Non-Penetrating Blast-Related Injuries of the Eye and Optic Nerve

Frontlines of Eye Care, Winter 2019

The incidence of combat ocular trauma has increased with each military conflict due to the evolution of combat weaponry and tactics. Ocular injuries were observed in 2.5% of reported combat injuries in World War II and in 9% of reported injuries in the Vietnam conflict.[1,2] The increased use of high-energy explosive devices in recent conflicts has contributed to a dramatic rise in the incidence of combat ocular injuries, which increased to 13% of all reported combat injuries during the Persian Gulf War and Operations Iraqi (OIF) and Enduring Freedom (OEF).[3,4] A total of 1,732 individual cases of ocular trauma that occurred between 2002 and 2011 in OIF, OEF, and Operation New Dawn have been recorded in the Joint

Image of a high-energy blast demonstrating multiple small and large objects projected outward that can result in significant ocular damage in the absence of eye protection. Also note the flames emanating from the blast center that can cause significant ocular burn injury. (Source: U.S. Marine Corps photo by Cpl. Olivia McDonald/ Released flickr.com/photos/39955793@N07/23764675906/)

Theater Trauma Registry. Of these cases, 92% resulted from a blast event.[5] Ocular injuries from high-energy explosives, however, are not limited to the combat environment. These injuries represent a significant portion of injuries sustained by survivors of mass casualty (MASCAL) events caused by improvised explosive devices (IEDs), such as those used during the Oklahoma City and Boston Marathon bombings, and industrial explosions similar to the fertilizer plant explosion in West, Texas. Ocular injury was reported in 8% of the patients in the Oklahoma City bombing, 13% of the patients in the Boston Marathon bombing, and 14% of the patients in West, Texas.[6,7]

In 2014, the Institute of Medicine (IOM) published *Gulf War and Health, Vol. 9: Long-term Effects of Blast Exposure*.[8] In this report, the IOM recognized the causal relationship between blast-related penetrating eye injuries (i.e., open-globe injuries) and long-term visual impairment. Although the IOM acknowledged that "more serious outcomes from closed-globe injuries are possible too – mainly from blunt trauma and primary blast injury (PBI) – and include hyphema, vitreous hemorrhage, commotio retinae, retinal detachment, macular holes, traumatic cataract, optic nerve damage, and orbital fracture" – conditions and consquences of blunt trauma that are well established and long regarded in ophthalmology to cause vision loss and long-term visual impairment – the report concluded that "there is inadequate/insufficient evidence of an association between blast-related acute non-penetrating eye injuries and long-term effects on vision."[8] Based on this knowledge and clinical incongruity, a literature search of peer-reviewed clinical, pre-clinical, and computational research was conducted to further

investigate the relationship between blast-related non-penetrating ocular injuries and long-term visual impairment and to reconcile the apparent discord between clinically relevant blast-related anatomical defects presented in the literature and the IOM's conclusion.

Blast Mechanisms and Blast Wave Physics

The Department of Defense has characterized blast-related damage into five categories based on mechanism of injury: (1) Primary; (2) Secondary; (3) Tertiary; (4) Quaternary; and (5) Quinary.[9,10] Primary blast injuries are caused solely by the overpressure wave generated by high-energy explosions in which the explosive material undergoes a near instantaneous transformation into a highly pressurized gas that expands outward at a supersonic speed. The outward expansion of gas compresses the air molecules ahead of the wave front and forms an overpressure wave known as the positive pressure phase. This rapid outward compression of air molecules results in a period of low pressure behind the wave front (known as the negative pressure phase), which causes air molecules to move back towards the explosion source.[11,12] The resulting pressure wave with its distinct phases causes tissue damage primarily through three mechanisms: *spallation*, *implosion*, and *shearing*. Spallation, commonly referred to as fragmentation, occurs when the overpressure wave force exceeds the tensile strength of the medium through which it propagates. While spallation primarily affects gas-tissue interfaces, it can theoretically damage any type of body tissue.

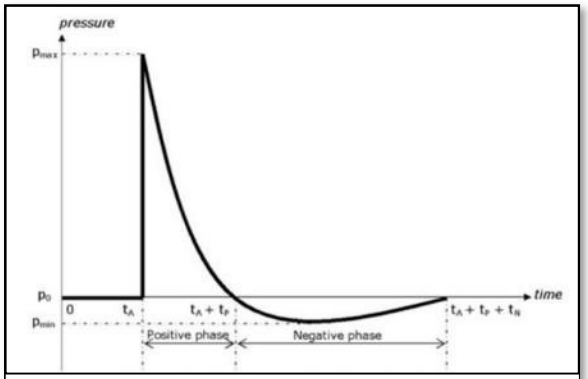
Implosion occurs when the Secondary blast injury results from debris or fragments displaced by the blast wave and wind that affect the eye. Tertiary blast injury occurs when the blast wave propels an individual through the air, causing them to strike solid objects; crush injuries, such as those caused by a building or a similar large structure collapsing on a person are also classified as tertiary injuries.

Quaternary blast injuries result from products of explosive devices, such as heat, light, or exposure to toxic substances, while quinary blast injuries are long-term effects of explosive debris and contaminants, such as chemical, biological, and radiological species.[9,10]

Blast-Related Non-Penetrating Injuries: Clinical Evidence

Several notable reports of non-penetrating eye injuries due to blast were published during the World War I and World War II time periods. The term "blast injury," however, was not commonly used at the time; instead terms such as "concussion" injuries were used to describe internal injuries caused by explosives that otherwise demonstrated no obvious external signs of penetrating or blunt injury.

In his book based on World War I experiences, *Atlas D'ophtalmoscopie de Guerre*, Pierre-Félix Lagrange, a French ophthalmologist, described lesions of the eye caused by "concussion at a distance" that results from the "violent displacement of air" from exploding shells and artillery.[13] He further hypothesized that such explosions can cause lesions that typically occur at the posterior pole, predominantly in the macular area. Additionally, the rapid movement of the eye that results from the blast causes damage to the uveal



Friedlander Waveform – the curve demonstrates the positive and negative overpressure phases of an idealized blast wave. (Source: Jerome TW, Karch SJ, Beech JC. Characterization of a 4-inch portable shock tube. USAARL Report No. 2015-04)

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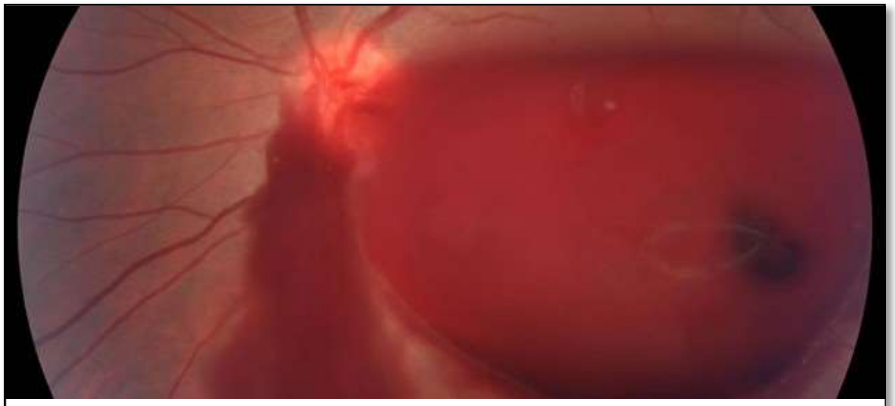
A visible blast wave from a conventional explosion. Primary blast injuries are caused by this blast wave. (Source: ke.army.mil/bordeninstitute/published_volumes/conventional_warfare/ch07.pdf)

membrane, leading to choroidal ruptures.[13] In 1919, after studying Lagrange's principles, U.S. Army Lt. Col. George de Schweinitz added that, in cases of "concussion lesions," there may not be any external evidence of injury and that the absence of anatomical signs is not enough to rule out significant intraocular lesions.[14] In fact, de Schweinitz described a case of an English soldier who presented with vitreous hemorrhage and extensive concussive damage in the fundus despite the absence of any external signs of injury.[14] A number of cases of individuals with "concussion" injuries were reported shortly after World War I. In 1923, Colonel S. Hanford McKee of the Canadian Army referenced the mechanisms elucidated by Lagrange when presented with choroidal atrophy, macular holes, traumatic choroiditis, and choroidal rupture.[15] Patients with choroidal rupture and macular hole had visual acuity (VA) of 6/60 and 4/60, respectively, in their injured eye.

Clinical evidence of blast- related ocular damage was also reported in World War II. In a case series, Bellows[16] described 13 soldiers who had sustained significant ocular trauma due to explosions but did not present with any apparent penetrating injuries or evidence of blunt trauma.

Changes in the iris, lens, and pupil; optic nerve atrophy; and choroidal and retinal lesions were among the abnormalities noted in these patients.[16] The resulting VA was 20/200 or worse in 5 of these patients and between 20/200 and 20/40 in 4 of these patients. During this time period, Sir William Stewart Duke-Elder provided further insight into the mechanism by which a blast wave causes ocular injury in humans.[17] He proposed that both the positive and negative pressure phases can contribute to injury. The blast wave causes distortion of the cornea and forces the aqueous humor, lens, and iris backwards, thereby pushing the vitreous humor toward the posterior pole. Due to the incompressible nature of the intraocular contents, this inward pressure causes the globe to expand perpendicularly to the direction of the blast.[17] Such mechanical stresses on the eye can lead to subconjunctival and intraocular hemorrhage, traumatic iritis, traumatic cataract, and secondary glaucoma.[17] Reports of non- penetrating blast-related eye injuries in military personnel have become more frequent in the recent conflicts due to an increase in the use of explosive devices on the battlefield. While high-explosive devices have been used in modern warfare since



Retinal hemorrhage secondary to blunt trauma. (Image courtesy of James Zimmerman, MD, LCDR MC (FS/ FMF) USN)

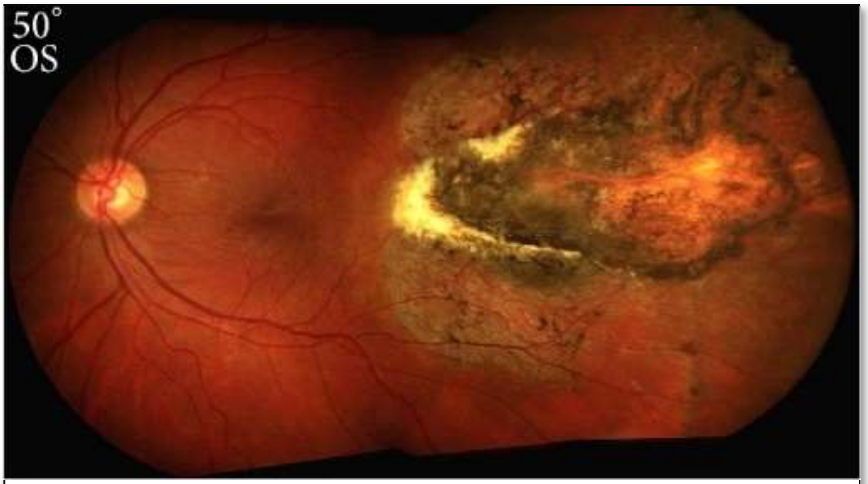
before World War I, the development of personal protective equipment has also increased the rate of survival amongst military personnel. It is likely that injury rates were actually higher in previous conflicts but were not reported because the casualty did not survive their injuries.

This additional factor may have also contributed to a rise in the frequency of noted cases of blast- related ocular trauma. However, clinical evidence of ocular injury caused solely by primary blast describing cases where the eye was damaged by "windage."[15] The cases (i.e., the blast wave) is limited and often confounded by blunt ocular trauma caused by other blast mechanisms. Nevertheless, several recent clinical studies have reported non-penetrating anterior segment, posterior segment, and optic nerve damage caused by blast in patients who otherwise had no evidence of external blunt trauma or penetrating injury caused by shrapnel and other displaced objects.

Clinical Evidence: Anterior Segment Damage

A recent literature review by Phillips et al.[18] described non- penetrating blast injuries to the anterior segment (Zone I and Zone II of the Ocular Trauma Classification System) (OTCS).[19] Blast-induced injuries involving Zone I included corneal abrasions and conjunctivitis. Zone II injuries included hyphema, iritis, iris synechiae, iris sphincter damage, angle recession, cataract, and lens luxation/subluxation.

Another review of non- penetrating anterior segment blast injuries in British soldiers noted corneal abrasions, iris and ciliary body contusions, cyclodialysis clefts, hyphema, lens contusion, and corneoscleral lamellar lacerations.[20] Cockerham et al.[21] published a prospective case series that evaluated 46 combat Veterans with blast-related traumatic brain injury (TBI) for the presence of closed-globe injuries. Eleven of the 46 patients (24%) had sustained closed-globe injuries to the anterior segment in Zone I (corneal scarring and rupture of Descemet's membrane), and 12 of the 46 patients (26%) sustained injuries in posterior synechiae, anterior subcapsular cataract, and posterior subcapsular cataract).[21] An observational cross-sectional study also examining Veterans with blast- related TBI reported a high incidence of non-penetrating anterior segment injuries, including angle recession (12 eyes of 65 patients), partial-thickness anterior stromal corneal scars (15 eyes), iridodialysis (8 eyes), and Descemet's membrane rupture (6 eyes).[22] The authors also noted significant abnormalities in the endothelial layer, including reduced endothelial cell density, increased pleomorphism, and polymegathism; these conditions have the potential to cause long-term visual dysfunction, bullous keratopathy, and corneal failure.[22]

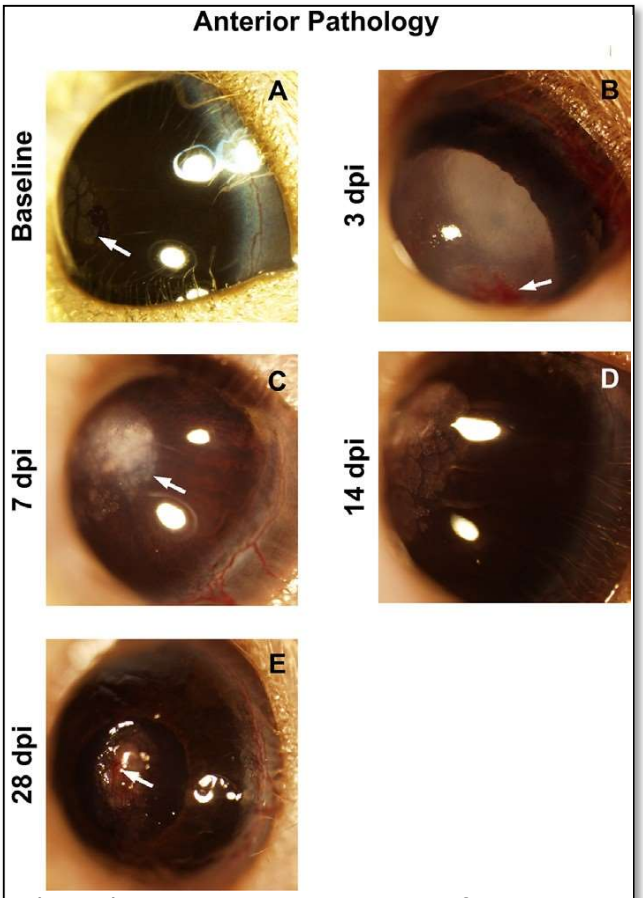


Chorioretinal scar as a result of trauma.
(Source: openi.nlm.nih.gov/detailedresult?img=P-MC5080503_CRIOPM2016-3918592.002&req=4)

It is difficult to study the specific effects of primary blast and conclusively rule out confounding secondary or tertiary blast injuries using the standard methodological techniques of clinical research; however, a few clinical studies have attempted to study the isolated effects of

primary blast waves on the eye. One study of 19 U.S. Army Soldiers who had sustained blast-related monocular injuries evaluated the effects of primary blast injury by examining the "seemingly uninjured eye" (opposite the injured eye) for corrected distance VA, automated endothelial cell density (ECD), central corneal thickness, corneal hysteresis (CH), corneal resistance factor (CRF), and cornea compensated intraocular pressure.[23] The seemingly uninjured eye was studied because, while it did not exhibit any anatomically visible signs of damage, it was nevertheless exposed to the same blast wave.

After follow-up (averaging 425 ±340 days; range: 115-1393 days post injury), only CH and CRF measures were found to be lower in the injured patients than the averages reported in healthy, uninjured patients. The authors noted that while primary blast-related ocular injury is not easily detected, it is important to conduct ongoing follow-up in patients injured by blast to determine any resulting long-term visual sequelae. A case-control study by Zone II (angle recession, traumatic mydriasis, iridodialysis, Capó-Aponte et al.[24] examined the effects of repetitive low-level blasts on ocular structures and function in 9 Marine breacher instructors who were exposed to approximately 500-600 low-level blasts per year as part of breacher training. Data from the instructors were compared to that from Marine breacher engineers who were not exposed to any blasts over a two-year period. A battery of clinical ocular tests, administered 10 times during the study period, revealed reduced corneal ECD in the breacher instructors. These results, obtained over a two-year period, suggest that repetitive primary blast may lead to long-term anatomic sequelae which could pose significant visual risk.[24]



Photos demonstrating varying amounts of anterior ocular injuries associated with mild blast trauma in a murine model. (A) Calcium deposits (arrow) are common in the normal D2 eye. (B) Hyphema (arrow), corneal edema and a cataract at 3 dpi. (C) Corneal edema and calcium deposits (arrow) at 7 dpi. (D) Corneal edema, corneal neovascularization and calcium deposits at 14 dpi.(E) A corneal scar and corneal neovascularization (arrow) at 28 dpi. (Source: Bricker-Anthony C, Rex TS. Neurodegeneration and Vision Loss after Mild Blunt Trauma in the C57Bl/6 and DBA/2J Mouse. PLoS One. 2015;10:1-23)

Clinical Evidence: Posterior Segment and Optic Nerve Damage

Numerous studies of combat eye injuries sustained in recent conflicts have produced evidence of blast-induced non-penetrating damage to the posterior segment and the optic nerve.

Injuries to these regions are classified into Zone III of the OTCS.[19] In addition to Zone I and Zone II injuries, Phillips et al.[18] reported several closed-globe Zone III injuries resulting from blast, including vitreous hemorrhage, commotio retinae, choroidal rupture, chorioretinitis sclopetaria, macular holes, retinal detachment, and traumatic optic neuropathy.

Notably, Phillips indicated that retinal detachment, severe macular injury, and traumatic optic neuropathy in particular can cause significant vision loss, and that closed-globe injuries can also lead to varying degrees of photoreceptor damage and retinal atrophy. Zone III injuries were also noted by Cockerham et al.[21] who reported that 13 of his 46 patients (28%) had sustained closed-eye Zone III injuries, including vitreous hemorrhage, peripheral chorioretinal scarring, retinal tears and holes, retinal detachment, peripheral choroidal ruptures, peripheral retinal hemorrhage, pigmented/hypopigmented scarring, macular holes, and optic nerve atrophy.

The retina and choroid, in particular, were found to be highly susceptible to blast-related injury; 12 of the 13 patients with Zone III injuries sustained damage in these regions.[21] Although vision in the majority of these eyes was 20/20 or better, the authors noted that a delayed loss of vision is possible from the injuries they reported.

Closed-globe injuries of the macular region were evaluated in further detail in a retrospective chart review of 33 soldiers (36 eyes) who sustained blast injuries in OIF and OEF.[25] A review of patient charts found that macular holes occurred in 8 eyes, macular retinal pigment epitheliopathy in 8 eyes, macular retinal pigment epitheliopathy with atrophy in 6 eyes, macular retinal pigment epitheliopathy with atrophy and foveal inner/outer segment (IS/ OS) junction disruption in 7 eyes, and macular scarring in 8 eyes.

Blurry or distorted vision were among the subjective complaints from these patients. In the 7 eyes with IS/OS junction disruption, final VA ranged from 20/30 to light perception; 5 of the 7 eyes (71.4%) had a final VA of 20/150 or worse. In addition to macular complications, optic neuropathy was observed in 7 of the 36 eyes (19%). IEDs were responsible for the majority of these injuries (86%), followed by rocket- propelled grenades and mortar blasts.[25]

A review of non-penetrating blast injuries in British soldiers by Scott et al.[20] also found damage to the posterior segment of the eye, particularly commotio retinae, retinal tears, retinal detachments, choroidal ruptures, chorioretinitis sclopetaria, retinal dialyses, optic nerve avulsion, and traumatic optic neuropathy. A prospective study evaluated non- penetrating blast-related injuries in patients presenting at a teaching hospital in Pakistan. Several cases of posterior segment damage were noted, such as vitreous hemorrhage, choroidal rupture, retinal detachment, commotio retinae, macular scars, retinal hemorrhages, and optic atrophy.[26]

Blast-Related Non-Penetrating Injuries: Pre-Clinical Evidence

Unlike clinical studies of blast-related trauma in which the individual effects of each blast mechanism cannot easily be distinguished, animal models of blast-induced injury allow researchers to isolate a particular blast injury mechanism (e.g., primary, secondary, tertiary) to understand its effect on the eye at the anatomical, cellular, and/or molecular levels.

Pre-Clinical Evidence: Anterior Segment Damage

Several animal studies have reported significant anterior segment damage resulting from primary blast. Sherwood et al.[27] reported angle recession, internal scleral delamination, and cyclodialysis in post-mortem porcine eyes exposed to a 7-22 pounds per square inch (PSI) primary blast wave generated by a shock tube. Jones et al.[28] also used a shock tube system to expose rabbit eyes to primary blast and reported clinically significant increases in corneal thickness in the eyes 48 hours after blast exposure. Several murine models have used a paintball gun blast induction method to elucidate blast-related trauma to the anterior segment, including corneal edema,[29-32] corneal neovascularization,[29,31] hyphema,[29,31] traumatic cataracts,[29,31] corneal scarring,[31] corneal abrasions,[31,32] corneal stromal scarring,[32] and thinning of the corneal epithelium.[31] Non- penetrating anterior segment damage has also been reported in

primary blast studies using rats. In a recent study, Shedd et al.[33] provided additional evidence of non- penetrating anterior segment damage in rats, including stromal and epithelial swelling, stromal scarring, corneal thickening, epithelial bullae, stromal inflammation, stromal vascularization, and subepithelial scarring. Anterior segment damage from primary blast has also been reported at the molecular level. In a shock tube experiment, Por et al.[34] demonstrated that both low-level single and repeated blast exposure resulted in increased expression of TRPV1, CGRP, SP, and ET-1 in the cornea, molecules involved in inflammatory signaling and pain perception. Low-level blast exposure in this rat model also resulted in increased neutrophil infiltration in the cornea and stromal layer.[34]

Pre-Clinical Evidence: Posterior Segment and Optic Nerve Damage

Compared to anterior segment trauma, a substantially larger literature base exists describing non-penetrating posterior segment damage to the eye and optic nerve in animal models of blast injury. Although much of this evidence may not show definitive impact on vision, it is reasonable to assume that this damage leads to increased risk to vision. In addition to angle recession, internal scleral delamination, and cyclodialysis, Sherwood et al.[27] reported radial peripapillary retinal detachment, chorioretinal detachment, and tissue damage in the optic nerve of post-mortem porcine eyes. In their shock tube study, Jones et al.[28] exposed rabbit eyes to varying levels of blast (7.52, 12, and 17.9 PSI [52, 82.7, and 123.4 kPa, respectively]) and observed an increase in retinal thickness immediately after blast exposure. Furthermore, their results indicated that peak pressure is positively correlated with post-injury retinal thickening (i.e., retinal thickness was greater when the specimens were subjected to higher peak pressures). In another rabbit model of blast injury, apoptosis of retinal ganglion cells (RGCs) was observed 20 days after exposure as measured by an increase in glutamate levels in the vitreous humor.[35]

Posterior segment and optic nerve damage has also been observed in experimental blast studies using rats. Several shock tube studies report apoptosis and gliosis in RGCs and the inner nuclear layer,[36] and damage to the retina and optic tracts.[37,38] Wang et al.[39] demonstrated bilateral apoptosis in the ganglion cell layer and inner nuclear layer of the rat retina as well as bilateral apoptosis in the optic nerve. Zou et al.[40] exposed rats to a trinitrotoluene detonation and found that, compared to control rats, blast- exposed rats had higher levels of proteins involved in inflammation, edema, and apoptosis of the retina (sustained up to 2 weeks post-blast). In addition, these rats also had greater retinal thickness at 72 hours and 2 weeks after blast exposure, higher glutamate levels peaking at 72 hours post-blast, and larger retinal lesions.

Similar results have been reported in murine models using a modified paintball gun as the method of blast induction. Posterior segment findings of these studies included retinal pigment epithelium vacuoles,[29-31,41] retinal detachment,[29,30,41] and retinal cell death.[31,41,42] Additionally, these experiments noted the presence of pyknotic nuclei in the retina, photoreceptor cell death, increased glial activity, disruption of the retinal pigment epithelium and Bruch's membrane, optic nerve avulsion, and optic nerve degeneration.[29-31,41,42] In a recent study, Evans et al.[43] used the shock tube platform to study blast-related vitreoretinal trauma in mice and found posterior vitreous detachments and hemorrhages that contained macrophages, foci of photoreceptor degeneration, evidence of detached and degenerating photoreceptor outer segments containing macrophages, subretinal hemorrhages, and lower RGC layer cellularity. Dutca et al.[44] attempted to study posterior segment damage in mice over a period of 16 weeks by evaluating RGC function using a multielectrode array and pattern electroretinogram (PERG). Their analyses revealed significant thinning of the RGC layer, a

significant increase in the firing rate of RGCs at 1 and 16 weeks post-blast, and a significant decrease in the dendritic field area 16 weeks post-blast compared to 4 weeks post-blast. These results demonstrate that blast exposure can lead to abnormal RGC physiology and progressive visual dysfunction. Furthermore, the dendritic retraction of RGCs noted 4 and 16 weeks after blast suggests that the associated visual deficits, both structural and functional, are likely permanent due to cell death and anatomically abnormal RGCs. Another study of blast-related RGC dysfunction in mice found a decrease in the retinal nerve fiber layer at 12 weeks post-blast and a small decrease in RGC count.[45] Using PERG, this study also noted decreased function of RGCs at 4 months post-blast as well as decreased axon density and increased glial scarring to the optic nerve up to 10 months after blast injury.[45] These findings, observed over several months, indicate the possibility of lasting posterior segment damage. The authors noted that both the acute and chronic deficits in PERG response after blast exposure may be indicative of potential long-term dysfunction of the retina and optic nerve.

Murine model systems have also been used to shed light on the underlying cellular, molecular, and transcriptional mechanisms involved in blast-induced eye injury. Mammadova et al.[46] demonstrated that blast exposure can lead to increased glial fibrillary acidic protein (GFAP) immunoreactivity in Müller glial cells, the principal glial cells in the retina. Increased GFAP immunoreactivity has been associated with hypertrophy of Müller cells and identified as a stress response in retinal degenerative diseases. There was a concomitant inflammatory response in the blast-exposed retinas, as demonstrated by immunoreactivity of microglia-specific proteins ba1 and CD68. Activated microglia may indicate the lack of a regulatory mechanism that would otherwise limit an immunological cascade that can contribute to retinal damage. A robust increase in phosphorylated *tau* species (Thr231 and Thr181) localized to the nerve fiber layer and outer plexiform layer was detected in blast-exposed retinas 30 days after injury. An increase in phosphorylated *tau* in Müller glia impacts microtubule assembly and stabilization and may contribute to the release of proinflammatory cytokines and other stress responses. Increased levels of phosphorylated *tau* in horizontal cells can potentially disrupt contrast sensitivity, as horizontal cells facilitate signal transmission from photoreceptors to bipolar cells. Retinal thickness, particularly in the outer layer, had also decreased by approximately 28.5% when measured 30 days after blast exposure. Because the outer layer contains cell bodies of photoreceptor cells (rods and cones), decreased thickness of the outer layer likely represents photoreceptor cell death.[46] Struebing et al.[47] explored transcriptional changes that occur in the mouse retina following blast exposure. Their findings demonstrate that blast overpressure is sufficient for causing dysregulation of genes related to metabolic function and protein synthesis in the retina, differential expression of genes in the retinal transcriptome, and altered genetic networks that are associated with the innate and acquired immune system response. They also noted that blast exposure causes progressive loss of visual function, decreased RGC soma size, and lymphocyte invasion into the retina.

Existing literature on animal models of primary blast-related ocular trauma strongly suggests that blast pressure alone is sufficient to produce clinically relevant non- penetrating anterior segment, posterior segment, and optic nerve damage that has been known to pose long-term risk to the eye and vision. However, it is clear additional research employing standardized experimental designs is needed. Future studies should collect data at further time points and determine how results apply to the human eye and the long-term effect they have on vision.

Blast-Related Non-Penetrating Injuries: Computational Modeling and Simulation

Computational modeling based on finite element (FE) analysis has been used to investigate interactions of the blast wave with the facial skeleton and the eye. A three-dimensional fluid-structure interaction (FSI) model demonstrated that blast waves reflect off the nose and brow ridges and re-direct towards the eye, causing amplification of pressure at the eye.[48] Another FSI model corroborated these results, and additionally found that blast waves produce asymmetric loading across the face; pressures were found to be higher at the medial aspect of the eye compared to the lateral aspect of the eye. When the simulated detonation was on the ground rather than in front of the face, peak pressure decreased by 40% and there was less reflection off the nose and brow ridges, suggesting that blast angle and direction play a significant role in blast loading.[49] Modeling of blast dynamics at the face and ocular regions can also determine efficacy of eye protection used by military personnel. A shock tube study found that while spectacles on the Authorized Protective Eyewear List (APEL) provided adequate protection against head-on blasts when worn, gaps between the face and the side and bottom of the spectacle lens lead to increased blast loadings reaching the cornea. Results also indicated that spectacles, particularly on large head forms, may actually lead to amplification of the blast wave on the eye. By contrast, APEL goggles, which have foam and/or rubber seals around the frame, leave no gaps between the lens and the face and were shown to have better protection coefficients against primary blast than spectacles.[50] This research suggests that variations such as anatomy of the face and blast angle must be considered to achieve optimal design and fit of eye protective devices.

Computational Modeling and Simulation: Anterior Segment Damage

Computational methods have been used to create biomechanical representations of the globe and orbit that can help predict types of injury that result from exposure to primary blast pressures. FSI models have demonstrated that asymmetric blast loading on the face and eyes may lead to globe distortion and stresses in the sclera, increasing risk of interfacial failure between scleral tissue and the orbit. Intraocular pressure (IOP) and scleral stress, however, were periodic, suggesting that the blast wave propagates and becomes scattered in the orbit.[49] FE models have also shown an increase in corneal stress and IOP as well as higher risk for hyphema and lens dislocation as blast size becomes larger and positioned closer to the eye.[51]

Another study used a three-dimensional computational model consisting of a deformable eye and its internal structures, a rigid skull, and a fluid domain in which blast wave propagation was simulated.[52] The authors applied three existing ocular injury risk models to assess potential injury outcomes of simulated blast explosions. Injury risk in one model was 8% for corneal abrasions, 11% for hyphema, and 0% for lens damage. However, when another model was applied, injury risk was found to be significantly higher for hyphema (78%) and lens damage (53%);[52] lack of uniformity between these two models may have been the likely cause of this discrepancy. The same study further explored interactions of the blast wave with intraocular structures and found that anterior structures including the lens, cornea, limbus, ciliary zonules, and ciliary muscle initially experienced a peak in maximum principal stress before the principal stress diminished significantly.[52]

Computational Modeling and Simulation: Posterior Segment and Optic Nerve Damage

Rossi et al.[53] developed a FE model consisting of the eye, orbit, and skull to study the effects of the blast wave as it propagates through the orbit. The authors noted that structures

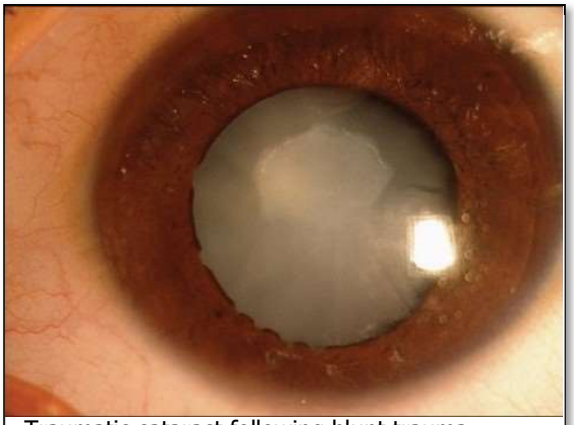
posterior to the vitreous base (e.g., equator, macula, and orbital apex) experienced a significantly higher level of pressure than anterior structures such as the cornea, indicating that orbital geometry plays a critical role in the reflection and amplification of the blast wave as it travels through the orbit. Compared to anterior structures, which experienced a relatively rapid peak pressure and a subsequent reduction in pressure, structures posterior to the vitreous base experienced much higher positive pressure phases and substantial negative pressure phases that oscillate in a sine wave-like pattern. This research team found that the pressures exerted on the retina, choroid, and optic nerve exceeded the tensile strengths that have been reported in the literature for these structures. As such, these structures are highly susceptible to damage caused by primary blast.[53] Similarly, Esposito et al.[54] suggested that retinal and optic nerve injury may result from blast due to the effects that the positive and negative pressure phases have on the macula and at the orbital apex. Other FE models have corroborated these results by demonstrating that primary blast can lead to high stresses on the macula and optic nerve[55] and an increased risk of retinal damage.[51]

Computational evidence of blast-related posterior segment damage, however, has also presented conflicting results. An FSI model suggested that while blast waves pose a risk for anterior segment injuries such as corneal abrasions and hyphema, they present a 0% risk for retinal damage.[49] Another study used a three-dimensional computational model and found that injury risk for retinal damage was 48% in one injury model, but 0% in another model.[52] However, they noted that throughout the blast simulation, reflection of waves against the bony orbit led to the observed oscillations of mean intraocular pressure, with maximum IOP occurring during the positive phase. Posterior structures such as the retina, macula, and optic nerve head demonstrated the highest oscillations and maximum principal stress.[49,52]

Computational studies have elucidated blast wave interactions with the eyes, orbit, and face. Through simulation, these models can inform continued development of improved forms of eye protection that can aid in the prevention of primary blast-related ocular injury. However, it is critical that these studies become standardized and accurately reflect the ocular effects of exposure to the types of blast encountered in combat and during civilian MASCAL events.

Discussion

The clinical, pre-clinical, and computational modeling literature reviewed here indicates that significant non-penetrating ocular injuries can occur as a result of primary blast exposure. These findings add to a growing body of evidence that casts doubt on the IOM's conclusion, which states "…there is inadequate/insufficient evidence of an association between exposure to blast that leads to acute nonpenetrating eye injuries and long-term effects on vision."[8] While the IOM acknowledges the possibility of significant blast-related non-penetrating ocular injury, their conclusion primarily stems from limitations in the literature, such as inadequately powered datasets, incomplete control populations, and lack of longitudinal studies that evaluate long-term visual deficits due to primary blast. Review of blast literature supports the IOM's conclusion to a certain extent. Very few studies have examined the long- term sequelae of non-penetrating blast



Traumatic cataract following blunt trauma. (Source: openi.nlm.nih.gov/detailedresult?img=PMC3159314_IJO-59-347-g001&req=4)

injuries, particularly for non- visible microscopic and subclinical aspects, and, despite increasing demonstration of anatomic and physiologic damage to ocular structures (e.g., corneal endothelium, RGCs, photoreceptors), the impact of these changes on acute and long- term vision remains speculative and inconclusive. On the other hand, this review's findings clearly disagree with the IOM in that the impact of anatomically visible derangements (e.g., macular holes, retinal detachments, lens dislocations) is clear and is supported by a plethora of clinical studies and reports of high-energy explosive injuries spanning more than 100 years. Unfortunately, the IOM does not distinguish between these conditions and fails to recognize this as a limitation in their conclusion.

Furthermore, it is well-established in ophthalmology literature that similar anterior and poster segment injuries also occur in patients who have sustained non-penetrating blunt trauma, and that these injuries can lead to long-term visual dysfunction, making it highly plausible that blast- related ocular damage causes similar long-term visual dysfunction. Long-term visual consequences resulting from non-penetrating blunt ocular trauma have been well documented in literature. One study evaluated patients who had sustained closed- globe injuries of various causes, including assault, sports, and motor vehicle accidents;[56] patients presented with retinal detachments, vitreous hemorrhage, proliferative vitreoretinopathy, epiretinal membrane, macular holes, and choroidal detachment, as well as certain anterior segment complications that included hyphema, traumatic cataract, zonular dialysis, angle recession, and iridodialysis.

Vision was measured after the patients underwent vitreoretinal surgery (pars plana vitrectomy and/ or scleral buckling) for treatment of posterior segment abnormalities. VA of 20/40 or better was achieved in only 33% of the patients, whereas 44% achieved VA between 20/400 and 20/50. Poor visual outcomes were noted in 24% of the patients, who had VA of 20/400 or worse at the last follow-up (average follow up = 11 months).[56] An additional study evaluated patients with severe vitreous hemorrhage following closed-globe blunt trauma.[57] Posterior segment injuries included retinal tears, retinal detachment, submacular hemorrhage, choroidal rupture, and macular holes. Anterior segment damage was also noted in these patients and included hyphema, traumatic cataract, lens dislocation, and iridodialysis. Final VA of 20/40 was achieved in only 21% of the eyes evaluated in this study. Notably, 54% of the eyes had final VA less than 20/200; macular scars were the primary reason for poor visual outcome in these cases.[57] Poor visual outcomes were also noted in a group of patients who had experienced lens dislocation or subluxation as a result of blunt trauma.[58] These patients also presented with hyphemas, afferent pupillary defects, iris sphincter tears, iridodialysis, vitreous hemorrhage, vitreous in the anterior chamber, and zonular abnormalities. After cataract extraction, 45% of the eyes still had VA worse than 20/40; macular scarring, retinal detachment, optic atrophy, cystoid macular edema, and corneal disease were the primary causes of poor vision in these eyes. Furthermore, 35% of the eyes had final VA worse than 20/200.[58]

Additional reports have demonstrated the association of closed-globe blunt trauma with the development of traumatic glaucoma. In a study of 40 eyes with closed-globe injuries, 43% had experienced persistent elevation of IOP (≥ 21 mm Hg) for at least 3 months.[59] Injuries including hyphema, angle recession of more than 180°, and lens displacement were significantly associated with the development of glaucoma.[59] Angle recession, in particular, has been shown to be a significant cause of traumatic glaucoma.[60,61]

A review of non-penetrating ocular damage resulting from blast and blunt trauma reveals that these two injury mechanisms can cause similar anatomic damage. Many of the

blast-related anterior and posterior segment injuries reported in the clinical and pre-clinical literature have also been observed in studies of closed-globe blunt trauma, as reported above, and likely carry the same risk of long-term vision loss. For example, injuries such as retinal detachments, macular holes, commotio retinae, and hyphema have the potential of causing long-term visual problems, regardless of whether they were a result of blunt trauma or blast exposure.

Therefore, it can be extrapolated that the same non-penetrating injuries caused by blast will lead to similar long-term visual problems. In light of this evidence, it is recommended that the IOM modify its conclusion accordingly and acknowledge that primary blast can cause significant anatomic injuries to the eye that are known to cause long-term vision loss and that these injuries require long-term follow-up. Additionally, it is important that the IOM recognizes this association to further emphasize to eye care providers that all patients who have been exposed to blast should receive a comprehensive eye exam, even if no obvious external signs of injury are present.

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