Pupillometry and intracranial pressure: a narrative review
Pupilometría y presión intracraneal: una revisión narrativa
Pupilometria e pressão intracraniana: uma revisão narrativa

Elisabetta Roberti[a,b], Nicola Zugni[a], Alessandra Beretta[a], Frank Rasulo[a,b]

Autor para correspondencia: *Elisabetta Roberti, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, 25123, Brescia, Italy, e-mail: e.roberti001@unibs.it*

[a] *Spedali Civili University Affiliated Hospital of Brescia, Department of Anesthesia, Critical Care and Emergency Services Italy*
[b] *University of Brescia, Italy, Department of Medical-Surgical Specialties, Radiological Sciences and Public Health Italy*

Abstract

Background: in clinical practice pupillary changes are often correlated to increased intracranial pressure (ICP); nevertheless, qualitative assessment of pupils is subjective and often inaccurate, regardless of examiner's experience. In this context, automated pupillometry may be helpful in identifying pupillary changes earlier than clinical assessment. Objectives: We aimed to discuss the feasibility of automated pupillometry monitoring as a predictor of increased ICP in critically ill patients at risk of developing intracranial hypertension.

Methods: A review of the available literature was performed; 3 prospective and 2 retrospective observational studies were selected.

Results: Data from the included studies show that variations in different automated pupillometry parameters are associated with changes in ICP.

Conclusion: Automated pupillometry may represent a useful tool to predict intracranial hypertension and may be included within a multimodal approach using other non-invasive tools such as cerebral ultrasound. Further studies are needed to explore the potential usefulness of this tool.

Keywords: Pupilometry, Intracranial pressure (ICP), Traumatic brain injury (TBI), Automated monitoring, Cerebral perfusion pressure (CPP).

Resumen

Antecedentes: En la práctica clínica, los cambios pupilares a menudo se correlacionan con un aumento de la presión intracraneal (PIC); sin embargo, la evaluación cualitativa de las pupilas es subjetiva y, a menudo, inexacta, independientemente de la experiencia del examinador. En este contexto, la pupilometría automatizada puede ser útil para identificar cambios pupilares antes que la evaluación clínica. Objetivos: Nuestro objetivo fue discutir la viabilidad de la monitorización de la pupilometría automatizada como predictor del aumento de la PIC en pacientes críticamente enfermos con riesgo de desarrollar hipertensión intracraneal.

Métodos: Se realizó una revisión de la literatura disponible; se seleccionaron 3 estudios prospectivos y 2 estudios observacionales retrospectivos.

Resultados: Los datos de los estudios incluidos muestran que las variaciones en diferentes parámetros de la pupilometría automatizada se asocian con cambios en la PIC.

Conclusión: La pupilometría automatizada puede representar una herramienta útil para predecir la hipertensión intracraneal y puede ser incluida dentro de un enfoque multimodal utilizando otras herramientas no invasivas, como el ultrasonido cerebral. Se necesitan más estudios para explorar la posible utilidad de esta herramienta.

Resumo

Antecedentes: Na prática clínica, mudanças pupilares são frequentemente correlacionadas com aumento da pressão intracraniana (PIC); no entanto, a avaliação qualitativa das pupilas é subjetiva e frequentemente imprecisa, independentemente da experiência do examinador. Nesse contexto, a pupilometria automatizada pode ser útil para identificar mudanças pupilares mais cedo do que a avaliação clínica.

Objetivos: Nosso objetivo foi discutir a viabilidade do monitoramento da pupilometria automatizada como preditor de aumento da PIC em pacientes criticamente enfermos em risco de desenvolver hipertensão intracraniana. Métodos: Foi realizada uma revisão da literatura disponível; 3 estudos prospectivos e 2 estudos observacionais retrospectivos foram selecionados.

Resultados: Os dados dos estudos incluídos mostram que variações em diferentes parâmetros da pupilometria automatizada estão associadas a mudanças na PIC.

Conclusão: A pupilometria automatizada pode representar uma ferramenta útil para prever hipertensão intracraniana e pode ser incluída dentro de uma abordagem multimodal usando outras ferramentas não invasivas, como o ultrassom cerebral. Mais estudos são necessários para explorar a utilidade

potencial dessa ferramenta.

1. Introduction

1.1. Rationale

Clinical pupillary evaluation, through measurement of the pupillary diameter, may be used to detect anisocoria or to assess the presence and the strength of the pupillary reflex to light stimulus. Multiple studies in the literature show a direct correlation between pupillary changes and increased ICP [Chen et al. (2011)]. However, qualitative assessment of pupils is subjective and often inaccurate regardless of the examiner's experience [Olson and Fishel (2016); Shoyombo et al. (2018)].

The consequences of increased ICP can be grouped into two categories: mechanical and vascular. When a space-occupying mass develops, a pressure gradient from this area causes a distortion of the brain tissue with displacement of the midline (herniation). Herniation of the brain parenchyma represents a medical emergency that requires prompt treatment to prevent irreversible and fatal brainstem damage. In contrast, the vascular effects of increased ICP cause a reduction in cerebral perfusion pressure (CPP), which is the driving force behind cerebral blood flow (CBF), which may become insufficient for adequate perfusion and oxygenation of brain tissue. Thus, ICP monitoring is essential in neurologic patients at risk of intracranial hypertension. In fact, Balestreri M. et al. showed that ICP values > 20 mmHg are associated with a marked increase in mortality, from 17% to 47% [Balestreri et al. (2006)]. The same result occurs with the reduction of CPP below 55 mmHg, with 81% mortality compared to 23% [Balestreri et al. (2006)]. Traumatic brain injury (TBI) is a leading cause of death and disability worldwide and accounts for approximately 30% of all injury-related deaths [Maas et al. (2017)]. Following the injury caused by the event, treatments are aimed at preventing secondary injury. In this context, early recognition of increased ICP is of paramount importance, as it can lead to transtentorial hernia and brainstem compression, worsening any already present neurological deficit, and, as a result, the overall outcome and mortality rate [Dostovic et al. (2016)]. In the management and prognosis of severe TBI, abnormalities of pupillary response or anisocoria (pupil size asymmetries) are often associated with neurological deteriorations and are correlated with poor neurological outcome [Choi et al. (1988); Braakman et al. (1980)]. Due to peculiar anatomic nerve fibers disposition, pupillary light reflex (PLR) allows to assess brainstem dysfunction. After a unilateral or bilateral light stimulus, neural impulse is conducted through the optic nerve (cranial nerve – CN II) and across both optic tracts via the optic chiasm down to the pretectal nucleus in the midbrain. Hence, the cells of the parasympathetic Edinger-Westphal nucleus in the midbrain are stimulated bilaterally by axons arising from the pretectal area. From here, preganglionic fibers leave bilaterally to reach the ciliary ganglia via the oculomotor nerve (cranial nerve – CNIII); finally, postganglionic fibers stimulate the iris sphincter muscle causing consensual bilateral myosis. Parasympathetic fibers that control pupillary function travel superficially in CNIII, while somatic efferent fibers directed towards elevator palpebrae and extraocular motor nerves (except for the superior oblique muscle and the lateral rectus) are in the inner portion. Therefore, parasympathetic fibers are more susceptible to extrinsic compression, as in case of intracranial hypertension and transtentorial herniation. Unreflective anisocoria, or more broadly PLR abnormalities are a sensitive marker for neurological status deterioration. Given these data, in critically ill patients PLR is commonly used to assess early midbrain function deterioration [Sandroni et al. (2022)]. Standard PLR assessment by penlight, although simple and inexpensive, is prone to errors and interrater variability; moreover, it relies on subjective and imprecise description, while automated pupillometry provides reproducible data, standardizing the intensity, the distance, and the duration of the light stimulus [Sandroni et al. (2022); Lussier et al. (2019); Bower et al. (2021)]. Measured parameters include maximum and minimum pupil size, constriction latency (Lat), velocity (CV), and percentage (CH), and dilation velocity (DV) **(Table 1)** [Taylor et al. (2003); Oshorov et al. (2021)]. The NeurOptics®pupillometer, using a proprietary algorithm, combines all these variables in the neurological pupil index (NPi®), whose values range from 0 to 5, the norm being ≥ 3 **(Table 1)** [Oshorov et al. (2021)] **(Figure 1)**.

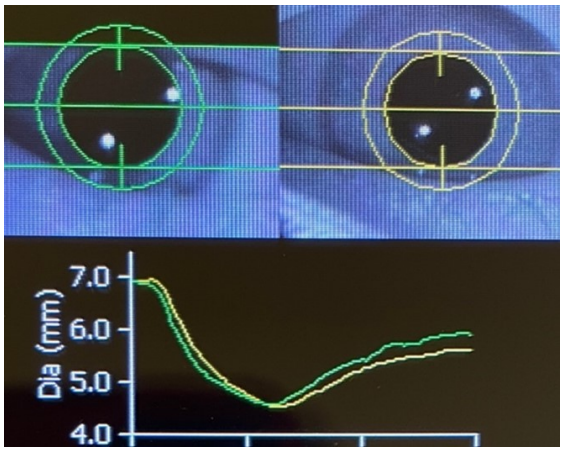

Figure 1: Study selection process flow-chart

Variable (unit of measure)	Normal value	Note
Npi® (Scalar Value)	≥ 3	Algorithm that takes all variables above as inputs and compares to normative model to give a composite score of pupillary response.
Maximum pupil size (mm)	4	The minimum pupil size is the pupil size at the peak of the constriction
Minimum pupil size (mm)	2.5	Maximum pupil size is the initial resting pupil size and is defined by the mean pupil size during the latent period.
Contraction percentage (%)	30-35	Maximum size minus minimum size divided by the maximum size.
Contraction velocity (mm/s)	1.5	The amount of the constriction divided by the duration of the constriction
Contraction latency (s)	0.3	Latency time from light stimulus and onset of constriction
Asymmetry (mm)	< 0.5	Difference in diameter of the two pupils

Table 1: Reference pupillometry parameters – modified from [Oshorov et al. (2021)]

NPi values are not influenced by external factors. While the remaining parameters are dependent on several factors: ambient light, temperature, pharmacological agents (especially opioids and sedatives) and pre-existing pathological conditions (cataract surgery, ocular trauma). In the intensive care unit

(ICU), it is the only one that is not influenced by medication, although it is also dependent on ambient light **(Table 2)**.

Drug	
Propofol	Reduction PLR
Ketamina	Reduction PLR
Benzodiazepines	Reduction CV
Dexmetomidine	Increase PLR
Opioids	Reduction pupil diameter, CV and PRD
Curare	No effect
Beta blockers	No effect

Table 2: Classes of drugs that modify pupillometer values.

Automated pupillometry seems to be most promising within the context of neuroprognostication in comatose patients following cardiocirculatory arrest. The presence of an NPI ≤ 2 from day 1 to 3 is associated with poor outcome (false positives 0 CI 95% 0-2) [Oddo et al. (2018)]. Furthermore, an abrupt change of these parameters on serial measurements may herald the occurrence of intracranial hypertension, prompting additional investigations or treatment. Within this context, automated pupillometry may be equivalent to other non-invasive tools for diagnosing intracranial hypertension, such as transcranial Doppler or optical nerve sheath diameter.

1.2. Objectives

With this narrative review, our aim is to assess the feasibility of automated pupillometry monitoring in the context of intracranial hypertension through an analysis of the available data. Although increasingly used in the ICU settings, the predictive value of automated pupillometry in detecting elevated ICP and its subsequent clinical implications are not well established. Worthy of note, is that a Systematic Review could not be performed due to the lack of published studies.

2. Methods

2.1. Search strategy and selection criteria

Literature search was performed on May 15, 2023, with MEDLINE via PubMed, and EMBASE databases. No restrictions were placed on date, language, or country of study publication. We developed a draft search strategy for MEDLINE via PubMed using the following medical subject heading terms: "Intracranial Hypertension"[Mesh] AND "Reflex, Pupillary"[Mesh] We used this as the basis for the search strategies in the other databases listed (Appendix 1). We included studies conducted on adult and pediatric populations with ICP monitoring, where automated pupillometry was employed to assess ICP trend. We excluded case report studies, and animal studies. We searched additional studies by cross-checking the reference list of all included studies identified by our electronic search. ER screened all studies for eligibility based on title and abstract and performed a full-text assessment for final inclusion. AB and NZ intervened if questions were raised. FR supervised the process.

3. Results

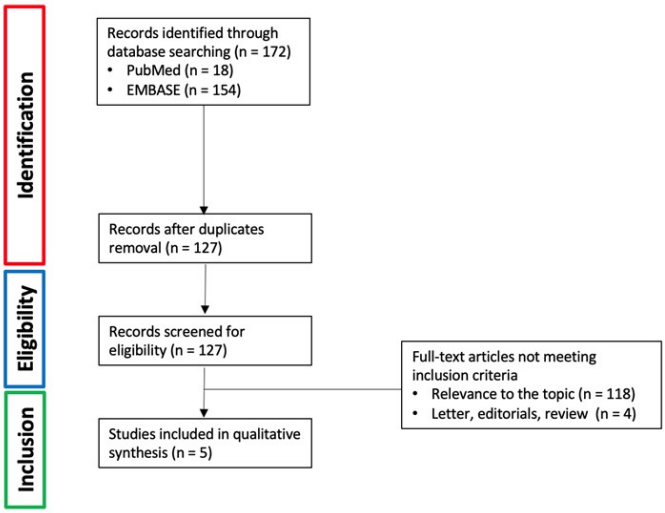

Figure 2: Study selection process flow-chart.
The selection process of the studies is presented in Figure 2, which details from the initial search to the articles finally included, according to the inclusion and exclusion criteria.

From the initial 172 results, after duplicate removal, 127 records were screened for eligibility, according to exclusion and inclusion criteria. This process led to the inclusion of 5 full text articles, enrolling an overall amount of 304 patients, as summarized in **(Table 3)**. Articles included were published from 2011 to 2022; 4 out of 5 were conducted in an adult population [Chen et al. (2011); Jahns et al. (2019); Giede-Jeppe et al. (2021); Pansell et al. (2022)], while 1 was conducted in pediatric patients [Freeman et al. (2020)].

Authors. Year of publication	Type of study	Population. Pathology	n. of patients	Automated pupillometry variables. Invasive method of comparison	Correlation with ICP
Jeff W. Chen et al. 2011	Prospective. (Multicentric: 8 ICU)	Adults. SDH, SHA, EDH, aneurysmal SAH, ICH.	134	NPi® vs not specified.	NPi® is associated with increased ICP
Fritz-Patrick Jahns et al. 2019	Prospective. (Single centric)	Adults. Severe TBI.	94	NPi® vs parenchymal Codman ICP probe®; Codman, Raynham, MS, USA	Elevated ICP episodes correlate with a concomitant decrease of NPi
Ashley D. Freeman et al. 2020	Prospective. (Single centric)	Pediatrics. TBI and Encephalopathy	28	NPi®, percent change in pupillary size, constriction velocity, dilation velocity vs external ventricular drain [EVD] or intraparenchymal device.	NPi®, percent change in pupillary size, constriction velocity, dilation velocity
Antje Giede-Jeppe et al. 2020	Retrospective. (Single centric)	Adults. Supratentorial ICH.	23	Constriction velocity, percent change in pupillary size, dilation velocity, latency vs parenchymal Codman ICP probe®; Codman, Raynham, MS, USA	Increased ICP negatively correlates with pupillary dynamic parameters, showing a high negative predictive value for ICP elevation
Jakob Pansell et al. 2022	Retrospective. (Single centric)	Adults. ESA, TBI, ICH.	65	NPi® vs parenchymal Codman ICP probe®; Codman, Raynham, MS, USA	Normal NPi® may rule out ICP elevation

Table 3: Overview of published papers. SDH: Subdural hematoma; SAH, subarachnoid hemorrhage; EDH: epidural hematoma; ICH: spontaneous intracerebral hemorrhage; ICU: intensive care Unit; PICU: pediatric intensive care unit; n: number.

Intracranial pressure was invasively monitored in all patients, while automated pupillometry variables were collected through use of the NPi®(described elsewhere [Chen et al. (2011); Jahns et al. (2019); Freeman et al. (2020); Giede-Jeppe et al. (2021);

Pansell et al. (2022)]. In all cases, (described elsewhere) increased ICP correlated with alteration in automated pupillometry variables. NPi®was considered in 4 out of 5 articles [Chen et al. (2011); Jahns et al. (2019); Freeman et al. (2020); Giede-Jeppe et al. (2021); Pansell et al. (2022)], whilst Giede-Jeppe et al. (2019) only considered constriction velocity, percent change in pupillary size, dilation velocity and latency [Giede-Jeppe et al. (2021)]. The first study evaluating the correlation between NPi®and increased ICP was that of Jeff W. Chen et al, where they enrolled 134 patients with: subdural hematoma (SDH), subarachnoid hemorrhage (SAH), epidural hematoma (EDH) induced from TBI, aneurysmal SAH, or spontaneous intracerebral hemorrhage (ICH) [Chen et al. (2011)]. Patients with normal NPi®values had lower ICP values than patients with abnormal NPi®values (NPi®<3) (19.6 mmHg vs. 30.5 mmHg, p = 0.0014). They also found how NPi values changed earlier than ICP values (average 15.9 hours) [cite1]. More recently, Fritz-Patrick Jahns et al. [cite15] studied 54 patients with severe TBI (defined as a Glasgow Coma Scale – GCS < 9) finding a progressive reduction in NPi®values as ICP increased. Administration of osmotic therapy to treat increased ICP values is associated with improved NPi®values. NPi®values also seem to be associated with neurological outcome at 6 months: patients with abnormal NPi®were higher in patients with Glasgow Outcome Scale (GOS) 1 and GOS 3 than in patients with GOS 4 and 5. Lack of NPi®normalization after decompressive craniectomy was consistently associated with a poor outcome [cite19]. In the study by Jakob Pansell et al. [cite18], linear regression yielded a significant negative correlation between mean NPi®and ICP. ROC analysis for elevated ICP with mean NPi®as classification variable yielded an area under the ROC curve (AUROC) of 0.72. The Youden analysis generated an optimal mean NPi cutoff at 3.85 (sensitivity 70%, specificity 66%, positive predictive value 13.4%, negative predictive value 96.7%) [cite18]. Giede-Jeppe et al. [cite17] did not evaluate NPi®, but other parameters. Best discriminative thresholds for ICP elevation were constriction velocity (CV) < 0.8 mm/s (AUC 0.740), percent change in pupillary size < 10% (AUC 0.743), dilation velocity (DV) < 0.2 mm/s (AUC 0.703), and latency (Lat) > 0.3 s (AUC 0.616). Thay found high negative predictive values of pupillary parameters [CV: 99.2% (95% CI 98.3–99.6), per-change: 98.7% (95% CI 97.8–99.2), DV: 98.0% (95% CI 97.0–98.7), Lat: 97.0% (95% CI 96.0–97.7)], while positive predictive value of all four parameters to indicate ICP elevation ranged between 7.2 and 8.3% only and was similarly low for CT abnormalities (9.1%) [cite17]. Only the study by Ashley D. Freeman et al. [16] included the pediatric population. When intracranial pressure was elevated, the Neurologic Pupil index, percent change in pupillary size, constriction velocity, and dilation velocity were significantly lower than when intracranial pressure was within normal range [cite16].

4. Discussion

The assessment of pupil size and its reflex mechanism to light is an integral part of the protocol for the treatment and management of patients with severe brain injuries in intensive care units around the world. As a matter of fact, guidelines of the American Association of Neurological Surgeons and the Brain Trauma Foundation recommend assessing asymmetry of pupil size or reactivity to light, as well as the presence of fixed and/or dilated pupils. Literature data agree in identifying how the absence of light reactivity and anisocoria correlate with patient outcome, as the appearance of anisocoria and the absence of light reflex are late and often non-reversible event [[Tien et al. (2006)]]. Pupillary light reactivity is a validated predictor in both the CRASH (Corticosteroid Randomization after Significant Head Injury) and IMPACT (International Mission for Prognosis and Analysis of Clinical Trials) TBI prognostic models [[Chen et al. (2011)]]. Pupillary assessment in the clinical setting is often performed very subjectively, with a pen torch for reactivity and a caliber for pupil size. On the opposite, automated pupillometry is based on a portable infrared device, allowing reliable, reproducible, and objective measurements of pupillary reflexes and pupil size. Furthermore, the numerical scale of the NPi®introduced for the first time in this report, allows for an automatic and rigorous interpretation and classification of pupil dynamics. The notion of normal or abnormal pupillary reflex is derived automatically by comparing the reflex with an NPi®model, which defines the behavior of the pupillary reflex mechanism in light. This reduces the subjectivity of the measurement. Altered NPi®values are associated with increased ICP values [1], [15-18]. This parameter appears to have an excellent negative predictive value, providing a possible screening tool for estimating ICP [[Giede-Jeppe et al. (2021); Pansell et al. (2022)]]. Furthermore, altered NPi®values can predict the occurrence of intracranial hypertension by several hours, allowing for a more careful clinical assessment [[Chen et al. (2011)]], [[Jahns et al. (2019); Freeman et al. (2020)]]. If confirmed, NPi®alteration could help identify patients with ischemic stroke who are candidates for early decompressive craniectomy. Moreover, The NPi®value can monitor the benefit of osmotic therapy in normalizing ICP values [Chen et al. (2011)]. Finally, the NPi®value appears to be a prognostic tool (neurological outcome at 6 months) in traumatic brain injured patients [Chen et al. (2011)]. Failure to normalize NPi®values is associated with unfavorable prognosis.

5. Conclusion

Automated pupillometry may be helpful in identifying patients with intracranial hypertension and assessing response to osmotic therapy. In addition, the pupillometer might be a prognostic indicator in traumatic brain injured patients. Further studies are needed to explore the potential usefulness of this tool.

Referencias

Balestreri, M., Czosnyka, M., Hutchinson, P., Steiner, L.A., Hiler, M., Smielewski, P., Pickard, J.D., 2006. Impact of intracranial pressure and cerebral perfusion pressure on severe disability and mortality after head injury. Neurocritical care 4, 8–13.

Bower, M.M., Sweidan, A.J., Xu, J.C., Stern-Nezer, S., Yu, W., Groysman, L.I., 2021. Quantitative pupillometry in the intensive care unit. Journal of intensive care medicine 36, 383–391.

Braakman, R., Gelpke, G., Habbema, J., Maas, A., Minderhoud, J., 1980. Systematic selection of prognostic features in patients with severe head injury. Neurosurgery 6, 362–370.

Chen, J.W., Gombart, Z.J., Rogers, S., Gardiner, S.K., Cecil, S., Bullock, R.M., 2011. Pupillary reactivity as an early indicator of increased intracranial pressure: the introduction of the neurological pupil index. Surgical neurology international 2.

Choi, S.C., Narayan, R.K., Anderson, R.L., Ward, J.D., 1988. Enhanced specificity of prognosis in severe head injury. Journal of neurosurgery 69, 381–385.

Dostovic, Z., Dostovic, E., Smajlovic, D., Ibrahimagic, O.C., Avdic, L., 2016. Brain edema after ischaemic stroke. Medical archives 70, 339.

Freeman, A.D., McCracken, C.E., Stockwell, J.A., 2020. Automated pupillary measurements inversely correlate with increased intracranial pressure in pediatric patients with acute brain injury or encephalopathy. Pediatric Critical Care Medicine 21, 753–759.

Giede-Jeppe, A., Sprügel, M.I., Huttner, H.B., Borutta, M., Kuramatsu, J.B., Hoelter, P., Engelhorn, T., Schwab, S., Koehn, J., 2021. Automated pupillometry identifies absence of intracranial pressure elevation in intracerebral hemorrhage patients. Neurocritical Care 35, 210–220.

Jahns, F.P., Miroz, J.P., Messerer, M., Daniel, R.T., Taccone, F.S., Eckert, P., Oddo, M., 2019. Quantitative pupillometry for the monitoring of intracranial hypertension in patients with severe traumatic brain injury. Critical care 23, 1–9.

Lussier, B.L., Olson, D.M., Aiyagari, V., 2019. Automated pupillometry in neurocritical care: research and practice. Current neurology and neuroscience reports 19, 1–11.

Maas, A.I., Menon, D.K., Adelson, P.D., Andelic, N., Bell, M.J., Belli, A., Bragge, P., Brazinova, A., Büki, A., Chesnut, R.M., et al., 2017. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. The Lancet Neurology 16, 987–1048.

Oddo, M., Sandroni, C., Citerio, G., Miroz, J.P., Horn, J., Rundgren, M., Cariou, A., Payen, J.F., Storm, C., Stammet, P., et al., 2018. Quantitative versus standard pupillary light reflex for early prognostication in comatose cardiac arrest patients: an international prospective multicenter double-blinded study. Intensive care medicine 44, 2102–2111.

Olson, D.M., Fishel, M., 2016. The use of automated pupillometry in critical care. Critical Care Nursing Clinics 28, 101–107.

Oshorov, A., Alexandrova, E., Muradyan, K., Sosnovskaya, O.Y., Sokolova, E.Y., Savin, I., 2021. Pupillometry as a method for monitoring of pupillary light reflex in icu patients. Zh Vopr Neirokhir Im N Burdenko 85, 117–23.

Pansell, J., Hack, R., Rudberg, P., Bell, M., Cooray, C., 2022. Can quantitative pupillometry be used to screen for elevated intracranial pressure? a retrospective cohort study. Neurocritical Care 37, 531–537.

Sandroni, C., Citerio, G., Taccone, F.S., 2022. Automated pupillometry in intensive care. Intensive Care Medicine 48, 1467–1470.

Shoyombo, I., Aiyagari, V., Stutzman, S.E., Atem, F., Hill, M., Figueroa, S.A., Miller, C., Howard, A., Olson, D.M., 2018. Understanding the relationship between the neurologic pupil index and constriction velocity values. Scientific reports 8, 6992.

Taylor, W.R., Chen, J.W., Meltzer, H., Gennarelli, T.A., Kelbch, C., Knowlton, S., Richardson, J., Lutch, M.J., Farin, A., Hults, K.N., et al., 2003. Quantitative pupillometry, a new technology: normative data and preliminary observations in patients with acute head injury. Journal of neurosurgery 98, 205–213.

Tien, H.C., Cunha, J.R., Wu, S.N., Chughtai, T., Tremblay, L.N., Brenneman, F.D., Rizoli, S.B., 2006. Do trauma patients with a glasgow coma scale score of 3 and bilateral fixed and dilated pupils have any chance of survival? Journal of Trauma and Acute Care Surgery 60, 274–278.