Blast-Induced Neurotrauma: Surrogate Use, Loading Mechanisms, and Cellular Responses

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Background: With the onset of improved protective equipment against fragmentation, blast-induced neurotrauma has emerged as the "signature wound" of the current conflicts in the Middle East. Current research has focused on this phenomenon; however, the exact mechanism of injury and ways to mitigate the ensuing pathophysiology remain largely unknown. The data presented and literature reviewed formed the fundamentals of a successful grant from the U.S. Office of Naval Research to Wayne State University.

Methods: This work is a culmination of specialized blast physics and energy-tissue coupling knowledge, recent pilot data using a 12-m shock tube and an instrumented Hybrid III crash test dummy, modeling results from Conventional Weapons effects software, and an exhaustive Medline and government database literature review.

Results: The work supports our hypothesis of the mechanism of injury (described in detail) but sheds light on current hypotheses and how we investigate them. We expose two areas of novel mitigation development. First, there is a need to determine a physiologic and mechanism-based injury tolerance level through a combination of animal testing and biofidelic surrogate development. Once the injury mechanism is defined experimentally and an accurate physiologic threshold for brain injury is established, innovative technologies to protect personnel at risk can be appropriately assessed. Second, activated pathophysiological pathways are thought to be responsible for secondary neurodegeneration. Advanced pharmacological designs will inhibit the key cell signaling pathways. Simultaneously, evaluation of pharmacological candidates will confirm or deny current hypotheses of primary mechanisms of secondary neurodegeneration.

Conclusions: A physiologic- or biofidelic-based blast-induced tolerance curve may redefine current acceleration-based curves that are only valid to assess tertiary blast injury. Identification of additional pharmaceutical candidates will both confirm or deny current hypotheses on neural pathways of continued injury and help to develop novel prophylactic treatments.

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Penetration and/or fragmentation injuries remain responsible for the greatest number of battlefield deaths and injuries. However, the ensuing conflict in Iraq and Afghanistan demonstrate a shift in injury patterns from penetration and/or fragmentation type injuries to increases in primary blast-induced neurotrauma, also known as traumatic brain injury (TBI), due to improved body armor and the ever-increasing use of improvised explosive devices (IEDs); hence, our discussion will focus mainly on primary blast injury.[1–3] Physicians at the Walter Reed Army Medical Center say that each war has a "signature wound"; World War I produced damaged lungs from poison gases, World War II caused cancer from radioactive bombs, and the Vietnam conflict led to skin disorders from Agent Orange.[1] Blast-induced TBI is emerging as the signature wound in the current conflicts.[4] Because information regarding blast-induced TBI is limited, research efforts are responding to the required needs. However, challenges to progress lie in (a) reliance on inappropriate testing surrogates for injury tolerance and mitigation design, (b) limited understanding of blast-induced mechanisms of TBI and secondary neurodegeneration, and (c) the ability to integrate this information into current protective equipment standards expediently.

One of two areas of greatest need is an appropriate physiologically based injury tolerance curve for primary blast-induced TBI so that manufacturers, academics, governments, and end users can base new protective equipment designs on valid injury criteria and help to develop appropriate personal protective equipment (PPE) standards. Recent published primary blast injury criteria include tolerances for lung damage and lethality percentage but does not include injury tolerance criteria for TBI.[5] Published pathology scoring systems for blast injuries, although considering many types of head injuries such as burns, fractures and lesions, have only recently considered TBI using surrogate head acceleration as a measure of tolerance.[6–9] The need for developing a physiologic and mechanism of injury-based tolerance curve for TBI is fundamental to progress.

The second area where additional research is most needed concerns the ability to retard the secondary neurodegenerative molecular effects of blast-induced TBI. Essentially, multiple brain cell pathways become "activated" soon after blast exposure. Many of these pathways continue to harm brain cells to the point of cell death (secondary neurodegeneration). These harmful pathways continue for some time after first exposure. Novel pharmaceutical mitigation designs that enhance but not replace PPE will capitalize on knowing the exact cell signaling pathways, which continue neurodegeneration soon after initial mechanical insult.[10] Currently, the main pathways involved in blast neurotrauma are hypothesized to be the production of nitric oxide synthase and glial cell activation.[11,12] Investigation using drugs that inhibit the main pathways as prophylactic treatments

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will clarify the major mechanism of injury and evaluate a novel treatment method.

NEW WAR AND ITS EMERGING INJURIES

It may be difficult to know the exact number of TBI cases that actually occur and compare those numbers to past conflicts because military epidemiology currently categorizes TBI as "head and neck" injury.[13] However, three indices implicate increased TBI in Iraq and Afghanistan when compared with previous conflicts. First, explosion exposure and fragmentation mortality have declined,[2] making it possible to track the resulting brain injury. Second, more advanced knowledge of the effects of closed head injury and mild TBI is being discussed in the literature between the treating clinicians.[14,15] Lastly, up to 88% of all injuries seen at second echelon medical treatment sites are due to blast exposure.[16,17] One study reported that injuries sustained by 97% of one Marine unit in Iraq were due to explosions, where 65% of these explosions were due to IEDs and 53% of the injuries involved the head and neck.[3] More than 1,700 persons or roughly 28% of all medically evacuated personnel are believed to have sustained some degree of TBI since the inception of the war despite challenging diagnosis.[18,19] Closed TBI accounted for 88% of 433 individuals studied at Walter Reed Army Medical Center.[20] These data confirm that blast injury (mostly primary and secondary) is the single most common injury etiology in the current conflicts.[3]

In many cases, the biggest threat associated with explosive munitions or IEDs is their associated fragmentation (e.g., the metal casing of military shells, nails, or other objects designed to fragment upon detonation) also referred to as secondary blast injury.[21,22] Current PPE such as the Outer Tactical Vest worn by U.S. Military personnel and associated standards are being revised to meet the shift in necessity, when compared with previous requirements based predominantly on ballistic threats. Therefore, the remaining mechanism of TBI is primary blast injury or the shock wave effects of these weapons.

In February, 2001, Dearden[23] recognized that a large number of weapon systems being developed and used during the 1990s seemed to implement blast as their primary damage mechanism. These enhanced-blast devices (Thermobaric, Fuel-Air, Metallized, and Reactive Surround)[24] significantly change the shape of the typical blast profile by increasing the duration and impulse for an equivalent peak pressure resulting in increased transmitted energy to the target.[25,26] Dearden predicted that the United Kingdom and coalition forces would have to face more of these types of weapons in future conflicts. Although IEDs became much more prevalent, just before the current conflicts in Iraq and Afghanistan, enhanced blast weapons were thought to become eventually used significantly by terrorists.[23]

SURROGATE USE FOR MECHANISM-BASED INJURY KNOWLEDGE

IED Threat and Surrogates

The sudden emergence of IED threats combined with the lack of existing adequate protection have required the need for rapid progress in the design of blast protective equipment. However, designing equipment for blast mitigation ideally requires an awareness of the underlying injury mechanisms. In absence of current solid knowledge of the injury mechanism, the effectiveness of blast protective equipment is currently validated through the use of existing standardized mechanical surrogates, which were in fact largely developed and validated for assessing the safety designs of automobiles,[7,27] potentially having low relevance to the blast-injury scenario. For instance, although the Hybrid III (HIII) manikin remains useful for assessing the global bodily motions induced by blast,[27] it might not be appropriate for more "local" blast injury predictions.

Ideally, surrogates should be "biofidelic," which implies that they should have similar biomechanical responses in relation to corridors established from human specimens for a given injury generating energy.[28–31] Several anthropomorphic surrogates having biofidelic tissue simulant materials have been developed (MABIL[32] and UK Thoracic rig[33]) in recognition of the critical importance that stress-wave mechanics has for assessing blast injuries. Once data from such biofidelic surrogates is available, injury criteria must be applied. A valid injury criterion has been defined as "a biomechanical index of exposure severity which, by its magnitude, indicates the potential for impact induced injury."[34] The most useful injury criterion for safety system development will give an increased understanding of the mechanism of injury and the time at which it occurs. Because surrogates can only record biomechanical measurements (linear/angular acceleration, velocity, displacement, force, torque, pressure), the link between the surrogate and the physiologic injury model (animal) requires significant supporting data.[35] Although injury criteria have been developed for the UK Rig, no such criteria exist yet for the MABIL surrogate.

Blast-Induced Neurotrauma

In the case of blast-induced neurotrauma, determining the injury mechanisms is challenging, particularly, because of the undefined sensitivity of brain function to the stress conditions that might be inflicted by the blast. As such, a relevant area to investigate is the direct effect of blast pressure on the brain. Recently, Chavko et al.[36] measured in vivo brain pressure during blast exposure in rats. They found that while cranium overpressure magnitudes were similar, the waveforms measured in vivo differed when the cranium was oriented longitudinally versus transversely to the shock tube flow. This indicates the geometrical dependence of how the wave is transferred into the brain and the ability to measure pressure in vivo during blast exposure. The geometrical differences between humans and animals will affect the transfer of the fraction of the blast that encroaches on the individual brain cells. Nevertheless, in vivo pressure may be an appropriate mechanical variable for the development of injury tolerance curves because it will relate the load experienced at the tissue level to neuropathophysiology rather than the external static overpressures typically recorded.

Unfortunately, in vivo pressure measurements are invasive and not suitable for the development and validation of PPE against blast. Therefore, one must rely on mechanical

variables that can readily be measured with surrogates and for which injury corridors have been defined. Unfortunately, blast-induced brain injury corridors are likely to be different from existing automotive-based head response corridors because it has been shown that different injury generating energies cause distinctly different biomechanical corridors in human specimens.[31] To find appropriate biomechanical corridors for blast-induced brain injury, one requires brain mechanical response data using a suitable biomechanical response measurement. Although brain kinematic response experiments have been performed for blunt head impacts,[37–39] experiments performing this measurement under blast conditions could not be found and are vital to understand the mechanism of brain injury from blast.

Surrogate Head Response to Blast

Three experimental trials were carried out in which a HIII head form was subjected to the venting flow exiting a shock tube. A typical resultant head acceleration from these tests, processed with the CFC 1000 filter, is shown in Figure 1, A. The resultant peak head acceleration was found to be of the order of 40*g*. The mean duration of the resultant head acceleration was 3.22 ms ± 0.14 ms (95% confidence interval), as measured by the Diadem 10.2 software using the standard for head acceleration pulse width measurements (SAE J1727). The duration over all peaks was estimated as 8.50 ms ± 0.23 ms. The mean peak side on pressure generated by the blast wave measured 155 cm inside the shock tube from the open end was 92.4 kPa ± 6.1 kPa, based on a 95% confidence interval.

Figure 1, B shows three high-speed video (3,000 Hz) frames depicting the shock wave exiting the tube (left, $t = 0$ ms), the vortex (arrow) produced by the exiting shock wave (middle, $t = 1.3$ ms), and the "blast wind" of accelerated air initiating motion of the instrument cables (arrow) through momentum transfer but before motion of the head form because its greater mass (right, $t = 7$ ms). A piece of Mylar (arrow) exiting the tube shows that cold, high-density air expanded from the driver portion of the shock tube (contact surface) is interacting with the headform.

An important observation from Figure 1, B is that the shock front transmits through and around the headform before any detectable motion of the head as a rigid body. This indicates that if the main injury mechanism is pressure based, the injury outcome will not significantly depend on the actual global body motion of the head, and the greatest harm is generated before any detectable motion.

Head Injury Criterion

The Head Injury Criterion (HIC)[40] relates resultant head acceleration to various brain injury and concussion levels. The application of HIC in the development and validation of safety features in the automotive field has lead to successful design improvements. The HIC was validated using injury indicators such as cadaver skull fractures from a single time point postimpact. HIC values

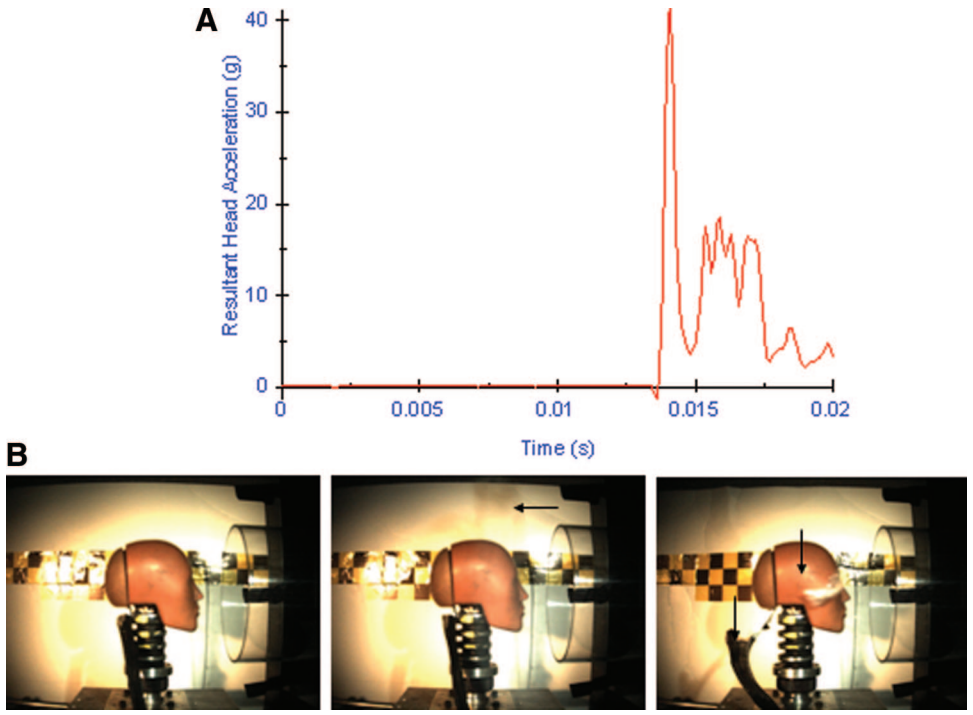
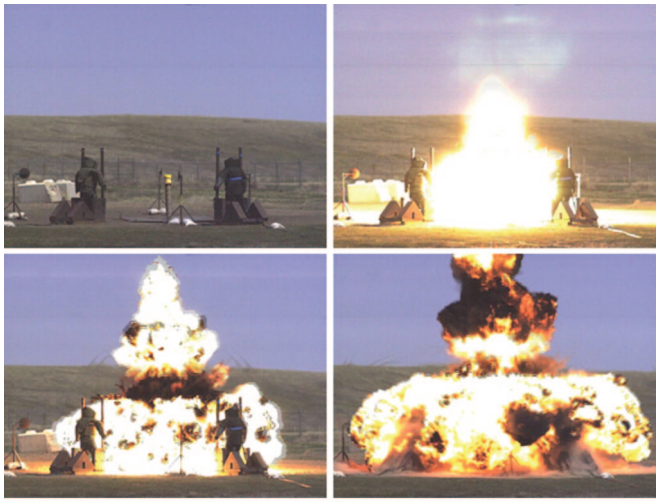


Figure 1. (*A*) A typical resultant head acceleration trace (CFC 1000 filtered) from tests using a Hybrid III head-neck set-up in the blast flow of a 12-m long shock tube. (*B*) Three high-speed video (3,000 Hz) frames depicting the shock wave exiting the tube (left, $t = 0$ ms), the vortex (arrow) produced by the exiting shock wave (middle, $t = 1.3$ ms), and the "blast wind" of accelerated air initiating motion of the instrument cables (arrow) (right, $t = 7$ ms). A piece of Mylar (arrow) exiting the tube shows that the driver portion of the shock tube (contact surface) is interacting with the headform.

are currently only validated for automotive-based impact durations that are >20 ms.[41–45]

Being calculated based on readily available engineering measurements taken from HIII manikins that can survive blast testing, the HIC was deemed practical for quickly developing and testing new head protective blast mitigation equipment. It was viewed as the single most effective engineering measurement that can be used as a "blast dosimeter" in these scenarios as a guide to head injury potential. However, many questions remain as to the validity of discounting the whole process of internal stress wave mechanics and possible superficial results when using mechanical surrogates like the HIII manikin and applying acceleration-based injury criteria to blast-induced neurotrauma in basic research.

In particular, resultant head acceleration durations significantly below 10 ms, and often below 1 ms,[7,8] have been observed during full-scale blast testing involving unprotected HIII manikins located in the near-field blast regime. In such tests, performed at the facilities of Defense R&D Canada, Suffield, the HIII manikins were subjected to the blast of 10 kg of C4 explosive at a standoff distance of 3 m. The very short durations, when compared with those obtained from automotive crash tests for which the HIC was validated, raises suspicion as to whether the HIC could be applicable for blast scenarios. The objective of these tests was to validate the effectiveness of Explosive Ordnance Disposal (EOD) ensembles (see Fig. 2 for high-speed video frames from these tests). When manikins were fitted with EOD helmets, the HIC durations were increased 5 ms to 12 ms, and the high frequency content was also significantly reduced. Although this provides more confidence in the use of HIC for the EOD helmet protected cases, these durations are still below those observed in the automotive crash tests.

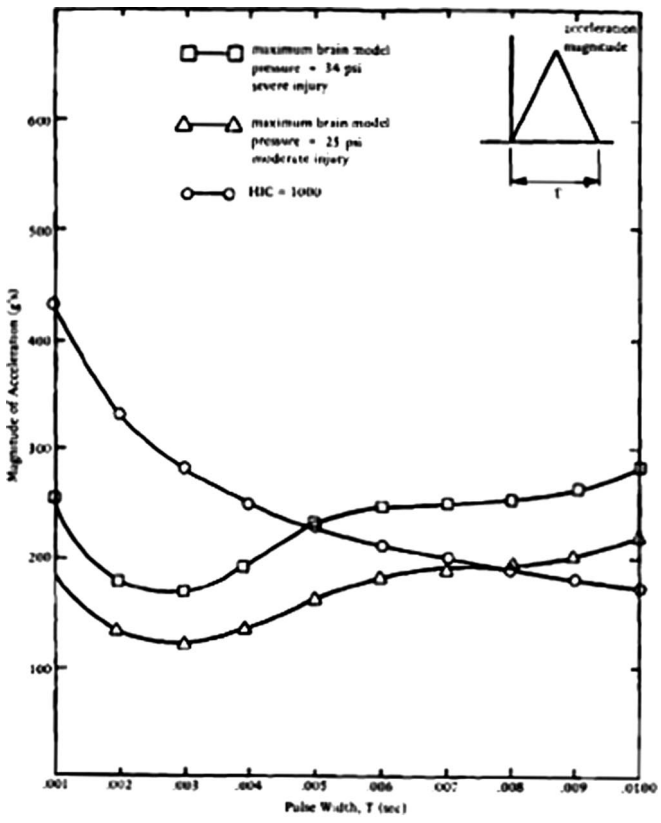


Courtesy: Defence R&D Canada – Suffield.

Figure 2. Images from a high-speed video of a full-scale blast evaluation of Med-Eng (now Allen-Vanguard) Explosive Ordnance Disposal Ensembles using Hybrid III mannequins, performed at the facilities of Defence R&D Canada, Suffield. Ten kilograms of C4 with a standoff distance of 3 m places the mannequins within the range of the fireball. Head accelerations were <10 ms in duration.

Similar to the 10 kg charges used to test EOD ensembles, typical "road side bomb" exposures occurring at ~1 to 10 times the fireball radius (mid-field blast regime) correspond to acceleration durations below 20 ms.[46] Although the far-field blast regime typical of nuclear weapons would sustain longer head acceleration durations, near-field and mid-field regimes are currently the greatest threats.

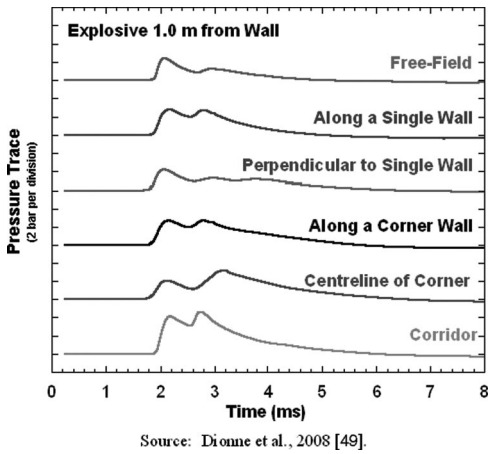
Ward et al.[47] found that brain injury tolerance using HIC (HIC = 1,000) and brain pressure plotted versus the duration of the acceleration pulse (Fig. 3) shows that HIC and pressure tolerances only coincide over a narrow region. If tissue pressure loading is indeed a primary mechanism of injury for blast exposure, HIC values of durations typical of current blast threats may not correlate well to injury severity. The complex cellular signaling that is initiated by mechanical injury accounts for prolonged central nervous system damage and cellular dysfunction.[35] A physiologically based tolerance curve will be dependent on a combination of incident tissue loading, genetic predisposition to initiate catastrophic cellular cascades and how long after the incident the patient is clinically evaluated. Although HIC may indicate injury risk, it only relates to the initial mechanical incident and therefore cannot be used to define physiologic injury tolerance levels over time.



Source: Reprinted with permission of the International Society of Automotive Engineers. Ward et al., 1980 [47].

Figure 3. Ward et al.[47] demonstrated that HIC of 1,000 and pressure-based tolerance do not coincide over a large region of durations.

For concerns related to the very short duration of accelerations for blast events and correlation with pressure tolerance, it can be argued that acceleration-based injury criteria such as the HIC might not be suitable for so-called complex blast. Examples of complex blast phenomena include waves reflecting, reverberating, and interacting with one another within building walls or within breached vehicles. These complex blast waves may experience peak reflected pressures greater than 10 times peak ambient static pressures outside these enclosed structures and a space volume dependent slower rise of quasi-steady pressure that can remain much longer (>100 ms).[46,48] To illustrate the effects of complex blast, results from numerical simulations of the interaction of a blast wave with rigid walls, performed using a 3D computational fluid dynamics software,[449] are shown in Figure 4. The detonation of a 5 kg charge of C4 explosive was modeled. The charge was located 1 m away from either a single wall (in two orientations—perpendicular to the wall or along the wall), a corner (two orientations—equidistant from both walls or along one of the two walls), as well as in a corridor configuration. For comparison, a reference free field case was also simulated. The pressure traces shown in Figure 4 clearly indicate the enhanced level of complexity introduced with rigid surfaces. In the most confined cases, the secondary pressure peaks become larger than the original one, and the pulse duration is more than doubled. These complex waves typically do not consist of a single traveling wave front followed by intense blast winds that interact with the human from a single orientation causing acceleration in a single direction.[48,50] Blast winds traveling in opposite directions might result in a near stagnant flow, minimizing the amount of head displacement for individuals subjected to such blasts. However, very high pressures and blast impulses are still capable of causing neurotrauma, which implies that using acceleration-based injury criteria could be erroneous in these situations.



Source: Dionne et al., 2008 [49].

Figure 4. Results from numerical simulations using 3D computational fluid dynamics software of the interaction of a blast wave with rigid walls are shown. Five kilograms of C4 explosive was modeled 1 m away from either a single wall (in two orientations—perpendicular to the wall or along the wall), a corner (two orientations—equidistant from both walls or along one of the two walls), as well as in a corridor configuration. For comparison, a reference free field case was also simulated.

The theory behind using acceleration as an injury criterion, as HIC does, is based on the second law of Newton relating acceleration to the force applied to a rigid body. Because the brain is viscoelastic in nature, its impact response is more complex than a rigid body.[37–39] The Viscous Criterion has been shown as a promising injury criterion for blast exposures to the torso in the 50 m/s to 100 m/s velocity of deformation range.[34] A similar approach might thus prove suitable for the development of brain injury models as deformation and strain and/or their rates can be considered good mechanical criteria for developing blast-induced TBI corridors.[35,51–54] In such a case, physical brain surrogates, involving for instance an actual brain stimulant inside a surrogate skull, would have to be developed.

Future Research

As outlined above, more knowledge on blast injury mechanisms and injury models is required to guide manufacturers of personal blast protective equipment in arriving at appropriate designs that will reduce the injury potential. Although the actual injury mechanisms, once discovered, are unlikely to be directly linked to engineering measurements made on physical surrogates (e.g., acceleration might not be the cause for blast-induced TBI), it can be hoped that the output from simple physical surrogates will be successfully correlated to the injury mechanisms and models. As a result, developers of protective equipment will be able to reliably test and validate their designs and provide superior protective solutions to the end users. The first step required to arrive at that goal is to pursue research on the true causes of blast neurotrauma. Some potential avenues are presented in the next sections.

TISSUE LOADING CAUSING SECONDARY MOLECULAR AFFECTS

Brain Pressurization Mechanism

Hypotheses regarding how the brain becomes pressurized as a result of blast exposure is generating much debate.[55] Several key fundamental studies,[56–61] during the post World War II era, may provide insight into the current problems. Studies were conducted where the location of the blast exposure (whole-body, head protected, body protected) of rabbits was controlled while measuring the transduction of the pressure wave in bone.[56,59,61] It was demonstrated that while bone reflects 71% ± 16% of the pressure of ambient shock waves, traveling at 580 m/s, the fraction transduced was "transmitted to the brain directly through the skull" at speeds in excess of 3,000 m/s despite differences in bone structure.[56,59,61] Studies investigating what fraction is reflected and transmitted by the impedance mismatch between the inner skull and brain or the fraction sent as a lateral shear wave around the skull could not be found. Total pressure within the skull, however, was amplified slightly (~8%) when compared with the external peak shock wave static pressure.[56,59,61] Shielding the specimen's head from the shock wave, <30% of the blast overpressure was transduced to the brain while thorax

transducers recorded <50%.[56,61] In a similar study using unprotected deceased rhesus monkeys, Romba and Martin[62] showed a 6% amplification in peak pressures within the brain when compared with peak external shock wave pressures which is in good agreement with Clemedson. Again, when shielding the head the brain pressure was minimally elevated with respect to external pressure. Further, during body-protected trials the brain pressure amplification remained.

Clemedson et al.[33,58,60] demonstrated that as the shock wave penetrates skin, bone, muscle, and various thoracic soft tissues, the pressure front (a) elongates its rise time up to several hundred microseconds (ambient, <40 μs; brain, 500–850 μs; muscle, 330–790 μs), and (b) the pressure decays as a function of distance from intrusion location (body surface, 1; under skin, 0.9; plura, 0.5; lung, 0.48; heart ventricle, 0.28). This is critically important because cellular injury is related more to stress rate than total stress[63] and pressures transduced by areas of the body below the neck will be damped by the tissue before arriving at the brain. It is likely that <30% of the blast static overpressures transduced to the brain during the above head shielding experiments most likely reflects transduction from exposed neck regions. The skull itself has openings such as the neck/gullet, ear canal, sinus, orbits through which the pressure wave can be propagated.

Pressure transduction through fluids of the circulatory or cerebrospinal systems remains another pressurization pathway. Clemedson[56] concluded that neither mechanism was significantly important, considering the large drop in peripheral resistance in highly vascularized tissue such as the brain. Further, while increased petechia (small hemorrhage) has been noted in both the mid-brain and cerebellar regions of blast victims, no direct evidence of circulatory system involvement could be found. The most recent modeling results show that intracranial pressure as a result of shock wave exposure tends to concentrate near the same anatomic regions as the noted petechia, indicating injury is due to local pressurization and not fluid percussion transduction.[64]

The competing hypotheses of the transduction of shock wave to pressure wave inside the brain lead to a combination of the following conclusions: (a) primarily macroscopic compression and in vivo transduction from soft tissues of the head such as the orbits and upper neck (<100% of external pressure), (b) there is a secondary direct transduction through the skull (29% ± 16% of external pressure), and (c) there may be minor involvement of in vivo transduction from soft tissues below the neck (<30% of external pressure).

Apart from mechanisms of direct stress wave transmission, it is also credible that brain pressurization occurs from the rapid global displacement compression of the skull as a shell structure, as would occur at depth under water for example. Because cranium pressure has been shown to be ~7% greater than the external blast level, the three mechanisms do not sum linearly. It is hypothesized that in vivo cranium pressure is ~7% greater than the external shock wave static pressures with a rise time of 500 μs to 850 μs. This is not in agreement with a recent in vivo study where only the plateau duration regions differed from external profiles.[36] However, this study only performed a single trial; therefore, this hypothesis needs to be tested in detail to determine the mechanism of injury so that preventions can be designed appropriately.

Cellular Stress Rate Effects

Mechanically, the cranium-cerebrospinal fluid-brain system acts like a homogeneous highly viscous liquid when compared with air-filled organs within the body.[61] Such a system transmits a pressure wave without appreciable deformation (<3.5 mm).[37–39,61,65,66] One study showed that cell injury was more sensitive to stress rate rather than total stress indicating that large deformations are not required to cause injury.[63] Using Conventional Weapons effects software (CONWEP) with a constant standoff distance of 5 m and a trinitrotoluene (TNT) equivalence of 1.149 to mimic cyclotrimethylenetrinitramine also known as RDX, shockwave velocities were calculated for various explosive charge quantities.[67] As blast static overpressure increases, so does the shockwave and flow velocities (Table 1).[68] This in turn decreases the time at which the external shock front arrives at brain case entry/compression points. It is therefore credible that the rise-time of the transduced pressure wave will decrease; increasing cellular stress rates that in turn increase injury. Measurements at the tissue level seem to be the only way to confirm or deny this hypothesis.

Secondary Molecular Responses

It is relatively well understood that blunt neurotrauma has two actions that proceed to destroy cells of the central nervous system: initial mechanical insult and secondary molecular responses including chemical induction and gene

TABLE 1. Relationship Between Net Explosive Quantity, Ambient Static Pressure, Shock Front Velocity, and Blast Wind Velocity

Net Explosive Quantity (kg)*	Static Over Pressure (kPa)*†	Shock Front Velocity (m/s)*	BIast Wind Velocity (m/s)†
185	1,379	1,205	929
72	689	886	633
29	345	673	418
9	138	501	224
1	34	387	73

* CONWEP software based on Ref. 67.
† CONWEP software based on Ref. 68.

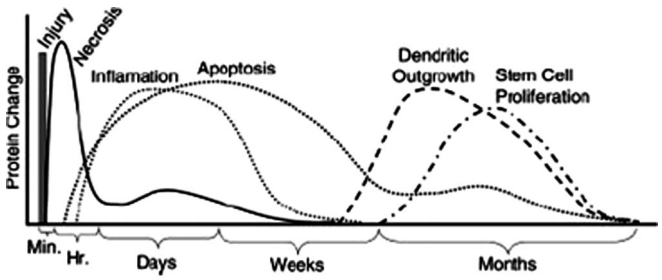


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Figure 5. Illustration of dynamic cellular events that occur posttraumatic brain injury (nonblast).

expression.[69–71] Some of the secondary responses are beneficial but many are detrimental and continue cell destruction well after the time of initial mechanical insult (Fig. 5).[35,71] Although in vivo cells during blast exposure are "stressed" by a high-speed pressure wave, cells exposed to shock waves in vitro have discrete central lesions with extensive cell death while surviving cells experience similar cascading problems that follow a specific time line.[72–74] The detrimental molecular responses specific to blast-induced neurotrauma should be studied in detail, as they could be a target for future therapeutic interventions.[75–77]

Glial Cell (a Structural/Immune Cell) Response

Kaur et al.[12,78] demonstrated that blast exposure induces global rat brain microglial activation most readily between 1 day and 14 days after insult. The hallmark of typical neurologic disorders causing degeneration such as Alzheimer's is strong microglial activation and increased expression of their cell surface antigens.[79–81] In both blast exposure studies immunohistochemistry showed a dramatic up-regulation of complement type three receptors (CR3) and major histocompatability complex I and II indicating elevated immunoreactivity and signs of continued neurodegeneration of dendrites located near activated glial cells. In 1995, Kaur et al. demonstrated that animals killed at 21 days showed reduced responses, whereas in 1997, he showed that animals killed at 28 days had returned to normal levels indicating that immunologic responses of the brain largely diminish at some time between 21 days and 28 days postexposure. The authors speculated that because activated microglial cells were located throughout the brain but generally focused in the superficial regions (cerebral and cerebellar cortices), this indicated that while the blast wave propagated throughout the entire brain, there was most likely greater blast pressure at the surface of the brain rather than its deeper regions.[12] This follows data showing the pressure wave being damped as it moves through tissue but disagrees with modeling results showing pressure concentration at deeper brain regions.[58,64]

Changes in macroglial cells (astrocytes) consist of displaced organelles and hypertrophy (swelling) with-in 1 day and 7 days after blast exposure in vivo.[82] These changes were not seen in experimental animals when survival intervals were prolonged >14 days. They suspected that a disruption in the blood-brain barrier could have caused the abnormal movement of serum-derived substances into the astrocyte, resulting in edema. Other macroglial cells (oligodendrocytes) tested remained unaffected.

Endogenous Nitric Oxide

Nitric oxide (NO) is a molecule that is produced in both pathologic and nonpathologic conditions. From L-arginine, NO is inducible or constitutively generated in the brain by three isoforms of the enzyme NO synthase (NOS): endothelial NOS, inducible NOS (iNOS), and neuronal NOS.[83] Gene expression of iNOS has been indicated in numerous neurotramatic injury modalities and models and now includes blast-induced neurotrauma.[11] iNOS produced NO is responsible for microglia/macrophage toxicity and increases glutamate-mediated neuronal damage leading to cognitive deficits as soon as 3 hours after blast exposure and lasting at least 24 hours.[11,84] Specifically, Faden et al.[85] suggested that neurodegenerative pathways after blunt neurotrauma are triggered by elevations in extracellular excitatory amino acids, primarily glutamate. Glutamate receptor (*N*-methyl D-aspartate) activation causes increased intracellular concentrations of both Ca++ and Na+ that have shown to have multiple detrimental results.[86–94] Besides serving as the primary mechanism responsible for inducing apoptosis (programmed cell death),[93] calcium overload is thought to uncouple mitochondrial electron transfer from adenosine triphosphate synthesis and over stimulating enzymes such as iNOS leading to oxidative stress and cell death.[95] However, only iNOS has been confirmed in blast induced neurotrauma.

Aminoguanidine inactivates the citrulline forming activity of iNOS at a rate of 0.46 minutes-l and Ki value of 16 μmol/L.[96,97] These observations support the assertion that aminoguanidine is a mechanism-based inactivator specific to iNOS. Aminoguanadine has been shown to reduce the detrimental neuronal and behavioral effects of blast exposure in rats and therefore helps confirm that iNOS induced NO is a key secondary mechanism in blast-induced neurotrauma.[98]

The postexposure cellular response to blast-induced neurotrauma is multifaceted, occurs quickly after initial insult, and is becoming more complex as research efforts intensify. Although key blast-induced secondary responses have been covered, the total amount of knowledge spanning all modalities of neurotrauma is outside the scope of this article and has not been addressed. The most up to date essential mechanisms underlying neurologic deficits from all modalities of TBI has recently been published (Fig. 6).[10] Besides initial mechanical tissue destruction in the form of a high velocity stress wave and cell cascade injury mechanisms discussed above, no evidence confirming these same pathways could be found for blast exposure. Investigations leading to the discovery of pharmaceutical agents that reduce or stop these secondary molecular responses from occurring will both detail primary mechanisms of continued cell death and help develop a pharmaceutical agent that could be used as a prophylactic treatment for blast exposure.

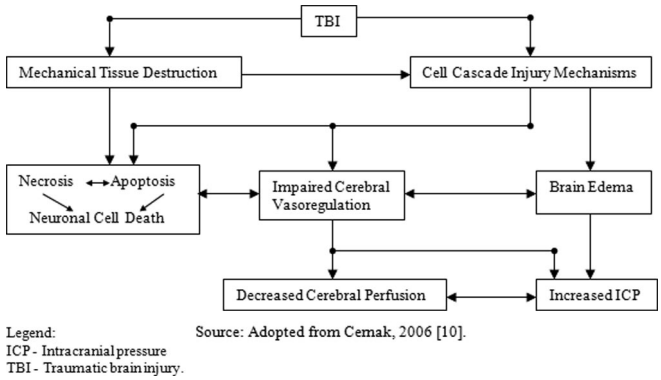

Figure 6. Schematic presentation of the most essential mechanisms underlying neurological deficits caused by multimodal TBI.

CONCLUSIONS

A physiologically based blast-induced tolerance curve may redefine current acceleration-based curves that are currently only valid to assess tertiary blast injury and therefore may help evaluate new primary blast injury mitigation designs more accurately. Further, the physiologically based tolerance curve could be easily adopted to add a "time since incident" component that would factor in the secondary molecular response so that total injury from the time of exposure could be determined.

Knowing that secondary neurodegenerative molecular responses continue cell death and military evacuation times to trauma centers range from 1 hour to several days,[99] depending on initial clinical assessment, amplifies the need for a prophylactic neuroprotective treatment. Many clinical trials are ongoing to test new neuroprotective drugs.[10] Unfortunately, many good candidates in animals are failing to show differences or even cause enhanced neurodegeneration in humans.[10] Identification of additional pharmaceutical candidates will both confirm or deny current hypotheses on mechanisms of continued injury and help to develop novel prophylactic treatments.

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