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Automated Pupillometry Value Differences Serve as a Prognostic Indicator Even When They are Within Normal Range

Różnice wartości zautomatyzowanej pupilometrii służą jako wskaźnik prognostyczny, nawet gdy mieszczą się w normalnym zakresie

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Abstract

Introduction. The pupillary light reflex (PLR) is an integral aspect of the neurologic exam. With the enhancement of automated infrared pupillometry (AIP), the Neurological Pupil index (NPi) is being increasingly used when performing a neurological examination. NPi difference (the absolute difference between paired NPi readings from the left and right eye) is a relatively unexplored variable in AIP assessment.
Aim. This study evaluates the association between Glasgow Coma Scale (GCS) scores and NPi differences between the left and right eyes, when the NPi is normal, in patients enrolled in a multi-center prospective database.
Material and Methods. Restricting observations to only include NPi values ≥3 (normal), there were 2,572 qualifying patients with 3,519 pupillometer readings linked to GCS values. Linear regression and ANOVA models were developed to investigate the relationship between GCS and NPi difference.
Results. Subject mean age was 55.88 (16.95) years and 54.5% were female. Mean NPi difference was 0.36 and mean GCS was 12.06. Regression analysis indicated a slight negative association between NPi difference and GCS (r^2=0.0696, P<.0001). When observations were dichotomized as either NPi difference ≥0.7 (large) or <0.7 (small), there was a statistically significant difference in the mean GCS (10.76 [3.90]) for large NPi difference vs. small NPi difference (13.15 [2.68]; P<.0001).
Conclusions. Even among patients with normal PLR, a large NPi difference is associated with lower GCS scores. Trending and evaluating the NPi difference may become an important aspect of patient assessment. **(JNNN 2021;10(4):168–174)**
Key Words: Glasgow Coma Scale (GCS), Neurological Pupil index (NPi), NPi Difference, pupillary light reflex (PLR), pupillometry

Streszczenie

Wstęp. Odruch źreniczny na światło (PLR) jest integralną częścią badania neurologicznego. Wraz z udoskonaleniem automatycznej pupilometrii w podczerwieni (AIP), wskaźnik neurologiczny źrenicy (NPi) jest coraz częściej używany podczas wykonywania badań neurologicznych. Różnica NPi (bezwzględna różnica między sparowanymi odczytami NPi z lewego i prawego oka) jest stosunkowo niezbadaną zmienną w ocenie AIP.
Cel. Niniejsze badanie ocenia związek między wynikami w skali Glasgow (GCS) a różnicami NPi między lewym i prawym okiem, gdy NPi jest prawidłowe, u pacjentów włączonych do wieloośrodkowej prospektywnej bazy danych.

Materiał i metody. Ograniczając obserwacje tylko do wartości NPi≥3 (normalne), zakwalifikowano 2572 pacjentów z 3519 odczytami z pupilometru powiązanymi z wartościami GCS. Opracowano modele regresji liniowej i ANOVA w celu zbadania związku między różnicami między GCS a NPi.
Wyniki. Średnia wieku badanych wynosiła 55,88 (16,95) lat i 54,5% stanowiły kobiety. Średnia różnica NPi wynosiła 0,36, a średnia GCS 12,06. Analiza regresji wykazała niewielki negatywny związek między różnicą NPi a GCS (r^2=0,0696, P<0,0001). Gdy obserwacje zostały rozdzielone jako różnica NPi≥0,7 (duża) lub <0,7 (mała), wystąpiła statystycznie istotna różnica w średniej GCS (10,76 [3,90]) dla dużej różnicy NPi vs małej różnicy NPi (13,15 [2,68]); P<0,0001).
Wnioski. Nawet wśród pacjentów z prawidłowym PLR duża różnica w NPi wiąże się z niższymi wynikami GCS. Trendy i ocena różnicy NPi mogą stać się ważnym aspektem oceny pacjenta. **(PNN 2021;10(4):168–174)**
Słowa kluczowe: Skala Glasgow (GCS), neurologiczny indeks źrenic (NPi), różnica NPi, odruch źreniczny na światło (PLR), pupilometria

Introduction

Despite abundant existing information about automated infrared pupillometry (AIP) to evaluate the pupillary light reflex (PLR), little is known regarding the comparison between the reaction of the left and right eyes to light [1–4]. The PLR pathway is well-described but has traditionally been evaluated subjectively by estimating the size or pupil diameter (PD), shape, and reactivity [3–6]. In brief, when retinal ganglion cells receive light stimuli from bipolar and amacrine cells, information is transmitted along their axons which form the optic nerve (cranial nerve II) [7]. The optic nerve projects to the ipsilateral pretectal olivary nucleus, which further connects bilaterally to the parasympathetic Edinger–Westphal nuclei (EWN). In turn, the EWN projects to the ipsilateral ciliary ganglion via preganglionic oculomotor nerve (cranial nerve III) fibers [7]. The last segment in the pathway is the postganglionic parasympathetic oculomotor nerve fibers innervating the iris sphincter muscle, leading to pupillary constriction [5,7].

Historically, the pupil was graded by using the terms *brisk*, *sluggish*, and *fixed* to describe the relative speed of the PLR. The advent of AIP is changing this paradigm [4,6]. When the PLR is assessed with the NPi-200 (NeurOptics, Inc) pupillometer, in addition to the minimum and maximum pupillary diameter, latency, & constriction and dilation velocities, one of the additional parameters that is obtained is the Neurological Pupil index (NPi). The NPi is a derived value that utilizes a unique algorithm (incorporating each of the measured elements of the PLR) to produce a score on a scale from 0 to 5, with a score ≥3.0 signifying normal pupillary response [1,2]. Prior work demonstrates that a pupil can have a rapid constriction velocity (CV) but still respond abnormally (e.g., delayed or incomplete constriction) [5]. Research has focused on unilateral PLR and reports NPi and CV either from both eyes individually [8], from the eye with the highest or lowest value [9], or as a combined (e.g. average) value of both eyes [10]. It is not known whether the difference between a left and a right NPi value is significant.

The Glasgow Coma Scale (GCS) is a widely used and well-established clinical assessment tool for patients with acute traumatic brain injury (TBI) [7,11], and has previously been explored as an associated variable with NPi [12–14]. The GCS scores 3 distinct components of behavioral response to external stimulation: eye opening, verbal response, and motor function [15]. Lower GCS scores are associated with increasing rates of mortality and unfavorable outcomes [16,17]. Recent studies have demonstrated that GCS, NPi, and a combination of GCS and PLR are prognostic factors in TBI [10,18,19]. However, there are no data examining associations between GCS and the absolute difference between the left and right eye NPi values. The NPi difference (NPi-Diff) is calculated as the absolute difference between paired NPi readings from the left and right eye. It is integral to investigate unilateral AIP changes and the NPi-Diff as previous work has highlighted how specific NPi changes may occur hours prior to delayed cerebral ischemia or herniation [20,21]. Recognition and identification of these changes by clinicians may provide opportunities for earlier intervention to decrease permanent damage. One might postulate that with an increase in intracranial pressure (ICP) or shift of the intracranial structures, the NPi may start to decline. Recent data suggests that even when the NPi is ≥3.0, subtle changes in PLR may indicate neurologic worsening [22]. With NPi changes usually indicating injury to the PLR pathway, and by extension, possibly to adjacent regions responsible for motor and cognitive functions, we expect to see effects on the GCS with its assessment of eye-opening, verbal response, and motor response.

The purpose of this study is to test the hypothesis that NPi-Diff is associated with GCS scores even when NPi values are in the normal range.

Material and Methods

This work examines data from the Establishing Normative Data for Pupillometer Assessment in Neuroscience Intensive Care (END-PANIC) Registry. The methods and design of this registry have been previously documented [1]; in short, END-PANIC is a prospective international registry of data from neurocritical care patients who received AIP assessments during their intensive care unit (ICU) stay [1]. The pupillometer used in the END-PANIC registry is the NPi-200 (NeurOptics, Inc). AIP variables include the NPi, resting PD, latency from light stimulus to initial constriction, CV, PD when fully constricted, and dilation velocity [23]. In addition to containing all of the variables obtained from the pupillometer, the registry also contains data abstracted from the electronic medical record including but not limited to: demographic data, admission severity scores, modified Rankin score (mRS), and daily GCS and stroke severity scores [1].

In each of the END-PANIC institutions, the use of AIP to assess PLR is the standard of care. This study was performed in accordance with all federal and state regulations and designated by the Institutional Review Board as exempt from written consent. Subjects enrolled in the registry between Oct 2015 and Jan 2020 were included if they were at least 18 years of age and had paired (left and right) NPi values obtained within 72 hours of admission. Additionally, we restricted the sample to include only patients with NPi values ≥3.0. At each level of GCS for a subject, only the observation with the greatest NPi-Diff was included.

Statistical analysis was performed utilizing SAS v 9.4 for Windows. Unless otherwise indicated, continuous data are expressed as mean (standard deviation), nominal data as frequency (percent), and ordinal data as median (interquartile range). Utilizing 1 observation per subject, we first examined appropriate measures of central tendency for each variable. Paired T-test models were constructed to evaluate statistical significance in the difference of left eye and right eye AIP variables. Wilcoxon's Rank Sum Test was used to compare mRS on admission and discharge mRS. A linear regression model was developed between GCS and NPi-Diff. Consistent with manufacturer recommendations, observations were dichotomized as NPi-Diff ≥0.7 (large difference) vs. <0.7 (small difference). ANOVA models were then developed to examine mean GCS for large vs. small NPi-Diff.

Results

There were 2,752 subjects (Table 1) with 3,519 pupillometry assessments linked to GCS scores that matched our inclusion criteria. Subjects had a mean age of 55.88 (16.95) years; 1,500 (54.51%) were female; there were 1,978 (71.88%) Caucasian, 424 (15.41%) African American, 90 (3.27%) Asian American or Pacific Islander, 6 (0.22%) Native American, and 254 (9.22%) other or non-reporting subjects. The top 2 primary diagnoses included 813 (29.54%) patients with brain tumor and 479 (17.41%) patients with stroke. Mean GCS was 12.06 (3.41) with a median of 14 (10–15).

Table 1. Demographics

Variable	Total (N=2,752)	Small NPi Difference (N=2,296)	Large NPi Difference (N=456)
1	2	3	4
Age* — years	55.88 (16.95)	55.91 (16.83)	55.71 (17.55)
Gender†			
Female	1,500 (54.51%)	1,234 (53.75%)	266 (58.33%)
Male	1,252 (45.49%)	1,062 (46.25%)	190 (41.67%)
Race†			
African American	424 (15.41%)	323 (14.07%)	101 (22.15%)
Asian American/Pacific Islander	90 (3.27%)	77 (3.35%)	13 (2.85%)
Caucasian	1,978 (71.88%)	1,681 (73.21%)	297 (65.14%)
Native American	6 (0.22%)	5 (0.22%)	1 (0.22%)
Other/Not reported	254 (9.22%)	210 (9.15%)	44 (9.64%)
Ethnicity†			
Hispanic	327 (11.88%)	260 (11.32%)	67 (14.69%)
Non-Hispanic	2,362 (85.83%)	1,986 (86.50%)	376 (82.46%)
Other/Not reported	63 (2.29%)	50 (2.18%)	13 (2.85%)

Table 1. Continued

1	2	3	4
Primary Diagnosis†			
Brain Tumor	813 (29.54%)	725 (31.58%)	88 (19.30%)
Stroke	479 (17.41%)	397 (17.29%)	82 (17.98%)
Other	1,460 (53.05%)	1,174 (51.13%)	286 (62.72%)
ICU LOS — days*	4.60 (6.65)	4.06 (6.18)	7.31 (8.11)
Hospital LOS — days*	8.38 (9.66)	7.58 (8.86)	12.40 (12.20)
mRS on admission*	1.06 (1.48)	0.97 (1.40)	1.50 (1.72)
mRS at discharge*	2.16 (1.91)	1.96 (1.85)	3.11 (1.93)

Small NPi Difference=NPi-Diff<0.7, Large NPi Difference=NPi-Diff≥0.7
NPi=Neurological Pupil Index, ICU=Intensive Care Unit, LOS=Length of Stay, mRS=Modified Rankin Score, *Reporting as mean (standard deviation), †Reporting as frequency (percent)

The mean ICU length of stay (LOS) was 4.60 (6.65) days and the mean hospital LOS was 8.38 (9.66) days. The median mRS on admission was 0 and the median mRS at discharge was 2; this difference was statistically significant (P<.001).

Including all observations, the mean NPi value for the left eye was 4.31 (0.47) and right eye was 4.30 (0.47);these were not statistically significantly different (P=.8945). Mean NPi-Diff between left eye and right eye was 0.36 (0.33). 571 (16.23%) of all observations had an NPi-Diff ≥0.7 (potentially clinically relevant). Anisocoria (≥1.0 mm difference in PD) was present in 282 (8.01%) of paired observations. Of the remaining metrics abstracted from the pupillometer (Table 2), the following variables were statistically significantly different: the resting PD of the left pupil and right pupil (P=.0002) and the smallest PD in response to light of the left pupil and right pupil (P=.0056).

The primary hypothesis was explored with simple regression (Figure 1) which revealed a slight negative association between NPi-Diff and GCS score (r^2=0.0696, P<.0001). We then sought to evaluate the statistical significance of the difference in GCS scores between observations with an NPi-Diff ≥0.7 or <0.7 (Figure 2). Utilizing 1 observation per subject, mean GCS for observations with NPi-Diff ≥0.7 (N=456) was 10.76

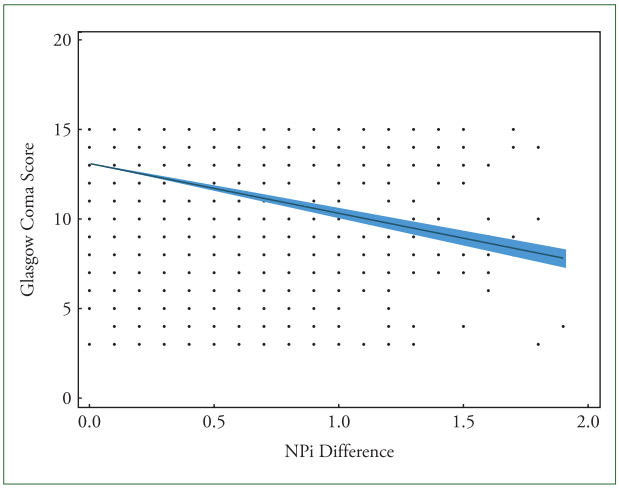

Figure 1. Regression Analysis of NPi-Diff and GCS

Table 2. AIP Variables of the Left and Right Eyes

Variable	Left Eye	Right Eye	p-value
NPi	4.31	4.30	.8945
Pupil diameter at rest (mm)	3.55	3.59	.0002
Pupil diameter — smallest (mm)	2.51	2.53	.0056
Percent change in size	27.42	27.62	.1324
Constriction velocity (mm/s)	1.87	1.88	.7280
Maximum constriction velocity (mm/s)	2.93	2.95	.2468
Dilation velocity (mm/s)	0.83	0.82	.7647
Latency (s)	0.25	0.25	.7113

Reporting as mean

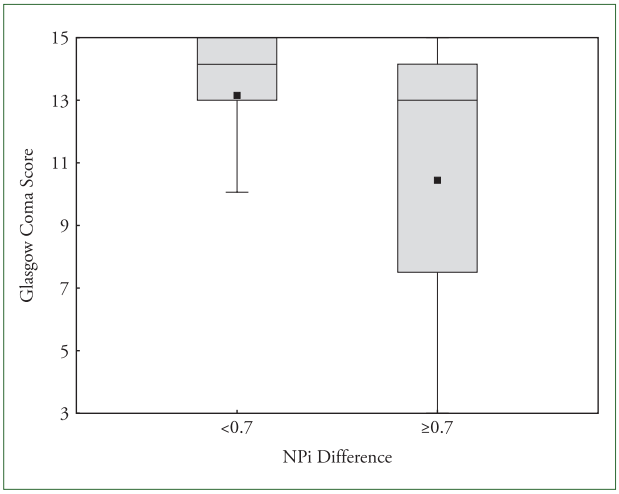

Figure 2. ANOVA Model of Small (<0.7) versus Large (≥0.7) NPi-Diff and GCS

(3.90), while mean GCS for observations with NPi-Diff <0.7 (N=2,296) was 13.15 (2.68) and these values were statistically significantly different (P<.0001).To further explore these relationships, we used Pearson's partial correlation coefficient. Controlling for age, sex, race, and diagnosis confirmed a statistically significant correlation between GCS and NPi-Diff (R=–0.26877, P<.0001). There was a statistically significant association between anisocoria and NPi-Diff (χ^2=117.0421; P<.0001) confirmed by chi-squared analysis.

To explore the relationships between additional AIP variables and GCS, we used simple regression which indicated a slight positive association between GCS and CV of the left (r^2=0.1074, P<.0001) and right eyes (r^2=0.1051, P<.0001). Utilizing 1 observation per subject, mean GCS for observations with anisocoria (N=226) was 12.14 (3.22), while mean GCS for observations without anisocoria (N=2,526) was 12.81 (3.03) and these values were statistically significantly different (P<.005).

Discussion

With the rise of AIP assessments into the standard of care, the NPi has emerged as a clinical indicator of neurologic status. Traditionally, an NPi≥3.0 has been considered to be indicative of a normal PLR. As the first research study to investigate the relationship between NPi-Diff and the GCS, these results provide novel insight into the prognostic ability of AIP for patients with neurological or neurosurgical diagnoses. This analysis highlights the association between increased values of NPi-Diff — even when paired NPi values are normal — and lower GCS scores.

An increase in the NPi-Diff is typically characterized by a decline in the NPi of one eye — one pupil becoming less reactive than the other. A variety of neurologic complications can lead to unilateral pupillary changes, including increased ICP, stroke, and herniation syndromes. Previously, it has been reported that patients with elevated ICP displayed a drop in left NPi values and a slight increase in right NPi values [24]. The NPi has also been shown to be significantly correlated to midline shift and herniation in acute and large hemispheric stroke patients [25,26]. Remarkably, Papangelou et al. [21] found abnormal NPi measurements in patients with supratentorial mass lesions approx. 7.5 hours before transtentorial herniation occurred, highlighting the critical role AIP can perform in patient management. It is noteworthy that other variables (e.g., anisocoria, CV) confirm our findings. Notably, NPi-Diff is a displayed variable on the pupillometer.

Analytics demonstrate that a clear relationship exists such that even when the NPi value is ≥3 (normal): the greater the difference between left and right eye NPi, the greater the likelihood that a functional neurologic deficit (FND) exists. The results are congruent with critical illness where monitoring trends is key to early detection of declining status. For example, while a resting heart rate of 98 bpm is still within normal limits, an astute practitioner who recognizes that the rate has steadily increased from 62 to 98 over the course of an hour would wisely assess the patient for a sinister cause such as sepsis. The NPi-Diff therefore reflects a trend where a FND is impacting one eye earlier (or more significantly) than the other eye.

Limitations

One limitation with this study is using GCS score as a marker of neurologic prognosis. For patients who are sedated and/or intubated, healthcare providers are unable to complete the verbal portion of the GCS and as a result, these subjects were excluded from our analysis. Another limitation with this study is the significantly larger number of subjects with small NPi-Diff values in comparison to those with large NPi-Diff values. As more subject data is incorporated in the END-PANIC registry, we hope to have a larger sample size of subjects with large NPi-Diff and further evaluate the results presented here.

Conclusions

Monitoring for NPi-Diff values ≥0.7 should be considered even when both NPi values reflect a normal PLR (≥3.0). Patients with greater NPi difference have lower GCS, indicating a negative relationship between the two measures. Further research is necessary to evaluate the association between NPi difference and other established, quantitative assessments (e.g., discharge mRS) to determine its efficacy as a marker of neurologic status.

Implications for Nursing Practice

The findings can be incorporated into practice because: 1) the results add to a growing body of evidence that supports nurses assessment of PLR with AIP and not with flashlight or penlights; and 2) differences in left and right eye AIP measures should be noted. Nurses no longer subjectively assess temperature by feeling the patients forehead and we should no longer rely upon subjective assessment of pupil diameter and reactivity when a superior alternative exists. Although an NPi value >3.0 is indicates that the PLR is within normal

limits, a difference in the left and right eye NPi values >.70 indicates that the patient is at risk for impending focal neurologic deficit. Nurses observing a large NPi difference should report their findings.

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References

[1] Olson D.M., Stutzman S.E., Atem F. et al. Establishing Normative Data for Pupillometer Assessment in Neuroscience Intensive Care: The "END-PANIC" Registry. *J Neurosci Nurs*. 2017;49(4):251–254.

[2] Lussier B.L., Stutzman S.E., Atem F. et al. Distributions and Reference Ranges for Automated Pupillometer Values in Neurocritical Care Patients. *J Neurosci Nurs*. 2019; 51(6):335–340.

[3] Chen J.W., Gombart Z.J., Rogers S., Gardiner S.K., Cecil S., Bullock R.M. Pupillary reactivity as an early indicator of increased intracranial pressure: The introduction of the Neurological Pupil index. *Surg Neurol Int*. 2011; 2:82.

[4] Lussier B.L., Olson D.M., Aiyagari V. Automated Pupillometry in Neurocritical Care: Research and Practice. *Curr Neurol Neurosci Rep*. 2019;19(10):71.

[5] Shoyombo I., Aiyagari V., Stutzman S.E. et al. Understanding the Relationship Between the Neurologic Pupil Index and Constriction Velocity Values. *Sci Rep*. 2018;8(1):6992.

[6] Meeker M., Du R., Bacchetti P. et al. Pupil examination: validity and clinical utility of an automated pupillometer. *J Neurosci Nurs*. 2005;37(1):34–40.

[7] Hall C.A., Chilcott R.P. Eyeing up the Future of the Pupillary Light Reflex in Neurodiagnostics. *Diagnostics (Basel)*. 2018;8(1):19.

[8] Cortes M.X., Siaron K.B., Nadim H.T., Ahmed K.M., Romito J.W. Neurological Pupil Index as an Indicator of Irreversible Cerebral Edema: A Case Series. *J Neurosci Nurs*. 2021;53(3):145–148.

[9] Oddo M., Sandroni C., Citerio G. et al. Quantitative versus standard pupillary light reflex for early prognostication in comatose cardiac arrest patients: an international prospective multicenter double-blinded study. *Intensive Care Med*. 2018;44(12):2102–2111.

[10] Natzeder S., Mack D.J., Maissen G., Strässle C., Keller E., Muroi C. Portable Infrared Pupillometer in Patients With Subarachnoid Hemorrhage: Prognostic Value and Circadian Rhythm of the Neurological Pupil Index (NPi). *J Neurosurg Anesthesiol*. 2019;31(4):428–433.

[11] McNett M.M., Amato S., Philippbar S.A. A Comparative Study of Glasgow Coma Scale and Full Outline of Unresponsiveness Scores for Predicting Long-Term Outcome After Brain Injury. *J Neurosci Nurs*. 2016;48(4): 207–214.

[12] Thakur B., Nadim H., Atem F., Stutzman S.E., Olson D.M. Dilation velocity is associated with Glasgow Coma Scale scores in patients with brain injury. *Brain Inj*. 2021; 35(1):114–118.

[13] Minami Y., Mishima S., Oda J. Prediction of the level of consciousness using pupillometer measurements in patients with impaired consciousness brought to the emergency and critical care center. *Acute Med Surg*. 2020;7(1):e537.

[14] McNett M., Moran C., Janki C., Gianakis A. Correlations Between Hourly Pupillometer Readings and Intracranial Pressure Values. *J Neurosci Nurs*. 2017;49(4):229–234.

[15] Teasdale G., Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet*. 1974;2(7872): 81–84.

[16] Majdan M., Steyerberg E.W., Nieboer D., Mauritz W., Rusnak M., Lingsma H.F. Glasgow coma scale motor score and pupillary reaction to predict six-month mortality in patients with traumatic brain injury: comparison of field and admission assessment. *J Neurotrauma*. 2015; 32(2):101–108.

[17] Leitgeb J., Mauritz W., Brazinova A. et al. Glasgow Coma Scale score at intensive care unit discharge predicts the 1-year outcome of patients with severe traumatic brain injury. *Eur J Trauma Emerg Surg*. 2013;39(3):285–292.

[18] Brennan P.M., Murray G.D., Teasdale G.M. Simplifying the use of prognostic information in traumatic brain injury. Part 1: The GCS-Pupils score: an extended index of clinical severity. *J Neurosurg*. 2018;128(6):1612–1620.

[19] Obling L., Hassager C., Illum C. et al. Prognostic value of automated pupillometry: an unselected cohort from a cardiac intensive care unit. *Eur Heart J Acute Cardiovasc Care*. 2020;9(7):779–787.

[20] Aoun S.G., Stutzman S.E., Vo P.N. et al. Detection of delayed cerebral ischemia using objective pupillometry in patients with aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 2019;132(1):27–32.

[21] Papangelou A., Zink E.K., Chang W.W. et al. Automated Pupillometry and Detection of Clinical Transtentorial Brain Herniation: A Case Series. *Mil Med*. 2018;183 (1–2):e113–e121.

[22] El Ahmadieh T.Y., Bedros N., Stutzman S.E. et al. Automated Pupillometry as a Triage and Assessment Tool in Patients with Traumatic Brain Injury. *World Neurosurg*. 2021; 145:e163–e169.

[23] Dance S., Scholefield B.R., Morris K.P., Kanthimathinathan H.K. Characteristics of a Brisk or Sluggish Pupillary Light Reflex: A Nursing Perspective. *J Neurosci Nurs*. 2020;52(3):128–131.

[24] Al-Obaidi S.Z., Atem F.D., Stutzman S.E., Olson D.M. Impact of Increased Intracranial Pressure on Pupillometry: A Replication Study. *Crit Care Explor*. 2019;1(10):e0054.

[25] Osman M., Stutzman S.E., Atem F. et al. Correlation of Objective Pupillometry to Midline Shift in Acute Stroke Patients. *J Stroke Cerebrovasc Dis*. 2019;28(7): 1902–1910.

[26] Kim T.J., Park S.H., Jeong H.B. et al. Neurological Pupil Index as an Indicator of Neurological Worsening in Large Hemispheric Strokes. *Neurocrit Care*. 2020;33(2):575 –581.

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A — Concept and design of research, B — Collection and/or compilation of data, C — Analysis and interpretation of data, D — Statistical analysis, E — Writing an article, F — Search of the literature, G — Critical article analysis, H — Approval of the final version of the article, I — Acquisition of assets [eg financial]

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