Distributions and Reference Ranges for Automated Pupillometer Values in Neurocritical Care Patients

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ABSTRACT

BACKGROUND: Automated pupillometry is becoming widely accepted as an objective measure of pupillary function, especially in neurocritical care units. Normative reference values and thresholds to denote a significant change are necessary for integrating automated pupillometry into practice. **OBJECTIVE:** Providing point estimates of normal ranges for pupillometry data will help clinicians intuit meaning from these data that will drive clinical interventions. **METHODS:** This study used a planned descriptive analysis using data from a multicenter registry including automated pupillometry assessments in 2140 subjects from 3 US hospitals collected during a 3-year period. **RESULTS:** We provide a comprehensive list of admission pupillometry data. Our data demonstrate significant differences in pupillary values for Neurological Pupil Index, latency, and constriction velocity when stratified by age, sex, or severity of illness defined by the Glasgow Coma Scale score. **CONCLUSION:** This study provides a greater understanding of expected distributions for automated pupillometry values in a wide range of neurocritical care populations.

Keywords: assessment, neurocritical care, neurology, pupillary light reflex, pupillometer

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Without normative data, it is hard to know what is abnormal. Research suggests that an abnormal pupillary light reflex (PLR) is reflective of early changes in intracranial physiology.[1–3] The pupillometer is a handheld device that was developed in response to a need for standardized and reliable pupil assessments. Because of the limitations of subjective observations of the PLR,[4,5] there is growing adoption of pupillometer technology.[6] Seeing these changes as trends is important. However, a lack of normative data specific to the population of neurocritically ill patients limits the interpretation of PLR data. The purpose of this analysis is to explore distributions for PLR data from automated pupillometry in a diverse cohort of neurocritically ill patients.

The full assessment of cranial nerve function, which includes the PLR, is a fundamental element of the neurological examination. A major portion of the functional status of the optic (cranial nerve II) and oculomotor (cranial nerve III) cranial nerves can be assessed by evaluation of the PLR.[7,8] Abnormalities in this examination reflect not only cranial nerve deficits but also pathologic changes in the nearby intracerebral environment, leading to cranial nerve dysfunction.[9,10] Recent literature supports that simply reporting a pupil as reactive, brisk, or sluggish fails to capture the entirety of the PLR.[8] A small pupil will not reach high constriction velocity (CV) because the

percent change in size is small. A large pupil may have a brisk response, but failure to fully constrict would be reflected as a low Neurological Pupil Index (NPi) value (eg, the pupil that briskly constricts from 6 mm to 5 mm).

There are limitations to the traditional method of assessing the PLR with a handheld flashlight. The pupil size, shape, and reactivity to light are influenced by ambient lighting, skin tone, eye color, quality of the light source, and subject cooperation.[4,5] Using the terms *brisk* and *sluggish* in clinical practice to describe the PLR is vague and subjective. Variables in the pupillary assessment such as CV are reportedly sensitive to changes in intracranial pressure.[11,12] Consistent and reliable pupil examinations with trending data may assist the team of providers in clinical decision making and lead to therapeutic interventions that may influence patient outcomes. Timely intervention (eg, hyperosmolar therapy, hyperventilation as a bridge to surgical intervention) after observation of a new pupillary abnormality has been associated with improved survival or recovery.[13]

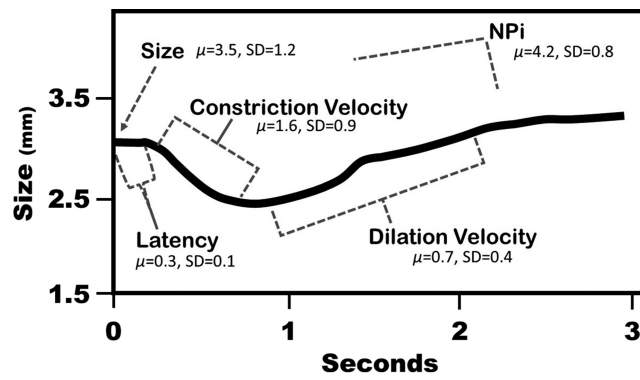
Having objective PLR data is important to provide high-quality clinical care. Providing clinicians with a deeper understanding of the reference ranges for those data is expected to drive clinical interventions.[14] There is currently only 1 handheld pupillometer sold in the United States; the NPi-200 (developed by Neuroptics, Inc) is used in acute and critical care settings.[10,15–18] In addition to providing a digital reading for the initial size of the pupil, the NPi-200 provides several unique values that are unavailable from the manual examination (Figure 1). These include the latency, CV, dilation velocity (DV), and NPi, and each of these elements can be evaluated in detail. Pupil size is measured is millimeters and documented to the hundredth place. Latency is the time from when the pupil is first exposed to light to the onset of pupil constriction (measured in seconds and documented to the hundredth). Both CV and DV are measured in millimeters per second (mm/s) and documented to the hundredth. Constriction velocity is the speed at which the pupil changes from baseline to its smallest size over time. Dilation velocity is the change from the smallest pupil size back to baseline over time.

These findings provide baseline values for clinicians and researchers using automated pupillometers.

The NPi is derived from a proprietary algorithm that incorporates constriction latency, CV, and DV. The NPi is indexed to a baseline set of samples obtained from healthy volunteers, with scores ranging from 0 to 5.[19,20] NPi scores greater than 3 are considered to be reflective of normal PLR, whereas a score of 0 indicates the absence of a PLR. Previous research in healthy volunteers found that larger pupil size was correlated with faster CV and higher NPi scores.[21] The NPi is a derived variable with no specific units and documented to the tenth. In contrast to the limited interrater reliability of human observations,[5] the pupillometer has a very high interdevice reliability.[22]

A major hurdle in interpreting pupillometry values is the diversity of pathophysiologic conditions and medical diagnoses hypothesized to impact PLR. For example, a distal middle cerebral artery infarct is expected to have less impact on PLR than would a large

FIGURE 1 The Discrete Elements of the Pupillary Light Reflex With Pooled Normative Values



Note. Neurological Pupil Index (NPi) is a derived variable reflecting the PLR compared with healthy individuals. Size = size before light stimulus; latency = period from light stimulus to first constriction; constriction velocity = speed at which pupils constrict; dilation velocity = speed at which pupil recovers to normal (prestimulus) size.

intracranial hemorrhage that results in central brainstem herniation.[7] The gap in literature is a lack of descriptive data and measures of central tendency for PLR values with respect to patients admitted to the neurocritical care unit (NCU). This work, therefore, is not intended to serve as the pinnacle of automated PLR research, nor is it intended to provide inferential analyses; rather, this study will serve as a foundation for future exploration.

Methods

This is a planned descriptive analysis of data from the Establishing Normative Data for Pupillometer Assessments in Neuro-Intensive Care (END-PANIC) registry, which is approved by the local institutional review board and registered with ClinicalTrials.gov (NCT02804438). All data were collected as standard of care, and subject consent was not required. Data collection methods have been previously described in detail.[23] In brief, END-PANIC is a prospective multicenter registry of pupillometer assessments and associated clinical data abstracted from patients admitted to the NCU at participating hospitals and prescribed to have PLR assessments as part of their standard care. Time and date values are stamped independently for left eye (OS) and right eye (OD). Pupillometer values for OS and OD (ie, NPi, minimum and maximum pupil size, DV, CV, and percentage of constriction) are obtained during routine care, and research staff downloads the values to an electronic spreadsheet. Similarly, data from the electronic medical record are abstracted such that pupillometer readings can be merged with electronic medical record data into a single time-stamped database. Shared data are maintained on a secured server, and statistical analysis is performed using SAS v9.4 for Windows (SAS Institute).

There were 72 472 PLR readings from 2140 patients included in this analysis. The END-PANIC registry currently includes 2655 patients admitted to 3 hospitals. Of these, there were 2371 patients with Glasgow Coma Scale (GCS) scores. Subjects in whom pupil examinations were not performed and observations without pupil reactivity were excluded (n = 231). The highest daily GCS (best neurologic function) was matched to automated PLR data without regard to medical diagnosis. Most observations provided OS and OD readings. Averaging OS/OD may fail to capture significant variation because of intracranial pathology (eg, mass effect with midline shift). Therefore, OS and OD values are evaluated separately (eg, a single assessment of both eyes from 1 patient would yield 2 PLR readings). Age was categorized as youngest (<25 years), middle (25–50 years), older (51–75 years), and elderly (>75 years). All values are reported as mean (standard deviation), unless otherwise noted.

To provide normative data in a large population of patients with variable severity of illness that might significantly impact the generalizability of those values, we chose to stratify patients using the GCS. Despite recognized limitations,[24–26] the GCS provides a common denominator for discussing patients with neurologic injury. One of the flaws of the GCS is that it is limited in measuring level of consciousness in specific conditions, such as sedated or intubated patients.[24] However, the GCS is a widely used organ-specific measure of severity of illness in neurocritical care wherein GCS 13–15 is mild, GCS 9–12 is moderate, and GCS 3–8 is severe. With a full understanding of the limitations, this analysis intentionally evaluates PLR data in relationship to GCS values.

This study provides only descriptive analytics. Nominal data are summarized using frequency, ordinal data were summarized using mean and interquartile range, and continuous data were summarized using mean and standard deviation. Central tendencies were developed for each PLR variable at each GCS level (mild, moderate, and severe). A random-effects mixed model for longitudinal data was constructed to account for clustering of subjects. This model was run using the Kenward-Roger degree of freedom.

Results

This analysis includes 2140 subjects from 3 US hospital NCUs, including 2 university hospitals and 1 community hospital. Subjects were predominantly white (n = 1345, 62.9%), non-Hispanic (n = 1582, 73.9%), and female (n = 1,134, 53.0%), and the mean age was 52.3 years (IQR, 40–69; Supplemental Digital Content 1, available at http://links.lww.com/JNN/A199). The PLR values and central tendencies for the entire sample taken as a single cohort, and stratified by GCS score severity, are provided in Table 1.

Neurologic Pupil Index

The mean (SD) NPi for OS (4.14 [0.83]) and OD (4.15 [0.80]) were similar ($P = .2199$). A paired t test also showed a statistically significant difference in NPi for OS and OD within subjects ($P < .001$). A random-effects mixed model indicates significant within-subject variation in OS and OD NPi values ($P < .001$). The NPi values for mild (4.3 [0.64]), moderate (4.2 [0.83]), and severe (4.1 [0.89]) injury were statistically significantly different ($P < .001$). The difference in NPi values for men (4.3 [0.73]) versus women (4.1 [0.86]) was significant ($P < .001$). There was a statistically significant difference in NPi values by age comparing youngest (4.0 [0.88]), middle

TABLE 1. Mean (SD) and Median [95% CI] Values for Pupillary Response Measures at Each Level of GCS

	Entire Cohort	Mild (GCS 13–15)	Moderate (GCS 9–12)	Severe (GCS 3–8)	*P*
NPi	4.2 (0.8) 4.4 [2.4–4.8]	4.3 (0.6) 4.4 [2.0–4.8]	4.2 (0.8) 4.5 [2.3–4.8]	4.1 (0.9) 4.4 [3.1–4.8]	<.001
Size, mm	3.5 (1.2) 3.4 [2.0–5.7]	3.2 (1.1) 3.0 [1.8–5.5]	3.6 (1.1) 3.4 [2.0–5.7]	3.8 (1.1) 3.7 [2.3–5.8]	<.001
Latency, mm/s	0.3 (0.1) 0.2 [0.2–0.4]	0.3 (0.1) 0.2 [0.2–0.4]	0.3 (0.1) 0.2 [0.2–0.4]	0.2 (0.0) 0.2 [0.2–0.3]	<.001
Constriction velocity, s	1.6 (0.9) 1.6 [0.4–3.2]	2.0 (0.8) 2.0 [0.2–2.8]	1.7 (0.8) 1.6 [0.5–3.1]	1.3 (0.8) 2.0 [0.7–3.4]	<.001
Dilation velocity, s	0.7 (0.4) 0.7 [0.1–1.4]	0.6 (0.4) 0.5 [0.1–1.3]	0.8 (0.4) 0.8 [0.2–1.4]	0.9 (0.4) 0.9 [0.3–1.5]	<.001

Abbreviations: CI, confidence interval; GCS, Glasgow Coma Score; NPi, Neurological Pupil Index.

(4.0 [0.84]), older (4.2 [0.73]), and elderly (4.4 [0.56]; $P < .001$) patients.

Pupil Size

For size, the OS (3.47 [1.16] mm) and OD (3.49 [1.17] mm) were clinically similar but statistically different ($P < .0027$). A paired *t* test also showed a statistically significant difference in size for OS and OD within subjects ($P < .001$). A random-effects mixed model indicates significant within-subject variation in OS and OD pupil sizes ($P < .001$). The size values for mild (3.2 [1.14] mm), moderate (3.6 [1.14] mm), and severe (3.8 [1.07] mm) injury were statistically significantly different ($P < .001$). The difference in size for men (3.3 [1.12] mm) versus women (3.6 [1.18] mm) was significant ($P < .001$). The difference in size values for youngest (3.6 [1.35] mm), middle (3.8 [1.33] mm), older (3.4 [1.05] mm), and elderly (3.2 [0.97] mm) patients was significant ($P < .001$).

Pupil Latency

Pupil latency is measured in seconds (s). Latencies for the OS (0.26 [0.06] s) and OD (0.26 [0.06] s) were similar ($P = .0607$). A paired *t* test showed a statistically significant difference in latency for OS and OD within subjects ($P < .001$). A random-effects mixed model indicates significant within-subject variation in OS and OD pupil latencies ($P < .001$). The latency values for mild (0.26 [0.06] s), moderate (0.26 [0.06] s), and severe (0.24 [0.05] s) injury were clinically similar but statistically significantly different ($P < .001$). The latency values for men (0.25 [0.05] s) versus women (0.26 [0.06] s) were also statistically significantly different ($P < .001$). The difference in latency values for youngest (0.25 [0.06] s), middle (0.25 [0.06] s), older (0.26 [0.05] s), and elderly (0.26 [0.05] s) patients was found to be significant ($P < .001$).

Constriction Velocity

The mean (SD) CVs for OS (1.62 [0.86] mm/s) and OD (1.62 [0.87] mm/s) were similar ($P = .8609$), and a paired *t* test found no statistically significant difference in CV within subjects ($P < .59$). A random-effects mixed model indicates significant within-subject variation in OS and OD CVs ($P < .001$). The CV values for mild (2.0 [0.82] mm/s), moderate (1.7 [0.82] mm/s), and severe (1.3 [0.80] mm/s) injury were statistically significantly different ($P < .001$). The difference in CV values for men (1.6 [0.82] mm/s) versus women (1.7 [0.9] mm/s) was statistically significant ($P < .001$). The difference in CV values for youngest (1.6 [0.95] mm/s), middle (1.8 [0.99] mm/s), older (1.6 [0.80] mm/s), and elderly (1.5 [0.74] mm/s) patients was significant ($P < .001$).

Dilation Velocity

For size, the OS (0.71 [0.39] mm/s) and OD (0.72 [0.39] mm/s) were similar ($P = .2623$). A paired *t* test also showed a statistically significant difference in DV for OS and OD within subjects ($P = .002$). A random-effects mixed model indicates significant within-subject variation in OS and OD DVs ($P < .001$). The DV values for mild (0.58 [0.37] mm/s), moderate (0.76 [0.37] mm/s), and severe (0.91 [0.37] mm/s) injury were statistically significantly different ($P < .001$). The DV values for men (0.67 [0.37] mm/s) versus women (0.74 [0.40] mm/s) were different ($P < .001$). The difference in DV values for youngest (0.68 [0.44] mm/s), middle (0.80 [0.44] mm/s), older (0.71 [0.36] mm/s), and elderly (0.67 [0.33] mm/s) patients was significant ($P < .001$).

Findings were explored based on admission diagnosis. The mean (SD) values for NPi ranged from 4.06 (0.81) for nonsurgical neurologic injuries other than stroke (eg, seizure) to 4.31 (0.69) for acute

ischemic stroke and were statistically significantly different by diagnosis ($P < .001$), although it is noted that these values are clinically similar. The mean (SD) pupil size ranged from 3.2 (1.10) mm for intracerebral hemorrhage (ICH) to 3.7 (1.13) mm for neoplasm ($P < .001$). Latency ranged from 0.24 (0.04) s for traumatic brain injury to 0.28 (0.05) s for acute ischemic stroke ($P < .001$). Constriction velocity ranged from 1.48 (0.91) mm/s for ICH to 1.86 (0.93) mm/s for neoplasm ($P < .001$). Dilation velocity values ranged from 0.63 (0.39) mm/s for ICH to 0.83 (0.40) mm/s for neoplasm ($P < .001$). Although these differences are statistically significant, we are unable to find literature discussing the clinical relevance of this finding.

Discussion

The results provide insight for clinicians who have already adopted or those transitioning their practice to incorporate automated pupillometry. These findings not only serve as a baseline for future comparisons and hypothesis testing that includes PLR data from automated pupillometry but also provide point estimates and variance for PLR measures when used in clinical practice. The ability of quantitative pupillometry to deliver replicable and reliable results, and its relationship to associated outcomes, has been previously established for pupillary measurements in previous studies.[2,9,12,21,22,27-30] However, until now, only a small cohort of healthy volunteers has been assessed for normative data.[12]

Paired testing of OS and OD values, including mixed methods, provides support that differences in measured values are expected. This finding confirms and extends clinical and pathophysiologic findings. The vast majority of intracranial lesions has some focality and would be expected to impact 1 eye PLR differently than the other eye. For example, a left frontal ICH would be expected to impact the left PLR differently than it would impact the right PLR up until the lesion expands to a terminal point (eg, downward herniation). The results provide insight into expected findings and emphasize the need for monitoring trends. The left and right PLR should be examined separately with OS values compared and trended with previous OS values, and OD values compared and trended with previous OD values.

Limitations

This analysis was not designed to provide inferential statistics or to describe PLR effects within discreet diagnoses. This analysis examines the distribution of pupil reactivity values. A recognized limitation is the use of nonrandomized sampling. All observations were obtained from patients admitted to NCUs and therefore were more likely to have abnormal PLR. However, this does represent the largest known sample of automated PLR readings, and the heterogeneity of the sample enhances external validity. It is a recognized limitation of the study that the registry does not collect specifically data on the presence or absence of second or third cranial nerve pathology. However, these are rare findings in the NCU and unlikely to impact the results.[31]

Conclusion

This report is the first to provide measures of central tendency for PLR values across a large cohort of subjects. Separate observations of OS and OD, including trends, should be monitored throughout the NCU stay. These data provide baseline normative values for future research into automated pupillometry in clinical practice.

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