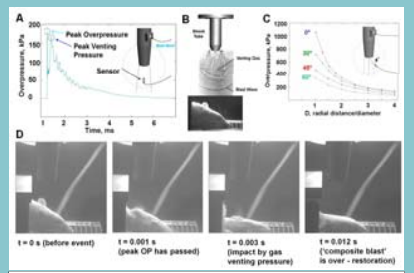
Task 3: Examine both acute (hours) and subacute (days) brain injury. Develop blast brain injury model based on rodent morphological and clinical data, discovery of relevant biomarkers.

Modeling Blast-Induced Brain Injury

Variable Length Driver allows adjustment of over-pressure and test duration. No other blast wave simulator in the literature has this unique feature

Adjustable blade cutter allows change of diaphragm materials and for range of operational pressures

Variable length driven allows device to turn a normal shock wave into a blast wave prior to exit

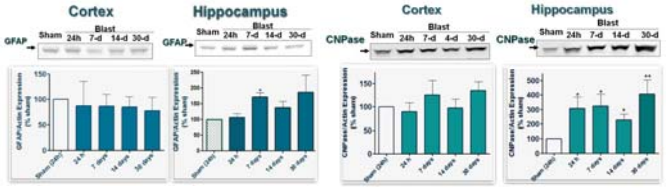


A,B: Components of shock tube-generated blast wave; C: Blast Peak Overpressure (OP) at the target as function of a radial distance and angle, and D: Rat head movement upon head-directed, body armored, blast wave load of 358 kPa for 10 msec. 1,000 Hz high speed video images using Schlieren optics shown.

BBI Mortality and Biomarkers in Brain

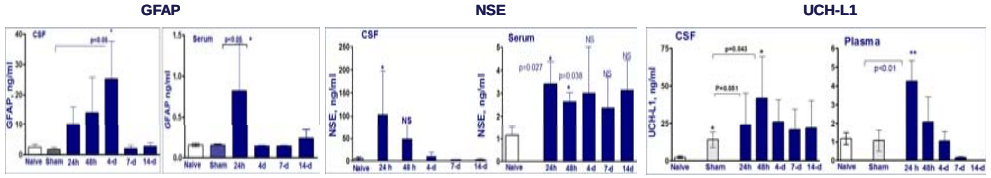
Peak Overpressure (kPa)	Total Blast Duration (msec)	Mortality
Total exposure (unprotected body)		
110 (n=3)	2	survived
170 (n=2)	4	lethal
358 (n=2)	1	lethal
Head-directed (body armored)		
172 (n=12)	4	all survived
358 (n=48)	10	all but one survived

Mortality after head-directed blast exposure of body-armored or nonprotected rats



Expression of GFAP and CNPase in cortex and hippocampus of rats after blast-induced non-penetrating injury.

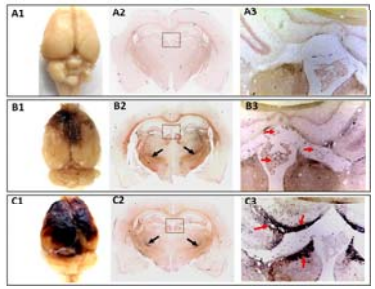
BBI Biomarkers in CSF and Blood



Banyan SW ELISA of GFAP, NSE and UCH-1 levels in CSF and blood of rats with blast-induced non-penetrating injury.

Brain Pathomorphology/Histology

Head-Directed Severe Blast Exposure (358 kPa/10 msec)



Gross pathology: typical focal intracranial hematomas (B1 and C1) shown from at least 3 animals at each time point. Histopathology: coronal sections in caudal diencephalon exhibit diffuse and local silver accumulation in Caudal Diencephalon section (B2 and C2). Black arrows indicate strong silver staining in Nucleus Subthalamicus. Representative microphotographs of whole brains with high resolution scan (1.5x, A2-C2) and corresponding or similar areas at higher magnification (10x) are shown (A3-C3). Red arrows point to silver accumulation in perivascular and periventricular tissue zone.

CONCLUSIONS

- An experimental model for studies of controlled blast wave impact in rats was designed to enable repeatable blast signatures of controlled duration and peak pressure and reproduce blast impact in laboratory animals in accurate fashion.
- The high speed imaging demonstrated strong head acceleration/jolting accompanied by typical intracranial hematomas and brain swelling.
- The microscopic injury was revealed by prominent silver staining in the deep brain areas including nucleus subthalamicus zone suggesting both diffused and focal neurodegeneration.
- GFAP and CNPase, markers of astroglia and oligodendroglia, accumulated substantially in hippocampus 24 h after blast and persisted for 30 days post-blast.
- In blood, GFAP significantly increased 24 h after injury, followed by a decline and accumulation in CSF in a time-dependent fashion. A similar profile is shown for UCH-L1 increase in blood, while increased CSF levels of UCH-L1 persisted throughout 14 days after blast and varied significantly in individual rats. NSE levels in blood were elevated within 24 and 48 hours post-blast.
- Our model of controlled non-penetrating blast in rats demonstrates the critical pathological and biochemical signatures of blast brain injury that may be triggered by cerebrovascular responses, including blood brain barrier disruption, glia responses and neuro-glial alterations.

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