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Research report

Linking blast physics to biological outcomes in mild traumatic brain injury: Narrative review and preliminary report of an open-field blast model

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HIGHLIGHTS

- Blast exposures are associated with traumatic brain injury (TBI); during recent conflicts most of these have been classified as mild TBI (mTBI).
- The role and mechanisms of primary blast wave injury remain controversial. We review blast models of TBI including shock tubes and open-field blast.
- Our analyses of behavioral and pathological findings show that low level blast exposures (peak pressure < 100 kPa) induced lower mortality rates, fewer motor disabilities, and absence of lung injuries as compared to high level blast (peak pressure > 200 kPa).
- We present preliminary findings obtained from a reproducible open-field blast murine model of mTBI representing a primary low level blast injury. Within scalability limits, this model closely mimics low level battlefield blast exposures and offers opportunities to advance the understanding of blast physics, resulting neuropathology, and underlying mechanisms leading to chronic effects of mTBI.

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ABSTRACT

Blast exposures are associated with traumatic brain injury (TBI) and blast-induced TBIs are common injuries affecting military personnel. Department of Defense and Veterans Administration (DoD/VA) reports for TBI indicated that the vast majority (82.3%) has been mild TBI (mTBI)/concussion. mTBI and associated posttraumatic stress disorders (PTSD) have been called "the invisible injury" of the current conflicts in Iraq and Afghanistan. These injuries induce varying degrees of neuropathological alterations and, in some cases, chronic cognitive, behavioral and neurological disorders. Appropriate animal models of blast-induced TBI will not only assist the understanding of physical characteristics of the blast, but also help to address the potential mechanisms. This report provides a brief overview of physical principles of blast, injury mechanisms related to blast exposure, current blast animal models, and the neurological behavioral and neuropathological findings related to blast injury in experimental settings. We describe relationships between blast peak pressures and the observed injuries. We also report preliminary use of a highly reproducible and intensity-graded blast murine model carried out in open-field with explosives, and describe physical and pathological findings in this experimental model. Our results indicate close relationships between blast intensities and neuropathology and behavioral deficits, particularly at low level blast intensities relevant to mTBI.

1. Introduction

Blast exposure is associated with traumatic brain injury (TBI), and also recognized as a potential risk factor for subsequent cognitive, behavioral disorders and possible chronic neurodegenerative disease [1–5]. During World War I, Frederick Mott first

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reported findings in post-mortem brains of three blast exposed soldiers with no physical evidence of external head trauma; petechial hemorrhages, mostly within the white matter of corpus callosum, and internal capsule, were noted [6,7]. Later reports contributed to the understanding of the effects of penetrating brain injury in warfare by studying those injured in World War II and among Vietnam Veterans [8–10]. During the current conflicts in Iraq and Afghanistan [Operation Iraqi Freedom (OIF), Operation Enduring Freedom (OEF), and Operation New Dawn (OND)], the focus on severe and penetrating brain injuries has shifted to more commonly observed closed brain injuries, particularly those referred as mild TBI (mTBI) [11]. Since 2000, Department of Defense (DoD)'s report indicated that the vast majority (82.3%) of TBI has been classified as mTBI/concussion; while only approximately 1% comprising severe injuries [12]. Additionally, screening of one million combat veterans by the Veterans Health Administration (VHA) showed that approximately 8.4% of OEF/OIF/OND Veterans reporting and screened have received a diagnosis of TBI, most characterized as mTBI and, in great proportion, related to blast exposures [13,14]. 2016 recent Quarter 1 data again showed that mTBI constituted 86% of the total numbers of TBI [12]. Introduction of new and improved protective body armor in 2003 led to a marked reduction of traditional combat injuries [15,16]. Deaths from pulmonary damage were greatly reduced by enhanced protection of the torso; however, soldiers surviving combat related blasts appeared to be at higher risk of chronic effects of mTBI caused by explosive weaponry including exposures to widely used improvised explosive devices (IEDs) [17–20]. More importantly, the pattern of neuropathology caused by blast exposure observed in the military personnel may hold unique features not observed in those who have suffered blunt TBI [20–22].

The Glasgow Coma Score (GCS) is used to evaluate TBI severity [23]. For mTBI, the GCS ranges 13–15 and is characterized by: a confused or disoriented state lasting less than 24 h; loss of consciousness less than 30 min; memory loss lasting less than 24 h, and excludes penetrating TBI [12,24,25]. In experimental models, mTBI has been found to be associated with a variety of ultrastructural, biochemical, molecular, cellular, brain circuit and behavioral abnormalities [26,27]. This type of blast induced injury, mostly from IEDs, has been described clinically as an invisible injury, except when accompanied by tympanic membrane rupture [1]. About 15% of mTBI cases chronically associate with headaches, comorbid posttraumatic stress disorders (PTSD), depression, memory disturbances, or other cognitive dysfunctions [22,28]. It is often difficult to differentiate between the effects of blast TBI and PTSD, which may be the results of psychological stress/trauma [29–31]. Reconciling clinical reports of TBI exposure to blast in combat [17,18], and data from experimental TBI blast models [32,33] offers the prospects of better insights into the chronic symptoms of blast mTBI. This reconciliation may provide information about blast biomechanics and elucidate specific relationships between blast injury and later cognitive, behavior and neurological dysfunction.

We review underlying physical mechanisms of contemporary explosive devices and the spectrum of injuries inflicted by blast exposure, current shock tube and open-field mTBI animal models, and their associated behavioral and neuropathological outcomes. This narrative review is based on searches of the PubMed database using each of the terms "shock tube", "blast" or "open field blast" in combination with the terms "traumatic brain injury" or "brain trauma". Additionally, we describe a highly reproducible and intensity-graded open-field blast-induced murine model of mTBI, its subsequent macroscopic pathology findings, and how this model of open-field blast correlates with blast battle field exposure.

2. Physical principles of blast injuries

2.1. Types of blast injuries

Most combat blast-induced mTBIs are caused by explosive weaponry such as IEDs, rocket propelled grenades, and mortars [34]. Explosive blasts can result in primary, secondary, tertiary and quaternary injuries. Primary blast injuries occur as the blast wave impacts bodily structures. Most of the shock wave impact relates to the expanding overpressure zone [35]. The primary blast wave generates internal stress and strain forces in tissues and organs to cause injury. Furthermore, depending on position in relation to blast direction and surrounding structures, subjects are also exposed to complex blast waves caused by multiple reflections from the walls, ground, and their interactions [36]. Helmets have been shown to protect the brain from lateral and posterior blast exposure [37]. Additionally, body armor protects military personnel from most ballistic projectiles to the torso, reduces lung injuries and thus increases survival [38] and, as mentioned, the likelihood of living to experience the effects of TBI.

Secondary blast injury occurs when fragments from the explosive device or ground debris impact and penetrate into the body, and is characterized as the effect of projectiles. IEDs have metal casings and are usually filled with metal fragments. Tertiary blast injury, mainly due to the blast wind, occurs when the body is thrown through space into a structure such as a building, wall or the ground. Quaternary blast injury is due to burns, asphyxia, radiation, exposure to toxic inhalants [39,40]. Ultimately, primary injury due to blast exposure, similar to blunt trauma and ballistic penetration, relates to energy transfer from the external environment through the skull and its apertures and into the brain [41]. However, in primary blast wave injury, the modes of injuring mechanisms and coupling to tissues and structures are not immediately apparent.

2.2. Physics of explosive blast and underlying mechanisms of the blast injuries

Here, we consider the physical properties of the blast wave, translational and rotational head acceleration mechanisms, and a novel phonon-based physical model as causes of mTBI. As mentioned, potential mechanisms for blast-induced mTBI in the military environment include direct blast wave impingement, penetrating impact, blunt impact, among others [42].

2.2.1. Blast wave

Modern explosives produce pressure waves along with acoustic, electromagnetic, light and thermal energies [39]. Understanding blast wave dynamics, how they interact with the human body and how the body responds is a critical step towards understanding the blast-induced mTBI.

The triggering event in an explosion is detonation. The fundamental physics of blast detonation is rapid chemical decomposition of an explosive into the shock front and blast wind [43,44]. When an explosion occurs, space formerly occupied by the explosive material is virtually instantaneously filled with gas under high pressure and temperature. The resulting energy expands radially outward as a blast wave moving at supersonic speed. Thereafter, the explosion may also generate nonlinear and complex blast waves depending on location of the explosive material and nearby structures [1]. The Friedlander equation [45,46] characterized by a peak overpressure, duration, and impulse (integration of overpressure with respect to time) describes propagation of an ideal blast wave through time and space. A Friedlander plot depicts a very fast rise-time in positive pressure followed by an exponential decay to below atmospheric pressure (depending in some degree on the magnitude of the positive pressure rise) and ends upon return to atmospheric pressure

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