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Abstract

Quantitative pupillometry provides a noninvasive and objective assessment within the neurological examination. This review details the physiology of the pupillary light response, the clinical significance of changes in pupillary reactivity, and the variables that compose the Neurological Pupil index or NPi are discussed. This article reviews the most recent applications and advances in quantitative pupillometry for noninvasive intracranial pressure monitoring, postcardiac arrest prognostication, and subarachnoid hemorrhage. Also discussed are the limitations and confounders of quantitative pupillometry in the modern neurological intensive care unit.

Keywords

pupillometry, out of hospital, cardiac arrest, reflex, pupillary, brain injuries, traumatic, intracranial pressure

Introduction

In the second-century AD, Galen of Pergamon found that the pupillary response could be used in identifying a multitude of clinical conditions. To this day, clinicians routinely use this basic examination finding as an essential part of a patient's neurological status.¹ Until recently, however, the paradigm of pupillary change evaluation was dependent on a clinician's subjective finding with significant interrater variability.^{2,3} Therefore, the application of automated quantitative pupillometry has been a significant advance in the effort to quantify and standardize this aspect of the neurological examination and by extension neurological care.

Physiology of Pupillary Response

The pupils are controlled by both parasympathetic (constriction) and sympathetic (dilation) systems. Light activates retinal photoreceptors and retinal neurons that signal down the optic nerve (CNII) and across both optic tracts via the optic chiasm. These fibers then synapse within the pretectal area located in the midbrain. Axons arising from the pretectal area travel bilaterally and synapse at both Edinger-Westphal nuclei. Parasympathetic fibers then leave both Edinger-Westphal nuclei via the oculomotor nerves (CNIII) and synapse at the ciliary ganglia. Parasympathetic fibers then emerge from the ciliary ganglia to innervate the pupillary constrictor muscles. Therefore, a light shone in 1 eye causes a direct response in the ipsilateral eye and a consensual response in the contralateral one (Figure 1).

The anatomical arrangement of the CNIII warrants brief review. Superficial parasympathetic fibers control pupillary

function. Somatic efferent fibers, located in the inner portion of the CNIII, control striated muscles of levator palpebrae superioris and all extraocular muscles except for the superior oblique muscle and the lateral rectus muscle. Therefore, with external compression of CNIII, the parasympathetic fibers may be affected first or in isolation presenting with pupillary dilation, while the inner somatic efferent fibers controlling extraocular movements may be preserved. In contrast, a complete CNIII palsy will result in the eye being displaced downward due to an unopposed superior oblique muscle innervated by trochlear nerve (CNIV) and outward due to an unopposed lateral rectus muscle innervated by abducens nerve (CNVI). Ptosis and pupillary dilation will also be present (Figure 1).

The sympathetic pathway is responsible for pupillary dilation. A descending sympathetic pathway from the hypothalamus travels down ipsilaterally to spinal cord levels T1 and T2. These first-order neurons synapse at the intermediolateral cell column of the upper thoracic cord. Second-order neurons exit the spinal cord at T1 and T2 and cross the apex of the lung

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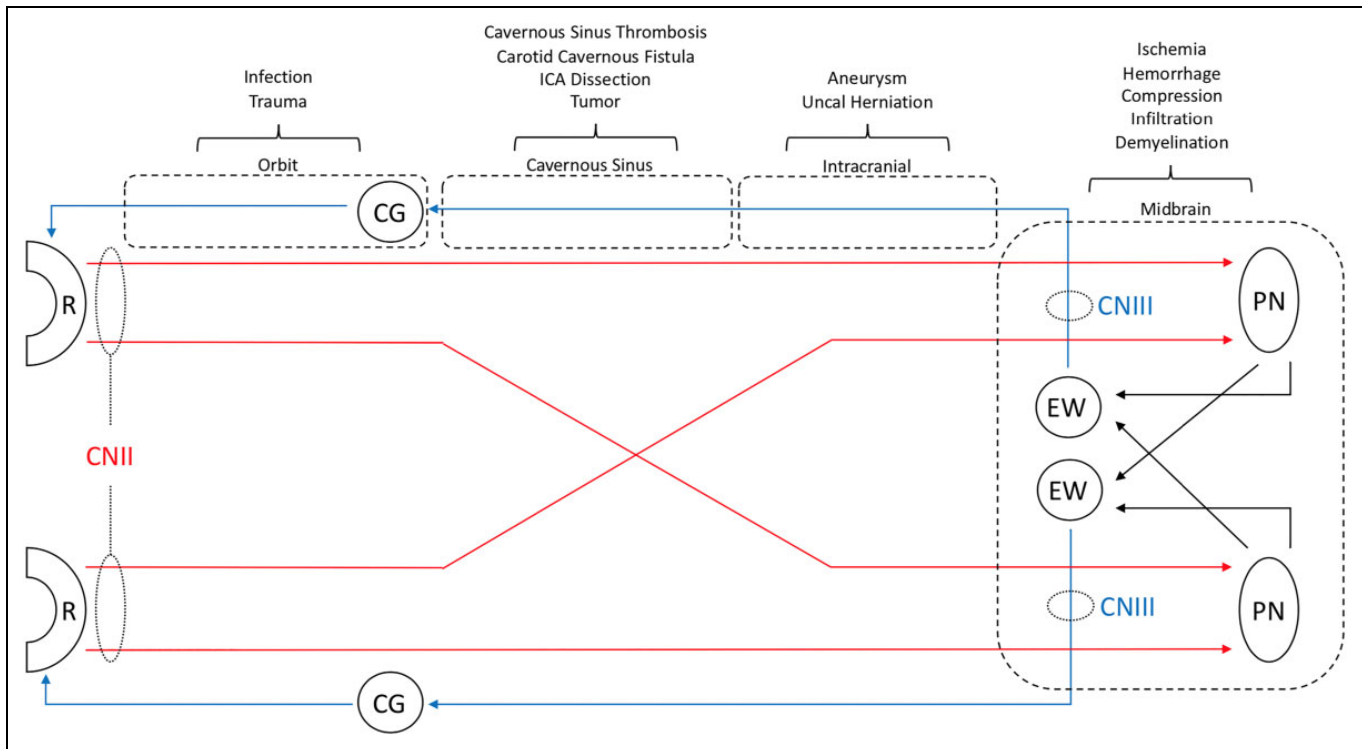


Figure 1. Schematic of the pupillary light reflex pathway with the anatomical location of pathological lesions.; CG indicates ciliary ganglion; CNII, optic nerve; CNIII, oculomotor nerve; EW, Edinger-Westphal nucleus; PN, pretectal nucleus; R, retina.

joining the sympathetic chain to synapse in the superior cervical ganglion. Third order neurons then ascend through the carotid plexus along the internal carotid artery then through the cavernous sinus eventually innervating the pupillary dilator muscle. Lesions affecting the first- and second-order neurons, such as lateral medullary syndrome or apical lung tumors, cause ipsilateral Horner syndrome, which is characterized by the triad of ptosis, miosis, and hemifacial anhidrosis.⁴ The sympathetic fibers responsible for facial sweating leave the pathway shortly after the cervical ganglion and continue along the external carotid artery. Therefore, more distal third-order neuron lesions such as internal carotid artery dissection do not cause anhidrosis. Of note, the symptoms of Horner syndrome will be ipsilateral, regardless of the location of the lesion which is unusual for the central nervous system. Also, the examiner should check for miosis in dim light as it can easily be missed.

Pathologies Affecting the Pupillary Light Reflex

Any condition that disturbs the balance of autonomic control of pupil size can affect the dynamics of the pupillary light reflex (PLR). Abnormalities of the PLR have been reported in a wide range of disorders. Metabolic disorders, such as diabetes, can impair the sympathetic system and affect the PLR.⁵ Significant differences in PLR have been noted in neurodegenerative conditions such as Alzheimer and Parkinson diseases, theorized to be due to the central cholinergic deficits in these conditions.⁶ In

fact, recent studies have shown quantitative pupillometry may be able to detect PLR changes in early Alzheimer disease^{7,8}

In the neurocritical care setting, pupillary size and reactivity to light often provides early information about impending intracranial problems, including elevated ICP, and should prompt an evaluation for critical pathologies.^{9,10} An accurate and prompt evaluation for such pathologies requires an understanding of the path of CNIII and its relationship with different lesions. For example, lesions at the Edinger-Westphal nuclei in the midbrain can cause bilateral palsies. Such a lesion may be caused by ischemia of the small, dorsal perforating branches of the mesencephalic portion of the basilar artery.¹¹ Approximately one-third of posterior communicating artery aneurysms cause CNIII palsy due to their proximity to the nerve.¹² CNIII palsies have also been attributed to aneurysms at the top of the basilar artery, superior cerebellar artery, and the anterior choroidal artery.¹³⁻¹⁵ Herniation of the uncus can also compress CNIII and its superficial parasympathetic fibers.¹⁶ Ischemia can also cause various midbrain stroke syndromes that affect the fascicles of the CNIII. These fascicles can also be affected by midbrain hemorrhage, compression, and infiltrative or demyelinating processes.¹⁷

Lesions such as tumors (eg, meningioma), cavernous sinus thrombosis, carotid cavernous fistulas, and vasculitis within the cavernous sinus or superior orbital fissure manifest with oculomotor palsy and frequently also with trochlear, trigeminal, and abducens nerve pathology. Infections of the orbit by *Pseudomonas keratitis* or herpes zoster ophthalmicus can also

Table 1. Quantitative Pupillometry Parameters.¹⁹

Parameter	Definition
Neurological Pupil index (NPI)	Proprietary algorithm using all parameters to determine pupillary response. Scale 0-5; <3 is abnormal.
Maximum and minimum	Pupil diameter (mm) at rest and peak constriction
Latency	Time (seconds) delay between light stimulus and initiation of pupillary constriction
Constriction velocity	Distance (mm) of constriction divided by duration (seconds) of constriction
Dilation velocity	Distance (mm) of redilation divided by duration (seconds) of redilation

induce a CNIII palsy.¹⁸ The PLR pathway and relevant pathologies are summarized in Figure 1.

Finally, Horner syndrome has multiple mechanisms and can manifest with miosis, ptosis, and anhidrosis. Stroke, encephalitis, meningitis, tumor, and syringomyelia can all interrupt sympathetic fibers and result in a full Horner syndrome. Distal third-order neuron etiologies such as carotid cavernous fistula or internal carotid artery dissection will present with ptosis and miosis without anhidrosis.⁴ However, changes in pupillometry do not warrant a broad evaluation for all aforementioned pathologies. Precise neurological examination with consideration for risk factors associated with initial clinical presentation and possible complications should guide evaluation.

Advantages and Limitations of Quantitative Pupillometry

Pupillary assessment is subject to interexaminer variability, has very low consistency, and relies on subjective and imprecise descriptions such as “brisk” or “sluggish.”^{2,3} Quantitative pupillometry provides more reliable measurements with a lower error rate.³ Pupillometry devices provide variables including maximum size, minimum size, constriction velocity (CV), constriction amplitude (CA), response latency, and Neurological Pupil index (NPI). The NPI is calculated by a proprietary algorithm from multiple variables including latency, CV, mean CV, size at baseline, percentage of change, and dilation velocity (Table 1). An NPI (NeuroOptics, Laguna Hills, CA, USA) of <3.0 is considered abnormal.¹⁹ Any of the previously mentioned variables are potential markers of changes in the PLR. However, an intact and brisk CV does not necessarily indicate a normal PLR.²⁰

Due to its advantages, quantitative pupillometry is increasingly being used as an adjunctive monitor in neurological intensive care units (neurological ICUs). A single-center evaluation of nursing colleagues found a preference for the pupillometer over the standard flashlight pupil assessment, herein referred to as qualitative pupillometry.²¹ Nevertheless, there are technical limitations to consider. Agitated or confused patients can be difficult to evaluate. Patients with scleral edema, periorbital edema, intraocular lens replacement, or

prior ocular surgical procedures can limit assessment with pupillometry.^{22,23} Consistency of pupillometric measurement can also be influenced by ambient light.^{24,25} Quantitative pupillometers are also expensive with reported prices up to US\$ 5000.^{26,27} A promising less expensive alternative is the development of smartphone-based software applications. Preliminary studies have shown comparable results between these smartphone applications and traditional infrared pupillometry.^{28,29}

Medication Effects on the PLR

Selected medications have been studied with quantitative pupillometry to understand their effects on the PLR, and many such medications are frequently used in the neurological ICU. For example, opioids are well known to produce miosis; however, they can also cause hypoxia and hypercarbia with associated sympathetic activation, which can blunt the parasympathetic response.³⁰⁻³³ In order to determine whether the PLR was preserved with opioids, 10 healthy volunteers received remifentanyl until bradypnea, desaturation, and/or hypercarbia were achieved. Baseline arterial blood gas and pupillometry were checked prior to administration. At the point of maximal hypercarbia and hypoxia (O₂ saturation <85%), the patients' pupils displayed a parasympathetic predominance with an average size of 2.5 mm. However, the volunteers had an intact but reduced PLR.³¹ These results are in agreement with a smaller early preliminary study (n = 6) with the same findings.³⁴ Thus, while opioids cause pronounced miosis, the PLR is preserved.

Paralytic agents are also commonly used in the neurological ICU. Gray et al conducted a study to determine the effect on pupillary response. Patients underwent tracheal intubation and were induced with propofol, fentanyl, and succinylcholine. General anesthesia was maintained with fentanyl and propofol. Vecuronium or pancuronium was then administered after the succinylcholine effect stopped. The study found that pupillary size, reflex amplitude, and CV were unaffected by neuromuscular blockade, and some patients had a preserved constriction response to isoflurane and preserved dilation response to noxious stimuli.³⁵

In general, states that decrease arousal usually cause miosis, and first-generation antihistamines such as diphenhydramine demonstrate this principal. Diphenhydramine 75 mg administered orally caused miosis, and the PLR remained intact. This was a surprising finding, given diphenhydramine's known anticholinergic properties. The authors postulate that miosis seen was due to reduced sympathetic tone from sedation.³⁶ Diphenhydramine overdose is known to cause mydriasis, and reports of diphenhydramine overdose range from 300 mg to >1.5 g.³⁷ The transition point between reduced sympathetic tone resulting in miosis and increased parasympathetic tone resulting in the mydriasis of overdose is unknown.

Benzodiazepines and propofol are also commonly used in the neurological ICU both for sedation and treatment of seizures. As such, it is critical to understand their effects on

pupillary dynamics. Two studies, with 16 and 15 healthy male volunteers each, found that diazepam 10 mg administered orally did not cause a change in pupil diameter or PLR.^{36,38} To our knowledge, there have been no studies involving continuous benzodiazepine infusion.

In a cross-sectional single-center cohort study of 19 adults, Haddock et al studied propofol sedation with quantitative pupillometry. All of the participants were in the ambulatory setting receiving either colonoscopy or esophagogastroduodenoscopy, which allowed the authors to eliminate potential confounders in the ICU setting such as other medications and comorbid conditions. Patients received a propofol bolus and maintenance dose that produced a significant decrease in maximum and minimum pupil diameter and decrease in mean CV. This study is valuable, as it is the only study to isolate propofol infusion and its effects on pupillary dynamics. However, it has limitations, namely, a small sample size and lack of a control group.³⁹

Barbiturates have been even less well studied. Taylor et al reported the effects in 3 patients on high-dose barbiturates for uncontrolled intracranial pressure (ICP). This study primarily evaluated the effects of high ICP on the PLR and was not designed to study medication effects directly. At burst suppression, the constriction velocities decreased to <0.6 mm/s, and the pupil constriction was <10% from baseline. Interestingly, these thresholds were the cutoffs found to be predictive of high ICP from the rest of the study's data. However, in these 3 patients, ICP was well controlled suggesting the medication effect was responsible.⁴⁰ Furthermore, the ciliospinal reflex, which is pupil dilation in response to painful stimuli of the neck or head, can be present and even exaggerated in a barbiturate coma.^{41,42} This phenomena has been confirmed by pupillometry.⁴³ These studies show that high-dose barbiturates can mimic the effects of high ICP on quantitative pupillometry, and recognizing this may prevent unneeded intervention.

Anti-emetics are also commonly used in the neurological ICU. Given that haloperidol is known to cause miosis, it was hypothesized that select anti-emetics may affect pupil size and reactivity based on shared anti-D2 receptor action as antipsychotics.⁴⁴ This study involved 47 patients undergoing lower abdominal surgery randomized to receive low- or high-dose metoclopramide, droperidol, or ondansetron. Pupillometry was performed every 5 minutes for 40 minutes to evaluate pupil size and pupillary reflex dilation (PRD), which is sympathetic reflex dilation in response to pain also called the ciliospinal reflex. Ondansetron did not affect PRD or pupil size, while metoclopramide and droperidol decreased PRD and pupil size. The effect on PRD was more sustained with droperidol than metoclopramide.⁴⁵ Overall, anti-emetic therapy is unlikely to confound pupillary response as the most common first-line therapy is ondansetron.

Less common effects have also been reported on a case report level. For example, ipratropium bromide is a derivative of atropine and has been reported to accidentally contaminate the eye when administered via nebulizer in the ICU. This can cause mydriasis and falsely suggest uncal herniation.⁴⁶

Table 2. Summary of Medication Effects on the Pupillary Light Reflex.

Medication	Dose	Effect on Pupil Size	Effect on Pupillary Dynamics
Remifentanyl ³¹	Titrated to respiratory depression	Miosis	Reduced PLR ^a
Vecuronium ³⁵	0.15 mg/kg	None	None
Diphenhydramine ³⁸	75 mg	Miosis	None
Diazepam ³⁶	10 mg	None	None
Propofol ³⁹	0.3-0.7 mg/kg bolus; 200-800 mg maintenance	Miosis	Reduced CV
Barbiturate ⁴⁰	Titrated to burst suppression	Not reported	Reduced CV
Ondansetron ⁴⁵	0.13 mg/kg	None	None
Metoclopramide ⁴⁵	0.5 mg/kg	Miosis	Reduced PRD
Droperidol ⁴⁵	0.02 mg/kg	Miosis	Reduced PRD

Abbreviations: CV, constriction velocity; NPi, Neurological Pupil index; PLR, pupillary light reflex; PRD, pupillary reflex dilation.

^aMeasured by change in pupil size in millimeters and NPi.

Quantitative pupillometry is a recent technology, and there is still much work to be done to quantify the effects of medications on the PLR. The field requires additional studies on other classes of medications (eg, antiepileptics) as well as more rigorous studies expanding on the preliminary works detailed earlier. Regardless, these studies illustrate that quantitative pupillometry should be interpreted in context with a consideration of medication influences (Table 2).

Applications of Quantitative Pupillometry

Postcardiac Arrest

The return of the pupillary light response has long been identified as an important prognostic sign after cardiac arrest (post-CA).⁴⁷⁻⁴⁹ As such, qualitative pupillometry has been used as an adjunct in prognostication. However, immediate post-CA prognostication based on pupillary response had previously been discouraged, as patients often receive atropine during resuscitation. Atropine blocks parasympathetic effects and is known to cause pupillary dilation, so neurological assessment was traditionally delayed due to concerns that atropine may confound the results.

In order to assess this, Goetting and Contreras studied 21 patients who had received atropine during resuscitation after a witnessed cardiac arrest and 28 patients who had received atropine prior to intubation in nonarrest situations. Both groups had increased pupillary dilation 30 minutes after atropine administration and 30 minutes after return of spontaneous circulation (ROSC), respectively. However, PLR was clearly preserved even with qualitative pupillometry in all patients in both groups. In summary, this study showed that while atropine may cause increased pupillary diameter, it does not cause nonreactive pupils post-CA. Therefore, if the PLR is absent, it is concerning for hypoxic-ischemic insult.⁵⁰

Building upon this findings, subsequent studies have evaluated the prognostic utility of the PLR both during resuscitation and immediately after CA. An early study showed that when PLR was measured during CPR, 83% of patients had a PLR at some point during resuscitation. The remaining 5 patients who had complete absence of a PLR all died, and the absence of the PLR for 5 minutes or more was associated with a poor outcome.⁵¹ Of note, all studies in this field standardize good or favorable outcome as Cerebral Performance Categories (CPC) 1-2 and poor or unfavorable outcome as CPC 3-5.

Immediate post-CA, PLR of <6% has also been shown to predict poor outcome. This study also evaluated later time points through 72 hours post-CA but found the zero-hour measurement to be most sensitive and specific for poor outcome.⁵² In addition to PLR, decreased NP_i and CV are also associated with poor outcome in the first 6 hours. In fact, there was 100% mortality in patients with NP_i 0 at 6 hours who did not receive targeted temperature management (TTM).⁵³ Outcomes for the TTM patients were slightly better for all NP_i ranges. For example, the mortality rate of TTM patients with NP_i 0 at 6 hours was 95%. Similarly, PLR <3% within 6 hours post-CA has been associated with 100% mortality.⁵² These immediate post-CA studies have small populations, and additional studies are required to validate the utility of pupillometry in this time frame.

Most studies have focused on pupillometry measurement performed at 1 and 2 days post-CA. Studies have shown that a PLR <9% to 13% at 1 day post-CA is associated with a poor outcome.^{54,55} Similarly, a PLR <13% on day 2 is associated with a poor outcome, and the cutoffs of 7% and 13% have both been shown to have 100% specificity.⁵⁴⁻⁵⁶ Decreased CV at day 1 and 2 also predicts poor outcome.⁵⁶ Finally, NP_i of <2 between day 1 and 3 had a 100% positive-predictive value for poor outcome.⁵⁷

While pupillometry is a promising modality, there are many tools in the post-CA prognostication toolbelt, and pupillometry is not performed in isolation but as an adjunct to these established methods. Using receiver–operating characteristic (ROC) curves, the area under the curve (AUC) for PLR alone was 0.81 at a cutoff of <13%, which was comparable to the AUC for electroencephalogram (EEG; 0.80) and somatosensory-evoked potentials (SSEP; 0.73) for predicting a poor outcome.⁵⁴ A PLR <13% was equal in specificity compared to absent activity on EEG or bilaterally absent N20 on SSEP at 48 hours. The addition of NP_i to SSEP augmented the sensitivity of SSEP from 48% to 58% and a specificity of 100% for predicting a poor outcome.⁵⁷ Reduced PLR had also been correlated with higher levels of neuron-specific enolase ($r = -0.52$, $P < .001$).⁵⁶

There has been a rapid increase in the number and robustness of studies evaluating the utility of quantitative pupillometry in post-CA prognostication. In summary, decreased PLR alone has been shown to be sensitive and specific within approximately the first 72 hours. The studies vary, but in general a PLR <13% is a poor prognostic sign. Given the finding that a zero-hour PLR <6% was the most sensitive and specific for poor outcome, in one study, this may serve as a valuable tool for emergency providers, as they often are the first to

Table 3. Summary of Studies Evaluating Quantitative Pupillometry in Post-CA Prognostication.

Time Post-CA	Findings	PLR AUC; Best Cutoff
Intra-CA	-All patients without PLR during CPR died ⁵¹ -Absence of PLR >5 minutes was associated with poor outcome ⁵¹	
Zero-hour post-CA	-Zero-hour PLR most sensitive and specific for poor outcome of all measurements within 72 hours ⁵²	0.84; <6% ⁵²
6 hours post-CA	-100% mortality when NP _i 0 ⁵³ -86% poor outcome when $0 < NP_i < 3$ ⁵³ -52% poor outcome when $NP_i > 3$ ⁵³ -PLR, NP _i , CV all predicted poor outcome at 6 hours, and AUCs not statistically different ⁵³	0.75; <5% ⁵³
24 hours post-CA	-Lower PLR associated with poor outcome ⁵⁴ -Slower CV associated with poor outcome ⁵⁵ -NP _i 2 or less had 100% PPV (FPR 0) for poor outcome ⁵⁷	0.79; <13% ⁵⁴ 0.76; <9% ⁵⁵
48 hours post-CA	-Lower PLR associated with poor outcome ⁵⁴ -Slower CV associated with poor outcome ⁵⁵ -PLR <7% was 100% specific for poor outcome ⁵⁵ -PLR <13% was 100% specific for poor outcome ⁵⁶ -NP _i 2 or less had 100% PPV (FPR 0) for poor outcome ⁵⁷ -Decreased PLR at 48 hours correlated with increased NSE at 72 hours ⁵⁶	0.81; <13% ⁵⁴ 0.82; <11% ⁵⁵
72 hours post-CA	-Higher PLR associated with better outcomes ($P < .001$) ⁵² -NP _i 2 or less had 100% PPV (FPR 0) for poor outcome ⁵⁷ -NP _i combined with SSEP increased sensitivity of SSEP alone ⁵⁷	

Abbreviations: AUC, area under the curve; CA, cardiac arrest; CPR, cardiopulmonary resuscitation; CV, constriction velocity; FPR, false positive rate; NP_i, Neurological Pupil index; NSE, neuron-specific enolase; PLR, pupillary light reflex; PPV, positive predictive value; SSEP, somatosensory evoked potentials.

encounter post-ROSC out-of-hospital cardiac arrest (OHCA) patients. The PLR alone is comparable to EEG or SSEP, but when used in combination PLR can enhance the sensitivity of these techniques while imparting 100% specificity in some studies. The key findings from the discussed studies are summarized in Table 3.

Overall, the results prove this technique is a valuable addition to the post-CA prognostication toolkit, both alone and as an adjunct to traditional methods such as EEG and SSEP (Table 3). Although quantitative pupillometry is already standard in many neurological ICUs, it is not as common in emergency departments or medical ICUs which care for post-CA patients on initial presentation and in subsequent days, respectively. The

studies are heterogenous, and there is currently no standardized parameter or value used to identify patients likely to have a poor outcome. However, multiple studies have shown that post-ROSC PLR <9% to 13% on the second day usually portends a poor outcome and can be up to 100% specific.⁵⁴⁻⁵⁶ These findings argue for wider adoption of quantitative pupillometry in all settings that treat post-CA patients, given the prognostic utility immediately post-ROSC as well as 24 to 72 hours later.

Increased ICP and Herniation

A “blown” pupil, which is unilateral pupillary dilation and loss of reactivity, is an ominous sign of life-threatening transtentorial herniation (TTH). Increased ICP and TTH have been shown to be preceded by changes in quantitative pupillometry.¹⁶ Based on the findings of a large study by Taylor et al, a CV of <0.6 mm/s has been identified as the threshold at which ICP is elevated or will become elevated. This is based on the findings that CV was <0.6 mm/s in only 8 measurements of 2432 paired measurement (0.3% of the time) in 310 normal volunteers. However, in patients with ICP >20 mm Hg and a midline shift of 3 mm or more (13 patients and 156 paired measurements), CV was <0.6 mm/s in the ipsilateral eye 51% of the time. In patients with diffuse swelling but no midline shift, CV did not start to decrease until an average ICP of 29 mm Hg.⁴⁰

The percentage of pupil size reduction is also a useful marker of increased ICP. Taylor et al found that in normal volunteers, the average reduction was 34% compared to 19% in patients with head injury. Only 1 of 2432 measurements was <10% in the normal group, but a measurement <10% in the head injury group was invariably associated with an ICP >20 mm Hg. Similar to CV, pupil size reduction was not <10% until ICP was >35 mm Hg.⁴⁰

Jahns et al studied quantitative pupillometry in the setting of increased ICP due to TBI in 32 patients with ICP elevations >20 mm Hg resulting in 43 episodes of ICP elevation. The study found that during these sustained ICP elevations (>20 mm Hg for >10 minutes), NPi became abnormal compared to baseline (4.2 vs 2.8, $P < .001$). Additionally, the rate of abnormal NPi was higher in patients who went on to have a poor outcome versus good outcome (15% vs 0%, $P = .002$) as defined by Glasgow Outcome Scale after 6 months.⁵⁸

In addition to detecting increased ICP, changes in pupillometry have been shown to precede TTH. A small study of 3 patients with a total of 12 independent TTH events evaluated with pupillometry found that the NPi was zero in 58% of cases of TTH and abnormal in the remaining cases. Given that NPi measurements were taken at fixed intervals, the authors speculated that the NPi would have progressed to zero in the remaining cases. Nonetheless, this finding offers a useful insight in that the blinded clinicians rated these pupils as completely fixed and dilated, which underscores the value of quantitative pupillometry. Abnormalities in NPi prior to herniation occurred in 73% of cases with the earliest alterations detectable at a median of 7.4 hours before TTH. A major limitation of this study is that 10 of the 12 herniation events occurred in 1 patient.⁵⁹

Since pupillometry can detect increased ICP and TTH, authors have begun to investigate whether response to osmotic therapy can also be assessed with pupillometry. Previously discussed studies had noted improvement in the PLR after treatment of increased ICP or TTH, but those reports were descriptive, and the response was not systematically evaluated.^{40,58,59} Taylor et al described 2 illustrative cases. In the first, the patient had sustained ICP >20 mm Hg and developed an unreactive pupil with CV <0.6 mm/s. After treatment with mannitol, the ICP decreased and CV increased to 0.73 mm/s within 9 minutes. In the second case, the patient had an ICP of 23 mm Hg with a CV <0.6mm/s, and after mannitol, the ICP decreased and CV increased to 0.79 mm/s.⁴⁰

Jahns et al also evaluated response to osmotic therapy in 15 patients and found that ICP reduction was associated with NPi improvement. However, there were 12 patients who showed no improvement in NPi after osmotic therapy, and all of those patients had a poor outcome.⁵⁸ In the study of 12 herniation events in 3 patients, Papangelou et al reported that NPi normalized with osmotic therapy after a median of 43 minutes.⁵⁹

Ong et al performed the first systematic study of treatment response and showed pupil reactivity improved after osmotic therapy in a prospective observational cohort of 72 patients with a total of 402 pupillometry measurements. The patients had various etiologies of increased ICP with the most common being intraparenchymal hemorrhage (36.1%), TBI (15.3%), and anterior circulation stroke (13.9%). Neurological Pupil index was significantly improved after intervention, and the effect lasted on average 5 hours. This is an important step toward quantifying the dose-dependent effect of hypertonic therapy and more individualized osmotic therapy.⁶⁰

However, other pathologies can affect CNIII and mimic critical pathologies such as TTH. Kim et al examined 171 patients including 60 normal controls and 111 patients with CNIII palsy. The etiology of the CNIII palsy was broadly divided into a microvascular ischemia group ($n = 60$) versus a nonischemic group including extrinsic compression (eg, tumor or aneurysm) or inflammation ($n = 51$). They found that pupillometry could differentiate microvascular ischemia from other etiologies, namely, extrinsic compression. Decreased pupillary constriction ratio was specific for compressive CNIII palsy and was seen in 60% of cases compared to 0% of the microvascular cases and only 20% of the inflammatory cases. When combined with a difference in pupil size of at least 0.45 mm, a decreased pupillary constriction ratio <7.5% had a sensitivity and specificity of 95% and 88%, respectively, for nonischemic palsy. This knowledge is important to identify critical pathologies versus a chronic condition such as diabetes resulting in microvascular ischemia or inflammatory conditions.⁶¹

These data show that quantitative pupillometry parameters such as CV <0.6mm/s, NPi <3, and pupil size reduction <10% can identify elevated ICP (Table 4). In addition, abnormal NPi can identify impending TTH, with the earliest warning signs occurring many hours in advance. Once TTH has occurred, osmotic therapy is the initial medical management, but the dose-response relationship is unknown. Pupillometry may

Table 4. Summary of Studies Evaluating Quantitative Pupillometry in Increased ICP and Herniation.

Pupillary Response Variable	Findings
Constriction velocity (CV)	-CV <0.6 mm/s is concerning for high ICP. Patients with ICP >20 mm Hg and midline shift met this cutoff in 51% of cases compared to 0.3% in normal volunteer ⁴⁰ -In diffuse swelling, CV did not reach <0.6 mm/s until ICP >35 mm Hg ⁴⁰
Pupillary size reduction	-Pupillary size reduction was <10% in 100% of cases with ICP >20 mm Hg but occurred only 0.04% (1/2432 paired measurements) of the time in normal volunteers ⁴⁰
Neurological Pupil index (NPi)	-ICP >20 mm Hg resulted in a change of NPi from baseline (4.2 vs 2.8, $P < .001$) ⁵⁸ -NPi was abnormal (<3) in all TTH events and 0 in 58% of events ⁵⁹ -NPi abnormalities occurred before TTH in 73% of events (earliest 7.4 hours prior) ⁵⁹ -Rate of NPi <3 was higher in poor outcome cases (15% vs 0%, $P = .002$) ⁵⁸ -ICP reduction was associated with NPi increase ⁵⁸ -NPi normalized in 43 minutes after hyperosmolar therapy ⁵⁹ -NPi improved within 2 hours of hyperosmolar therapy ⁶⁰ -No NPi change after osmotic therapy invariably led to poor outcome ⁵⁸

Abbreviations: ICP, intracranial pressure; NPi, Neurological Pupil index; TTH, transtentorial herniation.

provide a mechanism of quantifying a response and guiding further therapy. Finally, pupillometry shows promise in differentiating critical pathologies from nonemergent pathologies.

Vasospasm in subarachnoid hemorrhage. Most recently, Aoun et al demonstrated that vasospasm causing delayed cerebral ischemia (DCI) could be detected by pupillometry. The study, conducted at 3 centers, enrolled 56 patients with subarachnoid hemorrhage yielding 635 paired measurements of NPi and transcranial doppler (TCD). Neurological Pupil index was not associated with isolated sonographic vasospasm on TCD in the overall study population. In patients who developed DCI, there was an association with the development of an abnormal NPi ($\chi^2 = 38.4$, $P < .001$). In cases of DCI, there was also an association with sonographic vasospasm on TCD ($\chi^2 = 6.41$, $P = .011$). However, the odds ratio for NPi predicting DCI was higher than the odds ratio for sonographic vasospasm predicting DCI (3.39 vs 1.64). In total, 12 patients developed DCI of which 7 patients had a decrease of NPi to <3. Five (71.4%) patients had NPi changes more than 8 hours prior to clinical signs.

This study had limitations including a small sample size of patients with DCI. Also, since there were multiple NPi measurements per day (at least every 4 hours) and only 1 TCD per day, the authors selected the lowest NPi value from the day which may not have been temporally close to the TCD

measurement. Furthermore, NPi from both eyes were obtained, but only the lowest value between the 2 was included.⁶²

Overall, these results are not surprising, as TCD has a low positive-predictive value for DCI. The majority of patients with aneurysmal subarachnoid will have sonographic vasospasm, but a minority (25%-40%) of those patients have DCI.⁶³ Therefore, NPi is not associated with isolated vasospasm but rather with DCI, indicating it is more reflective of ischemia. These are important findings, given how frequently NPi can be measured and may provide significant advance warning to allow for intervention. Despite the study limitations, these are promising results and warrant further investigation.

Conclusion

The PLR has long been established as an important clinical tool in evaluating the autonomic nervous system and a wide variety of clinical conditions. The advent of digital pupillometry has provided not only more reliable and quantitative data but also adds more variables that can be used to differentiate between pathological processes. Studies have shown this technique has promise as an adjunct to traditional methods in post-CA prognostication, a method to assess for increased ICP and to better assess and quantify response to treatment, and finally a method for detecting vasospasm in subarachnoid hemorrhage. The PLR is affected by numerous pathologies due to its extensive pathway, and the role of quantitative pupillometry is poised to grow as researchers continue to discover additional applications.

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