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Prognostic value of automated pupillometry: an unselected cohort from a cardiac intensive care unit

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Abstract

Background: Patients admitted to a cardiac intensive care unit are often unconscious with uncertain prognosis. Automated infrared pupillometry for neurological assessment in the intensive care unit may provide early prognostic information. This study aimed to determine the prognostic value of automated pupillometry in different subgroups of patients in a cardiac intensive care unit with 30-day mortality as the primary endpoint and neurological outcome as the secondary endpoint.

Methods: A total of 221 comatose patients were divided into three groups: out-of-hospital cardiac arrest, in-hospital cardiac arrest and others (i.e. patients with cardiac diagnoses other than cardiac arrest). Automated pupillometry was serially performed until discharge or death and pupil measurements were analysed using the neurological pupil index algorithm. We applied receiver operating characteristic curves in univariable and multivariable logistic regression models and a calculated Youden index identified neurological pupil index cut-off values at different specificities.

Results: In out-of-hospital cardiac arrest patients higher neurological pupil index values were independently associated with lower 30-day mortality. The univariable model for 30-day mortality had an area under the curve of 0.87 and the multivariable model achieved an area under the curve of 0.94. The Youden index identified a neurological pupil index cut-off in out-of-hospital cardiac arrest patients of 2.40 for a specificity of 100%. For patients with in-hospital cardiac arrest and other cardiac diagnoses, we found no association between neurological pupil index values and 30-day mortality, and the univariable models showed poor predictive values.

Conclusion: Automated infrared pupillometry has promising predictive value after out-of-hospital cardiac arrest, but poor predictive value in patients with in-hospital cardiac arrest or cardiac diagnoses unrelated to cardiac arrest. Our data suggest a possible neurological pupil index cut-off of 2.40 for poor outcome in out-of-hospital cardiac arrest patients.

Keywords

Intensive care unit, acute cardiac care, out-of-hospital cardiac arrest, pupillometry, prognostication, prediction

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Introduction

Many patients admitted to a cardiac intensive care unit (ICU) experience cardiac arrest (CA), including out-of-hospital cardiac arrest (OHCA), or episodes of cerebral hypoperfusion or hypoxia because of their underlying condition. These conditions often lead to anoxic brain injury and coma and early prognostication of these patients remains difficult.[1–4] Approximately 50% of OHCA patients die before hospital discharge following severe anoxic brain injury, and survivors often have neurological deficits.[5–7]

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OHCA patients are different in baseline characteristics and outcome compared to patients with in-hospital cardiac arrest (IHCA) and other cardiac diagnoses.[8,9]

Electroencephalography (EEG) and somatosensory evoked potentials (SSEPs) are used for neurological prognostication in the ICU, but there is an unmet demand for simple, fast and non-invasive tools in the critical care setting.[10–12] Furthermore, assessment of pupil size and pupillary reactivity are believed to be associated with outcome.[13–15] Pupil measurements are currently usually performed manually by physicians and nurses, and each measurement is evaluated and described with varying consistency.[16,17] To overcome interobserver variability, handheld automated video-based quantitative pupillometry has become available at the bedside. With this technology, new parameters have emerged, among which is the neurological pupil index (NPi). This index was developed by NeurOptics (Laguna Hills, CA, USA), and allows objective and quantifiable assessment of the pupillary reflex in comatose patients.[15,18–20] However, there is a lack of evidence concerning the prognostic value of the NPi in critical care, and studies are needed to clarify if the NPi provides reliable prognostic information in the acute phase in the ICU.

Therefore, the primary aim of this report was to investigate the independent predictive value of automated infrared pupillary measurements on 30-day mortality and neurological outcome at hospital discharge in unselected patients admitted to a cardiac ICU.

Methods

The study was a retrospective, observational study including comatose patients admitted to the cardiac ICU at Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. Comatose patients admitted from April 2015 to June 2017 were assessed with the NPi-200 pupillometer from the start of admission until they regained consciousness, were discharged or died. Pupil measurements were performed as part of daily clinical practice and data were handled anonymised according to the data protection law. The ethics committee of the capital region of Denmark approved the study concept and the hospital administration waived the need for written consent from patients included as part of a quality assurance effort.

Study population

We performed pupil measurements in 248 unconscious patients. Data from 27 patients were excluded from further analysis due to erroneous social security numbers or inclusion in an ongoing clinical trial. A total of 221 patients were included in the present study. Patients experienced OHCA (n=135, 62%), IHCA (n=28, 12%) or other cardiac diagnoses (total n=58, 26%), with the latter group consisting primarily of patients with cardiogenic shock (n=25), ischaemic heart disease (n=14), valvulopathy (n=10) and arrhythmias (n=5). Automated pupillometry was performed by the physician and nursing staff, with at least one successful measurement during the first 24 hours of admission. The measurements were performed in unconscious or sedated patients, as prognostication is not relevant in awake patients. Patients had serial daily pupil measurements performed during admission depending on their clinical status.

Treatment of OHCA

All patients were treated in accordance with international guidelines and received standardised intensive care throughout the admission.

OHCA patients were primarily sedated with propofol and fentanyl to a Richmond agitation sedation scale of 4 or less and received targeted temperature management at 36°C. After 24 hours, patients were re-warmed (maximum 0.5°C per hour). Sedation was tapered at 37°C, and patients were weaned from the ventilator, if possible. Mean arterial pressure was maintained at over 65 mmHg with norepinephrine and dopamine as the primary vasopressors used.

Withdrawal of life-sustaining therapy (WLST) was decided at the earliest 3 days after sedation termination in accordance with international guidelines applying serial EEG, SSEPs and clinical examination.[21] The NPi measures or other quantitative measures of pupillary function were available in the patient chart but were not used for prognostication.

NPi measurements

Pupil measurements were made using the NPi-200 pupillometer from NeurOptics, a hand-held portable device which assesses pupil dynamics in patients.

A pupil measurement begins with the device placed at a fixed distance from the eye and the pupil targeted on an LCD screen. The distance is ensured by application of an individual 'chin guard' (SmartGuard) prior to each measurement. A fixed intensity burst of light with a duration of 0.8 seconds and a pulse intensity of 121 μW induces a pupillary reflex, and images are stored with more than 30 frames taken per second for 3.2 seconds, with numeric measurements deriving from these images. The pupillometer is calibrated by the manufacturer and re-calibration is not required.

Each pupil measurement provides the examiner with minimum and maximum pupil size, constriction percentage, constriction velocity, latency and NPi value. The NPi algorithm is derived from a normative model with pupil measurements made on healthy volunteers.[15] A pupil measurement is graded on the NPi scale from 0 to 5 with one decimal point. A NPi score below 3 is considered abnormal

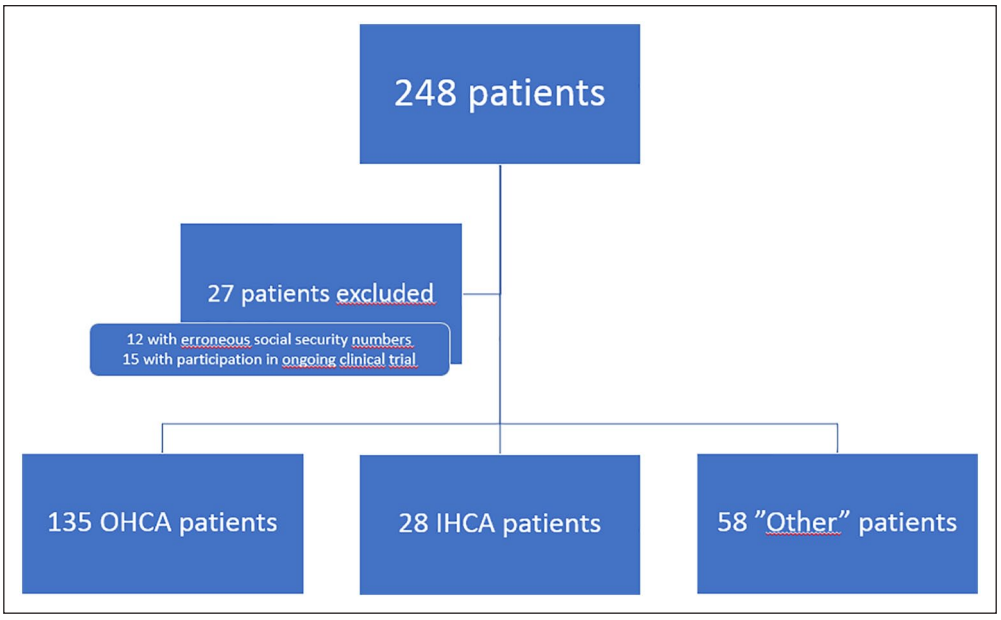

Figure 1. Study flowchart.

(a sluggish response) and a score greater than 3 is considered normal (a brisk response). The lower the NPi value, the more sluggish is the pupillary light reflex and vice versa. Hence, the NPi algorithm helps the examiner to track the pupillary response of each single patient over time in an objective and quantifiable manner.

Outcomes

The primary outcome of the study was 30-day mortality. The secondary outcome was neurological outcome at discharge from hospital assessed by the cerebral performance category (CPC)[22,23] scale. Patients were dichotomised into 'good neurological outcome' with CPC scores of 1–2 and 'poor neurological outcome' with CPC scores of 3–5. A CPC score of 5 indicates death. The individual CPC score was evaluated through chart review of patient journals.

Statistical analysis

We sought to analyse differences in baseline characteristics and clinical parameters between the three patient groups, 'OHCA', 'IHCA' and 'other'. The chi-square test was used for categorical data, the one-way analysis of variance (ANOVA) for continuous data and the Kruskal–Wallis test for non-parametric ANOVA tests between the three groups. We used the R package 'TableOne'[24] for these analyses.

Furthermore, we used the R packages 'pROC'[25] and 'Deducer'[26] to produce receiver operating characteristic (ROC) curves, and area under the curve (AUC) values were used for analysing the predictive value of NPi in the three groups in univariable and multivariable models. The multivariable models were adjusted for age, sex, ST-segment elevation myocardial infarction, shockable primary rhythm and time to return of spontaneous circulation that all are factors known to influence mortality in OHCA. Odds ratios (ORs), including 95% confidence intervals (CIs), were extracted from these models per 1.0 increase in NPi value. A Youden index[27,28] for the univariable model predicting 30-day mortality was made. We chose to optimise the Youden index for a specificity of 90–100% (i.e. false-positive rate of 0–10%) in increments of 1%. Positive predictive values (PPVs) and negative predictive values (NPVs) were calculated.

Finally, a sensitivity analysis was performed by identifying the lowest NPi on either eye and the lowest mean NPi value (calculated from the two lowest measures from each eye for each patient). This statistical analysis was applied for all three patient groups.

A P value below 0.05 was considered statistically significant, CIs are presented for outcome data. Adjustment for multiple testing using Bonferroni correction was performed as necessary.

R software, 3.2.2, was used for data analyses.

Results

A total of 221 patients were included in the study and divided into three groups (OHCA, IHCA, Other) (Figure 1). Baseline characteristics are shown in Table 1. Available NPi measurements were performed a median of 4.8 days after CA (interquartile range (IQR) 5.1 days) and the median number of pupil measurements performed was six (IQR nine). The median time from arrest to the minimal mean NPi was 3.2 days (IQR 4.4 days). In patients dying, the median time from the minimal mean NPi performed to

Table 1. Baseline characteristics.

	OHCA	IHCA	Other	*P* value
	n=135	*n*=28	*n*=58	
Demographics				
Male sex, n (%)	109 (80.7)	18 (64.3)	41 (70.7)	0.19
Age (mean±SD)	60.68 (11.71)	64.61 (12.37)	68.48 (10.18)	<0.001
Clinical characteristics at admission				
Serum lactate (mean±SD)	5.71 (4.83)	6.80 (0.42)	2.64 (1.06)	0.34
Serum blood glucose (mean±SD)	12.27 (5.84)	12.45 (5.81)	10.01 (4.72)	0.28
Serum creatinine (median (IQR))	106 (40)	147 (91)	125 (65)	<0.04
Serum pH (mean±SD)	7.22 (0.13)	7.10 (NA)	7.35 (0.09)	NA
LVEF (mean±SD)	36.49 (13.81)	33.25 (18.44)	24.86 (15.28)	<0.001
GCS (median (IQR))	3 (0)	3 (3)	4 (12)	<0.001
Cardiogenic shock*	43 (31.9)	14 (50.0)	24 (41.4)	0.13
ST-segment elevation myocardial infarction	57 (42.2)	14 (50.0)	12 (20.7)	0.006
Medical history, *n* (%)				
Arterial hypertension	69 (51.1)	13 (46.4)	35 (60.3)	0.50
Hypercholesterolemia	38 (28.1)	9 (32.1)	23 (39.7)	0.63
Diabetes mellitus type 1	1 (0.7)	0 (0.0)	1 (1.7)	0.87
Diabetes mellitus type 2	18 (13.3)	5 (17.9)	14 (24.1)	0.48
Active malignancy	9 (6.7)	3 (10.7)	6 (10.3)	0.82
Asthma or COPD	13 (9.6)	5 (17.9)	12 (20.7)	0.21
Nefropathy	8 (5.9)	5 (17.9)	4 (6.9)	0.22
Peripheral artery disease	9 (6.7)	3 (10.7)	7 (12.1)	0.72
Smoking**	75 (55.6)	12 (42.9)	35 (60.3)	0.10
Alcohol abuse**	16 (11.9)	4 (14.3)	5 (8.6)	0.92
Drug abuse**	2 (1.5)	1 (3.6)	1 (1.7)	0.60
Congestive heart failure	13 (9.6)	1 (3.6)	12 (20.7)	0.11
Atrial fibrillation	15 (11.1)	6 (21.4)	12 (20.7)	0.39
Ischaemic heart disease	22 (16.3)	5 (17.9)	11 (19.0)	0.93
Previous TIA or stroke	10 (7.4)	4 (14.3)	6 (10.3)	0.68
Previous acute myocardial infarction	12 (8.9)	5 (17.9)	11 (19.0)	0.22
Previous percutaneous coronary intervention	9 (6.7)	4 (14.3)	9 (15.5)	0.33
Previous coronary artery bypass grafting	6 (4.4)	1 (3.6)	1 (1.7)	0.82
Previous valve surgery	4 (3.0)	1 (3.6)	2 (3.4)	0.96
Implantable cardioverter-defibrillator	2 (1.5)	0 (0.0)	2 (3.4)	0.69
Pacemaker	3 (2.2)	0 (0.0)	1 (1.7)	0.89
OHCA characteristics				
TTM at admission	113 (83.7)	4 (14.3)	–	<0.001
Shockable primary rhythm	117 (86.7)	14 (50.0)	–	<0.001
Witnessed cardiac arrest	119 (88.1)	26 (92.9)	–	<0.001
Location of cardiac arrest (home)	67 (49.6)	–	–	–
Bystander CPR	106 (78.5)	–	–	–
AED used for resuscitation	20 (14.8)	–	–	–
Time to treatment, min, median (IQR)				
Time to basic life support	1 (1)	–	–	–
Time to advanced life support	5 (4)	1 (1)	–	<0.001
Time to return of spontaneuos circulation	15 (15)	10 (10)	–	0.008

* Cardiogenic shock at any time point during admission.
** Former or current user.
OHCA: out-of-hospital cardiac arrest; IHCA: in-hospital cardiac arrest; CPR: cardiopulmonary resuscitation; AED: automatic external defibrillator; IQR: interquartile range; LVEF: left ventricular ejection fraction; GCS: Glasgow coma scale; COPD: chronic obstructive pulmonary disease; TIA: transient ischaemic attack; TTM: targeted temperature management.

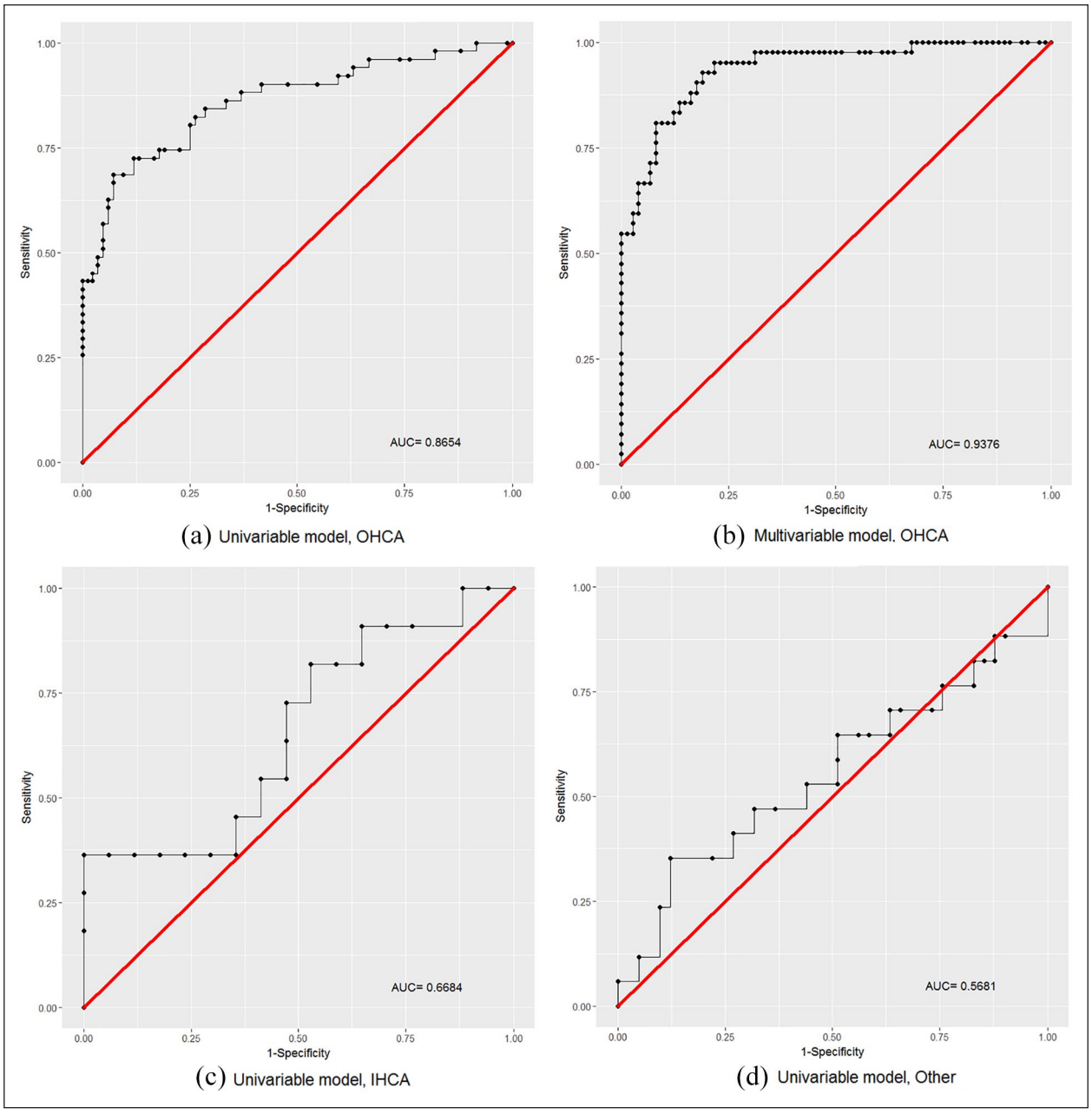

Figure 2. Predictive value of the neurological pupil index for 30-day mortality.

death was 4.7 days (IQR 7.8 days) with less than 10% in this group having their minimal mean NPi measured less than 8 hours before dying.

Mortality

Information about 30-day mortality was available in all patients in the three patient groups.

OHCA. A total of 135 patients experienced OHCA. Fifty-one (38%) patients died within 30 days. The median NPi values were 4.10 (IQR 0.60) in survivors compared to 2.80 (IQR 3.43) in non-survivors ($P<0.0001$). Higher NPi values were independently associated with a lower 30-day mortality (OR 0.15, 95% CI 0.06–0.29, $P<0.0001$), and the univariable model had an AUC of 0.87 (Figure 2(a)), with a maximal AUC area cut-off level for NPi being 3.30 (sensitivity 69% and specificity 93%, PPV 85% and NPV 83%). In the multivariable analysis adjusting for risk factors, higher NPi values remained significantly associated with 30-day mortality (OR 0.05, 95% CI 0.01–0.18, $P<0.0001$) (Table 2), and the multivariable model achieved an AUC of 0.94 (Figure 2(b)).

Table 2. Youden index.

	NPi threshold	Sensitivity (%)	PPV (%)	NPV (%)	Youden index
Specificity 90 (%)	3.40	69	81	83	0.59
Specificity 91 (%)	–	–	–	–	–
Specificity 92 (%)	–	–	–	–	–
Specificity 93 (%)	3.30	69	85	83	0.62
Specificity 94 (%)	3.25	63	86	81	0.57
Specificity 95 (%)	3.10	57	88	78	0.52
Specificity 96 (%)	2.80	49	89	76	0.45
Specificity 97 (%)	2.70	47	89	75	0.44
Specificity 98 (%)	2.60	43	92	74	0.41
Specificity 99 (%)	2.45	43	96	74	0.42
Specificity 100 (%)	2.40	43	100	74	0.43

NPi: neurological pupil index; PPV: positive predictive value; NPV: negative predictive value.

IHCA. Twenty-eight patients experienced IHCA. Twelve (44%) patients died within 30 days. The median NPi values were 3.85 (IQR 1.44) in survivors compared to 3.40 (IQR 2.90) in non-survivors (P=0.14). Higher NPi values were not independently associated with a lower 30-day mortality (OR 0.53, 95% CI 0.24–0.98, P=0.07), and the univariable model had a poor AUC of 0.67 (Figure 2(c)).

Other. Fifty-eight patients had diagnoses other than CA, with a total of 19 (28%) patients dying within 30 days. The median NPi values were 4.20 (IQR 0.85) in survivors compared to 4.25 (IQR 0.95) in non-survivors (P=0.42). Higher NPi values were not independently associated with a lower 30-day mortality (OR 0.98, 95% CI 0.65–1.59, P=0.95), and the univariable model had a very poor AUC of 0.57 (Figure 2(d)).

Neurological outcome

CPC scores at discharge were obtained through chart review and were available in 127 OHCA patients, 27 IHCA patients and 58 patients without CA.

OHCA. Seventy (55%) patients had a good neurological outcome, i.e. CPC 1–2, and 57 (45%) patients had a poor neurological outcome, i.e. CPC 3–5, with only six (5%) patients surviving with severe neurological sequelae, i.e. CPC 3–4. Higher NPi values were individually associated with good neurological outcome (OR 0.11, 95% CI 0.04–0.26, $P<0.0001$) and the univariable model had an AUC of 0.86. In the multivariable model higher NPi values remained significantly associated with neurological outcome (OR 0.012, 95% CI 0.001–0.08, $P<0.0001$), and the model achieved an AUC of 0.96 (0.83 without NPi values).

IHCA. Ten (37%) patients had a good neurological outcome and 17 (63%) had a poor neurological outcome, with four (15%) patients surviving with severe neurological disorders. No association was found between higher NPi values and good neurological outcome in the IHCA group (OR 0.49, 95% CI 0.17–1.01, P=0.15), and the univariable model had an AUC of 0.66.

Other. Thirty (52%) patients had a good neurological outcome and 28 (48%) had a poor neurological outcome, with nine (16%) patients surviving with severe neurological disorders. No association was found between higher NPi values and good neurological outcome (OR 0.80, 95% CI 0.50–1.18, P=0.32), and the univariable model had a very poor AUC of 0.58.

Predictive value

NPi measurements had a good predictive value for mortality in OHCA patients, while the predictive value was poor in IHCA patients and cardiac patients without CA.

To demonstrate the predictive accuracy of NPi measurements for mortality in OHCA patients at specificities of 90% or greater, we calculated a Youden index (Table 2). The Youden index, defined by sensitivity + specificity − 100%, is used to summarise ROC curves and identify the optimal threshold/cut-off for a predictive variable, in this case the NPi, at different sensitivities and specificities along with the calculated PPV and NPV. The NPi cut-offs at the highest specificities found were 2.40 (specificity 100%, Youden 0.43), 2.45 (specificity 99%, Youden 0.42), 2.60 (specificity 98%, Youden 0.41), 2.70 (specificity 97%, Youden 0.44), 2.80 (specificity 96%, Youden 0.45) and 3.10 (specificity 95%, Youden 0.52). Due to the relatively small sample size of our cohort and the small proportion of patients with low NPi values, it was impossible to obtain threshold values at every specificity between 0.90 and 1.00.

Sensitivity analysis

We found no statistically significant difference when using the lowest NPi measurement made on one eye (AUC 0.86) and the calculated lowest mean of both eyes (AUC 0.86) in

the univariable model for OHCA patients compared with the main model (AUC 0.87). For IHCA and 'other' patients the results remained unchanged.

Adjustment for multiple testing

All significant results of the primary analyses, as shown above, remained statistically significant following Bonferroni correction (i.e. $P<0.05$).

Discussion

The present study shows that automated pupillometry and the NPi have good predictive value for 30-day mortality in OHCA patients in the cardiac ICU. In contrast, in IHCA patients and patients with other cardiac diagnoses, the pupil measurements do not seem to have predictive value for 30-day mortality. Through calculation of a Youden index, we identified a relevant cut-off for NPi in OHCA patients of 2.40. Further studies should aim to validate this cut-off so that automated pupillometry and NPi can be implemented as an accessible prognostic tool in the future.

Assessment of pupillary status is important in ICU patients and influences therapeutic management and prognosis.[13,15] The pupillary light reflex and anisocoria are of interest when examining critically ill patients at risk of developing neurological damage, and need to be monitored continuously.[29] CA causes primary non-reversible anoxic damage to the brain during the first few minutes of arrest and secondary possibly reversible damage during reperfusion of the brain after resuscitation.[30] Increased intracranial pressure and incarceration with affected pupillary light reflexes can be seen in OHCA patients,[31] but often a return of the pupillary light reflex in resuscitated OHCA patients is found. This has been proved to be a prognostic indicator of good neurological outcome,[32] albeit the brain stem reflexes are often present in patients with significant hypoxic brain injury. However, manual pupil measurements using a handheld flashlight is subject to significant inter-examiner variability.[16]

Automated pupillometry, including the NPi algorithm, has been introduced in the critical care setting to quantify and plot changes in pupil measurements through comparison with a normative pupil response.[14] In this study we performed a retrospective analysis of the predictive value of NPi measurements in patients admitted to the cardiac ICU of a large tertiary centre during a period of 2 years. We found that NPi measurements had a good predictive value of 30-day mortality and neurological outcome (CPC) for OHCA patients, but not for IHCA patients and cardiac patients without CA. A possible explanation of this finding could be that OHCA patients primarily die from severe neurological injury leading to WLST, and thereby have affected NPi values, whereas IHCA patients and patients with other diagnoses than cardiac arrest also die from non-neurological complications, for example cardiogenic shock and sepsis not likely to affect the pupillary light reflex.[30,33,34]

In accordance with previous studies made in OHCA patients we found that automated pupillometry has a high predictive value, complementing clinical tools such as EEG, SSEPs and neuron-specific enolase.[35,36] One major advantage of pupillometry is the simplicity of the procedure. In contrast to the aforementioned techniques, automated pupillometry is a fast and non-invasive manoeuvre that can be performed by any staff member with a consistent high inter-device and interrater reliability, which avoids the subjectivity of traditional pupil examination.[37] It is therefore likely that automated pupillometry will increasingly be implemented in critical care procedures in the future.

We chose to optimise the Youden index for a specificity of 90–100%, because the clinical perspective of any prognostic tool used in critically ill patients is only relevant at high specificities. Thus for clinicians to consider WLST the tests used for prognostication must have very high specificities to avoid WLST in patients with plausible chances of survival.[34]

Finally, in the present cohort the number of patients alive at follow-up with a poor neurological outcome was low, and therefore the results of the analyses of NPi and survival with good neurological outcome are virtually similar. Therefore, the data on neurological outcome are summarised in the results section. We emphasise that predicting neurological outcome in OHCA patients is highly associated and correlates to the prediction of mortality, but we still believe that our results help strengthen the possible role of automated pupillometry as a forceful predictive tool after OHCA.

Limitations

As this was a retrospective analysis and pupil measurements were applied in different patient groups as part of different treatment protocols, measurements were not made on all patients admitted to the cardiac ICU or at similar time points, leading to a potential selection bias. Furthermore, the number of included IHCA patients was limited to 28, and the lack of predictive value in this patient group may be related to the small sample size. The retrospective nature of the study also implicated that precise information about levels of sedation were not always available. However, although recent studies have shown that some pupillary function in highly sedated patients may be altered, the pupillary light reflex remains intact and therefore useful even in sedated patients.[38–41] Yet neither fentanyl nor propofol, the drugs of choice at our facility, significantly alter the pupillary light reflex when used in above-minimum alveolar concentration anaesthetic levels.[42] Besides this, the NPi algorithm is reportedly calculated through pupillary assessments not

involving pupil size, and may therefore be relatively less biased by this factor.[42] The chin guards were collected when feasible; hence the present series constitutes a convenience sample of cardiac ICU patients. We decided to use the NPi mean value of the right and the left eye separately and did not assess anisocoria in this study. However, our sensitivity analysis showed no difference in results when applying the lowest NPi measurement made on one eye or the calculated lowest mean of both eyes.

Conclusion

Automated infrared pupillometry may be a useful tool in the acute critical care setting. Our data suggest that an NPi value below 2.40 is a strong predictor of poor outcome in OHCA patients. If this finding can be confirmed in other OHCA cohorts, automated pupillometry and the NPi may be useful in the multimodality approach to prognostication in cardiac patients who are unconscious after OHCA.

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Conflict of interest

The authors declare that there is no conflict of interest.

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