CEREBRAL BLOOD PRESSURE RISE DURING BLAST EXPOSURE IN A RAT MODEL OF BLAST-INDUCED TRAUMATIC BRAIN INJURY

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ABSTRACT

Blast-induced traumatic brain injury (bTBI) has been called the signature wound of war in the past decade. The mechanisms of such injuries are not yet completely understood. One of the proposed hypotheses is the transfer of pressure wave from large torso blood vessels to the cerebrovasculature as a major contributing factor to bTBI. The aim of this study was to investigate this hypothesis by measuring cerebral blood pressure rise during blast exposure and comparing two scenarios of head-only or chest-only exposures to the blast wave. The results showed that the cerebral blood pressure rise was significantly higher in chest-only exposure, and caused infiltration of blood-borne macrophages into the brain. It is concluded that a significantly high pressure wave transfers from torso to cerebrovasculature during exposure of the chest to a blast wave. This wave may lead to blood-brain barrier disruption and consequently trigger secondary neuronal damage.

INTRODUCTION

Blast injuries have been referred to as the signature wound of war in the past decade, Over 73% of US military causalities in recent operations are caused by explosive devices [1] and about 20% of troops in Iraq sustained some level of neurological impairment resulting from blast exposure [2]. The blood-brain barrier (BBB) breakdown is one of the important aftereffects of bTBI [3,4]. BBB is the mechanism that isolates brain's delicate extracellular fluid in the central nervous system (CNS) from the circulating blood and forms a protective network for the CNS. A dysfunctional BBB increases cerebrovascular permeability, causing vasogenic cerebral edema which in turn triggers secondary neuronal damage that may lead to cognitive and behavioral impairments [3,5]. This contributes to many diseases of the central nervous system, e.g., Meningitis, epilepsy, cerebral palsy, schizophrenia, Parkinson's disease, Alzheimer's disease and multiple sclerosis [5,6]. Ruptured BBB also plays an important role in the sequel that may follow the injury such as infection, ischemia, increased cranial pressure, swelling and edema. These are consequences of a complex series of interactions between vascular, cellular and biochemical systems in the brain and can last for hours to days and leave the patient in need of more intensive care and treatment and may contribute to chronic neurological disorders [7-11].

Although bTBI has been investigated in a number of studies [12-15], the injury mechanism has not yet been fully understood. Several studies have reported increase in BBB permeability after bTBI [3,4]. Some studies proposed that head exposure to blast can directly cause primary injuries [9,16], while more recent studies [1,17] and some clinical reports [18,19] hypothesized that transfer of pressure wave from large torso blood vessels to cerebrovasculature can be the major mechanism of bTBI.

A few studies reported increase in BBB permeability after bTBI which may last for days after blast exposure depending on the intensity and duration of overpressure [3,4]. It has also been shown that after closed head injury, BBB stays open up to 30 days [20]. The prolonged permeability of BBB may cause additional damage and lead to behavioral impairments. A recent study [21] of bTBI on a rat model showed that regions of BBB-rupture and axonal injury in brain were anatomically different, suggesting that their underlying mechanisms are not the same.

Since axonal injury is believed to be related to shear strain in brain tissue, it can be argued that shear strain does not result in BBB rupture. However, the arguments regarding mechanisms of BBB rupture is far from settled.

On the other hand, in hypertension related studies on small rodents [22-27], it has been shown that acute hypertension can lead to opening of the BBB. In these studies, mechanisms such as injection of circulatory stimulant hormones or vasoactive drugs, aortic coarctation and direct perfusion of saline in the circulatory system by a syringe pump have been used in order to increase the pressure in the carotid artery and subsequent arterioles and capillaries. These studies showed that a sudden change of the cerebral blood pressure can lead to opening of the BBB.

The aim of this study was to investigate the cerebral blood pressure rise in a rat model during blast exposure using a shock tube for two different blast exposure scenarios of head-only and chest-only.

MATERIALS AND METHODS

A) *Blast Wave Simulator:*

A 50-mm diameter compressed-gas (He and N_2) driven shock tube was designed and made based on the shock tube designs previously reported in the literature [4,28-32]. The shock tube has a modular driver (20-610 mm) and driven (610-1200 mm) sections (Fig. 1), capable of reproducing pressure shock waves with peak overpressure range of 60-300 kPa. This shock tube can simulate a blast wave and induce mild, moderate and severe levels of bTBI in small animals, e.g. mice and rats. The relatively small diameter of the shock tube makes it possible to target different body parts of the animal.

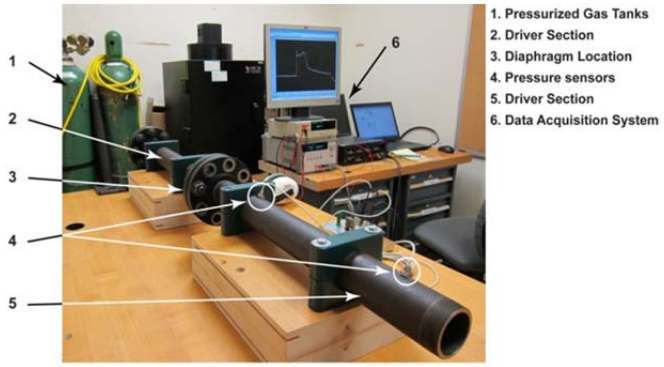

Figure 1. Shock tube experimental setup.

B) *Cerebral Blood Pressure measurement:*

Sprague-Dawley rat was chosen for this study because it has the most similar arterial circle (the Circle of Willis) to human among all rat species. Young adult rats (350-450g) were exposed to overpressure peaks of 65, 110, 160, and 185 kPa with two different "Head-Only" and "Chest-Only" exposure scenarios, such that the rest of body was shielded and protected from exposure to the shock wave (body surface pressure was measured to be less than 7kPa). In order to measure cerebral blood pressure, a cutting-edge miniature 1F (0.33 mm) pressure sensor (SPR-1000, Millar Instruments Inc., Houston, TX) was inserted in the internal carotid artery (ICA, diameter of about 0.7 mm in rats) before the arterial circle (the Circle of Willis). After proper anesthesia, a 30-mm incision was made in the anterior neck, and the right common carotid artery (CCA) and vagus nerve were exposed. Immediately before the bifurcation of CCA to ICA and external carotid artery, the artery was carefully separated from the nerve. After clamping the CCA using two vessel clips and two loosely tied sutures, a V-cut was made and the pressure catheter was inserted inside the artery and pushed toward the Circle of Willis and then sutures were tied tightly around the artery and catheter. Then the catheter was connected to the data acquisition system for real time observation of blood pressure, and proper positioning of the catheter was assured by observation of blood pressure pulsation. The surgery wound was closed by sutures and the animal was secured in a custom-made holder in front of the shock tube. Right ICA was instrumented and the animal was exposed to the blast from the left side to prevent any artifact.

C) *Histology Method:*

Immunohistochemical staining was assessed to investigate and compare the macrophage infiltration into the brain through the cerebral vessels (anti-CD68) in the two previously described exposure scenarios. Two groups of 4 animals (head-only or chest-only) were exposed to a 110 kPa peak overpressure for histological studies. One week post injury, animals were transcardially perfused with 4% paraformaldehyde and their brains were harvested and immersion fixed overnight. The brains were placed into 30% sucrose to prevent freeze artifact, and frozen sectioned into 40-µm thick coronal slices. The results are reported for two anatomical regions in the hippocampus (CA2) and the primary motor cortex (M1) as shown in Fig. 2.

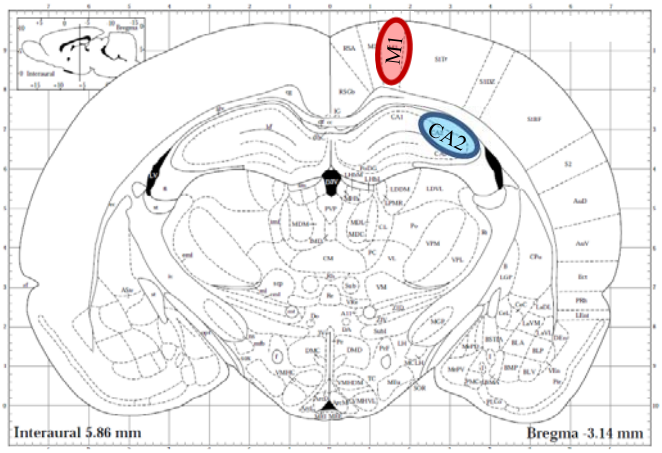

Figure 2. Injury was quantified in regions in hippocampus (CA2) and primary motor cortex (M1), utilizing Immunohistochemical staining. Photo from the Rat Brain Atlas of Paxinos & Watson.

RESULTS AND DISCUSSION

A significant cerebral blood pressure rise was observed for both head-only and chest-only exposures. Representative measured ICA blood pressures for both exposure scenarios are shown in Fig. 3. The blood pressure increased 2 to 10 times the physiological pressure (~14 kPa) and lasted for about 2 ms. Comparison of the ICA peak blood pressure for head-only and chest-only groups for four different peak overpressure are shown in Fig. 4. The pressure rise in the chest-only group was significantly higher (30%) than the head-only group, suggesting propagation of a high amplitude pressure wave from torso blood vessels to the cerebral vasculature.

Immunohistochemical staining for infiltrated blood-borne macrophages into the brain tissue showed that there was significantly more ($p < 0.05$) infiltration of macrophages into the brain tissue after chest-only exposure in comparison with head-only exposure in both CA2 and M1 regions (Fig. 5). This can be interpreted that higher level of BBB permeability is due to pressure rise in blood vessels. Further Immunohistochemical staining including APP, GFAP, and IgG are in progress.

The results of this study showed the existence of a significant pressure rise in cerebrovasculature during blast exposure. Moreover, chest exposure resulted in higher amplification of this pressure wave. In addition, observation of more infiltration of blood-borne macrophages after chest exposure could be correlated to the higher level of blood pressure rise during blast exposure. This cerebral blood pressure rise is diffusive in nature and therefore may explain the diffusive nature of brain injury after blast exposure.

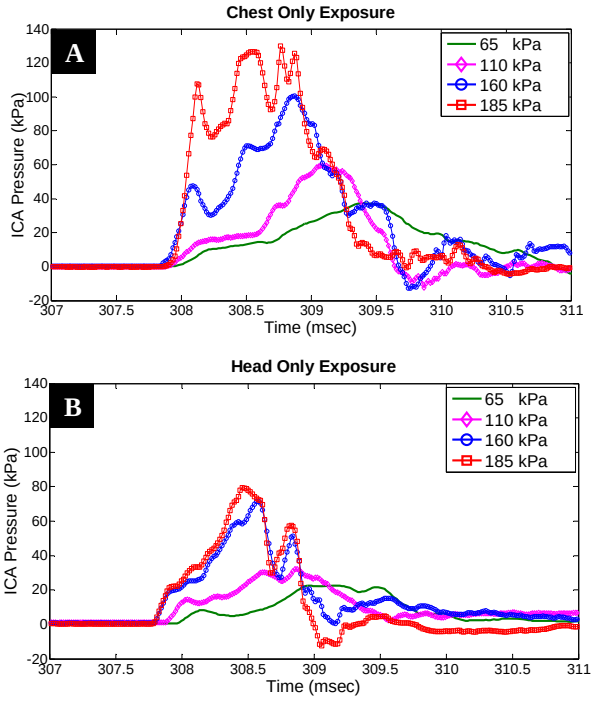

Figure 3. Representative blood pressure rise for different shock over pressures. (A) Chest-only exposure and (B) Head-only exposure.

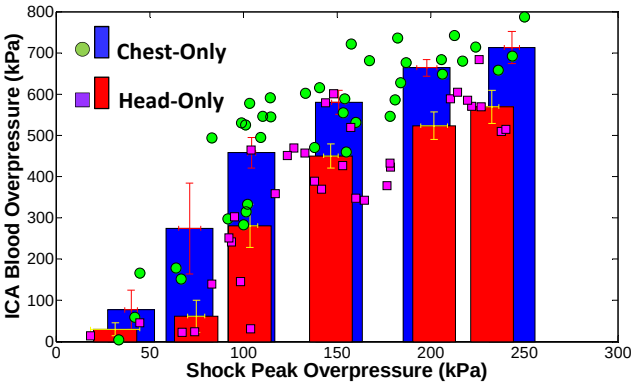

Figure 5. Comparison of peak ICA blood pressure in head-only and chest-only exposure to different shock peak overpressure.

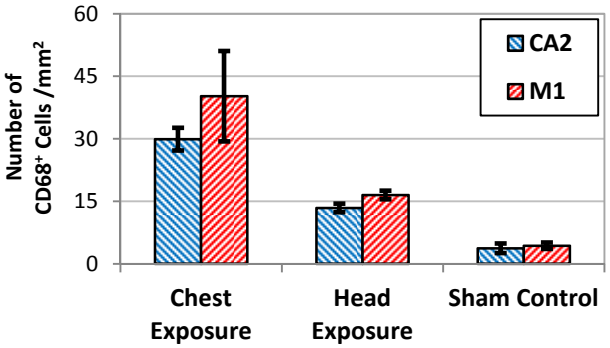

Figure 4. Immunohistochemical results for $CD68^+$ cells showing infiltrated macrophages into the brain.

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