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Protocol paper

Quantitative pupillometry for neuroprognostication in comatose post-cardiac arrest patients: A protocol for a predefined sub-study of the Blood pressure and Oxygenations Targets after Out-of-Hospital Cardiac Arrest (BOX)-trial

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Abstract

Background: Resuscitation guidelines propose a multimodal prognostication strategy algorithm at ≥72 hours after the return of spontaneous circulation to evaluate neurological outcome for unconscious cardiac arrest survivors. Even though guidelines suggest quantitative pupillometry for assessing pupillary light reflex, threshold values are not yet validated.

This study aims to validate pre-specified thresholds of quantitative pupillometry by quantitatively assessing the percentage reduction of pupillary size (qPLR) <4% and Neurological Pupil index (NPi) ≤2 and in predicting unfavorable neurological outcome. Both as an isolated predictor and combined with guideline-suggested neuron-specific enolase (NSE) threshold >60 μg L^{-1} in the current prognostication strategy algorithm.

Methods: We conduct this pre-planned diagnostic sub-study in the randomized, controlled, multicenter clinical trial "Blood Pressure and Oxygenation Targets after Out-of-Hospital Cardiac Arrest-trial". Blinded to treating physicians and outcome assessors, measurements of qPLR and NPi are obtained from cardiac arrest survivors at time points (±6 hours) of admission, after 24, 48, and 72 hours, or until the time of awakening or death.

Discussion: This study will be the largest prospective study investigating the predictive performance of automated quantitative pupillometry in unconscious patients resuscitated from cardiac arrest. We will test specific threshold values of NPi ≤2 and qPLR <4% to predict unfavorable outcome following cardiac arrest. The validation of pupillometry alone and combined with NSE with the criteria of the current prognostication strategy algorithm will hopefully increase the level of evidence and support clinical neuroprognostication with automated quantitative pupillometry in unconscious post-cardiac arrest patients.

Trial registration: Registered March 30, 2017, at ClinicalTrials.gov (Identifier: NCT03141099).

Keywords: Cardiac arrest, Post resuscitation care, Guidelines, Quantitative Pupillometry, Prognostication

Introduction

Background and rationale {6a}

The annual average out-of-hospital cardiac arrest incidence is 89 per 100,000 individuals in European countries (86 in Denmark). For patients admitted with a return of spontaneous circulation (ROSC), the survival rate is 35% (41% in Denmark).[1,2]

The subsequent active withdrawal of life-sustaining treatment (WLST) to irreversible hypoxic-ischemic brain injury is the leading cause of death in patients resuscitated from cardiac arrest.[3,4] To avoid falsely pessimistic predictions and to increase overall accuracy, current guidelines recommend a multimodal approach to the neuroprognostication strategy algorithm, with two or more predictors when patients are unconscious, with a Glasgow Motor Score ≤3, at ≥72 hours after ROSC.[5] The predictors include neurophysiology, with

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https://doi.org/10.1016/j.resplu.2023.100475

absent N20 Somatosensory Evoked Potentials or malignant electroencephalograms at >24 hours, biomarkers (e.g., neuron-specific enolase [NSE] >60 μg L^{-1} at 48 and/or 72 hours), extensive anoxic injury on brain imaging, and clinical examination with status myoclonus at ≤72 hours or absent pupillary and corneal reflexes at ≥72 hours.[5]

Quantitative pupillometry is favored over the standard manual evaluation for assessing pupillary light reflex, with quantitatively assessed percentage reduction of pupillary size (indicated as qPLR) and the neurological pupil index (NPi) as the most common parameters.[5–7]

Besides a completely absent pupillary reflex, several studies find that specific thresholds of reduced pupil reactivity predict outcomes with high specificity.[6,8–10] An NPi ≤2.0 and a qPLR <4.0% achieved a zero percent false positive rate when predicting unfavorable neurological outcomes in unconscious patients after cardiac arrest.[6,10] However, as results have been inconsistent across studies, thresholds are yet to be standardized. Thus, guidelines still recommend that only completely absent pupillary reflexes (equaling qPLR and NPi at 0) at ≥72 hours are used as predictors in the neuroprognostication strategy algorithm.[5]

If the full potential of quantitative pupillometry is to be utilized as a part of the multimodal neuroprognostication, proposed pupillometry thresholds must be prospectively validated in a large contemporary cohort.

Objectives {7}

BOX trial

All objectives will be investigated in the "Blood Pressure and Oxygenation Targets after Out-of-Hospital Cardiac Arrest-trial" (BOX trial, ClinicalTrials.gov no.: NCT03141099), a randomized, controlled multicenter trial, allocating unconscious survivors of cardiac arrest to either low (63 mm Hg) or high (77 mm Hg) mean arterial blood pressure target (double-blinded intervention) and restrictive (9–10 kPa) or liberal (13–14 kPa) oxygen target (open-label intervention) during Intensive Care Unit (ICU) stay with blinded outcome evaluation.[11,12]

Primary objective

The primary objective of this study is to perform an external validation of the prognostic value of the proposed quantitative pupillometry thresholds of qPLR <4.0 and NPi ≤2.0,[6,10] predicting the primary outcome for eligible patients in the BOX trial cohort.[11,13] Further, we will test the guideline-proposed prognostication strategy algorithm for unconscious patients (Glasgow Motor Score ≤3) at 72 hours, with pupillometry measured before 72 hours combined with 48-hour measurements of NSE.[5] In this study, the primary outcome is the incidence of an unfavorable neurological condition, defined as a Cerebral Performance Category of 3–5, after 90 days from randomization.

Secondary objectives

To evaluate the prognostic performance of qPLR and NPi alone and adjusted for clinical predictors, predicting the secondary outcomes from the BOX trial:

1. Death from any cause within 365 days from randomization.
2. Median modified Rankin scale score after 90 days from randomization.
3. Median Montreal Cognitive Assessment score after 90 days from randomization in patients attending follow-up.
4. Median plasma NSE level at 48 hours from randomization.

Hypotheses

In a population of unconscious cardiac arrest patients, the individual thresholds of qPLR <4.0 and NPi ≤2.0 will achieve a false positive rate <1% as early as 24 hours after ROSC for predicting the primary and secondary outcomes. Further, we will identify optimal thresholds predicting the outcome with a false positive rate of 0–5% for pupillometry thresholds alone and <1% when implemented in the prognostication strategy algorithm. With the multivariable adjustment, qPLR and NPi will contribute independently to prognostication.

Methods

Study design and eligibility criteria {8, 9,10}

The BOX trial comprised 789 unconscious cardiac arrest, survivors of presumed cardiac origin, included at two tertiary heart centers in Denmark (Odense University Hospital and Copenhagen University Hospital, Rigshospitalet), providing specialized cardiac care for 3.9 million citizens. The trial protocol[13] and the main results[11,12] have recently been published. With the additional exclusion criteria of pre-existing ophthalmic conditions that would inhibit or significantly affect pupillary reflexes (e.g., cataract and eye surgery),[14,15] all remaining patients from the BOX trial were eligible for this sub-study (Fig. 1).[13] We have written this protocol in accordance with the SPIRIT guideline[16] and summarized the inclusion and exclusion criteria for the main trial in Table 1.

Study procedure

Serial measurements of quantitative pupillometry, using NPi®-200 pupillometers (NeurOptics®, Irvine, CA, USA), will be performed at admission and 6, 12, 24, 36, 48, 72, 96, and 120 hours after cardiac arrest or until awakening or death, if earlier than 120 hours. The measurements at admission, 24, 48, and 72 hours, will be used in the further analysis for this study.

All measurements are automatically collected and directly stored in the SmartGuard® device (a single-use chin guard or spacer) developed for the device. Quantitative pupillometry measurements are not routinely recorded in the clinical charts, as it was implemented as a guideline-supported part of the prognostication in 2021,[5] and thus not at the time of the trial initiation.

Post-cardiac arrest care, prognostication, and WLST

All unconscious cardiac arrest survivors admitted to the ICU are subjected to the same protocol for post-cardiac arrest care, regardless of site. They are intubated, mechanically ventilated, and continuously sedated with propofol and fentanyl to reach a target Richmond Agitation-Sedation Scale score of −4.

With commercially available cooling devices, active cooling is initiated immediately after admission, achieving the predefined target core temperature of 36 °C as quickly as possible. To reduce shivering and subsequent energy consumption, neuromuscular blocking agents are administered when necessary. After maintaining the target temperature for 24 hours, normothermia of 37 °C ± 0.5 °C is achieved by rewarming of 0.5 °C per hour. As per protocol, the temperature is actively kept for 36 or 72 hours after ROSC, depending on the randomization in the subordinate fever management study of the BOX trial.[13,17]

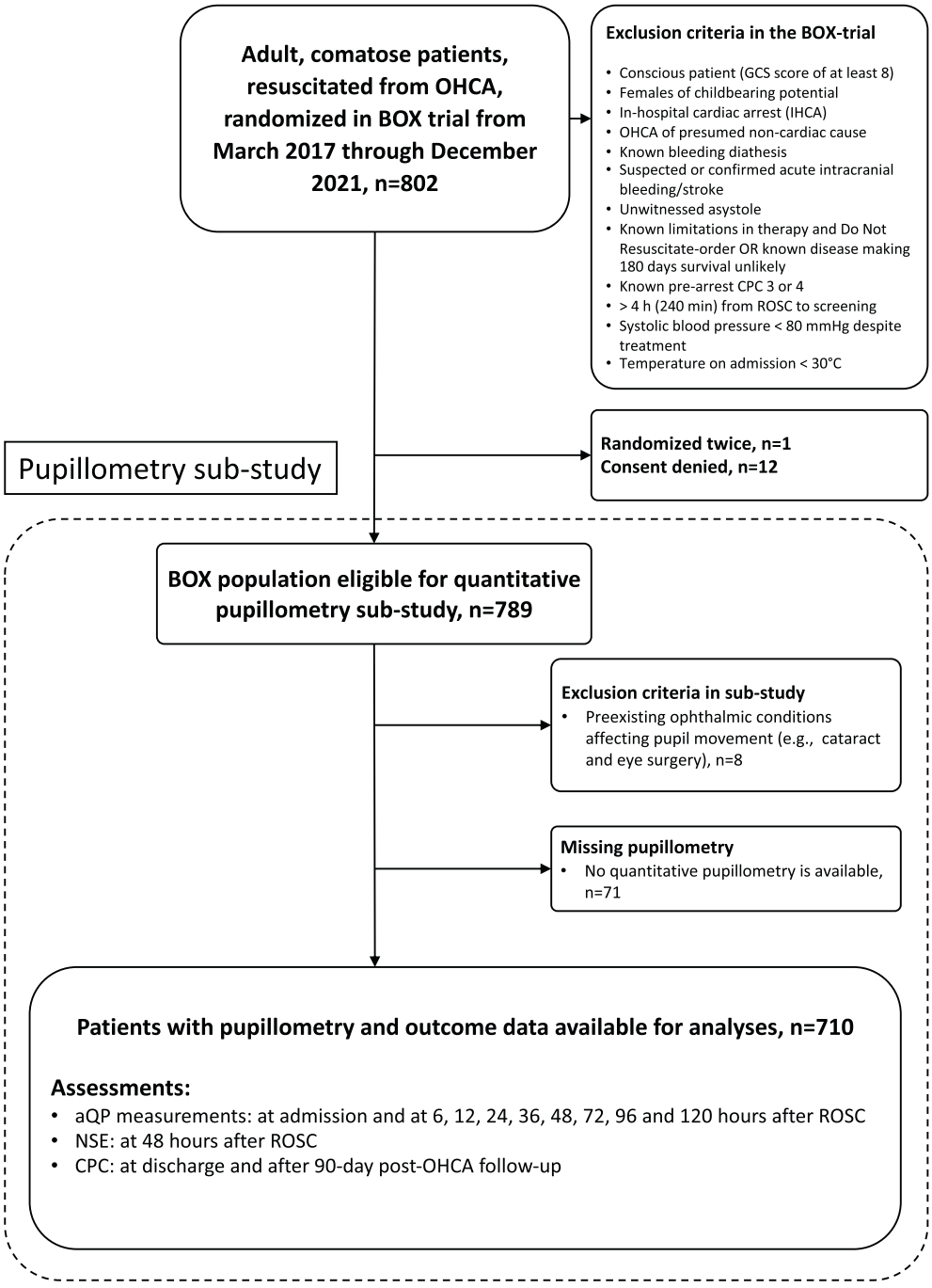

Fig. 1 – Consort diagram. Flowchart summarizing patient enrollment, exclusion, and assessments in the BOX trial pupillometry sub-study. OHCA: Out-of-hospital cardiac arrest; GCS: Glasgow coma scale; IHCA: In-hospital cardiac arrest; CPC: Cerebral performance category; ROSC: Return of spontaneous circulation; aQP: Automated quantitative pupillometry; NSE: Neuron-specific enolase.

An electroencephalogram will be performed when patients remain unawake 24 hours after tapering sedation and analgesics.[11] If still unconscious (Glasgow Motor Score $\leq$3) after 72 hours, neuroprognostication will be performed by externally blinded physicians based on clinical neurological examination (including evaluating consciousness and brain stem reflexes) and neurophysiology (Somatosensory Evoked Potentials or serial electroencephalograms). Subsequently, if patients have a bilateral absence of N20-peak on the median nerve or treatment-refractory status epilepticus (sequences [>10 s] of repetitive epileptiform discharges with an amplitude >50 μV and a medium frequency $\geq$1 Hz on electroencephalogram, constituting >50% of a 30-minute period in a patient with or without clinical manifestations) a decision of WLST can be made. However, if cerebral herniation leading to brain death is identified at any time or the patient has myoclonus status (generalized myoclonic convulsions in the face and extremities and continuous for a minimum of 30 min) combined with a bilateral absence of N20-peak on the median nerve is concluded, within the first 24 hours

Table 1 – Inclusion and exclusion criteria for BOX trial.

Inclusion criteria	Exclusion criteria
1. Age ≥18 years	1. Conscious patients (obeying verbal commands)
2. OHCA of presumed cardiac cause	2. Females of childbearing potential (unless a negative HCG test can rule out pregnancy within the inclusion window)
3. Sustained ROSC (defined as the time when chest compressions have not been required for 20 consecutive minutes and signs of circulation persist).	3. In-hospital cardiac arrest (IHCA)
4. Unconsciousness (GCS <8) (patients not able to obey verbal commands) after sustained ROSC	4. OHCA of presumed non-cardiac cause, e.g., after trauma or dissection/rupture of major artery OR cardiac arrest caused by initial hypoxia (i.e., drowning, suffocation, hanging)
	5. Known bleeding diathesis (medically induced coagulopathy (e.g., warfarin, NOAC, clopidogrel) does not exclude the patient)
	6. Suspected or confirmed acute intracranial bleeding
	7. Suspected or confirmed acute stroke
	8. Unwitnessed asystole
	9. Known limitations in therapy and Do Not Resuscitate-order
	10. Known disease making 180 days survival unlikely 11. Known pre-arrest CPC 3 or 4
	12. >4 hours (240 min) from ROSC to screening
	13. Systolic blood pressure <80 mmHg despite fluid loading/vasopressor and/or inotropic medication/intra-aortic balloon pump/axial flow device# 14. Temperature on admission <30 °C
	14. Temperature on admission <30 °C

OHCA: Out-of-hospital cardiac arrest; ROSC: Return of spontaneous circulation; GCS: Glasgow coma scale; HCG: Human chorionic gonadotropin; IHCA: In-hospital cardiac arrest; NOAC: novel oral anticoagulants; CPC: Cerebral performance category.

of admission, WLST can be instituted. Neither NSE nor quantitative pupillometry was part of the prognostication of this trial.

Quantitative pupillometry {11}

The pupillometer measures the human pupil sizing in the 1–9 mm interval, with an accuracy of 0.03 mm. With a calibrated light stimulation of fixed intensity (1000 Lux) and duration (3.2 s), it produces a rapid measure (0.05 mm limit) of pupil size and reactivity, expressed as several quantitative parameters, including qPLR (%). An internal algorithm produces the NPi, a scalar value from 0 to 5 (with 0.1 decimal precision), which is derived from the reactivity parameters and compared against the mean of a reference distribution of healthy subjects for the same variable.[18] A higher NPi is considered more reactive than a lower one. A score ≥3 (a brisk response) defines normal reactivity, an NPi <3 (a sluggish response) denotes abnormal reactivity, and an NPi value of 0 is considered non-reactive (an absent response).

All pupil reactivity parameters are obtained at every pupillary assessment; however, only qPLR and NPi are used in the analysis of this sub-study. To avoid falsely pessimistic predictions, the lowest value of the two eyes (if any difference is recorded) will be used when defining the threshold values associated with an unfavorable outcome, as done in similar studies.[6] However, when using threshold values in the clinical neuroprognostication, the higher value should be used as the representative to avoid over-decision of WLST.

Outcomes {12}

The primary outcome is the incidence of unfavorable neurological conditions, defined as Cerebral Performance Categories Scale 3–5, after 90 days from cardiac arrest.

The secondary outcomes comprise 1) death from any cause within 365 days, 2) median modified Rankin scale, 3) median Montreal Cognitive Assessment score after 90 days, and 4) median plasma NSE level at 48 hours.

Sample size {14}

The overall sample size is determined by the BOX trial (n = 789). The prevalence of unfavorable neurological outcomes in a previous study cohort (2015–2017) in the same cardiac ICUs[19] was 38%. When using sample size estimation for a diagnostic test for adequate specificity[20] with a specificity of 95% for both qPLR and NPi and a 95% confidence interval of 3%, a sample size of at least 534 patients is needed. This falls well within the sample size in the BOX trial.[13]

Blinding {17}

The results can be seen on the device monitor during the measurement procedure when obtaining the individual quantitative pupillometry measurements. However, all measurements are obtained by nursing staff only (with no involvement of doctors) and automatically stored in pupillometer SmartGuard until final analyses. As automated pupillometry was not a guideline-supported part of the prognostication when the trials were initiated, measurements are not included in clinical decision-making. Hence, the quantitative pupillometry measurements obtained during this sub-study will only be used for research analysis.

Data management {19}

Access to the electronic case report file requires a two-factor authentication process and is electronically logged. Collecting and maintaining data about potential and enrolled participants are handled with confidentiality, and all data from the trial are stored in a REDCap® database.[21]

Access is restricted to the selected medical staff with valid authorization from the Danish Health Care Authorities. In this sub-study,

quantitative pupillometry data collected and stored in the SmartGuard® device will only be accessed and handled by authorized investigators of the BOX trial.

Anonymized data for meta-analyses may be provided after the publication of the main manuscripts.

Statistical methods {20}

Statistical methods for primary and secondary outcomes {20a}

According to distribution, categorical variables will be presented as counts (percent of the total) and continuous variables as means (±SD) if parametric or medians (25th–75th percentile) if nonparametric.

Variables of baseline characteristics and pupillometry data will be compared between outcome groups and time points, and outcome data will be compared between groups of specific threshold values. Differences in continuous variables will be compared by the Kruskal-Wallis test for nonparametric data and the Student's t-test for parametric data. A chi-square test will be used when comparing group differences in categorical variables. To analyze the progression of mean values over days and differences across outcome groups, we will apply mixed models for repeated measures with the outcome groups, time points, and the interaction term of the outcome group with time as fixed effects.

Specificity, sensitivity, false positive rate, positive predictive value, negative predictive value, and Youden Index will be calculated for qPLR and NPi predicting the primary and secondary outcome.

The probability of time free from the primary outcome occurring in patients between groups of the specific threshold values will be depicted in Kaplan–Meier estimate plots, with differences calculated with the log-rank test.

The prediction of primary and secondary outcomes with qPLR and NPi will be estimated with univariable and multivariable regression models, adjusted for age, sex, time-to-ROSC, lactate level at admission, witnessed arrest, plasma NSE level at 48 hours, bystander cardiopulmonary resuscitation, shockable primary rhythm, and randomization site. The prognostic performance, at time points from admission to 72 hours after, will be evaluated by area under the receiver operating characteristics curves, with statistical differences calculated using the De Long method.[22]

All pupillometry and NSE will be measured in all patients (both awake and unawake patients) before 72 hours, and prognostic neurophysiology will only be performed in unawake patients after 72 hours. Hence, neurophysiology will not be included in the analysis. However, the significance of prediction by pupillometry will be analyzed against NSE and the other clinical predictors.

The parameters will be tested in combination with 48-hour plasma NSE >60 (±5 μg/L due to potential outliers) in unconscious patients at 72 hours to validate the threshold values of qPLR and NPi in the guideline-suggested prognostication strategy.

R Studio, version 1.2.5001, will be used for all analyses (RStudio Team [2020]. RStudio: Integrated Development for R. RStudio, PBC, Boston, MA; URL: http://www.rstudio.com/).

Methods for additional analyses (e.g., subgroup analyses) {20b}

Additional analyses will be performed for the following subgroups for interaction: Age (above/below median), sex (male/female), known hypertension at the time of the cardiac arrest, vasopressor at 48 hours, sedatives and opioids at 48 hours, site of inclusion, BOX interventions (targeted temperature management for 36 or 72 hours, high or low blood pressure, and liberal or restrictive oxygen).

Methods in analysis to handle protocol non adherence and any statistical methods to handle missing data {20c}

For patients missing quantitative pupillometry assessments, the pattern will be investigated by tabulating patients by missing vs. not missing and assessing the differences. Sensitivity analysis with multiple imputations by chained equations will be applied for data missing at random.

Plans to give access to the full protocol, participant-level data, and statistical code {31c}

The BOX trial steering group and a selected number of researchers appointed by the steering group will have access to the final trial dataset. Any data required to support the protocol can be supplied upon request and based on approval from relevant authorities. At the time of protocol publication, there are no plans to make patient-level data publicly available.

Ethics approval and consent to participate {24}

The BOX trial and this sub-study were approved by the Regional Ethics Committee at the Capital Region of Denmark.

The detailed procedure and requirement of written informed consent for participation in the BOX trial is described in the published trial protocol. Consent was obtained from relatives and a trial guardian as soon as possible and subsequently from patients if they regained consciousness and were cognitively preserved. No additional requirements were needed for the measurements of quantitative pupillometry evaluated in this sub-study.

The risks and discomforts for pupillometry were practically little to none, and manual pupillary assessment was part of the routine monitoring; thus, the excess risk associated with this sub-study was minimal.

Both tertiary heart centers, facilitating trial enrollment, have great experience conducting clinical trials of post-cardiac arrest patients. The trial was overseen by The Good Clinical Practice unit at the research department of the Cardiology Research Unit, ensuring the study was performed according to current agreements.

Dissemination plans {31a}

All positive or neutral results will be published in international peer-reviewed journals and presented at international congresses. Co-authorship will be granted in accordance with the Vancouver guidelines.

Discussion

The majority of in-hospital deaths for patients resuscitated from cardiac arrest are due to the active WLST when a hypoxic-ischemic brain injury is suspected.[3,23–25] Thus, thorough and accurate prognostication is essential to prevent inappropriate deaths in patients with the potential for recovery. However, the early identification of patients where meaningful recovery is unachievable due to irreversible neurological injury is likewise important to avoid prolonged futile treatment.

Besides being the recommended method for assessing pupillary reflexes, as part of the current 2021 prognostication strategy,[5] quantitative pupillometry is a bedside, easy-to-use tool with a high prognostic ability for determining unfavorable outcomes early after admission of unconscious cardiac arrest survivors. Compared to prognostic neurophysiology and brain imaging, pupillometry does

not require moving a potentially unstable patient from the ICU, using expensive advanced machinery or highly specialized personnel for performing or analyzing the measurements. However, even though cut-off values of qPLR and NPi have been proposed as predictors of unfavorable outcome in post-cardiac arrest prognostication, only completely absent pupillary reflexes are recommended in guidelines.[6,8,9] Therefore, specific threshold values must be validated for clinical neuroprognostication in large clinical trials.

The biomarker NSE is highly specific in predicting unfavorable neurological outcome,[8] and can be measured without highly specialized equipment or personnel. Further, NSE was previously validated combined with absent pupillary reflexes for the neuroprognostication strategy.[26] Thus, the combination of quantitative pupillometry thresholds with NSE could potentially be a very favorable match if validated in the 2021 prognostication strategy algorithm.

The BOX trial,[11] a randomized, controlled, multicenter clinical trial including 789 patients, will provide the clinical platform for this study. We will perform an external validation of proposed quantitative pupillometry thresholds, alone and combined with NSE, in the prognostication strategy algorithm, predicting unfavorable outcome in unconscious cardiac arrest survivors.

Conclusion

This study will be the most extensive prospective study investigating the predictive performance of automated quantitative pupillometry and validating thresholds for predicting outcome in unconscious cardiac arrest survivors. Hopefully, this will increase the evidence level and support the clinical use of automated quantitative pupillometry in clinical neuroprognostication.

CRediT authorship contribution statement

Benjamin Nyholm: Conceptualization, Methodology, Writing – review & editing, Visualization. **Johannes Grand:** . **Laust Emil Roelsgaard Obling:** . **Christian Hassager:** Conceptualization, Methodology. **Jacob Eifer Møller:** Conceptualization, Methodology. **Henrik Schmidt:** Conceptualization, Methodology. **Marwan H. Othman:** . **Daniel Kondziella:** . **Jesper Kjaergaard:** Conceptualization, Methodology, Writing – review & editing, Visualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: All co-authors were supported outside the submitted work. JEM's salary is supported by the University of Southern Denmark through an institutional research grant from Abiomed, and CH received grants from Lundbeck Foundation (R186-2015-2132), Novo Nordisk Foundation (NNF20OC0064043), and The Danish Heart Foundation (21-R151-A10091-22200). JG's salary is supported by a research grant from the Danish Cardiovascular Academy, which is funded by the Novo Nordisk Foundation (NNF20SA0067242) and The Danish Heart Foundation.

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