Automated Pupillary Measurements Inversely Correlate With Increased Intracranial Pressure in Pediatric Patients With Acute Brain Injury or Encephalopathy

Ashley D. Freeman, MD[1–3]; Courtney E. McCracken, PhD[2,3]; Jana A. Stockwell, MD, FCCM[2,3]

Objectives: The purpose of this study was to determine correlation and temporal association between automated pupillary measurements and intracranial pressure in pediatric patients with brain injury or encephalopathy requiring intracranial pressure monitoring. We hypothesized that abnormal pupillary measurements would precede increases in intracranial pressure.

Design: A prospective cohort study was performed. Automated pupillometry measurements were obtained at the same frequency as the patients' neurologic assessments with concurrent measurement of intracranial pressure, for up to 72 hours. Pupillary measurements and the Neurologic Pupil index, an algorithmic score that combines measures of pupillary reactivity, were assessed for correlation with concurrent and future intracranial pressure measurements.

Setting: Single-center pediatric quaternary ICU, from July 2017 to October 2018.

Patients: Pediatric patients 18 years or younger with a diagnosis of acute brain injury or encephalopathy requiring an intracranial pressure monitor.

Interventions: None.

Measurements and Main Results: Twenty-eight patients were analyzed with a total of 1,171 intracranial pressure measurements. 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 ($p < 0.001$ for all). There were mild to moderate negative correlations between concurrent intracranial pressure and pupillary measurements. However, there was an inconsistent pattern of abnormal pupillary measurements preceding increases in intracranial pressure; some patients had a negative association, while others had a positive relationship or no relationship between Neurologic Pupil index and intracranial pressure.

Conclusions: Our data indicate automated assessments of pupillary reactivity inversely correlate with intracranial pressure, demonstrating that pupillary reactivity decreases as intracranial pressure increases. However, a temporal association in which abnormal pupillary measurements precede increases in intracranial pressure was not consistently observed. This work contributes to limited data available regarding automated pupillometry in neurocritically ill patients, and the even more restricted subset available in pediatrics. (*Pediatr Crit Care Med* 2020; XX:00–00)

Key Words: acute brain injury; encephalopathy; neurologic examination; traumatic brain injury

Subjective pupillary measurements of size and reactivity are routinely used in the ICU as a marker of neurologic function, guiding therapy, and interventions. Additionally, pupillary reactivity has been used in traumatic brain injury (TBI) patients to predict survival and probability of unfavorable outcomes (1, 2). Pupillary size and reactivity are generally measured manually by pupillary gauge or estimation; however, significant variation exists between different examiners' measurements (3). Given inter-rater variance and the subjective nature of pupillary measurements, automated pupillometry is increasingly being used.

Automated pupillometers are handheld devices which take objective measurements of pupillary size and reactivity. Meeker et al (4) published a study showing subjective measurements of pupil reactivity had poor inter-rater agreement and twice the error of measuring pupil size than observed with automated pupillometry. These findings were corroborated by Couret et al (5) who demonstrated better correlation in pupillary measurements with an automated pupillometer than by manual assessment.

Given the importance of accurate pupillary measurements and the impact on patient care decisions, such as the need for additional neurologic imaging or neurosurgical intervention, ICUs have begun to adopt the use of automated pupillometers

[1]Division of Critical Care Medicine, Department of Pediatrics, Medical College of Georgia at Augusta University, Augusta, GA.

[2]Emory University School of Medicine, Atlanta, GA.

[3]Division of Critical Care Medicine, Department of Pediatrics, Children's Healthcare of Atlanta, Egleston Campus, Atlanta, GA.

DOI: 10.1097/PCC.0000000000002327

(6–8). One manufacturer of pupillometers has developed an algorithmic combination of pupillary measurements into a score called the Neurologic Pupil index (NPi), which defines the pupillary response as normal or abnormal. An NPi score of greater or equal to 3 is normal and less than 3 is abnormal. Adult studies demonstrate an inverse correlation between pupillary reactivity, NPi, and increased intracranial pressure (ICP), and instances of abnormal pupillary measurements preceding increases in ICP (9, 10).

Although the majority of the current literature regarding pupillometry is in adult populations, given the high frequency of TBI in the pediatric population (11) and other diagnoses requiring ICP monitoring (e.g., acute brain injuries and encephalopathy), we aimed to further define the association between automated pupillary measurements and ICP. We hypothesize that abnormal pupillary measurements will precede increases in ICP.

MATERIALS AND METHODS

This study was conducted as a prospective observational study of pediatric patients with traumatic or acute brain injury, or encephalopathy who required invasive ICP monitoring in the PICU at Children's Healthcare of Atlanta (CHOA), Egleston campus, from July 2017 to October 2018. CHOA Institutional Review Board (IRB) approved this study (IRB number 00094113) with a waiver of informed consent.

Patients were prospectively identified following admission, based on their diagnosis codes and enrolled if they were 18 years or younger with a diagnosis of brain injury or encephalopathy requiring invasive ICP monitoring. Patients were excluded if their pupils were unable to be visualized or examined.

Per study protocol, the patient's nurse obtained automated pupillary measurements at the frequency that neurologic assessments were ordered by the ICU team. Measurements were recorded on a data collection sheet provided by the study team. The ICP measurement at the time of pupillary assessment and the type of ICP monitoring device (external ventricular drain [EVD] or intraparenchymal device) was recorded. For patients with an EVD, the level the EVD was set above the external auditory meatus was also recorded.

Data points collected include as follows: demographics (age, gender, weight), Glasgow Coma Scale (GCS) at admission, diagnosis, use of hyperosmolar therapy (mannitol or hypertonic saline) in the hour preceding pupillary measurements, use of sedative, analgesic, or paralytic infusions, and presence of electroencephalography (EEG) monitoring. If the patient had EEG monitoring, it was noted if they were in burst suppression based on neurophysiology reports for that time period.

Data were collected for up to 72 hours following enrollment. The primary objective was to determine whether elevations in ICP, defined as an ICP of 20 mm Hg or greater, were preceded by abnormal pupillary measurements. We defined an ICP of 20 mm Hg or greater as elevated based on the Guidelines for the Management of Severe Traumatic Brain Injury, Third Edition (12). The correlative relationship between ICP and pupillary measurements was assessed as a secondary objective.

NeurOptics NPi-200 pupillometer system (Laguna Hills, CA) was used for the study. This pupillometer is a handheld device that takes measurements of pupillary size and reactivity. The device emits a light and an infrared camera captures and measures pupil size (maximum and minimum), percent pupil change, dilation velocity, constriction velocity, maximum constriction velocity, and latency. The measurements are combined algorithmically into a score called the NPi, which stratifies pupillary reactivity as normal (score of 3 to 5), abnormal (less than 3), or a score of zero which represents either a nonreactive pupil, or an immeasurable or atypical pupillary response. The device is U.S. Food and Drug Administration approved without an age restriction. The company did not provide any financial support for this study.

Descriptive statistics were calculated for all variables of interest and include means and SDs, medians, and ranges or counts, and percentages when appropriate. Because data were measured hourly over up to a 72-hour period, multiple measurements per patient were recorded. Rank order correlation coefficients with associated 95% CIs were used to measure the strength of association between ICP values and measures of pupillary response. Because subjects were measured repeatedly, the correlations were estimated on the ranked data using a mixed modeling approach proposed by Hamlett et al (13) to account for repeated measures, and a normal approximation using Fisher r to Z transformation was used to generate a 95% CI. Given the large number of measurement pairs, correlations greater than or equal to 0.32 were considered meaningful as this implies that approximately 10% of the variation in ICP values were associated with concurrent changes in pupillary reactivity. Wilcoxon rank-sum tests were used to compare pupillary measures when the ICP was greater than or equal to 20 compared to less than 20. Differences in measurements between ICP groups were further converted to effect sizes using the %*stddiff* macro in SAS v. 9.4 (SAS Institute, Cary, NC) (14). The effect size can be used to interpret the magnitude of differences between the high and low ICP cohorts when pupillary measures are on different scales. Finally, the area under the receiver operating curve (AUROC) was used to describe how well specific measure of pupillary response discriminated between normal and high ICP values.

In addition, for each ICP measurement at time *t*, a lagged measure of pupillary response was computed using a lag of one measurement (*t*–1), three measurements (*t*–3), and six measurements (*t*–6). These lagged measures were then correlated with ICP values at time *t* to determine whether or not preceding pupillary measures correlated with later ICP values. For a subset of patients with normal ICP values at the start of monitoring who subsequently developed elevation of ICP, individual time series plots of ICP versus different measures of pupillary response were generated. These plots were used to determine the pattern of pupillary responses prior to elevations in ICP. In addition, first-order autoregressive integrated moving average (ARIMA) models were used to explore the effect of lagged pupillary measures on ICP measurements at the patient level (data not shown). Analysis were conducted using SAS v. 9.4 and statistical significance was assessed at the 0.05 level unless otherwise noted.

RESULTS

Twenty-eight patients were enrolled prospectively from July 2017 to October 2018. Diagnoses included TBI, acute brain injury, and encephalopathy. Majority of patients (85.7%) were monitored with an EVD. At enrollment, 28.6% (8/28) had an abnormal NPi, 28.6% (8/28) had an elevated ICP, and three patients had both (**Table 1**). Given the diagnoses in our study population, many of the pupillary and ICP measurements were taken while patients were on a combination of sedative, analgesic, and paralytic infusions. Additionally, many patients received hyperosmolar therapy and EEG monitoring during the study period. Twenty percent of measurements were taken with patients in burst suppression as evidenced on EEG (**Table 2**).

The correlation between concurrent ICP measurements and measures of pupillary reactivity were evaluated. All measures of pupillary reactivity except latency had an inverse correlation with ICP. Percent change in pupil size, constriction velocity, maximum constriction velocity, and dilation velocity had the most meaningful correlations (all ≥ –0.32). NPi for the left eye measurements met our threshold for significant correlation, but the right eye measurements did not. Latency did not have a significant inverse or direct correlation (**Table 3**).

Next, we compared pupillary reactivity measurements when ICP was greater than or equal to 20 mm Hg versus when ICP was less than 20 mm Hg. All measurements were significantly lower ($p \leq 0.001$) when ICP was greater than 20 mm Hg compared to when ICP was less than 20 mm Hg (**Table 4**). The raw data of NPi versus ICP for each eye are provided in **Figure 1**. Additionally, we calculated the AUROC for each measure of pupillary reactivity when the ICP was greater than or equal to 20 mm Hg. Bilateral constriction velocities and maximum constriction velocities, and right eye NPi and percent change pupil size had AUROC greater than or equal to 0.7. Bilateral dilation velocities, left eye NPi and percent change pupil size, and right eye latency and NPi had AUROC between 0.6 and 0.7. Latency for the left eye had AUROC of 0.55 (**Table 5**).

Pupillary measurements were then assessed for correlation with future ICP measurements, to evaluate for a predictive pattern of changes in pupillary measurement preceding elevations of ICP. The ICP was correlated with the pupillary measurements from three prior assessments. The median time from the ICP to these preceding assessments was 1 hour, 3 hours, and 7 hours, respectively. These measurements had statistically significant and meaningful negative correlation with ICP for bilateral percent change in pupil size and constriction velocities and right eye dilation velocity at 1 lagged measure, and bilateral constriction velocities and right eye dilation velocity and percent change pupil size at 3 and 6 lagged measures (**Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/PCC/B254; **Supplemental Table 2**, Supplemental Digital Content 2, http://links.lww.com/PCC/B255; and **Supplemental Table 3**, Supplemental Digital Content 3, http://links.lww.com/PCC/B256).

Patients with a normal NPi and ICP less than 20 mm Hg at enrollment who subsequently had an ICP elevation greater than or equal to 20 mm Hg were individually analyzed for a predictive pattern of abnormal pupillary measurements preceding ICP elevation. Of these seven patients, one was noted to have decreased right eye NPi preceding the ICP elevation. Two patients were noted to have decreases in either dilation velocity, constriction velocity, or both preceding ICP elevations,

TABLE 1. General Demographics of the Study Cohort

Characteristics	*n* = 28
Age, yr, mean ± SD (minimum–maximum)	7.6 ± 5.9 (0.3–17.8)
Weight, kg, median (25–75th IQR)	24 (13–48)
Initial Glasgow Coma Scale, median (25–75th IQR)	4 (3–7.5)
Diagnosis, *n* (%)	
TBI, open	3 (10.7)
TBI, closed	14 (50)
Encephalopathy	4 (14.3)
Other[a]	7 (25)
Type of ICP monitoring[b], *n* (%)	
External ventricular drain	24 (85.7)
Intraparenchymal device	5 (17.9)
Number of measurements per patient, median (25–75th IQR)	44 (24.5–56.5)
Time between measurements, hr, median (25–75th IQR)	1.0 (1.0–1.5)
At least one instance of ICP ≥ 20 mm Hg during monitoring, *n* (%)	19 (67.9)

ICP = intracranial pressure, IQR = interquartile range, TBI = traumatic brain injury.

[a]Other includes arteriovenous malformation (5), intraparenchymal hemorrhage (1), and stroke with hemorrhagic conversion (1).

[b]More than one may apply so percentages add up to more than 100%.

TABLE 2. Infusions and Electroencephalography Findings

Infusions and EEG Findings	Measurements Taken, *n* = 1,171, *n* (%)
Hyperosmolar therapy given in preceding hour	82 (7)
Benzodiazepine infusion	498 (42.5)
Narcotic infusion	685 (58.5)
Pentobarbital infusion	248 (21.2)
Dexmedetomidine infusion	33 (2.8)
Paralytic infusion	254 (21.7)
Continuous EEG[a]	811 (69.3)
Burst suppression	236 (20.1)

EEG = electroencephalography.

[a]*n* = 1,170 measurements taken for this variable.

TABLE 3. Correlation of Intracranial Pressure With Measures of Pupil Reactivity

	Right			Left		
Measurement	*n*[a]	Correlation[b] (95% CI)	*p*	*n*[a]	Correlation[b] (95% CI)	*p*
Neurologic Pupil index	1,130	−0.31 (−0.53 to −0.10)	0.004	1,168	−0.32 (−0.52 to −0.12)	0.002
Change pupil size (%)	930	−0.36 (−0.58 to −0.15)	0.001	956	−0.37 (−0.57 to −0.18)	< 0.001
Constriction velocity (mm/s)	913	−0.36 (−0.58 to −0.15)	0.001	936	−0.39 (−0.58 to −0.20)	< 0.001
Maximum constriction velocity (mm/s)	923	−0.36 (−0.58 to −0.15)	< 0.001	950	−0.32 (−0.53 to −0.10)	0.003
Latency (s)	929	0.09 (−0.10 to 0.29)	0.348	953	0.11 (−0.05 to 0.27)	0.185
Dilation velocity (mm/s)	899	−0.34 (−0.55 to −0.12)	0.002	910	−0.34 (−0.54 to −0.15)	< 0.001

[a]Number of measurement pairs.

[b]Correlation is estimated from a mixed model using the estimates from the within subject variance matrix to account for repeated measurements made on the same subject.

but not within consistent time periods. Other patients had a positive correlation or no correlation between pupillary measurements and subsequent ICP.

DISCUSSION

Pupillary assessment is an integral part of the neurologic examination of critically ill patients, and it guides decision making for imaging and surgical intervention. Subjective pupillary measurements have high rates of inter-examiner variability (3). Therefore, automated pupillometry is becoming increasingly used, as it has less inter-rater disagreement, requires little training and can be performed at the bedside (4, 5).

Adult studies have previously shown an association between increased ICP and abnormal automated pupillary measurements. Chen et al (9) studied the relationship of pupillary reactivity, using NPi, to increases in ICP. They demonstrated that patients with normal NPi had lower peak ICP, and patients with one or more abnormal pupillary measurements had a higher mean ICP. In two patients, they also demonstrated a temporal relationship between changes in NPi and peak ICP, with a decrease in the NPi noted up to 15.9 hours prior to their peak ICP. Similarly, Park et al (10) found abnormal NPi correlated with both lower GCS and higher ICPs. Two more recent studies in adults have also shown NPi measurements to decrease with concurrent elevations of ICP (15), and an inverse correlation between ICP and NPi and constriction velocity (16).

Our study examined this relationship in pediatric patients with brain injury or encephalopathy requiring ICP monitoring. Although the right eye NPi score and bilateral latency measurements did not meet our criteria for meaningful correlation (a correlation of 0.32 or greater), all other measurements of pupillary reactivity demonstrated significant and meaningful inverse correlation with concurrent ICP (Table 3). Therefore, the constituents used to calculate an NPi score seem to have better correlation with ICP measurements than the absolute NPi score itself. Latency would not be expected to have an inverse correlation, given a slower reaction time would be expected as ICP increased; however, it also did not have a significant direct correlation. Our study did however demonstrate

TABLE 4. Comparison of Pupillary Measurements When Intracranial Pressure Is Greater or Less Than 20 mm Hg

Measurement	ICP < 20, *n* = 856	ICP ≥ 20, *n* = 315	*p*	Effect Size[a]
NPi right	4.4 (3.6–4.6)	3.4 (0–4.3)	< 0.001	−0.72
NPi left	4.4 (3.5–4.6)	3.3 (0–4.5)	< 0.001	−0.55
Pupil % change right (%)	16 (9–22)	11 (4–15)	< 0.001	−0.77
Pupil % change left (%)	16 (10–23)	11 (3–17)	< 0.001	−0.63
Dilation velocity right (mm/s)	0.32 (0.15–0.52)	0.21 (0.09–0.30)	< 0.001	−0.69
Dilation velocity left (mm/s)	0.33 (0.19–0.54)	0.24 (0.1–0.38)	< 0.001	−0.52
Constriction velocity right (mm/s)	0.97 (0.54–1.42)	0.51 (0.30–0.76)	< 0.001	−0.86
Constriction velocity left (mm/s)	1.02 (0.59–1.38)	0.62 (0.27–0.88)	< 0.001	−0.81

ICP = intracranial pressure, NPi = Neurologic Pupil index.

[a]Effect size is calculated using rank based means to calculate standardized mean differences between groups. Negative effect size implies lower values in the elevated ICP group.

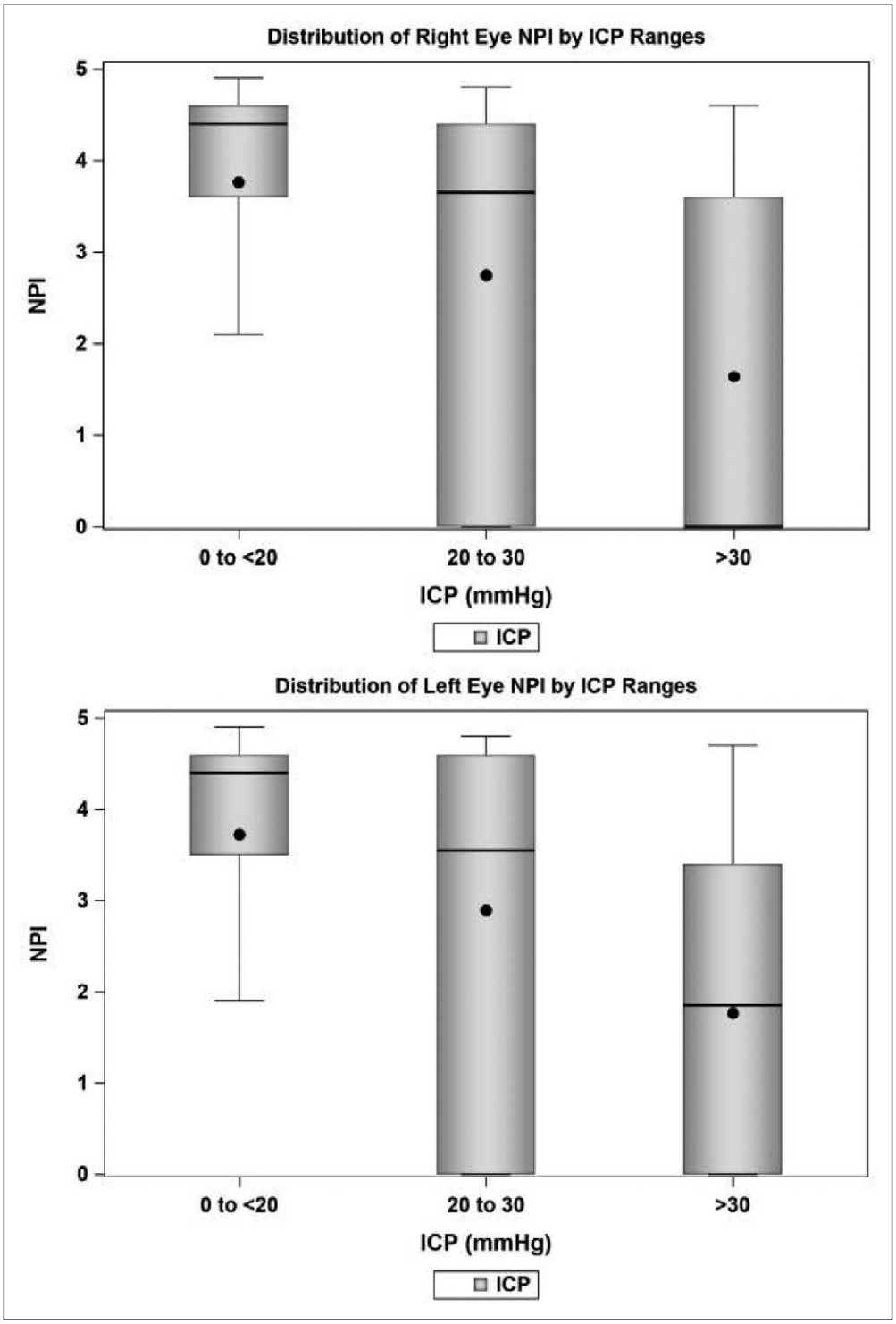

Figure 1. *Box plots* of Neurologic Pupil index (NPi) versus intracranial pressure (ICP) for right eye and left eye.

a greater inverse correlative relationship between NPi and constriction velocity compared to that done by McNett et al (16).

All measures of pupillary reactivity were significantly lower in patients whose ICP was greater than or equal 20 mm Hg versus those whose ICP less than 20 mm Hg (Table 4). Most of the AUROCs for measures of pupillary reactivity ranged between 0.65 and 0.72, indicating that the average sensitivity (across all ranges of specificity) of these measures of pupillary reactivity was 65% and 72%. Of these, constriction velocity appeared to be the most sensitive with AUROC values of 0.72 and 0.71 in the right and left eyes, respectively (Table 5).

Taylor et al (17) examined pupillary measurements in both healthy adult volunteers and patients with head injury. Thirteen patients with head injury and midline shift of more than 3mm had 156 paired measurements performed when ICP was greater than 20 mm Hg. In these patients, constriction velocity decreased to values of 0.8 to 0.6 mm/s or less. Additionally, they noted in 31-46% of patients with ICP greater than 20 to 30 mm Hg had a reduction in their percent pupil change to less than 10%. Similarly, we found that patients with an ICP greater than or equal to 20 mm Hg had a median constriction velocity of 0.51 and 0.62 mm/s, for the right and left eyes, respectively. However, our patients' median percent reduction in pupil size when ICP was greater than 20 mm Hg was 11% bilaterally. Normative data for quantitative pupillometry in pediatrics has been studied, with a mean percent reduction in pupil size of 36%, constriction velocity of 2.34 mm/s, and mean dilation velocity of 2.2 mm/s (18). All of our patients' median measurements, with or without ICP elevation, fell below these thresholds; reflecting that pupillary reactivity may be affected by any type of intracranial insult and worsened by increased ICP.

In correlating pupillary measurements with future ICP values, we found a statistically significant inverse correlation for bilateral percent change in pupil size and constriction velocities and right eye dilation velocity at 1 lagged measure, and bilateral constriction velocities and right eye dilation velocity and percent

TABLE 5. Measures of Pupil Reactivity and Predicting Elevated Intracranial Pressure (≥ 20 mm Hg)

	Right	Left
Measurement	AUROC (95% CI)	AUROC (95% CI)
Neurologic Pupil index	0.70 (0.66–0.73)	0.66 (0.62–0.69)
Change pupil size (%)	0.70 (0.66–0.75)	0.67 (0.63–0.71)
Constriction velocity (mm/s)	0.72 (0.68–0.75)	0.71 (0.67–0.74)
Maximum constriction velocity (mm/s)	0.71 (0.68–0.75)	0.71 (0.67–0.74)
Latency (s)	0.61 (0.57–0.66)	0.55 (0.51–0.60)
Dilation velocity (mm/s)	0.68 (0.64–0.72)	0.64 (0.60–0.68)

AUROC = area under the receiver operating curve.

change pupil size at 3 and 6 lagged measures (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/PCC/B254; Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/PCC/B255; and Supplemental Table 3, Supplemental Digital Content 3, http://links.lww.com/PCC/B256). These measures were done in an attempt to form a predictive model for abnormal pupillary measurements preceding an increase in ICP, as was shown in two subjects by Chen et al (9). However, this correlation could also represent a continuum of an inverse correlation between ICP and NPi across time rather than being predictive. Therefore, we analyzed patients who initially had a normal NPi and normal ICP and who subsequently had at least one ICP elevation during the study period. We found no consistent predictive pattern for abnormal pupillary measurements preceding increases in ICP. This analysis was limited by the number of patients, number of measurements preceding the first ICP elevation, and gaps in the time within which measurements were taken.

This study is a prospective cohort study, which is one of its strengths. Although the number of enrolled subjects was limited, a large number of measurements were taken and analyzed. The study also confirms, what has previously been noted in adult patients, that pupillary reactivity is affected by increases in ICP.

Although the median time between pupillary measurements was 1 hour, some patients had larger time gap between data points, likely related to clinical demand of the patient's condition and the bedside staff's ability to collect data congruently with providing clinical care. To this same point, data was collected by bedside nursing staff who were instructed on data collection methods at enrollment and provided an instruction sheet for reference, but it was not possible to regulate or guarantee consistency of data collection in real-time. Not every time point had values for each variable recorded. Also, the NPi score is a proprietary algorithm developed by NeurOptics and patients less than 18 years old were not included in the cohort used to generate the scoring system. Although many studies extrapolate adult data to pediatrics, this is a limitation of using this score in a pediatric population.

Additionally, the standard bedside management of EVDs in our unit is to leave the EVD open to drain and transduce the ICP hourly. As both ICP and pupillary measurements are dynamic, there is the potential that elevations of ICP or abnormal measures of pupillary reactivity were missed between assessments. Also, by having the EVD open to drain except for at times of ICP measurement, elevations of ICP are being treated by drainage of cerebrospinal fluid. We used a threshold of 20 mm Hg to define elevated ICP; however, the Guidelines for the Management of Severe Traumatic Brain Injury, Third Edition, also state that this threshold may be too high for younger patients (12). Therefore, using a threshold of 20 mm Hg for ICP elevation across all age groups could be a limitation of our study.

Last, we were unable to account for the effects of infusions (narcotics, benzodiazepines, barbiturates, and paralytics) or other patient medications on pupillary reactivity. Previous studies have shown correlation between pupil size and narcotic dose (5), and transient changes in constriction velocity and pupil size related to intermittent doses of narcotics and benzodiazepines (17). However, Hou et al (19) showed oral diazepam did not affect pupil diameter or light reflex. Additionally, neuromuscular blockade has been shown to not affect pupillary light reflex in anesthetized patients (20).

Moving forward, larger prospective studies are needed to validate these findings and would provide an opportunity to further evaluate if changes in pupillary reactivity precede increases in ICP.

CONCLUSIONS

Measures of pupillary reactivity inversely correlate with ICP. Pupillometry is a useful adjunct to supplement the bedside provider's examination of a patient in whom there is concern for ICP elevation. However, it remains to be elucidated if changes in pupillary reactivity precede increase in ICP and if so by what time period.

ACKNOWLEDGMENTS

We would like to acknowledge Dr. Rajit K. Basu of Emory University and Children's Healthcare of Atlanta for his contribution to the revisions of this article.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/pccmjournal).

The authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: afreeman1@augusta.edu

REFERENCES

1. Lieberman JD, Pasquale MD, Garcia R, et al: Use of admission Glasgow Coma Score, pupil size, and pupil reactivity to determine

outcome for trauma patients. *J Trauma* 2003; 55:437–442; discussion 442–443

2. Kuo JR, Lo CJ, Lu CL, et al: Prognostic predictors of outcome in an operative series in traumatic brain injury patients. *J Formos Med Assoc* 2011; 110:258–264
3. Olson DM, Stutzman S, Saju C, et al: Interrater reliability of pupillary assessments. *Neurocrit Care* 2016; 24:251–257
4. Meeker M, Du R, Bacchetti P, et al: Pupil examination: Validity and clinical utility of an automated pupillometer. *J Neurosci Nurs* 2005; 37:34–40
5. Couret D, Boumaza D, Grisotto C, et al: Reliability of standard pupillometry practice in neurocritical care: An observational, double-blinded study. *Crit Care* 2016; 20:99
6. Zafar SF, Suarez JI: Automated pupillometer for monitoring the critically ill patient: A critical appraisal. *J Crit Care* 2014; 29:599–603
7. Yan S, Tu Z, Lu W, et al: Clinical utility of an automated pupillometer for assessing and monitoring recipients of liver transplantation. *Liver Transpl* 2009; 15:1718–1727
8. Bower MM, Sweidan AJ, Xu JC, et al: Quantitative pupillometry in the intensive care unit. *J Intensive Care Med* 2019 Oct 10. [online ahead of print]
9. Chen JW, Gombart ZJ, Rogers S, et al: Pupillary reactivity as an early indicator of increased intracranial pressure: The introduction of the Neurological Pupil index. *Surg Neurol Int* 2011; 2:82
10. Park JG, Moon CT, Park DS, et al: Clinical utility of an automated pupillometer in patients with acute brain lesion. *J Korean Neurosurg Soc* 2015; 58:363–367
11. Centers for Disease Control and Prevention: Report to Congress: The Management of Traumatic Brain Injury in Children, National Center for Injury Prevention and Control; Division of Unintentional Injury Prevention, Atlanta, GA, 2018
12. Kochanek PM, Tasker RC, Carney N, et al: Guidelines for the management of pediatric severe traumatic brain injury, third edition: Update of the brain trauma foundation guidelines. *Pediatr Crit Care Med* 2019; 20:S1–S82
13. Hamlett A, Ryan L, Wolfinger R: On the Use of PROC MIXED to Estimate Correlation in the Presence of Repeated Measures. SUGI 29. Montreal, QC, Canada, SAS Institute, 2004
14. Dongsheng YDJ: A Unified Approach to Measuring the Effect Size Between Two Groups Using SAS®. Orlando, FL, SASGF 2012, 2012
15. Jahns FP, Miroz JP, Messerer M, et al: Quantitative pupillometry for the monitoring of intracranial hypertension in patients with severe traumatic brain injury. *Crit Care* 2019; 23:155
16. McNett M, Moran C, Janki C, et al: Correlations between hourly pupillometer readings and intracranial pressure values. *J Neurosci Nurs* 2017; 49:229–234
17. Taylor WR, Chen JW, Meltzer H, et al: Quantitative pupillometry, a new technology: Normative data and preliminary observations in patients with acute head injury. Technical note. *J Neurosurg* 2003; 98:205–213
18. Boev AN, Fountas KN, Karampelas I, et al: Quantitative pupillometry: Normative data in healthy pediatric volunteers. *J Neurosurg* 2005; 103:496–500
19. Hou RH, Samuels ER, Langley RW, et al: Arousal and the pupil: Why diazepam-induced sedation is not accompanied by miosis. *Psychopharmacology (Berl)* 2007; 195:41–59
20. Gray AT, Krejci ST, Larson MD: Neuromuscular blocking drugs do not alter the pupillary light reflex of anesthetized humans. *Arch Neurol* 1997; 54:579–584