The capacity of neurological pupil index to predict absence of somatosensory evoked potentials after cardiac arrest—A study protocol

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Abstract
Background: Anoxic-ischemic brain injury is the most common cause of death after cardiac arrest (CA). Robust methods to detect severe injury with a low false positive rate (FPR) for poor neurological outcome include the pupillary light reflex (PLR) and somatosensory evoked potentials (SSEP). The PLR can be assessed manually or with automated pupillometry which provides the neurological pupil index (NPI). We aim to describe the interrelation between NPI values and the absence of SSEP cortical response and to evaluate the capacity of NPI to predict the absence of cortical SSEP response in comatose patients after CA.

Methods: A total of 50 patients will be included in an explorative, prospective, observational study of adult (>18 years) comatose survivors of CA admitted to intensive care in a university hospital. NPI assessed with a hand-held pupillometer will be compared to SSEP signals recorded >48 hours after CA. Primary outcomes are sensitivity, specificity, and odds ratio for NPI to predict bilateral absence of the SSEP N20 signal, with NPI values corresponding to <5% FPRs of SSEP absence. Secondary outcomes are the PLR and SSEP sensitivity, specificity, and odds ratio for poor neurological outcome at hospital discharge and death at 30 days.

Discussion: The PLR and SSEP may have a systematic interrelation, and a certain NPI threshold could potentially predict the absence of cortical SSEP response. If this can be concluded from the present study, SSEP testing could be excluded in certain patients to save resources in the multimodal prognostication after CA.

KEYWORDS
cardiac arrest, neurological outcome, neurological pupil index, prognostication, pupillometry, somatosensory evoked potentials

Abbreviations: ALS, advanced life support; CA, cardiac arrest; CABG, coronary artery bypass grafting; CHF, congestive heart failure; CPR, cardio-pulmonary resuscitation; CT, computed tomography; EEG, electroencephalography; GCS-M, Glasgow Coma Scale-Motor Score; ICD, implantable cardioverter defibrillator; MRI, magnetic resonance imaging; mRS, Modified Rankin Scale; NPI, neurological pupil index;NSE, neuron specific enolase; PCI, percutaneous coronary intervention; PLR, pupillary light reflex; RLS, reaction level scale; ROSC, return of spontaneous circulation; sPLR, standard (manual) assessment of the pupillary light reflex; SSEP, somatosensory evoked potentials; WLST, withdrawal of life-sustaining treatment.

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The major cause of death among comatose survivors of cardiac arrest (CA) is global hypoxic-ischemic brain injury. The initial phase of anoxemia/ischemia damages the regions of the brain most sensitive to hypoxia: the hippocampus, thalamus, basal ganglia, and cerebral cortex. In the cortex, the synaptic activity ceases within seconds after CA. With prolonged CA, the injury also affects areas less sensitive to hypoxia, such as the brainstem. After successful resuscitation, the reperfusion may worsen the injury in all parts of the brain during the next several days.

To assess the neurological prognosis in comatose patients after primary resuscitation and stabilisation, international guidelines advocate a multimodal approach. Most tests are applied to identify brain injury consistent with poor neurological outcome. The recommended methods are electroencephalography (EEG), computed tomography, magnetic resonance imaging (MRI), pupillary and corneal reflex, somatosensory evoked potentials (SSEP), and biomarkers of brain injury, such as neuron specific enolase (NSE).

Each method tests different neurological functions, reflexes, or the extent of injury. A combination of methods enables neurological prognostication with high specificity. A stringent prognostication approach is vital as withdrawal of life-sustaining treatment (WLST) based on inadequate assessment of prognosis can result in death as a "self-fulfilling prophecy". However, it is both time consuming to include all the recommended methods in everyday practice prognostication. To establish the interrelation of NPI and SSEP have the potential to save resources in the multimodal approach to prognostic assessment by using only one of two clearly interrelated methods.

1.1 Pupillary light reflex

The pupillary light reflex (PLR) arc is dependent of an intact brainstem function. The afferent limb involves the optic nerve, which synapses on neurons in the pretectal nucleus and then the Edinger-Westphal nucleus located in the midbrain. The efferent limb involves the oculomotor nerve axons, and the ciliary ganglion which enables pupillary muscle contraction. A bilateral PLR absence indicates a severe injury in the midbrain and signifies a poor neurological outcome in comatose CA patients.

The manually assessed PLR, also called standard PLR (sPLR), is associated with imprecision due to human error, environmental and patient factors. Pupillometry is a semiautomated method that provides a quantitative measure of the PLR. With a standardized light stimulation, the handheld pupillometer measures the pupil size, latency, constriction-, and dilation velocity. Based on the values obtained, it calculates an index of the PLR known as the neurological pupil index (NPI). An NPI of 0 means that the PLR is absent, and an NPI of 1-5 ranges from an abnormally slow to normal PLR. A transiently absent PLR is common during the first hours following the CA. If the circulatory arrest was brief, the brainstem may recover fully. Patient factors that could make the PLR unreliable are ophthalmological pathologies such as asymmetric glaucoma, Argyll Robertson pupil, preexisting optic neuropathies.

1.2 Somatosensory evoked potential

Somatosensory evoked potentials measures the cortical response to median nerve stimuli. Stimulating electrodes are placed on the forearm and receiver electrodes are placed on the neck and scalp. The electrically induced signal travels from the median nerve along to the spinal cord, via the medial lemniscus in the midbrain to the contra-lateral somatosensory cortex. A signal peak can be detected by the electrodes at specific anatomical locations at specific time points. The N13 corresponds to the cervical spine and N20 corresponds to the primary somatosensory cortex. A bilaterally absent N20 signal concomitant with a confirmed N13 signal is a strong predictor of poor neurological outcome in comatose patients after CA.

1.3 Rationale and hypothesis

The PLR and SSEP are robust methods with low false positive rates (FPR) for poor prognosis in the multimodal prognostication after CA. As explained above, both PLR and SSEP depend on intact midbrain function. Anatomically, the medial lemniscus, the
Edinger-Westphal nucleus, and the oculomotor nerve nucleus are neighboring structures in the midbrain. A severe hypoxic lesion could affect these structures causing an absence of both PLR and SSEP response. Because the brainstem is more resistant to hypoxia than the cortex, the cortical response to SSEP is likely to cease prior to the PLR. Even so, if the ischemic injury is severe enough, it will affect the PLR. In theory, the reaction is first slowed down, before it finally fades completely—corresponding to a progressively decreasing NPi value.

Our reasoning is that there should be an interrelation between PLR and SSEP. A patient with ischemic brain injury who has an abnormal or absent PLR will most likely have a discontinued cortical SSEP response. We hypothesize that a certain NPi value is predictive of a bilaterally absent PLR will most likely have a discontinued cortical SSEP response. Because the brainstem is more resistant to hypoxia than the cortex, the cortical response to SSEP is likely to cease prior to the PLR. Even so, if the ischemic injury is severe enough, it will affect the PLR. In theory, the reaction is first slowed down, before it finally fades completely—corresponding to a progressively decreasing NPi value.

Our reasoning is that there should be an interrelation between PLR and SSEP. A patient with ischemic brain injury who has an abnormal or absent PLR will most likely have a discontinued cortical SSEP response. We hypothesize that a certain NPi value is predictive of a bilaterally absent N20 SSEP response. Ideally, there should be a numeric NPi cut-off, with a high specificity for absent cortical SSEP response. If the hypothesis can be confirmed, it would allow SSEP testing to be excluded in certain patients. Instead, the technically less demanding pupillometry could be used as its proxy in the multimodal prognostication after CA.

2 | METHOD

2.1 | Ethical approval

The study is approved by the Swedish Ethical Review Authority (DNR 2019-00823, 2020-00506). A consent is obtained from patients regaining consciousness or the next of kin when appropriate after receiving verbal and written information.

2.2 | Study design

An explorative, prospective, noninterventional, observational, cohort study with consecutive inclusion. The patients are submitted to clinical routine prognostication procedures, including pupillometry and SSEP. The study data will be collected from medical records and patient monitoring systems.

2.3 | Research aim

To describe the association between NPi and bilateral absence of the cortical SSEP N20 signal in patients remaining comatose after CA, and to define a NPi cut-off value that renders a <5% FPR for a bilaterally absent SSEP cortical response.

2.4 | Setting

The study will be conducted in the Sahlgrenska University Hospital, the referral center for specialized cardiac care for the 1.7 million inhabitants of western Sweden. The yearly admittance of resuscitated survivors of CA in the general ICU is 50-60 patients, and around 50% will remain comatose on day 3.

2.5 | Postcardiac arrest intensive care

The local standard operations procedure (SOP) for comatose survivors of CA includes 24 hours of targeted temperature management (TTM) at 36°C using a water mediated surface cooling device (Arctic Sun 2000 TTM; Bard Medical). The patient is sedated using remifentanil and propofol during TTM. Core temperature is measured via an indwelling urinary catheter. After 4 hours of rewarming, sedation is reduced at the earliest convenience to evaluate if the patient regains consciousness. Patients who do not regain consciousness are kept at ≤37.5°C. Blood samples are collected 24, 48, and 72 hours after CA for NSE analysis. The neurophysiological examinations, EEG and SSEP, are performed >48 hours after CA in patients remaining comatose. The clinical neurological examination and the results from the prognostic tests are evaluated at a minimum of 72 hours after CA. Poor neurological prognosis is deemed likely when the following criteria are fulfilled, in accordance with the 2015 European guidelines:

1. Unconscious (RLS 7-8, GCS-M 1-2) 72 hours after CA and bilaterally absent PLR and corneal reflex OR Unconscious (RLS 7-8, GCS-M 1-2) 72 hours after CA and bilaterally absent N20 signal on SSEP.
2. Unconscious (RLS 7-8, GCS-M 1-2) 96 hours after CA and at least two of the following:
   a. Status myoclonus with presentation <48 hours after CA
   b. NSE value > 60 µg/L at 48 hours and increasing trend 24-48 hours after CA
   c. Burst suppression or status epilepticus on EEG
   d. Signs of diffuse anoxic brain injury on CT/MRI

   Reaction Level Scale: 7 = abnormal extension, 8 = no response. Glasgow Coma Scale-Motor score: 2 = abnormal extension, 1 = no response.

2.6 | Population and study size

We will include a minimum of 50 adult (>18 years) survivors of CA remaining comatose > 48 hours during post resuscitation care in the intensive care unit.

Exclusion criteria will be regained consciousness <48 hours after CA, or before examination by pupillometry or SSEP is performed; pregnancy; intracranial bleeding; traumatic brain injury, palliative care and lack of next of kin.

2.7 | Outcome measures

Primary outcome: sensitivity, specificity, and odds ratio for NPi to predict bilateral absence of the N20 SSEP signal, including the NPi value corresponding to a 5% FPR for absent cortical SSEP response.

Secondary outcome: the PLR and SSEP sensitivity, specificity and odds ratio for poor neurological outcome at hospital discharge and death at 30 days.
2.8 | Procedures

Pupillometry is routinely performed together with SSEP (±1 hour) >48 hours after CA using a handheld device for automated infrared pupillometry (NeurOptics NPi®-200 Pupillometer; Neuroptics Ltd). All values provided by the pupillometer will be registered: NPi, maximum pupil diameter, minimum pupil diameter, change in pupil size, constriction velocity, maximum constriction velocity, latency of constriction, dilation velocity.

Somatosensory evoked potentials is routinely performed >48 hours after CA with the signal recorded on a standard electrodiagnostic system (KeyPoint G4, software v.2.32; Natus Technology Europe Gmbh). The median nerve in the right and the left forearm is stimulated with a bipolar surface electrode. A 2.7-Hz stimulation frequency is used with a 0.2-ms stimulus duration in two sets of at least 500 repetitions. The filter bandpass is 10 to 2 kHz. Surface electrodes (Ag/AgCl) are placed on Erb's point, cervical spine (C7) and 2 cm posterior to C3 and C4 (C3' and C4', respectively). Only contra-lateral leads are recorded. The amplitude cut-off is 0.3 µV for the N20 potential and 0.25 µV for the noise level. We will register the highest N20 potential amplitude on each side if present, and the amplitude of noise level in that registration.

2.9 | Neurological and survival outcome

Neurological outcome is assessed at hospital discharge from available medical records data according to the Modified Rankin Scale (mRS). A poor neurological outcome is defined as mRS 4-6 (unable to walk and attend bodily need without assistance, bedridden requiring constant nursing care, dead). Survival status at 30 days.

2.10 | Additional data collected

Demographic and clinical data along with test results will be retrieved from medical records. Physiological data during intensive care will be retrieved from patient monitoring systems.

1. Comorbidities
   a. Preexisting neurological deficit
   b. Preexisting ophthalmological pathology
   c. Previous myocardial infarction
   d. Previous percutaneous coronary intervention (PCI)
   e. Congestive heart failure
   f. Previous coronary artery bypass grafting.
   g. Presence of implantable cardioverter defibrillator
   h. Preexisting known atrial fibrillation
   i. Preexisting known diabetes mellitus
   j. Preexisting hypertension or antihypertensive medications.
   k. Clinical frailty scale

2. Cardiac arrest features and prehospital treatment provided by bystander and first responder personnel
   a. Scene of CA
   b. Witnessed CA
   c. Bystander CPR
   d. First registered rhythm
   e. CPR device used
   f. Defibrillation count
   g. Time of CA
   h. Time to Return of Spontaneous Circulation
   i. Time from CA to Advanced Life Support
   j. Pre-hospital airway device
   k. Adrenaline dose (mg)
   l. Cause of CA
   m. Angiography and/or PCI performed

3. Physiological data during intensive care
   a. The targeted temperature for TTM
   b. Highest temperature measured during ICU stay
   c. Fever at any time during ICU stay
   d. If WLST was performed prior to prognostication

4. Neurological prognostication
   a. NSE 24, 48, and 72 hours after CA
   b. Electroencephalography, presence of “highly malignant” or “benign” EEG pattern according to the Westhall classification
   c. Computed tomography
   d. Magnetic resonance imaging
   e. Clinical examination: sPLR, corneal reflex, presence of myoclonus, motor response to pain

2.11 | Statistical considerations and data analysis

Existing data applicable to a calculation of sample size were identified in the online supplement of a study by Oddo et al, reporting the accuracy of NPi as compared to manual assessment of PLR. Their data included the association between PLR, SSEP, and outcome in patients included by criteria similar to ours. Provided NPi values were median and interquartile range (IQR) on day 3 after CA, categorised according to neurological outcome at 3 months. NPi was 4.5 (4.2-4.7) in the favorable outcome group and 3.7 (3.3-4.2) in the unfavorable outcome group respectively. From the study by Moseby-Knappe, based on the “TTM trial” cohort we estimated the prevalence of absence of SSEP response to be 37% correspondingly. In order to find a significant difference in NPi of 0.7 with a power of 95% with two-sided Fisher’s nonparametric permutation test, 45 patients are needed, assuming a 2:1 allocation and unequal SD in the groups (0.37 and 0.67 calculated from the IQR above), and significance level 0.01. To account for uncertainty within these estimates, we aim to include 50 patients with a complete protocol.

A receiver operating characteristics curve will be used to find the NPi cut-off values resulting in a <5% FPR for absent SSEP to
predict poor neurological outcome. NPi values below the cut-off, that is, values consistent with poor outcome, will be used to calculate the predictive value for SSEP at its given prevalence. Fisher's exact test will be used to assess correlation between NPi and SSEP.

3 | DISCUSSION

The aim of this study is to assess the interrelation between PLR and SSEP, two robust tests used in the multimodal neurological prognostication of comatose patients after CA. Understanding the association between the different methods is essential in order to use the most appropriate and rational methods for the individual patient. We hypothesize that the PLR and SSEP have a systematic interrelation, and that a certain NPi value has the capacity to predict the absence of cortical SSEP response. If confirmed, the prognostication procedure could be rationalized to save resources in the assessment of neurological prognosis. Similar reasoning has been applied to the association between EEG and SSEP. With a normal or "benign" EEG, the cortical SSEP response was invariably present. Thus, it has been advocated that patients with such EEG patterns, SSEP is not required for the assessment of neurological prognosis after CA.

The absence of the PLR is a well-established clinical predictor of poor neurological outcome after CA if unaffected by sedation or other factors obtunding the reflex. Confounders to the manual assessment of PLR includes a small pupil size and darker eye colour. The use of automated infrared pupillometry is more reliable than manual assessment of PLR as it can detect even small changes, otherwise easily missed. Also, the use of pupillometry has been shown to be reliable, and the staff procedure training uncomplicated. However, if the eyes are rolling away or undulating, the examination cannot be performed. Certain ophthalmological pathologies are likely to cause unreliable pupillometry and sPLR results. If present, such obstacles will be recorded in the present study database.

The absence of the cortical N20 SSEP signal a strong predictor for poor neurological outcome after CA if recommended in international guidelines. Yet, no prognostication method is 100% certain and false positive cases exist. One important factor influencing the reliability of the interpretation is the noise level in the recording. Several false positive SSEP predictions of poor neurological outcome are associated with avoidable confounders such as noise and inconsistent interpretations. A standard recording technique and protocol for interpretation is preferred to raise the reliability of the method. Noise level can be reduced by administering muscle relaxant, and by turning off nonessental electrical ICU equipment during the SSEP registration.

3.1 | Limitations

There are some limitations to our study. The inherent limitations of an observational design apply. However, the prospective approach can ascertain good quality data and provide a good estimate for the interrelation of the applied methods. Although bilateral absence of the cortical N20 SSEP response has a high specificity for poor neurological outcome, its sensitivity rarely exceeds 50%. Furthermore, the capacity of NPi to predict the absence of SSEP will depend on the prevalence of SSEP. Consequently, the external validity of our results will be limited to patient populations with similar prevalence of absent SSEP. Although, if we can provide accurate sensitivity and specificity estimates for NPi to predict absent SSEP response, the values obtained can be used to calculate the NPi predictive value in other populations, given their specific prevalence of absent SSEP response.

3.2 | Clinical use

The interrelation between PLR and SSEP has not been detailed before and the results of the present study may infer alternative conclusions. If our hypothesis is confirmed, the additional use of SSEP may be superfluous if PLR can be reliably assessed using pupillometry and NPi. However, if the association between the methods turns out irregular, SSEP may be the preferred method in neurological prognostication if the PLR is not entirely absent. Regardless of the robustness of our results, the study will improve the understanding of the prognostication methods and can help to use the available resources more efficiently.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

This project is approved by the Swedish Ethical Review Authority (DNR 2019-00823, 2020-00506). Inclusion and management of patients will comply with the Helsinki Declaration for research in human subjects and data will be handled and stored according to the European General Data Protection Regulation (GDPR). Verbal and written consent to use routinely registered data for the study will be obtained at the earliest possible occasion with respect to the severity of the patient's condition and the likely emotional distress of family members. Consent can be withdrawn at any time. Patient ID will be registered and stored on a physical paper, stored in a locked space in the ICU department. Each patient will be assigned a unique serial number, used for data registration and analysis. The datafiles are stored on secure servers protected by firewalls and requiring authorised access.

TIMELINE

200201-220630.

AUTHORS’ CONTRIBUTIONS

CR conceptualized the study and obtained ethical approval. LL, SJ and MT designed the protocol. LL, SJ and MT wrote the manuscript,
which was revised by JN, PR, PL and CR. All the authors read and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT
The datasets generated and analyzed during the current study are not publicly available due to the intrusion of the patient’s privacy. But the datasets are available from the corresponding author on request. The results will be published in a peer-reviewed medical journal.

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