**ABSTRACT**

Military service members are often exposed to at least one explosive event, and many blast-exposed veterans present with symptoms of traumatic brain injury. However, there is little information on the intensity and duration of blast necessary to cause brain injury.

**METHODS:**

**SUBJECT TERMS**

Primary blast; brain injury; injury risk; ferret.
ABSTRACT

Military service members are often exposed to at least one explosive event, and many blast-exposed veterans present with symptoms of traumatic brain injury. However, there is little information on the intensity and duration of blast necessary to cause brain injury.

METHODS:

Varying intensity shock tube blasts were focused on the head of anesthetized ferrets, whose thorax and abdomen were protected. Injury evaluations included physiologic consequences, gross necropsy, and histologic diagnosis. The resulting apnea, meningeal bleeding, and fatality were analyzed using logistic regressions to determine injury risk functions.

RESULTS:

Increasing severity of blast exposure demonstrated increasing apnea immediately after the blast. Gross necropsy revealed hemorrhages, frequently near the brain stem, at the highest blast intensities. Apnea, bleeding, and fatality risk functions from blast exposure to the head were determined for peak overpressure and positive-phase duration. The 50% risk of apnea and moderate hemorrhage were similar, whereas the 50% risk of mild hemorrhage was independent of duration and required lower overpressures (144 kPa). Another fatality risk function was determined with existing data for scaled positive-phase durations from 1 millisecond to 20 milliseconds.

CONCLUSION:

The first primary blast brain injury risk assessments for mild and moderate/severe injuries in a gyrencephalic animal model were determined. The blast level needed to cause a mild/moderate brain injury may be similar to or less than that needed for pulmonary injury. The risk functions can be used in future research for blast brain injury by providing realistic injury risks to guide the design of protection or evaluate injury.
Continuation for Block 13

ARO Report Number 58155.52-LS-MUR
Brain injury risk from primary blast ...
Brain injury risk from primary blast

Karin A. Rafaels, PhD, Cameron R. 'Dale' Bass, PhD, Matthew B. Panzer, MA Sc, Robert S. Salzar, PhD, William A. Woods, MD, Sanford H. Feldman, DVM, PhD, Tim Wallko, PhD, Richard W. Kent, PhD, Bruce P. Capehart, MD, Jonathan B. Foster, BS, Burcu Derkunt, BS, and Amanda Toman, BS, Aberdeen, Maryland

BACKGROUND: Military service members are often exposed to at least one explosive event, and many blast-exposed veterans present with symptoms of traumatic brain injury. However, there is little information on the intensity and duration of blast necessary to cause brain injury.

METHODS: Varying intensity shock tube blasts were focused on the head of anesthetized ferrets, whose thorax and abdomen were protected. Injury evaluations included physiologic consequences, gross necropsy, and histologic diagnosis. The resulting apnea, meningeal bleeding, and fatigue were analyzed using logistic regression to determine injury risk functions.

RESULTS: Increasing severity of blast exposure demonstrated increasing apnea immediately after the blast. Gross necropsy revealed hemorrhages, frequently near the brain stem, at the highest blast intensities. Apnea, bleeding, and fatigue risk functions from blast exposure to the head were determined for peak overpressure and positive-phase duration. The 50% risk of apnea and moderate hemorrhage were similar, whereas the 50% risk of mild hemorrhage was independent of duration and required lower overpressures (144 kPa). Another fatigue risk function was determined with existing data for scaled positive-phase durations from 1 microsecond to 20 milliseconds.

CONCLUSION: The first primary blast brain injury risk assessments for mild and moderate/severe injuries in a gyrocerebral animal model were determined. The blast level needed to cause a mild/moderate brain injury may be similar to or less than that needed for pulmonary injury. The risk functions can be used in future research for blast brain injury by providing realistic injury risks to guide the design of protection or evaluate injury. (J Trauma Acute Care Surg. 2012;73: 985-901. Copyright © 2012 by Lippincott Williams & Wilkins)

KEY WORDS: Primary blast; brain injury; injury risk; ferret.

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bound for blast brain injury tolerance but did not address mild traumatic brain injury.

The current state of understanding of blast brain injury is certainly lacking: the mechanisms of the injury are inconclusive, the diagnosis is often difficult, the frequency of incidence is thought to be underreported, and the treatment plan is uncertain. Focusing on the overpressure and duration aspect of blast provides a reasonable quantification of the blast severity and can be related to previous research done with primary blast injury for the pulmonary system (cf 17). The goal of this study was to define the risk of intracranial hemorrhage and cardiorespiratory instability after exposure to a simulated blast, using a range of blast exposures that are relatable to real-world events.

**MATERIALS AND METHODS**

Sixty-four male ferrets (*Mustela putorius furo*) were grouped into a blast exposed group (n = 61) or a control group (n = 3). The ferret model was selected for this study because, unlike rodents or lagomorphs (e.g., rabbits), the ferret has a gyrencephalic cerebral cortex. In this study, the cerebral cortex of a ferret demonstrates a greater percentage of cerebral cortex thickness for supragranular neurons compared with a rodent. The Mean (SD) of body mass and head circumference are 1.2 (0.2) kg and 15.3 (1.0) cm, respectively. The experimental protocol was approved by the University of Virginia Animal Care and Use Committee.

Before anesthetic induction, glycopyrrolate (0.1 milligram per kilogram body weight subcutaneously administered; Robinul, Baxter Pharmaceutical, Deerfield, IL) was administered to diminish secretions in the upper and lower respiratory system. General anesthesia was induced with an intraperitoneal injection of urethane (1,500 milligram per kilogram body weight of a solution containing 0.5-g/ml urethane; Sigma-Aldrich, St. Louis, MO) and maintained with intermittent urethane injections of 150 mg/kg intravenously administered as needed based on jaw tension and/or toe pinch response. An endotracheal tube was inserted to allow for airway management in the event of apnea, with apnea defined as 10 seconds without spontaneous respiration.

The electrocardiogram was continuously monitored throughout the duration of the test. With the exception of approximately 5 minutes surrounding the blast exposure, heart rate and pulse oximetry were also continuously monitored. Body temperature was maintained at between 38°C and 40°C using heating pads or blankets. Arterial and venous lines were placed in the cephalic veins and/or tail vein to facilitate the drawing of blood at various stages of the experiment and to provide locations for the administration of medications. Blood samples were taken before and immediately after the blast exposure, 1 hour after the exposure, and 5 hours after the exposure for animals surviving to that time.

**Shock Tube and Test Fixure**

An 8-inch diameter shock tube was used to generate an overpressure shock wave that simulated free-field blasts as described by Rafaei et al. These blast waves were characterized by a sharp rising, exponentially decaying overpressure pulse. The ferrets were placed and secured into a rigid test fixture (see Figure, Supplemental Digital Content 1, http://links.lww.com/TA/A143) designed to protect the animal's body from the shock overpressure and to expose only the head, similar to the methods described by Rafaei et al. However, in this study, a 2-inch thick section of America Mat foam (Soundproofing America, Inc., San Marcos, CA) was used in place of the foam used in the study of Rafaei et al. Measurements taken in the steel tube indicate pressure reductions of more than 85% from the incident value, often near 98% reduction. The center of the head was placed approximately 3.8 cm from the opening of the shock tube.

Owing to physical constraints, the ferret position relative to the tube entrance in the direction of the propagation of the shock had a SD value of 111 mm across the data set. To derive overpressure conditions at the ferret location, a finite element blast model was used to provide overpressure and duration relative to the end of tube conditions. The correction for this effect was small, with a mean (SD) of 0.6% (0.4%) of the measured incident peak overpressure and 8.0% (5.1%) of the measured positive-phase duration.

**Species Mass Scaling**

Pulmonary blast injury research has historically used scaling based on positive-phase duration to differences in mass between animal surrogate and human (e.g., 13). This scaling principle has also been used widely in low-rate impact biomechanics. Consequently, this approach was also used in this study to account for the variation of brain size between species. There is, however, insufficient published blast blast test data to fully establish whether this procedure is appropriate for brain blast injuries. The mass scale factor is calculated using a simple dimensional relationship such that positive-phase duration is scaled using the cube root of body mass (Eq. 1). All results in this study were scaled to a reference mass of a 70-kg human.

\[
\Delta t_{scaled} = \lambda \Delta t, \quad \text{where} \quad \lambda = \left(\frac{M_{ref}}{M}\right)^\frac{1}{3}
\]

**Postexposure Evaluation**

Continuous electrocardiogram monitoring did not find any episodes of cardiac arrest during the blast exposure. Euthanasia was performed at 5 hours after the exposure or earlier if the clinical condition after the blast deteriorated despite resuscitation efforts. Heparin (APP Pharmaceuticals, Schaumburg, IL) was injected immediately at the start of euthanasia to reduce clotting during the perfusion fixation technique. A thoracotomy was performed to gain access to the heart, and the euthanasia solution (VirHac A4H, Inc., Fort Worth, TX) was administered. From an incision in the left ventricle, a cannula was inserted into the ascending aorta. The heart was perfused with saline at physiologic rates of flow out of the right atrium. After the saline flush, the perfusate was perfused with approximately 1 L of 0.1 mol/L phosphate buffer containing 4% paraformaldehyde (Electron Microscopy Sciences, Hatfield, PA). After perfusion fixation, the organs were examined macroscopically for gross changes, excised, and immersed in the paraformaldehyde solution for subsequent
TABLE 1. Test Conditions/Survival and Injury Assessment, Organized by the Severity of Brain Hemorrhage, Followed by Apnea, then Survival, and Finally Peak Incident Overpressure

<table>
<thead>
<tr>
<th>Subject</th>
<th>Peak Incident Overpressure, kPa</th>
<th>Scaled Duration, ms</th>
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microscopic study. The fixed organs were embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The stained sections were then examined using light microscopy.

Photographs of the brain and cranial vault taken during extraction of the brain were analyzed to grade cerebral hemorrhage severity. Surface area of the hemorrhages, the entire brain, and the cranial vault were calculated using ImageJ to obtain a normalized area of hemorrhaging. Hemorrhages were graded as none (no visible bleeding) or mild, moderate, and severe for the normalized area of hemorrhage (3%, 3-10%, and >10% of the dorsal and ventral brain surface, respectively).

Measures and Data Analysis

The primary measure of blast risk was fatality, which was measured as euthanasia before 5 hours after the blast or euthanasia at the 5-hour mark. Secondary measures include the presence of apnea after the blast and the grading of brain hemorrhages (none, mild, moderate, and severe). Risk functions for the outcome measures (Eq. 2, showing the example for fatality risk) were determined from experimental results by logistic regression (LogXact 8, Cytel Inc., Cambridge, MA). The regression model fit was assessed using the area under the receiver operating characteristic (ROC) curve for measuring the sensitivity versus 1 − specificity of the model fit and the Hosmer-Lemeshow goodness-of-fit statistic.

\[
\log \left( \frac{Pr(fatality \mid P_1)}{1 - Pr(fatality \mid P_1)} \right) = \beta_0 + \beta_1 P_1 + \beta_2 D_1
\]

RESULTS

A summary of the test conditions and the outcomes are shown in Table 1. Blast positive-pressure phase duration demonstrated an influence upon apnea. For shock tube exposures with scaled blast durations less than 8.5 milliseconds, all
peak incident overpressures greater than 625 kPa resulted in
immediate apnea, whereas all exposures to peak incident blast
overpressures less than 418 kPa did not experience immediate
apnea. For scaled blast durations greater than 8.5 milliseconds,
all peak incident pressures greater than 226 kPa experienced
immediate apnea, but peak incident pressure less than 197 kPa
did not cause apnea.

There were seven fatalities in the data set, concentrated
among the more severe exposure levels for both short and long
durations. The animals that did not survive 5 hours after the blast,
despite mechanical ventilation and administration of doxapram
(Dopram-V, Fort Dodge, Overland Park, KS), demonstrated a
similar clinical progression characterized by declining oxygen
saturation levels before bradycardia that progressed to asystole.
Intracranial hemorrhage, including subdural and subarachnoid
hemorrhage, and cerebral contusions were found in nonsurvivors,
often in the area on or around the brain stem. The calvarium
remained intact for all blast pressure and duration levels with
any evidence of fracture.

No serious pulmonary or gastrointestinal injuries were
found during the necropsy, indicating that the thorax was
suitably protected for the blast overpressure levels used in these
tests. Hematoxylin and eosin-stained tissue at the highest blast
levels demonstrated seven ferrets with minor intra-alveolar
pulmonary hemorrhage. Thirteen ferrets demonstrated minor
transmural, intramural, or submucosal hemorrhages in the
trachea, five of which also demonstrated lung injury. Micro-
sopic inspection of the liver, kidneys, stomach, spleen, and gut
did not reveal any pathologic findings.

Injury Criteria

The logistic regression for the 50% risk of mild and
moderate/severe subdural/subarachnoid bleeding for the ferrets
in this study is shown in Figure 1A. For reference, the pul-
monary blast fatality and threshold injury assessments of Bass
et al.14 are also included in the figures. Parameters for the re-
gression model with model statistics are shown in Table 2. For
mild bleeding, the coefficient for scaled duration ($\beta_2, p = 0.15$)
was not statistically significant, so a second model was fit
without scaled duration dependence. In both models, the
constant ($\beta_0$) and pressure coefficient ($\beta_1$) were
statistically significant ($p < 0.05$). The mild bleeding risk model
with no duration has good sensitivity and specificity with an
area under the ROC curve of 0.76. For this model, the Hosmer-
Lemeshow goodness-of-fit statistic indicates that there is no
evidence of a lack of model fit ($p > 0.2$). For moderate/severe
subdural/subarachnoid bleeding, all model coefficients were
statistically significant ($p < 0.0$). Furthermore, the model had
good sensitivity and specificity with an area under the ROC
curve of 0.81, and the Hosmer-Lemeshow statistic did not
exclude a fit ($p > 0.8$).

The model for 50% risk of initial apnea is shown in
Figure 1B. The apnea model has statistically significant
regression coefficients ($p < 0.01$). Furthermore, the model had
good sensitivity and specificity with an area under the ROC
curve of 0.91, and the Hosmer-Lemeshow statistic did not
exclude a fit ($p > 0.7$). For the fatality model with ferrets,
the pressure coefficient ($\beta_1$) was not statistically significant
($p = 0.051$). A second fatality model was fit with the addition
of scaled rabbit fatality data acquired using the same test
methodology.26 This model had statistically significant coefficients
($p < 0.01$), the area under the ROC curve was 0.91, indicating
a good sensitivity and specificity, and the Hosmer-Lemeshow
statistic did not exclude a fit ($p > 0.7$).

DISCUSSION

Typical injury metrics for unprotected blast have been
based on pulmonary or gastrointestinal injuries. Previous blast
research has long suggested that, at least for fatalities, the brain
is more tolerant to blast loading than the lungs or gastrointes-
tinal tract.57 However, there were no previous risk functions
for brain injury from primary blast. A few previous studies have
offered protection to the blast-sensitive thoracic and abdo-
menal regions while administering an isolated blast to the
head.20,28,31 These studies used blast pressure and duration
levels that would have likely exhibited significant pulmonary
injuries, yet the results demonstrated little evidence of brain
injury. Based on the observation that the heads and thoraces of
the experimental animals in primary blast pulmonary injury
criteria evaluations were given simultaneous exposure to the
blast, it appears likely that primary blast brain fatality may
be bounded by the primary blast pulmonary injury criteria
(e.g., 17). Blast exposure to the unprotected thorax and head
will result in fatal pulmonary injury at pressure and duration
levels less than that required to produce significant brain ab-
normality, an observation that may not be true when the thorax
and abdomen are protected. A comparison of the peak incident

Figure 1. Logistic risk functions, $n = 64$. A, Logistic risk function (50%) for mild and moderate/severe meningeal bleeding from
exposure to primary blast waves. B, Logistic risk function (50%) for initial apnea from exposure to primary blast waves.
overpressure and scaled blast duration in this study with our previous pulmonary injury risk assessment shows that the blast injury sensitivities of lung and brain are different, with the brain demonstrating a greater tolerance than that of the lung for primary blast injury (Fig. 2) at durations less than approximately 18 milliseconds. In this study, the majority (73%) of blast brain exposures that exceeded the 1% pulmonary survival curve survived. The results of this study indicate that the blast brain injury fatality tolerance is much greater than the pulmonary fatality tolerance when the thorax and abdomen are protected from blast. At the lowest positive-phase durations, the 50% fatality risk function for blast overpressure to the brain was more than twice the overpressure level for the same pulmonary lethality risk.

For nonfatal injuries, the 50% injury risk for mild intracranial bleeding occurred at peak overpressure values comparable to those for low probability fatal and threshold pulmonary injury, especially at positive-phase blast durations of 2 milliseconds or less. This suggests that human brain injuries, especially brain injuries that might result in altered cognition and/or emotion, may occur at peak overpressure levels lower than that necessary for pulmonary fatalities. In current military conflicts, the almost universal use of body armor generally acts to increase the effective tolerance of the pulmonary system relative to the brain. Wood et al. found that ballistic protective vests with hard body armor decreased the overpressure applied to the torso by a factor of 50 or more and decreased the overpressure rise time, with both effects substantially increasing the blast level required to create pulmonary injury. In fact, for ballistic armor with ceramic plates, the pulmonary injury threshold while wearing the vest was greater than the unprotected head 1% survival curve, indicating that the occurrence of pulmonary injuries from blast would be greatly diminished. An available human epidemiologic primary blast injury case with a M107 round from Raiaa et al. is compared with previous blast experiments with protected thoraces. These previous data are consistent with the case report and current fatality criteria reported in this study.

In addition to determining risk curves, several pathophysiological consequences were characterized. For instance, the bradycardia and apnea that were observed are not unique to isolated blast exposures to the head but have also been seen in blast exposure studies of the thorax. For thoracic blast exposures, it is thought that pulmonary congestion and edema in the intrathoracic space from blast lung injury stimulate the nerve endings of vagus nerve. The signals then reach the brain, causing a reflex response of increased cholinergic activity to induce the bradycardia and apnea. For isolated exposures to the head, it seems that injury to the brain, or medulla oblongata, could also cause downstream effects along the vagal pathway. Next, typical injuries seen during the tests were associated with subarachnoid and subdural bleeding as well as small contusions throughout the brain. This injury pattern suggests a mechanism of small displacement but rapid compression of the skull, leading to intracranial bleeding, as skull fracture was not seen in any tests.

Some of these pathophysiological consequences can be useful clinical measures for blast brain injury. Apnea is a good pathophysiological measure of blast brain injury because it is dependent on the amount of energy transmitted to the brain and has been shown to be a better predictor for the outcome from TBI than does the mechanism of the brain injury itself. Hemorrhagic lesions can also be a useful pathophysiological measure because lesion size has been related to brain injury severity for traditional TBI.

Results of this study may be helpful in attempts to mitigate blast injury among personnel at risk for such exposure. When applying the results of this study to humans, the principle unknown is the effect of body mass scaling. Although there is substantial evidence that such scaling is appropriate for blast impact (cf 24), its use in scaling blast injuries has not been completely validated. For example, both histologic and behavioral evidence of blast brain injury in rodents has been reported at incident pressure levels less than 20 kPa for very long scaled positive-phase durations. Further investigation into interspecies scaling for blast injuries will clarify questions related to blast scaling and perhaps also address the

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Table 2. Logistic Regression Model Coefficients (Mean [SD] Values) and Model Fit Statistics

<table>
<thead>
<tr>
<th>Model</th>
<th>Regression Coefficients</th>
<th>Model Fit Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta_0$</td>
<td>$p$</td>
</tr>
<tr>
<td>Mild bleeding (no duration)</td>
<td>-8.7 (3.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mild bleeding (with duration)</td>
<td>-10.6 (4.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Moderate/severe bleeding</td>
<td>-21.4 (6.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Apnea</td>
<td>-39.8 (10.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fatality</td>
<td>-34.4 (14.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Fatality with rabbit data (Raiaa et al.)</td>
<td>-45.0 (14.4)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

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Figure 2. Logistic risk function (50%) for fatality from exposure to primary blast waves with scaled rabbit data (Raiaa et al.) (ferret, $n = 64$; rabbit $n = 12$).

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possibility of differential physiologic and behavioral response by species. These experimental results were scaled to hypothetical human blast exposures, including determining the amount of explosive required to generate the corresponding blast wave. The Conventional Weapons Effects Program (ConWep), a computer program for calculating weapons effects, was used to compare these simulated blasts to real-world blast scenarios. The calculations indicate that the blast loads can be produced by free field blasts of ten to twenty thousand cubic metres of trinitrotoluene (see Figure, Supplemental Digital Content 2, http://links.lww.com/TA/A144), corresponding to real-world hemispherical blasts with charge sizes between 1 kg and approximately 800 kg of trinitrotoluene at standoff distances of 2.5 m to 20 m, which are realistic charge sizes and distances for terrorist attacks or combat scenarios. Future investigations are necessary to validate the mass scaling principles used in this study and to investigate additional histologic, physiologic, and behavioral injury criteria.

AUTHORSHIP

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DISCLOSURE
The authors declare no conflicts of interest.

REFERENCES

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