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Low-Level Primary Blast Causes Acute Ocular Trauma in Rabbits

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Abstract

The objective of this study was to determine whether clinically significant ocular trauma can be induced by a survivable isolated primary blast using a live animal model. Both eyes of 18 Dutch Belted rabbits were exposed to various survivable low-level blast overpressures in a large-scale shock tube simulating a primary blast similar to an improvised explosive device. Eyes of the blast-exposed rabbits (as well as five control rabbits) were thoroughly examined before and after blast to detect changes. Clinically significant changes in corneal thickness arose immediately after blast and were sustained through 48 h, suggesting possible disruption of endothelial function. Retinal thickness (RT) increased with increasing specific impulse immediately after exposure. Intraocular pressure (IOP) was inversely correlated with the specific impulse of the blast wave. These findings clearly indicate that survivable primary blast causes ocular injuries with likely visual functional sequelae of clinical and military relevance.

Key words: animal model; head trauma; models of injury; ocular blast trauma; primary blast trauma

Introduction

Ocular injury is the fastest-growing type of battlefield injury, increasing to about 22.5% in the two most recent U.S. conflicts. These injuries have generally been attributed to secondary blast (i.e., fragment- and blast driven debris-related) mechanisms but primary blast may be a significant contributor.[1] Primary blast injury has been extensively studied in the lungs, gut, and ears, mainly with regard to survivability[2] and traumatic brain injury (TBI),[3] but similar studies of the eye are sparse. However, a handful of case studies and recent experimental work have determined that primary blast (in the absence of secondary debris) can cause eye damage at survivable levels.[4] The increased interest is due to recent observations showing that ocular injury may be found in up to 28% of patients treated for blast exposure.[5] The most common blast-related eye injuries include decreased visual acuity, hyposphagma (subconjunctival hemorrhage or red eye), orbital fractures, retinal detachment, and globe ruptures.[6]

We previously reported significant damage to the *ex vivo* porcine eye following primary blast exposure using a large shock tube. The retina, choroid, sclera, angle, and optic nerve head were the most commonly damaged tissues.[4] *In vivo* studies of primary blast-induced ocular trauma have thus far been limited to rat and mouse models. Petras and colleagues exposed rats to overpressure using a shock tube yielding axonopathy within the retina, optic nerve, and brain.[7] Hines-Beard and associates and Bricker-Anthony and co-workers exposed mice to overpressure generated by a modified paintball gun resulting in significant retinal injury and decreased visual acuity.[8,9] Tzekov and colleagues produced retinal damage in a mouse model by provoking mild TBI using repeated head impacts.[10] However, scaling laws suggest that injury mechanisms may differ significantly based on eye size.[11] Thus, although these studies offer important insights into blast-induced ocular neurotrauma, it remains unclear under what conditions similar effects might be expected in humans.

The goal of the present study was to determine whether exposure to a survivable primary blast wave could cause clinically relevant, acute ocular injuries. A rabbit model was adopted because scaling laws suggest that a model larger than rat or mouse is needed to more accurately emulate the blast loading experienced by a human eye.[11] Rabbits are a better model than rats or mice because of their larger eyes and closer anatomical similarity to humans. We observed

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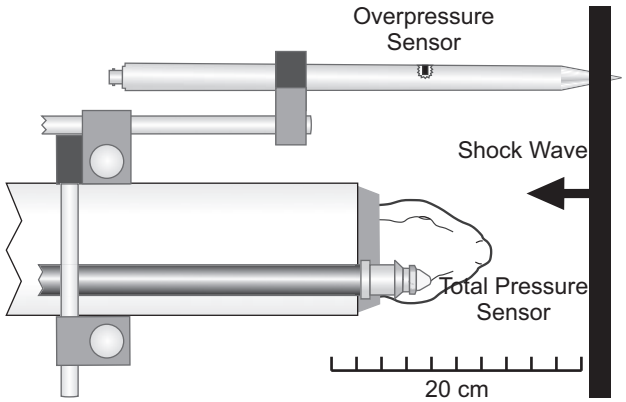

FIG. 1. Schematic of rabbit aligned axially toward the incoming shock wave.

statistically significant changes in corneal thickness (CT), retinal thickness (RT), and intraocular pressure (IOP) after blast exposure. These acute changes would cause clinically relevant visual deficits in humans and therefore likely affect the combat readiness of soldiers exposed to primary blast.

Methods

Experimental protocol

All experimental work was carried out at the U.S. Army Institute of Surgical Research (USAISR), Brooke Army Medical Center, San Antonio, Texas. This study was conducted in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Visual Research (http://www.arvo.org/about_arvo/policies/statement_for_the_use_of_animals_in_ophthalmic_and_visual_research/ Last accessed October 28, 2015), institutionally approved protocols, the Animal Welfare Act, the implementing Animal Welfare Regulations, and the principles outlined in the Guide for the Care and User of Laboratory Animals (National Research Council. Guide for the Care and Use of Laboratory Animals, Eigth Edition. Washington, DC. The National Academics Press, 2011).

A large, compression-driven shock tube was used in this study to simulate primary blast wave exposure. Detailed descriptions of this system have been provided previously.[4] The rabbit was placed in the expansion cone of the shock tube, downstream from the driven section and driver section (Fig. 1). Five control animals were treated identically with the exception of blast exposure (including placement in the shock tube). Eighteen animals were exposed to three peak blast overpressure ranges: 51.2–53.0 kPa (~8 psi), 78.8–88.7 kPa (~12 psi), and 120.4–132.1 kPa (~17 psi). These three exposure groups experienced peak blast overpressure specific impulses (impulse per unit surface area) of 56.0–59.3 kPa-msec (8.12–8.60 psi-msec), 96.5–104.3 kPa-msec (14.0–15.1 psi-msec), and 141.6–158.5 kPa-msec (20.5–23.0 psi-msec). Treatment groups are summarized in Table 1.

A total of 24 Dutch Belted male rabbits weighing 1.5–2.5 kg and 20 weeks of age were obtained for this study. It was necessary to examine each rabbit for pre-existing damage before each experiment to determine baseline biometric values and exclude animals with pre-existing abnormalities. During pre-blast ophthalmological examinations, one rabbit was excluded because it had pre-existing ocular damage. Another rabbit was lost due to atelectasis (collapsed lung) immediately following blast; however, the attending veterinarian attributed this primarily to the anesthesia rather than to blast wave exposure.

Each animal was weighed and anesthetized with an intramuscular injection consisting of 45/5 mg/kg of ketamine/xylazine. Supplemental sedation with isofluorane was used throughout the experiment for maintenance. IOP was measured in each eye using a TonoVET© rebound tonometer (Icare, Helsinki, Finland) followed by a photographic non-dilated slit-lamp examination. After dilation with 1% tropicamide, dilated fundus assessment using the Zeiss VisuCam fundus camera (Carl Zeiss Meditech, Dublin, CA) was performed. Direct ophthalmoscopy was then performed, followed by optical coherence tomography (OCT; Bioptigen, Inc., Durham, NC). Topical tetracaine was then applied prior to corneal confocal scanning laser microscopy (HRT 3, Heidelberg Engineering, Germany) and perilimbal ultrasound biomicroscopy (iScience, Menlo Park, CA). IOP measurements were then repeated, followed by withdrawal of 100 μL of aqueous humor from the anterior chamber of the right eye using a tangential 30-gauge needle paracentesis approach. Tetracaine and Vigamox© (Alcon, Fort Worth, TX) were then administered. Subsequently, the IOP of the right eye was repeatedly measured to determine if excess fluid was lost from the needle insertion point. The aqueous samples, along with arterial blood samples (2 mL) drawn from an ear, were obtained for biomarker analysis. An ophthalmic lubricant (GenTeal©, Alcon, Fort Worth, TX) was applied to the eyes; then the rabbit was placed in a recovery chamber until fully awake. Finally, the animal was returned to its cage. This protocol typically took approximately 2.5 h per animal and was performed throughout the mid-morning.

Approximately 24 h later, rabbits were anesthetized using ketamine/xylazine as above, along with 2 mg/kg buprenorphine injected subcutaneously as an analgesic. The rabbit was weighed and placed in a holder constructed from a 4-inch inner diameter PVC pipe to protect the body of the rabbit from the blast wave. The rabbit was then placed in the expansion cone of the shock tube for blast wave exposure, with IOP measurements obtained in both eyes. A 0.9% normal saline solution was used to keep the eyes moist throughout the experiment. The rabbits were aligned axially, directly into the shock tube so that both eyes would simultaneously receive the same exposure (Fig. 1). After exposure, the examination protocol given above was immediately repeated with exception of the aqueous sampling. Three h after blast wave exposure, an arterial blood draw (2.0 mL) was performed as described above.

The following day, 24 h after blast exposure, the rabbit was anesthetized using isoflurane gas. The IOP was measured in the

TABLE 1. BLAST EXPOSURE MATRIX

Group	n	*Peak overpressure*		*Duration*	*Specific impulse*	
-	-	*kPa*	*psi*	*msec*	*kPa-msec*	*psi-msec*
Sham	5	0	0	0	0	0
1	6	51.9	7.52	2.64	57.4	8.33
2	5	82.8	12.0	2.76	99.3	14.4
3	6	123	17.9	2.98	152	22.0

right eye and a 100 μL sample of aqueous humor was drawn from the right eye.

Two days after blast exposure, rabbits were anesthetized with ketamine and xylazine as described above. Tonometry, 100 μL aqueous draw (right eye only), blood draw, and corneal confocal imaging were repeated. Finally, the rabbit was euthanized with an intravenous or intracardiac dose of veterinary euthanasia solution Fatal-Plus (phenobarbital 390 mg/mL, propylene glycol 0.01 mg/mL, ethyl alcohol 0.29 m/mL, benzyl alcohol 0.2 mg/mL; total dose 150 mg/kg; Vortech Pharmaceuticals, Dearborn, MI). Animals were under general anesthesia when administered the euthanasia solution. Euthanasia protocols were in accordance with American Veterinary Medical Association guidelines.[12]

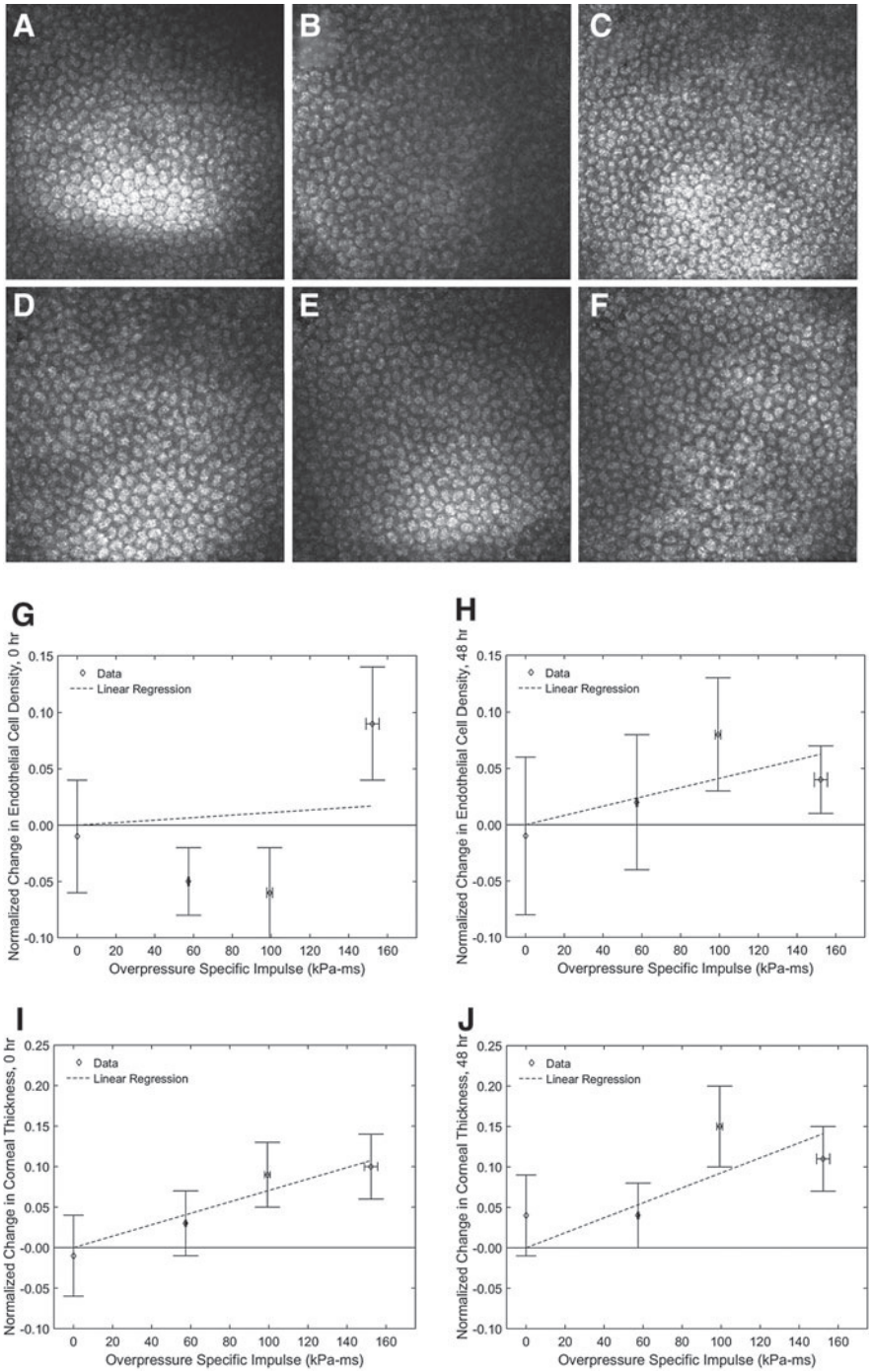

FIG. 2. Corneal effects of primary blast exposure. Top: Representative confocal microscopy images of corneal endothelial cells from a sham animal **(A–C)** and an animal exposed to a peak overpressure of 122 kPa (17.7 psi) **(D–F)** at time points (A, D) before, (B, E) immediately after, and (C, F) 48 h after placement in the shock tube. No clear differences were observed in cell density or morphology. Middle: Normalized changes in CECD as a function of specific impulse **(G)** immediately after and **(H)** 48 h after blast exposure. CECD was not significantly related to overpressure specific impulse at either time point. Bottom: Normalized changes in CT as a function of specific impulse **(I)** immediately after and **(J)** 48 h after blast exposure. CECD, corneal endothelial cell density; CT, corneal thickness.

The ocular tissue was carefully collected immediately following euthanasia to prevent surgical damage, then fixed for 24 h with modified Davidson's solution (64133-50, EMS, Hatfield, PA) followed by 10% of normal buffered formalin (NBF). Fixed samples were moved through increasing percentages of alcohol to 100% and then blocked in paraffin. Paraffin tissue sections, 5 μm in thickness, from the eye and optic nerve were deparaffinized in xylene, then rehydrated in descending grades of ethanol (100%, 70%, and 45%) to water for hematoxylin and eosin staining.

Image analysis

An apical z-stack of corneal confocal microscopy images was used to estimate CT and corneal endothelial cell density (CECD). CT was measured from the top of the epithelial cell layer to the bottom of the endothelial cell layer. CECD was estimated using

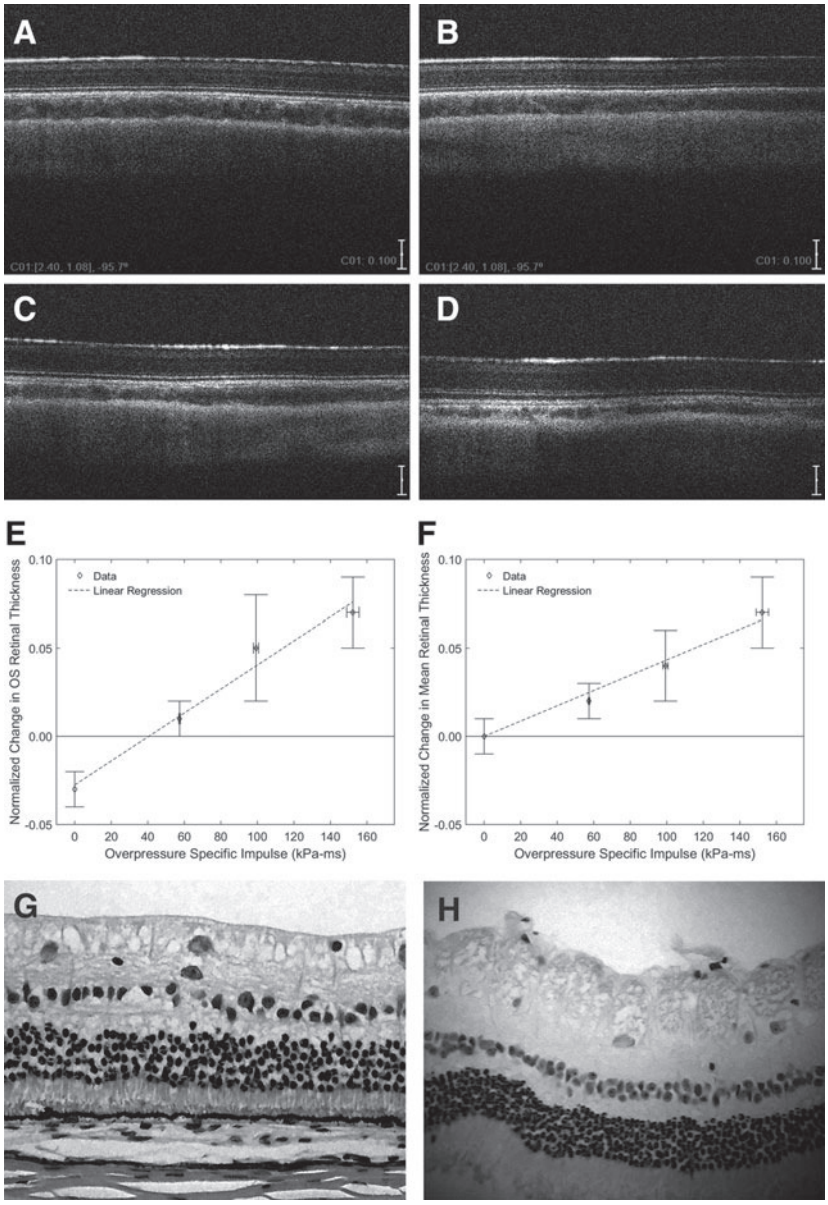

FIG. 3. Retinal effects of primary blast exposure. Top: OCT images used to measure retinal thickness taken from OCT images from the inner ganglion cell layer margin to the anterior surface of the retinal pigment epithelial layer. Typical images are shown for left eyes of a sham animal **(A)** before and **(B)** immediately after placement in the shock tube and an animal exposed to 117 kPa (17 psi) peak overpressure **(C)** before and **(D)** after blast exposure. Scale bar indicates 100 μm in the axial direction. Middle: Normalized changes in retinal thickness as a function of specific impulse immediately after blast exposure. **(E)** Left eye (the eye from which no aqueous samples were drawn) showed slight depression of retinal thickness in the sham group, probably resulting from anesthetic effects. **(F)** Mean of both eyes showed a linear trend with no offset. Values are averaged for both eyes for each animal. Bottom: Typical histopathological sections of the retina from **(G)** control rabbit eye and **(H)** an eye from a rabbit subjected to 117 kPa (17 psi) peak overpressure. The blast-exposed eyes showed disturbance to the microarchitecture of the inner retinal Müller cell structure and distortional redistribution of the axons and their interstitium. This type of injury when present was most prominent in the retinal midperiphery (approximately 3–4 disc diameters from the optic nerve head). OCT, Optical coherence tomography.

Table 2. Corneal Thickness, Corneal Endothelial Cell Density, Retinal Thickness, and Intraocular Pressure for Left Eye for Each Blast Group (Mean ± SEM)

	Corneal thickness (μm)			*CECD (cell/mm^2)*		
Blast group	*Pre*	*Post*	*48 h*	*Pre*	*Post*	*48 h*
Sham	351 ± 12.0	356 ± 9.6	363 ± 18.5	2735 ± 97	2711 ± 78	2674 ± 63
1	342 ± 9.6	346 ± 8.1	347 ± 8.5	2741 ± 39	2581 ± 43	2820 ± 89
2	316 ± 10.8	344 ± 4.2	373 ± 17.5	3017 ± 43	2826 ± 114	3284 ± 116
3	314 ± 10.4	354 ± 10.4	351 ± 14.5	2853 ± 89	3085 ± 78	2987 ± 46

	Retinal thickness (μm)		*IOP (mm Hg)*			
Blast group	*Pre*	*Post*	*Pre*	*Post*	*24 h*	*48 h*
Sham	148 ± 3.8	144 ± 3.8	11.3 ± 1.6	10.7 ± 1.7	15.5 ± 1.2	10.9 ± 1.3
1	151 ± 2.8	153 ± 2.4	13.1 ± 2.1	13.3 ± 2.1	14.2 ± 1.1	10.6 ± 1.5
2	146 ± 2.7	152 ± 3.0	15.5 ± 1.8	13.8 ± 1.4	17.8 ± 1.1	10.0 ± 0.9
3	147 ± 2.7	157 ± 1.4	14.1 ± 1.0	13.3 ± 0.7	19.2 ± 2.1	9.3 ± 0.7

CECD, corneal endothelial cell density; IOP, intraocular pressure; SEM, standard error of mean.

confocal images of an area of approximately 0.03 mm^2 (Fig. 2; HRT Rostock Cornea Module, Heidelberg Engineering). All image analyses were performed for both eyes in each animal.

RT was measured using In Vivo Vue Clinic v1.4 software (Bioptigen, Inc.) by measuring the distance from the inner ganglion cell layer margin (inner limiting membrane) to the anterior surface of the retinal pigment epithelium (Fig. 3). Reported values are averages from each of five inferior peripapillary images, each within 5 mm of the optic nerve head margin.

Statistical analysis

All responses were expressed as fractional changes relative to baseline values as

$$z(t) = \frac{y(t) - y_0}{y_0},$$

where $z(t)$ is the normalized response at time t, $y(t)$ is the experimental measurement at time t, and y_0 represents the baseline value at $t = 0$. This normalization accounted for inter-animal variability and changes due to confounding effects such as repeated anesthesia. Linear regression was then used to estimate the effect of overpressure specific impulse on each of the normalized responses. Due to the normalization, offsets were set to zero unless found to be statistically different from zero during regression. Statistical significance for the offset and/or linear effect was established if the p value was below 0.05.

Results

Table 2 summarizes the measured changes that occurred in each blast group.

CECD changes did not change significantly from baseline immediately after blast (Fig. 2G; $p = 0.50$) or 48 h after blast (Fig. 2H; $p = 0.21$). Although not statistically significant, the sudden decrease in density seen immediately after blast in the 8 and 12 psi groups could indicate clinically relevant cell loss (Fig. 2G). All CECD values returned to normal within 48 h following blast exposure (Fig. 2H). CT increased up to 10% with increasing specific impulse immediately following blast exposure (Fig. 2I; $p = 0.0027$) and up to 15% 48 h later (Fig. 2J; $p = 0.0016$). The progressive increase in CT after blast was most robustly seen in left eyes, which did not undergo multiple aqueous humor sampling procedures. Control eyes showed no significant change in either eye immediately following blast. Indeed, corneas in the left eyes of the control animals (i.e., eyes from which aqueous humor was not drawn) showed no change after 48 h.

RT increased by up to 7.5% with increasing specific impulse immediately after blast exposure (Fig. 3; $p < 0.0001$). Histopathological sections indicated disruption of the inner limiting membrane of the retina (Fig. 3G–H).

IOP was not correlated with specific impulse immediately (Fig. 4A; $p = 0.55$) or 24 h after blast (Fig. 4B; $p = 0.80$) but decreased with specific impulse 48 h after (Fig. 4C; $p = 0.020$). IOP at 24 h after blast was significantly elevated in all animals including sham (offset 35%, $p = 0.032$).

Discussion

These tomographic data confirm that primary blast wave insult, generated using a large shock tube, produced immediate changes in the retina and cornea of the living eye in rabbits. The immediacy of the effect on the cornea is perhaps not surprising given its superficiality and direct exposure, whereas the effects on the retina confirm that the effects of blast penetrate the entire globe.[4] Corneal changes persisted for the duration of the follow-up period (48 h). IOP was negatively correlated with specific impulse 48 h after blast. Together, these injuries would significantly compromise vision following low-level blast exposure.

Corneal edema was quantified using normalized thickness measurements from corneal confocal imaging of the cornea and was strongly correlated with the specific impulse ($R^2 = 0.928$ immediately after blast; Fig. 2I). This was confirmed by histological evidence of increased interlamellar voids corresponding to water infiltration that were observed. Edema was attributed to a pump-leak imbalance,[13,14] possibly owing to altered functionality of aquaporin (AQP) 1 in the endothelium.[15–17] These changes in CT would not significantly influence optical power (equivalent to a change of 0.1 D as calculated using the thick lens formula[18]). However, this increase in CT may compromise corneal transparency,[19–21] and corneal edema was also observed in a mouse model of blast injury.[22] Although transient corneal edema is commonplace and typically rapidly resolves, the fact that the observed thickening persisted and indeed increased at 48 h in left eyes exposed to higher blast energies suggests that endothelial function may have been compromised by a

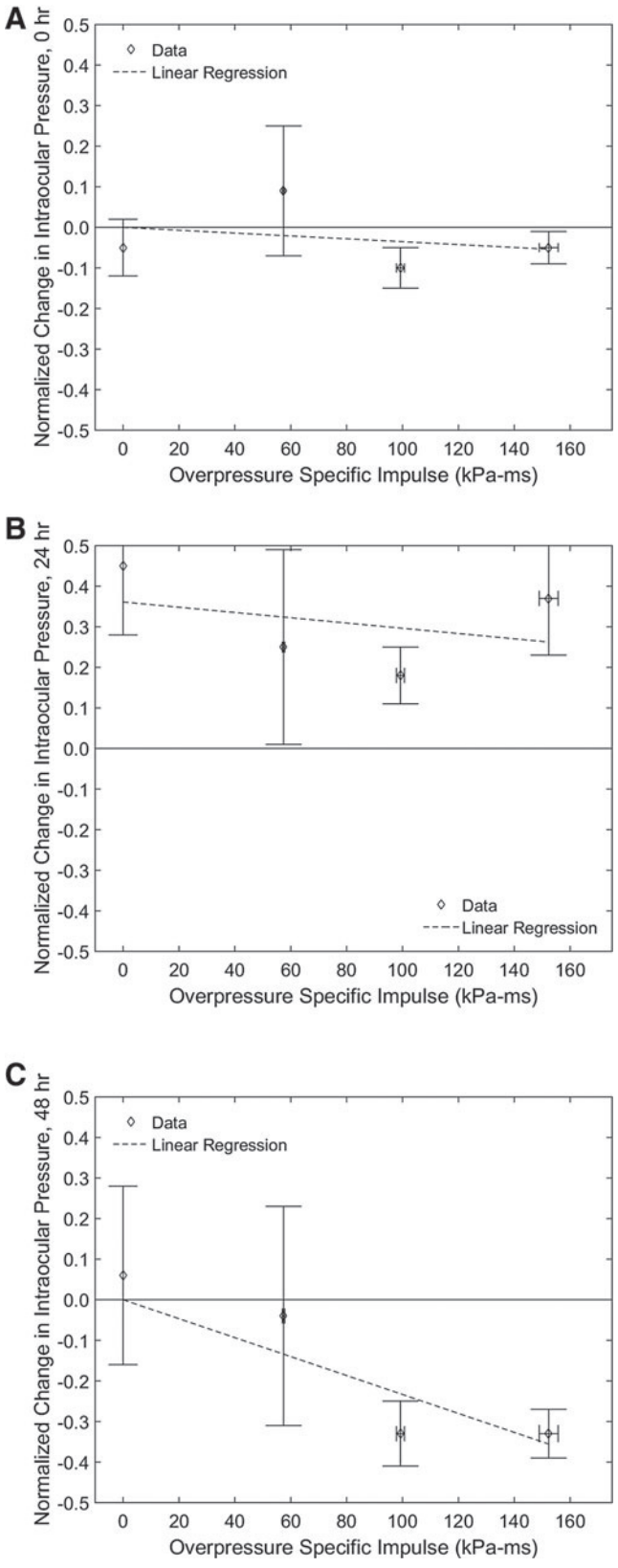

FIG. 4. Normalized change IOP. **(A)** IOP was unchanged immediately following blast, then significantly elevated 24 h later **(B)**; in both cases, IOP was not significantly related to specific impulse. IOP decreased significantly with increasing specific impulse 48 h after blast exposure **(C)**. IOP, intraocular pressure.

post-blast biological cascade. Sustained corneal thickening has been observed using other *in vivo* model systems.[8,23] Hess and Garner[19] reported edema-induced loss of contrast sensitivity at spatial frequencies above 3 cycles per degree. Specifically, a 6% increase in CT resulted in a contrast sensitivity deficit of up to 67% at high spatial frequencies,[19] whereas CT increases of up to 10% immediately after blast (Fig. 2I) and 15% 48 h later (Fig. 2J) were found in the present study. These changes would significantly compromise visual acuity and are likely to have a significant impact on daily tasks in civilian life such as driving[24,25] as well as combat effectiveness in a battlefield scenario.[26]

CECD changes were not statistically significant and no clear trend emerged, at least during the 48 h of post-blast monitoring employed in the current study (Fig. 2G–H). The prolonged increase in CT (Fig. 2J) may indicate loss of endothelial cell function. Variability in CECD values may have arisen due to difficulty locating the apex of the cornea, migration of the endothelial cells, anesthetic effects, or true changes in cell density. It may be possible that the 48-h observation window is insufficient to observe significant changes in CECD values. In addition, rabbits are able to regenerate their endothelial cells,[27] which may explain the observed increases in density of the same groups (8 and 12 psi) 48 h after blast exposure. Thus, although CECD may be an important metric for assessing corneal health in human patients,[28] it may not be a useful metric for ocular health in a rabbit model. Endothelial cell rearrangement has been observed and reported. It is possible that our observation of decrease in corneal endothelial cell density could be a result of cellular rearrangement and/or mitosis; both have been observed in rabbit endothelia to the extent of complete wound closure within 48 h.[29] Such rearrangement has been correlated with changes in AQP 1 activity, possibly linking corneal edema with rearrangement of the endothelium.[16]

Retinal thickening was observed immediately post-blast (Fig. 3E–F). The pathophysiological mechanism for the observed retinal thickening is evident upon close examination of the histopathological sections (Fig. 3G–H). Müller's fibers form a protoplasmic framework throughout the retina that surrounds the axons, cell bodies and dendrites. The inner ends of Müller cells form a mosaic that constitutes the inner limiting membrane (ILM) of the retina. This is in intimate association with the hyaloid membrane (HM) of the vitreous. Computational modeling studies of blast indicate that post-blast contra-coup oscillations of the vitreous arise out of synchrony with the oscillations of the corneosclera[30] that would be expected to result in repeated separation and reapproximation of the ILM and HM. At the relatively low blast overpressure levels applied in this study, it is evident that most of the cytoarchitecture of the retina is conserved, with the marked exception of the nerve fiber layer, which appears to be the principle site for the retinal thickening observed in these studies. Although rabbit eyes differ from human eyes in terms of size and anatomy (e.g., rabbits do not have foveas[31]), the functional implications of these findings for the macula, optic disc, and posterior pole of other foveated species are likely to be important.

The blast-related decrease in IOP 48 h after blast exposure (Fig. 4C) could be due to ciliary muscle dysfunction (uveitis) or damage to the eye's outflow facility resulting in decreased outflow resistance. IOP elevation in all animals (sham and blast exposed) 24 h after blast (Fig. 4B) was likely due to the use of ketamine anesthesia in the absence of isoflurane.[33] Ketamine is known to elevate IOP,[34] whereas isoflurane is known to suppress it.[35] It appears that the effects of isoflurane and ketamine negated each other during all measurements except at 24 h when supplemental isoflurane was not

used. IOP measurements were not significantly correlated with CT, although a slight negative trend was observed. Changes in IOP were inversely correlated with CT, indicating that the measured drop in IOP was not an artifact of edema.[32]

Continuing data analyses from this study population are ongoing, and correlations of various ocular injuries with both the positive and negative phases of the blast profile are underway. The roles of various biochemical intermediaries (biomarkers) in the post-blast scenario are also under detailed study and will be the subject of forthcoming articles. The present findings suggest that survivable isolated primary blast is capable of producing acute corneal injuries consistent with a Cumulative Injury Score of level 1, and retinal damage at a potentially much higher level.[4] Injuries of this magnitude would have considerable negative impacts on visual function.

Conclusions

Survivable primary blast wave exposure induced changes in CT and RT, which were statistically correlated with blast overpressure specific impulse. Changes of up to 15% in CT and 7.5% in RT were found in a live rabbit model with an actively perfused eye. Changes in CT were sustained through the 48-h post-blast follow-up period. These changes would significantly impair visual function if analogous changes occurred in humans following survivable primary blast exposure. Future work will extend the follow-up period to determine the time course of spontaneous recovery and/or permanence of injuries. We will also explore correlations between blast exposure and biomarker expression.

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Author Disclosure Statement

No competing financial interests exist.

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