ORIGINAL ARTICLE

Are There Predictive Pupillometry Markers in Determining External Ventricular Device (EVD) Weaning Failure or Success in Subarachnoid Hemorrhage Patients?

Tracy Bezner[1], Premkumar Nattanmai[1], Nakul Katyal[1], Keerthivaas Premkumar[3] and Christopher R. Newey[1, 2]

[1]University of Missouri, Department of Neurology, 5 Hospital Drive, CE 540, Columbia, MO 65212
[2]Cleveland Clinic, Department of Neurology, 9500 Euclid Avenue, Cleveland, OH 44195
[3]University of Missouri, Department of Biological Sciences, Columbia, MO 65212

Corresponding author: Premkumar Nattanmai, MD, University of Missouri, Department of Neurology, 5 Hospital Drive, CE 540, Columbia, MO 65211 (nattanmaip@health.missouri.edu).

Received: October 15, 2017 Accepted: February 2, 2018 Published: May 25, 2018

Am J Hosp Med 2018 Apr;2(2):2018.009 https://doi.org/10.24150/ajhm/2018.009

Introduction: Pupillometers objectively measure constriction (i.e., parasympathetic pathway) and dilation (i.e., sympathetic pathway) velocities of the pupillary reflex. These pathways may be affected by increases in ventricular size due to changes in cerebrospinal fluid (CSF) volume, such as during external ventricular device (EVD) weaning in aneurysmal subarachnoid hemorrhage (aSAH) patients. This pilot study evaluated if changes in pupillary responses could be predictive of EVD weaning failure in aSAH patients. Additionally, we analyzed ventricular size and pupillary reactions in these two groups.
Methods: Adult aSAH patients serially monitored with the pupillometer at an academic medical center were included. Patients were grouped into those successfully weaned from the EVD and those who were not. Pupillometer measurements (e.g. changes in constriction and dilation velocities), changes in intracranial pressure (ICP), changes in cerebral aqueduct diameter and 3rd ventricle diameter (measured via computed tomography head (CTH)) were evaluated between the two groups.
Results: Seven patients met the inclusion criteria. Three patients required ventriculoperitoneal shunting. There were no significant differences in the changes in constriction or dilation velocities between the groups. Additionally, there was no significant difference in ICP. There were significant differences between the changes in size of the cerebral aqueduct ($p=0.01$) and of the third ventricle ($p=0.01$) on CTH between those who weaned and those who did not. These did not correlate with pupillometer measurements.
Conclusions: We did not find predictive value in changes in constriction or dilation velocities or ICP on EVD weaning success in aSAH patients. Changes in the diameter of the third ventricle or cerebral aqueduct may be predictive of EVD weaning and suggests a further avenue for study.

Keywords: pupillometer, external ventricular device, subarachnoid hemorrhage

INTRODUCTION

Change in pupillary size is a commonly used prognostic indicator facilitating early recognition of a worsening neurologic condition, e.g. herniation. The fact that an

abnormal result in pupillary assessment (e.g. non-reactivity and/or mydriasis) triggers a cascade of diagnostic and therapeutic procedures underscores its importance.[1] While early, accurate, and reliable detection of pupillary changes is important, the problem of interobserver variability and varying evaluative schemas associated with manual pupillary observation are well known.[2,3] Recent studies continue to confirm inadequate levels of practitioner agreement in regards to pupillary reactivity when traditional, manual pupillary assessments for patients with neurologic injury are used.[2,3] Pupillometers may represent the next step in the evolution of neurocritical care because they are automated, computer-based, and use infrared digital video technology to objectively measure pupillary size and reactivity.[4] Pupillometers may have a role as a prognostic indicator of developing hydrocephalus which may occur in the weaning of external ventricular devices (EVD) in patients with aneurysmal subarachnoid hemorrhage (aSAH).

The etiology of hydrocephalus in patients suffering aSAH is either due to an obstruction in the ventricular system or decreased cerebrospinal fluid (CSF) absorption from fibrosis of the leptomeninges and arachnoid granulations caused by inflammation and deposition of blood products.[5] Regardless of etiology, CSF diversion is typically indicated in these patients. This is routinely accomplished via temporary EVD placement, with the hope of successful weaning and removal. [6] Patients who fail the weaning process are considered to have developed chronic hydrocephalus and require permanent shunting.[7] The purpose of our pilot study is to use pupillometers to evaluate subtle pupillary reactivity changes in patients with developing hydrocephalus secondary to aSAH. The goal is to identify a noninvasive prognostic marker that will aid in EVD weaning.

METHODS

Patients

We retrospectively reviewed prospectively collected data over a six-month period of adult patients (≥18 years of age) admitted with aSAH to the neurosciences intensive care unit (NSICU) at a tertiary, academic medical center. The Institutional Review Board approved this study.

The collected demographic data included age, sex, reason for admission, surgical intervention, Glasgow Coma Score (GCS), Hunt and Hess score, Fisher Grade score, temperature (Celsius), and serum sodium level. Additionally, EVD settings, cerebrospinal fluid (CSF) drainage over prior 24 hours, intracranial pressure (ICP) data, and computed tomography (CT) imaging data were also acquired.

Patients were excluded if pupillometer data was collected on intravenous sedation (e.g. propofol, dexmedetomidine) and/or analgesia (e.g. fentanyl). Figure 1 illustrates inclusion/ exclusion of patients.

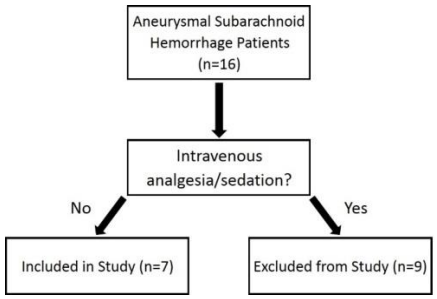

Figure 1: Patient Inclusion / Exclusion Flowchart.

Pupillometer

The NeurOptics pupillometer (NeurOptics, Irvine, CA, USA) was used in this study to evaluate pupillary physiology. In our NSICU, pupillometer assessments were collected by procedural protocol. A pupillometer headrest, specific to each patient, was attached to the pupillometer.

Table 1. Definitions of Pupillometer Variables

Variable	Definition
Npi (neurological pupil index)	Composite pupillary response number based on an algorithm using physiological pupil variables and comparing them to a normative model.
Latency (s)	The time difference between light stimulation and the onset of pupillary constriction.
Constriction velocity (mm/s)	An average velocity calculated by the pupil constriction divided by the duration of the constriction.
Maximum constriction velocity (mm/s)	Peak constriction velocity.
Dilation velocity (mm/s)	An average velocity calculated by pupil dilation divided by the duration of the dilation.

Prior to pupil assessment, all room lights were off, blinds were down, and hall curtain drawn closed. The pupillometer was powered on. The eye was scanned by positioning the headrest with the lower pad below the eye and holding the eyelid open. The eye was then scanned. The right eye (OD) was scanned first followed by the left eye (OS).

Pupillometer data collected from each eye included Neurological Pupillary Index (NPi), baseline size, minimum size after bright light, constriction velocity (CV), maximum constriction velocity (MCV), latency, and dilation velocity (DV). These variables have been previously explained and are summarized in Table 1.[1]

Neuroimaging

Axial CT head images were obtained on a 64-multislice scanner (General Electrics Healthcare, Chicago, IL). These were blindly reviewed by one of the authors (CRN). The diameter measurements of the ventricular system were obtained, including the cerebral aqueduct in the midbrain at the level of the superior colliculus and the third ventricle at the level of the hypothalamus. Figure 2 is an illustrative example.

Statistics

Continuous and categorical data were summarized with descriptive statistics including means and standard deviations (continuous data) and frequencies (categorical data). Average ICP values were calculated using data collected from 9AM to 12PM, the cluster of hours surrounding the pupillometer data collection. Pupillometer data was collected daily at 9AM, a time chosen to facilitate identification of transient changes in pupillary function because it follows changes made in EVD settings by the rounding neurosurgical team. Velocity measurements were compared to ICP and changes in ventricular diameter on axial computed topography (CT) scans of the head at the level of the third ventricle and at the cerebral aqueduct using Pearson Correlation. Student t-test was used to compare the continuous demographic data as well as CV and DV between those who pass EVD weaning from those who fail EVD weaning. If patients developed delayed hydrocephalus and required a ventriculo-peritoneal shunt, these patient(s) were included in the EVD weaning failure group for statistical analyses. A p value of ≤ 0.05 was considered significant. Data were analyzed using GraphPad Prism 7 (La Jolla, CA, USA).

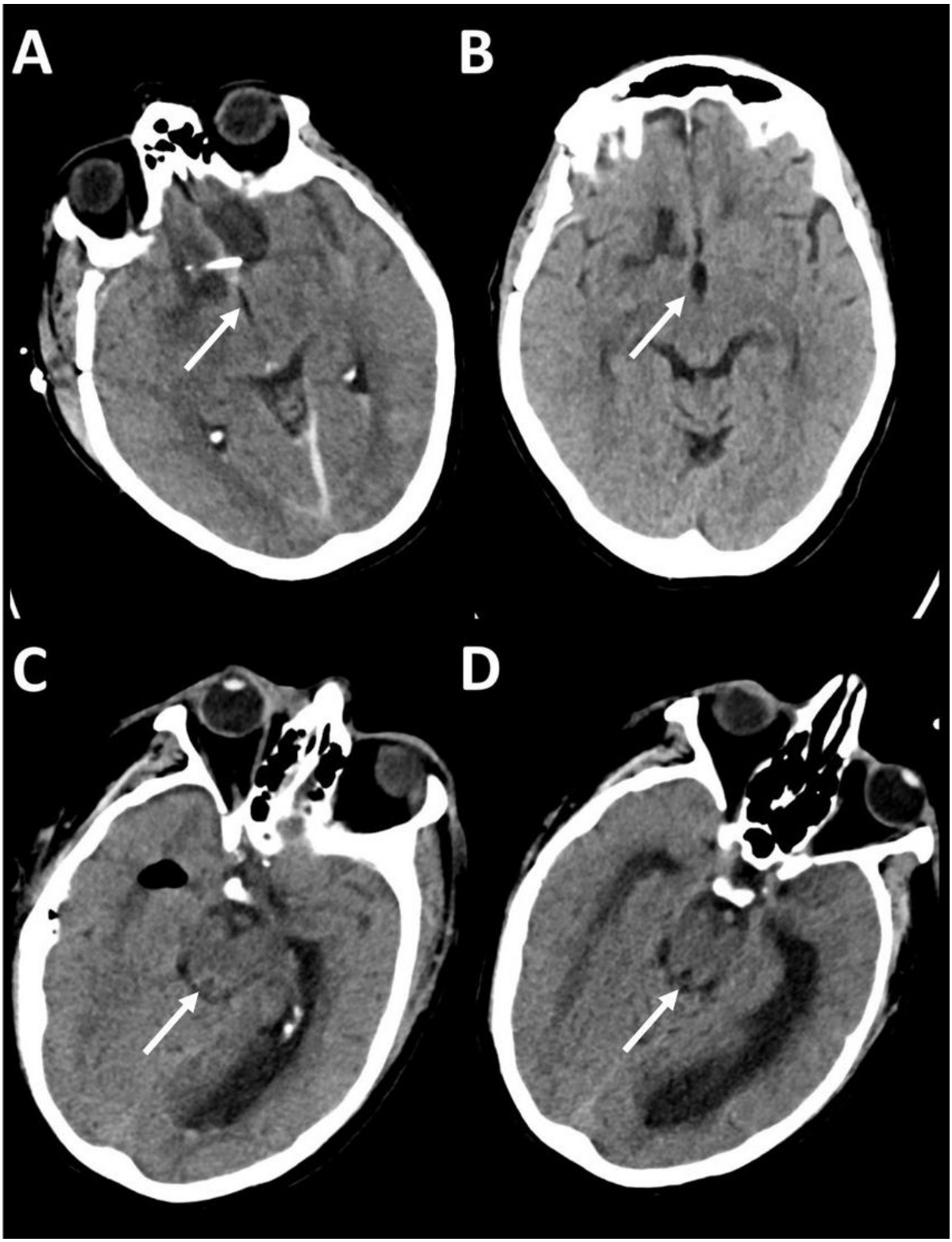

Figure 2. Computed Tomography (CT) Head. CT head showing the third ventricle prior to (A) and 24 hours after (B) external ventricular (EVD) clamping. There is marked enlargement of the third ventricle. CT head at the level of the cerebral aqueduct prior to (C) and 24 hours after (D) EVD clamping. The cerebral aqueduct had significant increase in diameter.

Table 2. Patient Demographics.

	Total (n = 7)	Passed EVD weaning (n = 4)	Failed EVD weaning (n = 3)	p value
Age (yrs; mean, SD)	58 (±14)	60 (±18)	55 (±10)	NS
Sex (Male, %)	4 (57.1%)	2 (28.6%)	2 (28.6%)	NS
Hunt and Hess Score (mean, SD)	2.43 (±1.13)	2 (±0)	3 (±1.73)	NS
Fisher Grade Score (mean, SD)	3.43 (±0.54)	3.25 (±0.5)	3.67 (±0.57)	NS
Temperature (^{o} C; mean, SD)	36.8 (±0.99)	36.7 (±0.88)	37.0 (±1.31)	NS
Sodium (mean, SD)	142.4 (±2.30)	142.8 (±1.26)	142.0 (±3.61)	NS
ICP (mmHg; mean, SD)	8.16 (±2.86)	7.67 (±2.76)	8.81 (±3.46)	NS

Abbreviations; yrs, years; SD, standard deviation; ^{o}C, degrees Celsius; ICP, intracranial pressure; n, number; EVD, external ventricular device; NS, nonsignificant

RESULTS

The mean age was 57.6 (±14) years, with a range of 35 to 76 years. Seven aSAH patients (3 males; 4 females) met the inclusion criteria. The average Hunt and Hess and Fisher Grade scores for all patients were 2.43 (±1.13) and 3.43 (± 0.54), respectively. These clinical variables did not change significantly comparing those who passed EVD weaning to those who failed. Additionally, serum sodium, temperature, and ICP did not change significantly in those who passed EVD weaning compared to those who failed EVD weaning. Table 2 summarizes the patient demographics.

Two patients immediately failed weaning and required ventriculoperitoneal (VP) shunting. One patient initially passed the weaning process, only to develop delayed hydrocephalus requiring VP shunting two-weeks later. Four patients did not develop hydrocephalus during EVD weaning. The average pupil sizes were 3.22 (±1.20) mm OD and 3.25 (±1.02) mm OS (p=0.97) among all patients. Those who passed EVD weaning showed average pupil sizes of 3.01 mm (±1.17) OD and 3.27 (±1.09) mm OS (p=0.76), and those who failed were 3.51 (±1.44) mm OD and 3.22 (±1.12) mm OS (p=0.79). The average change in OD CV among those passing weaning was 1.39 (±1.44) m/s, and in those who failed, it was 0.06 (±0.23) m/s (p = 0.18). The average change in OS CV between those who passed and failed weaning was 0.92 (±1.98) m/s and 0.43 (±0.29) m/s (p = 0.70), respectively. Comparison of the OD and OS change in DV among both groups also showed no significant difference (p = 0.16 and p = 0.65, respectively). Overall, there were no statistically significant differences in the pupillary function to distinguish those who passed EVD weaning from those who failed. Table 3 summarizes the pupillometer data.

The changes in the diameter of the cerebral aqueduct and 3rd ventricle measured on axial CT heads of patients showed significance between patients who passed versus those who failed EVD weaning. The average change in 3rd ventricle diameters were 0.04 (±0.03) cm and 0.93 (±0.40) cm (p = 0.01), respectively. Likewise, the average changes in aqueduct diameter were 0.07 (±0.05) cm in those who passed versus 0.46 (±0.21) cm in those who failed (p=0.01).

DISCUSSION

Changes in the CSF volume are well-known occurrences during EVD weaning in patients with aSAH. While hydrocephalus may be treated in the acute phase with EVD placement, markers enabling clinicians to identify patients requiring long-term CSF diversion are highly desirable. Our pilot study failed to show a pupillometer-based marker to reliably identify patients who

Table 3. Patients Pupil Physiological Variables.

	Passed			Failed			p value
Change in OD NPI (± SD)	-0.13	±	0.62	-0.03	±	0.68	0.85
Change in OS NPI (± SD)	-0.28	±	0.69	0.27	±	0.35	0.27
Change in OD CV (± SD)	1.39	±	1.44	0.06	±	0.23	0.18
Change in OS CV (± SD)	0.92	±	1.98	0.43	±	0.29	0.70
Change in OD DV (± SD)	0.59	±	0.63	-0.04	±	0.18	0.16
Change in OS DV (± SD)	0.53	±	0.90	0.26	±	0.33	0.65
Change in ICP (± SD)	1.58	±	1.28	2.61	±	4.08	0.65
Change in 3rd Ventricle (± SD)	0.04	±	0.03	0.93	±	0.40	**0.01**
Change in aqueduct (± SD)	0.07	±	0.05	0.46	±	0.21	**0.01**

Abbreviations: OD, right eye; OS, left eye; SD, standard deviation; ICP, intracranial pressure; CV, constriction velocity; DV, dilation velocity; NPi, neurological pupillary index

would fail or pass CSF diversion weaning. However, significant changes observed in the diameters of the cerebral aqueduct and 3rd ventricle measured via CT head were promising and represent a possible avenue of future study.

Changes in the pupil size are a well-known clinical finding used to identify intracranial changes. For example, compression of the posterior communicating (PCOM) and posterior cerebral (PCA) arteries by an aneurysm is a well-documented cause of oculomotor palsy with pupillary dilation.[8] Other causes of oculomotor nerve dysfunction resulting in concomitant pupillary changes are central nervous system tumors, midbrain infarction, trauma, and cavernous sinus lesions.[9] Among the classically known signs are small but reactive pupils found with injury to pupillodilator (i.e., sympathetic) fibers at the level of the hypothalamus and the pinpoint pupils associated with injury to the pontine region.[10] Likewise, an injury to both parasympathetic and sympathetic fibers results in midposition, fixed pupils similar to that associated with brain death.[11] Since the pupillometer enables rapid, easy measurement of CV (i.e., parasympathetic function) and DV (i.e., sympathetic function), evaluating these measurements in aSAH patients during the EVD weaning period may be a marker for EVD weaning success.

The pupilloconstrictor fibers (i.e., parasympathetic nervous system) originate in the Edinger-Westphal nuclei of the rostral midbrain at the level of the superior colliculus within paired nuclei located posteriorly to the oculomotor nucleus and anterolaterally to the cerebral aqueduct.[8] These fibers course along the peripheral aspect of the oculomotor nerve bundle as it exits the midbrain.[8] They then transit the interpeduncular cistern, course within the wall of the cavernous sinus, and finally pierce the dura to exit the cranium via the superior orbital fissure.[8] This course suggests obvious vectors for impingement resulting in pupillary abnormality. Similarly, the pupillodilator fibers (i.e., sympathetic nervous system) originate in the paraventricular nucleus within the hypothalamus.[8] They then descend uncrossed through the posterolateral tegmentum of the midbrain, pons, and medulla into the cervical spinal cord, synapsing at the lateral horn neurons of C8, T1, and T2 segments.[8,12] Preganglionic fibers then leave the cord (primarily at the T2 ventral root), traverse the stellate ganglion and then synapse in the superior cervical ganglion. Finally, postganglionic fibers form the carotid plexus, enter the

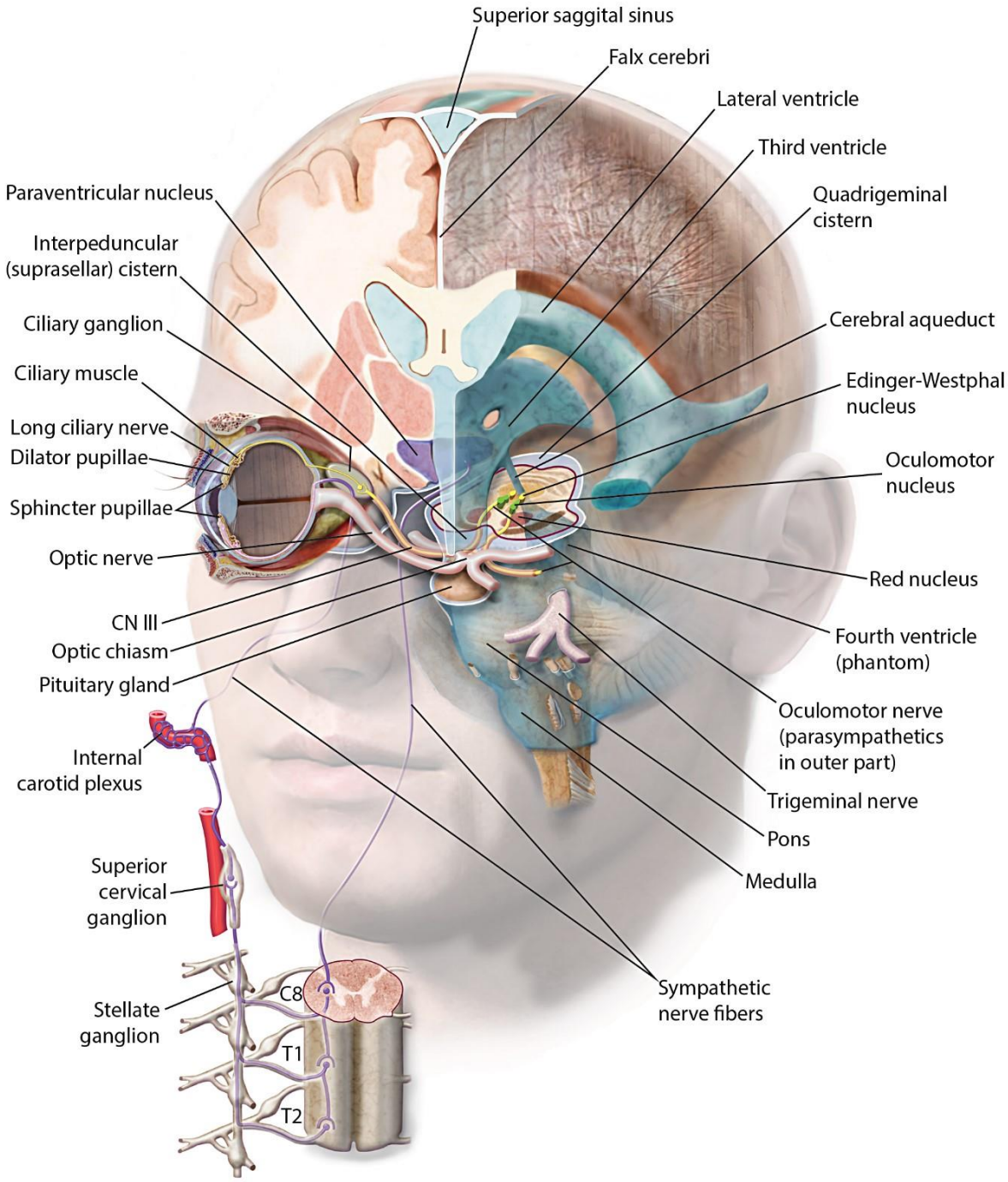

Figure 3. Cartoon of Cerebrospinal Fluid (CSF) and Proximity to Parasympathetic and Sympathetic Nervous Systems. The pupilloconstrictor fibers (i.e., parasympathetic nervous system) originate in the Edinger-Westphal nuclei of the rostral midbrain. These fibers are anterolateral to the cerebral aqueduct and transit the interpeduncular cistern. The pupillodilator fibers (i.e., sympathetic nervous system) originate in the paraventricular nucleus of the hypothalamus. These fibers could be affected by CSF volume at the level of the third ventricle, which is in close proximity to the paraventricular nucleus, and in the posterolateral tegmentum, which is close to the fourth ventricle.

cranial cavity, traverse the cavernous sinus, join the ophthalmic artery, and reach the eye as the long ciliary nerve innervating the dilator muscle of the iris.[8,13] The proximity of the paraventricular nucleus to the third ventricle and the course of the pupillodilator fibers present several locations for changes in CSF volume and ventriculomegaly to influence CV and DV. These sites include compression at the paraventricular nuclei, the posterolateral tegmentum close to the fourth ventricle, at the exit point of the spinal cord, within the wall of the cavernous sinus, and within the long ciliary nerve as it pierces the dura to exit the cranium and enter the orbit.

Figure 3 is a cartoon illustrating potential sites for CSF volume changes to influence CV and DV. We hypothesize that local changes at the level of the 3rd ventricle and/ or cerebral aqueduct could cause changes in the pupillary physiology in those who fail EVD weaning. Indeed, we found that changes at these levels on head CT do predict EVD weaning and failure. However, pupillary function was not found to be significantly affected by changes in CSF volume.

Because pupillary function can reflect intracranial changes, reliable methods of measurement are needed. In the setting of evaluation and management of brain injury, this need is great considering the vulnerability of pupillary measurements due to variations related to the examiner (e.g. experience level and visual acuity) and factors commonly found in the NSICU setting (e.g. variations in ambient lighting and equipment).[2,3] One study, while reporting high inter-rater reliability among nurses measuring pupillary size, reported low agreement when assessing pupillary reactivity.[14] A more recent study showed that different levels of staff (e.g. ambulance vs. hospital) recorded significant differences in pupil sizes.[15] Yet another study found senior neurology residents to have moderate inter-rater reliability for pupil size assessment and low agreement in discovering anisocoria.[16] By contrast, the pupillometer is an objective, consistent method of evaluating pupillary function.[1] It is important to note patients may have pre-existing ocular, systemic, or neurological disease.[1] Since the pupillometer is noninvasive and theoretically immune to inter-rater variability when used in a controlled manner, its use in identifying prognostic markers during EVD weaning is ideal.

Our data suggests that ICP was not an accurate predictor of EVD failure or variation in pupillometer-measured CV and DV values. In our study, the average ICP was 8.81 (± 3.46) mmHg in those who failed EVD weaning. It has been shown that measured ICP does not always correspond to the pressure being withstood by nerve fibers in various locations of the central nervous system (CNS). For example, CSF pressure in the optic nerve subarachnoid space and lumbar cistern is now known to be somewhat less than that of the intracranial space.[17] This finding is likely due to the buffering capacity of the CSF-filled ventricular system.

We excluded patients who were on continuous sedation and/ or analgesia since pupil size and function can be affected by these medications.[18,19] One recent study established that fentanyl decreased pupil size and altered pupil light reactivity but did not change the NPi.[18] Another study observed transient, symmetrical CV reductions in an outpatient population after administration of narcotics (oral or IV) and benzodiazepines.[20] For these reasons, we excluded patients who were on continuous sedation/analgesia infusion.

This was a retrospective study with strict inclusion criteria. It was limited by the low number of patients. Because of the

sample size, it is difficult to generalize to the population. However, no trend was observed in the patients we evaluated. Additionally, inter-rater reliability of the ventricular sizes was not calculated. Given the significance of ventricular size and weaning future studies should evaluate this as a marker for EVD weaning.

In conclusion, our data suggest that pupillary physiological variables were not reliable in differentiating which aSAH patients will pass and which will fail EVD weaning.

Notes

Author contributions: All authors have seen and approved the manuscript and contributed significantly to the work.

Financial support: Authors declare that no financial assistance was taken from any source.

Potential conflicts of interest: Christopher R. Newey has served on speaker's bureau for BARD medical. Drs. Bezner, Nattanmai, and Premkumar have no financial disclosures or conflicts of interests to report.

Acknowledgements: The authors would like to acknowledge Joe Chovan for creating the cartoon and Kristina Aldridge, PhD, for her review of the cartoon.

References

1. 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.
2. Kramer CL, Rabinstein AA, Wijdicks EF, and Hocker SE. Neurologist versus machine: is the pupillometer better than the naked eye in detecting pupillary reactivity. Neurocrit Care 2014; 21: 309-311.
3. Olson DM, Stutzman S, Saju C, Wilson M, Zhao W, and Aiyagari V. Interrater reliability of pupillary assessments. Neurocrit Care 2016; 24: 251-257.
4. Zafar SF and Suarez JI. Automated pupillometer for monitoring the critically ill patient: a critical appraisal. J Crit Care 2014; 29: 599-603.
5. Yolas C, Ozdemir NG, Kanat A, et al. Uncovering a new cause of obstructive hydrocephalus following subarachnoid hemorrhage: choroidal artery vasospasm-related ependymal cell degeneration and aqueductal stenosis-first experimental study. World Neurosurg 2016; 90: 484-491.
6. Suarez J, Tarr R, and Selman, W. Aneurysmal subarachnoid hemorrhage. NEJM 2006; 354: 1755-1757.
7. Connolly E, Rabinstein A, Carhuapoma J, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2012; 43: 1711-1737.
8. Haines D and Ard M. Fundamental Neuroscience For Basic And Clinical Applications, 4e. Philadelphia: Saunders, 2013
9. Suzuki K, Muroi A, Kujiraoka Y, Takano S, and Matsumura A. Oculomotor palsy treated by microvascular decompression. Surgical Neurology 2008; 70: 210-212.
10. Richerson G, Aston-Jones G, and Saper C. Principles Of Neural Science. New York: McGraw-Hill, 2013.
11. Fugate J, Eelco F, and Wijdicks M. Brain Death, Vegetative State, and Minimally Conscious States, Chapter 6. In: Daroff R, Jankovic J, Mazziotta J, Pomeroy S, Bradley W. Bradley's Neurology In Clinical Practice, 7e. London: Saunders, 2015.
12. Ropper AH, Samuels MA, Klein JP. Chapter 14. Disorders of Ocular Movement and Pupillary Function. In: Ropper AH, Samuels MA, Klein JP. eds. Adams & Victor's Principles of Neurology, 10e. New York: McGraw-Hill, 2014.
13. Thurtell M and Rucker J. Pupillary and Eyelid Abnormalities, Chapter 18. In: Daroff R, Jankovic J, Mazziotta J, Pomeroy S, Bradley W. Bradley's Neurology In Clinical Practice, 7e. London: Saunders, 2015.
14. Wilson S, Amling JK, Floyd SD, and McNair ND. Determining interrater reliability of nurses' assessment of pupil size. J Neurosci Nurs 1988; 20: 189–192.
15. Clark A, Clarke TNS, Gregson B, Hooker PNA, and Chambers IR. Variability in pupil size estimation. Emerg Med J 2006; 23: 440–441.
16. Litvan I, Saposnik G, Maurino J, et al. Pupillary diameter assessment: need for a graded scale. Neurology 2000; 54: 530.

17. Hou R, Zhang Z, Yang D, et al. Intracranial pressure (ICP) and optic nerve subarachnoid space pressure (ONSP) correlation in the optic nerve chamber: the Beijing Intracranial and Intraocular Pressure (iCOP) study. Brain Research 2016; 1635: 201-208.
18. Hou, R. H., Scaife, J., Freeman, C., Langley, R. W., Szabadi, E. and Bradshaw, C. M. Relationship between sedation and pupillary function: comparison of diazepam and diphenhydramine. Br J Clin Pharmacol 2006; 61: 752–760.
19. Shirozu K, Setoguchi H, Tokuda K, et al. The effects of anesthetic agents on pupillary function during general anesthesia using the automated infrared quantitative pupillometer. J Clin Monit Comput 2016; Feb 8 [epub ahead of print]
20. 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: 205–13.