The Selective Vulnerability of Foramen Magnum to Blast-TBI

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ABSTRACT

Over half of injuries in combat are caused by explosives, and blast-induced traumatic brain injury (blast-TBI) is one of the most serious wounds suffered. The skull's structure suggests that certain regions may be less protective, serving as portals of entry for a blast wave. We hypothesized that the foramen magnum is such an area of vulnerability. Using our recently described rodent cranium-only blast apparatus, which delivers a collimated blast wave, we compared brain injury when a blast wave is delivered to the foramen magnum by centering the blast over the occipital crest (caudal position) vs. when centered anteriorly and delivered to the full thickness skull (rostral position). In the caudal group, the LD50 was 785kPa peak overpressure, while the rostral group had zero mortality up to 1880kPa. Caudal blast injury was characterized by massive subdural hemorrhages, significant oxygen saturation abnormalities immediately after blast, and vestibulomotor deficits 24 hours later. Survivors of caudal blast exposure were sacrificed at 24 hours and the brains were studied with immunohistochemistry for Iba1, GFAP, and stained for FluoroJadeC. Caudal blast exposure resulted in: 1) widespread microglia/macrophage activation in the brainstem, cerebellum, and hippocampus; 2) reactive astrocytosis in the brainstem and cerebellum; and 3) neurodegeneration in the brainstem. These results indicate that the foramen magnum region is selectively vulnerable to blast wave exposure.

INTRODUCTION

Over half of injuries in combat are caused by explosives, and blast-induced traumatic brain injury (blast-TBI) is one of the most serious injuries. The skull's structure suggests that certain regions may serve as portals for a blast wave. We hypothesized that the foramen magnum is such an area of vulnerability.

METHODS

COBIA

Using our recently described rodent Cranium-Only Blast Injury Apparatus (Kuehn et al. 2011), which delivers a collimated blast wave, we compared brain injury when a blast wave is delivered to the foramen magnum by centering the blast over the occipital crest (caudal position) vs. when centered anteriorly and delivered to the full thickness skull (rostral position). Sham-injured animals (anesthesia and injury site prep only) were used as controls. The blast wave was generated by firing a .22 caliber crimped brass cartridge (power hammer load, "power level" 4 or 2, yellow or green color coding respectively; 179±5 or 129±5 mg of smokeless powder respectively). A "blast dissipation chamber" (BDC), of varying lengths, was used in the present experiments, yielding peak overpressures of 668 to 1880 kPa when measured at the aperture of the BDC-thoracic interface. In the first series of rats, survivors of blast exposure were sacrificed at 24 hours and the brains were studied with immunohistochemistry for Iba1, GFAP, and stained for FluoroJadeC. In the second series, animals were followed out to 28 days post-injury with neurobehavioral testing, including vertical rearing, accelerating rotarod, beam walk, beam balance, and Morris water maze.

Blast injury procedure

All procedures were approved by the Institutional Animal Care and Use Committee of the University of Maryland School of Medicine. This research was conducted in compliance with the Animal Welfare Act Regulations and other Federal statutes relating to animals and experiments involving animals and adheres to the principles set forth in the Guide for Care and Use of Laboratory Animals, National Research Council, 1996. Male Long-Evans rats (290-310 gm; Harlan, Indianapolis, IN) were anesthetized (60 mg/kg ketamine plus 7.5 mg/kg xylazine, intraperitoneally) and were allowed to breathe room air spontaneously. Core temperature was maintained at 37° C. After blast rat was observed for apnea. For sham injury, the above procedures were performed, except that the cartridge was not detonated.

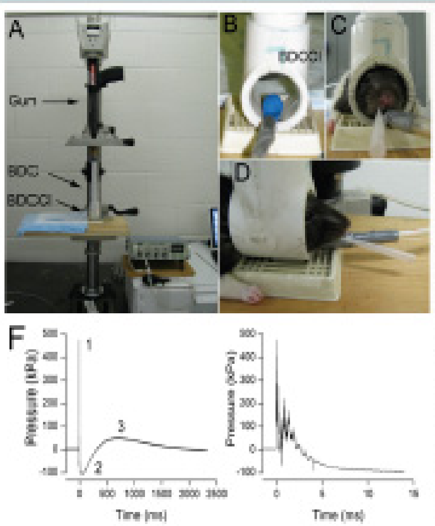


Figure 1. COBIA and the blast wave produced by COBIA. A,B: Overview (A) and close-up view (B,C,D) of COBIA with the rat positioned for blast injury. BDC, blast dissipation chamber; BDCCI, blast dissipation chamber cranium interface. E: BDC chambers of different lengths, BDCCI and BDC-gun interface on the left. F: Blast wave produced by COBIA shown at low and high temporal resolution; note the specific characteristics of the blast wave, including the initial brief peak overpressure (1), the underpressure (2) and the secondary slower overpressure (3), resemble closely the characteristic features of a free-field explosive blast (see Fig 2 in Ling et al.).

Figure 3 (Right). Blast injury in the caudal position is associated with subdural hemorrhage. Subdural hemorrhages were not observed in any subject in the rostral group. Subdural hemorrhages were observed in the caudal group in 16 out of 18 cases at 24 hours post-injury. Chronic subdural hemorrhages were observed in 3 out of 7 rats at 29 days post-blast injury. The top row (A-C) indicate animals blasted in the rostral position. The bottom row (D-F) indicate animals blasted in the caudal position. The left-most column (A,D) shows blast residue immediately post-blast. White circles indicate BDC position, and black lines indicate the occipital crest. The middle column (B,E) show brains of rats euthanized and harvested 24 hours post-blast and were blasted at 1349 kPa. The right-most column (C,F) show brains of rats harvested 24 hours post-blast at 762 kPa.

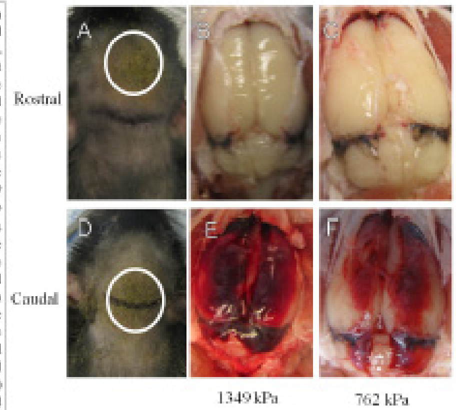
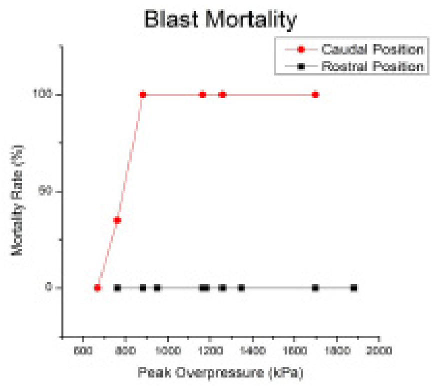


Figure 4 (Right). Caudal blast injury is associated with an LD50 of 785 kPa, while rostral blast injury has no mortality up to 1880 kPa. For all points, n≥3. At 762 kPa, n=28 in the caudal group, n=16 in the rostral group.



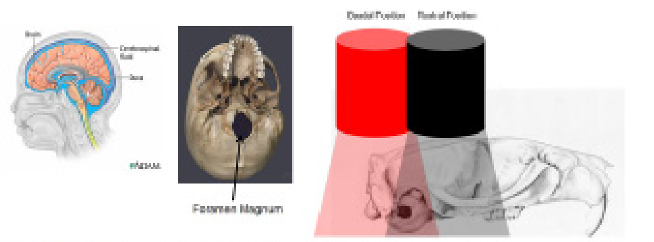


Figure 2 (Above). Skull anatomy and positioning of the blast wave. A-C: (A) Figure showing the ventricular system of the human brain. (B) Figure showing a human skull, with an arrow pointing to foramen magnum. (C) Figure indicating the positioning of the BDC aperture (solid) and the projection of the blast wave (transparent). The caudal position is colored in red while the rostral position is colored in black.

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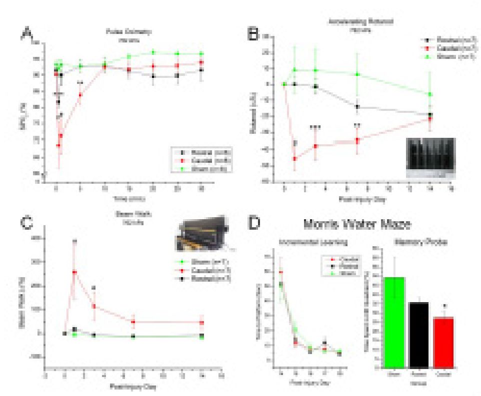

Figure 5 (left). Caudal blast injury results in oxygen saturation deficits up to 5 minutes post-injury, neuromotor deficits up to 7 days post-injury, and memory deficits 19 days post-injury. $^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; $^{\#}p<0.0001$. For all plots, sham-injured (green triangles), caudal (red circles), and rostral-injured rats (black squares) are shown. **A:** Time course of O_2 saturation (mean±SE), measured by pulse oxymetry. **B:** Time course of Accelerating Rotarod performance vs. day after injury. Change from baseline is shown as a percentage. **C:** Time course of beam walk performance vs. day after injury. **D:** Morris Water Maze performance is shown. Time to hidden platform is shown (left, mean±SE). Time spent in quadrant with platform removed is shown as a percentage of the first 30 seconds in the pool (right, mean±SE).

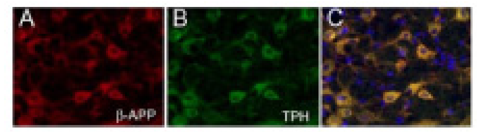

Figure 6. Blast injury in the foramen magnum area is associated with neurodegeneration in the dorsal raphe. A-C: Sections immunolabelled for β-APP (A) or Tryptophan Hydroxylase (B). A superimposed image is shown in C.

Figure 7 (left). Blast injury in the foramen magnum area is associated with cerebellar reactive astrocytosis. Cerebellar sections of brains with sham (A), rostral (B), or caudal (C) injury harvested 5 days post-blast and labelled with GFAP.

Figure 8 (left). Blast injury in the foramen magnum area is associated with hippocampal reactive astrocytosis. Hippocampal sections of brains with sham (A), rostral (B), or caudal (C) injury harvested 5 days post-blast and labelled with GFAP.

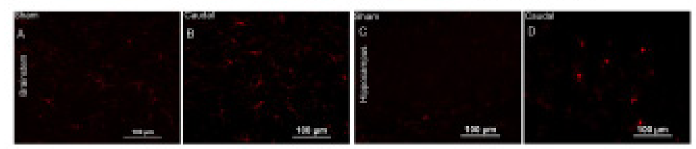

Figure 9 (above). Blast injury in the foramen magnum area is associated with microglia activation. Brainstem (A-B) or hippocampal (C-D) sections of brains harvested 24 hours post-blast and immunolabelled with Iba1.

CONCLUSION:

Numerous mechanisms by which blast waves alone cause neural injury have been proposed, ranging from thoracic transmission of the blast wave via major cervical blood vessels to direct interaction of the blast wave with the skull and with neural tissues. Our results suggest that a hydrodynamic pulse initiated in the CSF column by the blast wave is a key mechanism in blast-TBI, and that the foramen magnum region is selectively vulnerable to blast wave exposure.

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