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14. ABSTRACT We compared acute neurophysiological changes in rats following a blast-type TBI induced by a "shock tube" with more traditional models of TBI, i.e., midline fluid percussion (PERCUSSION) and controlled cortical impact brain injuries. Currently, insufficient data exists which compares the physiological brain changes induced by a blast-type injuries to those generated by more traditional animal models of TBI. We hypothesized in this proposal that brain damage from a blast-type injury (BLAST) may be very similar to those induced by a PERC injury model but fundamentally different than penetrating and ballistic-type brain injuries modeled by a pneumatic piston. We first documented neurophysiological and behavioral changes in rats following graded levels of PERCUSSION injury, which has been submitted for rapid publication in Neurosurgery Focus (see Appendix). In the second year, approved as a "no-cost extension", we are analyzing the data for BLAST injuries and comparing where on the severity scale, BLAST brain injuries fall when compared to PERCUSSION injuries of graded intensities.					
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Introduction

New models of experimental TBI are needed to fully understand the type of head injuries that are prevalent in OEF and OIF. Current animal models of TBI, e.g., lateral and midline fluid percussion, controlled cortical impact, Marmarou weight drop, Feeney weight drop and etc., all do an excellent job of simulating more focal injuries occurring following a fall, traffic accident, and to a lesser degree, bullet wounds to the head. However, it is unknown whether these traditional models of TBI also simulate an injury induced by a more global, blast-type injury (over-pressurization) induced by an IED.

In this study, we compared acute neurophysiological changes in rats following a blast-type TBI induced by a “shock tube” with more traditional models of TBI, i.e., midline fluid percussion and controlled cortical impact brain injuries. The traditional models of TBI have been used in our laboratory for over 10 years, and recently, we have adapted and characterized their use in juvenile rats (Smith et al, 1996). Acute neurophysiological changes which are routinely measured in our laboratory include immediate and sub-acute measurements of intracranial pressure, brain edema, extravasation of blood, blood-brain barrier permeability, acute and long-term changes in glucose and oxidative metabolism, neurochemical measurements using microdialysis, cerebral blood flow measurements and seizure-like EEG activity using depth electrodes (Kelly et al., 1997, 2000; Zanier et al., 2003, Lee et al., 1999). In addition, we have recently comparison studies of mild versus severe gene expression changes using the microarray technique (Li et al., 2004). Our comparative studies have also extended to radiographic findings in fluid percussed versus cortical impact injured rats using magnetic resonance imaging. These radiographic, whole animal studies include spectroscopic anomalies following ^{13}C glucose infusions in mild versus severe TBI (Bartnik et al., 2005, 2007; Obenaus et al., 2007).

In the first year (second year was approved as a “no-cost extension”), we first needed to document the full range of neurophysiological and behavioral changes induced by graded levels of fluid percussion brain injuries, from mild to severe. The graded levels of brain injuries produced by a penetrating brain injury, i.e., controlled cortical impact, was reported previously by my laboratory to be not as varied as the fluid percussion injury (Lee et al., 1999; Kelly et al., 1997, 2000). Graded severities of a penetrating injury primarily determined the rate at which the impact brain areas degenerated, not the size or volume. This baseline study of neurophysiological and behavioral response of rats following three different severities of fluid percussion injury was recently submitted for rapid publication in *Neurosurgery Focus* (Lee et al, 2010) and was found “acceptable pending minor revisions.” The submitted manuscript is included in the Appendix. The decision was made in the first year to expand the baseline study by more rigorously documenting the changes induced by the fluid percussion, since the primary objective of this study was to compare the changes induced by blast-type injuries to what is currently known about the injury-induced neurophysiological cascade. We are currently analyzing the data for blast-type brain injuries, which will be reported in full detail as the second-year Annual Report.

Body

MATERIALS AND METHODS

Surgical procedures

The rationale and experimental protocol for this study have been reviewed and approved by the Institutional Animal Care and Use Committee (IACUC). Fifty-one adult male Sprague-Dawley rats (300-325 g, Harlan Laboratories) were anesthetized with isoflurane (2-2.5% in 100% O_2) and their core temperatures were maintained at 37-38°C using a thermostatically-controlled heating pad (Harvard Apparatus, Holliston, MA). For measurement of mean arterial blood pressure (MABP), the femoral artery was cannulated using polyethylene tubing (PE-50).

Following cannulation, animals were placed in a stereotaxic head holder (Kopf Instruments, Tujunga, CA) fitted with an anesthetic nose mask, and the dura exposed through a 3.5 mm diameter craniotomy, which was centered -2 mm AP, 6 mm ML from bregma. A plastic injury cap, which was fashioned from the taper-tip end of a 1 cc syringe (BD, Franklin Lakes, NJ; OD 7.0 mm, ID 5.0 mm, 7.0 mm in length) was positioned directly over the craniotomy at approximately 45° from vertical and secured to the skull using silicone adhesive and acrylic dental cement (Fig. 1). A thin layer of silicone adhesive (Dow Corning) was applied to the outer margins of the craniotomy before the injury cap was positioned which served two purposes: 1) the silicone adhesive loosely held the injury cap in place as the dental cement was applied around the injury cap and 2) the silicone seal prevented any dental cement from leaking into the craniotomy. In order to facilitate the bonding of the dental cement to the skull, a thin coating of cyanoacrylate ("Krazy Glue", Borden, Columbus, OH) was applied to the skull and allowed to dry before the dental cement was applied, which minimized fluid buildup near the surface.

In addition to the injury cap, a 22-G needle was stereotaxically placed into the anterior horn of the right lateral ventricle (-1 mm AP, 1 mm ML from bregma) to acutely measure changes in intracranial pressure (ICP) during the injury process. The correct placement of the ICP catheter was confirmed by carefully observing pressure changes on an oscilloscope (Nicolet Model 310) as the catheter was advanced through the overlying cerebral cortex. While the catheter tip was slowly advanced, a small volume saline was infused (1 μ l/min) through a "Y" tubing that was connected in series with the ICP monitor. This slight buildup in pressure as the catheter tip advanced through tissue was abruptly lost as the catheter tip entered ventricular space. The ICP needle was then secured to the skull using acrylic cement. Prior to delivery of the fluid pulse, all wound margins were infiltrated with 1% xylocaine.

Injury induction and measurement of unconsciousness time

Detailed methods for the induction of FP brain injuries have been published elsewhere (Smith et al., 1996) and injuries for this study were conducted with only minor modifications. Following implantation of the injury cap and ICP monitor, animals were removed from the stereotaxic frame and the injury cap was connected directly to the FP injury device via a taper-tip to adapter "Luer-Lok" (Fig. 1). This short adapter replaced the usual extension tube used in previous studies from our laboratory (Lee et al. 1995). After ensuring a water-tight seal between the injury cap and FP device, animals were maintained at stage III-4 anesthesia for approximately 5 min before slowly being brought up to stage III-1 anesthesia by reducing the level of gas anesthesia. When animals displayed positive toe-pinch and corneal reflexes, the fluid pulse (1.5 - 3.1 atm) was delivered to the epidural space which induced a concussion resulting in stage III-4 to stage IV unconscious state. Thus, the duration of injury-induced unconsciousness was defined as the time animals took to return to stage III-1 state following injury (Fig. 2). Immediately after recovery to stage III-1, general isoflurane anesthesia was reinstated, and ICP and MABP were measured for an additional 30 min. Following this acute physiological monitoring, the injury cap and monitoring catheters were removed and

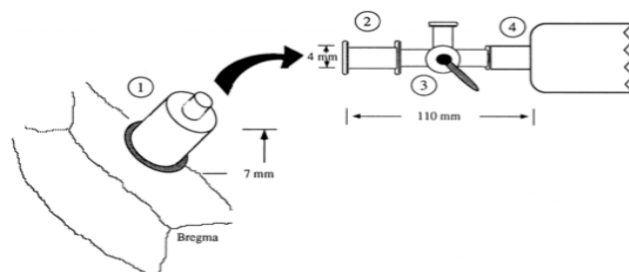


Figure 1 Schematic representation of the injury cap, location of the primary injury site and connectors between the injury cap and FP device. (1) injury cap, (2) "Luer-Lok" adapter, (3) three-way valve used to remove air bubbles from the FP device and (4) portion of the FP device. The injury cap was fabricated by cutting of the end of 1 cc syringe. The cut end was flared by gently melting it against a heat source.

wound margins sutured closed. Following recovery from anesthesia, animals were placed in a recovery chamber maintained at 37°C with warm, humidified air.

To minimize experimenter variability in testing for reflexes, a strict protocol was adhered to for determining states of unconsciousness/anesthesia. The corneal reflex was tested by gently touching the cornea with a sterile applicator every 1-2 s. The toe-pinch response was tested by gently squeezing the left hindpaw with a tissue forceps (Biomedical Research Instruments, Model 30-1355), which was modified to prevent complete closure by attaching a 3 mm spacer to one leg (30 mm from the end). For mild, moderate and severe injuries, the hindpaw was gently pinched with the modified forceps continually starting from 60 s, 140 s and 300 s, respectively, post-injury.

Mild FP Injury Group (2.5 atm, 250 ms fluid pulse)

ICP+EEG+MD	7 rats
Double-label autoradiography (6 x 4 time points)	24 rats
Edema+BBB+intracranial bleeding (6 x 4 time points)	<u>24 rats</u>
	55 rats

Severe/CCI Injury Group (4.0 atm, 250 ms fluid pulse)

ICP+EEG+MD	7 rats
Double-label autoradiography (6 x 4 time points)	24 rats
Edema+BBB+intracranial bleeding (6 x 4 time points)	<u>24 rats</u>
	55 rats

For blast-type TBI, compressed air delivered via a shock tube, which was composed of a 525 cm long, 30 cm diameter, horizontally mounted, circular steel tube divided into a 75 cm compression chamber separated from a polyester Mylar sheets (Du Pont Co, Wilmington, DE). The peak pressure obtained varied depending upon the number and thickness of the Mylar sheets placed. The relationship between Mylar sheet thickness and the pressure produced was linear. The peak pressure obtained was measured at the end of the expansion chamber by means of pressure transducers. Animals were injured while fully anesthetized, similar to traditional animal TBI studies, by opening a solenoid valve and thereby instantaneously releasing a pre-calibrated volume of compressed air (typically 50-100 kPa). Acute neurophysiological monitoring was conducted as described by previous publication from the PI's laboratory. ICP, EEG and microdialysis measurements was start 30 min prior to injury and continued for 6 hours post-injury. Double-label autoradiography was conducted for glucose metabolism and local cerebral blood flow at 30 min, 6h, 24 h and 72 h after injury, as described in previous reports from my laboratory. In a separate group of injured rats, brains was assessed for brain edema (wet weight vs. dry weight), intracranial bleeding (IgG immunocytochemistry) and BBB permeability (extravasation of Evans-Blue fluorescence) at the same post-survival time points as for autoradiography. The study groups for blast-type injuries was identical to what was approved in the SOW.

Blast Injury Group (75kPa, moderate injury)

ICP+EEG+MD	7 rats
Double-label autoradiography (6 x 4 time points)	24 rats
Edema+BBB+intracranial bleeding (6 x 4 time points)	<u>24 rats</u>
	55 rats

For control (sham) injuries, surgeries were identical to the FP injury group except that the fluid pulse was not delivered.

Sham Injury Group	
ICP+EEG+MD	7 rats
Double-label autoradiography (6 x 4 time points)	24 rats
Edema+BBB+intracranial bleeding (6 x 4 time points)	<u>24 rats</u>
	55 rats

The study groups for blast-type injuries were identical to what was approved in the SOW.

Acute monitoring

ICP and MABP were monitored for approximately 5 min before injury to obtain a stable pre-injury baseline and were stored digitally on a computer (Snap Shot Digital Oscilloscope). ICP and MABP values were continually measured during injury and for an additional 30 min post-injury to determine peak changes in ICP, MABP and cerebral perfusion pressure (CPP). Additional injury-induced responses monitored included the duration of apnea and post-traumatic seizures. Apneic periods were determined by visually observing for the lack of chest expansion. Post-traumatic seizures typically consisted of vibrissa or tail twitching, clonic/tonic seizures of the extremities or generalized seizures lasting less than 40 s. Four severely-injured cases with generalized seizures that lasted more than 40 s and accompanied by respiratory collapse were excluded from this study.

Behavioral/functional testing

All animals in this study were pre-trained on the beam walk and the Morris Water Maze for comparison of post-injury recovery performances to pre-injury, baseline values. Animals were trained on the Morris Water Maze using procedures described previously (Morris et al, 1982; Lee et al. 1993). Briefly, each animal was trained to “criterion” which involved finding a hidden platform in a pool of water made opaque using white organic paint (Stechlen Paint, San Diego, CA). Animals were trained to find the hidden platform using various cues located throughout the room. The task is often referred to as a “spatial” task since it is dependent on spatial memory retention involving the hippocampus and neocortex (Kolb et al, 1983; Morris et al., 1992). Each animal was given 8 trials per day until it reliably located and climbed onto the platform in less than 4 s from any one of four release points (defined as criterion). Upon reaching criterion, animals were also timed for their ability to locate and climb onto a visible platform (“cue task”). The cue task has been previously demonstrated to involve primarily non-memory associated motor structures, e.g., superior colliculus²⁹. Upon completion of training in the MWM, which typically lasted 2-3 days, animals were tested for their ability to cross a 1” wide beam. Animals were given 5 trials, and their best time to traverse 1.5 m was recorded.

Animals were injured the same day after reaching criterion and re-tested for their performance in the MWM (both spatial and cue tasks) and beam walk each day after injury for 7 days. At termination of the behavioral testing, animals were processed for quantitative [¹⁴C] 2-deoxy-glucose (2DG) autoradiography for determination of cerebral metabolic rates for glucose (CMR_{glc}).

2DG autoradiography

Procedures for the quantitative measurement of CMR_{glc} and its use following traumatic brain injury, have been described in detail previously (Yoshino et al., 1991). Briefly, 200 µCi/kg 2DG was injected into the femoral vein and blood samples collected through the femoral artery at pre-determined times. Blood samples were assayed for plasma glucose levels and ¹⁴C activity. Forty-five minutes after the injection of 2DG, animals were given a lethal dose of sodium pentobarbital (100 mg/kg, i.v.). The brains were quickly removed and frozen in powdered dry ice. Coronal section (20 µm) were cut at -18°C in a cryostat (Reichert, Cambridge, MA) and

processed for autoradiography. Alternate sections were stained with cresyl violet. Quantification of the tissue radioactivity was carried out using ^{14}C methylmethacrylate standards and a computer-based optical densitometry system (Image J, NIH).

Data analysis

Each animal following injury was assigned 4 acute injury-associated values: 1) duration of unconsciousness, 2) duration of apnea, 3) peak ICP change, 4) minimum CPP value and 5) duration of post-traumatic seizure. The acute injury values were blinded to those conducting the behavioral testing and 2DG autoradiography.

The ICMR_{glc} ($\mu\text{mol}/100\text{g}/\text{min}$) was calculated for the primary injury site and the underlying dorsal hippocampus. The correlations were determined using a linear regression model, and the 95% confidence interval was chosen to be significant. The cluster analysis was performed using Kmeans clustering method (Systat ver. 5.1), with an assumption of three distinct groups (mild, moderate and severe).

RESULTS

Acute response to fluid percussion and blast injuries

The range of unconsciousness induced by a fluid pulse delivered to the epidural space and from a blast injury ranged from 1 - 14 min (mild, 57.0 ± 5.0 ; moderate, 162.0 ± 9.8 ; severe, 331.0 ± 29.6 ; blast 61.2 ± 7.2 ; mean $\pm$ SEM). Mild, moderate, severe and blast injuries were categorized using a cluster analysis in which three distinct classifications were assumed (Fig. 2). In general, a strong correlation was seen between the duration of unconsciousness and peak ICP levels ($r = 0.67$, $p < 0.01$). However, regardless of the blast pressure (40-80 kPa), the resulting unconsciousness times were classified as "mild injuries."

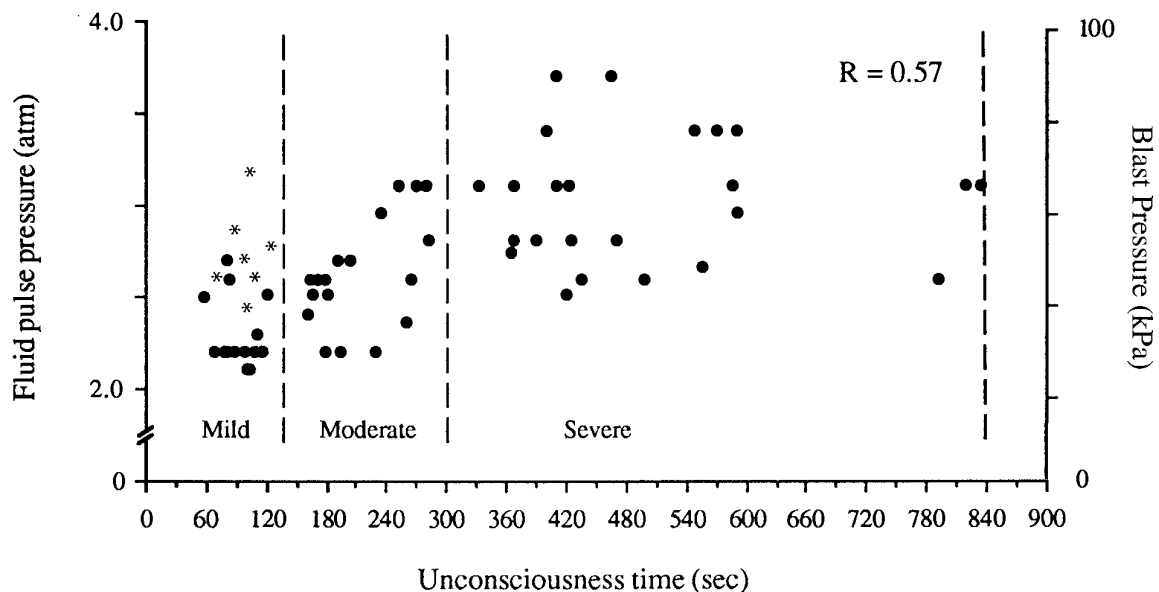


Figure 2 Scatter Plot of the fluid pulse and blast pressure and corresponding unconsciousness times for all 58 animals (51 fluid pulse, dots, and 7 blast, asterisks) injured for acute ICP measures for this study. The divisions between mild, moderate and severe injuries (dashed lines) were determined in previous studies from my laboratory using Kmeans cluster analysis (Systat ver 5.1). Four ultra-severely injured animals from high fluid pulse pressure never regained consciousness before respiratory collapse. These 4 animals were removed from this analysis. Note that all blast injuries, regardless of blast pressure used in these measurements (40-80 kPa), resulted in what my laboratory would characterize as mild injuries.

Changes in MABP correlated less well since the increase in the MABP, presumably due to an intact Cushing's Response, quickly reached to upper limits following a moderate injury (Fig. 3). Thus, CPP was severely reduced at high levels of unconsciousness. The periods of apnea induced by fluid pulse or blast injury showed a poor correlation with the duration of unconsciousness ($r = 0.38$, $p = 0.38$), as mild injuries (both FP and blast) produced significant levels of apnea. Post-traumatic seizures were never seen following mild or blast injury, but were prevalent and generalized following severe injuries. The significant correlation between the duration of unconsciousness and the occurrence of seizures indicate that both measures are strong indicators of injury severity following an experimental brain injury.

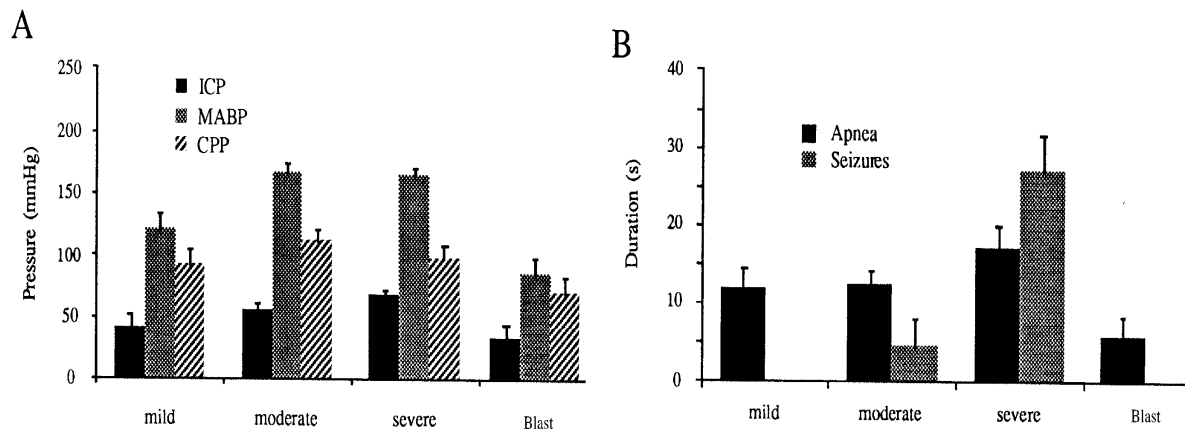


Figure 3 Plot of the acute physiological responses to FP and Blast injuries when categorized as mild, moderate, severe or blast injuries. All values represent mean $\pm$ sem. Note that the CPP is relatively independent of ICP acutely following both FP and Blast injuries due to an intact Cushing's response. ICP, MABP and seizure duration showed strong correlation to the duration of unconsciousness for FP injuries but not for Blast injuries, which were all relatively mild.

Long-term recovery

The functional recovery of brain-injured animals was assessed using three distinct measures: 1) return of motor function, 2) return of cognitive function (as tested by memory retention) and 3) regional glucose metabolism. Mild, moderate and severe injuries as categorized by the duration of unconsciousness, showed strong correlations with all three measures. Blast injuries, however, showed no such relation to blast pressure. Beam crossing times for our traditional model of brain injury significantly increased as the injuries became more severe since the traumatized animals had difficulty with coordinated motor movements ($r = 0.62$, $p < 0.01$), but their ability to escape a water-filled tank by climbing onto a visible platform (MWM cue task) showed a highly significant correlation ($r = 0.83$, $p < 0.001$, Fig. 4). More importantly, the spatial MWM task, which required the animal to remember a submerged platform based on room cues, displayed an almost perfect correlation with the duration of injury-induced unconsciousness ($r = 0.91$, $p < 0.0001$). As reported previously from our laboratory⁴⁹, glucose metabolism of parietal and hippocampal structures were significantly depressed 7 days following moderate FP injury when compared to normal or sham-injured animals. Seven days after a 50 kPa blast injury, cortex and hippocampus showed a similar depression in glucose uptake, at levels that were similar to those that were mildly injured using a fluid pulse (mild FP = 71.2 ± 3.6 vs. Blast = 76.8 ± 5.4 $\mu\text{mol}/100\text{g}/\text{min}$, $p = 0.27$). When glucose metabolism was

measured for graded levels of injuries as determined by the duration of unconsciousness, a strong negative correlation was seen. Such negative correlation was not seen for animals injured with blast pulse.

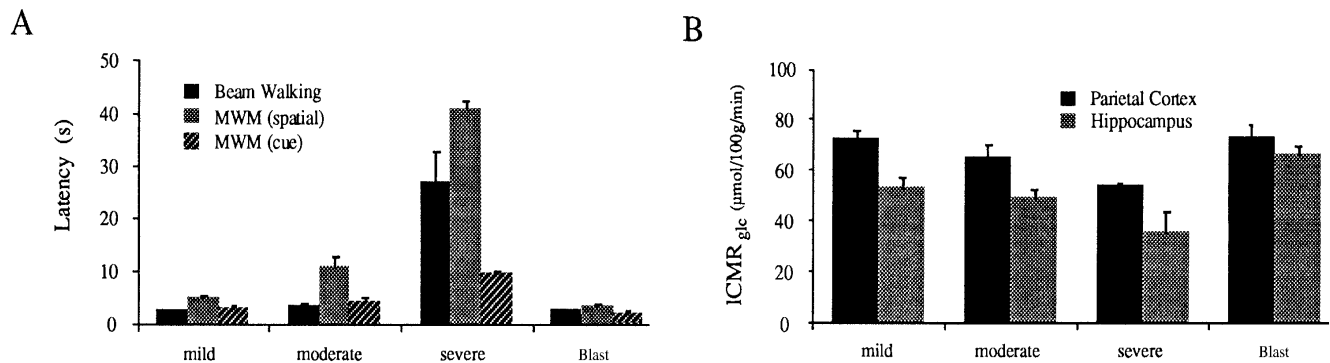


Figure 4 Plot of the functional recovery for mild, moderate and severe FP or Blast injuries at 7 days post-injury. Note that the beam walking performance was only affected by severe injuries, whereas mild, moderate and severe injuries progressively affected the animals' performance in the MWM. The loss of performance in the MWM may be due to the progressive depression of glucose metabolism in the ipsilateral cortex and hippocampus with increasing injury severity.

Key Research Accomplishments

- Lateral fluid percussion (FP) injuries, ranging from 0 to 3.7 atm, were induced in 165 adult male rats. Acute ICP and MABP were measured in 51 of these FP injured animals. Blast injuries, ranging from 40-100 kPa were induced in 55 male rats from which 7 representative cases were acutely monitored for ICP and MABP. Animals with the shortest duration of injury-induced unconsciousness (60 - 140 s; classified as mild injuries) displayed the least dramatic physiological responses to FP injury; these mildly injured animals showed complete functional recovery by 7 days
- FP injuries resulting in moderate (unconscious for 140-300 s) or severe (300-840 s) concussions showed remarkably similar early physiological responses, but recovered behaviorally at vastly different rates.
- All blast injured animals, regardless of blast pressure intensity tested in this study (40-100 kPa), showed acute responses that were categorized as "mild injuries"
- Seven of the 10 injury-induced physiological changes displayed a statistically significant correlation to the duration of unconsciousness ($r = 0.62 - 0.91$). No such correlations were seen for blast injured cases.
- These findings strongly suggest that the skull effectively mitigates blast energies at higher intensities, thus resulting in brain injuries are classified in our animal models as being "mild."

Reportable Outcomes

- Lee, S.M. Long-term consequence of moderate concussions: Increased vulnerability to epileptic seizures? *Neurosurgery Focus* (Manuscript #FOCUS-10-188, in press).
- Lee, S.M., Nahed, B.V. and Wong, M.D. Duration of injury-induced unconsciousness predicts functional outcome following experimental concussions. *Neurosurgery Focus* (Manuscript #FOCUS-10-189, in press).

- “New Advances in the Treatment of Traumatic Brain Injury” Trent Welles Neurosurgery Lecture, Department of Neurosurgery, University of Southern California, April 2009.

Conclusion

We conclude from our data that even the mildest percussion type of brain injury (including blast-type injuries) induces profound neurophysiological and behavioral deficits that last at least 1-2 days. The more severe the injury, the longer these deficits persist which may last weeks to months. These data also demonstrate that even the mildest blast-type injury that leads to an elevation of intracranial pressure will initiate a neurophysiological cascade resulting in alteration in cerebral blood flow, glucose metabolism and neurotransmitter imbalance that can lead to long-term decreased motor and memory performance.

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