

REVIEW

Non-impact, blast-induced mild TBI and PTSD: Concepts and caveats

YUN CHEN¹ & WEI HUANG²

¹*Tripler Army Medical Center, Honolulu, HI, USA, and* ²*Uniformed Services University of the Health Sciences, Bethesda, MD, USA*

(Received 21 September 2010; revised 6 February 2011; accepted 7 April 2011)

Abstract

Primary objective: A volumetric blood surge (rapid physical movement/displacement of blood) is hypothesized to cause the non impact, mild TBI and battlefield PTSD induced by a blast over pressure wave.

Research design: Systematic review of the literature.

Methods and procedures: Articles relating to the fields of blast injury, brain injury and relevant disorders were searched between the years 1968–2010 for keywords such as ‘brain injury’, ‘post traumatic stress disorder’ and ‘blast pressure wave’. Articles found through journal and internet databases were cross referenced.

Main outcomes and results: The blood surge, which is driven by elevated overall pressure in the ventral body cavity after exposure of the torso to blast wave, may move through blood vessels to the low pressure cranial cavity from the high pressure ventral body cavity. It dramatically increases cerebral perfusion pressure and causes damage to both tiny cerebral blood vessels and the BBB.

Conclusions: Three factors may be critical to the induction of blast induced brain injuries: (1) the difference in pressure between the ventral body cavity and cranial cavity; (2) blood that acts as a transmission medium to propagate a pressure wave to the brain; and (3) the vulnerability of cerebral blood vessels and the BBB to a sudden fluctuation in perfusion pressure.

Keywords: Mild traumatic brain injury, battlefield post traumatic stress disorder, blast over pressure wave, volumetric blood surge, cerebrovascular insults

Introduction

Unlike previous wars, improved body armour and helmets now successfully reduce the frequency of penetrating and blunt impact injuries caused by blasts and save the lives of many soldiers who suffer blast injuries in Iraq and Afghanistan [1]. However, soldiers who are still alive after exposure to a blast over-pressure wave are surviving with new and complex patterns of injuries—mild traumatic brain injury (TBI) and battlefield post-traumatic stress disorder (PTSD) [2].

A non-impact, blast-induced mild TBI is currently defined as damage to the brain, which is solely caused by the primary blast effect in war fighters exposed to an over-pressure wave that is generated by the blast itself but do not sustain penetrating and blunt impact injuries that are caused by secondary and tertiary blast effects. People who sustain blast-induced mild TBI have persistent symptoms including headache, dizziness, lack of motor co-ordination, difficulty balancing, memory loss, attention deficits, sleep difficulties, blurred vision or tired eyes, ringing

Report Documentation Page				Form Approved OMB No. 0704-0188	
Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.					
1. REPORT DATE APR 2011		2. REPORT TYPE		3. DATES COVERED 00-00-2011 to 00-00-2011	
4. TITLE AND SUBTITLE Non-impact, Blast-Induced Mild TBI And PTSD: Concepts And Caveats				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S)				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Tripler Army Medical Center,Honolulu,HI,96859				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release; distribution unlimited					
13. SUPPLEMENTARY NOTES Brain Injury, July 2011; 25(7-8)pgs.,641-650					
14. ABSTRACT Primary objective: A volumetric blood surge (rapid physical movement/displacement of blood) is hypothesized to cause the non-impact, mild TBI and battlefield PTSD induced by a blast over-pressure wave. Research design: Systematic review of the literature. Methods and procedures: Articles relating to the fields of blast injury, brain injury and relevant disorders were searched between the years 1968?2010 for keywords such as ?brain injury?, ?post-traumatic stress disorder? and ?blast pressure wave?.Articles found through journal and internet databases were cross-referenced. Main outcomes and results: The blood surge, which is driven by elevated overall pressure in the ventral body cavity after exposure of the torso to blast wave, may move through blood vessels to the low-pressure cranial cavity from the highpressure ventral body cavity. It dramatically increases cerebral perfusion pressure and causes damage to both tiny cerebral blood vessels and the BBB. Conclusions: Three factors may be critical to the induction of blast-induced brain injuries: (1) the difference in pressure between the ventral body cavity and cranial cavity; (2) blood that acts as a transmission medium to propagate a pressure wave to the brain; and (3) the vulnerability of cerebral blood vessels and the BBB to a sudden fluctuation in perfusion pressure.					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT Same as Report (SAR)	18. NUMBER OF PAGES 11	19a. NAME OF RESPONSIBLE PERSON
a. REPORT unclassified	b. ABSTRACT unclassified	c. THIS PAGE unclassified			

in the ears, bad taste in the mouth, aggression, anxiety, depression and may continue developing Alzheimer-like dementia and Parkinson's disease [3–5].

Battlefield PTSD is an anxiety disorder that may occur soon or develop gradually after exposure to a highly dangerous, terrifying and possibly life-threatening traumatic event (such as an improvised explosive device bomb blast) in combat operations or terrorist attacks. Patients sustaining PTSD have persistent re-experiencing symptoms (flashback memories, recurring distressing memories or dreams and frightening thoughts), avoidance symptoms (feeling emotionally numb, losing interest in any activities, memory loss, attention deficits and depression) and hyperarousal symptoms (sleep difficulties, aggression and anxiety) [6]. PTSD can be caused by either physical trauma or psychological trauma or, more generally, a combination of both [7]. However, battlefield PTSD is most likely to be a psychological consequence of physical trauma sustained in an explosion. It is solely caused by exposure to an over-pressure wave that is generated by the blast. This combat-related psychiatric disorder must be distinguished from other types of anxiety-related disorders caused by violent personal assaults, natural- or human-caused disasters and accidents. Combat-related stressors (such as insomnia, fear, fatigue, stress, depression, poor diet, pain conditions, substance use, etc.) and other risk factors for mental illness are not able to induce battlefield PTSD, although they may play a synergistic role in developing PTSD induced by a blast over-pressure wave and may worsen behavioural or psychological dysfunction associated with battlefield PTSD.

Blast-induced mild TBI is associated with the development of battlefield PTSD. Many PTSD symptoms (such as depression, anxiety, memory and attention deficits, sleep problems and emotional disturbances) overlap with symptoms of mild TBI [8–10]. Of all soldiers returning from Iraq and Afghanistan with blast-induced mild TBI, 43.9% of them have been shown to have PTSD [11]. Of the patients with non-blast mild TBI (i.e. Concussion, which is generally characterized by a transient loss of mental function or focal neurological deficits caused by acceleration or deceleration forces or by a direct blow), 48% of them have been proven to have PTSD 3–12 months after injury [12]. Surprisingly, some studies indicate that ~80% of patients with blast-induced and non-blast mild TBI develop chronic PTSD [13–15]. Blast-induced mild TBI and battlefield PTSD are frequently unrecognized and their severity underestimated, because they occur both without a direct blow to the head and in the absence of visible external injuries [16, 17]. Unfortunately,

to date, the mechanisms of blast-induced mild TBI and battlefield PTSD remain unknown.

Pathophysiology of battlefield PTSD and blast-induced mild TBI

The pathophysiology of battlefield PTSD is largely unknown [18]. Brain damage in patients with battlefield PTSD is not easy to detect with macroscopic imaging techniques (i.e. computed tomography and magnetic resonance imaging). The most feasible way of indentifying battlefield PTSD is cognitive and personality testing [19]. The amygdala is considered a key brain structure for emotional processing and it may play a significant role in developing PTSD [20]. The serotonergic and noradrenergic systems were considered to be involved in the pathophysiology of PTSD [21].

The most salient pathophysiological characteristics of non-impact, blast-induced TBI are described as the *pepper-spray pattern*—diffuse cerebral oedema, hyperemia, vasospasm and haemorrhage in the brain [22, 23]. However, in cases of closed head injury or penetrating brain injury, these pathophysiological changes can be observed only in the area bordering the injured site, not in entire brain. This suggests that blast-induced TBI might be a result of large-scale cerebrovascular insults that occur globally throughout the brain. Cerebral oedema, hyperemia, haemorrhage and vasospasm are primary consequences of cerebrovascular injury or rupture, which occur immediately or within a few days after injury.

A clinical investigation evaluating risk for repeat exposure to blasts demonstrates that soldiers with exposure to a first blast could have additive effects on the brain, thus greatly increasing the risk of death or permanent disability after the second blast [19]. Rapid and catastrophic cerebral oedema formation has been observed after a second blast. This effect is called a *second impact syndrome* [24]. Loss of the ability to auto-regulate and control over cerebral blood flow in cerebral arterioles is thought to be the major cause of second impact syndrome, which results in massive cerebral oedema [25]. The results support the hypothesis that cerebrovascular insults may be the leading contributor to blast-induced brain injuries.

The blood–brain barrier (BBB) damage also may play a critical role in blast-induced TBI. The BBB is a protective network of blood vessels and tissue that protects the brain from harmful substances or stimuli. Once the BBB is damaged, it increases cerebrovascular permeability, induces vasogenic cerebral oedema and causes secondary neuronal damage. Research has shown that loss of integrity of the BBB has been seen in the injured hemisphere

of mice at 4 hours and 24 hours after a closed head injury [26]. The BBB still remains open for up to 30 days, even though oedema disappeared by 7 days. These results suggest that the BBB is not only vulnerable to traumatic insults but also difficult to reconstruct after damage. The prolonged opening of the BBB may have harmful consequences and lead to additional tissue destruction and behavioural impairments. Recent studies have demonstrated that integrity of the BBB is disrupted in animal brains after exposure to blasts [27–29].

Cerebrovascular insults and BBB disruption will trigger secondary neuronal damage in the brain. Secondary neuronal damage is a cascade of progressive neural injury and neuronal cell death that is triggered by the initial injury and continues in the hours, days or weeks after the initial insult [30, 31]. This delayed neuronal damage has come to be recognized as a major contributor to serious neurologic and psychological impairments including memory loss, inability to concentrate, speech problems, motor and sensory deficits and behavioural problems [32].

As one of the most common and devastating types of secondary neuronal damage, diffuse axonal injury (DAI) is characterized by axonal separation and extensive lesions in white matter tracts. DAI occurs in ~50% of patients with severe TBI and also occurs in patients with moderate and mild TBI [33]. It is a major contributor to unconsciousness and persistent vegetative state after TBI [34]. It has been proven that axons are not typically torn or stretched on impact; but, rather, secondary neuronal damage is largely responsible for the damage to axons [33, 35]. Like battlefield PTSD, DAI triggered by the initial brain injury is typically difficult to detect by using neuroimaging techniques (i.e. computed tomography and magnetic resonance imaging), because the brain is made up of ~100 billion neurons and much of neuronal damage can be seen only under a microscope [34, 36]. Evidence of microscopic axonal injury has been found in the pathological examination of autopsy cases of head injury [37, 38].

Possible mechanisms of blast-induced mild TBI

Direct cranial transmission [39–42], skull flexure [43] and head acceleration [44, 45] were considered as the possible mechanical mechanisms by which the blast over-pressure wave may cause mild TBI. It has been well-known for several decades that the mean intracranial pressure is normally zero and 10 mm Hg (0–0.193 psi) and the upper limit of normal is 20–25 mm Hg (0.386–0.483 psi). However, even an intracranial pressure between 20 and 25 mm Hg is

likely to cause damage to the brain if prolonged [46]. Intracranial pressure rising beyond 40 mm Hg (0.772 psi) is usually fatal and it leads to brain infarction and brain death [47]. If a blast over-pressure wave can pass through the skull into the cranial cavity without any change in pressure magnitude [40], intracranial pressure will increase dramatically to more than 12-times the upper limit of normal up to 5.80 psi (40 kPa). Such extremely high intracranial pressure is a highly dangerous, serious and often life-threatening problem, which will squash the brain against bones, crush brain tissue and cause death immediately or soon after injury.

Fortunately, the skull is an incompressible solid bone structure of 6.5–7.1 mm thick, which resists compression of a blast over-pressure wave. A blast over-pressure wave may be quickly reflected by the skull surface and may not retain sufficient magnitude on the head to directly induce brain damage. In addition, because sutures of the skull have been shown to absorb 16–100% more energy per unit volume during impact loading than did bone [48], sutures may play an amazing protective role against possible skull deformation or flexure that results from the overall response of the skull to blast loading. Therefore, mild TBI may not be the result of direct cranial transmission of a blast wave or skull flexure caused by direct action of the blast wave on the head.

Sudden acceleration/deceleration forces to the head are known to be a mechanism for closed head injury. An impacting force to the head can produce linear acceleration, rotational (angular) acceleration or a combination of both, which causes discrete, focal lesions that affect only certain areas of the brain (the point of direct impact and at the site directly opposite the point of impact) and often occur as in motor vehicle accidents, sporting activities, accidental falls and assaults [49]. However, blast-induced mild TBI is the diffuse lesions that occur globally throughout the brain, not the discrete and focal brain lesions resulting from an impacting force to the head. Theoretically, sudden angular rotation of the head without an impacting force can cause shear strains resulting in neural damage in the brain. While in certain situations involving exposure of the head to a blast over-pressure wave, sudden linear acceleration or angular rotation (whiplash or jolting) of the head is most likely to cause an acute injury to the cervical spine or a cervical spine injury concomitant with a head injury. However, until now, no soldiers with a blast-induced mild TBI have been found to sustain a concomitant cervical spine injury. These characteristics suggest that a blast over-pressure wave cannot possibly cause a linear acceleration

and/or rotational (angular) acceleration injuries to the head.

Some animal studies of ballistic and blast wave exposure suggest that the vagus nerve may play a role in the central nervous system (CNS) response to over-pressure waves. Damage to the brain may not be due to direct exposure of the head to the over-pressure wave, but may instead be mediated by the vagus nerve [50–52]. The vagus nerve is the longest cranial nerve originating from the brain stem through organs in the neck, thorax and abdomen. The vagus nerve helps to regulate breathing and heart beat, to control the functions of the digestive system and muscular contractions of the stomach and intestines and to carry a wide assortment of signals that are responsible for several instinctive responses in the body, to and from the brain. When the vagus nerve is stimulated, it typically leads to a reduction in heart rate or blood pressure or both. Excessive nerve stimulation can cause a vaso-vagal response, resulting in coma induced by a sudden drop in heart rate and blood pressure. The vagally mediated CNS response may play a synergistic role in developing a secondary neuronal damage triggered by the initial brain injury. However, it may not be a major cause of blast-induced, mild TBI, because a transient ischemic attack that is a temporary loss of blood supply and oxygen delivery to a part of the brain within several minutes due to excessive vagus nerve stimulation does not cause permanent damage to the brain [53, 54].

Volumetric blood surges created by ballistic and blast pressure waves

When a shock wave strikes an incompressible fluid-filled organ (e.g. a large blood vessel), a sudden increase in pressure on the wall of the blood vessel will cause a volumetric blood surge (rapid physical movement or displacement of blood) that rushes through blood vessels to distant organs and tissues causing a ‘non-contact’, remote injury. The volumetric blood surge has been verified by wound ballistics experiments in animals and finite element simulation of blast loads on the torso.

Blood surge caused by ballistic pressure waves in animals

An experimental study of wound ballistics demonstrates that a ballistic pressure wave can cause a remote injury to distant organs and tissues [55]. The remote injury, characterized by diffuse milialy or spotty haemorrhage and oedema, was observed in the heart (mainly in the endocardium, an incidence of 70.6%), lung (an incidence of 35.3%) and liver (an incidence of 29.4%) after a missile affected

a dog or pig’s lower extremity. Blood flow in both the common carotid artery and ascending aorta increased 2–8-times within 30 seconds (a peak value was reached at ~10 seconds) after a gunshot wound to the lower extremity. The results suggested that drastic blood flow disturbance (or called volumetric blood surge) toward distant organs and tissues via large blood vessels (femoral artery, abdominal aorta, thoracic aorta and common carotid artery), which might be driven by increased pressure within the blood vessels around the wound channel, was largely responsible for the remote injury to distant organs and tissues.

Increased pressure within the blood vessels around the wound channel can be caused by an over-expanded temporary wound cavity (stretch cavity) that is created by the projectile impact and kinetic energy transfer in tissues. When the projectile (bullet or fragment) enters the body, it creates first a ballistic pressure wave that forces tissues out of the way, creating a temporary wound cavity that can be 30–40-times the diameter of the projectile [56]. The rapidly expanding temporary wound cavity compresses the blood vessels around the cavity to increase pressure within the blood vessels. Increased vascular pressure pushes blood rapidly flowing to distant organs and tissues where the atmospheric pressure is below that of the cavity. The temporary wound cavity is similar to a gas bubble created by an underwater explosion [57, 58], which can repeatedly expand and collapse owing to the difference in pressure to create secondary ballistic pressure waves during the time that the tissues move back into place. When the pressure inside the cavity falls below the pressure of the surrounding tissue, this causes the cavity to collapse, which again causes a rise in cavity pressure and cavity expansion until such time as the cavity pressure exceeds tissue pressure. This may be repeated several times until the cavity eventually disappears. The rapidly expanding/collapsing temporary wound cavity will compress and decompress repeatedly the blood vessels around the cavity to cause multiple volumetric blood surges travelling via large blood vessels to distant organs and tissues. Initial damage to distant organs and tissues may be caused by first volumetric blood surge that is driven by the rapidly expanding cavity or first ballistic pressure wave and this damage may be amplified by the subsequent volumetric blood surges that are driven by the cavity pulse or secondary ballistic pressure waves.

Blood surge verified by finite element simulation of blast loads on the torso

A simulation study using finite element modelling shows that a 294 psi blast loading against the torso

can produce ~ 0.2 ml of volumetric blood surge from the lungs to the heart and ~ 10 ml blood surge from the abdomen to the heart. Distortion of the thorax and abdomen, which was raised from the presence of air-containing organs in the torso, was observed under blast loading. In the thorax, an inward motion of the chest wall produces a compression wave in the lung that may exert a compressive force on the cardiovascular system. The blast loading delivered through the abdomen induces a direct compression effect on the abdominal contents, leading to an inward and/or upward motion that also exerts a force on the cardiovascular system. Both of these processes can lead to a surge in blood flow which may move quickly to the head. It is assumed that at least 2 ml of the blood surge will be delivered to the brain following exposure of the torso to blast. When this volumetric blood surge rushes to the brain, the sudden increase of blood volume may lead to a subsequent increase in intracranial pressure to nearly 147 psi [59].

Based on research findings obtained from wound ballistics and finite element simulation of blast loads, it can be inferred that blood plays a crucial role in inducing damage caused by ballistic and blast pressure waves. Blood is a liquid tissue. The liquid is basically incompressible and does not absorb any of the supplied energy, but it is an ideal pressure transmission medium that is capable of moving much higher pressure loads and providing much higher forces owing to its incompressibility. Without participation of blood, a shock wave alone may not be able to cause a 'non-contact' damage to distant organs and tissues (e.g. the brain).

Direct torso impact of blast pressure waves causes non-contact brain injuries

The surrounding (envelopment) and compression effects of a blast over-pressure wave on the human body are characteristic of a typical blast exposure [43]. When a blast over-pressure wave acts on the human body, it causes a sudden, transient (1–2 milliseconds) increase in atmospheric pressure on the organs and the cardiovascular system. The surrounding over-pressure causes people to be short of breath, feel dazed, lose consciousness or have a seizure [19], which are the typical symptoms of a concussion (mild TBI). A blast over-pressure wave affects primarily air-filled organs (such as the lung, gastrointestinal tract and the ear) and air–liquid interfaces (such as the walls of pulmonary alveoli and the intestine), but rarely damages solid and fluid-filled organs, because an over-pressure wave does not occur in incompressible solids and fluids [60].

While the torso is abruptly compressed by a blast over-pressure wave, the ventral body cavity (thoracic cavity and abdominal cavity) is similar to a tube of toothpaste that is being squeezed [19]. If the excess pressure is not strong enough to cause barotraumas, the over-pressure wave acting on the torso may lead to a sudden, transient increase in overall pressure inside the ventral body cavity, but cause no damage or only minor damage to the internal organs. The unprotected human body can survive relatively high blast over-pressure in an open field without experiencing barotraumas. A peak over-pressure of 10 psi appears to be a safe, non-damage pressure value for both the lung and gastrointestinal tract, because the threshold for lung damage and gastrointestinal tract damage is ~ 13 – 15 psi of peak over-pressure [61, 62]. However, such a 'safe' peak over-pressure is ~ 50 -times the upper limit of normal intra-abdominal pressure (11.45 mm Hg or 0.2210 psi) and ~ 96 -times the upper limit of normal intra-thoracic pressure (-3 mm Hg or -0.0579 psi). It will certainly lead to an increase in overall pressure inside both the thoracic cavity and abdominal cavity, although the thoracic cavity can be weakly protected by the sternum and the rib cage.

Elevated overall pressure in the ventral body cavity will increase pressure on the walls of thoracic and abdominal blood vessels to create a volumetric blood surge. This hypothesis has been supported by some experimental data. A volumetric surge of blood moved through the thorax and abdomen has been observed in a finite element model following a blast loading simulation of the torso [59]. In a swine model of closed head injury resulting from exposure to an explosive blast, the rapid increase in pressures within both common carotid and the left ventricle have been observed within the first 2 milliseconds after the blast. The delayed increase in pressure within the inferior vena cava (IVC) has been seen at ~ 4 – 5 milliseconds after the first and largest peak pressure within the carotid. Both the rapid increase in carotid and left ventricular pressures and the delayed increase in the IVC pressure might result from compression of the heart or the thorax. The results suggest that intravascular pressure pulse transmission may be one possible cause of blast-induced traumatic brain injury [39]. More recently, an innovative blast-resistant body armour that mitigates the effects of blast over-pressure waves on the human body by using artificial arteries to redirect hydraulic energy and release blast over-pressure from the outer surface of the body armour has been developed [63]. The body armour is comprised of a metal small arms protection insert (SAPI) plate, a Kevlar panel, a layer of polymer artificial arteries filled with the liquid that is similar to artificial blood and an outer layer of heat resistant clothing material.

The artificial-artery layer is arrayed vertically, where kinetic energy of the blast over-pressure wave will be transformed into liquid pressure and then be quickly released with liquid flowing out of the artificial arteries. A tethered rubber cap is attached to the lower end of the artificial artery. An air-driven shock tube that generates blast waves was used to test the body armour. The peak pressure in the driven chamber of the shock tube was ~ 140 psi and the peak pressure acting on the body armour was ~ 10 psi. When blast waves acted on the body armour, the end caps of artificial arteries were immediately knocked off and ~ 6 – 10% of liquid inside the artificial arteries sprayed out through the openings. The artificial-artery layer on the outer surface of body armour released $\sim 96\%$ of kinetic energy of blast over-pressures and reduced strike pressure that is behind the body armour and causes the behind armour blunt trauma (BABT) by at least 90% . The results suggest that the volumetric blood surge in blood vessels is the major cause of the non-impact, remote injuries including blast-induced traumatic brain injuries.

The volumetric blood surge may move quickly to the low pressure areas where the atmospheric pressure is below that of the ventral body cavity. As compared with the thoracic cavity and abdominal cavity, the cranial cavity should be a relatively low pressure area because the skull can resist compression of a blast over-pressure wave, avoiding a sudden increase in intracranial pressure. Therefore, the volumetric blood surge will certainly go through large blood vessels to the low-pressure cranial cavity from the high-pressure ventral body cavity. A recent study also suggests that kinetic energy of blast over-pressure can be transferred via great blood vessels in the abdomen and thorax to the brain [64]. When the blast over-pressure interacts with the body surface and compresses the body, it transfers its kinetic energy to the body's fluid phase (such as blood). Bodily fluids will deliver the kinetic energy of the blast pressure wave to the brain [65].

Unlike a ballistic pressure wave, a blast pressure wave seems to cause only a one-time rush of blood via large blood vessels to the brain, because it cannot create a temporary wound cavity in the body. A sudden rush of blood to the brain will increase dramatically cerebral perfusion pressure owing to the limited space inside blood vessels in the brain. Furthermore, because cerebral blood vessels and the BBB are vulnerable to sudden fluctuations in perfusion pressure, the extremely rapid increase in cerebrovascular pressure will cause damage to both tiny cerebral blood vessels and the BBB in the brain.

Cerebrovascular insults and the BBB damage may be the main causes of the non-impact, blast-induced

brain injuries, including mild TBI and battlefield PTSD (Figure 1). The potential mechanism of blast-induced brain injuries may be similar to the mechanism underlying haemorrhagic stroke caused by hypertension, that is damage to the brain is induced by increased cerebrovascular pressure. The difference between the two conditions is that the former is an acute, sudden cerebrovascular insult caused by a volumetric blood surge driven by elevated overall pressure in the ventral body cavity after exposure of the torso to blast over-pressure wave; while the latter is a chronic, progressive cerebrovascular insult induced by persistent high blood pressure in cerebral arteries.

As the results of cerebrovascular insults and BBB damage caused by a volumetric blood surge moving to the brain from the torso, the initial pathophysiological changes (diffuse cerebral oedema, hyperemia, vasospasm and haemorrhage) in the brain will trigger secondary neuronal damage. Cerebral hyperemia, resulting from increased blood flow, can lead to hypoxia and oedema. Vasogenic cerebral oedema (swelling) causes dangerous increases in intracranial pressure. Intracerebral haemorrhage (bleeding) can result in intra-axial and extra-axial lesions (epidural haematoma, subdural haematoma, subarachnoid haemorrhage and intraventricular haemorrhage) [66]. Cerebral vasospasm will lead to cerebral ischemia and neuronal necrosis. The delayed neuronal damages also include excitotoxicity, inflammation, ionic imbalance, oxidative stress, apoptosis and diffuse axonal injury. Secondary neuronal damage can be a major contributor to neurologic and psychological impairments after blast-induced brain injuries. Additional studies have shown both morphological and functional damage to brain structures due to kinetic energy transfer of blast over-pressure to the CNS [67–71].

Why can the volumetric blood surge cause brain damage, but not induce spinal cord injury? Unlike the cranial cavity (which is completely enclosed by the bones of the cranium), the spinal canal is enclosed within the vertebral foramen of the vertebrae. Large circular openings called *intervertebral foramina* for the transmission of the spinal nerves and blood vessels are formed by notches on the pedicles of the adjacent vertebrae. Intervertebral discs that are located between vertebrae can absorb shock and distribute vertical and horizontal compressive stress in each vertebral body. Intervertebral ligaments provide passive stability to the spine and help to prevent injury from hyperflexion and hyperextension movements. The unique anatomic characteristics enhance tolerance of the spinal cord to sudden fluctuation in vascular perfusion pressure. Hence, the volumetric blood surge created by elevated

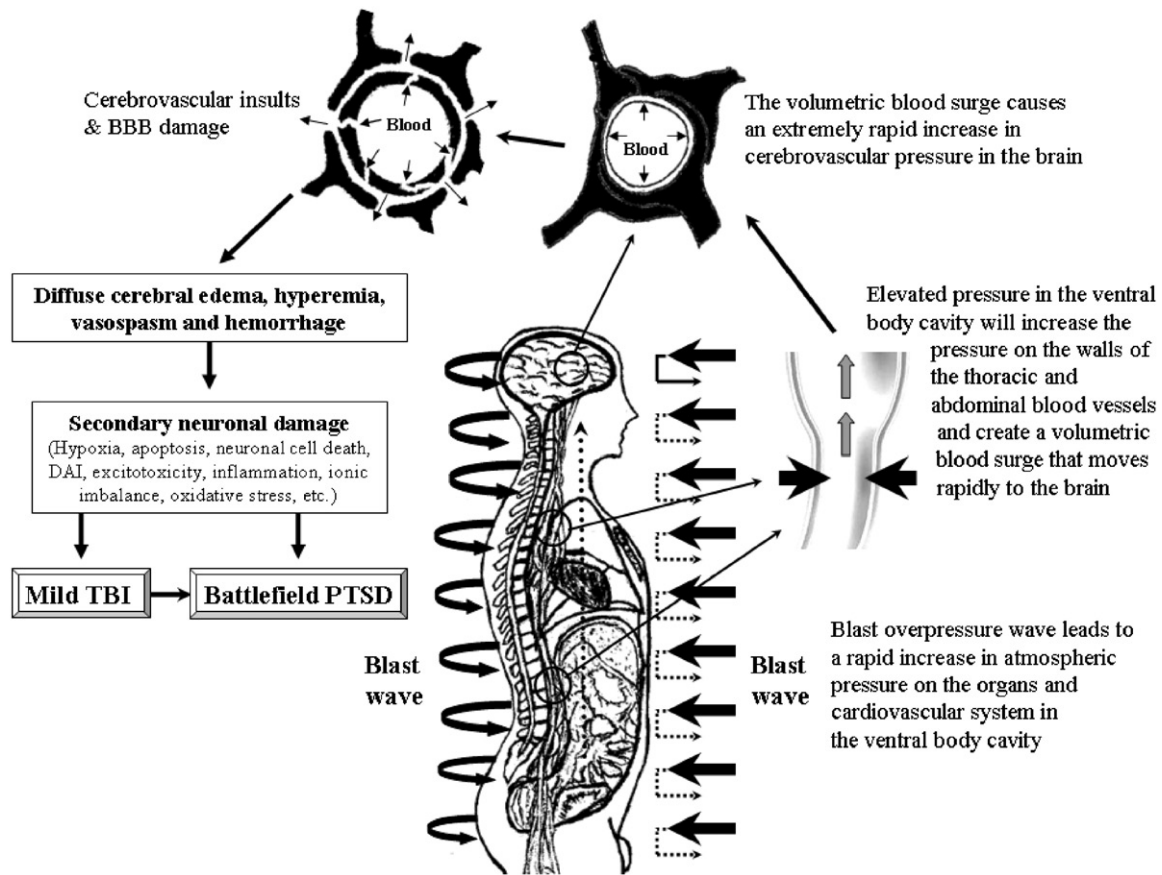


Figure 1. The potential mechanism underlying blast induced mild TBI and battlefield PTSD. Blast over pressure wave leads to a sudden increase in overall pressure inside both thoracic cavity and abdominal cavity. It creates a volumetric blood surge that moves quickly through large blood vessels to the low pressure cranial cavity from the high pressure ventral body cavity. The volumetric blood surge causes damage to both tiny cerebral blood vessels and the BBB, thus further triggering secondary neuronal damage in the brain. Secondary neuronal damage should be a major contributor to neurological and psychological impairments after mild TBI and battlefield PTSD.

overall pressure in the ventral body cavity will not cause vascular insults to the spinal cord.

Critical factors to induce the non-impact, blast-induced brain injuries

- (1) The difference in pressure between the ventral body cavity and cranial cavity, which is caused by the blast over-pressure wave acting on the human body, can be a critical factor creating the volumetric blood surge.
- (2) As an important pressure transmission medium, blood must play a crucial role in kinetic energy transfer of the blast over-pressure wave to the brain through large blood vessels.
- (3) The vulnerability of cerebral blood vessels and the BBB to sudden fluctuations in cerebral perfusion pressure can contribute to increased risk of mild TBI and battlefield PTSD after exposure to a blast over-pressure wave.

Conclusions

A volumetric blood surge, which has been verified by both wound ballistics experiments in animals and finite element simulation of blast loads on the torso, can possibly be the major cause of non-impact, blast-induced brain injuries. The blood surge may move quickly through large blood vessels to the low-pressure cranial cavity from the high-pressure ventral body cavity. It causes damage to tiny cerebral blood vessels and the BBB, thus further triggering secondary neuronal damage in the brain. The pathophysiological characteristics of non-impact, blast-induced TBI also suggests that damage to the brain might be a result of large-scale cerebrovascular insults that occur globally throughout the brain.

Battlefield PTSD and blast-induced mild TBI seem to have similar pathogenesis-related cerebrovascular insults and BBB damage. A battlefield PTSD should be a special delayed-onset mental

disorder caused by exposure to blast over-pressure in combat operations or terrorist attacks. It is more likely to be a psychological consequence of mild TBI and may result from secondary neuronal damage after a blast-induced mild TBI. This may be the reason why ~80% of patients with mild TBI develop chronic PTSD after injury and many battlefield PTSD symptoms overlap with symptoms of mild TBI.

To effectively prevent blast-induced mild TBI and battlefield PTSD, the thorax, abdomen and neck need to be well-protected from the blast.

Acknowledgements

The authors would like to thank Dr Amy Courtney and Dr Michael Courtney for their critical comments and useful suggestions and to thank Ms January Andaya for her valuable assistance in the preparation of this manuscript.

Declaration of Interest: The authors report no conflicts of interest. The views expressed in this manuscript are those of the author(s) and do not reflect the official policy or position of the Department of the Army, Department of Defense or the US Government.

References

1. MedicExchange [Internet]. Battlefield brain injury: the lessons from Iraq. 6 December 2007. Available online at: <http://www.medicexchange.com/Radiology/Articles/battlefield-brain-injury-the-lessons-from-iraq.html>, accessed 21 May 2010.
2. VA R&D Office [Internet]. Quality Enhancement Research Initiative (QUERI): Polytrauma and Blast Related Injuries, Health Services Research and Development Service, Minneapolis, June 2007. Available online at: <http://www.hsrd.minneapolis.med.va.gov/PTqueri>, accessed 5 June 2010.
3. Martin EM, Lu WC, Helmick K, French L, Warden DL. Traumatic brain injuries sustained in the Afghanistan and Iraq wars. *Journal of Trauma Nursing* 2008;15:94–99.
4. US National Academies of Science [Internet]. Committee on Gulf War and Health: Brain injury in veterans and long term health outcomes. 4 December 2008. Available online at: <http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=12436>, accessed 15 May 2010.
5. Warden D. Military TBI during the Iraq and Afghanistan wars. *Journal of Head Trauma Rehabilitation* 2006;21:398–402.
6. NIMH, National Institute of Mental Health [Internet]. What are the symptoms of PTSD? 12 January 2009. Available online at: <http://www.nimh.nih.gov/health/publications/post-traumatic-stress-disorder-ptsd/what-are-the-symptoms-of-ptsd.shtml>, accessed 10 June 2010.
7. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed (DSM IV). Washington, DC: American Psychiatric Association; 1994.
8. Kennedy JE, Leal FO, Lewis JD, Cullen MA, Amador RR. Posttraumatic stress symptoms in OIF/OEF service members with blast related and non blast related mild TBI. *Neurorehabilitation* 2010;26:223–231.
9. King NS. PTSD and traumatic brain injury: Folklore and fact? *Brain Injury* 2008;22:1–5.
10. Lew HL, Vanderploeg RD, Moore DF, Schwab K, Friedman L, Yesavage J, Keane TM, Warden DL, Sigford BJ. Overlap of mild TBI and mental health conditions in returning OIF/OEF service members and veterans. *Journal of Rehabilitation Research & Development* 2008;45:xi–xvi.
11. Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. soldiers returning from Iraq. *New England Journal of Medicine* 2008;358:453–463.
12. Mayou RA, Ehlers A, Hobbs M. Psychological debriefing for road traffic accident victims. *British Journal of Psychiatry* 2000;176:589–593.
13. Bryant RA, Harvey AG. Relationship between acute stress disorder and posttraumatic stress disorder following mild traumatic brain injury. *American Journal of Psychiatry* 1998;155:625–629.
14. Bryant RA. Posttraumatic stress disorder and traumatic brain injury: Can they co exist? *Clinical Psychological Review* 2001;21:931–948.
15. Elder GA, Cristian A. Blast related mild traumatic brain injury: Mechanisms of injury and impact on clinical care. *Mount Sinai Journal of Medicine* 2009;76:111–118.
16. Elsayed NM. Toxicology of blast overpressure. *Toxicology* 1997;121:1–15.
17. Owen Smith MS. Explosive blast injury. *Medical Bulletin of the US Army Europe* 1981;38:36–43.
18. Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL. Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *New England Journal of Medicine* 2004;351:13–22.
19. Reed KD. An innovative approach to blast injury recovery. *Military Review* 2008;Sept Oct:40–46. Available online at: <http://usacac.leavenworth.army.mil/CAC2/MilitaryReview/Archives/English/MilitaryReview-20081031-art010.pdf>, accessed 6 May 2010.
20. eMedicine [Internet]. Posttraumatic stress disorder. 19 March 2010. Available online at: <http://emedicine.medscape.com/article/288154-overview>, accessed 20 May 2010.
21. Maes M, Lin AH, Verkerk R, Delmeire L, Van Gastel A, Van der Planken M, Scharpé S. Serotonergic and noradrenergic markers of Post Traumatic Stress Disorder with and without major depression. *Neuropsychopharmacology* 1999;20:188–197.
22. Ling G, Bandak F, Armonda R, Grant G, Ecklund J. Explosive blast neurotrauma. *Journal of Neurotrauma* 2009;26:815–825.
23. Moore DF, Jérusalem A, Nyein M, Noels L, Jaffee MS, Radovitzky RA. Computational biology Modeling of primary blast effects on the central nervous system. *Neuroimage* 2009;2:10–20.
24. Kennedy K. Experts: Even mild head injuries put troops at risk. *Army Times Magazine* 2007;68:4–5.
25. Cantu RC. Second impact syndrome. *Clinical Sports Medicine* 1998;17:37–44.
26. Chen Y, Constantini S, Trembovler V, Weinstock M, Shohami E. An experimental model of closed head injury in mice: Pathophysiology, histopathology and cognitive deficits. *Journal of Neurotrauma* 1996;13:557–568.
27. Hicks RR, Fertig SJ, Desrocher RE, Koroshetz WJ, Pancrazio JJ. Neurological effects of blast injury. *Journal of Trauma* 2010;68:1257–1263.

28. Readnower RD, Chavko M, Adeeb S, Conroy MD, Pauly JR, McCarron RM, Sullivan PG. Increase in blood brain barrier permeability, oxidative stress, and activated microglia in a rat model of blast induced traumatic brain injury. *Journal of Neuroscience Research* 2010;88:3530-3539.
29. Svetlov SI, Prima V, Kirk DR, Gutierrez H, Curley KC, Hayes RL, Wang KK. Morphologic and biochemical characterization of brain injury in a model of controlled blast overpressure exposure. *Journal of Trauma* 2010;69:795-804.
30. Alvarez J, Selman WR. Mechanisms of secondary brain damage in cerebral ischemia and trauma. *Acta Neurochirurgica* 1999;44:682-683.
31. Siesjö BK, Siesjö P. Mechanisms of secondary brain injury. *European Journal of Anaesthesiology* 1996;13:247-268.
32. Beattie MS, Farooqui AA, Bresnahan JC. Review of current evidence for apoptosis after spinal cord injury. *Journal of Neurotrauma* 2000;17:915-925.
33. Abou Hamden A, Blumbergs PC, Scott G, Manavis J, Wainwright H, Jones N, McLean J. Axonal injury in falls. *Journal of Neurotrauma* 1997;14:699-713.
34. Emedicine.com [Internet]. Diffuse axonal injury imaging. 26 January 2008. Available online at: <http://emedicine.medscape.com/article/339912/overview>, accessed 17 June 2010.
35. Arundine M, Aarts M, Lau A, Tymianski M. Vulnerability of central neurons to secondary insults after *in vitro* mechanical stretch. *Journal of Neuroscience* 2004;24:8106-8123.
36. Granacher RP. Traumatic brain injury: Methods for clinical & forensic neuropsychiatric assessment. 2nd ed. Boca Raton, FL: CRC; 2007. pp 26-33.
37. Oppenheimer DR. Microscopic lesions in the brain following head injury. *Journal of Neurology, Neurosurgery & Psychiatry* 1968;31:299-306.
38. Smith DH, Meaney DF, Shull WH. Diffuse axonal injury in head trauma. *Journal of Head Trauma Rehabilitation* 2003;18:307-316.
39. Bauman RA, Ling G, Tong L, Januszkiewicz A, Agoston D, Delanerolle N, Kim Y, Ritzel D, Bell R, Ecklund J, et al. An introductory characterization of a combat casualty relevant swine model of closed head injury resulting from exposure to explosive blast. *Journal of Neurotrauma* 2009;26:841-860.
40. Chavko M, Koller WA, Prusaczyk WK, McCarron RM. Measurement of blast wave by a miniature fiber optic pressure transducer in the rat brain. *Journal Neurology Methods* 2007;159:277-281.
41. Nyein M, Jerusalem A, Radovitzky R, Moore D, Noels L. Modeling blast related brain injury. The 26th Army Science Conference; 14 December 2008; The Defense Technical Information Center; 2008. p 1-8. Available online at: <http://handle.dtic.mil/100.2/ADA504193>, accessed 12 June 2010.
42. Stuhmiller JH, Masiello PI, Ho KH, Mayorga MA, Lawless N, Argyros G. Biomechanical modeling of injury from blast overpressure. The RTO HFM specialists' meeting on Models for aircrew safety assessment: Uses, limitations and requirements; 26-28 October 1998; Ohio, USA: published in RTO MP 20; 1998.
43. Moss WC, King MJ, Blackman EG. Skull flexure from blast waves: A mechanism for brain injury with implications for helmet design. *Journal of Acoustic Society of America* 2009;125:2650.
44. Krave U, Hojer S, Hansson H. Transient, powerful pressures are generated in the brain by a rotational acceleration impulse to the head. *European Journal of Neuroscience* 2005;2:2876-2882.
45. Zhang L, Yang K, King A. A proposed injury threshold for mild traumatic brain injury. *Journal of Biomechanical Engineering* 2004;126:226-236.
46. Emedicine.com [Internet]. Initial evaluation and management of CNS injury. 13 June 2008. Available online at: <http://emedicine.medscape.com/article/434261/overview>, accessed 11 May 2010.
47. Emedicine.com [Internet]. Traumatic brain injury: Definition, epidemiology, pathophysiology. 30 March 2009. Available online at: <http://emedicine.medscape.com/article/326510/overview>, accessed 12 May 2010.
48. Jaslow CR. Mechanical properties of cranial sutures. *Journal of Biomechanics* 1990;23:313-321.
49. Maio Di, VJM, Maio Di, DJ. Forensic pathology. 2nd ed. Boca Raton, FL: CRC Press; 2001. p 165.
50. Cernak I, Savic J, Malicevic Z, Zunic G, Radosevic P, Ivanovic I, Davidovic L. Involvement of the central nervous system in the general response to pulmonary blast injury. *Journal of Trauma* 1996;40:100-104.
51. Gryth D, Rocksén D, Arborelius UP, Drobin D, Persson JK, Söndén A, Bursell J, Olsson LG, Kjellström BT. Bilateral vagotomy inhibits apnea and attenuates other physiological responses after blunt chest trauma. *Journal of Trauma* 2008;64:1420-1426.
52. Irwin RJ, Lerner MR, Bealer JF, Mantor PC, Brackett DJ, Tuggle DW. Shock after blast wave injury is caused by a vagally mediated reflex. *Journal of Trauma* 1999;47:105-110.
53. Ay I, Lu J, Ay H, Gregory Sorensen A. Vagus nerve stimulation reduces infarct size in rat focal cerebral ischemia. *Neuroscience Letters* 2009;459:147-151.
54. Lewandowski CA, Rao CP, Silver B. Transient ischemic attack: Definitions and clinical presentations. *Annals of Emergency Medicine* 2008;52:7-16.
55. Liu YQ, Chen Y, Chen L, Li SQ. Mechanism and characteristics of the remote effects of projectiles. *Journal of Trauma (China)* 1990;6:16-20.
56. Maiden N. Ballistics reviews: Mechanisms of bullet wound trauma. *Forensic Science, Medicine & Pathology* 2009;5:204-209.
57. Lee JJ, Gregson J, Rude G, Paulgaard GT. Underwater shock and bubble interactions from twin explosive charges. *Shock Waves* 2009; Part 2:1549-1554.
58. Reid WD. The response of surface ships to underwater explosions. Aeronautical and Maritime Research Laboratory, Defence Science and Technology Organization Canberra, Department of Defence (Australia); DSTO GD 0109, 1996. Available online at: <http://handle.dtic.mil/100.2/ADA326738>, accessed 6 June 2010.
59. Stuhmiller JH. Blast injury: Translating research into operational medicine. Army Medical Research and Materiel Command; BI QP JHS CH10, April 2008. Available online at: http://www.bordeninstitute.army.mil/other/pub/blast/Blast_monograph.pdf, accessed 7 June 2010.
60. Mayo A, Kluger Y. Terrorist bombing. *World Journal of Emergency Surgery* 2006;1:33.
61. Glasstone S, Dolan PJ. The effects of nuclear weapons. 3rd ed. Washington, DC: The Federal Emergency Management Agency, the U.S. Department of Defense and the U.S. Department of Energy; 1977.
62. Rice D, Heck J. Terrorist bombings: Ballistics, patterns of blast injury and tactical emergency care. *Tactical Edge Journal* 2000;Summer:53-55.
63. Chen Y, Huang W. A hydraulic energy redirection and release system for blast and ballistic protection. Unpublished data 2010.

64. Courtney AC, Courtney MW. A thoracic mechanism of mild traumatic brain injury due to blast pressure waves. *Medical Hypotheses* 2008;72:76-83.
65. Cernak I, Savic J, Ignjatovic D, Jevtic M. Blast injury from explosive munitions. *Journal of Trauma* 1999;47:96-103.
66. Barkley JM, Morales D, Hayman LA, Diaz Marchan PJ. Static neuroimaging in the evaluation of TBI. In: Zaske N, Katz D, Zafonte R, editors. *Brain injury medicine: Principles and practice*. New York: Demos Medical Publishing; 2006. pp 140-143.
67. Finkel MF. The neurological consequences of explosives. *Journal of Neurological Sciences* 2006;249:63-73.
68. Karmy Jones R, Kissinger D, Golocovsky M, Jordan M, Champion HR. Bomb related injuries. *Military Medicine* 1994;159:536-539.
69. DePalma RG, Burris DG, Champion HR, Hodgson MJ. Blast injuries. *New England Journal of Medicine* 2005;352:1335-1342.
70. Yang Z, Wang Z, Tang C, Ying Y. Biological effects of weak blast waves and safety limits for internal organ injury in the human body. *Journal of Trauma* 1996;40:81S-84S.
71. Axelsson H, Hjelmqvist H, Medin A, Persson J, Suneson A. Physiological changes in pigs exposed to a blast wave from a detonating high explosive charge. *Military Medicine* 2000;165:119-126.