Pupillometry Trends in the Setting of Increased Intracranial Pressure

Molly McNett, Cristina Moran, Dawnetta Grimm, Anastasia Gianakis

ABSTRACT

Serial pupil examinations remain a mainstay of neurological assessments performed by neuroscience nurses. Integration of pupillometer technology has increased in recent years, because of its ability to address limitations of manual examinations and to evaluate trended data over time. Preliminary research has linked pupillometer values to intracranial pressure (ICP) values, but data on pupillary changes in the setting of increased ICP remain sparse. The purpose of this study was to determine trends in pupillometer values in the setting of increased ICP among critically ill patients with neurological injury. This is a secondary analysis of data where serial pupillometer and ICP readings were recorded hourly on adult patients with neurological injury necessitating critical care management. More than 2100 paired serial pupillometer and ICP readings were obtained from 76 subjects, with a total of 2107 paired readings for the left eye and 2175 for the right eye. There were statistically significant differences in pupillometry values in the setting of increased ICP. Time series analysis indicates that spikes in ICP values resulted in corresponding variations in pupillometer values. Use of automated pupillometry remains a value adjunct to traditional invasive therapies. Evaluation of trended data may provide insight into ICP elevations in the absence of invasive monitoring and warrants additional research.

Keywords: assessment, brain injury, cranial nerves, intracranial pressure, pupil, pupillometer

Integration of pupillometer technology has increased in recent years, particularly in neurocritical care settings.[1–4] The pupillary assessment is a core component of neurological assessment, yet several studies have demonstrated substantial variability in pupillary assessment techniques, resulting in poor reliability and validity of measurements across provider groups.[5–8] Use of pupillometers in neurocritical care settings addresses limitations of the manual examination and provides standardized, trended values to aid in critical decision making.[8,9] Serial pupillometer values have been shown to correlate with intracranial pressure (ICP)[4,10,11] and signs of transtentorial brain herniation[12] and may be an important predictor of outcome after cardiac arrest.[13] Yet, few studies have investigated hourly trends of pupillometer values in the neurocritical care setting to determine temporal variations and congruence with readings from invasive ICP monitoring modalities. Therefore, the purpose of this study was to evaluate serial pupillometer values in the setting of increased ICP among a cohort of critically ill patients with neurological injury.

Questions or comments about this article may be directed to Molly McNett, PhD RN CNRN FNCS, at mmcnett@metrohealth.org. She is Director, Nursing Research and Evidence Based Practice, The MetroHealth System, Cleveland, OH.

Cristina Moran, MSN RN CCRN, is Clinical Nurse, Surgical Intensive Care Unit, The MetroHealth System, Cleveland, OH.

Dawnetta Grimm, MSN CCNS RN, is Clinical Nurse Specialist, Trauma/Critical Care/Burns, The MetroHealth System, Cleveland, OH.

Anastasia Gianakis, MSN RN CCRN, is Nurse Manager, Surgical Trauma Intensive Care Unit, The MetroHealth System, Cleveland, OH.

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Methods

This study is a planned secondary analysis of a prospective cohort, repeated-measures study examining correlations between ICP values and pupillometer readings within the first 72 hours of admission to an intensive care unit (ICU). Institutional review board approval was granted as a study of not greater than minimal risk. Inclusion criteria for subjects were adult patients (older than 18 years) with neurological injury necessitating admission to the ICU of an urban, academic, level I trauma and comprehensive stroke center. Exclusion criteria were those subjects with facial or ocular damage that would prevent serial pupillometer examinations. Serial pupillometer readings were recorded hourly on all patients as standard of care and documented in the electronic medical record. Readings included hourly constriction velocities (CV), Neurological Pupil index (NPi), and pupil size obtained for both the right and left eyes by the pupillometer. Data were also recorded hourly on

subjects who had ICP and cerebral perfusion pressure monitoring in situ as standard of care. Trained study staff recorded daily prospective data from patient rounds and/or the electronic medical record on patient clinical variables for the first 72 hours after ICU admission, which included age, sex, ethnicity, primary diagnosis, admission Glasgow Coma Scale (GCS) score, ICU and hospital length of stay (LOS), and Glasgow Outcome Scale (GOS) score at discharge.

Data were recorded and stored in Research Electronic Data Capture system.[14] Data were analyzed using the SPSS, version 20.0. Descriptive statistics, including mean, standard deviation, medians, and ranges for continuous variables and frequencies and percentages for categorical variables, were performed to describe the study sample and examine differences among variables based on ICP values. Serial, paired values for pupillometer and ICP readings were dichotomized by those recorded with ICP less than 15 mm Hg and those with ICP greater than or equal to 15 mm Hg. Student *t* tests were performed to compare mean pupillometer readings based on dichotomized ICP values. Time series analyses were conducted to graphically display trends of pooled mean paired values for pupillometer and ICP readings during the first 72 hours of ICU admission.

Pupillary changes were slight and likely would not have been detected with manual examination.

Results

More than 2100 paired serial pupillometer and ICP readings were obtained from 76 subjects, with a total of 2107 paired readings for the left eye and 2175 for the right eye. A summary of descriptive data is provided in Table 1. Most of the study sample were male (61%). Admission diagnoses included epidural hematoma (32%), aneurysmal subarachnoid hemorrhage (25%), intracerebral hemorrhage (20%), acute ischemic stroke (13%), nonaneurysmal subarachnoid hemorrhage (8%), and subdural hematoma (3%). Fifty-seven percent of the subjects were traumatic brain injury patients. Subjects who experienced increased ICP were generally younger (mean age: increased ICP, 52.3; normal ICP, 56.8), presented with lower mean GCS scores on admission (mean GCS: increased ICP, 4.8; normal ICP, 7.5), had

TABLE 1. Demographics

Characteristic	Statistic	All	ICP < 15	ICP ≥ 15	*P*
Age, y	Mean	55.4	56.8	52.3	.60
	Median	54.5	55.5	51.5	
	SD	16.7	12.9	18.0	
GCS admit	Mean	8.9	7.5	4.8	.11
	Median	9.0	8.0	3.0	
	SD	4.2	3.4	2.7	
ICU LOS	Mean	11.9	19.0	18.5	.93
	Median	9.0	14.5	20.0	
	SD	9.7	12.4	10.1	
Hospital LOS	Mean	14.3	23.1	19.2	.50
	Median	11.0	19.0	20.0	
	SD	9.7	13.6	10.1	
GOS score at discharge	Mean	3.7	2.6	2.0	.36
	Median	4.0	3.0	2.0	
	SD	1.4	1.3	1.4	
ICP	Mean	11.6	8.8	18.9	.41
	Median	11.0	8.0	18.0	
	SD	6.0	3.7	4.6	

Abbreviations: GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; ICP, intracranial pressure; ICU, intensive care unit; LOS, length of stay.

shorter hospital LOS (mean LOS: increased ICP, 19.1; normal ICP, 21.2), and had lower GOS scores at discharge (mean GOS: increased ICP, 2.0; normal ICP, 2.6) than those subjects who did not experience increased ICP. However, these differences did not reach statistical significance.

Table 2 displays the mean pupillometer values in the setting of increased ICP and normal ICP. Student *t* test analysis indicates statistically significant differences for pupillometer values based on ICP for left CV, left NPi, and left and right pupil size. In the setting of increased ICP, there were lower CVs for both the right and left eyes (left: 0.6, 0.8, $P < .000$; right: 0.7, 0.8, $P = .12$), as well as decreased left pupillary NPi (4.1, 3.8, $P < .000$) and size (2.5, 2.3, $P < .000$). Values for right eye NPi and size were comparable regardless of ICP values.

Time series analyses indicate that spikes in ICP values resulted in corresponding variations in paired pupillometer values for CV and NPi, but not necessarily for pupil size (Supplemental Digital Content 1, available at http://links.lww.com/JNN/A146). Temporal variations during the first 72 hours in paired values are displayed on the x-axis. In most instances, pupil size remained stable and within normal limits (mean, 2 mm). The Supplemental Digital Content figures display drops in CV and NPi values immediately after ICP spikes, along with slight increases in pupillary size during the first 72 hours. These changes are more profound for left pupillary reactions (Supplemental Digital Content 1, available at http://links.lww.com/JNN/A146), which correspond with the statistically significant reactions found with *t* test analyses. Supplemental Digital Content 2 (available at http://links.lww.com/JNN/A147) displays changes in pupillometer values when ICP is within normal limits. In these figures, there is a natural variation in values during the first 72 hours, all of which remain within normal limits.

TABLE 2. Hourly Pupillometer Values

Value (n)	Mean (SD)	*t* (*df*)	*P*
LCV		−4.3 (617)	.00
ICP < 15 (615)	0.8 (0.5)		
ICP ≥ 15 (311)	0.6 (0.5)		
LNPI		−6.9 (475)	.00
ICP < 15 (615)	4.2 (0.6)		
ICP ≥ 15 (311)	3.8 (0.9)		
L Size		4.0 (611)	.00
ICP < 15 (615)	2.3 (0.6)		
ICP ≥ 15 (311)	2.5 (0.6)		
RCV		−1.5 (709)	.12
ICP < 15 (615)	0.8 (0.5)		
ICP ≥ 15 (311)	0.7 (0.5)		
RNPI		0.8 (821)	.41
ICP < 15 (615)	4.2 (0.6)		
ICP ≥ 15 (311)	4.2 (0.4)		
R Size		−5.0 (831)	.00
ICP < 15 (615)	2.2 (0.5)		
ICP ≥ 15 (311)	2.3 (0.4)		
ICP		41.0 (671)	.00
ICP < 15 (615)	8.8 (3.7)		
ICP ≥ 15 (311)	18.9 (4.5)		

Abbreviations: ICP, intracranial pressure; L, left; LCV, left constriction velocity; LNPI, left neurological pupil index; R, right; RCV, right constriction velocity; RNPI, right neurological pupil index.

Discussion

Study findings contribute to the growing body of literature demonstrating use of automated pupillometry in detecting subtle changes in pupillary examinations that may occur with increases in ICP. Our original study demonstrated correlations between serial pupillometer values and ICP.[10] This is consistent with a recent study from Park et al[11] that evaluated pupillary light reflex (PLR) in the presence of idiopathic intracranial hypertension (IIH). The researchers evaluated and compared the PLR of study subjects under rod-, cone-, and melanopsin-mediated conditions. Subjects with IIH exhibited reductions in PLR under each of these mediation pathways. Overall, the study demonstrated a mean reduction in PLR in patients with IIH when compared with visually healthy subjects without evidence of neurologic or ophthalmic disease. Thus, there is increasing evidence that pupillometry readings can be indicative of changes in ICP.

A recent study by Papangelou et al[12] builds upon this evidence and examined pupillometer values in the setting of transtentorial brain herniation. In a case study of 3 patients, serial pupillometer data were compared with clinical observations, diagnosis, and treatment of transtentorial brain herniation. Findings indicate differences between right/left pupillometry readings hours before herniation episodes, with significant decreases in NPi at the time of herniation. Slowing of CV and increased latency were also observed. When pupillary response on clinical examination was reported to be fixed and dilated, there were occasions when the pupillometer recorded some change in size. Although this case series was small, it does demonstrate the value of trending automated pupillary data for the early identification of patients at risk of herniation and the ability of automated measurements to detect slight changes not detected with manual examinations.

Similarly, the pupillary changes reported in our study were slight and likely would not have been

detected with manual examinations. Solari et al[13] also reported slight differences in pupillary CV and size when comparing survivors with nonsurvivors after cardiac arrest. Pooled values in our study for CV and size were comparable with those reported after cardiac arrest, which ranged from 2.1 to 2.3 mm for pupil size and 0.6 to 0.7 mm/s for CV among both survivors and nonsurvivors.[13] Subtle changes measuring 0.1 to 0.2 mm/s on a pupil that is already small (2–3 mm) may not be detected with manual examinations, but trends in these values may hold clinical significance and relevance to neurological changes. There continues to be benefit for automated pupillometry in the setting of neurological injury, particularly when pupil sizes may be small and CV may be subtle, and because of the ability to trend these values over time.

A national trial establishing normative, trended values for pupillometry in the setting of neurological injury (END-Panic trial)[15] further suggests CV, size, and NPi be considered separately, because their values are not consistently correlated and can vary from predetermined thresholds because of sex, age, and diagnosis.[16] More than 30% of pupillometry readings from 1617 subjects revealed that often an abnormal NPi was found with a normal CV, with the converse also holding true (ie, normal NPi and abnormal CV). Thus, a brisk pupillary response may not always indicate a normal pupillary reaction to light.

As with other monitoring modalities, it has been suggested these pupillary trends be considered in combination with patient clinical assessment and trending values, rather than on sole, absolute values. Findings from the END-Panic[16] registry stimulate discussion regarding optimal thresholds for an abnormal response with an automated pupillometer. Our findings contribute to this discussion, as ICP spikes were associated with temporal drops in CV and NPi, yet decreases were transient and did not consistently fall within the range of predetermined abnormal readings. Similarly, pupillary size remained small and was not immediately impacted by ICP increases. Detection of these changes and associated trends would not have been observed with a manual examination yet occurred in conjunction with increases in ICP. For patients with serial neurological examinations, these trends may yield useful information in the absence of invasive monitoring.

There was a unilateral pupillary response that accompanied increased ICP values in our study. This is consistent with the range of pupillary responses reported in the END-Panic trial,[16] where 9.1% of subjects had an abnormal unilateral response and 10.8% experienced bilateral abnormal responses to light. Certainly, location of neurological injury can impact cranial nerves II and III, resulting in changes to PLRs. As with the END-Panic trial, we did not record location of cerebral injury, which remains a limitation of the study but certainly remains an area for future investigation.

Findings from our study highlight the importance of pairing serial values from the pupillometer with multimodal monitoring data and clinical assessment in the setting of neurological injury. We advocate for an evaluation of these serial trends instead of isolated, intermittent pupillometer values based on predetermined thresholds, because trends may be a better indicator of neurological status. Serial trends in our study demonstrate decreases in NPi before ICP spikes, normal NPi at the time of the spike, and then subsequent decreases again after spikes. Similar fluctuations in CV were also present, with values not consistently reading abnormal throughout the duration of increases in ICP. Fluctuations in trended values may not always be present bilaterally, as reported in our study.

Limitations to our study include the single-site design, which may impact generalizability, and that location of injury was not recorded to further explain the rationale behind the unilateral pupillary response. In addition, we did not include data on pupillary latency or dilation velocity, because these values are currently not recorded as standard of care in hourly assessments. Addition of these components is an important consideration for future research. Finally, not all subjects in our study had increased ICP; almost two-thirds of the subjects had normal ICP values. However, because this study was conducted in the context of routine clinical care, we were not able to stratify based solely on ICP increases, because we could not predict when these increases would occur. Nevertheless, paired, pooled data of ICP increases with pupillometer values were able to be obtained and compared with instances of normal ICP, which allowed us to capture and compare trends in values.

Conclusion

Use of automated pupillometry remains a value adjunct to traditional invasive therapies. Neuroscience nurses continue to integrate this technology into serial pupillary assessments to decrease subjectivity of examinations and allow for trending of values. Evaluation of trended pupillometer data not only yields more robust information about pupillary reactivity but may provide important insights into ICP elevations in the absence of invasive monitoring and warrants additional research.

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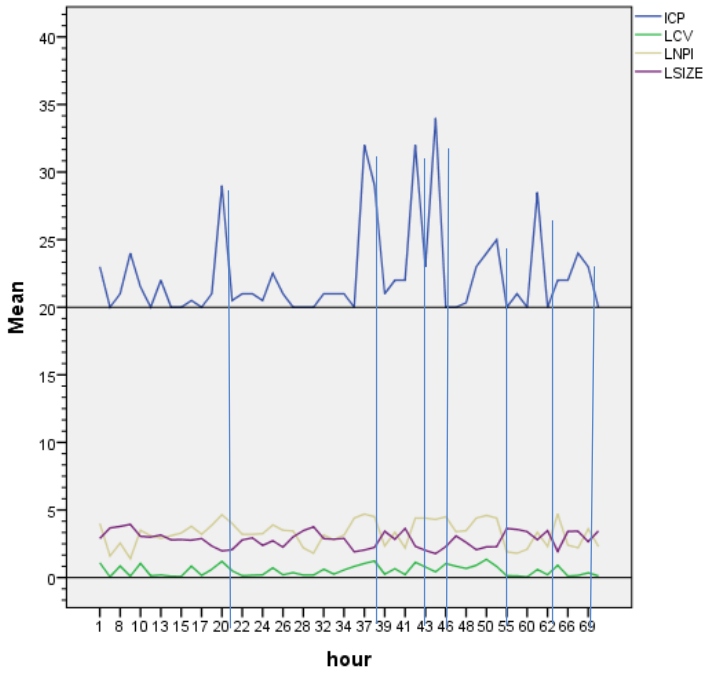
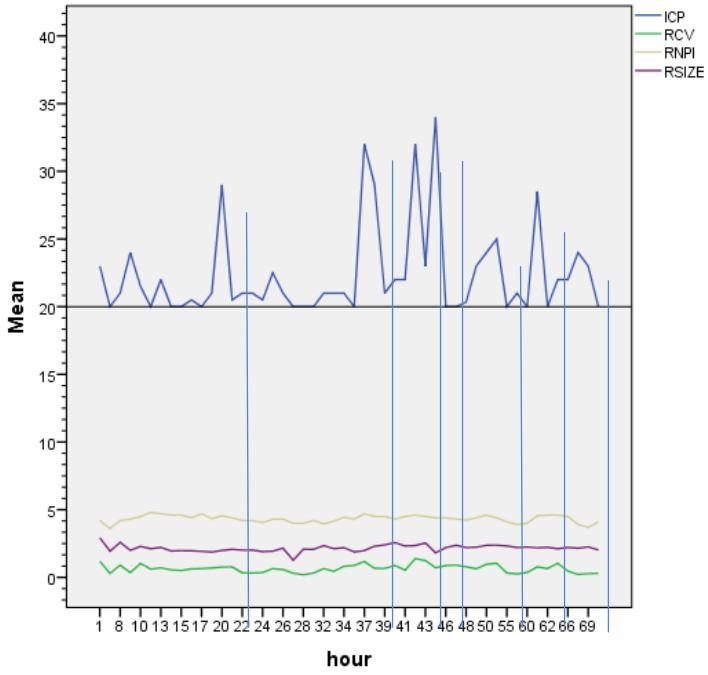
Supplemental Digital Content 1. Paired, Pooled Hourly Left and Right Pupillometer Values and Increased ICP

2.a. Left eye values

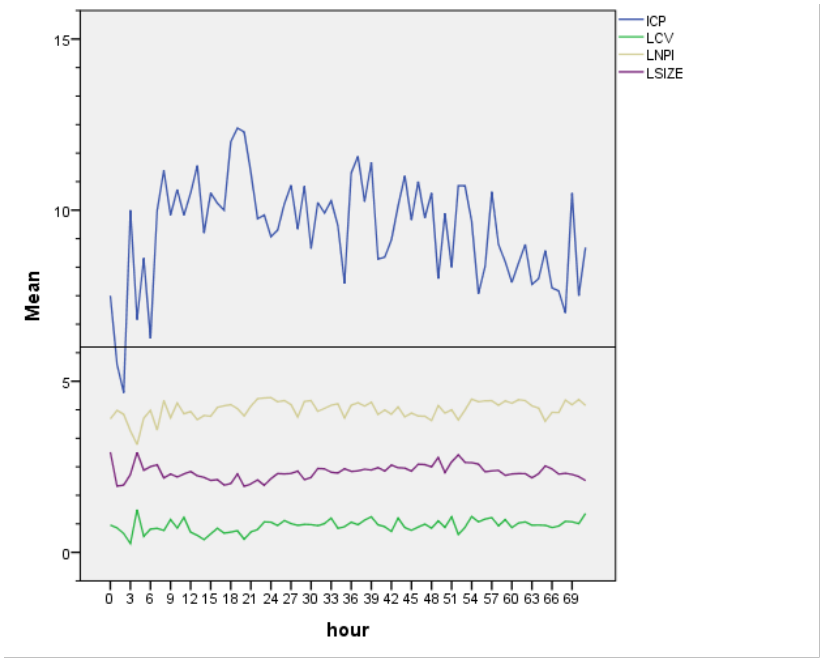


2.b. Right eye values



Supplemental Digital Content 2. Paired, Pooled Hourly Left and Right Eye Pupillometer Values and Normal ICP

2.a. Left eye values



2.b. Right eye values