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ORIGINAL WORK

Neurological Pupil Index and Pupillary Light Reflex by Pupillometry Predict Outcome Early After Cardiac Arrest

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Abstract

Background: The absence of the pupillary light reflex (PLR) 3 days after cardiac arrest predicts poor outcome, but quantitative PLR assessment with pupillometry early after recovery of spontaneous circulation (ROSC) and throughout targeted temperature management (TTM) has rarely been evaluated.

Methods: Fifty-five adult patients treated with TTM with available pupillometry data from the NeurOptics NPi-200 were studied. Discharge outcome was classified good if the cerebral performance category score was 1–2, poor if 3–5. Pupil size, PLR percent constriction (%PLR), and constriction velocity (CV) were determined at TTM start and 6 (± 2)-h post-ROSC ("early"), and throughout TTM using data from the worst eye at each assessment. The Neurological Pupil index (NPi) was also determined at each pupil assessment; the NPi is scored from 0 (nonreactive) to 5 (brisk) with values < 3 considered sluggish or abnormal. Prognostic performance to predict poor outcome was assessed with receiver operator characteristic curves.

Results: All nine patients with ≥ 1 nonreactive pupil (NPi = 0) within 6 (± 2) h after ROSC died, and 12/14 (86%) with sluggish pupils (0 < NPi < 3) had poor outcomes. 15/29 (52%) patients with normal pupil reactivity (NPi ≥ 3) had poor outcomes, four survived with cerebral performance category = 3, three died of cardiac causes, and eight died of neurologic causes. During TTM, 20/21 (95%) patients with nonreactive pupils had poor outcomes, 9/14 (64%) of patients with sluggish pupils had poor outcomes, and 9/20 (45%) with normal pupil reactivity had poor outcomes. Pupil size did not predict outcome, but NPi (AUC = 0.72 [0.59–0.86], $p < 0.001$), %PLR (AUC = 0.75 [0.62–0.88], $p < 0.001$) and CV (AUC = 0.78 [0.66–0.91], $p < 0.001$) at 6 h predicted poor outcome. When nonreactive pupils were first detected, 75% were < 5 mm.

Conclusions: Very early after resuscitation from cardiac arrest, abnormal Neurological Pupil index and pupillary light reflex measurements by pupillometer are predictive of poor outcome, and are not usually associated with dilated pupils.

Keywords: Cardiac arrest, Targeted temperature management, Therapeutic hypothermia, Pupillary light reflex, Prognostication

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Introduction

Predicting neurological outcome during targeted temperature management (TTM) after cardiac arrest remains challenging [1]. Practice recommendations have identified the reliability of an absent pupillary light reflex (PLR) 72 h after cardiac arrest to predict poor neurological outcome [2–5], and recommended further research with the PLR as a prognostic tool in severe brain injury [5]. The PLR may supplement data from other tools (such as the electroencephalogram [EEG] reflecting cortical activity) by providing a means to monitor changes in midbrain function.

Though traditionally categorized as a dichotomous variable (present or absent), the PLR has recently been quantified with pupillometer techniques to measure the percent constriction (%PLR) after a light stimulus in several types of brain injury, including traumatic brain injury [6] and hypoxic-ischemic encephalopathy after cardiac arrest [7–12]. In post-cardiac arrest care, published studies of pupillometry are limited to evaluations during cardiac arrest [10], or at only two or three daily evaluations after cardiac arrest [7–9, 12]. In addition, these reports have focused on the amplitude of the %PLR [7–9, 11] which varies depending on the pupil size before the light stimulus and is affected by anesthetic drugs including propofol [13]. In this diagnostic accuracy study, we wished to review our experience with pupillometry in the early time frame after cardiac arrest and throughout TTM using the Neurological Pupil index (NPi) comparing it to pupil size and %PLR to predict a poor outcome after cardiac arrest. The NPi is calculated based upon the reflex amplitude, constriction velocity, redilation velocity, and latency, appears to be independent of pupil size [13], and is reported as a continuous variable from 0 (nonreactive) to 5 (brisk). We hypothesized that NPi and %PLR would predict poor outcome better than pupil size.

Methods

Encephalopathic adults surviving an initial cardiac arrest (any location or rhythm) were treated with 24 h of surface cooling TTM with the Arctic Sun (Bard Medical, Covington, GA), usually at 33 °C, with a 12-h rewarming period. Our institutional protocol included continuous EEG monitoring and aggressive treatment of seizures, moderate sedation (e.g., propofol doses 10–30 mcg/kg/min) and analgesia (fentanyl doses of 20–50 mcg/h) with intermittent neuromuscular blockade [14, 15], and hemodynamic optimization targeting a mean arterial pressure of 80 mmHg during TTM [16]. Patients who did not waken within 48–72 h of rewarming followed a multimodal prognostication pathway recommended by the European Resuscitation Council including neurological exam, EEG data, neuron-specific enolase monitoring at 24, 48, and 72 h, and in select cases, magnetic resonance brain imaging and somatosensory evoked potential determination [16]. Outcome was classified as good if hospital discharge cerebral performance category (CPC) score was 1–2, and poor if CPC was 3–5. Data were prospectively entered into the International Cardiac Arrest Registry (INTCAR), (https://mmcri.org/ns/?page_id=15952). This project was approved by the Institutional Review Board with waiver of informed consent.

Objective pupil monitoring with the NeurOptics NPi-200 pupillometer was added to bedside assessment in June 2016 when our institution purchased these devices for clinical use. NeurOptics had no role in study design, data collection, or interpretation. No specific frequency of pupillometer use was mandated, but it was routinely used when pupil assessments were performed every 1–4 h. This handheld portable device measures pupil size with infrared light, emits a burst of visible light at 1000 lx for 0.8 s, then stores repeated video images at > 30 frames per second for 3.2 s [17]. The device records maximum and minimum pupil size in millimeters (mm), constriction velocity (CV) as mm/s, %PLR, the NPi, and the date and time of measurement simultaneously on the SmartGuard, a single patient use device attached to the pupillometer. The NPi values ≥ 3 are consistent with "normal" values, and $0 < \text{NPi} < 3$ represents an abnormal "sluggish" response [6, 13, 17, 18].

The SmartGuard for each patient was recovered before transfer from the ICU whenever possible for later downloading blinded to patient data. SmartGuards available for patients treated between June 28, 2016 and July 22, 2017 were downloaded, and data reconciled with prospectively entered INTCAR data. Patients with less than 12 h of pupillometry data or those who died during TTM before neurological outcome could be assessed were excluded.

Data are presented as median (interquartile range). Pupillometer results were grouped into initial data that includes the first pupil assessment whenever it occurred, early data (all data up to 6-h post-return of spontaneious circulation (ROSC) and any initial pupil evaluation between 6- and 8-h post-ROSC), and data during the total period of TTM which often extended as normothermic maintenance for up to 72 h. Within each time frame (early vs all TTM), patients were assigned the worst NPi category during that time (normal, sluggish, or nonreactive). For example, a patient with an initially sluggish pupil which improved to normal during the first 6-h post-ROSC would be classified as sluggish. If later during TTM the pupil worsened to again become sluggish and then nonreactive, it would be scored as nonreactive for the TTM period. Data from the worst scoring eye at each measurement was used (lowest size, NPi, %PLR, or CV).

Data and events occurring after any transition to comfort measures were excluded. Receiver operator characteristic curves to predict poor outcome were assessed using Analyse-IT® software. Optimal cutoff point values to predict poor outcome were determined using the maximum Youden index (J = sensitivity + specificity − 1) [19]. Additional descriptive data evaluated patients whose pupillary light reflex was "normal" (≥ 3), "sluggish" (0 < NPi < 3) or "nonreactive" (NPi = 0) during early and TTM time frames. Categorical data were analyzed with Fisher Exact and Chi-Square analysis as appropriate. All elements of the Standards for Reporting Diagnostic Accuracy (STARD 2015) are included in this report [20].

Results

A convenience sample of 55 adult patients treated with TTM after cardiac arrest had pupillometer SmartGuard data available. Three patients had their first data collected after the "early" data time frame (starting 9:26, 10:54, and 12:12 after ROSC) and are not included with the remaining 52 patients in "early" data. Demographics are displayed in Table 1, reflecting a mostly young, male cohort experiencing a witnessed, out-of-hospital cardiac arrest. An additional 58 patients treated with TTM after cardiac arrest during this interval were excluded (Supplemental Figure 1). The excluded group was similar to the study cohort for age, gender, initial rhythm, fraction of events witnessed, but more excluded patients experienced in-hospital or emergency department arrest (39% vs 20%, $p < 0.01$) and also had a shorter time to ROSC (14.5 [9–23] vs 23 [14–34], $p < 0.01$). Seventeen of 55 cohort patients (31%) were discharged from the hospital with a good outcome compared to 21/58 (36%, $p = 0.69$) excluded patients. When restricted to patients meeting Hypothermia After Cardiac Arrest (HACA) study criteria [21], good outcomes were noted in 12/19 (63%) cohort patients. Among the 55 patients we included, support was withdrawn from 30 (all of whom died) for neurologic reasons in 21 patients (median day of withdrawal was 5 days after ROSC, IQR 4–6), cardiac instability or death in 2, both neuro and cardiac in 2, prior living wills not to receive such treatment in 4, and 1 due to multisystem failure.

Table 1 Demographic data for 55 adult patients monitored with pupillometry during targeted temperature management after cardiac arrest

Age, years median (IQR)	57 (48–68)
Male, *n* (%)	36 (65%)
Initial rhythm	
VT/VF/shockable	28 (51%)
Asystole	14 (25%)
PEA	11 (20%)
Witnessed arrest	38 (69%)
Time to ROSC, min	23 (14–34)
OOHCA	44 (80%)

IQR interquartile range, *N* number, *OOHCA* out-of-hospital cardiac arrest, *PEA* pulseless electrical rhythm, *ROSC* return of spontaneous circulation, *VF* ventricular fibrillation, *VT* ventricular tachycardia

Enrolled patients underwent a median of 17 (IQR 11–24) assessments with the NPi-200 pupillometer during TTM, the median time to first assessment for the entire cohort was 4.5 h (range 33 min to 12.2 h) after ROSC. During the initial assessment, seven patients had a nonreactive NPi (two unilateral, five bilateral) a median of 3.8 (range 1.3–6.0) h after ROSC; all of these patients died. Two more patients started with sluggish pupils but progressed to nonreactive NPi in the early post-ROSC time period, and both died (see Supplementary Table 1 for summary data). Among 14 patients with an early sluggish NPi, 12 (86%) had a poor outcome. The sluggish NPi was bilateral in 12 patients, with nine not surviving and only one (11%) making a good outcome compared to two patients with unilateral sluggish pupils who both survived (CPC of 2 and 3). Bilateral sluggish pupils progressed to nonreactive pupils in six patients or never recovered normal pupil function (NPi ≥ 3) in one patient; all seven of these died. The five remaining early sluggish pupil patients recovered normal pupil function in 3–15 h, with two deaths and three surviving (CPC 2, 3, and 3). Among 29 patients whose early NPi remained normal, 15 (52%) experienced a poor outcome, including four surviving with a CPC of 3, three with cardiac death (repeat arrest or hemodynamic failure), and eight with neurologic death. Patients with a 0 < NPi < 3 in the first 6 h more frequently had poor outcomes (86%) compared to those with NPi > 3 (52%, $p = 0.03$).

When evaluating data during the total TTM time frame, 21 patients had a nonreactive NPi, with 20 (95%) experiencing a poor outcome. This included one brain dead organ donor, 15 other neurologic deaths, two patients with cardiac deaths, and two survivors with CPC of 3. The pupillometer assessment preceding the first NPi = 0 occurred 2.7 (1.8–4.4) h before, revealing an NPi of 3.7 (3.3–4.0), with three values < 3. The median time to first NPi = 0 was 6.4 (4.3–20.4) h after ROSC, at which time these nonreactive pupils were rarely dilated, with a median pupil size of 4.6 (range 1.6–7.8 mm). A nonreactive pupil was larger than 5 mm when first detected in only five of 21 patients (24%).

The single patient with a good outcome despite an NPi of zero was a 65-year-old man with a witnessed in-hospital ventricular fibrillation arrest with 10 min to ROSC. His NPi measured zero for a 36 min interval 19 h after ROSC when his pupil diameter was 1.6–1.8 mm. Of the

21 patients displaying an NPi of zero, 13 had pupil diameters less than 2 mm, 12 of whom recovered a measurable NPi later, including 11 patients whose NPi returned to normal values greater than 3. Of 461 pupil measurements less than 2 mm, 29 (6.3%) were NPi = 0, and 432 (93.7%) had an NPi > 0.

During TTM, a sluggish but reactive NPi occurred in 14 patients, with five good outcomes (all CPC = 2), and nine poor outcomes (three survived with CPC = 3, five experienced neurologic deaths, and one with cardiac death). A consistently normal NPi (≥ 3) during the entire TTM period occurred in 20 patients, of whom 11 (55%) had good outcomes (four with CPC = 1, seven with CPC = 2), and nine with poor outcomes (including three survivors with CPC 3, three with cardiac deaths, and three with neurologic deaths). Comparing all patients with an NPi < 3 (n = 35) to the 20 with a persistently normal NPi ≥ 3, only six of 35 experienced a good outcome (17%), compared to 11/20 who never developed an NPi < 3 (55%, $p = 0.009$). Among the NPi < 3 patients, 24 died (68%) compared to 6/20 who never developed an NPi < 3 (30%, $p = 0.01$).

As shown in Fig. 1a, b, increasingly severe impairments of the NPi were associated with higher rates of death and poor outcome. The lower NPi categories were associated with greater incidence of poor outcome for the 6-h post-ROSC data ($p = 0.007$) as well as for data during all of TTM ($p = 0.002$). As shown in Table 2, pupil size at initial evaluation and 6-h post-ROSC was not different between patients with a good versus poor outcome. The ROC curve analysis revealed that pupil size did not predict poor outcome, with an AUC of 0.58 (0.43–0.74, $p = 0.15$) for initial size, and 0.59 (0.43–0.74, $p = 0.13$) at 6-h post-ROSC. A pupil ≥ 4.5 mm was the best cutoff to predict poor outcome, with specificity of 1.0 and a false positive rate of 0 but a sensitivity of only 0.29. By comparison, the pupillometer-derived indices for NPi, constriction velocity, and %PLR were significantly different between patients with good and poor outcome. The 6-h post-ROSC values for NPi predicted poor outcome with an AUC of 0.72 (0.59–0.86, $p < 0.001$), with a

Table 2 Pupillometer data recorded at initial evaluation and 6 h (± 2) post-ROSC compared between patients with good (CPC 1–2) versus poor (CPC 3–5) outcome for 52 patients with early data

	Good outcome *N* = 16 (31%)	Poor outcome *N* = 36 (69%)	*p* value
Pupil size (mm)			
Initial	2.25 (2.03–3.45)	3.06 (2.11–4.7)	0.3
6 h	2.25 (2.03–3.45)	2.99 (2.11–5.18)	0.2
NPi			
Initial	4 (3.7–4.3)	3.4 (1.1–4)	0.02
6 h	4 (3.7–4.5)	3.1 (0.7–4.2)	0.02
Constriction velocity (mm/s)			
Initial	0.59 (0.32–1.04)	0.34 (0.23–0.59)	0.04
6 h	0.65 (0.37–0.95)	0.36 (0.2–0.6)	0.001
%PLR			
Initial	11 (5–17)	6 (4–13)	0.04
6 h	14 (6–22)	8 (4–12)	0.004

CPC Cerebral Performance Category, *mm* millimeter, *N* number, *NPi* Neurological Pupil index, *%PLR* percent constriction of pupillary light reflex, *ROSC* return of spontaneous circulation, *s* second

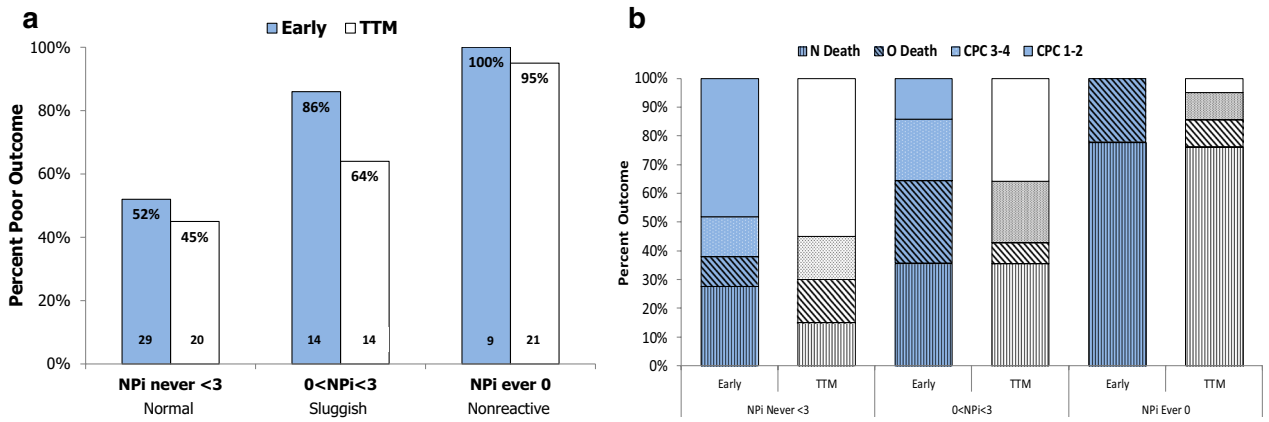

Fig. 1 **a** The lowest Neurologic Pupil index (NPi) early after ROSC (dark bars) and throughout TTM (white bars) identifies an increasing incidence of poor outcome despite TTM after cardiac arrest as the NPi worsens from normal (NPi ≥ 3) to sluggish (0 < NPi < 3) to nonreactive (NPi = 0) for 6 h values ($p = 0.007$) and entire TTM data ($p = 0.002$). **b** The lowest NPi early after ROSC (tinted stacked bars) and throughout TTM (black–white stacked bars) reveals an increasing percentage of neurological death (vertical bar blocks at bottom of stack) and decreasing percentage of good outcome CPC 1–2 (solid blocks at top of stack) as NPi worsens from normal to sluggish to nonreactive. Other causes of death (diagonal bar blocks) and survival with poor outcome CPC 3–4 (dotted blocks) appear similar

best cutoff of 3.7 to predict poor outcome. This threshold had a specificity of 0.82, sensitivity of 0.60, and a false positive rate of 0.17 (95% CI 0.06–0.41). The largest NPi with a false positive rate of zero was 1.5, and an NPi of 2 (as presented by Oddo et al. [12]) yielded a false positive rate of 0.06 (0.01–0.27). The 6-h constriction velocity had an AUC of 0.78 (0.66–0.91, $p < 0.001$) with a best cutoff of < 0.23 mm/s to predict poor outcome (specificity 1.0, sensitivity 0.47, false positive rate of zero (0–0.18), and the %PLR had an AUC of 0.75 (0.62–0.88, $p < 0.001$) with a best cutoff of < 5% to predict poor outcome (specificity 0.94, sensitivity 0.45, false positive rate of 0.06 (0.01–0.27). The AUCs for these three tests were not statistically different from each other.

Figures 2, 3, 4 and 5 show representative examples of patients with Good (CPC 1 and 2) or Poor (CPC 5) outcomes. Figure 2 shows the TTM course for pupil size and NPi for a 56-year-old woman with a witnessed out-of-hospital pulseless electrical rhythm cardiac arrest lasting 16 min to ROSC. Her NPi values for both eyes remained normal, and pupil size fluctuated between 1.7 and 3.2 mm. She made an excellent neurological recovery. Figure 3 represents a 66-year-old woman with severe diabetes who sustained a witnessed out-of-hospital cardiac arrest with a shockable rhythm defibrillated in 2 min to ROSC. Her initial NPi was sluggish (< 3) which normalized ~ 18 h after ROSC. She made a good neurological recovery (CPC = 2).

Figure 4 represents a 69-year-old woman with severe COPD, dialysis-dependent chronic kidney injury, and diabetes who sustained a witnessed pulseless electrical activity cardiac arrest which required 19 min to obtain ROSC. Her initial left eye NPi was barely above 3, and then normalized until 38–46-h post-ROSC when both pupils became nonreactive and remained ~ 2 mm in diameter. She did not waken, and family requested comfort measures honoring her living will. Figure 5 represents a 56-year-old woman with recurrent out-of-hospital ventricular fibrilation cardiac arrests with > 60 min total to obtain ROSC. Upon transfer to our hospital, her pupils were initially very sluggishly reactive and dilated. She received mannitol and hyperventilation, and a computed tomography scan revealed diffuse cerebral edema and uncal and subfalcine herniations. She progressed to brain death despite aggressive care.

Discussion

Though widely accepted as a measure of brain injury, the PLR has usually been described dichotomously as present or absent [1–5]. Pupillometers are more reliable than standard clinical pupillary assessments in intensive care unit patients, especially if pupils are small [18,

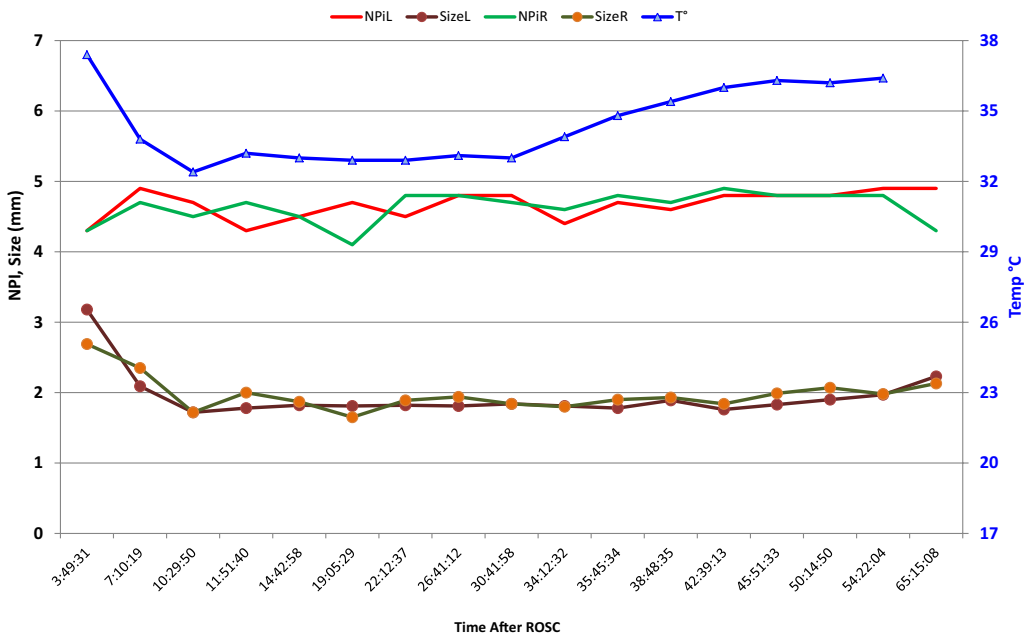

Fig. 2 Pupil diameter in mm (round markers) and the NPi (no markers) for the Left (red lines) and Right (green lines) eyes for a patient with a good outcome (CPC = 1). The NPi remains normal (≥ 3) throughout TTM. Core temperature (triangles—right axis) identifies phase of targeted temperature management (Color figure online)

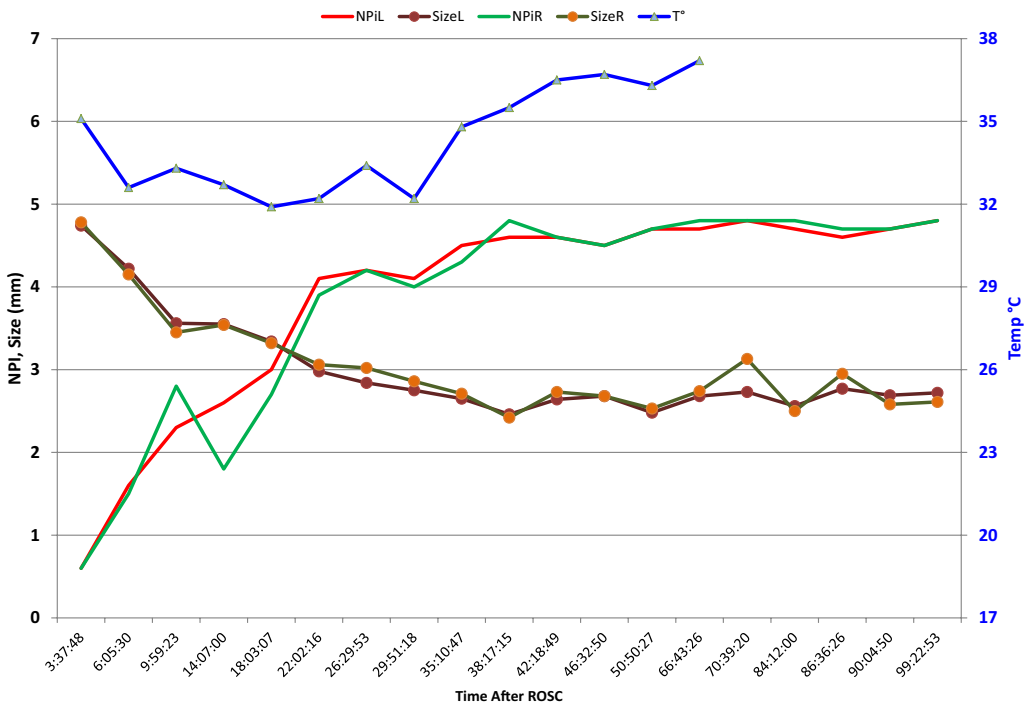

Fig. 3 Pupil diameter in mm (round markers) and the NPi (no markers) for the left (red lines) and right (green lines) eyes for a patient with a good outcome (CPC = 2). The NPi starts in the abnormal sluggish range (< 3), but recovers to normal by ~ 20 h after ROSC. Core temperature (triangles—right axis) identifies phase of targeted temperature management (Color figure online)

22]. These portable devices measure pupillary response using several different parameters, including the NPi, percent constriction or %PLR (depending on device), and constriction velocity. This study is the first to report frequent NPi and other pupillometry data after cardiac arrest during the initiation and maintenance of TTM, emphasizing the lack of pupillary dilation by pupillometer assessment commonly associated with nonreactive pupils during TTM after cardiac arrest, and describing the association between increasing impairment of the NPi and worse outcomes in this population.

After completing our study, we noted that NPi readings of zero were more commonly associated with very small pupils rather than the commonly linked "fixed and dilated" pupil. Figure 5 shows an early NPi of zero with dilated pupils, and later at 25-h post-ROSC, an NPi of zero with pupils less than 2 mm. Instructions for use of the pupillometer from NeurOptics reveal that the NPi-200 pupillometer requires at least a 30 micron (0.03 mm) change in pupil diameter to record a pupil response [23]. With very small pupils in which a change less than 30 μm is likely to occur, the device will report an NPi of zero and not report any data for constriction velocity or %PLR. In the setting of very small pupils, standard manual pupil assessment may also not detect a change in size. If the pupil later constricts by more than 30 μm, the device will again report these values and an NPi greater than zero.

Injury to the midbrain or other areas may induce very small pupils and be associated with worse outcomes (as with 95% of our patients with an NPi of zero). The single patient with an NPi of zero to make a good recovery had pupils measuring 1.6–1.8 mm when the NPi was zero, recovering to 3–5 once pupil size increased again. Additional evaluation is needed to determine whether the very small pupils and NPi of zero are due to brain injury or other causes such as increased age, general anesthesia, opiates, dim light stimulus, diabetic neuropathy, cataracts, or other factors [13].

We also noted occasionally that no data were reported for pupil size, NPi, or any other PLR parameter for one pupil. This is different than an NPi value of zero, and suggests a paired second measurement was never recorded. It is important to not confuse events with a true "zero" NPi value with events where no data are recorded for one pupil.

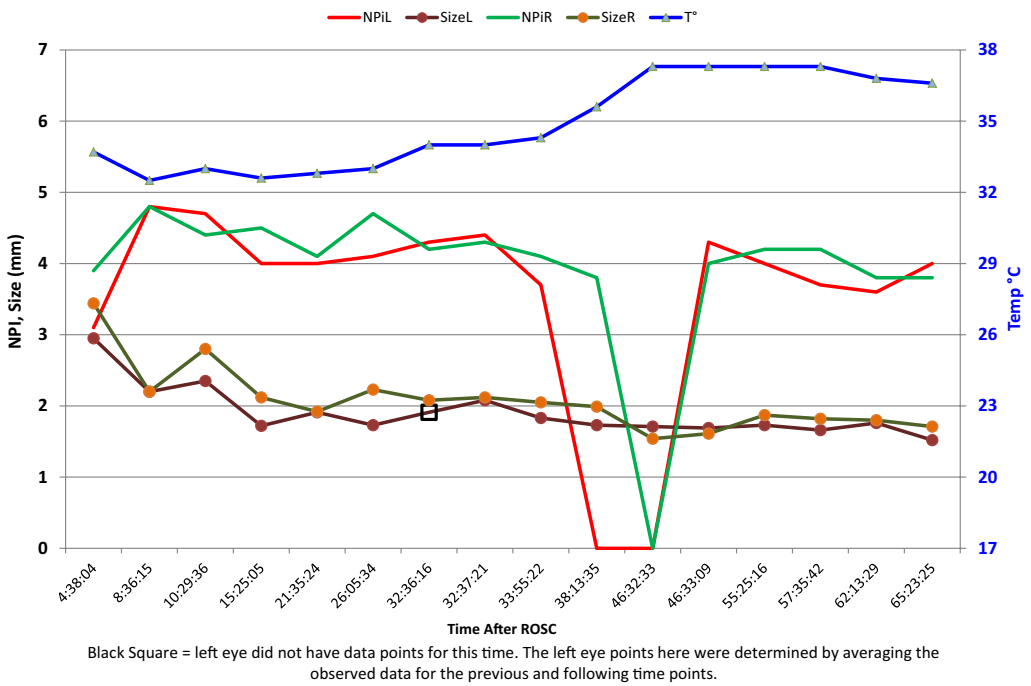

Fig. 4 Pupil diameter in mm (round markers) and the NPi (no markers) for the left (red lines) and right (green lines) eyes for a patient with a poor outcome (CPC = 5). The NPi starts in the normal range (≥ 3) but drops to nonreactive (NPi = 0) ~ 38 h after ROSC, associated with very small pupil size (< 2 mm). Core temperature (triangles—right axis) identifies phase of targeted temperature management. Black square represents interpolated value when left pupil data not reported (Color figure online)

Several investigators evaluated pupillometry in post-cardiac arrest patients during limited time frames such as intra-cardiac arrest, after 48 h, or only daily during TTM [7–10, 12]. Behrends et al. evaluated 30 patients during cardiac arrest with a NeurOptics pupillometer (Irvine, CA), finding a strong association with outcome [10]. Suys et al. evaluated 50 patients twice during TTM with the NeuroLight Algiscan (IDMED, Marseille, FR) [7], finding pupillometry superior to manual pupil assessment, and not affected by sedation, analgesics, or vasopressors. Their quantitative %PLR (equivalent to percent constriction reported by the NeurOptics device) was higher at both time points in patients with a good outcome, with a higher best cutoff value than we found (13% vs our 5%), and a similar AUC to predict poor outcome (0.79 vs 0.75).

Solari et al. evaluated 103 patients not awakening more than 48 h after ROSC, and found the %PLR predicted poor outcome better than pupil size and similar to EEG and somatosensory evoked potential [8]. Heimburger et al. evaluated 83 patients with the NeuroLight device at admission and again on day 2 during TTM, finding a higher %PLR value for patients with good outcome [9]. Tamura et al. evaluated 50 adult cardiac arrest patients, but only 34 treated with TTM, and 3 were non-comatose [11]. Using the NeurOptics-100 pupillometer a median of 32 min after cardiac arrest and again at 6, 12, 24, 48, and 72 h (but not in-between these time points), the %PLR was consistently greater in survivors and those with favorable neurologic outcomes. Oddo et al. performed a multicenter study using blinded pupillometer measurements once daily for the first 3 days after ROSC, finding the NPi was a better predictor of poor outcome than standard manual PLR assessment [12].

Our results confirm the findings from these five studies, but provide additional detail that may better define the role for pupillometry after cardiac arrest, especially during the very early time period when treatment decisions are being made. The pupillary light response is a dynamic physiologic variable, changing frequently even in healthy individuals, and as shown in Figs. 3, 4 and 5, even in the early hours after cardiac arrest. A single daily assessment for this important clinical parameter may miss critical changes, and we recommend more frequent assessments. Our best value in the first 6 h after ROSC to predict poor outcome was an NPi < 3.7, different than the < 2 value reported by Oddo [12]. This difference may reflect our earlier time frame or more frequent

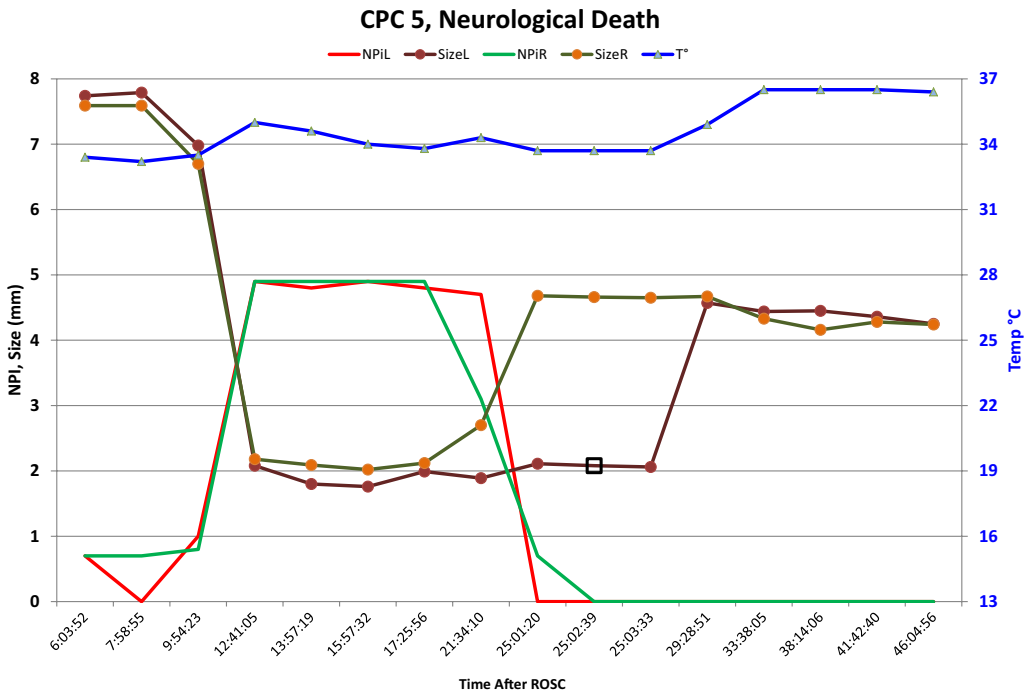

Fig. 5 Pupil diameter in mm (round markers) and the NPi (no markers) for the left (red lines) and right (green lines) eyes for a patient with a poor outcome (CPC = 5). The NPi starts in the abnormal sluggish range (< 3) associated with large pupils, but recovers to normal (≥ 3) ~ 12-h post-ROSC, dropping again to nonreactive (NPi = 0) ~ 25 h after ROSC and remaining there. Note the pupil diameter was dilated at first (7–8 mm), dropping to ~ 2 mm. Black square represents interpolated value when left pupil data not reported (Color figure online)

measurements, but additional research is needed to better understand this important threshold.

Previous pupillometer publications differed in other ways. Heimberger used the mean value of %PLR for both eyes [9], Tamura used the larger %PLR of two eyes [11], while the other investigators did not report how they dealt with two eyes [7, 8, 10, 12]. Suys, Solari, and Oddo used research nurses to record %PLR values (not shared with the bedside team), keeping the best value [7, 8] or the lowest for each eye [12]. Behrends recorded the %PLR data during CPR interruptions, also not sharing with clinical teams [10]. We chose to use the value for the worst scoring eye at each time point on the premise that a unilateral pupil change would prompt a clinical response (imaging, hyperventilation, osmolar therapy) even if the other eye remained normal.

Several limitations of our study deserve comment. We evaluated a modest sized cohort from a single center all treated with TTM, and did not include consecutive patients, so potential selection bias must be considered. Our cohort size of 55 patients is comparable to prior publications reporting 50, 67, 82, and 34 subjects [8–11] but smaller than the study by Oddo [12]. We made the decision a priori to exclude four patients who had withdrawal of life-sustaining therapies during TTM and never had an opportunity to be assessed neurologically, and three patients who had scant pupillometry data recorded; including these patients may have changed our results slightly. Many factors affect pupil function which we did not account for, including hemodynamics, preexisting medical and ophthalmologic diseases, type and severity of brain injury, and perhaps hypothermia itself [24, 25]. Pressors and neuromuscular blocking drugs administered intravenously do not appear to affect the iris [13]. Although sedative and analgesic medications can alter pupil function, and may contribute to the smaller pupils we observed [13], this is less likely with the moderate sedation protocol we use [14, 15, 26, 27]. Bedside nurses and physicians were aware of the pupilometer data, but the prognostication pathway did not incorporate this data and required a multimodal approach including clinical examination after sedation interruption, electrophysiology, biomarkers and imaging. Because of the exploratory nature of this study, we did not adjust statistics for multiple tests, and it is possible that some results may represent false positive results. We view these data as hypothesis generating rather than conclusive results, and further study is needed.

The majority of our patients (nearly 70%) experienced poor outcomes despite aggressive TTM therapy. Many

of our patients had unwitnessed cardiac arrests and nonshockable rhythms, likely explaining this higher rate of poor outcome. If we apply conservative criteria from the HACA study (witnessed cardiac arrest, ventricular fibrillation or nonperfusing ventricular tachycardia as the initial cardiac rhythm, age of 18–75 years, an interval ≤ 60 min from collapse to ROSC), 65% of our patients meeting those criteria had a good outcome [21].

Prior studies reported a strong association between manually detected loss of pupillary light reflex at initial assessment or 6 h after cardiac arrest and poor outcome [5, 28–30]. Because of the great variability in time from ROSC to first assessment in our patients, we selected the 6-h post-ROSC data a priori to standardize assessment. Many studies assessing pupil size did not define what is meant by "dilated", an important concept given the exact measurements now available with pupillometry. Non-dilated but nonreactive pupils have previously been described after cardiac arrest [28, 31, 32], and using the > 5 mm definition by Snyder [28], 75% of our patients with nonreactive pupils had non-dilated pupils when first detected. The implications of this finding, a dichotomy between "fixed" and "dilated," are unclear but suggests that the mechanisms leading to nonreactive pupils after cardiac arrest may be more complex than cerebral edema and cranial nerve III impingement, such as midbrain dysfunction or other ischemia-mediated mechanisms. In addition, the 30 micron minimum pupil change for the NeurOptics pupillometer to detect a response to light may confound assessment, though almost all patients with an NPi of zero suffered poor outcomes. Whether specific interventions in response to worsening pupil function can alter outcome for these patients, what those interventions should be, and whether a different strategy should be initiated if the pupil diameter is large versus very small is unknown.

Conclusions

Impairment of the pupillary light reflex as measured by pupillometry is associated with poor outcome after cardiac arrest, especially if sluggish and bilateral, progressing to nonreactivity, failing to normalize, or occurring early after ROSC. Pupils were most often not "fixed and dilated" when the pupils became nonreactive. Further research to define the role and timing of quantitative pupillometry after cardiac arrest, comparing to other prognostic indicators, assessing confounding by medications, evaluating response to targeted interventions, and incorporating into multimodal assessments is needed.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s12028-019-00717-4) contains supplementary material, which is available to authorized users.

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Conflict of interest
The authors declare that they have no conflict of interest.

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