Blast physics and central nervous system injury

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The effect of blast on biological tissue is well documented for particular organ systems such as the lung. This is not the case for the CNS, where the mechanism of CNS injury following a detonation and blast wave is unclear. The effect of blast on traumatic brain injury (TBI) has come into particular focus with the Global War on Terror and Operation Iraqi Freedom, and Operation Enduring Freedom where TBI has become known as the signature injury of these conflicts. The reason for the prominence of TBI in these particular conflicts as opposed to others is unclear, but may result from the increased survivability of blast due to improvements in body armor. In this review, we trace the historical context of blast injury and develop current concepts from this framework, in addition to highlighting many remaining unsolved questions.

The historical context of blast injury spans a number of centuries and conflicts with scientific and investigative contributions often related contemporaneously to specific conflicts such as the Great War (WWI) and the Second World War (WWII). The first suggested description of blast injury is attributed to M Jars in 1768, involving mining accidents in the North of England [1]. The description does not really sustain evidence for blast injury, but rather appears to emphasize the survivability of the ‘return of bad air’ following explosions within the mines of the late 18th Century. Interestingly, anecdotal evidence from a master miner indicated that survivability of blast explosions was enhanced by lying prone facedown in the mud. It is not clear, from the historical record, whether such survivability was caused by decreased surface area exposure to the blast wave or from the increased ability to evacuate because of the presence of air pockets. However, the increased survivability of blast in a supine position is known [2]. A more convincing description of blast injury was described in 1812 by Mr McTarnan’s as a Case of Death from the Wind of a Shot alluded to by WE Dickson in the Lancet in 1943 [3]. In this case, a marine died after exposure to a shot that did not result in any noted external injury, suggesting that the blast wind associated with the projectile resulted in sudden death. This provoked controversy about the existence of such causation, together with various hypotheses of the phenomenon, such as the ‘accumulation of electricity’, the ‘tremor of the atmosphere’ and ‘the development of subtile matter by the flight of the ball’ [4–6]. In effect, the transformation of chemical energy within a detonation into kinetic energy of fragments and shrapnel, the blast shockwave, acoustic energy, heat and electromagnetic field (EMF) energy, including the explosive ‘light flash’ and other EMF fields, have the potential to result in coupled fields with additive or synergistic damage to biological tissue. The strength and weakness of the coupling will depend on near- and far-field effects in each of these energy transformations with varying biological implications. The conceptual framework, however, is surprisingly reminiscent of the hypotheses generated several centuries ago. The current conflicts (Operation Iraqi Freedom [OIF] and Operation Enduring Freedom [OEF]) have seen a resurgence of interest in many of these issues related to blast, especially shell shock and mild traumatic brain injury (TBI), as has been well documented by the recent review of Jones et al. 2007 [7]. One of the earliest references to blast injury of the CNS was by Mott in his three Letorsian lectures, where concussion was attributed to ‘aerial compression’. Postmortem examinations of the CNS showed evident punctate hemorrhage and chromatolysis [8]. The diagnostic accuracy of Mott’s description was disputed by Denny–Brown, who negated an effect of blast on the CNS, however, a more balanced account was probably provided by Fulton, where the author states that ‘death from primary blast’ is a clinical entity that requires close study, because of its intimate connection with concussion and with the postconcussion syndrome of neuropsychiatry [9,10]. These remarks seem equally appropriate in the contemporary context. The global war on terror and the current operations in Iraq (OIF) and Afghanistan (OEF) have brought TBI into sharp focus,
especially military-related TBI. TBI is a significant cause of death and morbidity in the 0 to 40-year old range with a huge economic impact [11,12]. The military context of blast represents an added feature to TBI. However, it is unclear whether blast alters the natural history of TBI compared with blunt or impact injury in terms of the CNS injury cascade. We define blast according to Strehlow and Baker: an explosive in the atmosphere refers to the release of energy in such a period of time and within such a volume as to be small enough for the creation of a pressure wave of finite amplitude, spreading from the source of the explosion, the energy radiated can be nuclear, chemical, electrical or pressure energy [13]. However, this release of energy is not an explosion if it is insufficiently localized in time and space and does not result in the formation of an audible pressure wave.

Blast TBI is often associated with blunt or impact TBI so that convolution of clinical effects is very real, and significant difficulties exist in adequate parsing [14,15]. Blast injury is categorized as primary where injury is related to the shock-wave overpressure and underpressure, secondary where the injury results from blast-associated fragments or shrapnel, tertiary where injury occurs secondary to falling debris or throwing of the dismounted soldier or vehicle, and quaternary where injury develops from a variety of physical processes associated with explosive detonation such as thermal, toxic inhalation or electromagnetic and ionization fields [15,16]. TBI is broadly categorized into penetrating (pTBI) and closed (cTBI). cTBI itself is further categorized into mild (mTBI), moderate and severe, with mTBI representing approximately 70–80% of cTBI [17]. In non-military TBI, most pTBI is secondary to ballistic events, usually gunshot wounds, while for cTBI motor vehicle accidents (MVAs) are the predominant cause [18]. The categorization of cTBI, particularly mTBI, is often problematic with uncertainty surrounding both diagnosis and prognosis. This becomes of particular relevance in the military, where force health and readiness, together with soldier survivability, are singular issues. The question of whether primary blast has different CNS injury consequences is also an area of considerable uncertainty and active research. The answer to this question again has particular military relevance. Similarly, the overlap between TBI and post-traumatic stress disorder (PTSD) in the military population is a large and unanswered question [7,19]. This paper focuses on the relationship of blast and CNS injury by reviewing the TBI literature in relation to blast exposure. In order to set the context we first review the physics of blast.

**Blast & detonation wave physics**

The chemical reaction or rapid decomposition of explosives results in the formation of a detonation wave of altering chemical composition with the rapid formation of a propagated, nonlinear shockwave representing a large discontinuous increase in pressure, temperature and density in the gas flow. More importantly, an explosive event is stochastic with the characteristics of a 3D complex flow field that may be altered by ambient conditions and environmental boundaries that can result in wave reflections and field intensification up to eightfold [20,21]. In the ideal case, a blast wave is described by the Friedlander waveform with a rapid rise to the peak pressure, exponential fall-off of the overpressure, together with a relatively prolonged underpressure [22,23]. The blast waveform can be regarded as a combination of compressive and tensile components. When a blast wave interacts with materials, a shear or transverse wave is formed within the material usually several orders of magnitude less than the blast-wave intensity [24]. The formation of a transverse or shear wave, where the direction of particle motion is orthogonal to the direction of wave propagation, results in material shear stresses that may have a differential pathological effect on the anisotropic structures of the brain, especially white matter tracts where tissue properties vary with direction as a result of the fiber fasicular nature of white matter. Barotrauma is the mechanism of damage to air-filled organs, such as the lungs and middle ear. Rupture of the tympanic membrane is most frequently affected by blast overpressure of approximately 1 atm or 14.7 psi, with damage to air-filled organs unlikely unless associated with tympanic membrane damage [15]. More recently, an association has been described between tympanic membrane perforation and concussion [25].

Damage to the CNS may result from direct shock-wave effects or indirect effects resulting, for example, from transmission of pressure waves by way of the large vessels to the brain, in much the same way that the pressure pulse travels from the heart ahead of the moving column of blood. Similar indirect effects on the CNS have been noted in animal investigations following peripheral limb ballistic injury so that
indirect CNS effects following fragmentation and shrapnel injury can not be excluded [26, 27]. However, it is possible that mitigation of the thoracic and abdominal effects of blast by body armor has increased the ascertainment of direct blast on the brain owing to increased soldier survivability from these otherwise lethal injuries. Preliminary observation-derived numerical analysis [DFM & RPF Unpublished Data] suggests the feasibility of direct blast-wave transmission to the CNS [28]. Some recent experimental work using a rodent model exposed to primary blast generated by a shock tube indicates direct sensor transduction of the blast wave when the sensor was placed in the cerebral ventricles [29]. The coupling of the nonlinear blast wave into biological tissue results in increased energy deposition at high strain rates in fractions of microseconds. The relative amount of energy deposition is most simply dependent on the distance from the blast source (inverse cube law – Hopkinson Rule) together with the largely unknown high strain rate tissue material properties. Data suggests that tissue shear material properties may exhibit differing properties of state across a range of high strain rates as determined by Kolsky bar experiments. Similar experiments indicated that the bulk modulus, while nonlinearly related to the strain rate, did not exhibit more than one state [30]. It is possible to consider the blast waveform in terms of its frequency components, and this approach is isomorphic to a temporal domain solution [31]. Such an approach has been adopted by Cooper et al., where these investigators demonstrated decoupling of blast wave components and lung protection using differing material types. Other mechanisms of CNS injury may include air embolism secondary to blast wave transmission, with Clemedson particularly developing this viewpoint [32–34].

**Injury parameters & models**

The effect of TBI from impact or blunt TBI to blast may be considered along a dimension of increasing strain rate with impact injury occupying a lower strain rate, range while that of blast occupies a high strain rate range. Ballistic injury may occupy an overlapping and intermediate strain rate domain. The injury parameters at varying strain rates for CNS tissue remain to be determined. In particular, the blast wave metric that correlates most effectively with CNS tissue injury and concussion is unknown. There is a real need to determine this blast metric together with brain tissue injury blast intensity–duration curves for both single exposure events and cumulative blast exposure events, such as are available for blunt TBI [35]. Zhang and colleagues devised such metrics for blunt events and compared investigational data of mTBI in football injuries (National Football League) using a 3D finite element model of the head. The injury component input consisted of 6-degrees of freedom acceleration time courses, three orthogonal translational components (m/s²) and three orthogonal rotational components (rad/s²). A variety of injury metrics were calculated, including the head injury criterion over 15 ms (HIC). Using logistic regression for the binary mTBI or non-mTBI states, the midbrain shear stress was found to be most significant (p < 0.0001), with the maximum resultant translation acceleration (A_r) and the maximum resultant rotational acceleration (R_r) both having p values of p = 0.001. Of note, all the calculated injury metrics (midbrain shear stress, thalamic shear stress, intracranial pressure [ICP], HIC, Gadd Severity Index [GSI], A_r and R_r) were likely highly correlated, although this was not expressly examined by the authors. Metrics requiring characterization are the blast wavefront overpressure (ΔP), impulse duration (τ), duration of compression phase (τ+), duration of rarefaction phase (τ-), time of front pressure growth, peak pressure and the impulse (i) approximated for an idealized triangular pressure wave as i = 1/2ΔP τ+.

Other aspects of the blast wave interaction with CNS tissue may, however, be dominant, such as air embolism, the development of cavitation or the interaction of blast EMF fields with the pressure and induced stress fields. EMF measurement depends on the explosive type combined with a host of environmental factors with a frequency range of 1 Hz to 1 GHz within 80–600 µs from the initiation of detonation. The process of cavitation is somewhat akin to boiling, where the subatmospheric negative phase of the blast pressure wave causes local tissue pressure to fall below the interstitial fluid or tissue saturated vapor pressure. This may result in gas formation that can grow to cause tissue micro-bubble with subsequent collapse and the potential for associated tissue damage. The presence of a number of processes in a detonation blast, such as shock-wave propagation, thermal effects, EMFs and chemical by-products, make determination of relative
contributions to CNS injury difficult [36]. This situation is further complicated by the real possibility that such processes may not only be independent but also additive, with the potential for multiplicative effects. It is possible to consider these effects in terms of near and far field, with only shockwave having longer range or far field effects. Some modeling of the biological response to blast has been performed, and a robust lung injury model based on the work of Stuhmiller JH (1997) is available, allowing injury assessment in both the near and far field [37]. Using an energy equation and the amount of irreversible work produced by the blast, a lung injury model was generated. Interestingly normalization of blast-generated work by body mass allowed correlation of the lethality results between species. Because the brain is not a homogeneous tissue but contains significant anisotropy, this is likely to make determination of such injury curves more complex. Indeed, even at low strain rates regional alterations in porcine brain material properties were found [38]. This again is likely to be more complex at high strain rates, such as those seen in blast.

A number of animal model studies have demonstrated CNS injury in relation to blast effects using shock tubes (primary blast effects) and following detonation. Evidence of axonopathy was found together with edema, hypertrophic astrogliosis and alteration in the inducible nitric oxide synthetase gene expression in selected sample areas [39–45].

**Clinical context of CNS blast injury**

As previously discussed, TBI may be categorized as pTBI or cTBI. cTBI is defined as mTBI, moderate and severe according to the development of loss of consciousness (LOC), post-traumatic amnesia (PTA) and the Glasgow Coma Score (GCOS). mTBI is considered to have a GCOS of 13 to 15, or a LOC less than 1 h or PTA less than 24 h. Moderate TBI has a GCOS of 9 to 12, a LOC more than 1 h and less than 24 h or PTA greater than 24 h, or 7 days while severe TBI has a GCOS of 9 to 8, or a LOC more than 24 h or PTA greater than 7 days. These are either/or criteria with the most severe criterion used for categorization. It is often the case that not all TBI severity criteria will be appropriately recorded [18,46]. A further important differentiation is between primary and secondary TBI with primary TBI, resulting from the direct effects of the injury mechanism, such as a blast or blunt trauma, and secondary injury resulting from postinjury complications, such as raised ICP. The neurophysiological mechanisms associated with concussion in head injury were extensively reviewed recently by Shaw [47]. In this excellent review, the analogy between concussion and generalized seizure was suggested with a short-lived neuronal excitatory phase (paroxysmal depolarization shift) causing a loss of consciousness and postural control followed by a variable period of neuronal depression. This is the so-called convulsive theory of concussion, while PTA is considered to occur due to interference with memory consolidation by the concussive event (consolidation hypothesis of memory).

The earliest English language description of blast-associated TBI appears to be from Mott in 1916 where commotio cerebri produced by ‘direct aerial’ compression is described. The patients suffered varying intervals of unconsciousness associated with severe headaches and meningism [8]. More currently, there is some evidence that military TBI associated with traumatic vasospasm (TCV) may have a worse outcome as measured by the GCOS. However, there was no blast-associated increase in the proportion of patients with angiographically diagnosed TCV in the same cohort [48]. This recent study from OIF/OEF would appear to suggest that blast per se does not contribute to outcome status in military-associated pTBI and severe and moderate cTBI; however, the study was retrospective with a total of 57 patients with approximately 80% exposed to blast [48]. The Israeli experience was summarized recently in 2005 and derived from the case series at the Hedassah-Hebrew Hospital from 1 October 2000 to 1 September 2004. A total of 44 patients with head injury secondary to bomb attacks were seen, with nine severe TBIs, five moderate TBIs and 30 mTBIs [49]. Although there was no descriptive breakdown, the authors do note the critical nature of increased ICP measurement following blast injury as a complication of severe TBI. They emphasized management of cerebral swelling and edema. Such cerebral edema may be consistent with the effect of diffuse high-strain rate shockwave passage through cerebral tissue. Collation of the Israeli experience from 1982 to 1985 in Lebanon of 180 TBI patients suggested an increase in diffuse axonal injury (DAI) following cTBI associated with blast [50]. Some of the more anecdotal accounts of blast CNS injury are referenced [51–53].
In reference to mTBI, a further subclassification derived by the American Academy of Neurology in the form of a three point grading system is available, with Grade I consisting of transient confusion and no LOC with a duration of less than 15 min. Grade II consists of transient confusion and no LOC with a duration of more than 15 min, while Grade III consists of any loss of consciousness for any period of time. Diffuse axonal injury is considered to be the associated structural change following mTBI or concussion both in animal models of mTBI and human autopsy series where the patients with concussion died of unrelated causes. Ultrastructural changes consist of axonal microtubular and neurofilament disruption affecting rapid axonal transport. These injuries are consistent with shear injury and form the pathological basis of injury following blast. The pathology associated with this type of mTBI is the current focus of continued study, especially in association with PTSD.

Pharmacological treatment & diagnostics of TBI
Pharmacological therapy for TBI has been singularly unrewarding, with no randomized placebo-controlled clinical trials achieving efficacy. Most therapeutic advances have occurred because of more rapid delivery of the injured patient to healthcare facilities together with improvement in neurocritical care. Recently, in a relatively small Phase II trial (n = 100), 77 patients were randomized to receive progesterone (bolus 0.71 mg/kg over 1 h, then 0.5 mg/kg for the next 11 h, with a subsequent additional five infusions for a total treatment duration of 3 days) within 11 h of TBI, with 23 patients receiving placebo. GCOS ranged from 4 to 12 with 72 patients having severe and 38 with moderate TBI. The treatment and nontreatment group were well matched on basic demographics, such as age, race, index GCOS, mechanism of injury, Injury Severity Score, door-to-needle time and the Marshal computed tomography score. 30-day mortality was less in the treatment group, although not significantly, while the extended GCOS had significant efficacy in favor of progesterone therapy in the moderate TBI group. An interesting meta-analysis of progesterone in animal studies was performed by Gibson and colleagues. Extension of this Phase II trial to a large Phase III trial has recently been funded by the NIH with the hope of generalizing these initial results into clinical practice. Extension and development of current neuroimaging techniques, particularly diffusion tensor imaging (DTI), may well result in imaging surrogate markers for TBI. Recent studies have noted DTI evidence of white matter injury across the whole TBI spectrum, but only moderate and severe TBI resulted in irreversible myelin or white matter damage. The greater the white matter pathology the greater apparent cognitive deficit, with mTBI abnormalities resolving within a 6-month time frame.

Future perspective
Blast-related brain injury is gaining recognition in the medical community and public eye as a result of the current global military situation and increased awareness of a terrorist threat. Although the exact mechanisms remain to be determined, there is evidence that primary blast exposure results in neurological injury. Future endeavors in understanding primary blast TBI need to focus on two main avenues of research: prevention of blast-related TBI and treatment.

Prevention of blast injury will arise through objective monitoring of blast exposure, primarily in military cohorts, and the subsequent development of protective gear and armor. In the treatment realm, one of the key challenges is conducting large-scale, systematic studies of neuroanatomical, neurophysiological and cognitive changes resulting from primary blast. Advances in neuroimaging techniques make it possible to elucidate the anatomical and physiological consequences of blast TBI. These findings, in conjunction with cognitive and functional outcomes, can be used to guide acute treatment and long-term rehabilitation strategies. As increasing numbers of military personnel and civilians are exposed to blast, it may be possible to test these treatment strategies, ranging from cognitive and behavioral therapy to pharmacological interventions, via large-scale clinical trials.

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Executive summary

**Historical context of blast**

- Blast injury has been recorded across numerous conflicts since the Napoleonic Wars to the current conflicts of Operation Iraqi Freedom and Operation Enduring Freedom. Each conflict increases societal awareness of blast and contributes to efforts toward mitigation.

**Blast & detonation wave physics**

- The conversion of chemical energy rapidly into thermal, electromagnetic, acoustic, kinetic energy of projectiles, fragments and spall, together with the flow field of the shockwave are complex events with many stochastic, boundary and ambient conditions affecting the end product.
- The simplest model of a blast pressure is the Friedlander waveform, where the blast-overpressure decrements by the inverse cube of the distance (Hopkinson Rule).

**Injury parameters & models**

- There are no available injury criteria for blast related CNS injury. Injury criteria are available for impact injury and as such provide some insight into the type of criteria likely required in blast-related CNS injury criteria.
- There is a need to develop CNS injury criteria across a range of strain rates encompassing blunt or impact traumatic brain injury (TBI), ballistic-related TBI and blast.

**Clinical context of CNS blast injury**

- Blast CNS injury is often complicated by secondary, tertiary and quaternary blast events.

**Pharmacological treatment & diagnostics of traumatic brain injury**

- Neuroprotectants are not currently available for TBI and therapy consists of early access to advanced medical care with prevention of secondary complications.
- Application of diffusion tensor imaging may have utility in defining mild TBI from moderate and severe TBI.

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**Bibliography**

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