Doi: 10.5152/TJAR.2019.75418

Original Article
Resuscitation

Turkish Journal of Anaesthesiology & Reanimation

Pupil Reactivity in Refractory Out-of-Hospital Cardiac Arrest Treated by Extra-Corporeal Cardiopulmonary Resuscitation

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Cite this article as: Jouffroy R, Saade A, Philippe P, Guyard A, Carli P, Vivien B. Pupil Reactivity in Refractory Out-of-Hospital Cardiac Arrest Treated by Extra-Corporeal Cardiopulmonary Resuscitation. Turk J Anaesthesiol Reanim 2020; 48(4): 294-9.

Abstract

Objective: The objective of this study was to assess the association of early pupil evaluation with death occurrence on Day 28 in patients with refractory out-of-hospital cardiac arrest (ROHCA) admitted to the intensive care unit (ICU) and treated by extra-corporeal cardiopulmonary resuscitation (eCPR).

Methods: The pupil size (miosis, intermediary or mydriasis) and bilateral pupillary light reactivity (present or absent) were monitored in sedated and paralysed patients treated by eCPR. Mortality was assessed on Day 28.

Results: A total of 46 consecutive patients with ROHCA were included in the study. Thirty (65%) patients died on Day 28. Twenty-seven (90%) patients had pupils non-reactive to light, and 18 (60%) had mydriasis at the ICU admission. Using logistic regression, including age, gender, no flow, low-flow, size and pupil reactivity to light, only the pupillary reactivity to light remained associated with death on Day 28 (Odds ratio=0.12, 95%CI=[0.01-0.96]).

Conclusion: Pupils not reacting to light at the ICU admission were associated with mortality on Day 28 in patients with ROHCA. Pupillary light reactivity is a simple and easy tool that can be used to early detect a poor outcome in patients with ROHCA treated by eCPR.

Keywords: Death, extra-corporeal cardiopulmonary resuscitation, outcome, pupil reactivity, refractory out-of-hospital cardiac arrest

Introduction

Cardiac arrest (CA) is the cause of approximately 300,000 deaths per year in North America (1). Despite recent progress in advanced life support, the survival rate remains low, reaching 8%-10% at hospital discharge (2). Refractory CA results from the failure of advanced life support measures (3). In some countries, a time scale is used to define CA as refractory, set at 30 minutes in France (4). In the case of refractory CA, extra-corporeal cardiopulmonary resuscitation (eCPR) can be performed, with a positive impact on survival (4-6). In addition, the concept of a bundle of care. which includes eCPR, the control of oxygen and target temperature management, significantly improved patients' outcome after CA (5-12). In refractory CA, death mostly occurs early, within the first hours, from multi-organ failure despite eCPR. Delayed death results from care limitations motivated by the absence of neurological recovery (13). Both early and late prognostication after CA remain difficult (14).

With the use of eCPR and the development of prehospital care support, the early evaluation of patients with refractory CA is crucial to improve their management.

The aim of this study was to evaluate the association of pupil examination (size and pupil reactivity) at intensive care unit (ICU) admission, on death occurrence on Day 28 in patients with refractory out-of-hospital CA (ROHCA) treated by eCPR and admitted to the ICU.

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Received: 26.11.2018 Accepted: 11.02.2019
Available Online Date: 24.09.2019

Methods

Study population

The study was conducted in the ICU of Necker Academic Hospital. All patients aged <70 years, managed in the prehospital setting for ROHCA, were consecutively included in the study at ICU admission and treated with eCPR. Traumatic ROHCA were excluded from the study. Death that occurred within 28 days of hospital admission was retrospectively retrieved from medical records.

In compliance with the French legislation, our local ethical committee (Comité de Protection des Personnes, Est 3-Nancy, France-number: 17.12.05) considered that the consent of patients was waived for participation in this observational study.

Pupillary reactivity assessment

The pupil size and bilateral pupillary reactivity to light were subjectively assessed by a critical care nurse, trained for this purpose, at ICU admission and mentioned in the patient's medical report.

Pupil size was considered as following: miosis, intermediary or mydriasis. Pupillary reactivity to light was considered to be present when both pupils constricted to light and absent when no reactivity to light occurred. The pupil evaluation was not taken into account in the ROHCA management.

Therapeutic management of patients

All patients received medical care from the same medical team of critical care physicians, as previously described (15). Protocols for the management of patients with prehospital cardiac arrest did not change over the study period, ensuring no major discrepancies between patients in terms of organ support and therapies.

All patients were sedated using midazolam 0.1 mg kg^{-1} h^{-1} and sufentanil 0.2 µg kg^{-1} h^{-1}, and they were immobilised with atracurium 0.1 mg kg^{-1} h^{-1} (dose adjusted to obtain a neuromuscular response ≤2 at the 'trend-of-four' [TOF] monitoring). The sedation status was monitored using the bispectral index (BIS monitor, Covidien). Sedation and paralysis of patients was confirmed by a TOF ≤2/4. Sedation was stopped after rewarming, i.e., after 24 hours. Ventilation was adjusted to obtain a $PaCO_2$ of 40 mmHg and a PaO_2 ranging between 100 and 200 mmHg. Minimum lung ventilation was maintained to avoid pulmonary collapse with a tidal volume of 5 mL kg^{-1}, a respiratory rate of 8 movements min^{-1} and a positive end-expiratory pressure of 5 cmH_2O. $ScVO_2$ was continuously monitored to achieve an $ScVO_2$ >70%. Haemodynamic support was achieved by eCPR (Cardiohelp System, Maquet), which was set up via venous-arterial femoral cannulation by two experienced ICU physicians, either in the prehospital setting or immediately at hospital admission. Continuous veno-venous haemodiafiltration was initiated within the first 6 hours following ICU admission. To prevent coagulation of the eCPR membrane oxygenator, unfractionated heparin was administered intravenously at a low dose during eCPR, with repeated controls to maintain the activated clotting time ratio >2.0.

Fluid expansion (fluid administration 30 mL kg^{-1} day^{-1} of isotonic saline) and catecholamine (dobutamine 5 µg kg^{-1} min^{-1} and norepinephrine) were adjusted to obtain a mean blood pressure between 50 and 60 mmHg and to prevent pulmonary oedema. Blood transfusion was required to reach 10 g dL^{-1} haemoglobin, 100,000 mm^{-3} platelets, fibrinogen >1.5 g L^{-1} and a prothrombin rate >50%.

Mild therapeutic hypothermia was performed for all patients during the first 12-24 hours following ICU admission. Central corporeal temperature was maintained between 32 and 34°C using external cooling (ice packs placed on femoral and humeral vessels) and the thermoregulatory device of eCPR. All patients were rewarmed after 24 hours.

If spontaneous circulation recurred, the haemodynamic status was monitored by echocardiography and continuous cardiac output monitoring devices (Vigileo, Edwards Lifesciences).

Statistical analysis

The primary endpoint was mortality at Day 28 upon ICU admission.

The comparison of two means was performed using the unpaired Student's t-test. The comparison of two medians was performed using the Mann-Whitney U test, and the comparison of proportions was performed using the Fisher exact method. Correlation between two variables was assessed using linear regression analyses.

The association between the pupil size and reactivity with death were evaluated using the univariate and logistic regression models. No-flow duration (the lapse of time between the CA occurrence and the beginning of basic or advanced life support), low-flow duration (the lapse of time between the CA occurrence and the initiation of eCPR), gender and age, considered as confounding variables, were included in the final model.

All analyses were two-sided. A p-value <0.05 was considered statistically significant. Data were expressed as the mean±standard deviation (SD), or median with the interquartile range (25 to 75) for non-Gaussian variables (D'Agostino-Pearson omnibus test).

Table 1. Characteristics of patients with refractory out-of-hospital cardiac arrest treated by extra-corporeal cardiopulmonary resuscitation

	Overall population (n=46)	Deceased (n=30)	Alive (n=16)	p
Sex (M:F)	30:16	18:12	12:4	0.319
Age (years)	52±13	53±13	51±14	0.751
No-flow (minutes)	3±4	4±4	2±4	0.014*
Low-flow (minutes)	88±30	96±27	72±31	0.020*
Non-reactive pupils	31 (67%)	25 (83%)	6 (19%)	0.001*
Pupil size				
Mydriasis	22 (48%)	18 (60%)	4 (25%)	0.038*
Intermediary	8 (17%)	6 (20%)	2 (12%)	0.415
Miosis	16 (35%)	6 (20%)	10 (63%)	0.041*

Pupil examination was performed at ICU admission.

Data are expressed as the mean±standard deviation (SD) for quantitative variables and as the absolute number with percentage for qualitative variables.

The p-value corresponds to the comparison between alive and deceased patients.

Table 2. Aetiologies of refractory out-of-hospital cardiac arrest treated by extra-corporeal cardiopulmonary resuscitation

	n	%
Acute coronary syndrome	27	59
Cardiomyopathy	3	7
Drowning	2	4
Pulmonary embolism	2	4
Drug intoxication	2	4
Sepsis	1	2
Right ventricular dysplasia	1	2
Undefined	8	18

Data are expressed as an absolute number with percentage.

Table 3. Results of multinomial analysis

Variable	ORa	95 CI	p
Gender	2.29	0.27 - 22.73	0.443
Age	1.03	0.96 - 1.11	0.395
Pupillary light reactivity	0.12	0.01 - 0.96	0.045*
Pupil size	0.5	0.05 - 4.73	0.82
No-flow	1.19	0.96 - 1.57	0.119
Low-flow	1.03	1.00 - 1.07	0.069

Data are given as the odds ratio adjusted (ORa) with a 95% confidence interval (95%CI). *A p-value <0.05 is considered to be statistically significant.

All analyses were performed using the R 3.4.2 (www.R-project.org; the R Foundation for Statistical Computing, Vienna, Austria).

Results

Forty-six patients with ROHCA were included in the study from November 2011 to March 2014. The main characteristics of patients are summarised in Table 1. Thirty (65%) were male with the mean age of 52±13 years. The mean no-flow duration was of 3±4 minutes, and the mean low-flow duration reached 88±30 minutes.

The suspected aetiologies of CA are listed in Table 2, and they mainly include acute coronary syndrome, concerning 27 patients (59%).

At ICU admission, mydriasis was observed in 22 patients (48%), intermediary pupil size in 8 patients (17%), and miosis in 16 patients (35%). Thirty-one patients (67%) had pupils non-reactive to light.

Thirty (65%) patients died within 28 days. Miosis was more frequently observed in patients who stayed alive compared to deceased patients (63% vs. 20%), while mydriasis and intermediary pupil size more often occurred in deceased than in alive patients (60% vs. 25% and 20% vs. 12% respectively). In addition, non-reactive pupils to light were more often observed in deceased patients compared to alive patients (83% vs. 19%; Table 1).

At Day 28, 2 patients (7%) died from care limitations. Both patients had non-reactive mydriasis at ICU admission.

At Day 28, the cerebral performance category scale of alive patients ranked between 1 and 3.

In the univariate analysis, a significant difference was found between alive and deceased patients at Day 28 with miosis (p=0.041; Table 1). A significant difference was also found between alive and deceased patients at Day 28 with mydriasis (p=0.038), while no significant difference was found between alive and deceased patients with intermediary pupil size

(p=0.415). Lack of the pupillary light reactivity was significantly associated with mortality on Day 28 (p=0.001).

Using logistic regression including age, gender, no flow, low-flow, size and pupillary light reactivity, only the pupillary reactivity remained associated with death at Day 28 (OR=0.12, 95%CI=[0.01-0.96], p=0.045) (Table 3).

Discussion

In this study, we report an association between mortality at Day 28 and pupillary light reactivity at ICU admission of patients with ROHCA treated by eCPR. No association was found for the pupil size. Therefore, we suggest that the pupillary light reactivity early detects a poor prognosis of patients with ROHCA treated by eCPR.

CA is one of the most devastating conditions associated with a high mortality rate. Initially, the prognostication of patients with CA was only based on clinical approaches (16). A decade ago, a clinical neurological examination would be sufficient (17-19). The Glasgow coma scale motor score showed a strong predictive value for a poor outcome in non-sedated patients (20), but its diagnostic value has never been assessed in the early phase of CA (21-26). Loss of pupillary light reactivity is a recognised indicator of poor prognosis during and after cardiopulmonary resuscitation, even though it can be impaired in mild hypothermia, low cardiac output and modified by resuscitation drugs (21). Despite a high specificity for predicting a poor neurological outcome, its sensitivity is low (27-29). Consequently, pupillary light reactivity alone is not sufficiently accurate to determine the prognosis and the decision making (30-32). In this perspective, the clinical management of out-of-hospital CA, as previously described in the literature (33, 34), should be re-evaluated taking into account the recent progress made in the treatment of CA (18, 19). Due to the lack of objective tools for an accurate clinical approach, other prognosis factors were identified (35). Recent developments were made on medical devices and scoring systems to predict the neurological prognosis after CA, but few have been tested in the prehospital setting or in patients without return of spontaneous circulation (15, 16, 36-38). To date, a multimodal, clinical (Glasgow coma scale, neurological evaluation) and paraclinical (electro encephalography, visual evoked potential for examples) approaches (39, 40) are recommended for efficient evaluation (41). The latter requires 48-72 hours to evaluate a patient neurological outcome (42). Unfortunately, multimodal approach is only applicable to patients not subjected to eCPR. Delayed prognostication, at least no earlier than 72 hours, is preconised to be more reliable (32). Other parameters, such as the BIS to evaluate the cerebral activity sooner may be interesting (43). An examination of pupils is a simple parameter to monitor, and it may be an interesting tool to help the prognostication of patients with ROHCA. Automated pupillometry may increase the reliability and allow the quantification of pupils' response.

As eCPR is time consuming and is considered as an expensive treatment of refractory CA (44, 45), the early identification of patients with poor outcome is essential. An alternative to eCPR can be organ donation. Brain death is often marked by major haemodynamic instability (46), which can comprise organ function. Even though data lack on the consequences of eCPR on organ quality, it seems logical to suggest organ harvesting as soon as possible after brain death confirmation.

Study limitations

Some limitations in our study should be considered. First, this is a single-centre study with a small sample size. Second, this observational study showed an association between two variables, but it cannot lead to causality links. Inherent to the observational nature of this work, data concerning patient's comorbidities are lacking. Third, the study was performed in a country where the prehospital system is efficient and where physicians are quickly dispatched to the scene. Moreover, all patients with ROHCA were managed according to the French guidelines, and eCPR was set up as soon as CA was considered to be refractory, meaning 30 minutes following advanced life support corresponding to the definition of refractory CA in France (4). Consequently, prehospital management could potentially interfere with timing; therefore, it could have an effect on patient's outcome, and it may not therefore be extrapolated to other prehospital settings. Fourth, we cannot rule out a possible false-positive result in the evaluation of pupil size due to pharmacological interventions (32). All patients were sedated and paralysed. However, other therapeutics during resuscitation such as vasopressors and reoxygenation (12, 47) were not controlled, and thus they may have influenced the outcome. Fifth, data were not standardised on "no-flow" and "low-flow" durations, both known to be the major prognosis factors in CA (4). Sixth, we did not use a standardised protocol to assess pupillary reactivity to light. Actually, the type of light source, the intensity of light and duration of light illumination have been reported to influence the result. A clinical examination is reliable despite a growing body of literature reporting that quantitative pupillometry may be more accurate. Despite these limitations, our study suggests the use of pupils' examination and also supports a continued use of multimodal prognostication in patients with ROHCA treated by eCPR.

Conclusion

In refractory out-of-hospital cardiac arrest, pupils of patients treated with eCPR that were non-reactive to light illumination at ICU admission were associated with an early onset

of death at Day 28, whereas the pupil size was not. Pupillary light reactivity is a simple and easy tool useful in detecting a poor prognosis early in patients with ROHCA treated by eCPR.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Est 3-Nancy (Comité de Protection des Personnes, Est 3-Nancy, France-number: 17.12.05).

Informed Consent: Consent of patients was waived for participation in this retrospective observational study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – R.J.; Design – R.J., P.P.; Supervision – R.J.; Materials – R.J.; Data Collection and/or Processing – R.J.; Analysis and/or Interpretation – R.J.; Literature Search – R.J., A.S., P.P.; Writing Manuscript – R.J., A.S.; Critical Review – R.J., P.P., A.S., P.C., B.V.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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