Correlation of Objective Pupillometry to Midline Shift in Acute Stroke Patients

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Background: Pupillary dysfunction is recognized as a sign of acute neurological deterioration due to worsening mass effect in patients with hemispheric strokes. Recent neuroimaging studies suggest that horizontal displacement of brain structures may be more important than vertical displacement in explaining these pupillary findings. Pupillometers allow objective and standardized evaluation of the pupillary light reflex. We hypothesized that pupillary data (Neurological Pupil index [NPi] and constriction velocity [CV]) obtained with a hand-held pupilometer, correlate with horizontal intracranial midline shift in patients with ischemic and hemorrhagic strokes. *Methods:* The ENDPANIC registry is a prospective database of pupillometer readings in neurological patients. There were 134 patients in the database with an acute ischemic stroke or intracerebral hemorrhage who had at least 2 neurologic imaging studies (CT or MRI) and pupillometer assessments performed within 6 hours of the imaging. Horizontal shift of the septum pellucidum (SPS) was measured in 293 images. We computed the correlation between SPS and the following pupillary variables: size, NPi, CV (left, right, and left-right difference), followed by a regression model to control for confounders. *Results:* There were 94 patients (70.1%) with an ischemic stroke and 40 patients (29.9%) had an intracerebral hemorrhage. After controlling for age, race, and gender, there was a significant correlation between the SPS and NPi (left [$P < .001$], right [$P < .001$]), CV (left [$P < .005$], right [$P < .001$]) pupillary asymmetry (absolute difference between right and left; $P < .05$), but not between SPS and pupillary size (left or right). There was a significant correlation between the NPi and CV for the right pupil when there was a right-to-left SPS ($P < .001$ and $P < .05$, respectively), but none between the NPi and CV for the left pupil and left-to-right SPS. *Conclusions:* In patients with ischemic and hemorrhagic strokes, there is a significant correlation between SPS and the NPi, CV and pupillary asymmetry, but not with pupillary size.

Key Words: Midline shift—pupil—-stroke—intracranial hemorrhage—neurology

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Introduction

The art and science of assessing pupillary reactivity and responsiveness to light have developed over centuries. Healthcare practitioners have come to appreciate the pupil not only as an aperture that regulates the amount of light that enters the eye, but also a window into how physiologic changes in the brain may affect the signals carried by afferent and efferent cranial nerves that in turn affect its function. Similarly, the tools used to evaluate pupillary function have evolved from using natural light, to candle light, to electric light, and subsequently to miniature battery-powered penlights. More recently, portable hand-held pupillometers have substituted subjective interpretations of the pupillary light reflex such as brisk, sluggish, or nonreactive, with a scale of numerical measurements that are objective, precise, and reproducible.[1,2]

A change in the pupillary size, reactivity, and symmetry has long been known to be an indicator of worsening intracranial pathology. Information gathered from observing pupillary size and reactivity allows inferences to be made on the presence of intracranial mass effects and subsequently informs clinical decisions on medical or surgical intervention. The ability to accurately quantify pupillary size and reactivity now allows us to objectively measure the relationship between these findings and the patient's clinical status. The Neuroptics Neurologic Pupil index (NPI)-200 Pupillometer provides objective data on pupillary reactivity including pupillary constriction velocity (CV) and NPi, which is a proprietary algorithm which compares a patient's pupil measurements against a normative model of pupil reaction to light. The NPi is graded on a scale of 0-5. A score of 3 or more is analogous to a "brisk" response, while a score of less than 3 indicates a "sluggish" response, with value closer to 0 being more abnormal than values closer to 3. There have been multiple studies that demonstrated a significant correlation between abnormalities in these measurements and changes in clinical parameters such as Glasgow Coma Scale as well as intracranial pressure (ICP).[3,4] In addition, these studies have found that subtle abnormalities detected on pupillometry often preceded these changes by many hours. Questions remain, however, as to the physiology underlying the relationship between alterations in ICP, levels of sensorium, and pupillary function.

Traditionally, a unilaterally dilated pupil in the setting of increasing cerebral mass effect has been attributed to a mechanical compression of the oculomotor nerve by the uncus of the temporal lobe that is displaced downwards and medially. Much of our understanding in this area is based on pathological studies, obtained at a later time after the clinical observations. Moreover, many of these studies are based on patients with slowly growing tumors, which may not be reflective of the mechanism by which pupillary changes occur in the acute setting.

Neuroimaging has shed light on some of the structural changes seen preceding these late findings and may better explain earlier clinical findings. Ropper, in a series of 24 patients with intracranial mass lesions, demonstrated an association between different degrees of lateral shift (as opposed to vertical displacement) of intra-axial structures on head CT and levels of sensorium. Pupillary enlargement was observed to have a variable relationship to uncal herniation.[5] Based on a series of clinical observations, C. Miller Fisher proposed that pupillary changes may be due to horizontal shift in midline structures and distortion of the midbrain rather than downward displacement of the uncus exerting pressure on the oculomotor nerve. Indeed, there have been cases of progressive stupor and fixed dilatation of first 1 pupil and then the other where autopsy did not reveal temporal lobe herniation. Moreover, the sequential involvement of both pupils that is often seen within minutes of one another cannot be reliably explained by pressure being exerted on the third cranial nerve, especially when considering that the eyeball is almost never deviated inferolaterally, as would be expected in such cases.[6] These findings have challenged some of the tenets of clinical neurology that uncal and central herniation syndromes readily explain stupor and coma and the pupillary changes.[7]

There have been no studies combining data derived from a pupilometer and modern neuroimaging techniques. Such an approach may allow us to challenge current concepts underlying the physiologic changes that occur in the injured brain and to unravel some of its complexity. Utilizing data from the Establishing Normative Data for Pupillometer Assessments in Neuro-Intensive Care (END-PANIC) registry, we sought to test Miller Fisher's hypothesis on the correlation between lateral shift and pupillary changes. We compared objective measurements of pupillometry-derived pupil size, NPi and CV with the degree of lateral displacement of midline structures (midline shift) measured on neuroimaging to test the hypothesis. We also wanted to explore the use of pupillometery as a surrogate for predicting midline shift and possibly a valuable tool to guide intervention in early stages of pathology.

Methods

Study Patients

The ENDPANIC registry is a prospective database of pupillometer readings in Neurological and Neurosurgical patients admitted to 3 hospitals across the United States. The methodology of the ENDPANIC registry and pupillometer readings has been previously described.[8] The current study was conducted on patients with an ischemic stroke or an intracerebral hemorrhage in the supratentorial compartment, admitted to the Neurosciences Intensive Care Unit at a large University Hospital in the Southwestern United States from January 2nd, 2015

through September 29th 2017. All patients with infratentorial ischemic strokes or hemorrhages, and those with subarachnoid hemorrhages were excluded. Data collection was performed retrospectively after we obtained approval from the institutional review board. We collected patient baseline characteristics including age, race, gender, and primary diagnosis.

Neurological Imaging

We identified 134 patients with a primary diagnosis of acute ischemic stroke or intracerebral hemorrhage who had at least 2 neurologic imaging studies (CT head or MRI brain) performed within 6 hours of a pupillometer assessment. Patients with posterior fossa strokes or hemorrhages, and those with subarachnoid hemorrhages were excluded. All imaging was initially reviewed by a Neuroradiologist for clinical purposes and reported in the medical record, for the study purpose all imaging was then reviewed by a single investigator using a standardized protocol and who was blinded to the pupil data at the time of review. The image review and measurements were performed using Phillips Intellispace PACS enterprise software. We measured the lateral shift of the septum pellucidum (SPS), and also noted the presence or absence of basal cisternal effacement, and the side of the effacement if present, as well as the presence or absence of a decompressive hemicraniectomy or an external ventricular drain.

Pupillometer Data

All patients prospectively enrolled in the ENDPANIC registry underwent pupil assessment by the bedside nurse in the ICU. Pupil assessment was performed using the Neuroptics NPI-200 Pupillometer. Data were then transferred to a central database. The following data elements were retrospectively collected for analysis in our study; the pupil size, the NPi, and the CV for both eyes. Pupil data were then paired with the neurological imaging to include pupillary readings closest to the time of neuroimaging within 6 hours of the neuroimaging study.

Data Analysis

Statistical analysis was performed by a statistician using SAS software version 9.4. Baseline analysis was performed on the data utilizing the following variables: race, gender, age, primary diagnosis (ischemic or hemorrhagic stroke), as well as presence of a ventricular drain or decompressive hemicraniectomy. Race was analyzed as a categorical variable with: African-American, Caucasian, Asians, Native Americans, Pacific Americans and those who did not know their race. To compute the correlation between midline shift and other predictors, we normalized both variables by each SPS by its standard deviation and each predictor by its standard deviation and then fit a mixed effect linear regression model with observations ID as the random effect[9]. Since both the independent variable and the dependent variable are normally distributed and can be reversed, the estimate of the effect is the correlation coefficient and the P value is the corresponding P value for that correlation. Throughout the study, the type I error was maintained at 5%. We also performed a multivariate analysis where we controlled for age, gender, race, and primary diagnosis. We were not able to control for presence or absence as well as the side of a decompressive craniectomy, as well as an external ventricular drain due to small sample size.

A subanalysis was then performed using only observations with midline shift and separated in 2 groups based on the direction of shift. We used a similar mixed regression model to test correlation of NPi to midline shift in this subset of patients as well.

Results

We identified 357 patients admitted with a stroke diagnosis during the study period, 14 were excluded due to the lack of inpatient imaging studies, 20 patients were excluded for only having one imaging study during hospital stay, 11 were excluded for lacking abnormalities on MRI, 97 were excluded for having subarachnoid hemorrhage, 34 were excluded for having posterior fossa strokes, and 1 for having subdural hematoma as the primary finding. Furthermore, 46 were excluded for not having pupillometer readings within 6 hours of neurological imaging (Fig 1). There were 134 patients with 293 observations that were included in the analysis. Of the 134 patients, 29.9% had an ICH and 70.1% had an ischemic stroke (Table 1). The ratio of men to women was 1:1, and 20.9% of the cohort was African-American and 61.9% were Caucasian. The average age was 65.1 years with a standard deviation of 15.2. Of the paired observations that were analyzed in the study 151 of the 292 (51.7%) had a midline shift, with the direction of shift from left to right in 65(43%) of the reviewed imaging studies and right to left in 86(57%) of the studies.

A total of 16(11.9%) of the patients and 37(12.3%) neuroimaging studies had external ventricular drainage. Of the study patients 15 (11.2%) underwent decompressive hemicraniectomy, and evidence of craniectomy was present on 28(9.6%) of the studies reviewed.

Correlation Between Midline Shift and Pupil Assessment

We used all observations noted in the data that were complete to all variables needed for each analysis. As shown in Figs 2 and 3 and Table 2, our random effect mixed model showed good correlation for all observations between SPS and NPi for both pupils, with a correlation effect of $-.22$(P = .001) for the right pupil and $-.28$ for the left pupil (P = .001). Similarly, good correlation was noted for CV bilaterally; with a right coefficient $-.25$

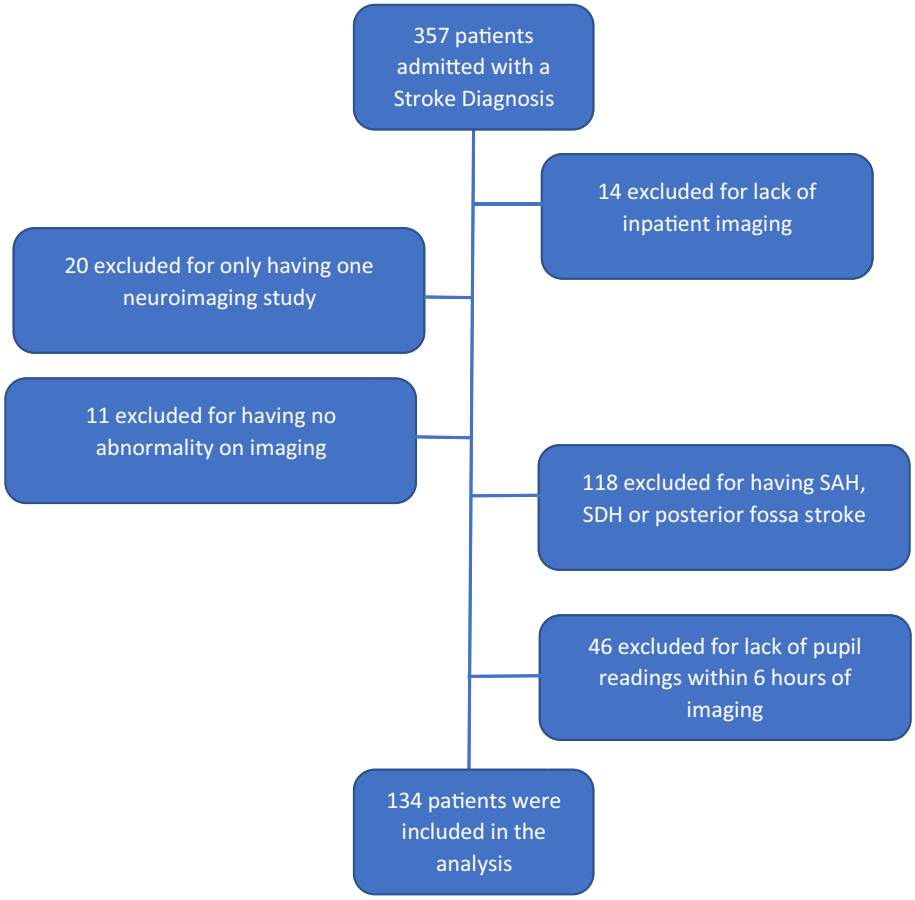

Figure 1. *Patient selection, the flow of study patient selection and patients that were excluded from that data that were analyzed.*

Table 1. *Baseline characteristics on the patients that were analyzed*

Variable	N(%)	Mean(SD) P25-P75
Primary diagnosis		
ICH	40 (29.9)	
Ischemic stroke	94 (70.1)	
Race		
African American	28 (20.9)	
Caucasian	83 (61.9)	
Others	23 (17.2)	
Gender		
Male	67 (50.0)	
Female	67 (50.0)	
Age		65.1(15.2) 53.0-76.0

(P = .001) and −.18(P = .002) in the left pupil. However, the individual pupillary size did not show statistically significant correlation (right pupil size −.09 [P = .136] and the left pupil size −.05[P = .383]). After controlling for possible confounding variables (age, gender, race, and primary diagnosis) the NPi still maintained good correlation to midline shift with P value of <.001 the left pupil and equal to .0001 for the right pupil (Table 3).

Correlation Between NPi and Cisternal Effacement

We performed mixed model analysis where repeated subjects were entered as random effect, and this showed significant correlation between NPi bilaterally and cisternal effacement. This estimate correlation for the right pupil was −.5923(P = .0118) and for the left pupil −.9225 (P = .0002, Table 2). The sample size was too small to dichotomize the relationship to each side of the effacement. The size of the pupil was also found to have significant estimate with cisternal effacement regarding the right pupil −.7453(P = .0053) and an estimate of −.4513 (P = .0608) for the left pupil (Table 2).

Subanalysis on Subgroups With Midline (SPS) Shift Only

We performed an additional subanalysis using only patients with midline shift. We evaluated the relationship of both pupils with midline shift based on the direction of shift, while controlling for age, gender, race, and primary diagnosis. We found that in the setting of right to left (leftward) shift, there is good correlation of midline shift with NPi in the right eye with coefficient of −.43(P = .001). In the setting of left to right (rightward) shift, the correlation coefficient of left pupil NPi with midline shift was −.23 and this failed to achieve statistical significance (Table 2).

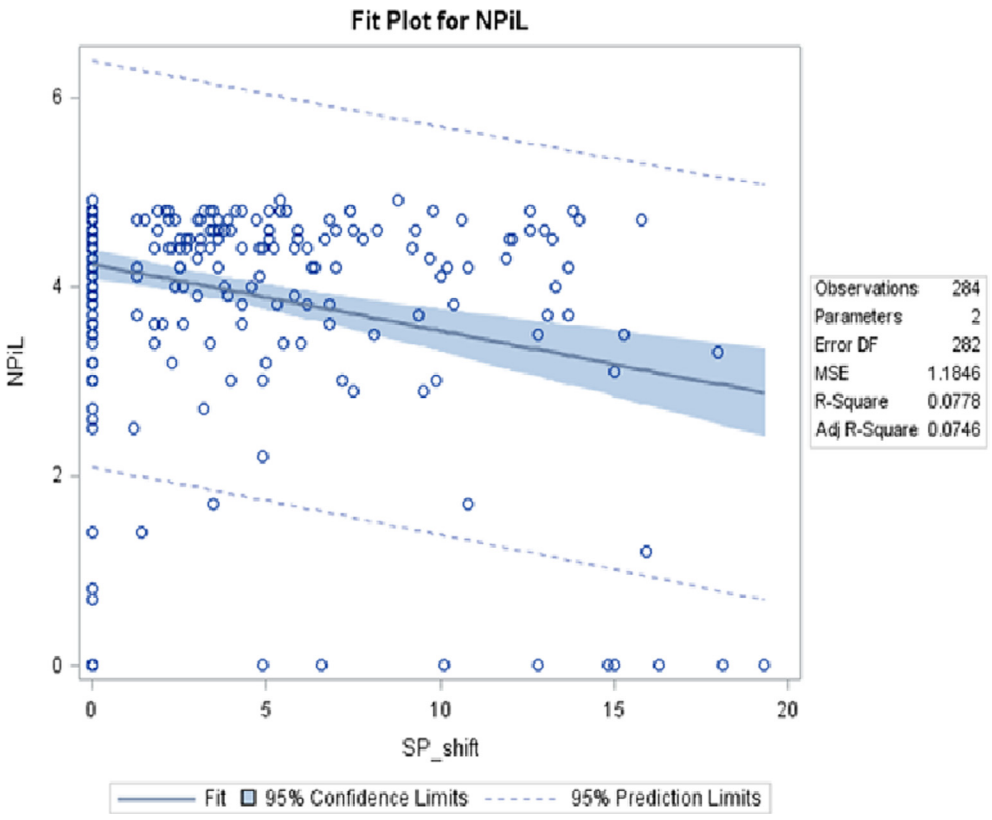

Figure 2. *Fit plot diagram demonstrating the relationship between NPi of the left pupil and the septum pellucidum shift.*

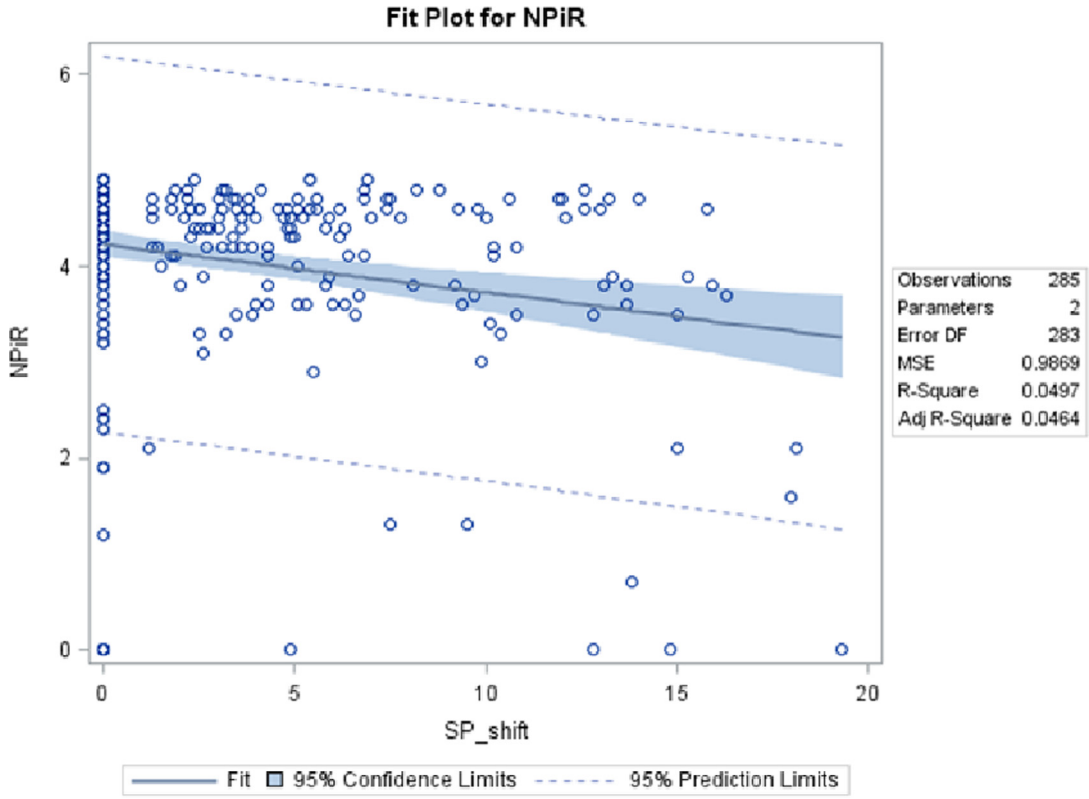

Figure 3. *Fit plot diagram demonstrating the relationship between NPi of the right pupil and the septum pellucidum shift.*

Table 2. *Correlation coefficient between septum pellucidum shift, cisternal effacement and the variables tested*

SP Shift	Variable 2	Correlation Coefficient (P-value)
SP Shift	NPIL	−.28 (.001)
SP Shift	NPIR	−.22 (.001)
SP Shift	Abs(NPiL-NPiR)	.18 (.003)
SP Shift	SizeL	−.05 (.383)
SP Shift	SizeR	−.09 (.136)
SP Shift	CVL	−.18 (.002)
SP Shift	CVR	−.25 (.001)
SP Shift	NPIL when SP_side=L2R	−.23 (.349)
SP Shift	NPIR when SP_side=R2L	−.43 (.001)
Cist E	NPIL	−.9225 (.0002)
Cist E	NPIR	−.5923 (.0118)
Cist E	SizeR	−.7453 (.0053)
Cist E	SizeL	−.4513 (.0608)

Abbreviations: CVL, constriction velocity left pupil; CVR, constriction velocity right pupil; L2R, left-to-right shift; NPIL, NPi left pupil; NPiR, NPi right pupil; R2L, right-to-left shift; SizeL, size of left pupil; SizeR, size of right pupil.

Discussion

Our results support the hypothesis that objectively derived measures of pupillary reactivity correlate with horizontal displacement of the cerebral structures as measured by SPS and supports that notion that automated pupillometry could be a valuable tool in the neurological ICU for as a monitor of worsening intracranial pathology in patients with stroke. What is also of interest is the failure to demonstrate a similar effect with pupil size. The value of automated pupillometry is noteworthy, as it eliminates the inter-rater variability in pupillary assessment. A recent study by Olson et al[1] demonstrated that there is limited inter-rater reliability for subjective assessment of the pupil. On the other hand, automated pupillometry has very good inter- and intradevice agreement.[10]

We also attempted to study if the direction of the midline shift was correlated with the side of the abnormal pupillary findings. Our analysis was able to demonstrate significant correlation between midline shift and changes in the pupil by automated pupillometry, specifically the NPi, when the direction of the shift was from right to left. However, we were not able to find a statistically significant correlation in the opposite direction of shift (left to right) with regards to the left eye. We do not know the exact reason for this discrepancy in correlation. We speculated that the presence of a decompressive craniectomy (which are performed more often in right hemispheric strokes) or even decompression of the ventricular system with an external ventricular drain (which is more often placed on the right side) might explain the absence of the correlation in rightward shift. However, our sample size was too small to analyze the effect of these variables.

As a surrogate for uncal herniation, we analyzed the relationship between pupil reactivity and size with cisternal effacement alone as seen on imaging. To our knowledge, there no standardized techniques for quantifying uncal herniation. Cisternal effacement also significantly correlated with NPI, but correlated with pupil size only for the right pupil.

Automated pupillometry can detect early pupil changes that in some patients can precede the onset of further clinical decline as demonstrated by Papangelou in trauma patients.[11] Pupillometry has also been shown to be a surrogate for elevation in ICP as demonstrated by Chen.[4,12] This concept would be of paramount benefit in aiding clinicians in the neurocritical care setting regarding the need for imaging or intervention for patients with stroke. Cerebral edema and midline shift are considered a significant cause for mortality and morbidity in acute stroke patients.[13,14] Large landmarks trials have attempted to investigate interventions that can ameliorate that effect and improve patient outcome. Decompressive craniectomy has been the only effective intervention for mortality reduction as demonstrated by the popular DECIMAL and HAMLET trials[15,16] as well as in the latter studies DESTINY I and in older patients DESTINY II.[17,18] More recently the timing of such intervention has been evaluated Dasenbrock et al.[19] There is evidence that early intervention carried better outcome for patients, and Dasenbrock postulates that hemicraniectomy before a decline in sensorium is the likely key to have the best outcome. Unfortunately, we do not have good noninvasive tools to serially follow the evolution of cerebral edema and mass effect in these patients. We continue to rely on detection of changes in the level of sensorium and assessing pupillary size and reactivity with hand-held flashlights to serially monitor stroke patients at risk for significant mass effect. Out results indicate that with further evaluation, the use of automated objective pupillometry could be a useful tool in detecting worsening midline shift.

Limitations

Our study has several limitations. The retrospective design which limited our ability to have good pairing of pupillary data and imaging data significantly reduced our sample size. We did not collect or correlate the timing of the pupil readings and neuroimaging to any osmotic therapy or other measures that were clinically implemented that could affect midline shift and ICP. Moreover, the time interval between the pupil readings and the neuroimaging and the order of which either was performed was not standardized and had a lot of variability given the retrospective nature of the study. In this sample, a large range of midline shift was used to demonstrate correlation; future prospective studies may benefit from within-subject comparisons not available in this study. Not all patients had baseline pupil readings in the absence of midline shift. We also did not collect clinical data such

Table 3. *Multivariate analysis of the data*

Effect	Estimate	Standard error	*P*
NPiL			
Intercept	10.2863	1.4786	<.0001
NPiL	−1.1075	.2258	<.0001
Age	−.01922	.01761	.2762
Gender	−.1025	.5306	.847
Race (African American vs Caucasian)	.636	.9967	.5239
Race (other vs Caucasian)	1.331	.8316	.1106
Ischemic stroke	−2.0375	.5545	.0003
NPiR			
Intercept	10.0061	1.5434	<.0001
NPiR	−.9776	.2539	.0001
Age	−.02311	.01785	.1965
Gender	−.1012	.5355	.8502
Race (African American vs Caucasian)	1.386	1.0048	.1689
Race (Other vs Caucasian)	1.5415	.8465	.0697
Ischemic stroke	−2.0917	.5589	.0002
CVL			
Intercept	9.1484	1.3401	<.0001
CVL	−1.0211	.2486	<.0001
Age	−.04618	.01664	.0059
Gender	.1474	.4993	.7681
Race (African American vs Caucasian)	.5252	.9552	.5829
Race (other vs Caucasian)	1.4913	.7642	.0521
Ischemic stroke	−2.2905	.5174	<.0001
CVR			
Intercept	10.5644	1.4008	<.0001
CVR	−1.3416	.2478	<.0001
Age	−.06064	.01737	.0006
Gender	.004555	.5144	.9929
Race (African American vs Caucasian)	1.3567	.9436	.1517
Race (other vs Caucasian)	1.5703	.7968	.0498
Ischemic stroke	−2.005	.5336	.0002
L2R NPiL			
Intercept	13.0307	3.8434	.0011
NPiL	−.6895	.8932	.4425
Age	−.04045	.03499	.2512
Gender	−.4132	.9713	.6717
Race (African American vs Caucasian)	−1.5808	1.6143	.3305
Race (other vs Caucasian)	.8875	1.1928	.4591
Ischemic stroke	−1.9202	.8847	.033
SizeL			
Intercept	12.2055	2.7206	<.0001
SizeL	−.4183	.3817	.2765
Age	−.05192	.03338	.1239
Gender	−.3483	.9711	.7208
Race (African American vs Caucasian)	−1.0155	1.6263	.5342
Race (other vs Caucasian)	.9104	1.1876	.4456
Ischemic stroke	−2.014	.8887	.0262
R2L NPiR			
Intercept	15.5786	3.3192	<.0001
SizeL	−1.7234	.4538	.0004
Age	−.02742	.0397	.4925
Gender	1.2652	1.2087	.2996
Race (African American vs Caucasian)	4.8474	2.1297	.0265
Race (other vs Caucasian)	.02917	1.9661	.9882
Ischemic stroke	−1.8187	1.3501	.1832

(*Continued*)

Table 3 (*Continued*)

Effect	Estimate	Standard error	*P*
CVR			
Intercept	12.4398	3.1517	.0002
SizeL	−1.1701	.5178	.0279
Age	−.06097	.03945	.128
Gender	1.1546	1.2608	.3639
Race (African American vs Caucasian)	5.0629	2.1309	.0211
Race (other vs Caucasian)	1.1721	2.0666	.573
Ischemic stroke	12.4398	3.1517	.0002

Abbreviations: CVL, constriction velocity left pupil; CVR, constriction velocity right pupil; L2R, left-to-right shift; NPIL, NPi left pupil; NPiR, NPi right pupil; R2L, right-to-left shift; SizeL, size of left pupil; SizeR, size of right pupil.

as NIHSS or Glasgow Coma Scale at the time of the assessments and neuroimages. We hope that a subsequent prospective study can produce better understanding of the relationship and further solidify the role of automated objective pupillometry as a useful tool in stroke patients.

Conclusions

We conclude that there is statistically significant relationship between midline shift and objective measures of pupillary reactivity (NPi and CV) but not with pupillary size. This indicates that, if validated in a larger prospective study, NPi assessment by automated pupillometry could be considered as a useful surrogate to noninvasively monitor midline shift in stroke patients and help in utilization of imaging and indicate the need to intervention. Prospective trials are needed to further assess the role of objective-automated pupillometry in predicting impending herniation and neurological decline in stroke patients.

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DaiWai Olson: Dr. Olson serves as the Primary Investigator of the END PANIC Registry. Dr. Olson receives research support from NeurOptics, and he is the editor for Journal of Neuroscience Nursing.

Sonja Stutzman: Dr. Stutzman is the Project Manager for the END PANIC Registry and coordinates data collection, data cleaning, and data monitoring. Dr. Stutzman's salary is supported by funding from NeurOptics. Dr. Stutzman is a guest editor for Nursing Clinics of North America.

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