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CLINICAL ARTICLE

Detection of delayed cerebral ischemia using objective pupillometry in patients with aneurysmal subarachnoid hemorrhage

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OBJECTIVE Cerebral vasospasm causing delayed cerebral ischemia (DCI) is a source of significant morbidity after subarachnoid hemorrhage (SAH). Transcranial Doppler is used at most institutions to detect sonographic vasospasm but has poor positive predictive value for DCI. Automated assessment of the pupillary light reflex has been increasingly used as a reliable way of assessing pupillary reactivity, and the Neurological Pupil Index (NPi) has been shown to decrease hours prior to the clinical manifestation of ischemic injury or herniation syndromes. The aim of this study was to investigate the role of automated pupillometry in the setting of SAH, as a potential adjunct to TCD.

METHODS Our analysis included patients that had been diagnosed with aneurysmal SAH and admitted to the neuro–intensive care unit of the University of Texas Southwestern Medical Center between November 2015 and June 2017. A dynamic infrared pupillometer was used for all pupillary measurements. An NPi value ranging from 3 to 5 was considered normal, and from 0 to 2.9 abnormal. Sonographic vasospasm was defined as middle cerebral artery velocities greater than 100 cm/sec with a Lindegaard ratio greater than 3 on either side on transcranial Doppler. Most patients had multiple NPi readings daily and we retained the lowest value for our analysis. We aimed to study the association between DCI and sonographic vasospasm, and DCI and NPi readings.

RESULTS A total of 56 patients were included in the final analysis with 635 paired observations of daily TCD and NPi data. There was no statistically significant association between the NPi value and the presence of sonographic vasospasm. There was a significant association between DCI and sonographic vasospasm, $\chi^2(1) = 6.4112$, $p = 0.0113$, OR 1.6419 (95% CI 1.1163–2.4150), and between DCI and an abnormal decrease in NPi, $\chi^2(1) = 38.4456$, $p < 0.001$, OR 3.3930 (95% CI 2.2789–5.0517). Twelve patients experienced DCI, with 7 showing a decrease of their NPi to an abnormal range. This change occurred > 8 hours prior to the clinical decline 71.4% of the time. The NPi normalized in all patients after treatment of their vasospasm.

CONCLUSIONS Isolated sonographic vasospasm does not seem to correlate with NPi changes, as the latter likely reflects an ischemic neurological injury. NPi changes are strongly associated with the advent of DCI and could be an early herald of clinical deterioration.

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KEYWORDS objective pupillometry; neurological pupil index; aneurysmal subarachnoid hemorrhage; cerebral vasospasm; delayed cerebral ischemia; transcranial Doppler; vascular disorders

ABBREVIATIONS DCI = delayed cerebral ischemia; EMR = electronic medical record; MCA = middle cerebral artery; NICU = neuro–intensive care unit; NPi = Neurological Pupil Index; PLR = pupillary light reflex; SAH = subarachnoid hemorrhage; TCD = transcranial Doppler ultrasound; UTSW = University of Texas Southwestern.

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The aftermath of aneurysmal subarachnoid hemorrhage (SAH) remains devastating despite modern advances in neurocritical care.[3,4,7,10,11,16,26,28] Patients who do not succumb to the initial insult from the aneurysmal rupture are at risk for cerebral vasospasm, which occurs angiographically and sonographically in 70% of patients.[11,16,19] Approximately 25% to 40% of these patients develop delayed cerebral ischemia (DCI), with neurological deficits and possible cognitive decline.[10,16] Transcranial Doppler ultrasound (TCD) has been shown in a recent meta-analysis to be predictive of DCI,[16] but with poor positive predictive value. TCD lacks solid specificity and is only reliable for monitoring middle cerebral artery (MCA) vessel flow through the transtemporal acoustic window.[10,16,19]

The negative predictive value of TCD makes it a useful tool for recognizing patients who are unlikely to develop DCI when there is absence of sonographic vasospasm, but its low specificity prevents the reliable identification of those who will eventually suffer from an ischemic injury. As a result, most centers tend to obtain catheter angiograms in patients whose TCD indices enter the severe vasospasm range, even when they remain neurologically intact. This also means that while patients receive modern adaptations of triple-H therapy (hypertension, hypervolemia, and hemodilution) during the vasospasm period, second-tier therapies for severe spasm, such as intravenous or intra-arterial infusions, are usually held back until clinical ischemia is detected because of the high-risk profile associated with these treatments.[1,15,17] The discrepancy between the presence of sonographic vasospasm and the advent of delayed ischemia likely results from the fact that DCI is only partially due to flow restriction, and that an added inflammatory and microvascular thrombotic component may be present.[4,10] To account for these intrinsic brain factors, multiple diagnostic modalities have been investigated. However, because they either are invasive or require specialized teams and services, their availability is limited to referral academic centers.[3,27]

Automated assessment of the pupillary light reflex (PLR) has recently emerged as an objective means of assessing pupillary reactivity across a broad spectrum of neurological disease, including stroke,[8,15,24,30] traumatic brain injury and edema,[5,6,29] tumoral herniation syndromes,[15,25] and sports or war injuries.[6,22] Pupillometers use infrared technology to assess an array of objective pupillary variables including size, constriction velocity, latency, and dilation velocity which are normalized and standardized to compute the Neurological Pupil Index (NPi).[6,8,13,23,24,30,31] The NPi values range from 0 to 5, with values 3 or greater considered normal.

The NPi changes are thought to reflect direct injury to the oculomotor nerve or indirect damage to the brain that would affect efferent and afferent visual-motor pathways.[25] Given the span of these pathways throughout the structures of the midbrain,[12,14] their proximity to the skull base vasculature, and their influence by cognition and neocortical functions,[2,20] as well as by sympathetic and parasympathetic responses,[14] we postulated that these pathways could be affected by the focal or global DCI that occurs after aneurysmal SAH. More importantly, the NPi has been reported to decrease hours prior to the clinical manifestation of ischemic injury or herniation symptoms, as a potential herald of irreversible neurological damage.[21,25] In this study, we investigated the role of automated pupillometry reading changes in the setting of SAH, as a potential adjunct to TCD.

Methods

The data for this study were abstracted from the Establishing Normative Data for Pupilometer Assessments in Neuroscience Intensive Care Registry (END-PANIC), which is registered with clinicaltrials.gov (registration no. NCT02804438). Data collection for this multicenter registry is ongoing, with data being collected at 3 US centers—Mission Hospital, Saint Joseph Health System, in Mission, California; University of Texas Southwestern (UTSW) Medical Center, in Dallas, Texas; and Riverside Methodist Hospital, Ohio Health, in Columbus, Ohio, although only data from UTSW were used in the present study. The purpose of the registry is to collect information on automated pupillary readings and physiological patient measures throughout the course of the neurological patient's stay in the hospital. The END-PANIC registry and methodology have been previously described in detail.[24] Institutional review board approval was obtained prior to the initiation of this study.

This analysis included patients who had been diagnosed with an aneurysmal SAH and admitted to the neuro–intensive care unit (NICU) of one of the participating institutions between November 2015 and June 2017. Patients were identified using the ICD-10 diagnosis code 160.7 ("nontraumatic subarachnoid hemorrhage from unspecified intracranial artery") and chart review. Data collection only included time spent in the NICU. Patients with nonaneurysmal SAH, such as peri-mesencephalic angiography-negative SAH, were excluded. Patients who had no TCD data stored in the electronic medical record (EMR) were also excluded. A dynamic infrared NPi-200 pupillometer (NeurOptics, Inc.) was used for all pupillary measurements. Pupillometer assessment is currently standard of care at UTSW. Pupillometer readings are acquired at least once every 4 hours as part of routine nursing care, and more frequently (hourly) if the readings or the clinical exam are abnormal or changing. Parameters collected include the NPi, maximum and minimum pupillary diameter, constriction velocity, dilation velocity, and latency time. The measurements are displayed on the device screen and obtained for each eye by the patient's nursing staff. The NPi is recorded in the EMR and the remaining variables are logged in an electronic spreadsheet, as a paired set of readings. An NPi value ranging from 3 to 5 is considered normal, and a value ranging from 0 to 2.9 is considered abnormal.

Given that multiple sets of pupillometer readings were obtained daily, and only one set of TCD readings, the set of pupillometer readings with the lowest NPi for the corresponding 24-hour period was included. The paired left and right eye pupillometer readings were studied as a single data unit observation, as making the distinction between left and right eye measurements was beyond the scope of this study. Only the lowest NPi value for the pair

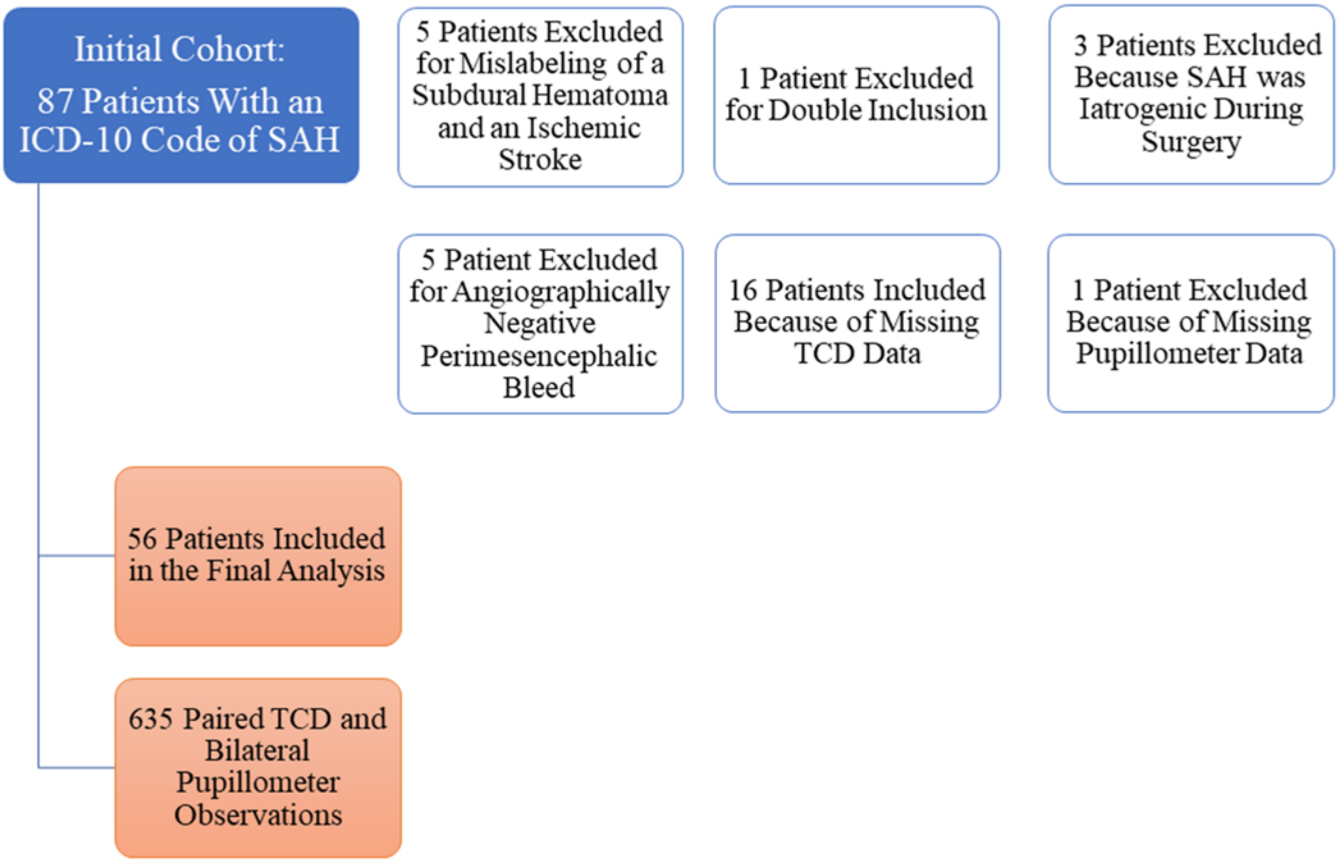

FIG. 1. Flow diagram illustrating patient selection for the analysis. Figure is available in color online only.

for the day was retained. Pupillometer data were not included for any day where TCD was not performed. TCD and NPi measurements were obtained for the duration of the NICU stay until the patient has floor transfer orders. In each case, clinical examinations were performed twice daily by the neurosurgery team, and hourly by the nursing staff, and findings were abstracted from the patient's EMR. Transcranial Doppler studies occurred daily 6 days a week, and were obtained using an ST3 Transcranial Ultrasound System (Spencer Technologies, Inc.). Bilateral transtemporal windows were used to obtain MCA velocities and to compute Lindegaard ratios.[18] Sonographic vasospasm was defined as TCD MCA velocities greater than 100 cm/second with a Lindegaard ratio greater than 3 on the left or right side. Data were imported from the EMR to an Excel spreadsheet and subsequently entered into SAS v.9.4 (SAS Institute Inc.) for analysis. Pearson chi-square tests of independence were performed to study the relationship between categorical variables, with a predetermined alpha level of significance of 0.05. We aimed to study the relationship between NPi and TCD readings, as well as the association between the presence of DCI and sonographic vasospasm and the presence of DCI and abnormal NPi values. Delayed cerebral ischemia (DCI) was defined clinically as the development of a new focal neurological deficit, and/or the sudden deterioration in the level of consciousness lasting longer than 1 hour.[9]

Results

The initial search using the ICD-10 code 160.7 yielded 87 patients. After individual chart review, 30 patients were excluded from the analysis for reasons listed in Fig. 1. Among the 56 patients who were included, 40 were female. The ruptured lesion belonged to the anterior circulation in 45 patients. Thirty-two patients had a Hunt and Hess grade of I or II on admission. We collected 635 paired observations in total, with each observation consisting of 1 set of daily bilateral TCD readings and a bilateral set of pupillometer values. Most patients had multiple bilateral daily pupillometer readings in the NICU, and we selected the one with the lowest NPi to facilitate the final analysis. There was no statistically significant association between the NPi value and sonographic vasospasm in the study population ($p = 0.1404$, OR 1.4748, 95% CI 0.8778–2.4779). A Pearson chi-square test of independence was performed to examine the relationship between DCI and sonographic vasospasm. There was a significant association between DCI and sonographic vasospasm: $\chi^2(1) = 6.4112$, $p = 0.0113$, OR 1.6419 (95% CI 1.1163–2.4150) (Table 1). The Pearson chi-square test of independence was also used to examine the relationship between DCI and abnormal NPi observation (NPi value 0–2.9). There was a significant and strong association between the development of DCI and the abnormal decrease in NPi: $\chi^2(1)$

TABLE 1. Contingency table: NPi and DCI

NPi	DCI–Clinical Vasospasm		
	Yes	No	Total
Abnormal: NPi 0–2.9	65 (10.24%)	74 (11.65%)	139 (21.89%)
Normal: NPi 3–5	102 (16.06%)	394 (62.05%)	496 (78.11%)
Total	167 (26.30%)	468 (73.70%)	635 (100%)
$\chi^2(1)$	6.4112		
p Value	<0.0001		
OR (95% CI)	3.3930 (2.2789–5.0517)		

TABLE 2. Contingency table: sonographic vasospasm and DCI

Sonographic Vasospasm	DCI–Clinical Vasospasm		
	Yes	No	Total
Yes	56 (8.82%)	110 (17.32%)	166 (26.14%)
No	111 (17.48%)	358 (56.38%)	469 (73.86%)
Total	167 (26.30%)	468 (73.70%)	635 (100%)
$\chi^2(1)$	38.4456		
p Value	0.0113		
OR (95% CI)	1.6419 (1.1163–2.4150)		

= 38.4456, $p < 0.001$, OR 3.3930 (95% CI 2.2789–5.0517) (Table 2). Twelve patients experienced DCI during their NICU stay. Ten of these patients had sonographic vasospasm on TCD. Eight patients had a generalized cognitive decline, and 4 had a new-onset monoparesis. Seven of these 12 patients showed a decrease in their NPi to values < 3 after initially presenting with normal bilateral readings. None of these patients presented with or developed a third cranial nerve palsy that would explain the decrease in their NPi. An emergent catheter angiogram was obtained in all 12 patients showed severe vascular stenosis in each case. All 12 patients had partial or complete resolution of their symptoms after endovascular mechanical or chemical treatment and had returned to their neurological baseline at the time of their discharge from the NICU. In 5 of these patients, the decrease in the NPi occurred > 8 hours before their clinical neurological decline was detected on hourly neurological examination. The NPi had renormalized to values > 3 in all patients the day of their discharge from the NICU. The improvement of the NPi tended to occur progressively after our intervention, lagging behind the clinical resolution of neurological deficits.

Discussion

Trancranial Doppler ultrasonography is a widely accepted tool for detecting cerebrovascular vasospasm in the setting of SAH, and sonographic observations have been shown to correlate well with catheter angiogram findings.[3,10,26] However, sonographic spasm does not progress to brain ischemia and DCI in the majority of cases.[16] A meta-analysis of the neurosurgical literature showed that TCD has a good negative predictive value, but low specificity. This makes it a good tool for ruling out the advent of DCI but an unreliable instrument for identifying patients who are likely to have ischemic symptoms with accuracy.[16] We postulated that the PLR could be affected by ischemic changes due to vasospasm after SAH and that automated pupillometry readings could help us identify patients who will develop or who are undergoing DCI more reliably. This assumption is based on the theory that the circuits responsible for the PLR can be affected by ischemia and that the change in reactivity will be detected by the pupillometer as the NPi decreases to abnormal levels.

Our study confirms the discrepancy between the presence of sonographic narrowing of the intracranial vessels after SAH and the advent of ischemic injury, as there was no correlation between abnormally high TCD readings and NPi decrease. As expected, abnormally high TCD readings in the vasospasm category were associated with the development of DCI, and that correlation was moderate. This is not surprising given the known low specificity and high sensitivity of Doppler ultrasonography. Pupillometer changes with NPi decrease to < 3 was strongly associated with the advent of DCI. These changes were observed in 7 of 12 patients who developed DCI (58.3%) and, interestingly, occurred 8 hours or more prior to clinical deterioration 71.4% of the time.

The potential advantage of adding hourly automated pupillometry data collection to daily TCD examinations when treating NICU patients with SAH, especially in the setting of continuously increasing TCD indices, resides in the fact that it could provide the treatment team with several hours of warning prior to the installment of potentially irreversible injury, and enable the preemptive escalation of care. Escalation could range from more aggressive fluid bolus administration, to early return to the angiography suite for endovascular treatment. This early-onset change of the NPi has been previously reported by Papangelou et al.[25] in the setting of transtentorial herniation, where pupillary reactivity became abnormal prior to 73% of 12 herniation events studied (occurring a median of 7.4 hours prior to herniation). As in our study, pupillometry readings in that series returned to the normal range after treatment of increased intracranial pressure.

There are recognized limitations with our work. The initial size of our cohort was small (n = 87). Excluding 17 patients because of missing EMR data may have skewed our results and affects the generalizability of our conclusions. We also did not have regular hourly pupillometer data available, which could account for the 71.4% rate of NPi changes in patients with DCI. The lack of hourly data before and after vasospasm treatment in the 12 patients with DCI also prohibited us from defining the timeframe of NPi recovery after the ischemic insult had been reversed. Hourly collection of automated pupillometer data is now standard at our institution for all SAH patients during their NICU stay. Similarly, we did not repeat TCD examinations in the event of acute clinical decline for practical reasons, since we would be rushing the patient for an emergent procedure. Accordingly, that paired TCD/NPi measurement following a neurological change could not be available for analysis. Finally, we did not independently look at left and right eye changes and instead considered paired readings as a unit. Future studies will allow us to establish a correlation between the side of the brain predominantly affected by vasospasm and ipsilateral eye abnormalities.

Conclusions

In this sample, an NPi decrease in patients with SAH was associated with DCI. Pupillometer changes may occur hours prior to the clinical neurological decline. This may provide the treatment team with enough warning to initiate pre-emptive therapeutic measures before the development of irreversible neurological damage, especially in the context of elevated TCD readings and in patients who have significant clinical and radiological risk factors for DCI. Pupillometry is not meant to replace a good clinical, radiological, and sonographic examination, but instead to complement it—and add a piece to the puzzle of the larger picture. These results are interesting and warrant further investigation.

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Disclosures

Dr. Olson reports receiving a salary from NeurOptics as a PI of the End-PANIC database. Dr. Stutzman reports receiving a salary from NeurOptics as a Co-I of the End-PANIC database. Drs. Stutzman and Aiyagari both report receiving clinical or research support from NeurOptics for the study described.

Author Contributions

Conception and design: Aoun, Batjer, Olson. Acquisition of data: Aoun, El Ahmadieh, Neeley, Plitt, Caruso. Analysis and interpretation of data: Aoun, Stutzman, Aiyagari, Atem, Welch, White, Olson. Drafting the article: Aoun. Critically revising the article: Stutzman, El Ahmadieh, Osman, Aiyagari, Welch, White, Batjer, Olson. Statistical analysis: Stutzman, Vo, Atem. Study supervision: Olson.

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