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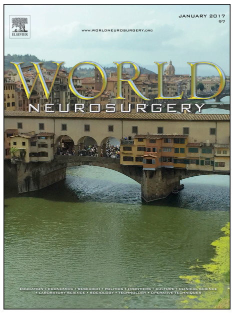

Objective Pupillometry As an Adjunct to Prediction And Assessment For Oculomotor Nerve Injury And Recovery: Potential for Practical Applications

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Abstract

Background

The pupillary light reflex examination is an intrinsic part of any good neurological exam. It can be affected by injury to the eye itself, the afferent and efferent pathways, and more importantly the brain due to stroke, traumatic brain injury, or toxicity. There has been consistent evidence that automated pupillometry assessment can provide superior accuracy and interrater correlation compared to bedside eye examination. Pupillary indices such as the Neurological Pupil Index (NPI) may also provide the treatment team with several hours of warning prior to the advent of herniation syndromes, or third nerve palsy. Pupillometer use is being increasingly implemented on the battlefield, and the playing field after sports-related concussions.

Methods

We aimed to portray the unique temporal relationship between NPi change and third nerve palsy occurrence and recovery, in a hospitalized patient that was initially neurologically intact. A 53-year-old woman presented with aneurysmal subarachnoid hemorrhage and headaches. Her aneurysm was treated surgically without complication. After lumbar drainage for hydrocephalus she developed an isolated left third nerve palsy that slowly recovered over the following weeks. Pupillometer data was obtained throughout her hospital stay.

Results

A total of 121 sets of pupillary measurements were obtained. The NPi decreased to abnormal levels of less than three, 12 hours before she became symptomatic. The NPi also started improving 24 hours prior to the improvement of her clinical exam. The patient did not display signs of neurological dysfunction related to vasospasm during her stay.

Conclusion

The NPi value seems to reliably correlate with third nerve function, and appears to possess predictive temporal properties that could allow practitioner to anticipate neurological injury, as well as recovery. These findings could heavily impact the fields of Neurosciences, Trauma, Military Medicine, Critical Care, and Ophthalmology.

Keywords:

Objective pupillometry; Third nerve palsy recovery; Neurological Assessment tool; Prognostic Neurological tool; Neurological Pupil Index; Pupillometer

Introduction

Observing the pupillary light reflex (PLR) whether in the hospital setting or on the field after traumatic civilian, military, or sports-related head injury remains a cornerstone of neurological assessment.[1-4] Pupil examination provides practitioners and first responders with a direct interpretation of the patient's global neurological state. The PLR is useful in guiding patient care in situations of malignant cerebral infarction and traumatic brain edema, where the cerebrum is at risk of transtentorial herniation. Pupillary dilatation is often an ominous sign of impending irrecoverable brain injury, and usually prompts the implementation of aggressive medical and surgical maneuvers. However, the interrater reliability of the subjective assessment by human practitioners is poor[5-7] and loss of the PLR is usually a late sign that potentially irreversible neurological injury has already taken place.

Automated pupillometric assessment using infrared technology has emerged as a means of reliably assessing pupillary function that can be standardized between users as well as medical institutions.[4,6,8] Pupillometers provide an array of objective and independent pupillary variables, which include size (resting and constriction), latency, constriction velocity, and dilatation velocity. These variables are then normalized and standardized using a stored databank of normal values to compute the Neurological Pupil Index (NPi).[8] The NPi ranges from zero to five, with a value equal or greater than three considered normal.[8] Differences between left and right eye indices are considered to be abnormal.

The NPi has been reported to potentially reflect disruption of the oculomotor nerve's (CN-III) capability to accurately convey motor stimuli. An abnormal NPi could reflect direct damage to CN-III itself, or, more frequently, indirect damage to the brain affecting afferent and efferent visual-motor pathways.[1-3] Preliminary studies have shown promise in the context of war and sports-related traumatic brain injury and edema,[2,9] increased intracranial pressure,[10] transtentorial herniation from tumoral compression,[1] chemical warfare exposure,[11] Horner Syndrome,[10] and malignant middle cerebral artery infarction.[12,13] Interestingly, the main clinical benefit from serial monitoring of the NPi may reside in its predictive ability, as is appears to abruptly decrease hours prior to clinical ischemic or herniation symptoms,[1,10] and could potentially provide the treatment team with sufficient time to intervene and perhaps prevent irreversible brain injury. The aim of this manuscript is to report technical data from an index clinical case that seems to convincingly support these claims, and where the NPi decrease appears to predict a neurological deficit hours prior to its occurrence, and the NPi increase may be an indicator of future clinical recovery.

Methods

This study used a dynamic infrared pupillometer (NPi-200; NeurOptics, Inc., Irvine, CA, USA) for all pupillary measurements. Pupillometer assessment is standard of care in our institution. Pupillometer readings are acquired at least once every four hours as part of routine nursing care, and more frequently (hourly) if the readings or the clinical exam are abnormal or changing. Pupillometer acquisition is done at the bedside and takes approximately 15 seconds per eye. Parameters collected include the NPi, maximal and minimal pupillary diameter, the constriction velocity and latency time. The measurements are displayed on the device screen and obtained for each eye by the patient's nursing staff. The device is capable of storing the entirety of the recorded data for the duration of the patient's stay. Data is stored in a SmartGuard® single-patient-use device that attaches to the pupillometer, and averages less than 50$ per patient. The pupillometer itself only needs to be purchased once and becomes part of tools available in each intensive care unit (ICU) room. Observations are documented in both the electronic medical record and a prospectively collected institutional review board approved registry (The "Establishing Normative Data for Pupillometer Assessment in Neuroscience Intensive Care"; END-PANIC multi-institutional registry).[6] Daily transcranial doppler (TCD) velocities for anterior and posterior circulations are obtained for each hemisphere as is standard in our institution after subarachnoid hemorrhage for the entirety of the ICU stay, and a catheter angiogram was performed on day eight after aneurysmal rupture. A full neurological assessment was also performed hourly during the neurocritical care unit (NCU) length of stay. No funding was received for this study. Institutional review board approval was waived given the retrospective nature of this analysis of a single patient's chart, in accordance with our institutional protocol.

Results

Clinical Case

A 53 year-old woman was transferred to our NCU 4-hours after complaining of severe and sudden headaches. Her head computed tomography (CT) scan (figure 1) showed significant subarachnoid hemorrhage as well as some intraventricular hemorrhage (Fisher score of 4). She was otherwise neurologically intact, and her extraocular muscles and pupillary responses were intact bilaterally. A CT-angiogram was performed and revealed a 3 mm left posterior communicating artery aneurysm that was likely the cause of her hemorrhage (Figure 2). She was taken to the operating room and underwent a left craniotomy with clip obliteration of the aneurysm. A lumbar drain was placed to allow for cerebrospinal fluid drainage since she suffered from moderate hydrocephalus. She was neurologically intact immediately after surgery and was transferred to the NCU for cerebral vasospasm monitoring and management. Her NCU stay duration was 17 days. Although her TCD values went into the sonographic vasospasm range, she had no clinically symptomatic delayed cerebral ischemia (DCI) and remained neurologically intact. A catheter angiogram performed on day eight, at the peak of her sonographic vasospasm period, only showed mild to moderate spasm.

Pupillometer Data

A total of 121 sets (bilateral) of objective pupillary measurements were obtained for each eye during her stay. Both eyes had values within normal range that were symmetrical during the first 3 days of her admission, and unchanged before and after her surgery. On the third day the NPi of her left eye started decreasing to levels below 3 and her left pupil minimal constrictive diameter started to increase (figures 2 and 3). On the morning of the fourth day (12 hours after the NPi had decreased), she began to complain of diplopia and had a moderate left third nerve palsy on clinical examination. Her lumbar drainage rate was initially set at 30 ml every two hours but was decreased to 30 ml every four hours based upon concern for oculomotor neuropraxia in the setting of spinal fluid drainage. Her CT angiogram scan did not show any signs of brain sag nor new bleeding or significant vasospasm (figure 3). During her next drainage session four hours later, she complained of severe spinal headaches and upon clinical examination her CN-III palsy had become complete. At this time, the NPi values in the left eye dropped below 1.0 and her pupil was maximally dilated despite light stimulation (figures 4 and 5).

She required eye patching on the left to be able to orient herself and work with physical therapy. Although it is very unusual for lumbar drainage to cause an isolated third nerve palsy, she had no signs of new bleeding nor of vascular spams on her CT and CT angiogram scans, and she remained very alert. The decision was made to stop her lumbar drainage. Three days later, her pupillometer indices started to improve with an NPi greater than 1.0 and a minimal pupillary diameter of less than 5 mm. The following day (24 hours after the NPi had started to normalize) she reported clinical improvement of her diplopia. Her oculomotor nerve function continued to recover during her stay, and at discharge, her NPi had normalized above 3.0. At discharge, she no longer required an eye patch to perform daily activities. At her 6-week postoperative clinic visit her oculomotor function had been restored, and her NPi was bilaterally within normal range.

Discussion

The consistent use of automated pupillometry to assess pupillary responsiveness and the integrity of neurological pathways is still in its infancy stages. Observations in the 1950's had already shown that infrared measurements would eliminate discrepancies in inter- and intra-rater assessments,[9] but its use in routine clinical practice has been questioned until recently. Although a more accurate and reliable evaluation of the PLR can be useful from a documentation standpoint, some clinicians argue that a good clinical examination is adequate to guide clinical decisions. However, recent publications have shown that a more accurate assessment of PLR pathway function may help with the management of critically ill patients.[1,3,4,9,11-13]

Papangelou et al.[1] assessed three patients at risk for transtentorial herniation from supratentorial mass lesions, with objective pupillary measurements obtained in an NCU setting in addition to routine clinical examination. Twelve episodes of clinical transtentorial herniation were recorded. The NPi index was abnormal in 73% of cases, and interestingly, seemed to change a median of 7.4 hours prior to the herniation event, and appeared to be foretelling. This early sign could potentially provide critical care teams with several hours of warning before patients become clinically symptomatic. NPi changes preceded clinical and electronic pupillary dilatation and constriction abnormalities in all cases. In the setting of an unresponsive patient where herniation may occur, but could be medically or surgically mitigated if foreseen, this preemptive information could prove very useful.

Kim et al.[13] used pupillometer data to monitor for transtentorial herniation in the setting of malignant middle cerebral infarction, and noticed a correlation between herniation events and NPi value decrease. Chen et al.[9] had comparable conclusions when they examined five patients with traumatic brain injury and a unilateral third nerve palsy with pupillary dysfunction. The NPi was abnormal on the side of the deficit, and its early improvement seemed to predict clinical recovery of pupillary activity at the long-term follow-up. During a study assessing the routine use of pupillometry among military personnel,[11] Mease et al. determined that it could potentially be used as a quick and seamless method to detect organophosphate and chemical warfare agent exposure.

The data from our reported index case aligns with previously published results. We had the opportunity to monitor a patient who was neurologically intact on admission, and then suddenly experienced a neuropraxic injury, followed by clinical recovery. DCI was not a contributing factor to neurological injury. The variations in the NPi clearly preceded both the clinical deficit and the recovery of third nerve function. In addition, right eye indices remained normal and acted as a control set in the same patient, which automatically negated intrinsic bias factors that are usually encountered when comparing individuals. This change in NPi could potentially prompt us in the future to obtain angiographic studies assessing vasospasm earlier, or even to discontinue/reduce lumbar drainage pre-emptively prior to the advent of clinical symptoms. NPi computation could also be used in outpatient follow-up visits to further track the recovery of the third nerve function of injured patients. This tool may provide Neurosurgeons, Neurologists, and Ophthalmologists with the means to acutely assess an oculomotor nerve palsy in the inpatient setting -a tool which was previously unavailable- and to potentially predict and track future recovery in a non-invasive and reproducible fashion.

Evidence from current pupillometer data is prone to several limitations. The number of reported cases where a clinical correlation with the changes in objective pupillary measurements and NPi variation has been sought out, is limited to a handful of studies with a small sample of subjects where clinical confounders may have affected the data. In our particular case, even though clinical and observational pupillary changes appear to correlate, they may not be accurately representative of the train of events in the general population. In addition, even though we are making the assumption that the left third nerve palsy may be linked to lumbar drainage, this is a rare event, and it could have been facilitated by moderate vasospasm or even by the irritative effect of the subarachnoid blood around the third nerve. However, the NPi change seems to correlate and perhaps predict neurological injury, regardless of the cause. These trends are encouraging and show enough promise to warrant further investigation in larger cohorts.

Conclusion

Automated pupillometry may provide an accessible, portable, and easily reproducible means of detecting direct neurological injury to the oculomotor nerve, or more importantly to detect secondary injury due to cerebral edema from traumatic or ischemic insults. It could also have uses on the battle or the athletic fields as part of the initial workup for military or sports-related impacts, and to rule out exposure to chemical warfare agents. The NPi variation may have value as a non-invasive marker with predictive properties, providing several hours of warning prior to the installment of potentially irreversible injury. Early normalization of NPi values could also reflect a greater potential for clinically significant recovery at follow-up. Much of the evidence currently available remains anecdotal but is encouraging, easy to obtain, and inexpensive enough to warrant additional research. There is work currently underway to assess the generalizability of these findings at a larger scale.

Figure Legends

Figure 1:

Axial cut of a non-contrasted computed tomography scan of the brain showing pan-cisternal subarachnoid hemorrhage and intraventricular hemorrhage.

Figure 2:

Three dimensional reconstructions demonstrating the left posterior communicating aneurysm (yellow circle)

Figure 3:

Axial cut of a computed tomography angiography scan of the brain at the time of initial complaint of third nerve malfunction, showing no vasospasm with a normal-sized left middle cerebral artery, and no new bleeding or mass effect on the left third nerve.

Figure 4:

Quantitative pupillary findings for the neurological pupil index (NPi) in function of the duration of hospital stay in days, for the right eye (red line) and left eye (blue line). Full black arrow: time of initial clinical manifestation of the left eye third nerve malfunction. Diamond arrow: time of subsequent worsening with full third nerve paralysis. Striped black arrow: time of initial clinical recovery.

Figure 5:

Quantitative pupillary findings for the minimal constriction diameter after exposure to light, in function of the duration of hospital stay in days, for the right eye (red line) and left eye (blue line). The black arrow indicates the time of initial clinical manifestation of the left eye third nerve malfunction.

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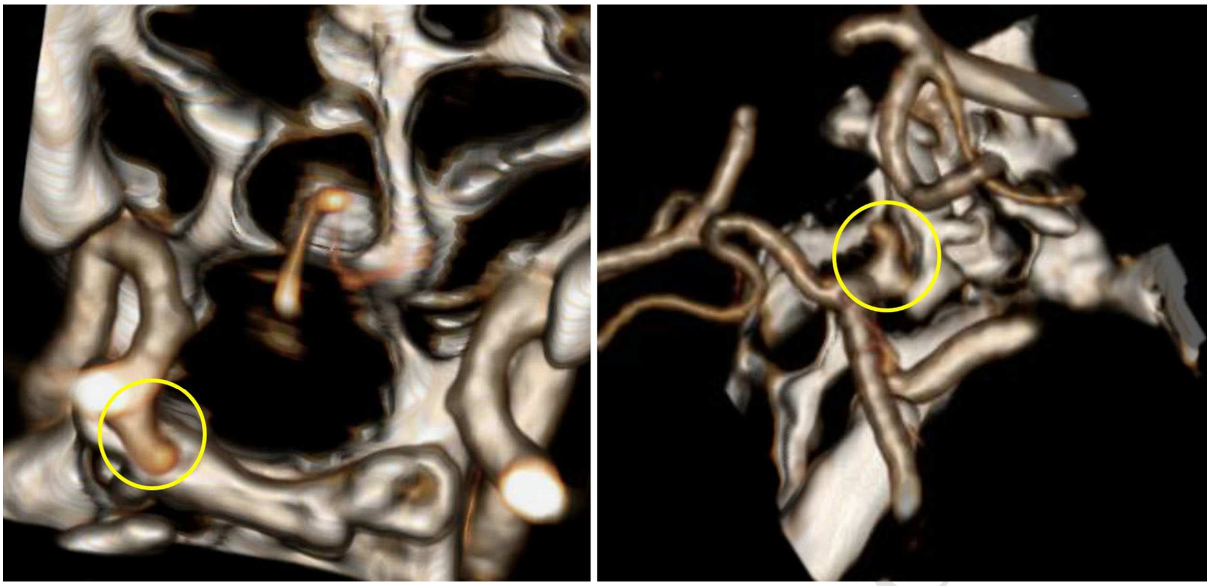

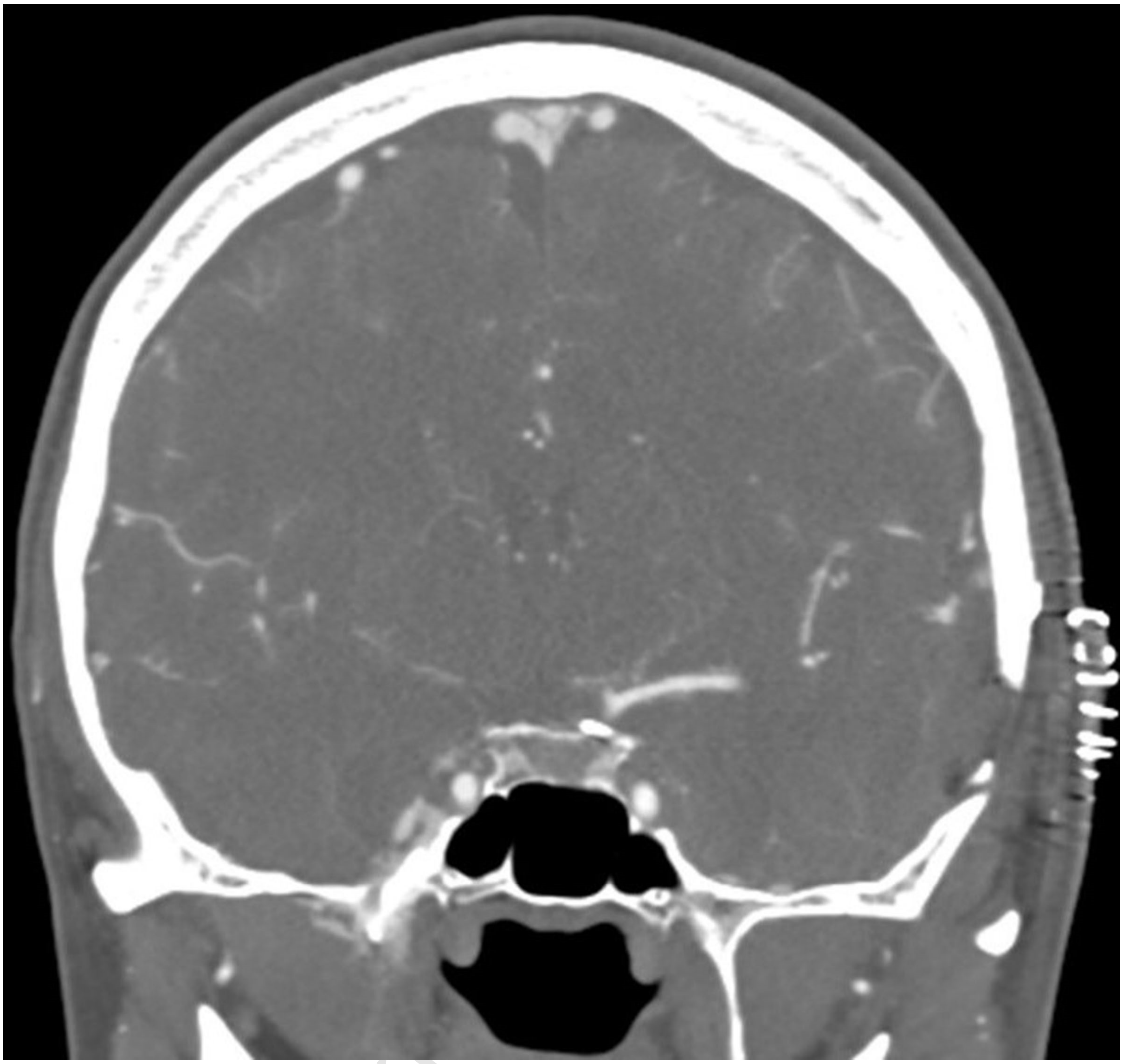

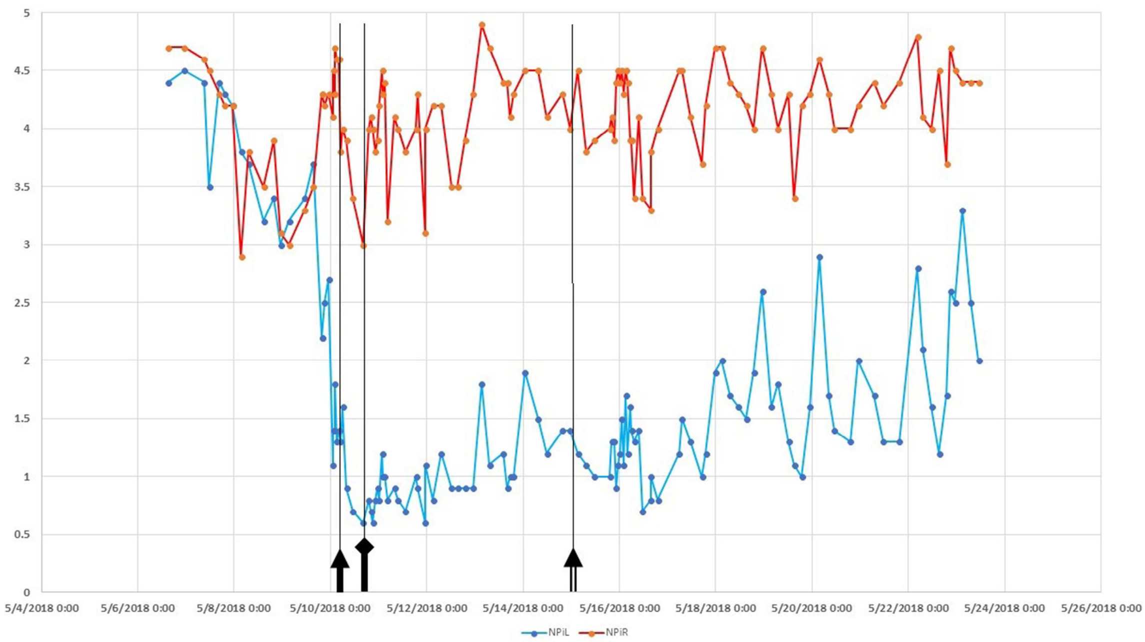

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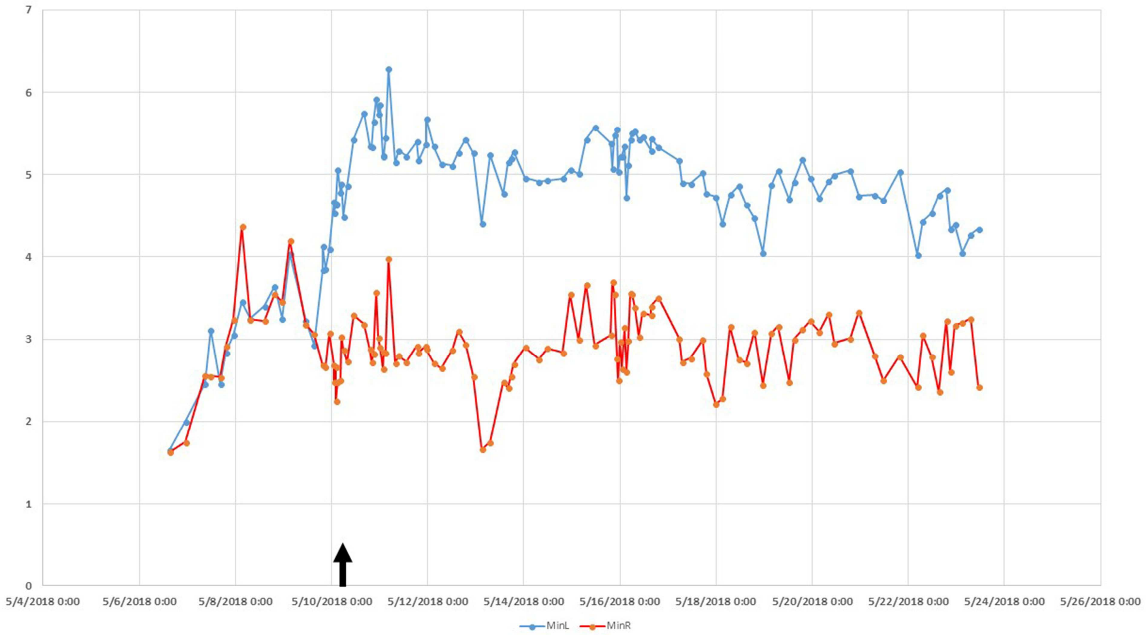

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- Objective pupillometry can reliably detect pupillary changes
- An oculomotor nerve palsy can be reflected by a in the NPi<3
- NPi decrease can predict oculomotor dysfunction by several hours
- Early NPi increase may be a predictor of future neurological recovery
- Future applications of pupillometer measurements could involve stroke, vasospasm, and trauma

Abbreviations:

- NPI: Neurological Pupil Index
- CN: Cranial Nerve
- TCD: Transcranial Doppler
- NCU: Neurocritical Care Unit
- CT: Computed Tomography
- DCI: Delayed Cerebral Ischemia