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Clinical paper

A feasibility study for the continuous measurement of pupillary response using the pupillography during CPR in out-of-hospital cardiac arrest patients

Hui Jai Lee[a], *Jonghwan Shin*[a,b,*], *Ki Jeong Hong*[a], *Jin Hee Jung*[a], *Se Jong Lee*[a], *Euigi Jung*[a], *Kyoung Min You*[a], *Tae Han Kim*[a]

[a] *Department of Emergency Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, 20, Boramae-ro 5-gil, Dongjak-gu, Seoul 07061, Republic of Korea*

[b] *Department of Emergency Medicine, Seoul National University College of Medicine, 103 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea*

Abstract

Purpose: We investigated the change in pupil size and pupil light reflex (PLR) using a pupillography capable of continuous measurement both during CPR and immediately following the return-of-spontaneous circulation (ROSC) in out-of-hospital cardiac arrest (OHCA) comatose patients in an emergency department.

Methods: Pupil size and PLR were continuously measured both during CPR and immediately following ROSC until intensive care unit (ICU) admission. The changes in pupil sizes during CPR were categorized into three groups (no change – N, decreased – D, and increased – I groups).

Results: Pupillography was applied for 118 and 60 patients during CPR and immediately following ROSC, respectively. Only two patients had a PLR during CPR. The number of patients included each group were 58 (N-group), 21 (D-group) and 39 (I-group). In the D-group, the proportion of witnessed arrest was higher than in the N-group and I-group (81% vs. 55% and 49%, respectively; $p = 0.049$). There were statistically significant shorter prehospital time in the D-group than the N-group and I-group (13 vs. 23 and 24 min, respectively; $p = 0.012$). PLR was observed immediately following ROSC in 14 patients. PLR was maintained in seven of these patients until admission to intensive care unit. Six of the seven patients who remained with PLR until ICU admission had survival to hospital discharge, and three of them had good neurological recovery.

Conclusion: Our study demonstrated that measurement of the continuous pupillary response can be feasible. Patients with the presence of PLR following ROSC had better outcomes.

Keywords: Pupillary reflex, Out-of-hospital cardiac arrest, Prognosis, Cardiopulmonary resuscitation

* Corresponding author at: Seoul Metropolitan Government Seoul National University Boramae Medical Center, 20, Boramae-ro 5-gil, Dongjak-gu, Seoul 07061, Republic of Korea.

E-mail addresses: skyshiner@naver.com, skycpr@snu.ac.kr (J. Shin).

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Introduction

The reason for performing adult advanced life support (ALS) in case of out-of-hospital cardiac arrest (OHCA) is to achieve the return of spontaneous circulation (ROSC) with no response to basic life support (BLS). The cardiopulmonary resuscitation (CPR) team conducting ALS should provide high quality CPR, manual defibrillation, cardiovascular drug administration, airway management, assessment of patient status, and reversible cause treatment.[1] In order to perform ALS, which ic complex and difficult, the CPR team must mobilize all available medical equipment in order to assess the patient's condition and current CPR quality. There are a number of methods and emerging technologies for monitor patients during CPR that can potentially help guide ALS interventions. These include clinical signs, CPR feedback devices, pulse checking, electrocardiography (ECG), end-tidal carbon dioxide with waveform capnography, blood gas values, invasive cardiovascular monitoring, ultrasound, and cerebral oximetry using near-infrared spectroscopy. However, many of these methods have no clear guidelines and are still under investigation. In particular, there is no available way to evaluate the degree of brain injury or predict neurological recovery during ALS. A method for measuring cerebral oxygen saturation using near-infrared spectroscopy is currently being studied.[2–4] However, this technique has yet to be established.

In an animal study using a visual examination during CPR, the change in pupil diameter and reactions to light predicted the ROSC and recovery of cerebral function.[5] In a clinical study of 244 patients, it was found that the proportion of ROSC and survival to hospital discharge were more frequent in cases of PLR or decreased pupil size.[6,7] The importance of this study is that the pupillometer can measure light reflexes in case that the traditional pen light method cannot confirm light reflexes. However, the patients enrolled in that study experienced IHCA, and the use of a portable pupillometer may interfere with CPR. Therefore, we prospectively assessed differences in PLR and pupillary size both during CPR and after ROSC in OHCA patients using continuously measurable pupillography.

Methods

Study design, setting, and population

We conducted a prospective clinical study of OHCA patients who were admitted to the emergency department (ED) at a university hospital between October 2015 and May 2017. This study was approved by the Boramae Medical Center institutional review board for clinical study, data collection, and follow-up of OHCA patients (20150812/16-2015-111/091). The ED volume of the involved hospital is 60,000 patients per year. The hospital is equipped with facilities, equipment, and medical personnel teams to provide the final intensive treatment to OHCA patients. All data collected from OHCA patients were maintained in a prospective OHCA registry according to the standardized Utstein-style guideline. Good and poor neurological outcomes were defined as CPC 1–2 and CPC 3–5 at one month, respectively. OHCA patients who had ROSC with recovery of consciousness before hospitalization, underwent trauma, or were under the age of 18 were excluded from this study. Patients who did not provide informed consent from family were also excluded. Patients were also excluded if their eyelids could not be opened or if their pupils were not exposed for any other reason. Patients who recovered consciousness immediately following prehospital ROSC or hospital ROSC were excluded from this study as well.

Measurement of the pupillary response was conducted using a pupillography system following modification of the videonystagmography. A pupillography system is a device that continuously and automatically measures a patient's pupil using infrared light. Because hypoxic brain injury due to cardiac arrest occurs as a global ischemia, pupillography was only conducted on the patient's left pupil. When the OHCA patients arrived at the ED, pupillography was conducted after performing an endotracheal intubation with capnography. A silk tape was then attached to the eyelid and the eyelid was opened. Because the patient was shaken due to chest compression during CPR, we firmly fixed the pupillography to the patient's head with rubber straps. The patient's pupil was positioned at the center of the image while viewing the pupil image in the monitor of the pupillography system. The pupil size was measured and light was reflected in the pupil every five seconds in order to confirm PLR. Normal saline was administered to the cornea every five minutes in order to prevent drying of the cornea. The measured PLR and pupil size were recorded in the system and the data were extracted in an Excel format. The presence or absence of PLR can be confirmed by a graph, and the pupil size can be confirmed by numerical variables and a change graph in the extracted Excel database (Supplemental Fig. 1). There was no interruption in any medical practice related to CPR while wearing the pupillography, such as ventilation with bag-valve-mask (BVM), endotracheal suction, or capnography. The measurement of pupillary response using the pupillography began approximately 10 min after the start of ALS in the ED. If the patient had a ROSC before the measurement of pupillary response, the patient was excluded from the analysis of CPR patients. If the patient did not recover consciousness after ROSC, we measured their pupillary response and included it in the analysis after ROSC. After ROSC, monitoring via pupillography was continued until the patient was admitted to the intensive care unit.

Outcome analysis of pupillary response

We initially planned to divide PLR into three groups: (A) PLR was not present at first, but appeared during CPR; (B) PLR was present at first, but disappeared during CPR; and (C) there was no PLR from the beginning to the end of CPR. A change in pupil size was defined as at least a 10% difference from the value of the first measure. The pupil size changes were also divided into three groups: (A) pupil size was bigger than at first (I-group), (B) pupil size was gradually smaller than at first (D-group), and (C) pupil size was not different from at first (N-group). Among the patients with ROSC, PLR was categorized into whether there was PLR and PLR persistence in the ER until ICU admission. This classification was made by analyzing both pupil images and numerical values. Cases that could not be confirmed by image or numerical value were excluded from the analysis.

Statistical analysis

The Shapiro–Wilk test was used to evaluate the normality of the continuous variables. Continuous data were expressed as the mean and standard deviation (SD) or medians and interquartile ranges

(IQR) according to the normal distribution. The Student's T test or Mann–Whitney U test was used as appropriate. Categorical data were expressed as frequencies and percentages and compared using the chi-square test or Fisher's exact test as appropriate. Bonferroni correction and Bonferroni corrected p-value were used for multiple comparisons. Statistically significant variables from the univariate analysis were those with a p-value of less than 0.05. Data were analyzed using the SPSS, version 20.0 (IBM., Armonk, New York, USA). The primary outcome was good neurologic recovery (CPC 1 or 2) at 30 days after ROSC.

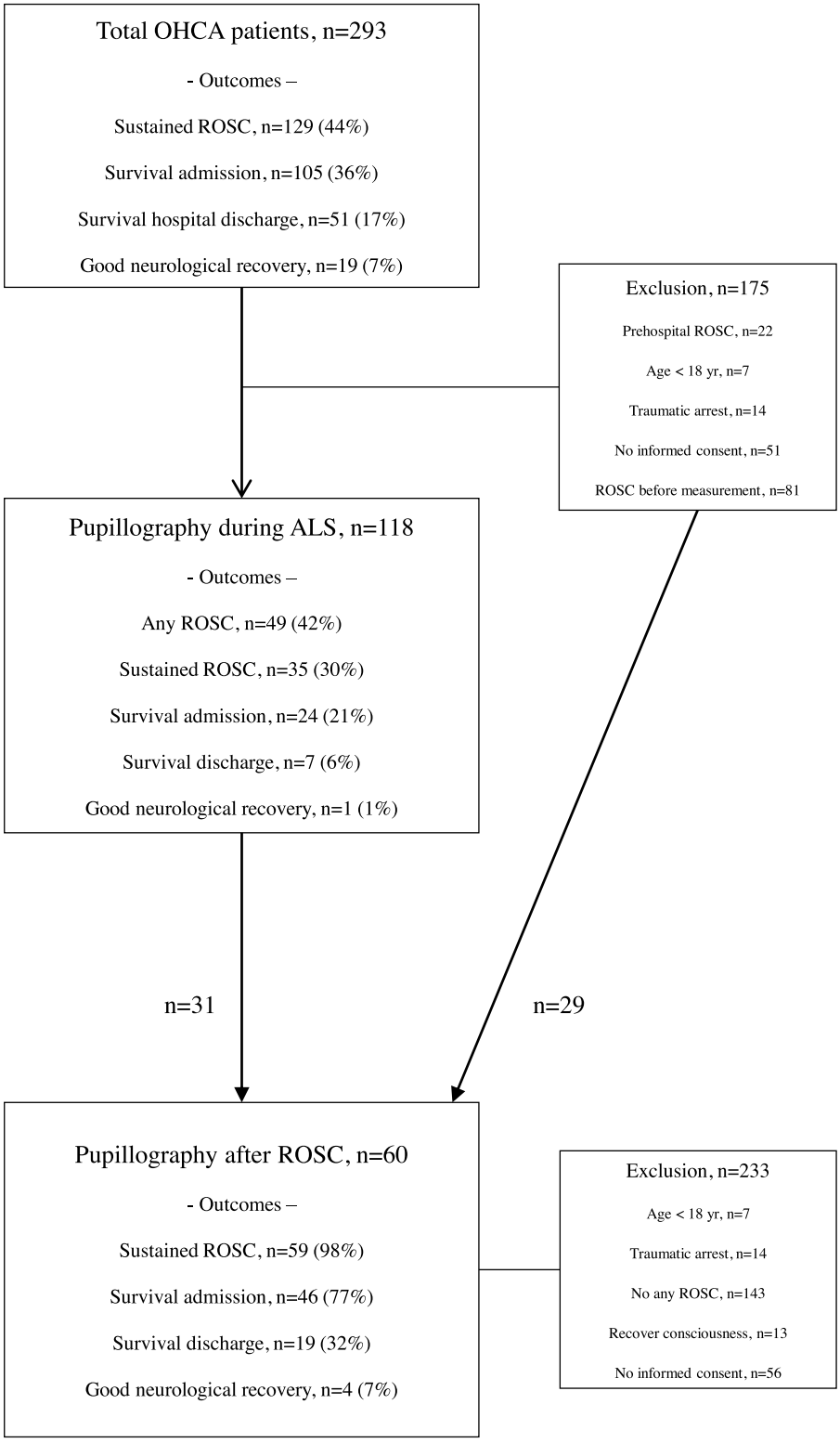

Fig. 1 – Study population and outcomes of out-of-hospital cardiac arrest (OHCA) patients. ROSC: return of spontaneous circulation, ALS: advanced life support.

Results

Enrolled patients

A total of 293 OHCA patients visited the ED during the study period. A total of 148 patients were ultimately enrolled in the study. Patients who did not have measurements of their pupillary response and patients who did not provide informed consent were excluded. A total of 118 and 60 patients were measured during CPR and immediately after ROSC, respectively (Fig. 1).

The change in pupil size and the PLR during CPR

Among the 118 patients whose pupillary response was measured during CPR, the total number of patients in the D-group, N-group, and I-group were 21, 58, and 39 patients, respectively. The baseline characteristics are provided in Table 1. There was a statistically significant difference in the number of witnessed cases in the D-group as compared to the N-group and I-group (81% versus 55% and 49%, respectively, p = 0.049). The prehospital arrest time (no + low-flow time) was significantly shorter in the D-group than in the N-group and I-group (13 min versus 23 min and 24 min, respectively, p = 0.012). There were no statistically significant differences in the laboratory results, CPR drugs, total energy of defibrillation, and outcomes between the three groups.

PLR was observed in only two patients during CPR, and classification of the PLR was not feasible. One OHCA patient was a 52-year-old man who underwent ALS in the ER with an initial shockable rhythm and three shocks of defibrillation. After performing 44 min of ALS, the patient recovered spontaneous circulation; he underwent immediate coronary angiography and percutaneous coronary intervention but died of myocardial dysfunction. His pupil size became larger than at the beginning, but ROSC was confirmed immediately after PLR was first recognized. Another 92-year-old male

Table 1 – The results according to the change of pupil size during ALS.

		D-group, n = 21	N-group, n = 58	I-group, n = 39	p-Value
Gender/age	Gender, male/female, n	9/12	37/21	21/18	0.228
	Age, median (IQR)	75 (55–82)	75 (64–81)	71 (59–87)	0.895
Prehospital	Witnessed arrest, n (%)	17 (81)	32 (55)	19 (49)	0.049
	Bystander CPR, n (%)	10 (48)	26 (45)	19 (49)	0.927
	Advanced airway, n (%)	8 (38)	28 (48)	14 (36)	0.440
	Shockable rhythm, n (%)	3 (14)	7 (12)	5 (13)	0.966
	No flow time (min), median (IQR)	0 (0–5)	3 (0–7)	3 (0–9)	0.094
	Low flow time (min), median (IQR)	12 (2–19)	19 (13–23)	18 (14–24)	0.036
	No + low flow time (min), median (IQR)	13 (2–25)	23 (17–28)	24 (17–30)	0.012
Hospital	Shockable rhythm, n (%)	1 (5)	9 (15)	7 (18)	0.844
	Presumed cardiac origin, n (%)	8 (38)	20 (35)	12 (31)	0.843
	ALS time in ED, median (IQR)	26 (20–33)	20 (14–27)	23 (17–35)	0.039
	Epinephrine (mg)	5 (4–8)	5 (3–6)	6 (4–7)	0.186
	Energy of defibrillation (J)	0 (0)	0 (0)	0 (0)	0.361
	Bicarbonate (mEq)	0 (0–80)	0 (0–80)	0 (0–80)	0.339
	Amiodarone (mg)	0 (0)	0 (0)	0 (0–300)	0.766
Laboratory	PH, median (IQR)	6.89 (6.76–6.96)	6.96 (6.79–7.09)	6.99 (6.82–7.08)	0.836
	PCO2 (mmHg), median (IQR)	74 (57–90)	83 (50–95)	67 (54–88)	0.273
	PO2 (mmHg), median (IQR)	31 (0–44)	15 (0–35)	27 (11–35)	0.858
	HCO3 (mEq/L), median (IQR)	13 (12–17)	17 (13–19)	16 (14–17)	0.211
	Lactate (mmol/L), median (IQR)	12 (7–13)	11 (9–15)	13 (9–16)	0.394
	Sodium (mmol/L), median (IQR)	141 (135–145)	138 (135–144)	139 (134–144)	0.313
	Potassium (mmol/L), median (IQR)	5.9 (5.5–7.0)	6 (5.0–7.6)	66 (5.4–8.0)	0.193
	Hemoglobin (g/dL), median (IQR)	11 (10–14)	10 (8–14)	12 (9–15)	0.233
	Troponin-I (ng/mL), median (IQR)	0.15 (0.09–1.92)	0.08 (0.04–0.55)	0.08 (0.03–0.52)	0.531
Post cardiac arrest care	TTM, n (%)	3 (14)	3 (5)	2 (5)	0.323
	CAG (emergency), n (%)	2 (10)	3 (5)	2 (5)	0.746
	PCI (emergency), n (%)	2 (10)	3 (5)	1 (3)	0.507
	ECPR, n (%)	0 (0)	2 (3)	2 (5)	0.580
Outcomes	Any ROSC, n (%)	9 (43)	22 (38)	18 (46)	0.716
	Sustained ROSC, n (%)	5 (24)	19 (33)	11 (28)	0.722
	Survival admission, n (%)	4 (19)	15 (26)	5 (13)	0.290
	Survival hospital discharge, n (%)	3 (14)	4 (7)	2 (5)	0.425
	Good neurological recovery, n (%)	0 (0)	1 (2)	0 (0)	0.594

ALS: advanced life support, CPR: cardiopulmonary resuscitation, IQR: interquartile range, ED: emergency department, TTM: target temperature management, CAG: coronary angiography, PCI: percutaneous coronary intervention, ECPR: extracorporeal CPR, ROSC: return of spontaneous circulation.

patient was transferred to an ambulance, and cardiac arrest was confirmed before he arrived at the hospital. This patient had a no flow time of one minute with a witnessed arrest by a paramedic. At first, there was PLR, but PLR disappeared within minutes of ALS. Eventually, he died without ROSC despite 50 min of ALS in the ED.

The change in pupil size and PLR after ROSC

After ROSC, a total of 60 patients underwent pupillography in the ED until ICU admission. Among the 60 patients who had pupillary responses measured after ROSC, the total numbers of patients in the D-group, N-group, and I-group were 25, 20, and 10, respectively. For five patients, the duration of pupil monitoring was too short, and the pupil size changes after ROSC could not be evaluated. There were no statistically significant differences in clinical characteristics and outcomes between the three groups (Table 2).

Of the 60 patients, 14 had PLR, and seven of these patients with pupillography remained with PLR until ICU admission. Six of the seven patients who remained with PLR until ICU admission had survival hospital to discharge and three of them had good neurological recovery. Conversely, there was no survival to hospital discharge or good neurological recovery among the seven patients whose PLR were not maintained consistently and died at the hospital. There was one patient (2%) that had good neurological recovery among the 46 patients who were found to have no PLR in the ED until ICU admission (Table 3).

Discussion

This study is the first to suggest a method with which to continuously monitoring the change in pupil size and PLR without interfering with

Table 2 – The results according to the change of pupil size immediately after ROSC.

		D-group, n = 25	N-group, n = 20	I-group, n = 10	p-Value
Gender/age	Gender, male/female, n	18/7	13/7	4/6	0.203
	Age, mean (IQR)	70 (59–75)	70 (56–81)	78 (55–84)	0.363
Prehospital	Witnessed arrest, n (%)	17 (68)	11 (55)	5 (50)	0.524
	Bystander CPR, n (%)	11 (44)	6 (30)	3 (30)	0.561
	Advanced airway, n (%)	8 (32)	10 (50)	5 (50)	0.403
	Shockable rhythm, n (%)	5 (22)	2 (13)	1 (11)	0.662
	No flow time (min), median (IQR)	1 (0–10)	5 (0–9)	9 (5–13)	0.081
	Low flow time (min), median (IQR)	18 (11–24)	18 (5–21)	15 (8–24)	0.676
	No + low flow time (min), median (IQR)	23 (11–30)	22 (6–30)	27 (10–35)	0.722
Hospital	Shockable rhythm, n (%)	1 (4)	3 (15)	1 (11)	0.464
	Presumed cardiac origin, n (%)	9 (36)	6 (30)	2 (20)	0.648
	ALS time in ED, median (IQR)	10 (7–21)	10 (6–19)	13 (8–20)	0.765
	Epinephrine (mg), median (IQR)	3 (2–5)	2 (1–6)	3 (2–4)	0.879
	Energy of defibrillation (J), median (IQR)	0 (0–0)	0 (0–0)	0 (0–40)	0.311
	Bicarbonate (mEq), median (IQR)	0 (0–10)	0 (0–40)	0 (0–40)	0.921
	Amiodarone (mg), median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0.678
Laboratory	pH, median (IQR)	6.79 (6.75–7.04)	6.89 (6.82–6.98)	6.98 (6.89–)	0.993
	PCO2 (mmHg), median (IQR)	92 (77–119)	85 (74–121)	76 (46–)	0.646
	PO2 (mmHg), median (IQR)	24 (0–44)	24 (0–70)	81 (50–)	0.396
	HCO3 (mEq/L), median (IQR)	21 (13–23)	17 (14–20)	18 (4–)	0.673
	Lactate (mmol/L), median (IQR)	9 (6–10)	11 (10–13)	7 (4–)	0.163
	Sodium (mmol/L), mean (IQR)	139 (134–143)	136 (130–140)	132 (124–)	0.240
	Potassium (mmol/L), median (IQR)	5.2 (4.3–5.9)	5.9 (4.6–6.6)	5.7 (55–)	0.476
	Hemoglobin (g/dL), median (IQR)	12 (10–14)	11 (8–13)	14 (9–)	0.620
	Troponin-I (ng/mL), median (IQR)	0.05 (0.03–0.13)	0.04 (0.02–0.14)	0.27 (0.22–)	0.237
Post cardiac arrest care	TTM, n (%)	8 (32)	5 (36)	3 (30)	0.919
	CAG (emergency), n (%)	4 (16)	4 (20)	2 (20)	0.744
	PCI (emergency), n (%)	4 (16)	1 (5)	2 (20)	0.440
	ECPR, n (%)	1 (4)	1 (5)	0 (0)	0.771
PLR	PLR Present, n (%)	7 (28%)	4 (20%)	2 (20%)	0.787
Outcomes	Sustained ROSC, n (%)	24 (96)	20 (100)	10 (100)	0.543
	Survival admission, n (%)	19 (76)	15 (75)	6 (60)	0.483
	Survival hospital discharge, n (%)	10 (40)	5 (25)	3 (30)	0.555
	Good neurological recovery, n (%)	3 (12)	1 (5)	0 (0)	0.414

ALS: advanced life support, CPR: cardiopulmonary resuscitation, IQR: interquartile range, ED: emergency department, PLR: pupillary light reflex, TTM: target temperature management, CAG: coronary angiography, PCI: percutaneous coronary intervention, ECPR: extracorporeal CPR, ROSC: return of spontaneous circulation.

Table 3 – The results according to the presence and persistence of pupil light reflex immediately after ROSC.

		Presence of pupil light reflex			Persistence of pupil light reflex		
		Yes, n = 14	No, n = 46	p-Value	Yes, n = 7	No, n = 7	p-Value
Gender/age	Gender, male/female, n	11/3	27/19	0.177	7/0	4/3	0.051
	Age, median (IQR)	66 (58–72)	71 (57–79)	0.340	59 (30–76)	69 (58–71)	0.405
Prehospital	Witnessed arrest, n (%)	9 (64)	27 (59)	0.709	4 (57)	5 (71)	0.577
	Bystander CPR, n (%)	4 (29)	19 (41)	0.391	2 (29)	2 (29)	1.000
	Advanced airway, n (%)	2 (15)	22 (48)	0.036	1 (14)	1 (14)	1.000
	Shockable rhythm, n (%)	4 (36)	4 (10)	0.030	3 (60)	1 (17)	0.137
	No flow time (min), median (IQR)	2 (0–7)	5 (0–10)	0.379	1 (0–5)	3 (0–13)	0.505
	Low flow time (min), median (IQR)	15 (2–20)	18 (10–24)	0.082	4 (0–13)	18 (17–21)	0.084
	No + low flow time (min), median (IQR)	18 (4–25)	25 (12–30)	0.080	5 (3–20)	25 (17–31)	0.085
Hospital	Shockable rhythm, n (%)	3 (27)	2 (4)	0.016	1 (20	2 (33)	0.621
	Presumed cardiac origin, n (%)	3 (25)	15 (33)	0.424	2 (29)	1 (14)	0.515
	ALS time in ED, median (IQR)	9 (3–18)	11 (7–19)	0.180	7 (0–9)	13 (5–56)	0.045
	Epinephrine (mg), median (IQR)	2 (0–4)	3 (2–5)	0.083	1 (0–2)	3 (1–14)	0.037
	Energy of defibrillation (J), median (IQR)	0 (0–0)	0 (0–0)	0.424	0 (0–0)	0 (0–225)	0.901
	Bicarbonate (mEq), median (IQR)	0 (0–0)	0 (0–40)	0.533	0 (0–0)	0 (0–80)	0.079
	Amiodarone (mg), median (IQR)	0 (0–0)	0 (0–0)	0.137	0 (0–0)	0 (0–75)	0.802
Laboratory	PH, median (IQR)	6.85 (6.77–7.12)	6.9. (6.77–7.02)	0.802	7.19 (6.76–)	6.80 (6.66–6.91)	0.250
	PCO2 (mmHg), median (IQR)	85 (49–115)	82 (69–110)	0.641	46 (37–)	104 (85–125)	0.036
	PO2 (mmHg), median (IQR)	20 (3–72)	25 (13–72)	0.558	81 (27–)	11 (0–29)	0.071
	HCO3 (mEq/L), median (IQR)	14 (11–24)	18 (13–21)	0.594	14 (8–)	15 (11–23)	1.000
	Lactate (mmol/L), median (IQR)	10 (9–19)	10 (7–12)	0.275	14 (9–19)	9 (9–16)	0.343
	Sodium (mmol/L), median (IQR)	139 (135–147)	139 (133–142)	0.377	140 (136–148)	139 (134–145)	0.690
	Potassium (mmol/L), median (IQR)	5.6 (4.0–6.2)	5.4 (4.3–6.3)	0.785	5.7 (3.8–6.4)	5.5 (4.1–6.1)	1.000
	Hemoglobin (g/dL), median (IQR)	13 (12–15)	12 (10–14)	0.091	12 (10–16)	13 (12–16)	0.690
	Troponin-I (ng/mL), median (IQR)	0.04 (0.01–0.15)	0.05 (0.02–0.22)	0.601	0.11 (0.01–0.38)	0.04 (0.03–0.08)	0.841
PCAS	TTM, n (%)	4 (31)	13 (28)	0.860	2 (29)	2 (33)	0.853
	CAG (emergency), n (%)	1 (7)	9 (20)	0.733	1 (14)	1 (17)	0.906
	PCI (emergency), n (%)	2 (15)	5 (11)	0.657	1 (14)	1 (17)	0.906
	ECPR, n (%)	1 (8)	2 (4)	0.628	0 (0)	1 (7)	0.261
Outcomes	Sustained ROSC, n (%)	13 (93)	46 (100)	0.068	7 (100)	6 (86)	0.299
	Survival admission, n (%)	2 (86)	34 (74)	0.361	7 (100)	5 (71)	0.127
	Survival hospital discharge, n (%)	6 (43)	13 (28)	0.304	6 (86)	0 (0)	0.001
	Good neurological recovery, n (%)	3 (21)	1 (2)	0.011	3 (43)	0 (0)	0.051

ALS: advanced life support, CPR: cardiopulmonary resuscitation, IQR: interquartile range, ED: emergency department, PCAS: post cardiac arrest care, TTM: target temperature management, CAG: coronary angiography, PCI: percutaneous coronary intervention, ECPR: extracorporeal CPR, ROSC: return of spontaneous circulation.

other important resuscitative efforts during CPR. We observed that the change in pupil size during CPR was related to prehospital arrest time (no-flow and low-flow time). In addition, PLR was observed during CPR in a few OHCA patients. Immediately following ROSC, 14% of patients had PLR. Among them, the outcome was good in patients whose PLR was maintained.

According to the 2015 adult ALS guideline, it may be reasonable to monitor physiologic parameters when feasible in order to monitor and optimize CPR quality, guide vasopressor therapy, and detect ROSC.[1,8] However, there have not been many clinical studies related to this topic, and accurate target values have yet to be established. There are many limitations on the use of these physiologic parameters during actual ALS. More importantly, there is no method that can be used to objectively assess brain injury during ALS. Although there have been some studies on the use of new techniques for brain injury during ALS or post-cardiac arrest care, additional studies are still necessary before widespread application. New equipment will also have limited application during dynamic and complex ALS.

Recently, there have been studies on pupillary response during CPR or post-resuscitation care using portable infrared pupillography. In a study of portable infrared pupillometery in IHCA patients, 25 out of 30 patients had PLR throughout or during CPR.[7] The continuous presence of the PLR or absence of the PLR less than five minutes during CPR was associated with good neurological recovery. Thus, they concluded that serial measurements of the PLR were useful in predicting the outcomes of cardiac arrest survivors. They also showed that PLR was not interrupted by the administration of epinephrine or muscle relaxants. IHCA is most often witnessed by a health care provider and the no flow time is very short due to the immediate CPR. Therefore, PLR may be more likely to occur during CPR. In a clinical study of 103 OHCA survival patients who had quantitative automated pupillography performed for 48 h during post-resuscitation care, reduced quantitative PLR was correlated with postanoxic brain injury

and, when compared to standard multimodal assessment, was found to be highly accurate in predicting long-term prognosis after cardiac arrest.[9] They suggested that quantitative pupillometry may be used for the multimodal assessment of prognosis in patients in coma following cardiac arrest.

In recent guidelines for predicting prognosis during post-resuscitation care, the absence of a pupillary reflex at 72 h or more after cardiac arrest predicts poor outcomes for patients with targeted temperature management (TTM) as well as those who are not treated with TTM as the false positive rate (FPR) approaches 0% (FPR 1 [0–3] and 0 [0–8], respectively).[11,12] In prognostic tests of OHCA patients during post-resuscitation care, there are situations in which most inspection methods cannot be performed. It may be difficult to perform most of the methods (brain imaging, electrophysiology, biomarkers, etc.) recommended in the guidelines during the appropriate period of time for many reasons, such as non-working time, hospital situation, patient's hemodynamic instability, and the economic statuses of the patient and caregivers.[12–14] Therefore, most of the relevant studies inevitably have a selection bias. However, the pupillary response test can be performed in most patients without these various obstacles. Therefore, the selection bias is relatively small compared to that in other predictive examinations. Therefore, the pupillary response test should be recommended as a necessary test to predict the prognosis, and further prospective studies should be conducted on this matter.

There are some limitations in the measurement of pupillary response using portable pupillometry during CPR or after ROSC. The portable pupillometry system requires an additional medical person because the measurement must be taken directly. This may interrupt the performance of CPR and CPR treatment. The measurement position may also be changed whenever measuring with the portable pupillometry system. Therefore, it may be difficult to accurately compare changes in pupil size during CPR. Additionally, it is not capable of continuous measurement. By contrast, our fixed-type pupillography can take continuous measurements during CPR without disturbing any resuscitative efforts and can overcome the limitations of portable pupillometry. It can also be used for all cardiac arrest patients without eye or periorbital injury.

In previous studies, PLR was reported to be almost unaffected by drugs.[15,16] Specifically, drugs used during ALS or post-resuscitation care will not affect PLR.[7] Therefore, PLR can be effectively used during CPR regardless of ALS management. An important parameter for the recovery of brain function in OHCA patients is the duration of resuscitation. It is difficult to identify no flow time and prehospital resuscitation duration during ALS; this is especially true for unwitnessed OHCA patients. Patients with positive PLR or decreased pupillary size during ALS had a shorter ischemic time. This information can be helpful in decision-making in post-resuscitation care, and it is also thought that it will contribute to not treating after unnecessary post-resuscitation care after ROSC. If the pupillary response can be continuously measured during post-resuscitation care from the beginning of ALS, it will be possible to better predict the brain injury of the OHCA patient with other prognostic studies before and during post-resuscitation care.

There were some limitations in this study. First, this study involved feasible trials of continuous measurement of the pupillary response during CPR using the pupillography in the ER only, and not in the ICU. As a result, the pupillary response during post-cardiac arrest care was not included in this study. Further study must involve continuous measurement of the pupillary response from CPR to the end of post-cardiac arrest care. Based upon the results, the relationship between the outcome and pupillary response can then be confirmed. Typically, the change in pupillary response during the early reperfusion period should be investigated for its prediction of the outcome. Second, as this is an observational preliminary study, the necessary sample size was not calculated. Moreover, the number of patients with good neurologic outcome was small. However, the calculated power for good neurologic outcome between PRL being present and not present was 0.91 and showed statistical significance. Further large-scale multicenter study of pupillary response can be helpful in overcoming a small number of good neurologic outcome patients. Third, we did not monitor the pupillary response in the prehospital area or immediately following admission to the ED. If the pupillary response could be measured during prehospital CPR by paramedics, one would be able to identify the pupillary changes during BLS at the beginning of a sudden cardiac arrest. Fourth, we did not measure the degree of brain perfusion while measuring the pupillary response. Fifth, there was a time when the pupillography could not be attached to the patient because of the clinical studies requiring patient movement and transportation from the resuscitation room. It is necessary to make the pupillography system smaller and lighter so that it can be attached even when a patient is being moved in the hospital.

Conclusions

This study demonstrated that continuous measurement of the pupillary response can be feasible both during and immediately after CPR for OHCA patients. There were a few OHCA patients who had PLR during CPR. In this feasibility study, subjects whose pupil sizes were decreased during CPR had shorter arrest time. Moreover, patient whose PLR were present after ROSC had better outcomes. These findings did not reach statistical significance. Further prospective multicenter large-scale studies are needed that extend the measurement from CPR in the ED to post-resuscitation care in the ICU.

Conflicts of interest

None of the authors has any financial or personal relationships with people or organizations that could inappropriately influence this study.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.resuscitation.2018.11.016.

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