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ORIGINAL RESEARCH

Neurological pupil index during cardiopulmonary resuscitation is associated with admission to ICU in non-traumatic out-of-hospital cardiac arrest patients

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Abstract

Pupillary light reflex (PLR) is a simple method to assess brainstem function and can be measured objectively and accurately using pupillometry. We sought to investigate the relationship between PLR measured with pupillometry during cardiopulmonary resuscitation (CPR) and early prognosis of out-of-hospital cardiac arrest (OHCA) patients. This study was a single-centre prospective observational study. All OHCA patients who received CPR in the emergency department (ED) from August 2019 to January 2021 were registered, and adult patients whose neurological pupil index (NPi) was measured with an automated pupillometer during CPR in the ED were included. The primary outcome was admission to the intensive care unit (ICU). A total of 109 patients were included, and the mean of the NPi measurements of all the patients was 0.1 ± 0.7. The mean of the NPi was higher in the patients admitted to the ICU than in those who died in the ED, 0.5 ± 1.2 *vs.* 0.0 ± 0.1 ($p = 0.031$). Receiver operating characteristic analysis was performed to determine the cut-off value of the NPi, and the optimal cut-off value for ICU admission was 2.0 with sensitivity and specificity 0.769 and 0.652, respectively. Patients with NPi >2.0 showed higher rates of admission to ICU, ICU survival, and good neurologic outcomes at hospital discharge and at 3 months following cardiac arrest, than the patients with NPi ≤ 2.0. Firth's bias-reduced penalised-likelihood multivariable logistic regression analysis showed that the odds ratio of the group with NPi >2.0 was 14.37 (95% confidence interval, 1.80–179.12), which was an independent variable associated with admission to ICU. NPi of higher than 2.0 is one of the indicators associated with an early favourable outcome of OHCA patients.

Keywords

Pupillary reflex; Out-of-hospital cardiac arrest; Prognosis

1. Background

Many studies have been conducted to predict the prognosis of out-of-hospital cardiac arrest (OHCA) patients, and recent focus has been on intensive care unit (ICU) survival rate and good neurological outcomes. According to the American heart association (AHA) guideline, prediction of such prognosis is made through tests such as those for pupillary light reflex (PLR), corneal reflex, and myoclonus [1]. To avoid the confounding effects of medication or the short, and often poor, examination in the early post-injury period, these tests are performed on patients who have had an adequate time after return of spontaneous circulation (ROSC) and play an important role in determining whether to continue intensive care [1].

On the other hand, prediction of early prognosis of patients undergoing cardiopulmonary resuscitation (CPR) is important in terms of continuing CPR and considering active treatment in the field or ED, and conversely, in preventing death due to "inappropriate discontinuation of treatment" [1, 2]. According to the study by Drennan *et al.* [3], ROSC should not be used as the sole criterion for discontinuation of CPR, and deciding to terminate CPR should take into consideration the universal termination of resuscitation rule and other factors that can more accurately predict the patient's prognosis.

Testing the PLR is a simple method to assess brainstem function and is used to evaluate neurological prognosis in patients with cerebrovascular disease or cardiac arrest [1, 4]. Recently, pupillometry has been used to objectively and accurately assess the PLR, by measuring the pupil min/max size, constriction %, latency, constriction velocity, maximum constriction velocity, and dilation velocity. Based on all these variables, the neurological pupil index (NPi) can be obtained [5].

There have been studies on the association between the PLR and patient prognosis during CPR [6, 7]. Specifically, there

are studies suggesting that the NPi in patients admitted to the ICU after ROSC is related to their prognosis [8–10]. However, there are no studies on the association between the NPi measured during CPR and patient prognosis. Therefore, we aimed to investigate the relationship between the NPi measured during CPR and early prognosis of OHCA patients.

2. Materials and methods

2.1 Study design and setting

This pilot study was a single-centre prospective observational study. The study, conducted from August 2019 to January 2021, was designed to evaluate the relationship between the NPi measured during CPR at the time of arrival to the emergency department (ED) and the rates of admission to ICU of the OHCA patients. All OHCA patients with a presumed medical cause for the arrest, who received CPR in the ED, and whose NPi was measured with an automated pupillometer during the initiation of CPR were eligible for the study. The exclusion criteria were ages $<$18 years, cardiac arrest due to a non-medical cause, ROSC upon ED arrival, baseline cerebral performance category (CPC) 3 or 4, CPR discontinued in ED due to "do not resuscitate" (DNR) status, underlying end-stage malignant diseases, and refusal to participate in the study.

The emergency medical service (EMS) system in the study area during the study period was a two-tiered dispatch system, and EMS providers performed basic life support at the scene (30:2 chest compression and ventilation, automatic external defibrillator applied) and, if possible, advanced airway management under direct medical supervision. If a qualified team capable of providing advanced life support (ALS) was dispatched, ALS under direct medical supervision was performed. When paramedic teams capable of ALS arrived at the scene, an intravenous line was secured and medications such as adrenaline (epinephrine) were administered according to the guidelines.

After the patient arrived at the ED, ALS was provided according to the AHA guidelines [1, 11]. When the Emergency Medical Services team informed that an OHCA patient would visit the ED, at least three physicians, including a CPR leader, four emergency medical technicians (EMT), three nurses, and one researcher, prepared for CPR. When the patient arrived, the patient was first lifted and placed on the CPR bed, and the Lund University Cardiopulmonary Assist System 2 (LUCAS-2) device (Physio-Control, Redmond, WA, USA) was applied by three EMTs while one EMT performed chest compressions. Once the patient was in bed and chest compressions were initiated with LUCAS, one physician maintained the airway and performed bag-valve-mask ventilation, a researcher measured the NPis in both eyes of the patient with a pupilometer while one nurse applied the defibrillator patch and the patient monitoring devices such as electrocardiography and pulse oximeter. Subsequently, another nurse secured an intravenous route and administered drugs, and the doctor in charge of the airway placed an advanced airway. The other nurse was responsible for recording the patient chart, and the patient's medical history was recorded by the other physician who was not the CPR leader or the one responsible for the airway. At the time of the NPi measurement, since high-quality chest compressions were performed with LUCAS, chest compressions were not interrupted, and attention was paid not to interfere with the bag-valve-mask ventilation.

Written informed consent was obtained from the legal representative of the patient at the same time. If the legal representative could not visit the ED during the initiation of CPR, informed consent for NPi measurement was obtained from the patient or legal representative when possible, after the measurements. Although the NPis of the patient were measured, if the legal representative refused to participate in the study or when informed consent was not obtained for any reason, the patient was not enrolled in the study. According to the AHA guidelines, the termination of resuscitation was decided by the emergency physician considering many factors, including witnessed versus unwitnessed arrest, time to CPR, initial arrest rhythm, time to defibrillation, comorbid disease, prearrest state, and whether there is ROSC at some point during the resuscitative efforts [12]. If the patient achieved sustained ROSC in the ED, ICU admission proceeded as soon as possible for post-cardiac arrest care. The treatment in the ICU was stopped when the patient did not respond to treatment, or when two or more physicians judged that life-sustaining therapy was meaningless when the legal representative officially stated that they had no longer wanted to provide life-sustaining treatment to the patient.

2.2 Automated pupillometer and the measurement of NPi

The NPi®-200 pupillometer (Neuroptics, Laguna Hills, CA, USA) was used to measure and calculate the NPi [5, 13]. It is a hand-held, non-invasive device with an infrared camera that automatically tracks and measures the size of the pupil and the series of dynamic pupillary variables (including the percentage of pupillary constriction, latency, constriction velocity, and dilation velocity) while a light of fixed intensity and duration is simultaneously shone, effectively stimulating the PLR. The measurement takes 3.2 s, allowing for a full or partial recovery of the pupil size following light stimulation. The NPi algorithm was developed to quantify pupillary reactivity and to eliminate the subjectivity of measurement. Pupil variables such as size, latency, constriction velocity, and dilation velocity are parameters for the NPi algorithm, and each value measured using the pupillometer is compared with a baseline set of the samples from healthy subjects. The variables are then graded and expressed in points from 1 to 5. If the NPi is $>$3 points, it is considered as normal pupillary reflex. An NPi value of 0 reflects an absent PLR, a value closer to 1 is reflects a sluggish PLR, and a value closer to 5 reflects a brisker PLR [5, 14].

During the initiation of CPR, the NPi values of both eyes were measured, and the smaller value was used in the analysis.

2.3 Data collection and processing

Data were recorded on a standardised collection form completed by the research nurse. Age, sex, location of arrest, presence of a witness, first monitored rhythm, bystander CPR, no-flow time (defined as the reported time from cardiac arrest to the start of bystander CPR), and low-flow time (defined as

the total amount of time CPR was performed on the patient during the pre-hospital and hospital stages) were recorded. Arrest location was classified as public or non-public. The first monitored rhythm was classified as shockable and non-shockable [15]. Pupil size and NPi were measured in both eyes and data from the worse scoring eye were used (lowest size, NPi) [9]. The primary outcome of this study was admission to ICU with sustained ROSC. Secondary outcomes were ICU survival and favourable neurologic outcomes at hospital discharge and at 3 months following cardiac arrest, which was investigated with a structured telephone follow-up protocol performed by trained research personnel.

2.4 Statistical analyses

Continuous variables were evaluated with the Shapiro-Wilk test to determine the normality of the distribution and were expressed as the mean ± standard deviation or the median (interquartile range (IQR)). Student's *t*-tests or Wilcoxon rank-sum tests were performed as deemed appropriate, depending on the normality of the distribution. Categorical variables were described as a number with percentage and compared using the χ^2 test or Fisher's exact test.

To minimise the possibility of misclassifying patients with good outcome as those with poor outcome, the smaller value of the NPi measured in both eyes was used for analysis. Receiver operating characteristic (ROC) analysis was performed to determine the cut-off value of the NPi, which was predicted to suggest poor outcomes.

A Firth's bias-reduced penalised-likelihood multivariable logistic regression analysis was performed to evaluate the independent association between the NPi and the admission to ICU with sustained ROSC, and the results were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Considering that this was a pilot study, the Firth's logistic regression was used to calculate the OR from the data of small sample size including rare events. Factors known to be associated with patient prognosis in previous studies, such as age, sex, location of arrest, presence of the witness, bystander CPR, presumed no flow time, first monitored rhythm, and low-flow time were included in the multivariable analysis.

A post hoc statistical power analysis was performed with the probability of admission to ICU for each group. Because a small number of patients were included in the NPi >2.0 group, statistical power analysis based on Fisher's exact test was performed. With the sample size of each group divided according to the NPi and admission to ICU, and with the α level of 0.05, the statistical power was calculated as 0.85.

All data processing and statistical analyses were performed using R-package software, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed *p*-value < 0.05 was considered statistically significant.

3. Results

A total of 265 adults OHCA patients were eligible to participate in the study. Among them, 156 patients were excluded (58 experienced cardiac arrest due to non-medical causes, 28 had ROSC upon arrival at ED, 5 had resuscitation discontinued because legal representatives refused further treatment, 22 had underlying end-stage malignant diseases, 43 refused to participate in the study by the patient or legal representatives). A final sample of 109 OHCA patients was included, and the mean of the NPi measurements of all the patients was 0.1 ± 0.7. The mean of the NPi was higher in the patients admitted to the ICU than in those who died in the ED, 0.5 ± 1.2 *vs.* 0.0 ± 0.1 ($p = 0.031$) (Fig. 1). The clinical characteristics of patients according to the admission to ICU are shown in Table 1. The median age was 78 IQR, 62–84) years, and most of the participants were male (65.1%, n = 71). The patients who could be admitted to the ICU with sustained ROSC were observed to be younger, to have arrests mostly in public locations, and to have shorter prehospital low flow times as compared with those who died at the ED.

In the ROC analysis, the optimal cut-off value for ICU admission was NPi score of 2.0. The area under the ROC curve was 0.708 (95% CI, 0.673–0.742), and the sensitivity and specificity at the cut-off value of 2.0 were 0.769 and 0.652, respectively. The patients were divided into two groups based on NPi 2.0; 103 (94.5%) were classified under the NPi ≤2.0 group and 6 (5.5%) fell under the NPi of >2.0 group. Table 2 shows the clinical characteristics of these two groups classified according to NPi. There were no statistically significant differences in age, sex, comorbidity, location of arrest, presence of witnesses, bystander CPR, no-flow time, or low-flow time between the two groups. The proportion of patients who were admitted to the ICU with sustained ROSC in the NPi >2.0 and NPi ≤2.0 groups was 83.3% and 25.2%, respectively ($p = 0.009$). The proportion of patients who achieved ICU survival in the NPi >2.0 and NPi ≤2.0 groups was 66.7% and 2.9%, respectively ($p < 0.001$). Among the patients who survived the ICU stay, three patients showed good neurologic outcome (CPC 1 or 2) at 3 months after cardiac arrest in the NPi >2.0 group, while no patients showed good neurologic outcome after 3 months in the NPi ≤2.0 group.

The results of Firth's bias-reduced penalised-likelihood multivariable logistic regression analysis are shown in Fig. 2. After adjusting the factors known to be associated with the outcome of cardiac arrest patients, the OR of NPi >2.0 was 14.37 (95% CI, 1.80–179.12), which was an independent variable associated with admission to ICU.

4. Discussion

In this study, an automated pupillometer was used to determine the association between the NPi and outcome during CPR. Further, patients with NPi >2.0 showed a higher frequency of admission to ICU than patients with NPi ≤2.0. This is consistent with the results of previous NPi studies and studies on PLR measurement during CPR. The OR of admission to ICU was 14.37 times higher for patients with NPi >2.0 than for patients with NPi ≤2.0 (OR, 14.37; 95% CI, 1.80–179.12).

PLR stems from the interaction between the sympathetic and parasympathetic nervous systems with respect to light. The sympathetic stimulation results in pupillary dilation, and the parasympathetic stimulation results in pupillary constriction. Severe anoxia or ischaemia can cause anoxia in the brain and brainstem and result in fixed and dilated pupils. If the blood

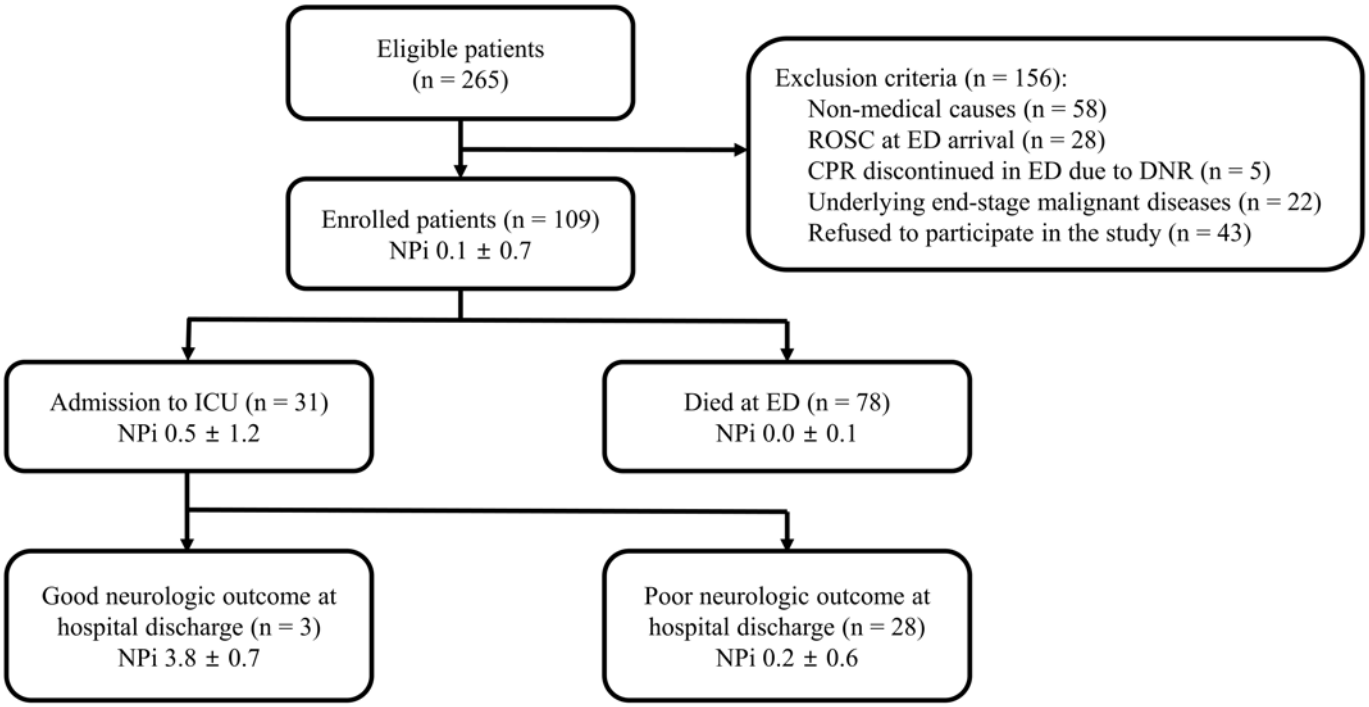

FIGURE 1. Flow chart of the study population. ROSC, return of spontaneous circulation; ED, emergency department; CPR, cardiopulmonary resuscitation; DNR, do not resuscitate.

TABLE 1. Baseline characteristics of patients according to the admission to ICU.

	Total (n = 109)	Admission to ICU (n = 31)	Dead in ED (n = 78)	*p*
Age	78.0 (62.0–84.0)	67.0 (57.0–81.5)	79.0 (70.0–84.8)	0.039
Male	71 (65.1%)	23 (74.2%)	48 (61.5%)	0.304
Comorbidities				
Hypertension	49 (45.4%)	18 (58.1%)	31 (40.3%)	0.142
Diabetes	22 (20.4%)	7 (22.6%)	15 (19.5%)	0.922
Hyperlipidaemia	8 (7.4%)	2 (6.5%)	6 (7.8%)	1.000
Public location	39 (35.8%)	17 (54.8%)	22 (28.2%)	0.017
Witnessed arrest	51 (47.7%)	19 (61.3%)	32 (42.1%)	0.112
Bystander CPR	64 (59.3%)	16 (51.6%)	48 (62.3%)	0.418
No flow time (min)	0.0 (0.0–8.0)	0.0 (0.0–8.0)	0.0 (0.0–7.8)	0.943
Shockable rhythm	16 (16.0%)	6 (22.2%)	10 (13.7%)	0.468
Prehospital low flow time (min)	27.0 (12.5–37.0)	25.0 (18.0–37.0)	28.0 (23.0–38.0)	<0.001
Mechanical CPR device by EMS	16 (14.7%)	5 (16.1%)	11 (14.1%)	1.000
Advanced airway by EMS	92 (84.4%)	23 (74.2%)	69 (88.5%)	0.119
Adrenaline administration by EMS	33 (30.3%)	7 (22.6%)	26 (33.3%)	0.384
Low flow time in ED (min)	15.0 (8.5–21.5)	15.0 (8.5–21.5)	15.0 (9.0–23.0)	0.324
NPi >2.0	6 (5.5%)	5 (16.1%)	1 (1.3%)	0.009

Data are expressed as median (interquartile range) or n (%) as appropriate.
ICU, intensive care unit; ED, emergency department; CPR, cardiopulmonary resuscitation; EMS, emergency medical service; NPi neurological pupil index.

flow or the arterial oxygen tension is reduced, then the pupil is dilated. If the blood flow disappears, it can cause wide dilation and the pupillary reaction to light also disappears [16–19].

The PLRs have been used to predict the survival and evaluate the neurological prognosis in post-CPR patients [20, 21]. However, the standard use of pupillary evaluation using a penlight can be highly subjective, and interobserver differences can occur [22, 23]. Automated pupillometers are accu-

TABLE 2. Baseline characteristics and patient outcomes according to the NPi measured during CPR.

	NPi >2.0 (n = 6)	NPi ≤2.0 (n = 103)	*p*
Age	81.5 (61.8–84.8)	77.0 (62.0–83.5)	0.858
Male	4 (66.7%)	67 (65.0%)	1.000
Comorbidities			
Hypertension	4 (66.7%)	45 (44.1%)	0.512
Diabetes	1 (16.7%)	21 (20.6%)	1.000
Hyperlipidaemia	0 (0.0%)	8 (7.8%)	1.000
Public location	3 (50.0%)	36 (35.0%)	0.757
Witnessed arrest	3 (50.0%)	48 (47.5%)	1.000
Bystander CPR	6 (100.0%)	58 (56.9%)	0.096
No flow time(min)	0.0 (0.0–0.0)	1.0 (0.0–8.5)	0.072
Shockable rhythm	3 (50.0%)	13 (13.7%)	0.033
Prehospital low flow time (min)	32.0 (26.0–36.0)	27.0 (21.5–37.0)	0.687
Mechanical CPR device by EMS	1 (16.7%)	15 (14.6%)	1.000
Advanced airway by EMS	5 (83.3)	87 (84.5)	1.000
Adrenaline administration by EMS	2 (33.3)	31 (30.1)	1.000
Low flow time in ED (min)	23.0 (17.5–24.0)	24.0 (15.0–32.0)	0.328
Outcome			
Admission to ICU	5 (83.3%)	26 (25.2%)	0.009
ICU survival	4 (66.7%)	3 (2.9%)	<0.001
Good neurologic outcome at hospital discharge	3 (50.0%)	0 (0.0%)	<0.001
Good neurologic outcome at 3 months	3 (50.0%)	0 (0.0%)	<0.001

Data are expressed as median (interquartile range) or n (%) as appropriate.
NPi, neurological pupil index; CPR, cardiopulmonary resuscitation; EMS, emergency medical service; ED, emergency department.

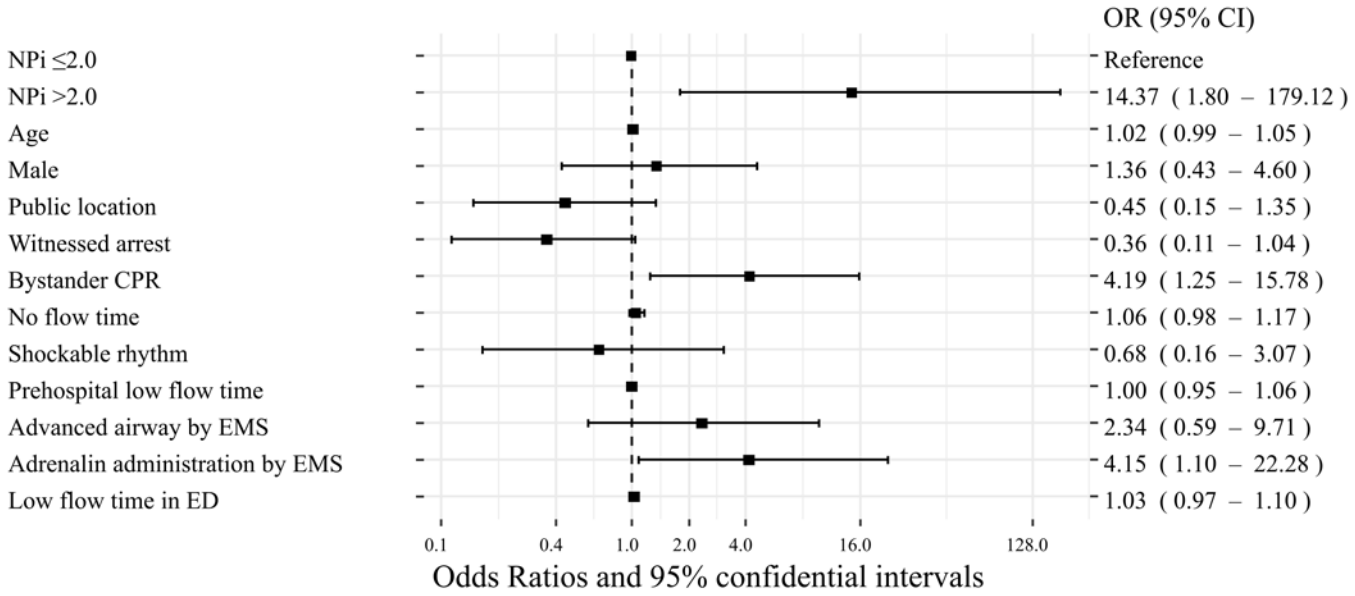

FIGURE 2. Odds ratio plot from the Firth's bias-reduced penalized-likelihood multivariable logistic regression analysis of admission to ICU as the dependent variable. NPi, neurological pupil index; CPR, cardiopulmonary resuscitation; EMS, emergency medical service; ED, emergency department.

rate, reliable, and objective compared to the traditional pen-light examination [4, 5, 24]. In particular, the NPi is related to the prognosis of patients with cardiac arrest, and reports have demonstrated an independent association between high NPi values and mortality [8, 10]. Additionally, a study by Oddo *et al.* [25] showed 100% specificity for predicting unfavourable 3-month neurologic outcomes when NPi values were $\leq$2. However, these studies measured the NPi after ROSC, which differs from this study, which measured the NPi during CPR.

Meanwhile, experiments on pig studying the correlation between PLR and prognosis measured during CPR reported that dynamic change of the pupil diameter and reaction to light during the cardiac arrest was associated with coronary perfusion pressure, and was a predictive factor for spontaneous circulation [26]. In the study by Steen-Hansen *et al.* [27], there were more cases of ROSC and ICU survival in patients with continuous contraction of the pupil as well as those who experienced recontraction after a period of dilation, compared with patients who experienced continuous dilation and those who experienced dilation after a period of contraction. There was also a case series reported by Behrends *et al.* [7] that found the presence of PLR during CPR correlated with ROSC and favourable neurologic status at 3 days.

All patients included in this study were administered adrenaline in accordance with AHA guidelines, and therefore, there may be concerns about the resulting PLR changes. However, the study by Behrends *et al.* [7] showed that the presence of the PLR in patients during CPR or at ROSC was related to the patient's prognosis regardless of the drug used, and the PLR was not blocked by adrenaline, atropine, or muscle relaxants. In addition, a study by Achamallah *et al.* [28] conducted pupillometry on in-hospital cardiac arrest patients who achieved ROSC and reported that the use of adrenaline or atropine during ACLS did not eliminate the PLR. These findings suggest that the absence of pupillary response in post-arrest patients is an important prognostic sign, which supports that the NPi measured during CPR in this study is meaningful.

5. Limitations

There are some limitations to this study. First, since the study was conducted at a single centre, it makes it difficult to apply the results to other institutions. Second, the PLR was measured using a pupillometer during CPR, and the time between the onset of cardiac arrest and PLR measurement was not constant for each patient. Therefore, the possibility of variation in results due to different low flow times cannot be excluded. Nevertheless, considering that the PLR reflects preserved coronary perfusion pressure, the results of this study are still significant. Third, the pupillometer check was performed only once during CPR. Therefore, the link between changes in the PLR and prognosis was not investigated. Fourth, of the 109 patients, only 7 survived, and among them, only 3 showed good neurologic outcome. Lastly, the withdrawal of therapy was not based on a protocol but on clinical decision.

6. Conclusions

NPi higher than 2.0 proved as an indicator of favourable early prognosis in patients after OHCA. Future large multicentre studies are warranted to arrive at strong conclusions.

AUTHOR CONTRIBUTIONS

DWK—wrote original draft; YHJ—supervised and reviewed; SMP—designed the study; DKL—designed the study, reviewed and edited; DHJ—analysed the results, reviewed and edited; all authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was reviewed and approved by the Institutional Review Board of Seoul National University Bundang Hospital (B-1905/538-305). Informed consent was obtained from the legal representatives of the patient or the patient enrolled in the study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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