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The best available pupil response predicts neurological outcome following cardiac arrest—a prospective cohort study

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Abstract

Background: Early neuroprognostication after cardiac arrest (CA) remains challenging. Manual pupillary light reflex assessments can be inconsistent, leading to interest in automated, quantitative pupillometry. This study used the better Neurological Pupil Index (NPi) and pupillary percentage values from bilateral measurements for neuroprognostication following CA.

Methods: We evaluated 90 adult survivors of in- and out-of-hospital CA admitted to a medical ICU at a tertiary care university hospital in Berlin. Automated pupillometry was performed every 8 hours for 5 days post-admission using the NeurOptics NPi-100 pupillometer. The better measurement from either eye was selected for analysis. Outcomes at hospital discharge were classified as good (cerebral performance category scale [CPC] 1–2) or poor (CPC 3–5) using the Pittsburgh CPC scale.

Results: Patients with favorable neurological outcomes consistently showed higher NPi values ($P < 0.001$) and greater percentage changes in pupillary diameter ($P < 0.001$). At 72 hours, the median NPi was significantly higher in the good outcome group (4.7 [interquartile range (IQR), 4.5–4.8] vs. 4.1 [IQR, 3.7–4.5]; $P < 0.05$). However, NPi values overlapped between groups, and most patients with unfavorable outcomes still exhibited values within the normal range (NPi > 3.0). A receiver operating characteristic analysis of the pupillary percentage change revealed a threshold of 16% to discriminate between the prespecified outcome groups.

Conclusion: Higher NPi values and/or greater pupillary diameter changes of the better reading in bilateral measurements were associated with favorable neurological outcomes after CA. However, previously proposed cutoff thresholds could not be confirmed in our cohort.

Keywords: Automated quantitative pupillometry, Cardiac arrest, Cerebral Performance Category, Infrared pupillometry, Neurological prognostication, Neurological Pupil Index

Introduction

Nontraumatic cardiac arrest (CA) remains a major cause of death worldwide with high mortality rates.[1] Standardized post-arrest care in the intensive care unit (ICU) has improved survival rates and neurological recovery.[2–4] However, accurately predicting neurological outcomes in unconscious patients remains difficult, particularly in the first days after CA.[4–6]

In the era of targeted temperature management (TTM), all unresponsive patients after successful resuscitation receive deep sedation, which has been shown to interfere with the accuracy of clinical examination during TTM.[7] Advanced electrophysiological assessments, such as electroencephalography and somatosensory evoked potentials, can yield false-positive results under TTM and require specialized expertise.[8] Consequently, a multimodal approach to neurological prognostication is strongly recommended, with assessments conducted no earlier than 72 hours post-arrest.[6,9] At this time point, absent brainstem reflexes, such as the absence of the pupillary light reflex (PLR), remain reliable predictors of unfavorable outcomes.[6,10–12]

The manual assessment of PLR, typically performed with a penlight, is the standard of care in the ICU. However, this method is prone to interobserver variability and is influenced by sedation and other pharmacological agents.[13,14] Automated pupillometry offers a more objective and quantitative assessment of the PLR, providing prognostic value by detecting subtle changes earlier, even in sedated patients with miotic pupils.[15]

Automated pupillometry was first developed in the 1960s, with its clinical applications emerging in 1989, primarily for assessing pupillary responses under general anesthesia.[16,17] Despite its early development, robust data on the use of infrared pupillometry in post-CA patients remain limited. Initial investigations evaluated PLR during resuscitation in 30 patients.[17] Their findings indicated that the absence of PLR for more than 5 minutes correlated with failure to achieve return of spontaneous circulation (ROSC) or poor neurological outcomes. Subsequent studies have further explored the role of quantitative pupillometry in predicting outcomes following CA. A lower percentage change in pupil size has been associated with poor neurological outcomes,[18,19] with some studies reporting 100% specificity for poor outcomes when PLR was markedly diminished (<13%) at 48 hours post-arrest.[20] Others have shown that early measurements, even immediately after return of ROSC,

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may offer predictive insight.[21] However, the prognostic performance of the Neurological Pupil Index (NPi) appears most reliable at 72 hours post-arrest, consistent with European Resuscitation Council guidelines.[6,22] Despite these findings, defining an optimal cutoff value and timing for using NPi to guide decisions—particularly regarding withdrawal of life sustaining treatment—remains a significant challenge

This study aimed to evaluate the best NPi from bilateral measurements for its predictive potential in neurological outcome assessment. Additionally, we analyzed the prognostic value of the maximum percentage change in pupil size over the first 5 days of intensive care unit (ICU) treatment.

Materials and methods

We report a single-center observational study performed on the medical intensive care unit (MICU) at a tertiary care university hospital in Berlin, Germany (Charité—Universitätsmedizin Berlin). The study followed the principles of the Declaration of Helsinki as revised in 2013. This study was approved by the internal review board (IRB) and ethics committee of Charité University Hospital Berlin (IRB No. EA2/011/15, 2015). Written consent was obtained from all patients included in the statistical analysis, either directly after awakening or from a court-appointed Legally Authorized Representative (LAR), as required by the IRB. The study enrolled unconscious survivors of in-hospital (IHCA) and out-of-hospital CA (OHCA), regardless of initial rhythm. Eligible patients were 18 years or older and admitted to the MICU for post-CA care following successful resuscitation. Patients with known ocular pathologies were excluded. A total of 103 patients were initially included in the study. Thirteen patients were excluded due to missing written consent, death within 24 hours of admission, ocular pathology, or immediate transfer for cardiac surgery (Figure 1).

Measurements

We conducted serial measurements of pupillary function using the NeurOptics NPi-100 pupillometer (NeurOptics, Irvine, CA, USA). This device emits a 1000-lux light burst for 0.8 seconds, followed by 3.2 seconds of recording the pupillary reaction at 30 frames per second.[23] The NPi is automatically calculated during the measurement, based on various pupillary characteristics, including minimum and maximum diameter, constriction velocity, dilation velocity, latency, and percentage change. These characteristics are compared to reference values obtained from healthy volunteers.[24] Values between 3 and 5 indicate normal pupillary function, with higher values closer to 5 representing a stronger pupillary light reaction compared to values nearer to 3. Values below 3 are considered pathological, with lower numbers signifying worse pupillary responses.[24] Additionally, we analyzed the percentage change in pupil size from baseline.[13,19]

Each patient included in the study underwent an initial pupillary measurement upon admission, performed by the physician or nurse on duty. Subsequently, measurements were conducted every 8 hours for 5 consecutive days, resulting in a total of 15 PLR measurements per patient. To minimize the false-positive rate, only the better pupillary response from either eye in each measurement was used for analysis when differences were observed between the 2 eyes. We did not evaluate inter-eye differences. The ICU staff was trained on the measurement protocol using healthy volunteers to ensure consistent and accurate data collection.

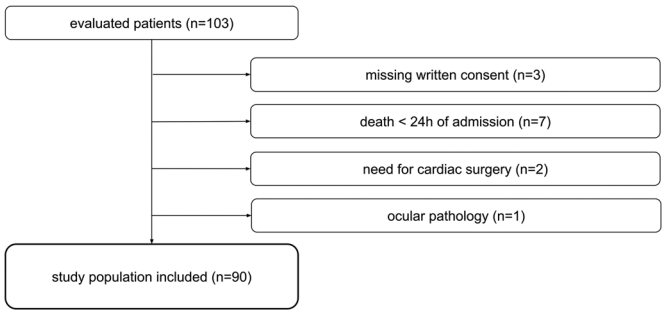

Figure 1. Patient selection criteria.

Post-arrest treatment

In accordance with our internal protocol and current guidelines, all patients underwent TTM at a temperature of 33°C, regardless of the cause of CA or the initial rhythm.[6] Disease severity upon admission was assessed using the Acute Physiology and Chronic Health Evaluation score.

Sedation was maintained using a continuous infusion of propofol/sufentanil, targeting a Richmond Agitation Sedation Scale score of −5, indicating deep sedation with no response to external stimuli. In cases of shivering, management followed protocol guidelines, including counterwarming of the extremities and further deepening of sedation. Neuromuscular blocking agents, such as pancuronium, were administered only if these measures failed. TTM induction involved the infusion of 1 L of cold crystalloid fluid and the use of an automated surface-cooling feedback device (Arctic Sun 2000 and Arctic Sun 5000; CR Bard, Murray Hill, NJ, USA). Controlled rewarming was performed at a rate of 0.25°C per hour until reaching 37°C, followed by a maintenance phase at 37°C for 24 hours. Sedation was discontinued upon reaching 36°C, provided there were no signs of (multi-) organ failure. All patients were mechanically ventilated to maintain normocapnia ($PaCO_2$ 35–45 mm Hg) and underwent blood glucose control to achieve normoglycemia (<200 mg/dL).

Decisions to withdraw life-sustaining therapy were made according to a previously published multimodal protocol and were not initiated earlier than 72 hours after CA. Consulting neurologists were blinded to the pupillometry results, which had no influence on decisions regarding withdrawal of care.

Outcome measures

For outcome assessment, we used the Pittsburgh Cerebral Performance Category (CPC) scale and divided patients into 2 groups. CPC 1–2 represented good neurological recovery, indicating no or only mild deficits, whereas CPC 3–5 signified unfavorable outcomes, including severe deficits, a persistent vegetative state, or death. This dichotomization is widely used in numerous studies.[22,25,26] CPC evaluation was conducted at hospital discharge.

Statistical Analysis

We used R version 4.4.2 (R Core Team. R: A Language and Environment for Statistical Computing; R Foundation for Statistical Computing, Vienna, Austria). The analysis was conducted in 2 main steps: first, evaluating each measurement time point individually, and second, analyzing trends over the first 5 days following ROSC. With 3 measurements performed daily, a total of 15 measurements per patient were available during this period.

We analyzed differences at all given measurements while focusing on baseline values at admission and measurements 48 and 72 hours after CA.

Data are presented as mean with standard deviation, median with interquartile range (IQR), or frequencies, depending on the scale and distribution. Baseline values were compared between groups using the *t* test, Mann-Whitney *U* test, or chi-square test, as appropriate. Statistical analyses were performed in accordance with standard biostatistical practice as described in *Principles of Biostatistics by* Pagano et al.[27] The specific test applied for each parameter is indicated in the tables.

For group comparisons of longitudinal data, a nonparametric repeated-measures analysis was performed. We used a Brunner-type nonparametric analysis for repeated measures using the f1.ld.f1 function from the R package nparLD. This method is suitable for longitudinal data in factorial designs and allows for the analysis of main effects and interactions without assuming normality or homoscedasticity. For group comparisons with 2 independent samples, Mann-Whitney *U* test for nonparametric data was used.

The level of significance was set at 5% (2-tailed) without adjustment for multiple comparison. All *P* values constitute exploratory analysis and do not allow for confirmatory generalization of results. Given the observational and exploratory nature of the study, no power analysis was performed, and no alpha adjustment was applied.

To assess the discriminatory ability of the maximal percentage change in pupil diameter of the better eye between outcome groups, a receiver operating characteristic (ROC) analysis was performed using the results of the 15 predefined measurement time points. The optimal cutoff was determined by maximizing Youden's Index.

Results

Patient characteristics

Our study included 90 patients after CA and successful resuscitation admitted between November 2015 and December 2018. Demographics of the study cohort are given in Table 1. Seventy-eight percent of the patients suffered from OHCA. The patients' mean age was 61.1 years, and 30% of the patients were female. Underlying etiologies for the arrest were most commonly a cardiac cause (ie, myocardial infarction or malignant arrhythmia) in 51% of the patients, followed by a respiratory cause in 37%, pulmonary embolism in 3%, and other causes in 9% of the cases. Seventy-one percent received a cranial computed tomography (CT) scan to calculate the gray-white matter ratio (GWR) for prognostication.

Forty-seven patients were discharged from the hospital (52%). Of those, 39 had a good neurological recovery at discharge (82%). Hence, all-cause mortality was 48% with 43 patients dying in hospital. Sixty-five percent of them died from withdrawal of life-sustaining therapy (WLST).

There were no differences in overall severity of illness, gender, OHCA, and time to ROSC between the groups (Table 2). Median ICU stay was significantly longer in patients with good outcomes (12 vs. 8 days, $P = 0.001$), whereas those with poor outcomes were older (mean age, 65.2 vs. 55.9 years; $P = 0.005$).

Patients with good outcomes more often had shockable rhythm at first medical contact and required less epinephrine (Table 2). Patients with good outcomes had lower neuron-specific enolase levels and higher GWR values on CT compared to those with unfavorable outcomes (Table 2). A total of 1350 pupil measurements were scheduled according to the study protocol, of which 819 were successfully completed (61%). Missing data were primarily due to early patient deaths or unavailability for scheduled measurements (eg, procedures such as cardiac catheter or CT scans).

Table 1

Baseline Characteristics on Admission

Characteristics	Overall (n = 90)
Age, y	61.1 (15.9)
Female gender	27 (30.0)
Epinephrine (cumulative), mg	2.00 [1.0–3.1]
Time to ROSC, h	12.00 [8.0–24.0]
APACHE II score	29 [22.5–34]
First rhythm	
Shockable	45 (50)
Non-shockable	45 (50)
OHCA	70 (77.8)
Good outcome (CPC 1–2)	39 (43)
Unfavorable outcome (CPC 3–5)	51 (57)
Head CT scan with GWR	64 (71.1)
CPC 1	31 (34.4)
CPC 2	8 (8.9)
CPC 3	4 (4.4)
CPC 4	4 (4.4)
CPC 5	43 (47.8)

Data are mean (standard deviation), absolute number (percent), or median [IQR].

APACHE II, Acute Physiology and Chronic Health Evaluation II; CPC, cerebral performance category; CT, computed tomography; GWR, gray-white matter ratio; OHCA, out-of hospital cardiac arrest; ROSC, return of spontaneous circulation.

NPi evaluation

Throughout the study period, patients with good neurological outcomes had significantly higher NPi values than patients with unfavorable outcome ($P < 0.001$). Table 3 and Figure 2 present the median NPi values across the entire study period. On ICU admission, median NPi values were within the normal range and without significant differences in both outcome groups (4.1 [IQR, 3.8–4.5] in CPC 1–2 vs. 4.0 [IQR, 3.7–4.3] in CPC 3–5; $P = 0.24$). Forty-eight hours post-CA (measurement 7), patients with good outcomes demonstrated significantly higher NPi values, with a median of 4.5 (IQR, 4.2–4.7) compared to 3.7 (IQR, 3.3–4.4) in the group with severe hypoxic encephalopathy ($P < 0.001$) (Table 3). Seventy-two hours after CA, both patient groups showed NPi values within the reference range with significantly higher values in the group with good outcome (4.7 [IQR, 4.5–4.8] vs. 4.1 [IQR, 3.7–4.5]; $P = 0.01$) (Table 3). Patients with good outcomes continued to show higher values (Table 3). However, NPi values overlap between the 2 outcome groups (Figure 3).

Quantitative analysis of the pupil change

The percentage change in pupil diameter was significantly higher in patients with good neurological outcomes over the whole study period ($P < 0.001$) (Table 3). Median percentage change over time is visualized in Figure 4. Across both outcome groups, the PLR was compromised on admission, as evidenced by a low percentage change in pupil diameter (9.4% [IQR, 6.1%–17.1%] in CPC 1–2 vs. 9.7% [IQR, 5.1%–13.5%] in CPC 3–5; $P = 0.37$) (Table 3). At 48 hours after CA (measurement 7), patients with favorable outcome showed significantly higher changes than patients with poor outcome (17.0% [IQR, 12.8%–21.2%] vs. 7.9% [2.7%–15.1%]; $P < 0.001$) (Table 3). Seventy-two hours post-CA (measurement 10), patients with good outcomes demonstrated a higher percentage change (21.9% [IQR, 16.3%–35.2%] vs. 15.0% [IQR, 8.4%–24.9%]) but without reaching statistical significance ($P = 0.06$).

Table 2

Baseline Characteristics in Outcome Groups

Characteristics	CPC 1–2 (n = 39)	CPC 3–5 (n = 51)	*P*
Age, y*	55.9 (14.2)	65.2 (16.1)	0.005
Epinephrine (cumulative), mg†	1.0 [0.0–3.0]	2.0 [1.0–3.7]	0.023
Time to ROSC, min†	12.0 [6.0–20.0]	13.0 [9.5–25.0]	0.222
APACHE II score†	27 [19–34]	29.5 [23–34.2]	0.235
OHCA‡	30 (76.9)	40 (78.4)	0.865
Shockable rhythm‡	27 (69.2)	18 (35.3)	0.003
Female sex‡	10 (25.6)	17 (33.3)	0.578
NSE, µg/L†	17.9 [12.8–27.3]	95.3 [43.5–202.0]	<0.001
CT, yes‡	24 (61.5)	40 (78.4)	0.129
GWR†	1.26 [1.23–1.29]	1.20 [1.16–1.24]	0.002
Time on ventilator, h†	208.0 [144.5–430.0]	175.0 [98–314.5]	0.084
ICU length of stay, d†	12.00 [8.5–23.0]	8.00 [4.0–14.0]	0.001

Data are mean (standard deviation), median [IQR], or absolute number (percent).

**t* Test.

†Mann-Whitney *U* test.

‡Chi-square test.

APACHE II, Acute Physiology and Chronic Health Evaluation II; CPC, cerebral performance category; CPC1–2, good outcome; CPC 3–5, poor outcome; CT, computed tomography; GWR, gray-white matter ratio; ICU, intensive care unit; NSE, neuron-specific enolase; OHCA, out-of-hospital cardiac arrest.

ROC analysis of the best pupillary percentage change showed an optimal cutoff of 16% for the maximum percentage change in pupil diameter. This threshold best separated patients with good neurological recovery from those with unfavorable outcomes in our cohort. The ROC analysis yielded an area under the curve of 0.79, and sensitivity was 66% with a specificity of 86.7%. Figure 5 shows the ROC analysis.

Table 3

NPi and Percentage Change in Outcome Groups

		Day	1			2			3			4			5			
Variable	**Group**	**Measurement**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	***P***
NPi	CPC 1–2	n	38	28	26	33	34	30	30	28	23	23	22	20	16	12	16	<0.001
		Median	4.1	4.2	4.4	4.1	4.3	4.5	4.5	4.5	4.5	4.7	4.7	4.6	4.6	4.6	4.7	
P25	3.8	3.7	3.8	3.5	3.8	4	4.2	4.4	4.2	4.5	4.5	4.3	4.5	4.5	4.4			
P75	4.5	4.4	4.5	4.5	4.6	4.6	4.7	4.7	4.8	4.8	4.8	4.7	4.7	4.7	4.8			
CPC 3–5	n	48	43	40	28	33	34	31	28	26	24	19	27	21	18	20		
	Median	4.0	4.0	3.9	3.6	3.8	3.8	3.7	4.2	4.2	4.1	4.3	4.2	4.3	4.3	4.2		
P25	3.7	3.5	3.2	1.6	2	1.4	3.3	3.5	3.6	3.7	4.1	3.8	3.9	3.3	3.7			
P75	4.3	4.5	4.2	4.4	4.3	4.3	4.4	4.4	4.5	4.5	4.7	4.4	4.6	4.5	4.5			
CPC 1–2 vs. 3–5	*P*		.24	.80	.01	.11	.02	.001	.001	.001	.04	.01	.1	.01	.02	.01	.01	
Min/Max (perc. change)	CPC 1–2	Median	9.4	10.0	13.0	11.1	12.3	16.0	17.0	16.1	18.1	21.9	24.2	23.8	30.6	35.3	28.1	<0.001
		P25	6.1	5.0	9.8	5.0	7.9	9.3	12.8	12.4	10.8	16.3	17.9	14.5	14.1	28.0	19.5	
		P75	17.1	12.5	15.3	16.1	16.8	17.7	21.1	22.9	24.1	35.2	28.1	31.2	37.5	39.9	36.4	
	CPC 3–5	Median	9.7	9.9	10.3	5.3	8.2	7.3	7.9	11.2	12.4	15.0	14.4	21.0	17.5	14.8	13.6	
		P25	5.1	4.5	6.3	1.0	3.3	3.6	2.7	5.3	6.2	8.4	8.9	11.0	11.6	9.5	11.0	
		P75	13.5	14.6	14.6	12.3	16.0	16.9	15.1	16.7	22.6	24.9	28.0	28.5	26.4	25.8	27.9	
CPC 1–2 vs. 3–5	*P*		.37	.92	.01	.04	.05	.06	.001	.02	.12	.06	.18	.17	.07	.1	.03	
Max	CPC 1–2	Median	2.0	2.0	2.1	2.1	2.2	2.3	2.3	2.1	2.3	2.3	2.6	2.9	2.6	3.6	2.9	0.500
		P25	1.8	1.9	1.8	1.9	1.9	1.8	2.1	1.9	2.0	2.0	2.1	1.9	2.0	2.5	2.3	
		P75	2.3	2.2	2.2	2.4	2.5	2.4	3.1	2.5	2.6	3.2	3.3	3.7	4.0	4.6	3.9	
	CPC 3–5	Median	2.1	2.1	2.1	2.2	2.3	2.4	2.3	2.3	2.4	2.6	2.4	3.2	2.5	2.9	2.7	
		P25	1.8	1.8	2.0	1.9	1.9	1.9	2.0	2.0	2.1	2.2	2.3	2.3	2.3	2.0	2.1	
		P75	2.4	2.4	2.6	2.5	3.0	3.1	2.8	2.8	2.8	3.0	2.8	4.4	3.5	3.7	4.0	
Min	CPC 1–2	Median	1.9	1.9	1.8	1.9	1.9	1.9	2.0	1.8	1.9	1.8	1.9	2.1	1.9	2.4	2.2	0.055
		P25	1.6	1.7	1.6	1.7	1.7	1.7	1.7	1.6	1.6	1.7	1.6	1.8	1.6	1.8	1.8	
		P75	2.0	2.0	2.1	2.2	2.3	2.2	2.5	2.0	2.4	2.1	2.2	2.7	2.5	2.9	2.6	
	CPC 3–5	Median	1.9	1.9	2.0	2.0	2.0	2.2	2.1	2.1	2.1	2.4	2.0	2.6	2.2	2.5	2.3	
		P25	1.6	1.6	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.9	1.8	1.9	2.0	1.9	1.9	
		P75	2.2	2.4	2.5	2.5	2.9	2.6	2.6	2.4	2.6	2.6	2.3	2.9	2.6	2.9	3.0	

Day refers to the time points relative to patient admission. *P* compares both groups longitudinally (Brunner-type nonparametric analysis) over the study period and each time point separately (Mann-Whitney *U* test).

CPC, cerebral performance category; CPC1–2, good outcome; CPC 3–5, poor outcome; n, number of patients per measurement; NPi, Neurological Pupil Index; P25, 25th percentile; P75, 75th percentile.

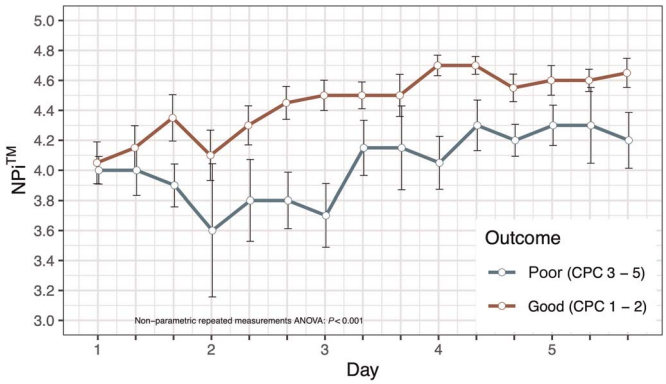

Figure 2. Median NPi value during the study in outcome groups over time. NPi, Neurological Pupil Index.

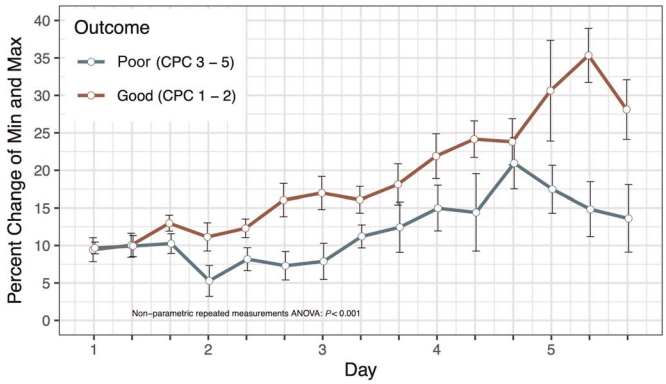

Figure 4. Median percentage change of the pupil during the study in outcome groups over time.

Discussion

In this study, we evaluated the predictive values of the NPi and the maximum percentage change of the pupil in patients resuscitated from IHCA and OHCA. We assessed pupillary function over 5 days, a longer observation period compared to previous studies. We only recorded the better reading from bilateral measurements. Patients with good neurological outcomes (CPC 1–2) had significantly higher NPi values and a greater percentage change in pupil size, which is consistent with current literature. The baseline characteristics and neurological outcomes of our study cohort align with published data.[28]

NPi values differed significantly between the outcome groups throughout the study period (Table 3). We observed that hypoxic encephalopathy alters pupillary function, as measured by NPi, even when the PLR is not completely absent. However, we observed frequent overlaps in NPi values across groups, especially in the first days after CA. On day 3 post-arrest, NPi values appear to stabilize in both groups, which may be attributed to the cessation of TTM or the process of weaning from sedation. Many patients with severe neurological impairment displayed normal pupillary function within the first 3 days based on the manufacturer's reference range ($3 \leq NPi \leq 5$).[25] Notably, only 2 patients with poor neurological outcomes presented an overall best NPi of 3 or less. This complicates both the reliable prediction of outcomes based solely on NPi values and the establishment of definitive NPi cutoff thresholds.

Bilaterally absent pupillary reactions at 72 hours post-CA are considered a reliable predictor for unfavorable neurological outcome in current guidelines.[5] Yet, absent PLR is observed in only 11%–21% of patients at this time point.[11,29] In our cohort, automated pupillometry detected subtle pupillary reactions in all but one patient. This highlights the higher sensitivity of pupillometers compared to manual penlight examinations, which can fail to detect faint pupillary responses.[13,14] Importantly, false-positive results for absent light reflex can have serious consequences, including inappropriate withdrawal of care. Automated pupillometry thus offers an objective and more reliable measurement to reduce such errors. Despite the overall poor neurological outcomes seen in approximately 50%

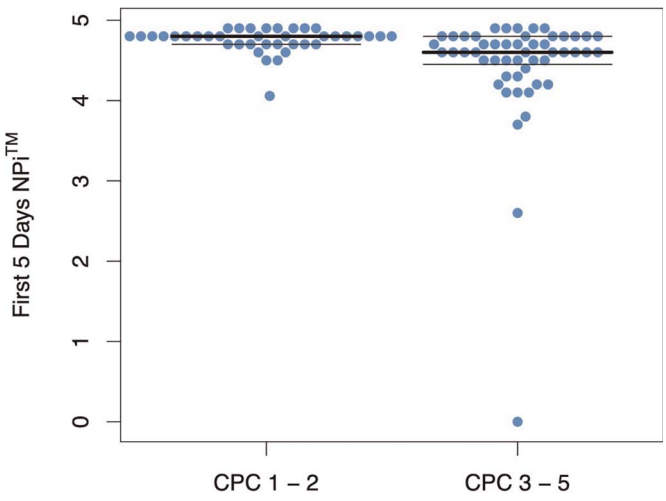

Figure 3. Best overall NPi value per patient during the study. NPi, Neurological Pupil Index.

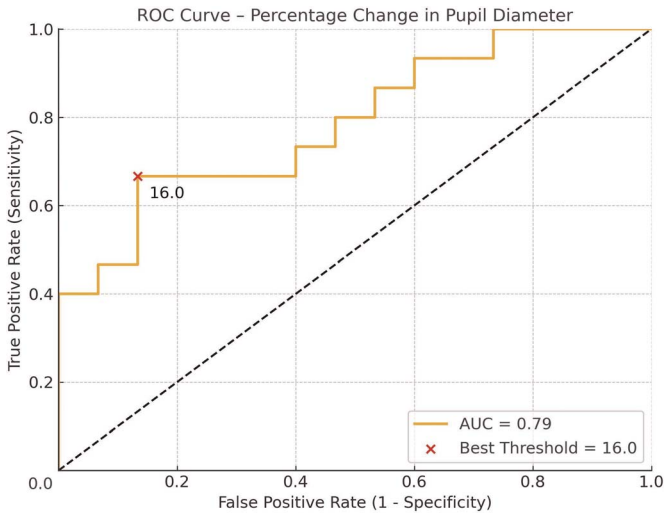

Figure 5. ROC analysis for the prediction of favorable neurological outcome (CPC 1–2) based on maximal pupillary percentage change. CPC, cerebral performance category; ROC, receiver operating characteristic.

of CA patients, we observed a discrepancy between the proportion of patients with severe hypoxic encephalopathy and those with absent PLR.[28] This suggests that further discrimination of pupillary function may be valuable. We hypothesize that patients with impaired but not absent pupillary reactions may represent a subgroup at increased risk for poor outcomes, warranting further diagnostics and tailored management.

Several studies have proposed NPi thresholds between 2.0 and 2.45 within the first 72 hours after CA as highly predictive of poor neurological outcomes, with some reporting 100% specificity for values ≤2.0 on day 1.[15,25,26,30] Despite these findings, only 2 patients with poor outcomes in our cohort had a best NPi value below 3, suggesting that such thresholds may apply to only a small subset of patients. Overall, our data did not support a clear NPi cutoff for outcome prediction.

Previous studies have shown that a percentage change in pupil diameter below 11% was associated with unfavorable outcomes.[18,19] Additionally, 100% specificity for poor outcomes was reported in patients with a pupillary change <13% at 48 hours post-CA.[20] Our findings generally support these observations. In our cohort, a threshold of 16% was determined by ROC analysis to discriminate between the outcome groups. A maximal pupillary percentage change below 16% might indicate poor outcome after CA. However, due to the use of only the better percentage change in bilateral measurements, this threshold should be interpreted cautiously. We could not confirm that impaired pupillary function during the first 2 days is a strong predictor of unfavorable outcomes. In our cohort, 24 of 39 patients with good outcomes had PLR values below 13% at 48 hours post-CA but later showed improvement. This suggests that pupillometry may be prone to false-positive results in the early post-arrest phase.

Furthermore, early outcome prediction can be challenging, as patients are often deeply sedated, intubated, and recovering from rewarming, all of which can significantly affect neuroprognostication. Therefore, the European Resuscitation Council guidelines recommend delaying prognostic assessments until at least 72 hours after CA.[6] Other studies indicate that the prognostic value of pupillary function may be more accurate at later time points, such as 72 hours post-sedation withdrawal or 96 hours post-arrest.[31]

Based on our findings, we do not recommend withdrawing care solely based on pupillary measurements, especially during the first 2 days, as this could result in the premature death of patients with the potential for full neurological recovery. The NPi thresholds for poor outcomes proposed by various studies should be interpreted with caution. It is crucial to provide state-of-the-art neuroprotective intensive care for several days and adopt a multimodal approach for outcome prediction. This is also reflected in the current guidelines for hypoxic-ischemic encephalopathy in adults established by the German Society for Neurology. In cases of inconclusive prognostic findings at 72 hours post-arrest, all prognostic tests—including pupillometry—should be repeated on day 7 after CA.[32]

Limitations

The main limitation of this study is the single-center design and the sample size. With NPi differences being small between the groups, larger samples and results from multiple centers would facilitate the identification of a cutoff value between the groups. Further, we did not obtain the results from the regular pupillary testing with a penlight for comparison.

Another limitation is that CPC scores were only evaluated at hospital discharge, and potential changes in neurological status at later time points are not reflected in our data.

Our study population was treated with targeted TTM at 33°C. Since the publication of the TTM trials, many centers have adopted a target temperature of 36°C.[33] At our institution, however, we have continued to use 33°C based on the characteristics of our patient population, which includes a higher proportion of patients without bystander CPR and with longer no-flow times compared to those included in the TTM trials. We believe that under these conditions, a lower target temperature may offer greater neuroprotective benefit. This approach is consistent with current ILCOR guidelines, which recommend maintaining a target temperature between 32°C and 36°C.[6] Notably, variations in body temperature may potentially influence the PLR and neurological outcomes.

Furthermore, our analysis did not differentiate between IHCA and OHCA. Some studies suggest that the predictive value of NPi in patients with IHCA may not be as reliable as in those with OHCA.[25]

A general limitation when comparing studies is the variability in the types of pupillometers used. Different devices apply varying light intensities, and the calculation of the NPi may differ depending on the software version.

Additionally, we selected the best pupillary response for NPi and the best percentage change of either eye after bilateral measurements for analysis. This led to the inability of analyzing inter-eye differences in NPi and percentage change, which might have added additional value to our study. In neurologically injured patients (eg, intracranial hemorrhage or stroke), data exists that NPi differences >0.7 are associated with poor outcome.[34] Data for outcome prediction with anisocoria after CA are lacking. We also selected the best NPi and percentage change independently, which may have led to the use of different eyes for each parameter.

Another limitation of this study is the time gap between data collection (2015–2018) and publication. This delay resulted from changes within our research team, shifting priorities, limited resources, and personal circumstances that affected the continuity of data analysis and manuscript preparation. However, the findings remain highly relevant.

Strengths of our study include its prospective design with a comprehensive 5-day monitoring period, providing robust data on pupillary function post-CA.

Conclusion

Patients with higher NPi values and/or greater percentage change are more likely to have a good neurological outcome following CA, when looking at the best value of bilateral measurements.

Conflict of interest statement

The authors declare no conflict of interest.

Author contributions

Marcy F and Schroeder T planned the analysis and contributed to data interpretation, manuscript writing, and review. Storm C assisted with data acquisition, manuscript drafting, and data interpretation. Krannich A was the primary contributor to the statistical analysis. Schueler B supported data acquisition and analysis. Nee J contributed to data interpretation and reviewed the manuscript. All authors reviewed and approved the final manuscript.
During the preparation of this work, the authors used ChatGPT (OpenAI) in order to correct grammar and spelling errors. After using this service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Ethical approval of studies and informed consent

The study was approved by the internal review board (IRB) and ethics committee of Charité University Hospital Berlin (IRB No. EA2/011/15), and was conducted in accordance with the Declaration of Helsinki, as revised in 2013.

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