Experimental Eye Research 99 (2012) 63–70

Contents lists available at SciVerse ScienceDirect

Experimental Eye Research

journal homepage: www.elsevier.com/locate/yexer

A mouse model of ocular blast injury that induces closed globe anterior and posterior pole damage

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ARTICLE INFO

Article history:
Received 11 January 2012
Accepted in revised form 27 March 2012
Available online 7 April 2012

Keywords:
mouse
eye
blast
model
traumatic
injury
cell death
visual acuity

ABSTRACT

We developed and characterized a mouse model of primary ocular blast injury. The device consists of: a pressurized air tank attached to a regulated paintball gun with a machined barrel; a chamber that protects the mouse from direct injury and recoil, while exposing the eye; and a secure platform that enables fine, controlled movement of the chamber in relation to the barrel. Expected pressures were calculated and the optimal pressure transducer, based on the predicted pressures, was positioned to measure output pressures at the location where the mouse eye would be placed. Mice were exposed to one of three blast pressures (23.6, 26.4, or 30.4 psi). Gross pathology, intraocular pressure, optical coherence tomography, and visual acuity were assessed 0, 3, 7, 14, and 28 days after exposure. Contralateral eyes and non-blast exposed mice were used as controls. We detected increased damage with increased pressures and a shift in the damage profile over time. Gross pathology included corneal edema, corneal abrasions, and optic nerve avulsion. Retinal damage was detected by optical coherence tomography and a deficit in visual acuity was detected by optokinetics. Our findings are comparable to those identified in Veterans of the recent wars with closed eye injuries as a result of blast exposure. In summary, this is a relatively simple system that creates injuries with features similar to those seen in patients with ocular blast trauma. This is an important new model for testing the short-term and long-term spectrum of closed globe blast injuries and potential therapeutic interventions.

1. Introduction

An estimated 300,000 service members have traumatic brain injury as a result of exposure to improvised explosive devices in the recent wars in Iraq (http://veterans.rand.org). While improvements in body armor have led to fewer fatalities, there has been an increase in surviving service members with eye damage. Thirteen percent of all injuries treated at an in-theater hospital were to the eye (Heier et al., 1993). And during the current wars in Afghanistan and Iraq, 186,555 eye injuries were diagnosed in actively serving military personnel at fixed medical facilities (Hilber, 2011). This is despite the availability of protective eyewear, which can be explained in two ways: 1) non-compliance in the use of eyewear (Blanch and Scott, 2009; Thomas et al., 2009); and 2) lack of efficacy of the protective eyewear. Twenty four percent of soldiers with ocular blast injuries had documentation of wearing eye protection at the time of injury indicating that some explosions were so powerful that eye protection was insufficient to prevent ocular damage (Weichel and Colyer, 2008; Mader et al., 2006).

There is a lack of consensus on the ability of a blast wave to induce damage to the eye (primary blast injury). Since service members are not exposed to blasts in a sterile environment, they are often also exposed to foreign bodies in the orbit (secondary blast injury). This makes dissecting out any potential effects of the blast wave on the eye impossible. Chalioulias et al., 2007 reported on one case of primary blast injury to the eye, demonstrating that blast exposure alone may be sufficient to damage the eye. More recently others have reported ocular pathology in blast-exposed patients with closed globes including corneal abrasions, hyphemas, cataracts, corneal edema, angle recession, hemorrhage, retinal tears or detachments, macular holes, choroidal rupture, commotio retinae, and optic neuropathy (Blanch and Scott, 2009; Cockerham et al., 2011). Despite the accumulation of data implying that the

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doi:10.1016/j.exer.2012.03.013

blast wave by itself can induce ocular injury, there is a need for an animal model to test the effects of a pure blast wave.

Very few studies report on the effects of blast injury on the eye or visual system. Whole body exposure to a blast overpressure wave of 129–173 kPa induces axonal degeneration in the central visual pathways of 83% of exposed rats (Petras et al., 1997). The retina was not analyzed. Long et al., 2009, performed similar experiments and showed diminished neuronal degeneration by covering the trunk of the rat with Kevlar, demonstrating that at least some of the damage was possibly due to air emboli. More recently a whole body mouse model of blast exposure was developed (Koliatsos et al., 2011; Cernak et al., 2011). The model induced an open waveform primary blast that caused axonal degeneration in the optic tract 14 days after exposure to a 32 psi blast and a few dying cells in the retinal ganglion cell layer of the far peripheral retina 5 days after exposure to a 29 psi blast. As in the Long et al., 2009 study, less neuronal damage was detected when the trunk was protected from blast exposure. They did not assess visual function or examine other regions of the retina or eye.

To study the effects of a primary blast injury to the eye while avoiding confounding complications due to blast exposure to the body of the mouse, we developed a novel model that directs a primary blast with an open-field waveform directly to the eye only. Here we characterize our mouse model of primary blast injury to the eye.

2. Materials and methods

2.1. Blast device

A commercially available paintball gun (Invert Mini, Empire Paintball, Sewell, NJ), pressurized air tank, and *x*–*y* table were secured onto medium density fiber boards (Fig. 1A). The commercial barrel was replaced with a machined barrel at half the original diameter to increase pressure output. The paintball gun has a regulated input so that the output forces can be controlled. In front of the barrel a plexiglass clamp was secured to an *x*–*y* table (Velmex, Bloomfield, NY) for fine movement. The *x*–*y* table allowed measurements to be made at increasing distances away from the barrel. A hole was machined into the tube to match the size of a mouse eye and was positioned directly in front of the barrel. A hole was also drilled into the opposite side of the pipe to fit the machined barrel of the pressure transducer. A slightly smaller PVC tube, which slides into the larger tube, was machined to create a housing chamber for the mouse (Fig. 1B).

2.2. Measurement of output pressures

A machined pipe the same diameter as the eye hole was attached to the end of a Sensotec pressure transducer model STJE (Honeywell, Morristown, NJ) and was positioned through the PVC pipe so that the end was abutted to the eye-sized hole. This allowed for precise measurement of pressure at the future site of injury. Pressures were measured before and after exposure of each eye to a blast. The pressures detected by the pressure transducer were sent to a laptop and were recorded and analyzed using Labview software (National Instruments, Austin, TX).

2.3. Animals

Adult female C57Bl/6 mice were purchased from Jackson Laboratories (Bar Harbor, ME). Prior to blast exposure, mice were anesthetized with ketamine/xylazine (25/10 mg/kg body weight) and secured into the mouse holder with surgical tape. A cushion was secured on the opposing side of the mouse housing to provide head support and modeling compound was secured to the bottom of the mouse housing next to the cushion for further head support and positioning. The mouse was positioned adjacent to the blast-side PVC, so that the mouse eye was in contact with the hole and surrounding pipe and could be visualized in the hole. Mice received 35 mg/ml acetamenophen in the drinking water for a minimum of one day prior to exposure and seven days after blast exposure. In initial experiments, an average of 5% drop in body weight was noted so all remaining mice received gel food for at least 3 days post-blast. All animal studies were performed in accordance with an UTHSC Institutional Animal Care and Use Committee approved protocol and complied with the guidelines of the Association for Research in Vision and Ophthalmology. All experiments were conducted in AALAC approved laboratories. The number of mice used for each experimental condition is shown in Tables 1, 3 and 4.

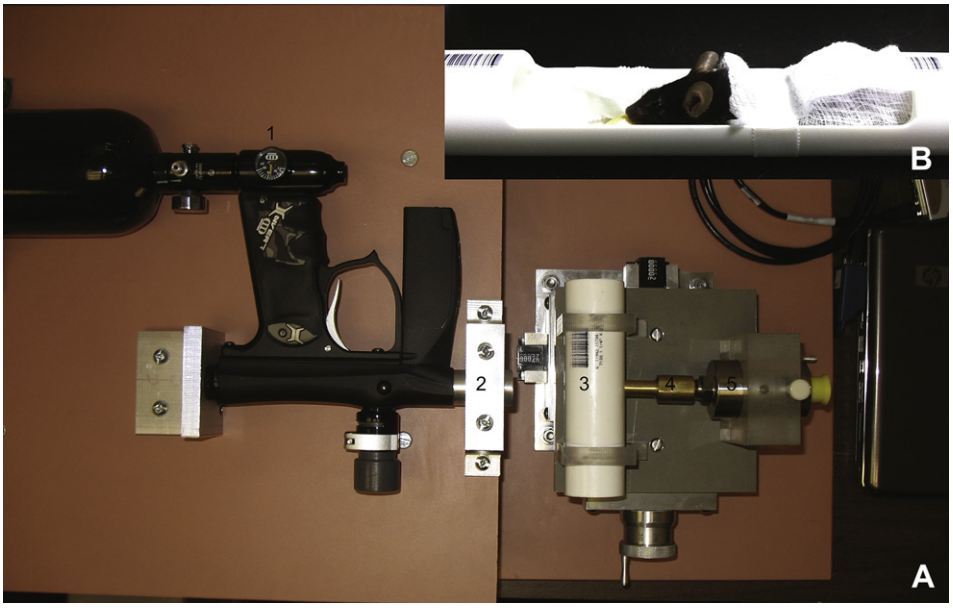

Fig. 1. A. Image of the ocular blast injury device. B. Image of the mouse housing. Arrows indicate: 1) pressure regulator; 2) machined barrel at the end of the paintball gun; 3) chamber with mouse eye-sized hole facing the barrel into which the mouse housing (B) slides; 4) machined barrel on the pressure transducer; 5) pressure transducer that connects to the laptop.