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Automated Pupillometry in Neurocritical Care: Research and Practice

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Abstract

Purpose of Review The purpose of this review is to examine the impact of pupillometer assessment on care and research of patients with neurological injury.

Recent Findings Recent studies demonstrate that automated pupillometry outperforms manual penlight pupil examination in neurocritical care populations. Further research has identified specific changes in the pupillary light reflex associated with pathologic conditions, and pupillometry has been used to successfully identify early changes in neurologic function, intracranial pressure, treatment response to osmotherapy, and prognosis after cardiac arrest.

Summary Automated pupillometry is being increasingly adopted as a routine part of the neurologic examination, supported by a growing body of literature demonstrating its reliability, accuracy, and ease of use. Automated pupillometry allows rapid, non-invasive, reliable, and quantifiable assessment of pupillary function which may allow rapid diagnosis of intracranial pathology that affects clinical decision making.

Keywords Automated pupillometer · Pupillary light reflex · Neurological examination · Outcomes · Intracranial pressure · Traumatic brain injury

Introduction

The neurological exam remains the most vital and relevant bedside diagnostic evaluation of neurological function that is available to the clinician. Examination of the pupillary light reflex (PLR) has long been a standard element of this exam for patients with known or suspected neurologic injury. The standard pupil examination most commonly involves visual assessment of pupil size, shape, symmetry, and pupillary light reflex [1]. Modern pupilometers provide accurate and reliable evaluation of various aspects of the PLR at precision levels that were heretofore unobtainable [2•, 3–5]. While automated pupillometry has not replaced any portion of the neurological exam, it has changed the accuracy and reliability of the PLR assessment. Therefore, the purpose of this review is to examine the impact of pupillometer assessment on care and research of the patient with neurological injury.

This article is part of the Topical Collection on *Critical Care*

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Neuromonitoring is essential for detecting changes in cerebral function to identify pathology and support interventions to prevent impending secondary brain injury [6]. PLR deterioration is a strong predictor of outcome after acquired brain injury [7, 8•, 9]. The importance of accurate, reliable, and valid data is not disputed, but the methods and tools for neuromonitoring are debated [10]. In the past 5 years, there has been a substantial increase in data supporting the utility, reliability, and predictive value of PLR data from automated pupillometry (Table 1) [3, 9, 11, 13, 14, 16, 20–29].

The Pupillary Light Reflex

Pupil "correctopia" was identified in 1907 [30]. Abnormal size and shape were later associated with changes in intracranial pressure (ICP) [31–33]. Under normal conditions with the PLR intact, light delivered to the entire pupil will produce a decrease in pupil size [34]. The pupillary response is under direct control of the autonomic nervous system, and maximum constriction velocity and relative constriction amplitude are felt to be effective means for detecting parasympathetic dysfunction [35, 36]. The dynamics of the PLR follow a consistent pattern involving 4 phases which can be mapped out

Table 1 Recent literature on pupillometry in the neurocritical care population

Reference	Description	Findings
Pupillometry compared with standard practice in neurocritical care population		
Shoyombo et al. [11•] (2018)	Observational, Prospective analysis of registry data Aim: Identify prevalence of normal constriction velocity in population with normal NPi in neurocritical care population $N = 1617$	CV greater than 0.8 mm/s was associated with high likelihood of normal NPi and low likelihood of having an abnormal NPI (< 3) CV less than 0.8 mm/s was associated with low NPi (< 3) Increasing pupil size and % change in pupil size were predictive of CV ($r^2 = 0.72$ and $r^2 = 0.457$, $p < 0.001$). 30.9% of observations had one or both eyes showing normal NPi with slow CV or low NPi with brisk CV. Brisk CV does not rule out an abnormal PLR; slow CV does not rule in abnormal PLR
Zhao et al. [12] (2016)	Prospective observational study Aim: Determine inter-device reliability of NPi-100 pupillometers $N = 20$	Mean maximum pupil size at rest for left eye (3.8 (1.1 SD) vs. 4.0 (1.6 SD), $p = 0.27$) and right eye (3.6 (1.1 SD) vs. 3.8 (1.1 SD), $p = 0.74$). Minimum pupil size with light stimulation for left eye (2.8 (1.2 SD) vs. 3.0 (1.5 SD), $p = 0.64$) and right eye (2.6 (1.0 SD) vs. 2.6 (0.6 SD), $p = 0.44$). Mean pupil reactivity for left eye (3.9 (1.2 SD) vs. 3.9 (1.4 SD), $p = 0.36$) and right eye (4.2 (1.0 SD) vs. 4.3 (0.8 SD), $p = 0.82$) Cohen's kappa assessments for pupil size and reactivity by independent investigators were nearly perfect between 2 pupillometers for max and min pupil size and reactivity
Olson et al. [2•] (2016)	Prospective, single blinded observational study Aim: Establish inter-rater reliability of pupil examination between two independent practitioners and an automated pupillometer $N = 127$	For manual assessment, inter-rater reliability was moderate for pupil size ($k = 0.54$, 95% CI, 0.50–0.57), and agreement on pupil size was fair ($k = 0.29$, 95% CI 0.27–0.32 and $k = .031$, 95% CI 0.2–0.34) for first and second practitioners respectively. Low agreement in detection of anisocoria between practitioners and pupillometers. 33.3% of pupils scored as not reactive by practitioner were not reactive by pupillometry. Practitioner agreement by manual pupillary assessment of non-reactive vs. sluggish vs. brisk pupils was fair ($k = 0.40$, 95% CI 0.36–0.44). Concluded that automated pupillometry may increase reliability of measuring pupil reactivity and standardize assessment
Utility of automated pupillometry in identifying acute changes		
Jahns et al. [13•] (2019)	Observational cohort Aims: Examined relationship between NPi and invasive ICP in patients with severe TBI (GCS < 9) $N = 54$	Among subjects with intracranial hypertension secondary to severe TBI, elevated ICP correlated with decrease in NPi. Episodes of sustained high ICP ($n = 43$, 172 matched ICP-NPi samples; baseline ICP[T-6 h] 14 ± 5 mmHg vs. ICPmax[T0 h] 30 ± 9 mmHg) associated with concomitant decrease in NPi (baseline 4.2 ± 0.5 vs. 2.8 ± 1.6, $p < 0.0001$). Abnormal NPi values were more frequent in patients with refractory intracranial hypertension ($n = 17$; 38 [3–96]% of monitored time vs. 1 [0–9]% in patients with non-refractory intracranial hypertension and 0.5 [0–10]% in those without intracranial hypertension; $p = 0.007$). Abnormal NPi associated with unfavorable 6-month outcome (15 [1–80]% in GOS 1–3 vs. 0 [0–7]% in GOS 4–5; $p = 0.002$)
Aoun et al. [14] (2019)	Retrospective analysis of prospectively collected data, observational Aim: Investigate role of automated pupillometry in setting of SAH as adjunct to TCD $N = 56$	For 635 paired observations of daily TCD and NPi, data showed statistically significant association between NPi value and sonographic vasospasm. There was a significant association between DCI and sonographic vasospasm χ^2 (1) = 6.4112, $p = 0.0113$, OR 1.6419 (95% CI 1.1163–2.4150), and between DCI and an abnormal decrease in NPi, χ^2 (1) = 38.4456, $p < 0.001$, OR 3.3930 (95% CI 2.2789–5.0517). 7/12 subject with delayed cerebral ischemia had a decrease of their NPi to abnormal range > 8 h prior to the clinical decline 71.4% of the time. NPi normalized in all patients after treatment of their vasospasm. Concluded sonographic vasospasm may not correlate with NPi change, but NPi changes are strongly associated with onset of delayed cerebral ischemia and may be of predictive value.

Table 1 (continued)

Reference	Description	Findings
Assessing severity		
Osman et al. [15] (2019)	Prospective observational registry, retrospective analysis Aim: Correlation of NPi and CV with acute ischemic or hemorrhagic stroke with presence of midline shift on CT or MRI of brain. $N = 134$	There was a significant correlation between septum pellucidum shift and NPi (left [$p < .001$], right [$p < .001$]), CV (left [$p < .005$], right [$p < .001$]) pupillary asymmetry (absolute difference between right and left; $p < .05$) There was no significant correlation between midline shift and pupillary size (left or right). There was significant correlation between the NPi and CV for the right pupil when there was a right to left midline shift ($p < 0.001$ and $p < 0.05$) but none between NPi and CV for left pupil during left to right midline shift. Concluded there was a significant correlation between NPi and CV and pupillary asymmetry, but no correlation was found with size.
Natzeder et al. [16•] (2018)	Retrospective analysis of prospective registry data, observational Aim: Evaluate aspects of NPi in relation to clinical severity and outcomes after aSAH $N = 18$	Mean NPi was lower in clinically severe (WFNS 4–5) vs. non-severe (WFNS 1–3) aSAH (mean ± SE: 3.75 ± 0.44 vs. 4.56 ± 0.06, $p = 0.171$). Pathologic NPi values observed more frequently in clinically severe (WFNS 4–5) vs. non-severe (WFNS 1–3) aSAH (mean ± SE: 16.3% ± 8.8% vs. 0.0% ± 0.0%, $p = 0.002$). Mean NPi was lower in patients with GOS 1–3 vs. GOS 4–5 (favorable outcome) at discharge (mean ± SE, 3.64 ± 0.48 vs. 4.50 ± 0.08; $p = 0.198$). Inverse correlation between NPi and ICP (Spearman $r = -0.551$, $p < 0.001$).
Assessing treatment effect		
Ong et al. [17•] (2019)	Prospective observational study Aim: To assess effect of osmotic therapy on pupillary indices by pupillometry $N = 72$	NPi significantly improved within 2 h of osmotic therapy when controlled for additional interventions $\beta = 0.08$, $p = 0.0168$. The most significant effect was observed in patients with an abnormal NPi prior to intervention ($\beta = 0.057$, $p = 0.0235$). Concluded that pupil reactivity improves after osmotic therapy and effect should be considered to help determine dose-dependent effects and timing.
Wildemeersch et al. [18] (2018)	Prospective cohort observational study Aim: Compare PDR vs. nociception flexion reflex as pain assessment tool in mechanically ventilated patients receiving opioids or propofol $N = 40$	Automated pupillometry was used to determine pupillary dilatation reflex during nociceptive stimulations applied by an inbuilt pupillary pain index protocol. After opioid administration patients needed a higher stimulation intensity to produce pupil dilation of > 13% (45.26 mA vs. 30.79 mA, $p = 0.00001$). Concluded that pupillary dilation during tetanic stimulation may reflect opioid effect under general anesthesia
Lukaszewicz et al. [19] (2015)	Prospective, observational study Aim: Evaluate automated pupillometry to predict pain and assess adequacy of analgesia for ICU procedures $N = 37$	% variation in pupil size > 19% predicted presence of pain during a dressing change, correlated to behavioral pain scale score of > 3. Sensitivity 100% (95% CI) and specificity of 77% (95% CI, 54–100%). Patients with largest pupil diameter and greatest variation were those who presented pain behavior during the procedure. Suggested pupillometry may be used as part of nonverbal assessment of pain.

based on changes in size (diameter) over time (seconds). These phases are response latency, maximum constriction, pupillary escape, and recovery [36]. Automated pupillometry provides measured values for three of these phases: latency, constriction velocity (CV), and dilation velocity (Fig. 1).

Latency is measured in milliseconds and describes the delay in pupil constriction following the application of the light stimulus [37]. The latency period, which may be shortened by higher intensity light stimulus, is due to delay in iris smooth muscle contraction with minimal effect from innervation pathways [38]. Latency is followed by constriction of the pupil. Constriction is measured in millimeters per second (mm/s) and reported or analyzed as CV, and also as maximum CV. The maximum CV is seen during initial constriction, and the velocity diminishes as the minimum pupillary diameter is reached [11•]. Following peak constriction, the pupil quickly escapes to a partially constricted state before returning to its initial size [36]. The recovery phase occurs when the light

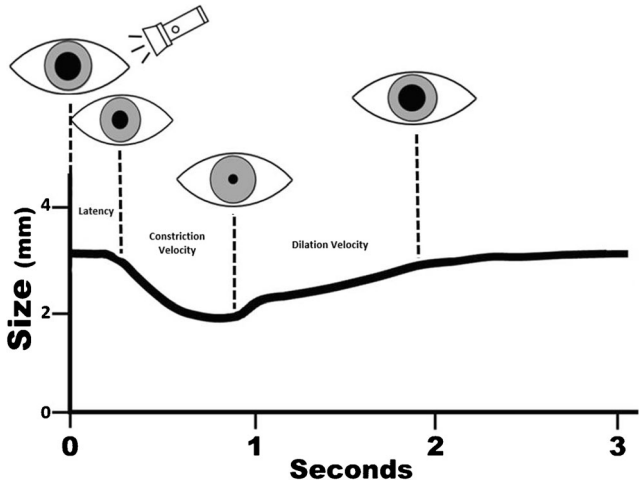

Fig. 1 Key components of the pupillary light reflex

stimulus is removed and is measured in mm/s and reported as the dilation velocity (DV) [37]. Post-illumination recovery can be sustained for up to 3 min depending on properties of the light and retina [36].

Sympathetic and parasympathetic pathways help regulate the PLR. An arousing stimulus, whether noxious or loud, applied to an awake subject dilates the pupil by activating the sympathetic radial muscle [39]. The pupil dilation reflex (PDR) following a stimulus occurs through integrated processes driven by sympathetic neurons. The parasympathetic innervation to the pupil sphincter is suppressed by supranuclear inhibition (central sympathetic neurons primarily in the reticular activating system which inhibit preganglionic parasympathetic neurons at the Edinger-Westphal nucleus) resulting in relaxation and pupillary dilation. Additional dilator muscle activation occurs via the α1-adrenergic sympathetic pathway. The mechanics of these pathways are mediated by both acetylcholine at synaptic junctions, and dilator muscle response to noradrenaline [36].

Pupillometry Basics

The amplitude or magnitude of the contraction, the CV, and the DV depend on the intensity and duration of the applied stimulus [40]. Whereas traditional assessment of the PLR is dependent on clinician assessment skills and light source (intensity and duration), pupillometry capitalizes on technological advancements in high-speed camera and computing technology [41]. The modern pupillometer is a handheld device that performs quantitative, reproducible, precise measurements [2•, 12, 42].

Solid-state microchips sensitive to infrared light allow continuous measurement of the pupil without simultaneously altering the pupil size and movement. A light-emitting diode infrared light is applied toward the pupil, and a sensor detects the reflected infrared light from the iris. The pupil is a blank circle in the middle of the reflected image, and the computer calculates the area of the pupil. This diameter is measured rapidly and repeatedly (every 30 ms). This generates not only the size of the pupil over several seconds but also the fluctuations in pupil size.

The Neuroptics NPi-200 is currently the only handheld pupillometer marketed in the USA. This device provides measured values for pupil size a baseline and maximum constriction, latency, CV, and DV, and a derived (proprietary formula) for the Neurological Pupil Index (NPi) [37]. While criticized for not having full control of ambient light, the very gradual nature of dark adaptation would not be feasible to incorporate into the neurological examination, with or without pupillometry [43]. Research into pupillometry is challenging the traditional evaluation of a normally reactive pupil. New data now demonstrate that a pupil can be briskly reactive, but abnormal (e.g., a 6-mm pupil that only partially constricts to 5 mm) [11•].

Primary Neurological Conditions

Pathologic changes in the PLR have been associated with clinical outcomes in a wide variety of neurological conditions [29]. Park et al. demonstrated a detectable difference in admission NPi values with patients with poor 1-month neurological outcomes (GOS 1–3) for all comers with acute brain injury due to subarachnoid hemorrhage, TBI, cerebral infarction, or intracerebral hemorrhage using an NPi cutoff for 3.4 with a specificity of 84.2% and sensitivity of 86% for a "poor" vs. "favorable" outcome [44]. Pupillary changes are often a harbinger of secondary brain injury, cerebral edema, hydrocephalus, intracranial shift, and raised ICP [6, 7, 13•, 24, 45–47]. A plethora of data generated within the field of ophthalmology predating the advent of handheld pupillometry documents the effect of intrinsic (preexisting) eye pathology influences pupil size and light reflex. Preexisting optic neuropathies, Argyll Robertson pupil, asymmetric glaucoma, and retinal disease may impact both manual and automated pupil examination, and these will not be addressed in this review. It is important to emphasize documentation of accurate baseline examination and consider intrinsic eye pathology in the differential for baseline abnormalities whether or not pupillometry has been employed.

Traumatic Brain Injury

A 2003 study [33] launched research examining pupillometry in acute traumatic brain injury (TBI). In patients with acute traumatic epidural hematoma and Glasgow Coma Score (GCS) < 8, anisocoria (pupillary size difference of > 2 mm) was present in 67% of patients and reducing the surgery

interval to less than 90 min was associated with a better outcome [48]. Whereas TBI patients with a GCS = 3 and fixed and dilated pupils had no reasonable chance for survival, a cohort of patients with GCS = 3 whose pupils were not fixed and dilated survived their injury [49]. DV has been noted to be altered even in mild TBI and concussion [47].

Elevated ICP is a common sequela of TBI, and a growing body of evidence supports that elevated ICP is associated with decreased NPi [13•, 22, 23, 50]. Patients with elevated ICP were found to have improvement in NPi values after osmotic therapy (20% mannitol or 23.4% saline), indicating that pupillometry has potential use as a noninvasive tool to assess the efficacy of osmotic therapy [17•]. The use of pupillometry as a non-invasive means to detect elevated ICP is further supported by Soeken et al. [51] in a study of idiopathic intracranial hypertension.

Oculomotor Nerve Palsy and Horner's Syndrome

Pupillometry has also been used to differentiate compressive and ischemic third nerve palsy. Reduced CV was found to be the most specific parameter for detecting non-ischemic third nerve palsy. For diagnosing compressive third nerve palsy, an inter-eye difference of > 0.45 mm in minimum pupil diameter or < − 7.5% constriction ratio had a sensitivity and specificity of 95% and 88% respectively [25]. Aoun et al. [52] reported a case in which abnormal NPi values preceded subjective assessment of third nerve palsy by 12-h. Pupillometric assessment of inter-eye differences of the maximum pupil diameter or the time taken by the pupil to recover to 75% of maximum diameter has been shown to have a sensitivity of 94.7% and specificity of 93.3% in the diagnosis of Horner's syndrome. This is comparable to the diagnostic accuracy of the apraclonidine test [53].

Ischemic and Hemorrhagic Stroke

Assessment of the PLR is equally important in stroke. Osman et al. [15] studied the relationship between intracranial midline shift and PLR indices in a retrospective study of 136 patients with an acute stroke (70% ischemic, 30% hemorrhagic). There was a significant correlation between midline shift and NPi, CV, and pupil asymmetry, but not pupil size [15]. However, pupillary size and DV were correlated in controls and patients with left hemispheric infarctions but not in patients with right hemispheric infarctions [54].

Pathological NPi values were more commonly seen in patients with high-grade subarachnoid hemorrhage (SAH) where the World Federation of Neurological Surgeons (WFNS) grade was > 3 compared with less severe SAH (WFNS grade 1–3) [16•]. Following subarachnoid hemorrhage, there is a significant correlation between the standard deviations for NPi, pupil size, CV, and DV and the discharge mRS score [8•]. There was a significant association between delayed cerebral ischemia and an abnormal decrease in NPi, but no association between NPi and sonographic vasospasm and the NPI preceded clinically detectable neurological changes by > 8 h in 2/3 of the cohort [14].

Seizure

Pupillometry research in seizure is limited. In a series of 89 electroconvulsive therapy sessions, patients' pupillary constrictions were significantly smaller (greater change in size) in the group with an adequate seizure when compared with the inadequate group [55].

Brain Death

The absence of a PLR is required for the diagnosis of brain death, and assessment with a flashlight is subject to error [2•]. This is highlighted by a case study in which flashlight assessment revealed fixed pupils. Upon use of pupillometry, his pupils were found to be reactive and he was taken for hematoma evacuation, eventually having good recovery [1]. There is an additional case series in which pupillometry found intact PLR for 3 patients in whom the PLR by flashlight was evaluated as absent [56]. Olgun et al. [57] measured pupil sizes in 57 infants, children, and adults diagnosed with brain death. The median right and left pupil sizes were 5.01 ± 0.85 mm and 5.12 ± 0.87 mm, respectively, with a range between 3.69 and 7.34 mm and not affected by vasopressor agents. The pupil sizes were larger in pediatric subjects [57].

Medical Conditions

Cardiac Arrest

Assessment of the pupillary light reflex has been recognized as an essential part of the prognostic neurological examination performed after hypoxic-ischemic cerebral damage after a cardiac arrest. Mild hypoxia dilates the pupil and depresses light reflex [41]. In a study of out-of-hospital cardiac arrest, the maximum pupillary diameter was found to be a strong predictor of return of spontaneous circulation and was also significantly correlated with neuron-specific enolase concentrations [58]. A prospective multi-center study of out-of-hospital cardiac arrest noted that the PLR values of survivors and patients with favorable neurological outcomes were consistently greater than those of non-survivors (poor outcome (sensitivity = 0.87; specificity = 0.80) vs. favorable neurological outcomes (sensitivity = 0.92; specificity of 0.74)) and a 6-h PLR of < 3% uniformly predicted mortality at 90 days [59•]. In a separate study, a PLR of less than 13% within the first 48 h of resuscitation was predictive of mortality [27]. Similar studies support

the prognostic value of pupillometry after cardiac arrest (Table 2).

Pupillometry has been used for prognostication of survivors of cardiac arrest. In a prospective cohort of 103 adult patients who were comatose 48 h after cardiac arrest, a quantitative PLR < 13% had 100% specificity and positive predictive value to predict poor recovery and performed as well as EEG and SSEP [27, 63•]. Higher NPi (better PLR responsiveness) is associated with improved 30-day outcomes in out-of-hospital, but not in-hospital cardiac arrest [60]. A reduced percent change in pupillary size was associated with worse electroencephalographic prognosis compared with those with great change in pupil size [61]. An international multi-center double-blinded prospective study validated the use of pupillometry using the NPi to predict outcome after cardiac arrest. At any time between day 1 and day 3, an NPi of ≤ 2 had a 51% negative predictive value and a 100% positive predictive value for the prediction of unfavorable outcome. The NPi performed better than the manual PLR. The addition of NPi to other tests like SSEP increased sensitivity of outcome prediction, while maintaining 100% specificity [26]. Several recent publications have studied the predictive value of quantitative pupillometry in patients treated with hypothermia after cardiac arrest. Higher PLR amplitudes have been associated with good outcomes, and a PLR amplitude of < 7% on day 2 predicted 3-month poor outcome with a specificity of 100% and sensitivity of 42% [21, 62].

Drugs

A drug or intervention that has an effect on the PLR would be expected to change the light reflex amplitude. With preserved integrity of the 2nd and 3rd cranial nerves and uninterrupted neural pathways through the pretectum and upper midbrain, the patient should have a normal light reflex. A review by Dr. Larson in 2015 summarizes the known neurotransmitter role in ciliary ganglion and pupillary sphincter activity (nicotinic and muscarinic respectively), but the pretectal and Edinger-Westphal nuclei appear to be possibly glutamate excitatory synapse junctions based on the timing and shape of the reflex arch suggestive of a rapidly acting ligand gated channels [41]. This leads to further need to clarify pharmacologic effect of neurotropic drugs on pupillary dynamics.

During general anesthesia, the sympathetic activity of the pupil is absent but present in other areas of the sympathetic nervous system [41, 64]. In anesthetized subjects, the pupillary changes during anesthesia are a result of alterations in pupillary sphincter tone directly controlled by neuronal activity within the upper mesencephalon [41, 65]. Similarly, with slow-wave sleep or during anesthesia with propofol, barbiturates, or inhaled anesthetics, the Edinger-Westphal (EW) neurons are thought to be spontaneous pacemakers, disinhibited by quiescence of various centers in the midbrain and posterior hypothalamus leading to rapid intrinsic firing. With lack of background inhibition to overcome the EW firing, pupils will fail to dilate in the dark. Sympathetic tone of the pupil during anesthesia is also lost, contributing to miosis. After approximately 10 min of full sedation with inhaled anesthesia, for example, the pupil stabilizes at a "basal diameter" of about 2 mm [41, 64].

Alcohol has also been shown to affect both pupil diameter as well as peak constriction amplitudes and velocities, though data is discrepant showing both increases and decreases in size, amplitude, and velocity depending on dose, time of ingestion, and dose of ingestion [66]. Similarly, recreational drugs with increased sympathomimetic activity due to increased noradrenalin and serotonin signally, such as 3,4-methylenedioxymethamphetamine and tetrahydrocannabinol (THC), have demonstrated increased latency and decreased constriction amplitude and velocity, as well as reduction in PLR recovery time [67, 68].

Despite the sympatholytic effect of diazepam, there was no significant effect on pupil diameter or pupillary light reflex [69]. Dexmedetomidine was examined in a similar way and produced no change in pupil size and light reflex recovery time but increased the light reflex from 0.30 ± 0.14 to 0.37 ± 0.12 mm and significantly reduced pupillary reflex dilation by 72 ± 62% [70, 71].

Organophosphate poisoning and botulinum toxins that block release of acetylcholine receptors have the expected response of paralysis of sympathetic and parasympathetic innervation to the iris resulting in pupil dilation and attenuation of the PLR. There is discrepant data, but the majority of effect of organophosphate and antimuscarinic agents appears to be from direct application and effect on ocular tissue rather than systemic absorption [36, 72].

Other Factors Affecting Pupillometry Output

Age is known to affect pupillary size. The resting aperture of the pupil decreases approximately 0.4 mm during each decade of life after 16 years of age. Sex and iris color, the latter of which would be expected to have a profound effect on manual penlight examination, have been suspected limitations of pupillometry [73]. PLR changes have been investigated as a nonverbal marker of pain [18, 41, 74–76]. Notably, because PRD is an evoked reflex, patients in constant pain may have small or mid-position pupils [41, 77] but will demonstrate changes in pupillary dilation when painful stimulus is administered [19, 78–80].

There have been several analyses regarding alteration in pupil size and particularly the pupillary light reflex in patients with Parkinson disease and Alzheimer disease. Most studies focused on the PLR parameters most

Table 2 Recent literature examining the prognostication value of pupillometry after cardiac arrest

Reference	Description	Findings
Obling et al. [60] (2019)	Prospective observational cohort study Aim: Assess prognostic value of NPi for 30 day mortality and outcome for comatose patients in the cardiac ICU $N = 221$	For patients with out of hospital cardiac arrest, higher NPi values were associated with lower 30-day mortality (AUC 0.87). Youden index identified a NPi cutoff for out of hospital cardiac arrest patients of 2.40 for a specificity of 100%. For patients with in-hospital cardiac arrest and other cardiac diagnoses, there was no association with NPi and 30-day mortality.
Beuchat et al. [61] (2018)	Retrospective analysis of prospective observational registry data Aim: Compare standardized EEG patterns and outcomes predictors during and after TTM after cardiac arrest $N = 202$	Correlation between benign EEG on day 1 and PLR. Correlation between highly malignant patterns and PLR were stronger. On day 1 after TTM, presence of highly malignant EEG pattern was associated with lower % change in PLR. Benign EEG had a higher % change PLR compared with patients with a non-benign EEG (26.6 ± 14.2 vs. 19.6 ± 11.8, $p < 0.023$). On day 2 after TTM, patients having a highly malignant EEG had a lower % change PLR compared to patients without a highly malignant EEG (12.8 ± 7.8 vs. 22.1 ± 12.6, $p < 0.001$).
Tamura et al. [59•] (2018)	Multicenter single-arm, uncontrolled prospective observational study Aim: Determine predictive value of pupillometry in post-cardiac arrest $N = 50$	PLR at 0 h was best predictor of 90-day survival and good neurologic outcome. PLR values consistently higher in patients with good neurological outcomes (CPC 1–2) compared to those with CPC 3–5 at 90 days. PLR values consistently higher in survivors compared with nonsurvivors at 90 days. PLR value was associated with 90-day survival ($p < 0.001$).
Solari et al. [27] (2017)	Prospective, blinded observational cohort Aim: Determine predictive value of pupillometry during first 48 h after cardiac arrest $N = 103$	Survivors had higher quantitative % change PLR (median 20% vs. 11%; $p < 0.0001$) and % change CV (1.46 mm/s vs. 0.94 mm/s, $p < 0.0001$) than nonsurvivors. 48 h data demonstrated a PLR of 13% was 100% specific for poor recovery (Cerebral Performance Category). Quantitative PLR had sensitivity of 61% and 71% NPV for good outcome
Heimburger et al. [62] (2016)	Prospective observational study Aim: Assess quantitative pupillometry vs. transcranial Doppler to predict outcomes after cardiac arrest during TTM $N = 82$	PLR amplitude of < 7% on day 2 after 24 h of targeted temperature management and sedation predicted poor outcome (CPC 3–5) at 3 months with 100% specificity and 42% sensitivity. Data at day 1 and 2 from AUC-ROC curves were 0.76 and 0.82 respectively. Determined best cutoff for predicting poor outcome at 3 months was PLR % change less than 9% on day 1 and < 11% on day 2.
Suys et al. [21] (2014).	Prospective, observational, double-blinded study Aim: Evaluate use of automated pupillometry within first 48 h to predict outcome post cardiac arrest compared to standard pupil exam, EEG and SSEP $N = 50$	Patients with good outcome (CPC 1–2) more likely to have higher PLR at days 1 and 2 than those with poor outcome (CPC 3–5); (16 [9–23]% vs. 10 [1–30] % at day 1, and 20 [13–39]% vs. 11 [1–55] % at day 2, both $p < 0.001$] for good vs. poor outcome respectively. A cutoff for outcome prediction was % change in PLR < 13%. AUC values for quantitative PLR to predict poor outcome was higher on day 1 (0.79 vs. 0.56, $p = 0.005$) and day 2 (0.81 vs. 0.64, $p = 0.006$) than manual PLR. There was comparable prognostic accuracy for quantitative PLR, EEG and SSEP (AUC values (0.81 vs. 0.80, $p > 0.20$) for quantitative PLR versus EEG and (0.81 vs. 0.73, $p > 0.20$) quantitative PLR versus SSEP)

affected by acetylcholine-dependent mechanisms and found significant reduction in CV and constriction amplitude when compared with normal age-matched subjects, though the duration of light stimulus during these studies has been implicated in discrepancies among the existing data [81, 82]. Similarly, pupillometry data with variable abnormalities in CV and size have been associated with severity in neurodegenerative conditions including multisystem atrophy [83] and autism spectrum disorders [36, 81, 84, 85].

Discussion

Though it is superior to routine penlight examination in general, the standardization and generalization of pupillometry data for use in assessment, therapeutics, and research must take into account population-related differences in baseline pupil size and function. Over the decades, baseline differences in pupil size and function have been recorded in different populations, all of which may be encountered within the neurocritical care

population. This underscores the importance of having baseline and serial measurements as well as well-established normative data for reference.

Additional factors should be considered when using automated pupillometry. As with a standard penlight examination, topical drugs such as pilocarpine or atropine, iris-lens adhesions, uveitis, and syndromes including Adie pupil, Argyll Robertson pupil, Horner's syndrome etc. may alter clinical interpretation of pupillometry data.

It is important to note that not all data prior to pupillometry can be compared across populations, as studies used different duration of light, control of ambient light, intensity and color of light, and devices. This makes comparison across studies difficult. While the accuracy and reliability of these measured variables has been demonstrated, the advent of pupillometry has provided a host of unique new variables. There is a need for research to determine the utility of each variable, and within context of various pathophysiologic conditions. The variables CV, DV, latency, and NPi are relatively new to clinical practice. Future research will provide insight to the full utility of high-fidelity PLR assessments.

Automated pupillometry has many potential applications. It is portable, and, compared with most other neuroimaging modalities, inexpensive. The true cost efficacy of replacing the standard penlight examination is difficult to determine, as emerging literature suggests early prediction of ICP and treatment effect may be a measurable outcome, but there is unlikely to be a global mortality benefit from incorporation of any monitoring tool. Moreover, there is no research demonstrating any adverse effects from pupillometer assessments. Therefore, the technology allows safe, serial evaluation of patients and permits rapid assessment of a vital portion of the neurologic examination.

Conclusion

Pupillometry allows for rapid assessment of a vital component of intracranial pathology. We already know that the findings from this assessment clearly affect clinical decisions. The prognostic value of incorporating automated pupillometry results when assessing for brain death or outcomes after out of hospital cardiac arrest supports its clinical use, but more data is needed to determine what normative values in these populations and timing of evaluation with sensitive and accurate data. Similar to clinical evolution of the echocardiogram, with increasing diagnostic use, hopefully identification of population norms and characterizing abnormalities will allow for augmentation of the traditional pupil examination, and over time we will learn how to incorporate the additional data from pupillometry into clinical practice and research. At a minimum, the ability of pupillometry to generate an objective, repeatable, and reliable pupil examination far superior to that of a flashlight supports the assertion that this technology should become standard practice.

Compliance with Ethical Standards

Conflict of Interest Bethany L. Lussier and Venkatesh Aiyagari each declare no potential conflicts of interest. DaiWai M. Olson reports grants from Neuroptics Inc., outside the submitted work; and he also serves as the editor for the *Journal of Neuroscience Nursing*.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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