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Modeling clinically relevant blast parameters based on scaling principles produces functional & histological deficits in rats

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ABSTRACT

Blast-induced traumatic brain injury represents a leading cause of injury in modern warfare with injury pathogenesis poorly understood. Preclinical models of blast injury remain poorly standardized across laboratories and the clinical relevance unclear based upon pulmonary injury scaling laws. Models capable of high peak overpressures and of short duration may better replicate clinical exposure when scaling principles are considered. In this work we demonstrate a tabletop shock tube model capable of high peak overpressures and of short duration. By varying the thickness of the polyester membrane, peak overpressure can be controlled. We used membranes with a thickness of 0.003, 0.005, 0.007, and 0.010 in to generate peak reflected overpressures of 31.47, 50.72, 72.05, and 90.10 PSI, respectively. Blast exposure was shown to decrease total activity and produce neural degeneration as indicated by fluoro-jade B staining. Similarly, blast exposure resulted in increased glial activation as indicated by an increase in the number of glial fibrillary acidic protein expressing astrocytes compared to control within the corpus callosum, the region of greatest apparent injury following blast exposure. Similar findings were observed with regard to activated microglia, some of which displayed phagocytic-like morphology within the corpus callosum following blast exposure, particularly with higher peak overpressures. Furthermore, hematoxylin and eosin staining showed the presence of red blood cells within the parenchyma and red, swollen neurons following blast injury. Exposure to blast with 90.10 PSI peak reflected overpressure resulted in immediate mortality associated with extensive intracranial bleeding. This work demonstrates one of the first examples of blast-induced brain injury in the rodent when exposed to a blast wave scaled from human exposure based on scaling principles derived from pulmonary injury lethality curves.

Introduction

Blast-induced traumatic brain injury has been described as the hallmark injury of modern warfare (Elder and Cristian, 2009; Nakagawa et al., 2011) with ~25,000 members of the armed services (U.S. and Coalition forces) injured or killed by explosive devices in Iraq and Afghanistan conflicts in the past decade (Champion et al., 2009). The prevalence of blast exposure is associated with an immense financial and societal burden with estimates of 13–22% of combat veterans having sustained a traumatic brain injury (TBI) during time in service (Panzer et al., 2012; Schneiderman et al., 2008; Terrio et al., 2009). Consequently, there is a clear clinical need for increased understanding of blast injury pathogenesis and the development of improved therapeutics for the treatment, or prevention, of blast-induced brain injury. Increasing efforts to study blast injury has resulted in the propagation of numerous preclinical models of blast injury with the shock tube representing the most widely used model type. Despite the extensive use of shock tube models, model parameters such as size of the driver and driven sections, membrane material and thickness, and gas used seem to vary across laboratories. As such, the shock waves produced vary significantly in peak overpressure and duration.

Recent work by Panzer and colleagues has identified potential discrepancies between many preclinical models and real-world recorded blast parameters with models often exposing small rodents to long duration blasts (Panzer et al., 2012). Assuming the same scaling principles apply as those discovered with regard to pulmonary blast injury, many current rodent models, in which overpressure exposure durations frequently exceed 4 ms and in some cases as much as 10 ms or more, may be subjecting animals to the equivalent of a human exposed to detonation of 27,000-kg of TNT from over 70 m away (Panzer et al., 2012). In other words, many preclinical models may be exposing animals to

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the equivalent of long-duration nuclear blasts rather than the more common high explosive blasts (Bass et al., 2012). Therefore, a preclinical blast model capable of delivering high peak overpressures over a short duration may be of value, particularly should similar scaling laws exist in the brain, as is the case in pulmonary-based work.

In this work we demonstrate the ability to model blast injury with clinically relevant peak overpressure and duration based on scaling laws from humans to rodents with a novel, tabletop shock tube model. Furthermore, we show the ability to model blast injury of varying severity with different polyester membranes that result in reflected peak overpressures ranging from approximately 30–90 PSI while consistently being of short duration (<3 ms). Animals exposed to blast-induced traumatic brain injury across this range of pressures exhibit alterations in total activity as well as clear histological changes as determined utilizing common markers of neural injury.

Methods

Animals

All procedures involving live animals were approved by the Institutional Animal Care and Use Committee of West Virginia University and were performed according to the principles of the *Guide for the Care and Use of Laboratory Animals*. This worked used thirty-eight 350 g male animals acquired from Hilltop Lab Animals (Hilltop Lab Animals, Inc.). Animals were acclimated for 1 week prior to experimental use and were housed under 12-hour light/12-hour dark conditions with food and water available *ad libitum*.

Design of blast model

A 4-piece, machined aluminum shock tube apparatus was constructed and driven using compressed nitrogen gas. The driver and driven sections were separated by clear polyester membranes (Ridout Plastics Co.) of varying thickness (0.003″–0.010″) to achieve a range of peak overpressure exposures. A tapered design of the driver section (Fig. 1) was included in an effort to minimize wave reflection and alterations of the blast wave by the expansion wave. This feature is similar in nature to blast tubes utilizing explosives in which the explosive is often detonated in a conical or parabolic-shaped driver section. The driver section was kept short in length (overall length = 6.7″; taper length = 4.63″; diameter = 2.8″) in an effort to reduce the amount of gas required for membrane rupture and subsequent blast duration, regardless of membrane thickness. The overpressure duration and impulse are reduced as described previously due to the shortened driver section (Bass et al., 2012). For additional details concerning design of the blast model, please see Supplemental information.

Blast waveform acquisition & analysis

Shock wave pressures were detected using piezoelectric sensors (PCB Piezotronics) that were placed in both reflected and incident positions at the exit of the shock tube (Fig. 1). Data was acquired and processed using the National Instruments input module (NI 9223) connected to the National Instruments receiver USB chassis (CDAQ-9171). Signals were recorded using a custom-designed Labview 12.0 program and the NI data acquisition system (National Instrument) with a sampling rate of 500 kHz as described previously (Ahlers et al., 2012; Chavko et al., 2011).

Blast exposure

Prior to blast exposure, animals were anesthetized by intraperitoneal injection of ketamine (90 mg/kg; Webster Veterinary) and xylazine (5 mg/kg; Webster Veterinary). Animals were oriented with the long axis of the animal perpendicular to the blast front. In other words, the blast was delivered side-on to the head only, with the wave first encountering the right side of the head (direct) prior to passing through

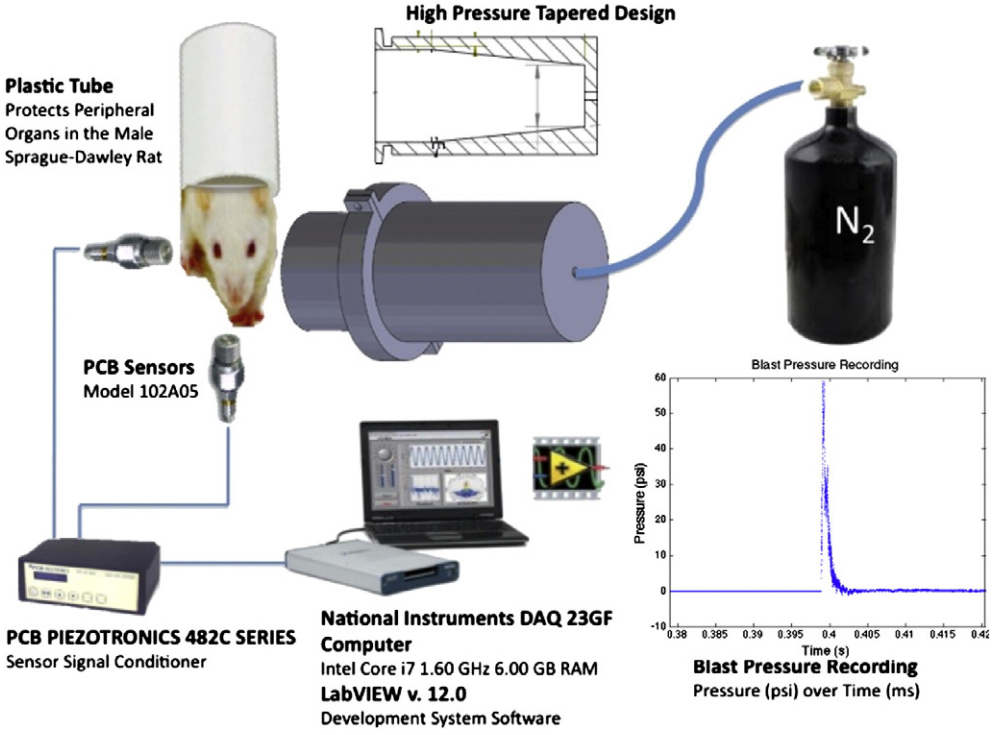

Fig. 1. Experimental setup utilized in this work demonstrating the novel shock tube apparatus for simulating blast-induced brain injury and data acquisition procedures. The shock tube utilizes a tapered driver section to reduce wave reflection and alterations of the shock wave by the expansion wave. The driver section was kept short to reduce the volume of gas required to produce membrane rupture and therefore, reduced overpressure duration and impulse. The abdomen and thorax of animals were protected using a rigid apparatus. Note: the orientation of the animal has been inverted for illustration purposes but the blast was delivered to the right side of the head initially rather than the left as pictured.