Journal of Spine
ISSN: 2165-7939

Capó-Aponte et al., J Spine 2013, S4
DOI: 10.4172/2165-7939.S4-004

Research Article Open Access

Pupillary Light Reflex as an Objective Biomarker for Early Identification of Blast-Induced mTBI

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Abstract

Purpose: There is an increase in mild traumatic brain injury (mTBI) in US Warfighters resulting from exposure to explosive devices. However, there is a lack of objective biomarkers to accurately identify mTBI in order to make a return-to-duty (RTD) determination in the battlefield. The present study examined pupillary light reflex (PLR) as a potential objective biomarker for early identification of mTBI.

Methods: The PLR-200™ monocular infrared pupillometer was used to quantify PLR under mesopic conditions in 20 U.S. military personnel with blast induced-mTBI and 20 age-matched non-TBI military personnel. Eight PLR parameters were assessed: maximum diameter; minimum diameter; percent of constriction; constriction latency; average constriction velocity; maximum constriction velocity; 75% recovery time; average dilation velocity.

Results: Four of the eight PLR parameters were statistically different between the groups: constriction latency, average constriction velocity, dilation velocity, and 75% recovery time.

Conclusions: This study demonstrates the potential application of PLR as an objective index of autonomic nervous system activity and the value of using PLR, in conjunction with other biomarkers, to optimize the diagnosis of mTBI in the battlefield and to facilitate the RTD decisions by deployed healthcare providers.

Keywords: Military; Pupil; Pupillary Light reflex; PLR; Pupillary dynamics; Mild traumatic brain injury; mTBI; Blast

Introduction

During the last decade, the US military has experienced an increase in the incidence of traumatic brain injury (TBI) resulting from the use of explosive devices by enemy forces [1,2]. The Department of Defense (DoD) reported that 273,859 new cases of TBI have been clinically confirmed from 2000 to the first quarter of 2013, with mild TBI (mTBI) accounting for 82 percent of all cases [3]. Unfortunately, Warfighters with TBI are often identified only when moderate or severe head injuries have occurred, leaving more subtle mTBI cases undiagnosed. The diagnosis of mTBI has been a challenge for the military primarily because of the lack of objective assessment tools [4,5], the overlap of symptoms with co-morbid conditions such as post-traumatic stress disorder (PTSD) [6], and the interpretation of the signs and symptoms by healthcare providers relies on self-reported symptoms from injured Warfighters [4,7]. Cognitive and neurosensory abilities potentially degraded by mTBI are crucial for military personnel in combat since their lives and safety depends on accurate and rapid situational awareness and perception of the environment. Prompt and accurate diagnosis and management of mTBI generally increases an individual's prognosis for neurological recovery [8-10] and safe return-to-duty (RTD) [11-13]. Premature RTD places Warfighters at greater risk of disability if they suffer additional concussive trauma [14]. Consequently, there is a quest for objective biomarkers (e.g., protein, imaging, cognitive, neurosensory) to accurately diagnose Warfighters with mTBI [5,15]. Valid objective biomarkers are particularly important in the combat zone to assist deployed clinicians in making an accurate determination of fit-for-duty (FFD) and RTD or evacuation from theater [4].

While the pupillary light reflex (PLR) has long been used as an indicator of neurological function in severely brain-injured patients [16-18], there is no research describing PLR as a potential objective biomarker for mTBI. The pupillary examination is the cornerstone for the neurological assessment by healthcare providers; however, it has relied on the standard manual "swinging flashlight" pupillary assessment performed with a penlight. Unfortunately, the manual pupillary assessment is highly subjective and does not provide the level of accuracy necessary to detect subtle deficits of dynamic pupillary function [19-21]. Advances in technology have significantly improved the accuracy and repeatability of automated infrared pupillometers allowing for precise quantification of pupil dynamics [19,22]. However, changes in the PLR have not been systematically characterized as a potential biomarker for mTBI. Therefore, the present study was designed to identify potential PLR parameters that can serve as objective biomarkers for early identification of Warfighters with mTBI. More specifically, this study compared eight PLR parameters between subacute blast-induced mTBI military personnel and normal controls.

Methods

Subjects

Forty U.S. military personnel participated in this study, equally divided in two groups: blast induced-mTBI group and non-TBI group. The non-TBI subjects who had deployed, but had no history of TBI or concussion were tested at the U.S. Army Aeromedical Research Laboratory. The age-matched blast-induced mTBI subjects were recruited during the subacute stage, i.e., between 15 and 45 days post-injury [23], and were receiving medical care at Walter Reed Army Medical Center (WRAMC). Subjects in the blast-induced mTBI group

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Received September 14, 2013; **Accepted** October 03, 2013; **Published** October 07, 2013

Citation: Capó-Aponte JE, Urosevich TG, Walsh DV, Temme LA, Tarbett AK (2013) Pupillary Light Reflex as an Objective Biomarker for Early Identification of Blast-Induced mTBI. J Spine S4: 004. doi:10.4172/2165-7939.S4-004

had a documented history of mTBI based on the criteria of the American Congress of Rehabilitation Medicine: 1) loss of consciousness of no more than 30 min; 2) post-traumatic amnesia of no more than 24 hours; 3) a Glasgow Coma Scale from 13 to 15; 4) alteration of mental stage [24]. For this study, "blast-induced mTBI" included mTBI caused by improvised explosive devices (IEDs), rocket propelled grenades (RPGs) and mortars. Subjects in the mTBI group were enrolled regardless the level of symptomatology. The study protocol was approved by the U.S. Army Medical Research and Materiel Command Institutional Review Board and the WRAMC Department of Clinical Investigation. Informed consent was obtained from all volunteers before participating in the study. All subjects underwent a comprehensive medical history review and eye examination to determine refractive error and ocular health using standard clinical procedures [25].

Pupillary Light Reflex (PLR) assessment

The PLR-200™ (NeurOptics, Irvine, CA) monocular infrared pupillometer was used to quantify PLR under mesopic conditions (approximately 3 cd/m^2). This is an FDA-approved hand-held cordless device that measures pupil size and dynamics (Figure 1). This pupillometer has a rubber eyecup that was placed over the tested eye to standardized stimulus distance and intensity [26]. Monocular PLR measurements were taken under binocular viewing conditions. The subject was asked to fixate with the non-tested eye on a distance target located at 10 feet away to avoid changes in pupil size due to accommodation and to prevent recording artifacts by blinking during PLR recordings. The PLR was recorded twice in the right eye and then twice in the left eye with an interval of about 30 second between the first and second recording. The pupillometer presented a 180 microWatts light stimulus for 167 milliseconds using a 32-frames per second sampling rate. Eight PLR parameters were assessed: maximum diameter; minimum diameter; percent of constriction; constriction latency; average constriction velocity; maximum constriction velocity; 75% recovery time; average dilation velocity. Figure 2 illustrates a schematic of the pupil response curve and PLR recorded parameters [27]. The maximum and minimum diameters refer to the diameter of the pupil during the resting stage before the light stimulation and at the peak constriction amplitude, respectively. The percent of constriction indicates the percent of relative constriction, whereas the constriction latency indicates the reaction time to constriction onset. The average and maximum constriction velocities represent the constricting movement of the pupil diameter after the light stimulation. The 75% recovery time indicates the total time for the pupil to recover 75% of its initial resting pupil size after reaching peak constriction. The typical pupillary recovery response after stimulated pupil constriction is characterized by an initially brisk dilation followed by a relatively slower dilation phase [19]. The average dilation velocity refers to the initial brisk phase after the reaching peak constriction. The PLR-200™ pupillometer is programmed to record PLR for 5 seconds.

Figure 1: PLR-200™ (NeurOptics) monocular infrared pupillometer.

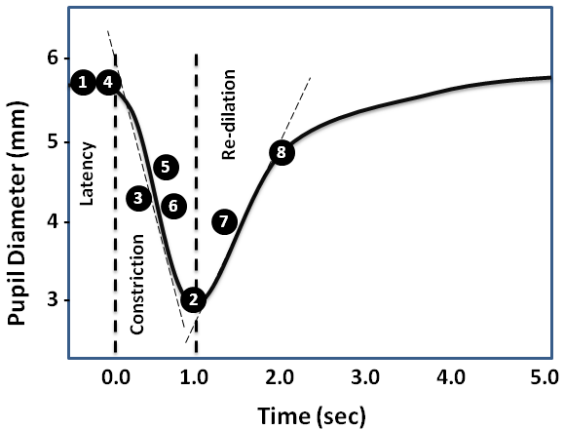

Figure 2: Schematic diagram of the pupillary reaction curve illustrating PLR recorded parameters: 1) maximum diameter; 2) minimum diameter; 3) percent of constriction; 4) constriction latency; 5) average constriction velocity; 6) maximum constriction velocity; 7) average dilation velocity; 8) 75% recovery time.

PLR recordings were automatically saved by the pupillometer after each measurement and data were later transferred as an ASCII text file to an external computer via an infrared transreceiver. The mean of the two readings per eye was used for the analysis. Descriptive statistics (mean ± SD) were used to characterize the eight individual PLR parameters for the two groups. All significance levels were $p < 0.05$. Statistical analyses were performed with Statistical Package for Social Sciences (SPSS) software.

Results

The current study compared PLR of 20 Warfighters with mTBI (14 males and 6 females) during the subacute stage post blast injury and 20 age-matched controls (18 males and 2 females) who had neither experienced an mTBI nor been exposed to a blast event. The participants' mean (SD) age was 31.2 (7.4), ranging from 20 to 43 years. All subjects were corrected to 20/20 and had similar spherical equivalent refractive error (mTBI -0.49 ± 2.07 D; non-TBI +0.12 ± 0.98 D; $p = 0.25$). All subjects, in both groups, had normal pupil response and no afferent pupil defect with the manual penlight examination. Additional clinical data and demographics for these participants were recently reported [25,28].

Figure 3 shows images of the typical pupillary response curve for the right and left eye for a subject with blast-induced mTBI and an age-matched control. There was no statistically significant difference for any of the PLR parameters between the right and left eye within each group based on Student's paired *t*-test analysis (Table 1). Consequently, the data for the right and left eye were combined for further between-group comparison of PLR parameters.

Table 2 summarizes the mean (SD) for the eight PLR parameters for the blast-induced mTBI and non-TBI groups. Student's paired *t*-test showed that four of the eight PLR parameters were statistically different between the groups. The constriction latency was higher for

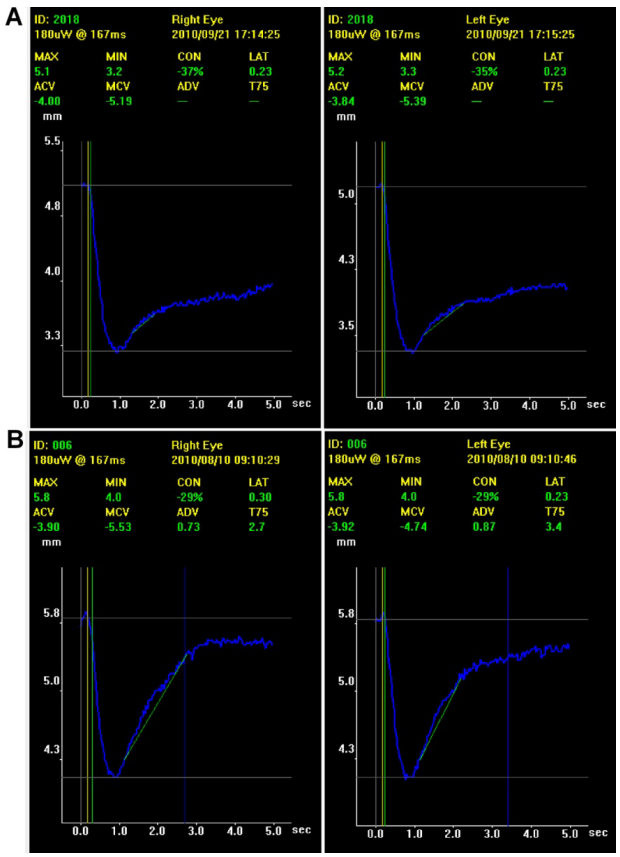

Figure 3: Images of the typical pupillary response curve for a subject with blast-induced mTBI (A) and age-matched non-TBI (B). Note: MAX = maximum diameter; MIN = minimum diameter; CON = percent of constriction; LAT = constriction latency; ACV = average constriction velocity; MCV = maximum constriction velocity; ADV = average dilation velocity; T75 = 75% recovery time.

the mTBI group indicating slower reaction time compared to the control group. Similarly, the average constriction velocity was slower for the mTBI group. In addition, the dilation velocity was slower for the mTBI group, and consequently, the time required for the pupil to reach 75% of its original size was also slower. There were no significant between-group differences for mean pupil diameter during the resting state, peak constriction, percent of constriction and maximum constriction velocity.

Discussion

Pupil abnormalities have been found in various conditions such as Alzheimer's disease, opiate withdrawal, headaches, recurrent abdominal pain, familial dysautonomia, diabetes, glaucoma, exophthalmos, and transtentorial uncal herniation [18,29-35]. To our knowledge, this is the first study describing defective PLR in blast-induced mTBI subjects during the subacute stage. The results of the present study indicate that four of the eight PLR parameters are better suited toward differentiating normal subjects from blast-induced mTBI patients. Specifically, the average constriction latencies and velocities were significantly slower in the mTBI group. In addition, the 75% re-dilation rate and average dilation velocity were slower in the mTBI group. The 75% re-dilation rate appears to be the most sensitive of the four significant parameters. Furthermore, in the majority of the mTBI cases a complete re-dilation was not observed in the 5-second recording window for the PLR-200™ pupillometer (Figure 3). It is worth mentioning that even though the ADV and 75% recovery values are not presented on the pupillary response curve summary for the mTBI subjects (Figure 3A) that did not completely recover during the recordings time, the stored pupillometry quantitative data had these values, which were used for the analysis. While PLR is normally expected to be completed within a 5-second window, PLR can be delayed by neuro-ophthalmic pathology or neurological deficit, as shown in this and other studies. While a 5-second recording window was adequate to detect PLR deficits, longer recording times are recommended to accurately characterize PLR re-dilation deficits in blast-induced mTBI patients.

PLR Parameter	mTBI			Non-TBI		
	OD	OS		OD	OS	
	Mean (SD)	Mean (SD)	P	Mean (SD)	Mean (SD)	P
Maximum Diameter (mm)	5.53 (0.76)	5.46 (0.75)	0.22	5.71 (0.74)	5.54 (0.91)	0.08
Minimum Diameter (mm)	3.65 (0.47)	3.59 (0.49)	0.25	3.84 (0.51)	3.72 (0.66)	0.09
Percent Constriction (%)	34.08 (3.40)	34.25 (0.02)	0.42	32.78 (0.33)	33.03 (0.04)	0.34
Constriction Latency (ms)	240.73 (25.73)	237.48 (28.66)	0.27	214.48 (18.31)	209.03 (12.80)	0.17
75% Recovery Time (sec)	4.49 (0.63)	4.46 (0.50)	0.43	1.81 (0.48)	1.72 (0.42)	0.21
Average Constriction Velocity (mm/sec)	-3.45 (0.99)	-3.72 (0.55)	0.13	-4.13 (0.43)	-4.09 (0.51)	0.30
Maximum Constriction Velocity (mm/sec)	-4.86 (0.78)	-4.96 (0.70)	0.29	-5.18 (1.37)	-5.11 (1.49)	0.44
Dilation Velocity (mm/sec)	0.83 (0.41)	0.77 (0.27)	0.28	1.02 (0.17)	1.02 (0.23)	0.48

Table 1: Between-eye comparison of mean PLR parameters for the mTBI and non-TBI groups. OD = right eye; OS = left eye; mTBI = mild traumatic brain injury; PLR = pupillary light reflex; minus value indicates a constriction response.

PLR Parameter	mTBI	Non-TBI	
	Mean (SD)	Mean (SD)	P
Maximum Diameter (mm)	5.50 (0.73)	5.63 (0.79)	0.29
Minimum Diameter (mm)	3.62 (0.45)	3.78 (0.56)	0.14
Percent Constriction (%)	34.16 (2.16)	32.90 (3.09)	0.10
Constriction Latency (ms)	**239.10 (24.58)**	**211.75 (9.51)**	**<0.001**
75% Recovery Time (sec)	**4.47 (0.48)**	**1.77 (0.38)**	**<0.001**
Average Constriction Velocity (mm/sec)	**-3.58 (0.61)**	**-4.11 (0.44)**	**0.003**
Maximum Constriction Velocity (mm/sec)	-4.91 (0.62)	-5.15 (0.99)	0.19
Dilation Velocity (mm/sec)	**0.80 (0.27)**	**1.02 (0.17)**	**0.001**

Table 2: Between-group comparison of mean PLR parameters. mTBI = mild traumatic brain injury; PLR = pupillary light reflex; minus value indicates a constriction response. Bold value indicates statistical significance at $p < 0.05$.

These results are not surprising given the close relation of the pupillary pathways to brain structures. Pupil constriction and dilation in response to a light stimulus are controlled by the autonomic nervous systems (ANS), specifically, the parasympathetic (PNS) and sympathetic nervous system (SNS), respectively [36]. Pupil constriction results from an increase in PNS activity and decrease in SNS activity. The reverse process is required for pupil dilation. Thus, an equilibrium between PNS and SNS is a prerequisite for optimal PLR. Because of these dual innervations, PLR deficits could be caused by a defective PNS or SNS activation. Therefore, the slower pupil constriction parameters and the slower pupil re-dilatation observed in this study suggest reduced parasympathetic and sympathetic activity. Additional studies of PNS and SNS activity inhibition utilizing pharmacological agents will be required to determine the specific ANS mechanism affected in mTBI patients. An alternate explanation for the significant sympathetic pupillary deficit found on the present study is the presence of a neuroendocrine dysfunction (NED). The hypothalamus links the nervous and endocrine systems via the pituitary gland. Therefore, it is expected that, in addition to the primary damage to the hypothalamus and/or the pituitary gland induced by mTBI, the production of pituitary hormones will be impacted. In particular, changes in pituitary hormone secretion can be observed during the acute phase after TBI as part of the adaptive response to the injury [37]. Post-traumatic hypopituitarism can result in adrenal insufficiency [38], which can cause decreased sympathetic activity and consequently a reduced dilating response. Recently, the DoD has placed a strong emphasis in the screening of NED on those patients with persistent mTBI symptomatology [39]. Additional studies will be needed to correlate indicators of PLR and NED.

It has been established that ANS dysfunction can occur in those with mTBI/concussion-type injuries. Increases in heart rate and fluctuations in blood pressure have been observed with autonomic testing procedures [40]. In addition, variability in heart rate has been seen with low/moderate exercise in athletes who have had a concussive event [41]. Furthermore, a recent case study of a teenage gymnast three weeks post-concussion revealed attention and recall deficits in addition to, "sympathetic dysfunction with the absence of a late phase II rise in blood pressure with Valsalva, suggesting altered vascular tone and heart rate response compared with normal controls" [42]. However, in this case study, all the signs and symptoms improved six weeks post-injury with physical, cognitive, and emotional rest.

Despite the defective pupillary dynamics observed in the present study, there was no significant difference in the pre-stimulated resting pupil size or the peak constriction size for either of the groups. Anisocoria (i.e., unequal pupil size) has not been reported in mTBI, therefore equal response by the contralateral eye observed in the present study is expected and consistent with a previous study involving the quantitative evaluation of PNS and SNS control of iris function [31].

While PLR can be affected by systemic and ocular disease processes and age, the subjects included in this study were relatively young and did not have any other concomitant systemic or ocular disease. In addition, subjects were age-matched to control for age-related differences in pupil size.

Digital infrared pupillometry provides an effective method to assess ANS control of PLR; it is an objective test, non-invasive, quick to perform, accurate causes reproducible measurements, requires no specialized training and causes no added discomfort or risk to the patient. Its PLR data are retrievable for further analysis and can easily transferred to electronic health records. This technology can be easily implemented in the operational environment to assess brain injuries secondary to combat trauma. It is hand-held, light-weight, portable, battery-operated, and relatively inexpensive. Digital infrared pupillometry also eliminates the inter-examiner variability inherent in the standard penlight technique [19]. In addition, the pupillary response curve displayed on the pupillometry screen provides the user with an instant visual representation of the defective curve (Figure 3). While additional studies are required to standardize the use of infrared pupillometry for different conditions, the present study suggests that this methodology could be used as the standard of care for PLR assessment when suspecting a neuro-ophthalmic disease or neurological deficit. If infrared pupillometry is performed during pre-deployment evaluations, not only could PLR help with the initial ANS assessment, but also to monitor subsequent recovery, or lack of recovery, after ANS deficit.

There were three limitations to this study. First, the small sample prevented further analysis of PLR and levels of symptomatology to determine which PLR parameters are indicators of continuing pathology in asymptomatic individuals, who have presumably recovered from their mTBI. Second, the pupils were assessed monocularly, therefore no consensual pupillary response was assessed. The assessment of consensual pupillary response could potentially identify subtle cases of afferent pupillary defect not readily identified through subjective manual testing. Finally, PRL measurements were taken over a 5-second period. More information about the pupil reflex may have been demonstrated if the measurements had been taken over a longer time period.

In conclusion, the evidence presented in this study demonstrates the potential application of PLR as an objective index of ANS activity and the value of using PLR, in conjunction with other biomarkers, to optimize the diagnosis of mTBI in the battlefield and to facilitate the RTD decisions by deployed healthcare providers. Consequently, the results support the implementation of digital infrared pupillometry in the clinical and operational setting. Further research with a larger sample size, as well as during different mTBI stages, levels symptomatology, and mechanisms of injury (blast vs. non-blast), could shed light on the specific PLR parameters to accurately diagnose mTBI, monitor recovery, and make RTD determination. Additional studies are also needed to correlate PLR and NED screening labs.

Disclaimer

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Acknowledgement

This research was funded by the Military Operational Medicine Research Program of the US Army Medical Research and Materiel Command.

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This article was originally published in a special issue, **Brain & Spinal Cord Injury** handled by Editor. Dr. Chen Gaung Yu, University of Kentucky, USA