Correlations Between Hourly Pupillometer Readings and Intracranial Pressure Values

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ABSTRACT

Introduction: Automated pupillometry is emerging as a mainstay in neurocritical care primarily because it overcomes limitations of manual pupillary examinations. Although several recent studies show improved assessment accuracy with a pupillometer, few investigate clinical use, specifically how well parameters correlate with multimodality monitoring and outcomes. The primary aim of this study was to examine correlations between serial pupillometer readings and intracranial pressure (ICP) values among neurocritically ill patients. **Design:** Prospective cohort, repeated measures. **Sample:** The study sample was composed of adult patients with neurological injury who were admitted to intensive care unit, requiring hourly neurological assessment and pupillary checks within a level I trauma, urban, academic medical center. **Procedures:** Hourly pupillometer readings and corresponding ICP values were consecutively recorded for 72 hours after intensive care unit admission. **Results:** Serial assessments resulted in more than 2100 pupillometer readings from 76 subjects. Mean age of the study sample was 55.4 years, with a mean Glasgow Coma Scale score of 8.9. The mean pupillometer values for the enrolled subjects included left constriction velocity of 1.22, left neurological pupil index of 4.21, left pupil size of 2.69, right constriction velocity of 1.18, right neurological pupil index of 4.18, and right pupil size of 2.57. The mean ICP of the study sample was 12, with mean cerebral perfusion pressure of 77. Pupillometer values significantly correlated with ICP values in bivariate ($P < .001$, $r = 0.13–0.23$) and multivariate regression models ($F(6) = 17.63$, $P < .001$). **Conclusions:** Automated pupillometry in neurocritical care is a valuable adjunct to traditional invasive monitoring. Integration of routine pupillometer assessments not only improves accuracy of examinations but also correlates with ICP values.

Keywords: neurologic injury, pupil assessment, pupillometer

The pupillary examination is a key component of serial neurological assessments in neurocritical care settings, and research indicates its usefulness as a prognostic tool.[1–8] The pupilloconstrictor response is a parasympathetic reflex caused by stimulation of the third cranial nerve. The third cranial nerve is adjacent to the medial temporal lobe and the midbrain third nucleus; therefore, damage to these areas of the brain controlling consciousness can disrupt third cranial nerve pathways, resulting in a decreased pupillary response, manifested as pupillary dilation.[1,9] Whereas constriction of pupils is controlled by the parasympathetic response, the normal pupillary dilation is due to sympathetic response, resulting in numerous different abnormal responses to light in the presence of neurological injury.[10] Thus, serial pupil assessments are a critical component to any neurological examination.

Despite the importance of pupillary assessments, there are significant limitations to manual pupillary examinations.[11,12] Reliability and validity of manual pupillary examinations are poor, and previous prognostic findings of pupil response are limited to correlations solely between unresponsive pupils and negative outcome.[2,8,11,12] Emerging evidence suggests potential benefits of automated pupillometry, specifically improved reliability and accuracy of assessments.[13–16] The next logical step in determining clinical use of the pupillometer is to establish correlations with invasive multimodality monitoring

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techniques. Therefore, the purpose of this study was to examine associations between hourly pupillometer readings and intracranial pressure (ICP) values among a cohort of neurocritically ill patients.

Background

Introduction of the pupillometer in neurocritical care addresses the inherent research and clinical limitations of a manual pupil examination. The pupillometer provides an objective measure of pupil size (PS) and velocity of pupillary constriction to light.[14] The device records serial readings of each eye on every patient, allowing for visualization of trends and subtle changes in pupillary response that may be indicative of acute neurological changes. Preliminary pupillometer research suggests a correlation between readings and neurological changes. Taylor et al[15] compared quantitative pupillometry results between a sample of 300 healthy volunteers and 26 patients with head injury. Findings indicate slower constriction velocities (CVs) in the head-injured group compared with healthy controls. Velocities were especially decreased in head-injured patients who experienced sustained increases in ICP (defined as ICP > 20 mm Hg for longer than 15 minutes) and a 3-mm midline shift on computed axial tomography examination. Asymmetry of pupillary size greater than 0.5 mm Hg was rarely seen in the healthy volunteers and only observed in the head-injured group when ICP values were greater than 30 mm Hg. When comparing nurses' pupillary examinations with those performed using the pupillometer, pupillary asymmetry was present 81% of the time in the head-injured patients according to the pupillometer but was only detected by nurses' assessments 22% of the time.[16]

More recently, use of a neurological pupil index (NPi) has been introduced.[17] The NPi is created using an algorithm that incorporates quantitative pupillometer values and compares the reading against the mean distribution of scores obtained from healthy subjects. Values are standardized into z scores and combined to create an NPi score that ranges from 0 to 5.[17] An NPi score greater than 3 indicates normal pupillary reactivity, whereas a score less than 3 reflects an abnormal pupillary light reflex. Chen et al[17] examined NPi in 134 patients from 8 different intensive care units (ICUs) using a pupillometer. Patients were monitored continuously for 72 hours, and pupillary responses were recorded every 30 minutes, along with ICP values. Subjects with lower NPi scores experienced higher increases in ICP when compared with subjects with normal NPi scores. When classifying subjects into groups based on normal (3–5) versus abnormal (<3) NPi, there were statistically significant differences between ICP values for the 2 groups (ICP mean for the group with normal NPi, 19.6 mm Hg; ICP mean for the group with abnormal NPi, 30.5 mm Hg; $P = .0014$). Finally, when examining a separate subgroup of the study with nonreactive pupils, the mean ICP value was 33.8 mm Hg. In these subjects, the first observance of pupillary abnormality was documented, on average, 15.9 hours before the corresponding peak in ICP (range, 0–60). Findings suggest that use of the NPi and pupillometer readings may be predictive of impending ICP spikes, yet no studies have examined correlations between pupillometer and ICP values. Therefore, the aim of this study was to examine associations between hourly pupillometer readings and ICP values among a cohort of neurocritically ill patients.

Findings from this study establish hourly correlations between serial pupillometer values and ICP.

Methods

Patients and Procedures

This study was a prospective cohort, repeated-measures study. Subjects included patients older than 18 years who were admitted to the ICU with acute neurological injury, requiring hourly neurological and pupillary assessments from February 2016 to September 2016. Diagnosis types included traumatic brain injury, closed head injury, cerebral contusion, concussion, subdural hematoma (SDH), epidural hematoma (EDH), intracranial hemorrhage, intracranial hematoma, diffuse axonal injury, intraparenchymal hemorrhage/bleed, subarachnoid hemorrhage (SAH), aneurysmal SAH, and acute ischemic stroke. Exclusion criteria were facial or ocular injury preventing pupillary examination and subjects who received pupillary examinations without a pupillometer. A power analysis indicated that 600 paired readings were sufficient to detect a modest correlation with a 2-tailed α at 5% and β of 0.20 (80% power). The study took place within a large, urban, academic public health system that has designation as a level I trauma center and comprehensive stroke center and has American Nurses Credentialing Center Magnet designation. The study was reviewed by the institutional review board (IRB) and granted a waiver for written consent because all data were observational and gathered as standard of care.

Baseline clinical variables were abstracted prospectively by trained study staff on subjects meeting

eligibility criteria upon admission to the ICU. Variables were selected to describe the study sample and determine distributions of pupillometer values across categories. These baseline variables included patient age, gender (male/female), ethnicity (Hispanic/non-Hispanic, white, African American, Asian, Middle Eastern, other), primary diagnosis (traumatic brain injury, closed head injury, cerebral contusion, concussion, SDH, EDH, intracranial hemorrhage, intracranial hematoma, diffuse axonal injury, intraparenchymal hemorrhage/bleed, SAH, aneurysmal SAH, acute ischemic stroke), mechanism of injury (fall, motor vehicle accident, struck pedestrian or object), presence of ocular or facial injury (yes/no), and admission Glasgow Coma Scale (GCS) score (total GCS on admission to ICU). Daily clinical variables were documented hourly as standard of care and abstracted daily by study staff for the first 72 hours after ICU admission. Variables were selected to meet the study aims and determine relationships between pupillometer values and traditional invasive monitoring approaches. These variables included pupillometer-obtained PS (millimeters), CV (millimeters per second), NPi (NPi-100; NeurOptics), GCS scores (hourly total score recorded as standard of care), ICP (Integra Camino; hourly value recorded as standard of care), and cerebral perfusion pressure (CPP) (hourly value recorded as standard of care). Upon discharge, ICU and hospital length of stay, mortality (alive/dead), and discharge disposition (home/skilled nursing facility/inpatient rehabilitation/died) were recorded by study staff.

Data Analysis

Study data were recorded and stored in the Research Electronic Data Capture system.[18] Descriptive statistics were performed and included means, standard deviations, medians, and ranges for continuous variables and frequencies and percents for categorical variables. Bivariate analyses included Spearman rank correlation for nonparametric data and Pearson's r for normally distributed parametric data. Multivariate regression analyses were used to identify predictors of ICP based on serial pupillometer values within the study population.

Results

There were more than 2100 serial pupillometer readings from 76 subjects paired with simultaneous hourly ICP monitoring (2107 readings for the left eye and 2175 for the right eye). Variations in the total number of readings for each eye were due to occasional intentional dilatation of the pupils for ophthalmic examinations, which prevented recording of pupillometry data on some subjects. Data for these missing values were coded as such and not included in the final analyses. Demographic data of the study sample are displayed in Table 1. The mean age was 55.4 years, and mean GCS on admission to ICU was 8.9. Most patients has sustained EDHs (n = 24), aneurysmal SAH (n = 19), or intracerebral hemorrhage (n = 15). Other diagnoses included acute ischemic stroke (n = 10), nonaneurysmal SAH (n = 6), and SDHs (n = 2). Approximately half of the study sample (n = 43) were patients with traumatic brain injury, with the most frequent mechanism of injury being caused by falls (n = 22) and motor vehicle accidents (n = 13). Patients were discharged to inpatient rehabilitation (n = 30), skilled nursing or long-term care facilities (n = 20), or home (n = 12). An additional 14 subjects died before hospital discharge.

Mean values for specific pupillometer indices for the first 72 hours of ICU admission are included in Table 1. Mean values for CV were 1.2 mm/s, mean NPi was 4.2, and mean PSs were 2.57 and 2.69 (right and left, respectively). Scatterplots for CVs and NPi values against ICP values are displayed in Figure 1 (Supplemental Digital Content 1, available at http://links.lww.com/JNN/A89). Higher NPi values that reflect reference limits (>3) were found in the upper left corner (Fig 1A), consistent with the lower distribution of scores for ICP values among the study sample. Similarly, the plots for pupillary CVs were clustered in the lower left corner (Fig 1C), indicating brisk (normal) CVs when ICP values were within reference limits.

Because distributions of pupillometer data were not normally distributed, nonparametric Spearman's ρ analyses were used for bivariate correlations. Correlational analysis indicates an inverse statistically significant relationship between CV, NPi, and ICP values. Pupil size was positively correlated with ICP. Table 2 displays the correlation coefficients and significance level for all pupillometer values with ICP and with CPP.

A multivariate regression model was created using CVs, NPi, and PS for both the right and left eyes to determine the strongest predictors of ICP. Overall, the model was significant for predicting ICP ($R^2 = 0.14$, $F(6) = 17.63$, $P < .001$). When examining the individual values for ability to predict ICP, both the right and left NPi were strongest predictors ($\beta = 3.64$, $t = 5.96$, $P < .001$; $\beta = 3.40$, $t = 6.120$, $P < .001$, respectively). Constriction velocities for both the right and left eyes were also significant predictors in the model (right CV, $\beta = 3.26$, $t = 4.17$, $P < .001$; left CV, $\beta = 2.04$, $t = 2.65$, $P < .005$). Pupillary size was a predictor, but level of statistical significance

TABLE 1. Summary of Patient Characteristics

Characteristic (*n*)	Statistic/ Category
Age (76), mean (SD), y	55.42 (16.72)
Range	23-92
Median	54.50
Admission GCS scores (76), mean (SD)	8.93 (4.25)
Range	3–15
Median	9.00
ICU length of stay (76), mean (SD)	11.95 (9.79)
Range	1–51
Median	9.00
Hospital length of stay (76), mean (SD)	14.39 (10.90)
Range	1–51
Median	11.00
Pupillometer value	
LCV (2107), mean (SD)	1.22 (0.95)
Range	0.00–6.51
Median	1.45
LNPI (2107), mean (SD)	4.21 (0.76)
Range	0.49–4.90
Median	4.40
LSIZE (2107), mean (SD)	2.69 (0.89)
Range	0.59–7.98
Median	2.74
RCV (2175), mean (SD)	1.18 (0.91)
Range	0.00–13.00
Median	1.21
RNPI (2175), mean (SD)	4.18 (0.97)
Range	1.06–4.90
Median	4.40
RSIZE (2175), mean (SD)	2.57 (0.99)
Range	0.10–6.16
Median	2.82
CPP (1560), mean (SD)	76.99 (16.24)
Range	0–157
Median	69.50
ICP (1560), mean (SD)	11.64 (6.02)
Range	0–46
Median	9.00

Note. CPP = cerebral perfusion pressure; GCS = Glasgow Coma Scale; ICP = intracranial pressure; ICU = intensive care unit; LCV = left constriction velocity; LNPI = left neurological pupil index; LSIZE = left size; RCV = right constriction velocity; RNPI = right neurological pupil index; RSIZE = right size.

and values were not as strong as those for pupillometer values (right size, $\beta = 1.35$, $t = 1.90$, $P = .05$; left size, $\beta = 1.03$, $t = 1.58$, $P = .12$).

Discussion

Findings from this study are the first to establish hourly correlations between serial pupillometer values and patient ICP. Values for both CVs and NPi were significantly correlated with ICP values, supporting validity in both values. Both had a negative correlation with ICP, further supporting recommended trends and interpretation of those values to guide clinical care. Normal values for NPi are considered those greater than 3 in the clinical setting; thus, because values displayed in the scatterplots were within this range, ICP values also tended to be within reference limits. Similarly, CV should be brisk, although there are no set recommended parameters to establish reference limits. As evidenced in the scatterplots, faster CVs were also associated with ICP values within reference limits.

Bivariate correlations were significant for both ICP and CPP, with stronger values and more significant correlations for ICP. This supports earlier findings from Chen et al,[17] which suggest changes in pupillometer values in the presence of increased ICP, when compared with healthy controls with no evidence of neurological injury. To date, no other studies have reported on serial pupillometer readings and concurrent ICP values. Our study is the first to establish baseline correlations between these 2 important parameters. Interestingly, correlations between left eye size and CPP were not significant in our study. Future research investigating injury type (lesion or diffuse), as well as specific injury location, may provide additional insight into the exact interaction between specific pupillometer indices and cerebral perfusion. Future research efforts should therefore continue to investigate both ICP and CPP as important correlates with pupillary response.

Findings from the multivariate model in our study lend further support to the notion of an association between serial pupillometer values and ICP. Pupillometer NPi and CV were strong predictors of ICP in the model. Interestingly, PS did not emerge as a strong predictor in the model, particularly when compared with NPi and CV. Numerous previous studies before integration of the pupillometer have reported PS as a powerful predictor of outcome and neurological injury.[2–8] Specifically, when pupil assessment (size, response to light) is combined with patient age and GCS scores in previous studies, accurate outcome prediction is as high as 78% to 84%.[2,3,8] However, pupil response in these previous studies was only recorded as absent or present, and study findings were based on the presence of dilated or nonresponsive pupils as predictors of poor outcome. With the introduction of the pupillometer, practitioners and clinical researchers now have the ability to consider

TABLE 2. Correlations for Pupillometer Values and ICP

	ICP		CPP	
	Correlation Coefficient (*n*)	*P*	Correlation Coefficient (*n*)	*P*
Pupil NPI				
Right eye	−0.126 (670)	.001	−0.238 (556)	.000
Left eye	−0.225 (677)	.000	−0.083 (563)	.055
Pupil constriction velocity				
Right eye	−0.195 (654)	.000	−0.067 (540)	.119
Left eye	−0.199 (676)	.000	−0.073 (562)	.091
Pupil size				
Right eye	0.166 (674)	.000	0.281 (560)	.000
Left eye	0.133 (677)	.001	0.068 (563)	.116

Note. CPP = cerebral perfusion pressure; ICP = intracranial pressure.

more than only PS (or the absence of a pupil reaction) when performing a neurological examination. This advancement is important not only for clinical decision making but also for future research on prognostication and correlations with other multimodality monitoring measures.

The main limitation to this study is the use of a single-site design, which limits generalizability of findings. A second limitation is that the data were not gathered on the presence of narcotics and sedatives, which may impact pupillary response and pupillometer readings,[19,20] nor were findings separated by brain injury type (ie, mass lesion, diffuse injury), which can also affect readings.[21] Finally, data were only gathered for the first 72 hours and thus would not capture herniation or neurological deterioration that may have occurred after the study period had ended. Nevertheless, study findings are an important starting point in establishing correlations between pupillometer values and invasive monitoring values in neurocritical care. Findings may also be used to determine optimal ranges of CVs and implications for clinical care. Additional research is currently underway to examine trends in specific pupillometer values in the presence of intracranial hypertension and to create a national registry of pupillometer values to further delineate optimal parameters. Future research efforts will substantiate preliminary findings using multisite, national data sets and may ultimately be used to validate and establish specific parameters to guide clinical care and correlate with other methods of traditional invasive monitoring.

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Figure 1: Scatterplots for mean pupillometer and ICP values

NPI values and ICP

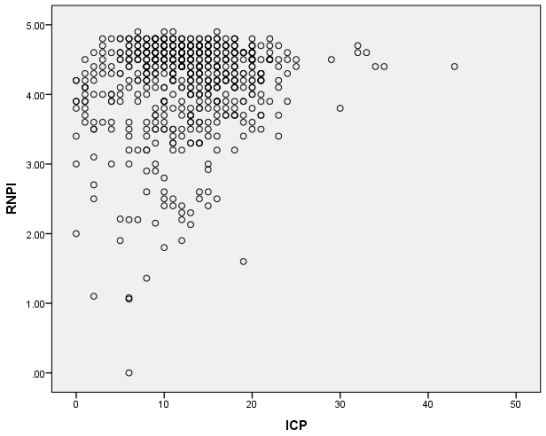

Figure 1a: Distribution of right eye NPi and ICP.

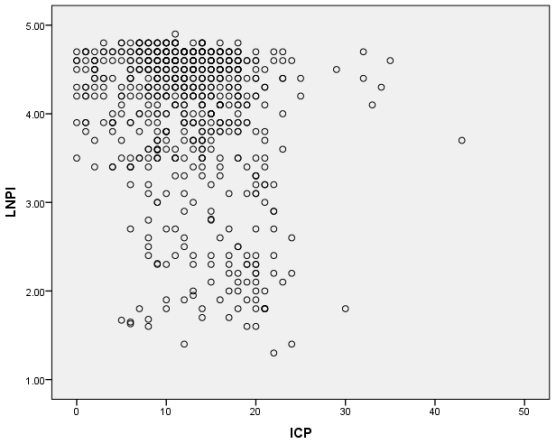

Figure 1b: Distribution of left eye NPi and ICP.

CV Values and ICP

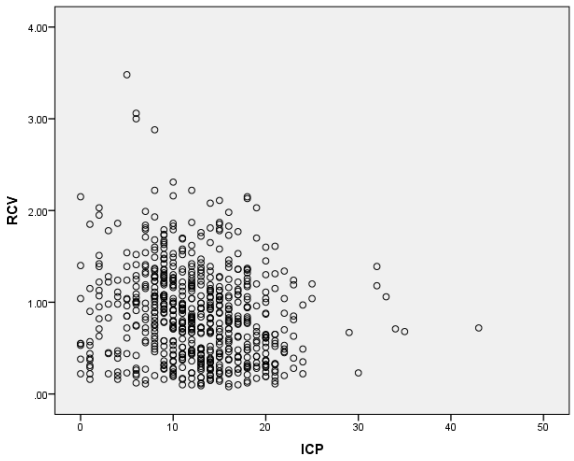

Figure 1c: Distribution of right eye constriction velocities and ICP.

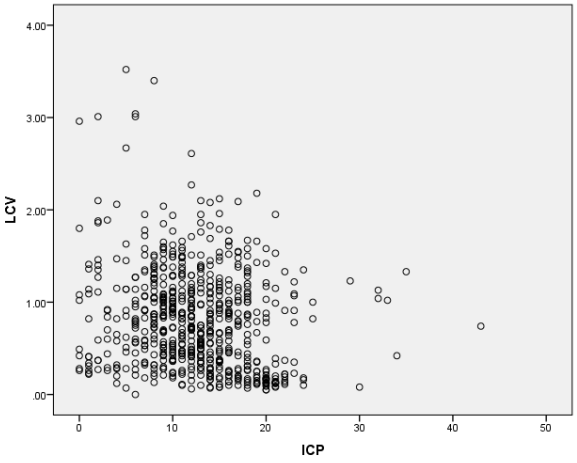

Figure 1d: Distribution of left eye constriction velocities a