Pain pupillary index to prognosticate outcome in comatose cardiac arrest patients

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Abstract

Background: The Neurologic Pupil Index (NPI), derived from automated pupillometry, can accurately predict poor neurological outcome in post-anoxic brain injury. The prognostic role of another index, called Pupillary Pain Index (PPI), remains unknown in this setting.

Methods: Monocentric study in adult comatose cardiac arrest (CA) patients. Quantitative PPI and NPI were concomitantly recorded on day 1 and day 2 after CA. The primary study outcome was to assess the prognostic value of PPI to predict 3-month unfavourable outcome (UO, defined as Cerebral Performance Category of 3–5). Secondary outcome was the agreement between PPI and NPI to predict unfavourable outcome.

Results: A total of 102 patients were included; 69 patients (68%) patients had UO. Patients with UO showed a lower NPI (4.2 [3.5-4.5] vs. 4.6 [4.3-4.7]; $p < 0.01$ on day 1 - 4.3 [3.8-4.7] vs 4.6 [4.3-4.8] on day 2), and PPI (3 [1-6] vs. 6 [3-7]; $p < 0.01$ on day 1 - 3 [1-6] vs 6 [4-8]; $p < 0.01$ on day 2) than others. PPI and NPI had similar predictive accuracy on day 1 and day 2 for UO. A PPI=1 on day 2 showed a sensitivity of 26 [95% CI 16-38]%, a specificity of 100 [95% CI 89-100]%, a NPV of 39 [95% CI 36-43]% and a PPV of 100% [95% CI 100-100]% to predict UO. On day 2, a total of 6 patients had concomitant PPI=1 and NPI ≤ 2 , while 12 showed NPI > 2 and PPI=1; the coefficient of agreement was 0.42. Moreover, NPI and PPI values showed a moderate correlation both on day 1 and day 2.

Conclusions: In this study, PPI=1 on day 2 could accurately predict UO in comatose CA patients, with 100% specificity and a higher sensitivity than NPI. The agreement between PPI and NPI values was moderate.

Introduction

Accurate neuro-prognostication in unconscious patients following cardiac arrest (CA) is mandatory to avoid inappropriate withdrawal of life support therapies (WLST) or to provide futile treatment in patients with irreversible brain damage, as well as to effectively communicate with patients' relatives [1]. As such, recent international guidelines updated the prognostic algorithm for these patients and recommended the concomitant presence of at least two specific patterns (i.e. highly malignant patterns at electroencephalography [EEG]; neuron-specific enolase [NSE] > 60 mcg/L; absence of cortical response at short-latency somatosensory evoked potentials [SSEPs] at day 3; onset of status myoclonus within 72h; extensive brain injury at brain imaging; absence of pupillary and/or corneal reflex at > 72 h) to predict unfavorable neurological outcome (UO) [2].

In particular, for pupillary reactivity, the most commonly method used at bedside remains manual pupillary light reflex (PLR) performed by clinicians and/or nurses. Nevertheless, this approach is hampered by a reduced inter-observer reproducibility and incorrect identification of unreactive pupils, especially among patients with small pupil size [3]. Some studies have therefore assessed the role of automated pupillometry to increase the accuracy of altered PLR to prognosticate UO in cardiac arrest

patients [4-6]. A prospective multicentric study also demonstrated that the best parameter derived from automated pupillometry was the Neurological Pupil Index (NPi); when this quantitative score was ≤ 2 at either day 1, 2 or 3 after CA, 100% of patients presented UO, and its prognostic accuracy was higher than manual pupillary examination or quantitative pupillary constriction [7]. Interestingly, no study has assessed the prognostic role of another index derived by the automated pupillometry, the Pupillary Pain Index (PPI), a score derived from pupillary dilation to nociceptive stimulation, which is currently used to monitor the adequacy of analgesia during surgical procedures [8-10].

The aim of this study was therefore to assess the prognostic value of PPI to predict UO in unconscious CA patients and to compare PPI with NPi in this setting.

Methods

Study design

This pilot retrospective monocentric study was conducted in the Department of Intensive Care at Erasme Hospital, Brussels (Belgium), between 1st October 2019 and 31th August 2021. Eligible patients were adult (≥ 18 years old) patients being unconscious (i.e. Glasgow Coma Scale < 9) at hospital admission after resuscitated CA and who survived for at least 24 hours. Patients with pupillary disease (i.e. Adie's pupil, Argyll Robertson pupil), multiple sclerosis, severe periorbital edema and recent ocular surgery were excluded from the study.

The study protocol was approved by the local Ethical Committee (P2019/650), which waived the need for an informed consent because both indices were routinely used as standard monitoring in unconscious brain injured patients. The design and methodology of the study is in accordance with STARD guidelines regarding the diagnostic accuracy of the reported data [11] and the Standards for Studies of Neurological Prognostication in Comatose Survivors of Cardiac Arrest edited by American Heart Association [12].

Post-resuscitation care

In all unconscious patients with post-anoxic brain injury, a standardized therapeutic protocol was used. Regardless of CA location and initial rhythm, patients were treated with targeted temperature management (TTM) for 24 h with a target temperature of 33°C. Cooling was started immediately after ICU admission with a combination of cold fluid bolus (15-20 ml/kg of a crystalloid solution in 30 min) and a cooling pads or intravascular catheter with a temperature-feedback system. Analgesia and sedation were provided using propofol and sufentanil, while cisatracurium was administered to control shivering in the induction phase and, if needed, as a continuous infusion thereafter. More information on post-resuscitation care have already been previously reported [13].

Automated pupillometry assessment

Automated pupillometry was performed using two different automated pupillometer. The first measurement was performed using the NeuroOptics NPi-200 device (Neuroptics, Irvine, CA, USA), which uses an infrared camera that integrates a calibrated light stimulation of fixed intensity (1000 Lux) and duration (3.2 s) to compute the NPi, based on an integrated algorithm, for each eye. A NPi score ≤ 2 defines the threshold that has been identified to have 100% specificity to predict UO in CA patients [7]. In our ICU, NPi was assessed every 8 hours.

After the NPi assessment, the Algiscan pupillometer (NeuroLight, ID-MED, Marseille, France) was used; briefly, an electrical stimulation with gradual and stepwise intensity (increasing from 10 mA to a maximum of 60 mA) was applied on the left forearm of the patients through two electrodes connected with a cable to pupillometer. This assessment was performed once daily and only in unconscious patients in our ICU. Baseline pupil size (mm), pupillary dilation to pain (i.e., the difference between post-stimulation and baseline pupil size, expressed as a %) and PPI were recorded during the stimulation for each eye. PPI measures pupil dilation in response to the increasing electric stimulus; once the threshold of 13% in pupil dilation is detected, electrical stimulation is automatically interrupted and PPI is calculated, ranging from 1 (pupillary reflex dilation < 5% to the maximal stimulation intensity of 60 mA) to 9 (pupillary reflex dilation > 13% with 10 mA stimulus)[9]. For this study, we collected NPi and PPI that were performed on each eye within 24 hours (day 1) and between 24 and 48 hours from CA (day 2).

Data Collection

Patients' demographics, medical and clinical history as well as main biological data were collected; initial rhythm, categorized as shockable (i.e. ventricular fibrillation or tachycardia) vs. non-shockable (asystole or pulseless electrical activity) and duration of CA were also collected. The use of drugs that might interfere with pupillary activity (i.e. sedatives or opioids) and their doses were also reported. To assess the severity of brain damage, we also collected the highest NSE value within the 72 hours after CA, the absence of cortical N20 waves at SSEP performed within 72 hours from arrest and the presence of highly malignant patterns (HMPs) at continuous EEG (i.e. presence of burst-suppression and persistent suppression), according to recent definitions [14].

Neurological outcome was assessed at 3 months after CA, using the Glasgow–Pittsburgh Cerebral Performance Categories (CPC) [15], categorized as favorable outcome (CPC 1 = full recovery and 2 = moderate disability, returned home) or UO (including CPC 3 = severe disability, at rehabilitation facility, 4 = vegetative state and 5 = death). The outcome was evaluated during follow-up visits and/or by telephone interview.

Study Outcomes

The primary endpoint of this study was to examine the prognostic accuracy of PPI in predicting UO in comatose patients after CA. Secondary outcome included the agreement between PPI and NPi to predict UO in this patients' population.

Statistical Analysis

Discrete variables were expressed as counts (percentage) and continuous variables as means $\pm$ standard deviation (SD) or median [25th to 75th percentiles], as appropriate. The Kolmogorov-Smirnov test was used, and histograms and normal-quartile plots examined to verify the normality of distribution of continuous variables. Differences between groups was assessed using a χ -square or Fisher's exact test for categorical variables, as appropriate, a t-test or a Mann-Whitney-U test for comparison of continuous variables between two groups and an ANOVA test or Kruskal-Wallis test for comparison of continuous independent variables among more the 2 groups. In the latter case, to assess the pairwise comparison, a Bonferroni correction was used. To assess the predictive value of the NP_i and PPI, we calculated the area under the receiver operating characteristics curve (AUROC); comparison between AUROCs was performed using the DeLong test. The prognostic performance of each predictor was analyzed calculating the specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV). False positive rate (FPR) for each tool was calculated as False Positive / FO. We therefore used an NP_i $\leq$ 2 as the most specific threshold to predict UO (as previously described) [7] and identified the PPI threshold showing 100% specificity; the agreement between the two indices was evaluated by comparing the number of patients with "predicted UO" with the two pupillometries, using the Cohen's kappa coefficient. Correlation between PPI and NP_i was performed using Pearson's correlation analysis; the degree of correlation was defined according to the coefficient of correlation as strong (higher than 0.6), moderate (between 0.4 and 0.6) or weak (below 0.4). A $p < 0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics 25.0 for Macintosh. We considered this study as a pilot study and no sample size calculation was performed, therefore a "convenient" sample size of 100 patients was selected.

Results

Study population

Over a total of 134 patients suffering from CA over the study period, 32 were excluded (early deaths, $n=5$; no PPI available, $n=27$), 102 patients were included in the analysis. The characteristics of study population are shown in Table 1. The median age was 66 [56-74] and 66% of the patients were males. Fifty-four (53%) patients were admitted after out-of-hospital CA, seventy-one (71%) had a witnessed CA and 68% received bystander-initiated resuscitation. Twenty-two (22%) patients had a shockable rhythm and the median time to return of spontaneous circulation was 20 [12-30] min. ICU mortality occurred in 60 (59%) patients, while 69 (68%) patients had UO. Patients with UO were older, had less frequently a witnessed CA, a shorter ICU stay and presented more frequently previous neurologic disease than others (Table 1). Patients with UO also showed higher NSE values and had more frequently bilaterally absent N20 waves and HMPs on EEG than those with favorable outcome.

Pupillary assessment

Patients with UO showed a lower NPi (4.2 [3.5-4.5] vs. 4.6 [4.3-4.7]; $p<0.01$), a lower pupillary constriction to light (16 [9-22]% vs. 20 [15-23]%; $p=0.01$), a lower PPI (3 [1-6] vs. 6 [3-7]; $p<0.01$), and a lower dilation rate to pain (12 [5-20]% vs 21 [16-31]%; $p<0.01$) on day 1 than others (Figure 1). Also, on day 2, patients with UO presented a lower NPi (4.3 [3.8-4.7] vs 4.6 [4.3-4.8]), a lower PPI (3 [1-6] vs 6 [4-8]; $p<0.01$) and a lower dilation rate to pain (14 [4-23] vs 23 [16-30]; $p<0.01$) than those with favorable outcome. All the different values derived from both pupillometers are reported in Table 2.

NPi, PPI and Neurological Outcome

PPI had an AUROC of 0.69 ([95% CI 0.58-0.79] – all patients on opioids) on day 1 and AUROC of 0.74 ([95% CI 0.64-0.84] – 76/102, 75% on opioids) on day 2 to predict UO, respectively. Similarly, NPi had an AUROC of 0.67 ([95% CI 0.56-0.78]; $p=0.79$ vs. PPI) on day 1 and an AUROC of 0.69 ([95% CI 0.58-0.79]; $p=0.36$ vs. PPI) on day 2 to predict UO, respectively (Supplemental Table 1). PPI values on day 2 were similar between patients with and without opioids (Supplemental Figure 1).

A PPI =1 on day 1 showed a sensitivity of 25 [95% CI 15-37]%, a specificity of 97 [95% CI 84-100]%, a NPV of 39 [95% CI 35-42]% and a PPV of 94% [95% CI 70-99]% to predict UO, while a PPI=1 on day 2 showed a sensitivity of 26 [95% CI 16-38]%, a specificity of 100 [95% CI 89-100]%, a NPV of 39 [95% CI 36-43]% and a PPV of 100% [95% CI 100-100]% to predict UO. The number of patients with PPI=1 on day 2 was similar between patients with and without opioids (13/76, 17% vs. 5/26, 19%; $p=0.80$). Similarly, a NPi ≤ 2 on day 1 showed a sensitivity of 12 [95% CI 5-22]%, a specificity of 100 [95% CI 89-100]%, a NPV of 35 [95% CI 34-37]% and a PPV of 100% [95% CI 100-100]%, while a NPi ≤ 2 on day 2 showed a sensitivity of 10 [95% CI 4-20]%, a specificity of 100 [95% CI 89-100]%, a NPV of 35 [95% CI 33-37]% and a PPV of 100% [95% CI 100-100]%. The presence of PPI=1 or NPi ≤ 2 on day 2 showed a specificity of 100 [89-100]% with a sensitivity of 28 [95% CI 17-40]% (Table 3).

Agreement and correlation between PPI and NPi values

On day 1, a total of 7 patients had concomitant PPI=1 and NPi ≤ 2 , while 11 showed NPi >2 and PPI=1. Among the remaining 83 patients, 1 had NPi ≤ 2 with PPI >1 and 82 had PPI >1 with NPi >2 . Thus, the Cohen's k coefficient was 0.48. On day 2, a total of 6 patients had concomitant PPI=1 and NPi ≤ 2 , while 12 showed NPi >2 and PPI=1; the coefficient of agreement was 0.42. Moreover, NPi and PPI showed a moderate correlation both on day 1 and day 2 (Figure 2).

Characteristics of the patients according to predictors of UO at 3 months

On day 2, 6 patients showed both NPi ≤ 2 and PPI=1, 13 patients showed either NPi ≤ 2 or PPI=1 and 83 had no pathological NPi and PPI. Patients with both NPi ≤ 2 and PPI=1 received a higher dose of epinephrine during resuscitation attempts and had higher lactate on admission when compared to patients with no pathological NPi and PPI. Moreover, patients with no pathological NPi and PPI showed lower NSE levels and less frequently HMPs on EEG than others (Supplemental Table 2).

Discussion

This is the first study evaluating the prognostic role of PPI to predict unfavorable outcome in comatose CA patients. Our findings showed that a PPI on day 2 presented a specificity of 100% to predict UO, with a higher sensitivity than NPi. Also, a moderate agreement between PPI and NPi values was observed, suggesting that these two indices are not inter-changeable.

Pupillary size depends on the balance of sympathetic and parasympathetic systems that are connected into the midbrain, and by the neurons that originate in locus coeruleus, colliculi and cingulate cortex [16]. The pupillary dilation reflex is usually considered under the influence of the sympathetic system. Sympathetic innervation of the radial muscle arises from pre-ganglionic neurons located in the C8-T2 spinal cord (i.e. the so-called ciliospinal center of Budge), and a painful stimulus, in particular when arising from the neck and upper trunk, can activate these groups of cells via a spinal reflex and project to the noradrenergic postganglionic neurons in the superior cervical ganglion, which innervate the dilator pupillae muscle [17].

Although several studies assessed the role of pupillary constriction to light reflex to predict unfavorable outcome after CA [7, 18, 19], no data are available on pupillary dilation to pain. Interestingly, pupillary dilation to nociceptive stimulation was 100% specific and more sensitive than other pupillary variables derived from light stimulation, including NPi. Among 19 patients who presented $PPI=1$ or $NPI \leq 2$, only 6 of them had both concomitant present and most presented only a pathological PPI value. A possible explanation of these results may be due to the different location of the structures implicated in the genesis of the reflex. PPI might be considered as a “quantification” of the spinocilial reflex. Previous studies showed that such reflex is mediated by supraspinal structures, located mostly in the thalamus [20]. In fact, Yang et al. assessed the role of sympathetic nervous system on spinocilial reflex concluding that its origin is sympathetic in awake subject. Moreover, in brain dead patients, spinocilial reflex was absent after a high-intensity tetanic stimulation of somatic nociceptors [21]. A second explanation would be related to the different ischemic tolerance of cerebral structures involved in pupillary light reflex and spinocilial reflex after CA. In one study, the recovery of cranial nerve reflexes occurred in a fixed order, irrespective of patients’ outcome, and was characterized by a progressive return of pupillary light reflexes, which preceded spinocilial reflexes [22]. As one patient had a $PPI=1$ on day 1 and eventually presented a favorable neurological recovery, one may argue that early assessment of PPI, in particular during sedatives and opioids administration, would result in false prediction of neurological outcome. However, the proportion of patients with $PPI=1$ was similar between those with and without opioids on day 2. Interestingly, PPI of 1 can be observed, although rarely, in the operative room in patients without brain injury, because of analgesic administration during surgical procedures [8, 23] (i.e. it is not always a sign on extended brain injury). However, abnormal NPi in the absence of severe post-anoxic brain damage has also been reported in association with sevoflurane and ketamine therapy [24] thus underlying how all prognostic index might have suffer from confounders and be potentially biased with false prediction of poor outcome. As such, future studies should evaluate PPI in larger cohorts of CA patients in the absence of any confounders and correlate PPI findings with additional predictors of poor outcome in this setting,

such as biomarkers or brain imaging. Finally, we were unable to assess whether clinical characteristics of the patients might explain the discrepancies between patients with both abnormal NPi and PPI and those with only one of them, due to the limited number of events.

This study had several limitations to acknowledge. First, this was a pilot study and the number of patients included was relatively small. Second, the study was monocentric and local protocol of post-resuscitation care and/or limitation of life-sustaining therapies may differ from other centers, which would potentially limit replicability and generalizability of findings. However, PPI values were not used as a prognostication tool, therefore reducing the risk of self-fulfilling prophecy. Third, we did not specifically consider the cumulative dose of opioids and sedatives, but only their administration. Fourth, the resting size of the pupil progressively decreases after the fourth decade of life and this aspect may have interfered with pupillary response to light or pain. Finally, no data on brain imaging (CT-scan, MRI) are available, this aspect would have provided a more precise characterization of the brain injury showing the structures of the brain involved.

Conclusions

Our study showed that PPI=1 on day 2 after arrest was 100% specific to predict unfavorable outcome in comatose cardiac arrest patients, with a higher sensitivity than NPi. Further larger multicentric studies are necessary to better define the prognostic role of different pupillometry derived indices in clinical practice.

Declarations

Ethics approval and consent to participate

The original study protocol was approved by the ethics committees and the informed written consent was waived as pupillometry, in our institution, is standard of care.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

FST is scientific advisor for NeurOptics inc. Other authors have no conflict of interest to declare.

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No funding was obtained to this study

Authors' contributions

LP and FST conceived the study; EM, AB and LP selected the population; EM, AB, EGB, AQC and FA performed the pupillometries; EM, FST and LP conducted the statistical analysis and wrote the first draft of the paper; AM, JC, FA, FST and LP revised the text for intellectual content.

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References

1. Sandroni C, D'Arrigo S, Cacciola S, Hoedemaekers CWE, Kamps MJA, Oddo M, Taccone FS, Di Rocco A, Meijer FJA, Westhall E, Antonelli M, Soar J, Nolan JP, Cronberg T: **Prediction of poor neurological outcome in comatose survivors of cardiac arrest: a systematic review.** *Intensive Care Med* 2020, **46**(10):1803-1851.
2. Nolan JP, Sandroni C, Bottiger BW, Cariou A, Cronberg T, Friberg H, Genbrugge C, Haywood K, Lilja G, Moulart VRM, Nikolaou N, Mariero Olasveengen T, Skrifvars MB, Taccone F, Soar J: **European Resuscitation Council and European Society of Intensive Care Medicine Guidelines 2021: Post-resuscitation care.** *Resuscitation* 2021, **161**:220-269.
3. Zafar SF, Suarez JL: **Automated pupillometer for monitoring the critically ill patient: a critical appraisal.** *J Crit Care* 2014, **29**(4):599-603.
4. Peluso L, Boisdenghien T, Attanasio L, Annoni F, Mateus Sanabria L, Severgnini P, Legros B, Gouvêa Bogossian E, Vincent J-L, Creteur J, Oddo M, Gaspard N, Taccone FS: **Multimodal Approach to Predict Neurological Outcome after Cardiac Arrest: A Single-Center Experience.** *Brain Sciences* 2021, **11**(7):888.
5. Obinata H, Yokobori S, Shibata Y, Takiguchi T, Nakae R, Igarashi Y, Shigeta K, Matsumoto H, Aiyagari V, Olson DM, Yokota H: **Early automated infrared pupillometry is superior to auditory brainstem response in predicting neurological outcome after cardiac arrest.** *Resuscitation* 2020, **154**:77-84.
6. Riker RR, Sawyer ME, Fischman VG, May T, Lord C, Eldridge A, Seder DB: **Neurological Pupil Index and Pupillary Light Reflex by Pupillometry Predict Outcome Early After Cardiac Arrest.** *Neurocrit Care* 2020, **32**(1):152-161.
7. Oddo M, Sandroni C, Citerio G, Miroz J, Horn J, Rundgren M, Cariou A, Payen J, Storm C, Stammet P, Taccone F: **Quantitative versus standard pupillary light reflex for early prognostication in comatose cardiac arrest patients: an international prospective multicenter double-blinded study.** *Intensive care medicine* 2018, **44**(12).
8. Vincinclair M, Schilte C, Roudaud F, Lavolaine J, Francony G, Bouzat P, Bosson JL, Payen JF: **Using Pupillary Pain Index to Assess Nociception in Sedated Critically Ill Patients.** *Anesth Analg* 2019, **129**(6):1540-1546.

9. Fratino S, Peluso L, Talamonti M, Menozzi M, Costa Hirai LA, Lobo FA, Prezioso C, Creteur J, Payen JF, Taccone FS: **Evaluation of Nociception Using Quantitative Pupillometry and Skin Conductance in Critically Ill Unconscious Patients: A Pilot Study.** *Brain Sci* 2021, **11**(1).
10. Sabourdin N, Diarra C, Wolk R, Piat V, Louvet N, Constant I: **Pupillary Pain Index Changes After a Standardized Bolus of Alfentanil Under Sevoflurane Anesthesia: First Evaluation of a New Pupillometric Index to Assess the Level of Analgesia During General Anesthesia.** *Anesth Analg* 2019, **128**(3):467-474.
11. Cohen JF, Korevaar DA, Altman DG, Bruns DE, Gatsonis CA, Hooft L, Irwig L, Levine D, Reitsma JB, de Vet HC, Bossuyt PM: **STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration.** *BMJ Open* 2016, **6**(11):e012799.
12. Geocadin RG, Callaway CW, Fink EL, Golan E, Greer DM, Ko NU, Lang E, Licht DJ, Marino BS, McNair ND, Peberdy MA, Perman SM, Sims DB, Soar J, Sandroni C, American Heart Association Emergency Cardiovascular Care C: **Standards for Studies of Neurological Prognostication in Comatose Survivors of Cardiac Arrest: A Scientific Statement From the American Heart Association.** *Circulation* 2019, **140**(9):e517-e542.
13. Peluso L, Belloni I, Calabró L, Dell'Anna AM, Nobile L, Creteur J, Vincent JL, Taccone FS: **Oxygen and carbon dioxide levels in patients after cardiac arrest.** *Resuscitation* 2020, **150**:1-7.
14. Hirsch LJ, Fong MWK, Leitingner M, LaRoche SM, Beniczky S, Abend NS, Lee JW, Wusthoff CJ, Hahn CD, Westover MB, Gerard EE, Herman ST, Haider HA, Osman G, Rodriguez-Ruiz A, Maciel CB, Gilmore EJ, Fernandez A, Rosenthal ES, Claassen J, Husain AM, Yoo JY, So EL, Kaplan PW, Nuwer MR, van Putten M, Sutter R, Drislane FW, Trinka E, Gaspard N: **American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version.** *J Clin Neurophysiol* 2021, **38**(1):1-29.
15. **A randomized clinical study of cardiopulmonary-cerebral resuscitation: design, methods, and patient characteristics.** Brain Resuscitation Clinical Trial I Study Group. *Am J Emerg Med* 1986, **4**(1):72-86.
16. Joshi S, Li Y, Kalwani RM, Gold JI: **Relationships between Pupil Diameter and Neuronal Activity in the Locus Coeruleus, Colliculi, and Cingulate Cortex.** *Neuron* 2016, **89**(1):221-234.
17. Mullaguri N, Katyal N, Sarwal A, Beary JM, George P, Karthikeyan N, Nattanamai P, Newey CR: **Pitfall in Pupillometry: Exaggerated Ciliospinal Reflex in a Patient in Barbiturate Coma Mimicking a Nonreactive Pupil.** *Cureus* 2017, **9**(12):e2004.
18. Suys T, Bouzat P, Marques-Vidal P, Sala N, Payen JF, Rossetti AO, Oddo M: **Automated quantitative pupillometry for the prognostication of coma after cardiac arrest.** *Neurocrit Care* 2014, **21**(2):300-308.
19. Tamura T, Namiki J, Sugawara Y, Sekine K, Yo K, Kanaya T, Yokobori S, Abe T, Yokota H, Sasaki J: **Early outcome prediction with quantitative pupillary response parameters after out-of-hospital cardiac arrest: A multicenter prospective observational study.** *PLoS One* 2020, **15**(3):e0228224.
20. Loewenfeld IE: **Mechanisms of reflex dilatation of the pupil; historical review and experimental analysis.** *Doc Ophthalmol* 1958, **12**:185-448.

21. Yang LL, Niemann CU, Larson MD: **Mechanism of pupillary reflex dilation in awake volunteers and in organ donors.** *Anesthesiology* 2003, **99**(6):1281-1286.
22. Jorgensen EO: **Course of neurological recovery and cerebral prognostic signs during cardio-pulmonary resuscitation.** *Resuscitation* 1997, **35**(1):9-16.
23. Wildemeersch D, Peeters N, Saldien V, Vercauteren M, Hans G: **Pain assessment by pupil dilation reflex in response to noxious stimulation in anaesthetized adults.** *Acta Anaesthesiol Scand* 2018.
24. Peluso L, Legros B, Caroyer S, Taccone FS, Gaspard N: **Falsely predictive EEG and clinical signs after post-anoxic brain injury under sevoflurane anesthesia.** *Clin Neurophysiol* 2021, **132**(5):1080-1082.

Tables

Table 1. Characteristics of study population, according to neurological outcome at 3 months (FO = favorable; UO = unfavorable).

	ALL (n=102)	FO (n= 33)	UO (n=69)	<i>p</i> values
Age, years	66 [56-74]	61 [48-73]	69 [62-74]	0.01
Male Gender, n (%)	67 (66)	24 (73)	43 (62)	0.38
CA witnessed, n (%)	72 (71)	30 (91)	42 (62)	<0.01
Bystander CPR, n (%)	69 (68)	25 (76)	44 (65)	0.36
Time to ROSC, min	20 [12-30]	20 [8-30]	21 [15-30]	0.28
Epinephrine, mg	2 [1-5]	2 [0-5]	3 [1-4]	0.18
Out of hospital, n (%)	54 (53)	17 (53)	37 (54)	1.00
Shockable rhythm, n (%)	22 (22)	10 (31)	12 (19)	0.20
Lactate at admission, mEq/L	4.5 [2.2-8.8]	3.1 [2.1-6.1]	5.6 [2.8-9.7]	0.05
ICU stay, days	5 [3-10]	9 [5-21]	4 [3-6]	<0.01
ICU mortality, n (%)	60 (59)	-	60 (87)	<0.01
Comorbidities				
Chronic Heart Failure, n (%)	30 (29)	10 (30)	20 (29)	1.00
Hypertension, n (%)	48 (47)	12 (36)	36 (52)	0.15
Coronary artery disease, n (%)	25 (25)	8 (24)	17 (25)	1.00
Diabetes, n (%)	24 (24)	7 (21)	17 (25)	0.81
COPD/Asthma, n (%)	20 (20)	3 (9)	17 (25)	0.11
Previous Neurologic Disease, n (%)	20 (20)	2 (6)	18 (26)	0.02
Chronic Kidney Disease, n (%)	12 (12)	5 (15)	7 (10)	0.52
Liver Cirrhosis, n (%)	5 (5)	1 (3)	4 (6)	1.00
ICU Treatments				
TTM at 33°C, n (%)	97 (95)	31 (94)	66 (96)	0.66
Temperature at 24 hours after CA, °C	33.8 [33.3-34.2]	33.9 [33.2-34.5]	33.8 [33.4-34.1]	0.71
Temperature at 48 hours after CA, °C	36.6 [36.0-36.9]	36.7 [36.0-37.0]	36.6 [36.0-36.9]	0.39
Vasopressor, n (%)	97 (95)	31 (94)	66 (96)	0.66

Inotropes, n (%)	29 (28)	12 (36)	17 (25)	0.25
Sedatives at 24h, n (%)	98 (96)	33 (100)	65 (94)	0.30
Opioids at 24h, n (%)	95 (93)	32 (97)	63 (91)	0.42
Sedatives at 48h, n (%)	65 (64)	25 (76)	40 (59)	0.12
Opioids at 48h, n (%)	76 (75)	27 (82)	49 (72)	0.33
Mechanical Ventilation, n (%)	102 (100)	33 (100)	69 (100)	1.00
CRRT, n (%)	16 (16)	6 (18)	10 (15)	0.77
ECMO, n (%)	8 (8)	4 (12)	4 (6)	0.27
Prognostication parameters				
Highest NSE values, mcg/L	43 [28-73]	33 [24-43]	54 [35-125]	<0.01
Bilateral N20 absent, n (%)	23/41 (56)	0/4 (0)	23/37 (62)	0.03
HMPs, n (%)	41/97 (42)	2/31 (6)	39/66 (59)	<0.01

Data are expressed as counts (percentage) and median [Interquartile Range]. CA = Cardiac arrest; CPR = Cardiopulmonary resuscitation; ROSC = Return of spontaneous circulation; ICU = Intensive care unit; COPD = Chronic obstructive pulmonary disease; CRRT = Continuous renal replacement therapy; ECMO = Extracorporeal membrane oxygenation; NSE = Neuron specific enolase; HMPs = Highly malignant patterns, TTM = targeted temperature management

Table 2. Pupillometry values on day 1 and day 2 after arrest, according to neurological outcome at 3 months (FO = favorable; UO = unfavorable).

	Day 1			Day 2		
	FO	UO	<i>p values</i>	FO	UO	<i>p values</i>
NPi	4.6 [4.3-4.7]	4.2 [3.5-4.5]	<0.01	4.6 [4.3-4.8]	4.3 [3.8-4.7]	<0.01
Size, mm	2.55 [2.20-3.30]	2.54 [2.10-3.38]	0.91	3.05 [2.24-3.50]	2.90 [2.37-4.05]	0.27
CH, %	20 [15-23]	16 [9-22]	0.01	22 [18-27]	21 [13-25]	0.06
PPI	6 [3-7]	3 [1-6]	<0.01	6 [4-8]	3 [1-6]	<0.01
Dilation, %	21 [16-31]	12 [5-20]	<0.01	23 [16-30]	14 [4-23]	<0.01

Data are expressed as counts (percentage) and median [Interquartile Range]. NPi = Neurological pupil index; CH = percentage of constriction, PPI = Pupillary pain index

Table 3. Accuracy of pupillary parameters to predict unfavorable neurological outcome (FO = favorable; UO = unfavorable) at 3 months.

		UO (n = 69)	FO (n = 33)	<i>p</i> <i>values</i>	Sensitivity [95%. CI] Specificity [95%. CI]	PPV [95%. CI] NPV [95%. CI]	FPR
DAY 1	PPI =1	17 (25)	1 (3)	< 0.01	25 [15-37]% 97 [84-100]%	94 [70-99]% 39 [35-42]%	3%
	NPi ≤ 2	8 (12)	-	0.05	12 [5-22]% 100 [89-100]%	100 [100- 100]% 35 [34-37]%	0%
	NPi ≤ 2 or PPI = 1	18 (27)	1 (3)	<0.01	26 [17-39]% 97 [84-100]%	95 [72-99]% 39 [35-43]%	3%
DAY 2	PPI =1	18 (26)	-	< 0.01	26 [16-38]% 100 [89-100]%	100 [100- 100]% 39 [36-43]%	0%
	NPi ≤ 2	7 (10)	-	0.09	10 [4-20]% 100 [89-100]%	100 [100- 100]% 35 [33-37]%	0%
	NPi ≤ 2 PPI = 1	19 (28)	-	<0.01	28 [17-40]% 100 [89-100]%	68 [58-77]% 100%	0%

Data are expressed as counts (percentage). UO = Unfavorable outcome; FO = Favorable Outcome; PPI = Pupillary Pain Index; NPi = Neurological Pupil index; PPV = Positive Predictive Value; NPV = Negative Predictive Value; FPR = False Positive Rate.

Figures

Figure 1

Pupillary Pain Index (PPI) and Neurologic Pupil Index (NPi) values on day 1 and day 2 after arrest, according to neurological outcome (FO = favorable; UO = unfavorable)

Figure 2

Correlation between Pupillary Pain Index (PPI) and Neurologic Pupil Index (NPi) values on day 1 and day 2 after arrest.

Supplementary Files

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