


BMJ Open Early Neurological ASsessment with pupillometrY during Cardiac Arrest REsuscitation (EASY-CARE): protocol for an observational multicentre prospective study

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ABSTRACT

Introduction Out-of-hospital cardiac arrest is burdened with a high rate of ineffective resuscitation and poor neurological outcome among survivors. To date, there are few perfusion assessment tools during cardiopulmonary resuscitation and none of them provide reliable data. Despite the lack of information, physicians must decide whether to extend or terminate resuscitation efforts.

Method and analysis This is a multicentre prospective, observational cohort study, involving adult patients, victims of unexpected out-of-hospital cardiac arrest. Early Neurological ASsessment with pupillometrY during Cardiac Arrest Resuscitation aims to primarily describe the reliability of quantitative pupillometry through use of the Neurological Pupillary Index (NPI) during the manoeuvre of cardiopulmonary resuscitation, as a predictor of the return of spontaneous circulation. The second objective is to seek and describe the association between the NPI and neurological outcome in the surviving cohort. Patients will be excluded if they are less than 18 years of age, have sustained traumatic brain injury, cerebrovascular emergencies, direct injury to the eyes or have pupil anomalies. Neurological outcome will be collected at intensive care unit discharge, at 30 days, 6 months and at 1 year. The Glasgow Coma Scale (GCS) will be used in the emergency department; modified Rankin Score will be adopted for neurological assessment; biomarkers and neurophysiology exams will be collected as well.

Ethics and dissemination The study has been approved by Ethics Committee of Milano. Local committee acceptance is required for each of the centres involved in the clinical and follow-up data collection. Data will be disseminated to the scientific community through original articles submitted to peer-reviewed journals and abstracts to conferences.

Trial registration number NCT05192772.

INTRODUCTION

Background

Unexpected cardiac arrest represents the third cause of death in industrialised countries. Incidence of out-of-hospital cardiac

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Results from this multicentric regional study will provide information about the role of quantitative pupillometry in course of cardiac resuscitation as prognosticator of return of spontaneous circulation.
- ⇒ The main strength of this study relies on the possibility of introducing automated pupillometry as a safe, rapid and user-friendly assessment tool for the evaluation of cardiopulmonary resuscitation performance.
- ⇒ The results of this study will generate hypothesis regarding the role of pupillary reactivity as the earliest neurological prognosticator in surviving patients.
- ⇒ The main limitation of this study relies on the observational design and limited cohort dimension with consequent difficulty to draw causal inferences.

arrest (OHCA) in Europe, estimated according to the European Registry of Cardiac Arrest registry, ranges from 67 to 170 cases over 100 000 residents.¹

The diffusion of automatic external defibrillator and bystander cardiopulmonary resuscitation (CPR) phone-guided Emergency Medical Service has had a positive effect on survival, nevertheless, the discharge survival rates remain low, roughly 8% (0%–18%).²

Good neurological long-term outcome in countries where withdrawal of life-sustaining therapy (WLST) is routine, exceeds 90%. In countries where WLST is not applied, poor neurological outcome rates are higher, with cases of survivors in a vegetative state reaching up to 50%.^{1,3} On the other hand, application of termination of resuscitation care using the preset criteria seems to lead to missed survivors.⁴

Although among the different tools available as indicators of CPR effectiveness, only end-Tidal CO₂ (ETCO₂) is proposed

for reperfusion monitoring in guidelines during CPR. However, there are different aspects to consider regarding this parameter: the accuracy of ETCO_2 is affected by the administration of certain drugs used during ACLS (eg, sodium bicarbonate and epinephrine) and by variations in ventilation settings.⁵ Furthermore, it represents a global indicator of reperfusion without providing information regarding cerebral oxygenation.

Information derived from indicators of cerebral function in course of CPR, even in presence of potentially effective extracerebral perfusion (as witnessed by ETCO_2), could be useful in deciding whether to continue or suspend CPR.

Quantitative pupillometry is a non-invasive, rapid and reliable technology, which is associated with a rapid learning curve. The applicability of this method in various fields is broad and provides the information regarding pupillary variables, including size, percentage constriction, constriction velocity, dilation velocity and latency, all of which have been included to derive the so-called Neurological Pupil index (NPi).^{6,7} The NPi is a scalar value (between 0 and 5), which is calculated based on an algorithm which accounts to the aforementioned measured variables.

Oddo *et al* demonstrated that in post-anoxic patients an NPi value <2 predicts poor neurological outcome with 100% of specificity. When NPi is associated with evoked potentials sensibility also rises to 58% including the ECMO-VA population selected.^{8,9}

In patients treated with target temperature management at 6 hours from return of spontaneous circulation (ROSC), NPi has been shown to be superior pupilar diameter evaluation in predicting neurological outcome.¹⁰ At 24 hours after rewarming, infrared pupillometry associated with corneal reflex seems to show 100% specificity in regards to poor outcome in a multicentre retrospective analysis.¹¹

Application of pupilar evaluation during CPR is reported in various studies: in a cohort of in-hospital cardiac arrest the presence of light reflex or its absence less than 5 min was related to a good neurological recovery; whereas in the out-of-hospital setting, only few case series are described confirming the feasibility of this method.^{2,3}

METHODS

Study design

This is a multicentre, double-blind prospective observational cohort study, including adult victims of unexpected OHCA.

Objective

To demonstrate a correlation between the intra-CPR infrared q-pupillometry (CPR-NPi) and ROSC using the NPi parameter value.

Secondary objectives will be:

- ▶ To describe the predictivity of NPi during CPR associated to ETCO_2 and ROSC.
- ▶ To describe the association between NPi during CPR and neurological outcome in prolonged resuscitation manoeuvres (> 30 min) survivors.
- ▶ To describe which CPR-NPi measure best correlates with poor outcome (dead or poor neurological score at follow-up).
- ▶ To describe the association between the CPR-NPi trend and outcome.
- ▶ To describe the association between the CPR-NPi trend and outcome in the automated CPR (m-CPR) population.
- ▶ To describe the association between CPR-NPi and outcome in the bystander CPR population (only BLS or BLS-D for example: phone guided from Emergency Medical Service Dispatchers).
- ▶ To describe the association between the CPR-NPi trend and neuroprognostication tools in survivors during their hospital stay (biomarkers; neurophysiology; prognostic MRI).

Study population

Data pertaining to consecutive adult patients, victims of unexpected, sudden OHCA, within the Lombardy Region, will be collected.

Inclusion criteria

- ▶ Age >18 years.
- ▶ Non-traumatic, out-of-hospital, unexpected cardiac arrest.
- ▶ Advance Life Support Team involved.

Exclusion criteria

Age <18 years.

- ▶ Traumatic brain injury.
- ▶ Recognisable acute cerebrovascular cause of cardiac arrest.
- ▶ Diagnosis of cerebral lesions (including haemorrhages, neoplasia, ischaemia) confirmed by CT scan.
- ▶ Cortical or peripheral blindness.
- ▶ Absence of one or both eyes.
- ▶ History of iridium palsy or peripheral anisocoria.
- ▶ Do not resuscitate criteria (terminal pathology, cadaveric signs).

The presence of acute brain injury is considered a relative exclusion criterion since it will be recognised only in the surviving patients after hospital admission and imaging.

Outcomes

Enrolled patients will be included in a follow-up programme along four different time frames:

The first outcome involves ROSC or ascertainment of death.

In the surviving patients' cohort, we will assess neurological status as follows:

Table 1 Time-frames for neuroprognostic exams in surviving patients admitted to intensive care facilities

Tool	Time from ROSC	Question	Note
Brain CT scan	Within 2 hours	Oedema quantification	Optional*
NSE	24–48 – 72 hours		
EEG	24–48 hours	Burst-suppression or suppression	ACNS terminology
SSEP	At 72 hours	N20 presence, side	
Q-Pupillometry	First 72 hours, each 2 hours	NPi, latency, etc.	Only if routinely used
MRI	4th day	DWI	Optional*

*Only if radiological facilities available.
 ACNS, American Clinical Neurophysiology Society; DWI, Diffusion Weighted Imaging; EEG, electroencephalogram; N20, Negative peak at 20 ms; NSE, neuron-specific Enolase; SSEP, Somato-Sensorial Evoked Potentials.

- ▶ After hospital admission, in the emergency department once cardiorespiratory stabilisation is achieved, using the GCS.
- ▶ At intensive care unit (ICU) discharge by Modified Rankin Score Scale (mRS).
- ▶ At 30 days from cardiac arrest by mRS.
- ▶ At 6 months from cardiac arrest, by mRS.
- ▶ At 1 year from cardiac arrest, by mRS.

The following data Regarding the comparison of neuroprognostication tools with intra CPR-NPi will be collected:

- ▶ EEG: following ACNS criteria, within 48 hours from ROSC.¹²
- ▶ Somato-Sensorial Evoked Potentials (SSEP): presence or absence of negative peak at 20 ms (N20) during median nerve stimulation at 72 hours.
- ▶ Neuron-specific enolase (NSE): blood samples will be collected at 24; 48 and 72 hours.
- ▶ NPi: only in centres where it is used routinely and will be collected in the first 72 hours.

Imaging CT scan at 2 hours from ROSC and MRI from 2nd to 5th days from ROSC are optionals (table 1).

Study procedures and settings

The protocol has been endorsed by Italian Resuscitation Council and registered on ClinicalTrials.gov with NCT:05192772. The study time-line is resumed in table 2.

We selected Neuroptics NPi-200 pupillometer (Irvine California, USA) since the NPi index pertains to this device. The emergency medical system in Lombardy is based on three different levels of rescue teams, most advanced level being Advanced Life Support 2 (ALS2), which consists of a technician, an emergency nurse and a physician consultant in anaesthesia and intensive care.

For Early Neurological ASsessment with pupillometry during Cardiac Arrest Resuscitation (EASY-CARE), we chose the seven ALS2 posts in Lombardy with the highest number of cardiac arrest admissions during the 2019 pre-pandemic period. The selection was limited to the ALS2 (ambulance with doctor, nurse and technician) since the technician in this team is least involved during the resuscitation effort, making this figure the ideal

subject to carry out pupillometry without introducing delay or changes in the resuscitation protocol.

Moreover, technicians are not trained to interpret pupillometry results, and they are trained not to reveal information or data to other team members. This is necessary in order to guarantee first level of blindness.

To evaluate the effectiveness and feasibility during resuscitation, the protocol was tested in a high-fidelity simulation (HFS) environment.

A two-part training course, consisting of distance learning and practical hands-on skills, was designed in order to ensure a high level of standardisation in data collection.

In a second phase, EASY-CARE will involve the ICUs, which admitted the enrolled survivors.

Data Collection

At ALS2 arrival on the rescue scene, the patient will be screened for inclusion criteria. In case of eligibility,

Table 2 The EASY-CARE time-line available at the moment

EASY-CARE protocol time line	
Protocol finalisation	08 Sep 2021
NCT reg.	25 Nov 2021
Ethical approval	09 Nov 2021
*EMT training start	29 May 2022
EMT training completed	08 Aug 2022
Patients enrolment start	Waiting for protocol publication (approximately Dec 2022)
Patients enrolment completed	Jul 2023
Follow-up start	n/a
Data analysis	n/a

The enrolments will follow the protocol publication; follow-ups will start accordingly with protocol when the first patient will be enrolled.

*EMT (Emergency Medical Technician)

EASY-CARE, Early Neurological ASsessment with pupillometry during Cardiac Arrest Resuscitation; n/a, not applicable; NCT, ClinicalTrials.gov registration ID.

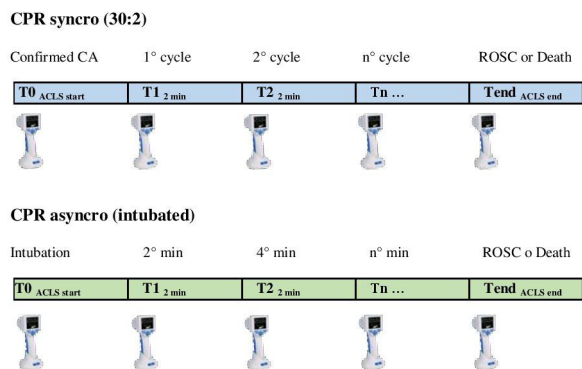


Figure 1 Timing of pupillary measurements during resuscitation manoeuvre. (A) During synchronised resuscitation (CPR performed in non-intubated patient at a compression/ventilation rate of 30:2) pupillometry is performed at diagnosis of cardiac arrest and at the end of every CPR cycle (2 min). (B) Non synchronised resuscitation (CPR performed in an intubated patient at a compression rate of 100 bpm and a ventilation rate of 15 ventilations/min) pupillometry is performed every 2 min starting from immediately after intubation. CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation. CA, Cardiac Arrest; ACLS, Advanced Cardiovascular Life Support.

pupillometry will be performed bilaterally in the following time frames (figure 1):

- ▶ T_0 : time of enrolment.
- ▶ T_1 : after the first resuscitation cycle (approximately 2 min according to guidelines).
- ▶ $T_2 \dots T_n$: every CPR cycle (or every 2 min in the intubated patient) bilateral pupillometry data will be collected.
- ▶ T_{end} : the last pupillometry exam at ROSC or death.

The CPR manoeuvre will be performed according to the European Resuscitation Council guidelines.¹³ Pupillometry measurements will be collected approximately during the rhythm check, and in intubated patients the ETCO₂ will be recorded simultaneously with the pupillometry measurement.

Other information regarding time of no/low flow, presence of bystander CPR, use of mechanical CPR will be extracted from the AREU's dispatch database (EmmaWeb V.6.9.2 11/03/2021, powered by Beta80 Group).

In the surviving patients, data regarding the neuro-prognostication exams (NSE, EEG, SSEP, CT and MRI) will be collected from the ICU to which the patient will be admitted following the indications displayed in table 1. EEG data will be reporting according to the American Clinical Neurophysiology Society standards.¹² At hospital admission, information regarding the neurological status assessment will be collected. Outcome data, including the mRS, mortality etc, will be collected as previously described through phone interview. In order to guarantee an appropriate blindness (second level of blindness), the interviewer will be unaware of any information regarding pupillometry measurements.

Data management

Anonymisation of the collected data is guaranteed through use of a mission specific numerical code, AREU generated for each patient enrolled. Pupillometry data will be automatically saved within device and subsequently extracted as excel files. This data will be inserted in a password-protected web-based electronic case report form provided to single users. Data will be checked for consistency and completeness by the study coordinator and scientific committee to ensure the highest possible quality of the collected data presented for statistical analysis, and to limit the rate of errors and missing data. Data will be stored and secured in SIAARTI database for a period of 5 years.

Statistical analysis

Sample size calculation

We hypothesised that the specificity of the NP_i described in previous studies can be assumed the same during resuscitation manoeuvres and the power analysis based on the performance described in these diagnostic studies.^{6 14-16}

Table 3 modified Rankin Scale used to assess neurological outcome in surviving patients following ROSC admitted to the intensive care unit

Modified rankin scale		
Grade	Description	
0	No symptoms at all	Good outcome
1	No significant disability: despite symptoms, able to carry out all usual duties and activities	
2	Slight disability: unable to perform all previous activities but able to look after own affairs without assistance	
3	Moderate disability: requiring some help but able to walk without assistance	Poor outcome
4	Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance	
5	Severe disability: bedridden, incontinent and requiring constant nursing care and attention	
6	Death	

Right column showing how patients are divided into 'good' or 'poor' outcome. ROSC, return of spontaneous circulation.

Therefore, NP_i ≤2 was considered as a predictor of poor outcome (defined as: severe disability, vegetative state, death) and an expected specificity of 100% and minimal acceptable specificity of 94% were established, above which, the lower limit of the 95% CIs is expected to fall (type I error=0.05).

Assuming a 45% prevalence, and a power test of 80%, a sample size of 88 subjects (48 controls and 40 cases) is estimated. Considering a 50% attrition rate and a 15% dropout, the sample size rises to 214 subjects.

Plan of analysis

The patients in each analysis will be included into an intention-to-treat (ITT) population. The ITT population will contain all patients enrolled in the study and will be used for primary, secondary and explorative outcomes analysis.

Quantitative data will be summarised by appropriate descriptive statistics (ie, mean, SD, median, minimum and maximum). Results will be expressed as mean±SD or median (IQR). Qualitative data will be summarised by absolute and relative frequency distribution and expressed as number of events (%). Kolmogorov-Smirnov and Shapiro-Wilk normality tests will be used to test if data are well modelled by a normal distribution.

The study variable, NP_i, usually indicated in value within 0 (unreactive) and 5 (normal light reflex), will be aggregate in three ranks:

- ▶ NP_i 0: unreactive.
- ▶ NP_i 0–3: sluggish
- ▶ NP_i 3–4.9: brisk.

In case of different NP_i value from both eyes, the lowest one will be considered as precautionary purpose. Second the concordance of value between the two eyes will be analysed as a further prognostic tool.

Neurological outcome valued by mRS scale, will be dichotomised as good recovery (mRS ranges from 0 to 3) and poor recovery (mRS ranges from 4 to 6) as showed in [table 3](#).

Other pupillometric parameters taken into account will be: latency and percentage of pupilar constriction.

Comparison between groups

Quantitative normal variables will be compared with the ANOVA (analysis of variance) and Student's t-test. Inter-group differences in quantitative variables distribution at different time points will be assessed with ANOVA for repeated measures. Ordinal qualitative variables or non-normal quantitative variables will be compared Mann-Whitney and Kruskal-Wallis tests. Binary outcome variable will be evaluated using a logistic regression model.

For the primary objective sensitivity, specificity, ROC (receiver operating characteristic curve) and AUC (area under the curve) curves will be used in order to evaluate the diagnostic test performance, while logistic regression models will be used for secondary endpoints.

The methodology adopted is conforming to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting guidelines.¹⁷

Discussion and expected impact of the study

EASY-CARE is designed to obtain information regarding brain stem perfusion status in course of CPR. Since the pupillary reactivity is the result of balance between parasympathetic and orthosympathetic vegetative nervous system; we hypothesise that vitality of brain stem, confirmed by q-pupillometry may be useful in two ways: first, the vitality of the autonomic system could contribute to ROSC by restoration of its effects on heart and cardiovascular system, and second, the recovery of pupilar reflexes could be a good indicator of the CPR effectiveness.

The other hypothesis for designing EASY-CARE, is the possibility that NP_i index could provide more information regarding early prognosis during refractory cardiac arrests.

In a setting where the prehospital setting represents a hostile environment for clinical research, EASY-CARE could represent a break-through study. Digital pupillometry operated by technicians allows to obtain information minimising behavioural difference in CPR/ALS protocol adherence. The double blindness during the pupillometry phase guarantees high quality of data, excluding the risk of self-fulfilling prophecy. Furthermore, the protocol's test in HFS has permitted to optimise the insertion of pupillometry within the sequence time frame.

Several limitations are worthy of note. Due to the nature of the out-of-hospital emergency setting, there has to be a limited choice of parameters and measurements that can be collected during CPR.

Another possible source of limitation in data collecting is attributable to the ambient-light sensitivity of NP_i-200 camera. This device is not protected from external light source and in some cases this may affect the acquisition of data.¹⁸

Despite the observational design of this study should limit any possible causal inferences, the results of EASY-CARE could represent a novel approach to evaluate the effectiveness and appropriateness of prolonged resuscitation efforts. The scientific committee is confident that results will support the design of a future international multicentre trial, which will have the objective of confirming this hypothesis.

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REFERENCES

- Gräsner J-T, Wnent J, Herlitz J, *et al.* Survival after out-of-hospital cardiac arrest in Europe - Results of the EuReCa TWO study. *Resuscitation* 2020;148:218–26.
- Behrends M, Niemann CU, Larson MD. Infrared pupillometry to detect the light reflex during cardiopulmonary resuscitation: a case series. *Resuscitation* 2012;83:1223–8.
- Breckwoldt J, Arntz H-R. Infrared pupillometry during cardiopulmonary resuscitation for prognostication--a new tool on the horizon? *Resuscitation* 2012;83:1181–2.
- Tamura T, Namiki J, Sugawara Y, *et al.* Early outcome prediction with quantitative pupillary response parameters after out-of-hospital cardiac arrest: a multicenter prospective observational study. *PLoS One* 2020;15:e0228224.
- Sandroni C, De Santis P, D'Arrigo S. Capnography during cardiac arrest. *Resuscitation* 2018;132:73–7.
- Chen JW, Gombart ZJ, Rogers S, *et al.* Pupillary reactivity as an early indicator of increased intracranial pressure: the introduction of the neurological pupil index. *Surg Neurol Int* 2011;2:82.
- Morelli P, Oddo M, Ben-Hamouda N. Role of automated pupillometry in critically ill patients. *Minerva Anestesiol* 2019;85:995–1002.
- Oddo M, Sandroni C, Citerio G, *et al.* Quantitative versus standard pupillary light reflex for early prognostication in comatose cardiac arrest patients: an international prospective multicenter double-blinded study. *Intensive Care Med* 2018;44:2102–11.
- Miroz J-P, Ben-Hamouda N, Bernini A, *et al.* Neurological pupil index for early prognostication after Venous arterial extracorporeal membrane oxygenation. *Chest* 2020;157:1167–74.
- Riker RR, Sawyer ME, Fischman VG, *et al.* Neurological pupil index and pupillary light reflex by pupillometry predict outcome early after cardiac arrest. *Neurocrit Care* 2020;32:152–61.
- Kim JH, Park I, Chung SP, *et al.* Optimal combination of clinical examinations for neurologic prognostication of out-of-hospital cardiac arrest patients. *Resuscitation* 2020;155:91–9.
- Hirsch LJ, Fong MWK, Leitinger M, *et al.* American clinical neurophysiology Society's standardized critical care EEG terminology: 2021 version. *J Clin Neurophysiol* 2021;38:1–29.
- Soar J, Böttiger BW, Carli P. European Resuscitation Council Guidelines 2021: Adult advanced life support [published correction appears in *Resuscitation*. 2021 Oct;167:105-106]. *Resuscitation* 2021:115–51.
- Flahault A, Cadilhac M, Thomas G. Sample size calculation should be performed for design accuracy in diagnostic test studies. *J Clin Epidemiol* 2005;58:859–62.
- Chu H, Cole SR. Sample size calculation using exact methods in diagnostic test studies. *J Clin Epidemiol* 2007;60:1201–2.
- Liu CamdCY. The saw-toothed behavior of power versus sample size and software solutions: single binomial proportion using exact methods. *Am Stat* 2002;56:149–55.
- Chan A-W, Tetzlaff JM, Götzsche PC, *et al.* Spirit 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
- Couret D, Simeone P, Freppel S, *et al.* The effect of ambient-light conditions on quantitative pupillometry: a history of rubber cup. *Neurocrit Care* 2019;30:492–3.