Clinical & Experimental Ophthalmology
RANZCO The Royal Australian and New Zealand College of Ophthalmologists
Clinical and Experimental Ophthalmology 2015; 43: 197–199 doi: 10.1111/ceo.12502

Editorial

Elucidating the effects of primary blast on the eye

Ocular injury is among the most common terrorist blast morbidities, arising in up to 28% of survivors. *Secondary* blast injury, in which penetrating and perforating foreign body damage arises from flying debris, is a familiar source of ocular tissue disruption, inflammation and infection. Remarkably, however, the nature and extent of ocular injury from the *primary* blast itself, independent of flying debris, has remained an enigma for almost half a century beyond the time its traumatic and lethal effects were first characterized for other organ systems.[1] It seems obvious that forces that can severely damage or destroy other less delicate and exposed organ systems could wreak havoc on the eye, but until very recently, no systematic analysis of ocular responses to *primary blast* had ever been performed, post-mortem or *in vivo*. A better understanding of the patterns of injury, inflammation and neurodegeneration arising from primary blast would be of great value in the development of diagnostics, therapeutics and in the design of better eye protection. Among American warfighters alone, the cost of active-service visual damage arising between 2000 and 2010 exceeded $25 billion.[2] This is not just a military issue: Trauma is the fourth leading cause of blindness worldwide; in the US, 50 000 civilians lose vision every year as a consequence of ocular trauma. Clinicians lack therapies for these patients because there has been a dearth of models available to explore mechanism and test therapeutics. We are now at an exciting time in the field, with tremendous potential to develop vision-preserving treatments for trauma victims.

Collaboration among physicists, ballistics experts, computer scientists, biomedical engineers, biochemists, neurobiologists and clinicians has begun to unravel the mysteries of primary ocular blast injury. In San Antonio, we recently reproduced the blast effects generated by improvised explosive devices, using a 4.0×0.5-m shock tube to generate a range of biphasic blast waveforms upon gelatin-mounted fresh bovine eyes in acrylic orbits. Pre- and post-impact B-scan and ultrasound biomicroscopy ultrasonography, high-speed ballistic videography and histopathology[3] were performed. Rapid axial oscillation of the eyes occurred even at very low, very survivable blast levels, with accompanying angle recession, chorioretinal detachment and other characteristic traumatic ocular damage. These studies led on to computational modelling (Watson, Gray, Sponsel, *et al*. ARVO 2015;2176328) and *in vivo* rabbit studies (Jones, Choi, Sponsel *et al*. ARVO 2015;2164006) that have yielded evidence of primary blast-associated changes in the cornea and retina at very low levels of primary blast exposure. Blast injuries to the anterior chamber appear to arise from inertial displacement of the lens and ciliary body, whereas posterior damage seems to arise from contrecoup interactions of the vitreous and retina. Cytokines and other protein markers in blast-exposed rabbits exhibited significant changes in both the aqueous and serum (Hernandez, Reilly, Gray, *et al*. ARVO 2015; 2164084). At Vanderbilt University, the capacity of primary positive phase blast impact upon the murine eye to produce intact globe changes commensurate with those observed in closed- or open-globe injury was confirmed.[4–6] These studies convincingly demonstrated that over the course of 1 month, damage arose in the anterior chamber, with corneal oedema, hyphema and in severe cases, retinal detachment and epiretinal membrane formation and associated vision loss. A summary of the work to date on the effects of various forms of primary blast on the eye is provided in Table 1. Remarkably, for both of our research teams, the pathway toward better understanding of blast injury began with very meticulous use of a simple paintball gun.[4–9]

In this issue of *Clinical and Experimental Ophthalmology*, an important new contribution to the literature on primary blast ocular injury makes its debut.[10] The importance of recurrent metabolic compromise upon ocular neurologic survival cannot be overemphasized, because it seems to have both a positive and a negative potential (e.g. see Roth 2004 for neuroprotective effects).[11] Indeed, this area of eye/brain research may bear relevance toward a major health conundrum facing footballers and boxers, chronic traumatic encephalopathy, now shown to

Conflict of interest: None.

Funding sources: WES and MAR were supported by US Department of Defense Vision Research Program Award Number W81XWH-12-2-0055. TSR was supported by the National Eye Institute, Grant Number R01 EY 022349.

Table 1. Animal models of blast injury to the eye

System	Waveform	Pressure (kPa)	To peak (ms)	Duration (ms)	Head position	Blast aspect	Area of injury			References
							OR	IR	ON	
Eye-directed blast studies										
Paintball marker	Over pressure	179	3	7	Fixed	Primary	Yes	Yes	Yes	4–6
Cannon	Friedlander	48–152	2	10	Fixed	Primary	Yes	Unk	Yes	3
Head-directed blast studies										
Cannon	Over pressure	172–310	2	7	Fixed	Primary	Unk	Yes	Yes	13–15
TNT	Unk	180; 480	-	-	Fixed	Primary	Yes	No	Unk	16
Cannon	Over pressure	150	2	15	Free	Primary and tertiary	No	Yes	Yes	14, 17
Cannon	Friedlander	120	2	9	Fixed	Primary	No	Yes	Yes	18
Cannon	Friedlander	70	2	9	Free	Primary and tertiary	No	Yes	Yes	8

OR, outer retina; IR, inner retina; ON, optic nerve.

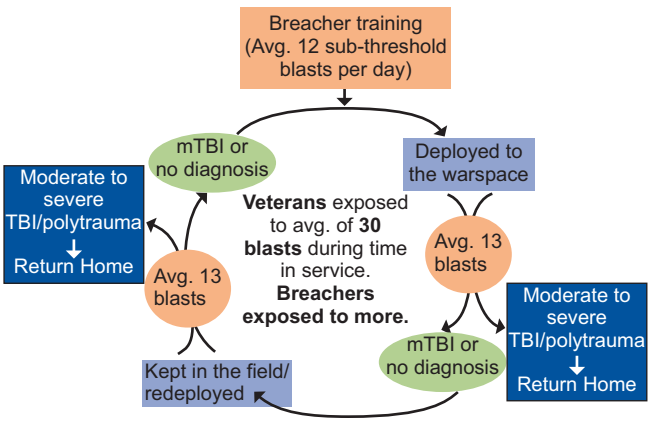

Figure 1. SCHEMATIC of the frequency of blast exposure in the active duty military. Based on data from: USAARL Report No. 2010-16, http://www.dtic.mil.[19] mTBI, mild TBI; TBI, traumatic brain injury.

also have visual consequences.[12] Figure 1 shows a schematic representation of the likely importance of repeated trauma in the development of visual loss in warfighters exposed to repeated blast, including breachers and their trainers who are exposed to frequent blasts.

In today's *CEO* article, the authors use a shock tube model of injury to the rat that has been well characterized.[14] Their positive phase blast parameters are comparable with those used by other groups including ours, in which an output pressure level of 179 kPa (26 psi) results in a time to peak of 3 ms and a total blast time of 6.9 ms.[3–6] The authors show alterations in optic nerve glia, suggesting both glial reactivity and death. It is unclear if they assessed the myelinated or unmyelinated regions of the optic nerve and, therefore, in the absence of double labelling, we do not know what type of glial cells were dying in their model; oligodendrocytes, astrocytes or microglia? The timing of neuroinflammation needs to be studied to determine if it is a result of the cell death, or if it is causative. If it occurs prior to onset of cell death after blast, blocking neuroinflammation would be an important therapeutic avenue to explore. In future efforts, we hope the authors will assay axonal degeneration by silver staining of longitudinal sections and myelin staining of cross-sections through the optic nerve. Currently, although they show evidence of a glial response and some ganglion cell death, it is unclear how much axonal degeneration occurs. The blast traumatic brain injury literature suggests that there should be damage to the axons in the optic nerve; future work should characterize such changes in this model. Also, despite the implications of the titles of both of their papers, which begin with the term, 'Pathophysiology', the authors do not perform any physiological assessments. It is very important to know if vision is perturbed in this model, and if so, what measures of visual function detect the deficits best. Their histological data suggest that they should assess retinal ganglion cell function through either visually evoked potentials or pattern ERGs (PERGs). Recently, retinal deficits from blast were detected using flash, standard and provoked PERGs.[4–7] Double labelling with cell-specific markers will be necessary to better understand the molecular underpinnings of blast injury to the eye and develop therapeutic interventions.

Notwithstanding these concerns, the new work of Choi *et al.* represents a landmark in our field, approaching the issue of repeated exposure to low level blast overpressure in a very definitive and experimentally controlled way. We are delighted and

eagerly await the further contributions of this group and hopefully many others, so that the scourge of traumatic ocular trauma can be addressed in the definitive manner that we now take for granted in so many other realms of modern ophthalmologic practice.

Tonia S Rex PhD,[1] Matthew A Reilly PhD[2] and William Eric Sponsel MD FRANZCO[2,3,4]

[1]Vanderbilt Eye Institute, Vanderbilt Brain Institute, Vanderbilt University, Nashville, Tennessee, [2]Department of Biomedical Engineering, University of Texas, [3]Vision Sciences, Incarnate Word University, San Antonio, Texas, USA; and [4]Australian Research Council Centre of Excellence in Vision Research, Australian National University, Canberra, Australia

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