


## RESEARCH ARTICLE

# Quantitative pupillometry in comatose out-of-hospital cardiac arrest patients: A post-hoc analysis of the TTH48 trial

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## Funding information

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## Abstract

**Background:** Quantitative pupillometry is an objective method to examine pupil reaction and subsequently grade the response on a neurological pupil index (NPI) scale from 0 to 5. The aim of the present sub-study was to explore the long-term prognostic value of NPI in comatose out-of-hospital cardiac arrest patients undergoing targeted temperature management (TTM).

**Methods:** This planned sub-study of the “Targeted temperature management for 48 versus 24 h and neurological outcome after out-of-hospital cardiac arrest: A randomized clinical trial.” NPI was assessed from admission and throughout day 3 and linked to the Cerebral Performance Categories score at 6 months. We compared the prognostic performance of NPI in 65 patients randomized to a target temperature of  $33 \pm 1^\circ\text{C}$  for 24 or 48 h.

**Results:** The NPI values were not different between TTM groups ( $p > .05$ ). When data were pooled, NPI was strongly associated with neurological outcome at day 1 with a mean NPI of 3.6 (95% CI 3.4–3.8) versus NPI 3.9 (3.6–4.1) in the poor versus good outcome group, respectively ( $p < .01$ ). At day 2, NPI values were 3.6 (3.1–4.0) and 4.1 (3.9–4.2) ( $p = .01$ ) and at day 3, the values were 3.3 (2.6–4.0) and 4.3 (4.1–4.6), respectively ( $p < .01$ ). The prognostic ability of NPI, defined by area under the receiver operating characteristic curve was best at day three.

**Conclusion:** Quantitative pupillometry measured by NPI was not different in the two TTM groups, but overall, significantly associated with good and poor neurological outcomes at 6 months. NPI has a promising diagnostic accuracy, but larger studies are warranted.

## KEYWORDS

cardiac arrest, neurological pupil index, pupillometry

## Editorial Comment

Assessment for neurological prognosis using pupillometry in post-cardiac arrest patients was explored in a secondary analysis of a trial cohort for post-arrest temperature management.

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Different thresholds for this test result during the first 3 post-arrest days were analyzed for screening accuracy to predict later wake up or not.

## 1 | INTRODUCTION

Prognostication in the intensive care unit (ICU) of comatose patients resuscitated after out-of-hospital cardiac arrest (OHCA) is challenging and resource-demanding. Withdrawal of life sustaining therapy (WLST) is the most frequent cause of death in these patients.<sup>1</sup> This emphasizes the crucial importance of appropriate neurological prognostication. Accordingly, international guidelines now recommend a multi-modal approach.<sup>2</sup>

In the multi-modal prognostication model, pupillary assessment is a part of the clinical neurological examination. Former studies have compared standard pupillary light reactivity (PLR) with quantitative measurement of PLR using a handheld device such as NeuroOptics NPI100™ and found quantitative pupillometry using the Neurological Pupil Index (NPI) to be well-correlated with good versus poor outcomes.<sup>3,4</sup> The ERC 2021 updated guidelines on post-resuscitation care thus recommend use of automated pupillometry in the ICU.<sup>5</sup> Automated pupillometry may become an essential and easily available part of ICU neuro-prognostication. However, data on use of pupillometry and comparison with other prognostic parameters such as EEG patterns, biomarkers like neuron specific enolase (NSE) and somatosensory evoked potentials (SSEP) are scarce.<sup>6,7</sup>

The aim of the present study was to compare the predictive properties of the NPI in patients resuscitated from OHCA during TTM at 33°C for 48 or 24 h in the ICU (TTM48 versus TTM24), as well as evaluate the overall properties of NPI in this patient group.

## 2 | METHODS

### 2.1 | Study design

The present study is a planned sub-study of the “Targeted temperature management for 48 versus 24 h and neurological outcome after out-of-hospital cardiac arrest: A randomized clinical trial (TTH48 trial).”<sup>8</sup> In brief, the TTH48 trial was an assessor-blinded, randomized investigator-initiated, pragmatic clinical trial, where comatose OHCA patients between 18 and 80 years with a presumed cardiac origin and time to initiation of cooling was less than 4 h, were randomized to TTM at 33 ± 1°C for 24 or 48 h. Both surface or intravascular cooling systems were used, and patients were sedated with infusion of propofol/midazolam and remifentanyl/fentanyl until normothermia was reached. Maximum rewarming rate was 0.5°C/h. Further information, including exclusion criteria, is available in the protocol paper.<sup>9</sup> The study was approved by the Danish Data Protection Agency, the Central Denmark Region Committee on Health Research Ethics (number 20110022), and the Regional Ethics Committee of Western Norway (ref 2013/1486).

### 2.2 | Patients and pupillometry measurements

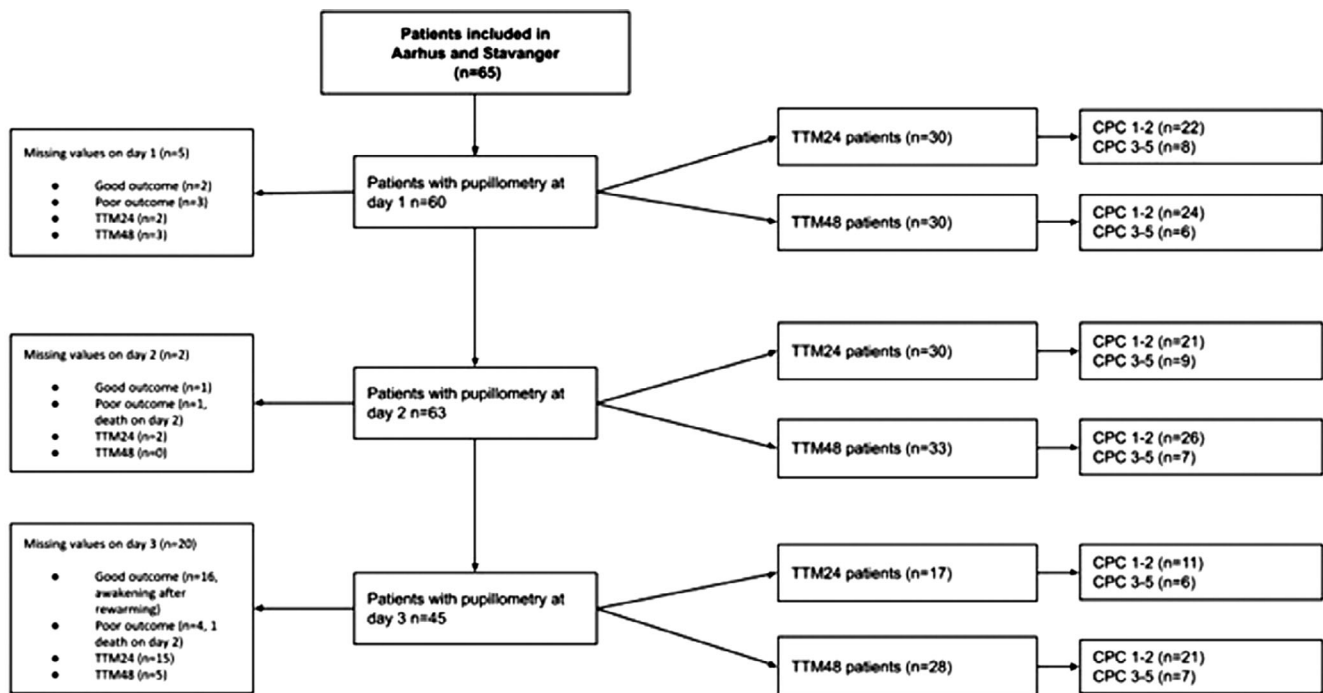
Pupillary assessment was made using the handheld NeuroOptics® NPI100™ (NeuroOptics, California). In this sub-study, two out of 10 centers were able to implement the NeuroOptic device and collect data on pupillometry. 65 patients were included from May 1, 2015 to the May 30, 2016 in the ICUs at Aarhus University Hospital, Denmark, and Stavanger University Hospital, Norway (Figure 1, Table 1). The device measured PLR using a video screen and infrared light. The NPI was automatically generated using the following parameters: Maximum size of pupil, minimum size of pupil, percent change in pupil size, latency from light stimulation to movement of pupil, average and maximum constriction velocity, and average dilation velocity.<sup>10</sup> The pupil measurements were compared with a normative dataset of pupil reaction to light and subsequently graded on the NPI scale with a value from 0 to 5 with 0.1 decimal precision. NPI >3 indicates normal pupil reaction and as an example, a NPI of 4.4 is considered more reactive than a NPI of 3.4. NPI < 3 suggests abnormal pupil reaction and as an example, a NPI of 1.2 is considered more abnormal than 1.8.<sup>3</sup> A trained ICU nurse performed the NPI measurements once every 8 h from admission until 72 h after reaching the target temperature or awakening of the patient. We chose the lowest NPI recorded at day 1 (0–24 h after reaching the target temperature), day 2 (24–48 h), and day 3 (48–72 h) for analysis of outcome prediction.

### 2.3 | Outcome assessments

The primary outcome measure was the NPI recordings in patients with good or poor neurological outcome assessed by cerebral performance category score (CPC) 6 months post-cardiac arrest. The CPC score was dichotomized, meaning that a CPC score of 1 and 2 was considered a good neurological outcome, and a CPC 3–5 was considered a poor outcome.<sup>11</sup> A CPC of 1 was no neurological deficit, CPC 2 was mild to moderate dysfunction, while CPC 3 was severe dysfunction requiring help for activities of daily living, CPC 4 was coma, and CPC 5 death.

### 2.4 | Statistical analysis

Baseline characteristics are presented as mean with 95% confidence interval for continuous data and as counts and percentages for categorical data. The data for grouped comparison and ROC curve analysis was checked for normal distribution using Q-Q plots before nonparametric analysis was used. Specificities and sensitivities were calculated using nonparametric ROC analysis and reported as area under the curve (AUC) with a 95% CI. Comparison of ROC curves in the two



**FIGURE 1** Flowchart of patients with out-of-hospital cardiac arrest where pupillometry was performed. TTM24 = Target temperature management for 24 h and TTM48 = Target temperature management for 48 h

**TABLE 1** Baseline characteristics of study participants

	Pooled data (n)	%	TTM24 (n)	%	TTM48 (n)	%
Patients	65	100%	32	49%	33	51%
Age, years (mean and CI)	58 (55–61)		59 (54–64)		57 (52–62)	
Male	57	88%	27	84%	30	91%
Bystander CPR performed	59	91%	29	91%	30	91%
Primary non-shockable rhythm	9	14%	7	22%	2	6%
Time to ROSC, minutes (mean and CI)	22 (19–25)		22 (18–27)		22 (18–26)	
PCI performed	31	48%	16	50%	15	45%
TnT at arrival (µg/L)	230 (152–308)		293 (129–458)		179 (119–238)	
Previous AMI	11	17%	5	16%	6	18%
Diabetes mellitus	11	17%	7	22%	4	12%
Renal failure	4	6%	1	3%	3	9%
Hypercholesterolaemia	9	14%	4	13%	5	15%
Known IHD	8	12%	3	9%	5	15%
Hypertension	17	26%	5	16%	12	36%
Alcohol abuse	2	3%	0	0%	2	6%
Time from CA to TT (mean and CI)	337 (306–369)		348 (302–395)		327 (282–371)	
SAPS II (median and IQR)	54 (49–58)		54 (45–63)		53 (48–59)	
Neurological outcome (CPC)						
Good outcome	48	74%	22	69%	26	79%
Poor outcome	17	26%	10	31%	7	21%

study groups as well as in the two outcome groups was made by the method described by De Long et al.<sup>12</sup> Sensitivity and specificity were calculated at the following cut-off points: NPI < 2.0, NPI < 3.0, and by

calculating the Youden index.<sup>13</sup> The NPI differences were compared using the Mann–Whitney *U* test. To test for difference in NPI over time, we used analysis of variance methods. A multiple logistic

**TABLE 2** NeuroOptic data compared between outcome and TTM groups

	Poor outcome	Samples (n)	Good outcome	Samples (n)	p value
NPI					
Day 1	3.6 (3.4–3.8)	14	3.9 (3.6–4.1)	46	.01
Day 2	3.6 (3.1–4.0)	16	4.1 (3.9–4.2)	47	.01
Day 3	3.3 (2.6–4.0)	13	4.3 (4.1–4.6)	32	.00
Pupil size (mm)					
Day 1	2.2 (1.6–2.8)	12	2.2 (2.0–2.4)	31	.5
Day 2	2.1 (1.7–2.5)	10	2.3 (2.0–2.7)	18	.16
Day 3	2.9 (1.9–3.9)	6	2.7 (1.2–4.1)	3	.79
Constriction velocity (mm/s)					
Day 1	0.62 (0.47–0.77)	14	1.2 (0.46–1.9)	10	.03
Day 2	1.1 (0.60–1.6)	16	1.1 (0.96–1.3)	47	.14
Day 3	1.3 (0.7–1.8)	13	1.9 (1.5–2.2)	32	.007
% Pupil light reflex					
Day 1	13.4 (11.2–15.5)	14	19.6 (16.2–22.9)	46	.004
Day 2	18.1 (11.7–24.5)	16	24.2 (20.0–28.4)	47	.01
Day 3	17.8 (11.3–24.2)	13	28.9 (25.5–32.3)	32	.002
TTM24			TTM48		
NPI					
Day 1	3.8 (3.4–4.0)	30	3.9 (3.7–4.0)	30	.59
Day 2	4.0 (3.8–4.3)	30	3.9 (3.6–4.1)	33	.06
Day 3	4.0 (3.5–4.4)	17	4.0 (3.7–4.3)	28	.77
NPI chance					
Day 1–2	0.35 (–0.04–0.76)	28	–0.04(–0.24–0.16)	30	.29
Day 2–3	0.02 (–0.43–0.47)	17	0.17 (–0.05–0.38)	28	

regression adjusted for minutes to ROSC, primary rhythm (shockable and non-shockable), and age was tested for association between good (CPC 1–2) and poor neurologic outcomes (CPC 3–5) at 6 months for each of the three time points (day 1, day 2, and day 3) (Table S1). Because multiple comparisons were considered, in the absence of any post-hoc adjustment of the significance level, the results should be considered as hypothesis generating and interpreted as exploratory. We aimed to include as many patients as possible in the time frame available and did not perform a pre-study power calculation. Statistical analysis was performed using STATA 13 (StataCorp LP). A *p*-value <.05 was considered statistically significant.

### 3 | RESULTS

#### 3.1 | Prognostic performance of NPI in TTM48 versus TTM24

In the 65 included patients (Figure 1, Table 1), we obtained pupillometry measurements in 60 patients on day 1, 63 patients on day 2, and 45 patients on day 3 (Table 2). We did not find a significant difference in NPI values between TTM48 and TTM24 on specific time

points (Table 2). Similarly, we did not find a significant difference in NPI change over time or a difference in prognostic ability, defined as AUC, on specific time points.

#### 3.2 | Automated quantitative pupillometry

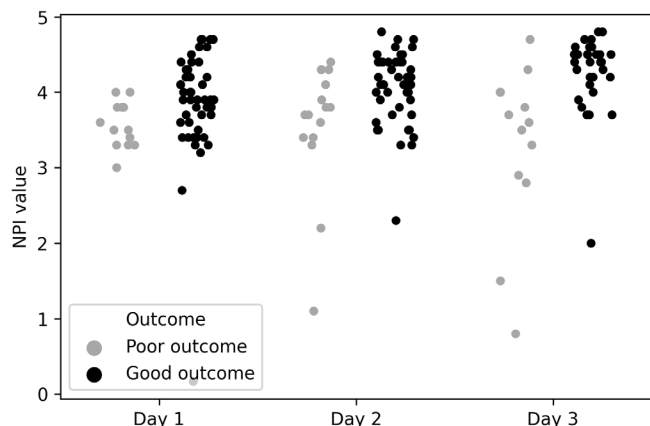
Since no significant difference was found between the two intervention arms, we used the pooled data to compare NPI in the two outcome groups.

Constriction velocity, percentage change in pupil size after light stimulus (%PLR), and NPI values are presented in Table 2. No significant difference was seen in pupil size between patients with poor and good outcomes. Constriction velocity was significantly different between outcomes groups on day 1 and 3 but was not observed at day 2. A significant difference was observed in %PLR on day 1–3.

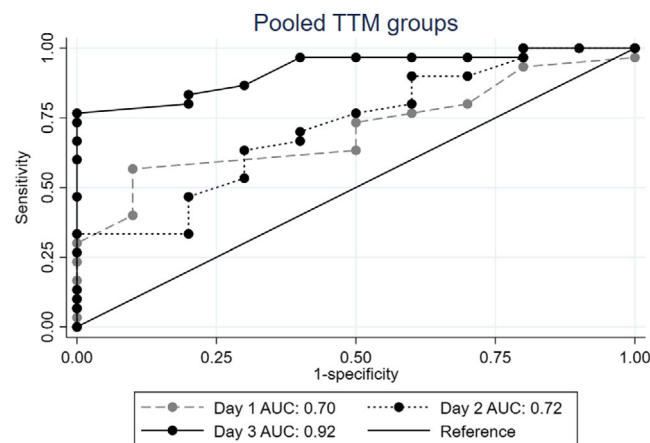
#### 3.3 | Outcome prediction using NPI

Overall, 48 of the 65 included patients (74%) had a good neurological outcome. There was a significant difference in NPI values between

the two outcome groups (good versus poor neurological outcome) on days 1, 2 and 3 (Table 2), but no linear relation between NPi and cerebral performance category score was observed on a scatterplot. Distribution of individual NPi values across outcome groups at day 1 to



**FIGURE 2** Neurological Pupil index. Distribution of individual Neurological Pupil index (NPi) value from day 1–3. Poor outcome CPC 1–2 (gray circle), good outcome (black circle)



**FIGURE 3** Figure illustrates the area under the ROC curve (AUC) of Neurological Pupil index (NPi) at day 1 to 3 for pooled data. Gray line day 1 and black lines on day 2 and 3. AUC, Area under the curve

3 are illustrated in Figure 2. The ability to predict poor outcome measured by AUC (95% confidence interval) increased from day 1 to 3, with an AUC of 0.70 (0.54–0.87) on day 1, 0.72 (0.53–0.90) on day 2, and 0.92 (0.84–1.0) on day 3, respectively (Figure 3). The best performance of the AUC was on day 3, with a significant difference between day 1 and 3 and between day 2 and 3 ( $p < 0.05$ ). When a cutoff value for NPi  $< 3.0$  was chosen, the specificity ranged from 96–98% with a 95% confidence interval between 84%–100% from day 1–3. The sensitivity increased from 0 (95% CI 0–23) on day 1 to 13 (95% CI 2–38) on day 2 and 31 (9–61) on day 3.

The Youden index was 0.67 on day 1 and day 3 with a cut-off value of NPi  $< 3.8$ , and on day 2, NPi  $< 3.9$ . However, to allow comparisons a cut-off value of 3.8 was chosen for all 3 days (Table S2, Table 3).

#### 4 | DISCUSSION

In the present study of resuscitated patients with OHCA undergoing TTM at  $33 \pm 1^\circ\text{C}$  for 24 or 48 h, we explored the prognostic ability of the automated Neurological Pupil index using the NeuroOptics® NPi100™. While we did not find any significant differences in NPi values between the two TTM groups, we demonstrated a significant difference in NPi values between patients with good and poor prognosis when using the pooled data. Further, the prognostic performance of NPi improved over time in the 3-day study period.

Automated pupillometry using the NPi scale from 0–5 may categorize the degree of anoxic brain injury following out-of-hospital cardiac arrest with a high inter-device reliability.<sup>14</sup> Recent studies suggest that NPi may be superior to standard pupil light reflex,<sup>3,15</sup> which is why post-resuscitation guidelines<sup>5</sup> suggest use of automated pupillometry to determine pupil reaction. Evaluation of NPi in former studies showed a 100% specificity already at day 1.<sup>3,16</sup> Similar findings were observed in this study, however, the prognostic performance estimated by the area under the roc curve improved over time and was best at day 3. We think our findings lend support to the current guidelines for post-resuscitation care recommending pupillometry and full neurological prognostication at 72 h or later.<sup>5</sup>

In general, NPi values  $< 3$  are considered abnormal,<sup>17</sup> but recent studies seek to optimize the cut-off value for NPi to gain maximum

	Cutoff	Sens (95% CI)	Spec (95%CI)	PPV (95%CI)	NPV (95%CI)
Day 1	<2.0	0 (0–23)	98 (89–100)	0 (0–98)	76 (63–86)
	<3.0	0 (0–23)	96 (85–100)	0 (0–84)	76 (63–86)
	<3.8	57 (29–82)	65 (50–79)	83 (67–94)	33 (55–16)
Day 2	<2.0	6 (0–30)	100 (93–100)	100 (3–100)	76 (63–86)
	<3.0	13 (2–38)	98 (89–100)	67 (9–99)	77 (64–87)
	<3.8	50 (25–75)	77 (62–88)	42 (20–67)	82 (67–92)
Day 3	<2.0	15 (2–45)	100 (89–100)	100 (16–100)	74 (16–100)
	<3.0	31 (9–61)	97 (84–100)	80 (28–100)	76 (62–89)
	<3.8	57 (29–82)	89 (76–96)	87 (74–95)	62 (32–86)

**TABLE 3** Outcome prediction

specificity and thereby avoid withdrawal of life sustaining therapy in patients with plausible survival odds. In our study, three different NPi cut-off values were tested to define the highest specificity. At day 1, we were not able to define a cut-off value with a 100% specificity. On day 2 and 3, we found cut-off values with a 100% specificity, but the confidence intervals ranged from 93–100 and 89–100, respectively. When the Youden index were used, the NPi cut-off value had a larger numerical value, and consequently, the specificity decreased. A study by Oddo et al.<sup>3</sup> found a 100% specificity on day 1 with a sensitivity of 22% with a cut-off value of NPi <2.0. In another study by Obling et al.,<sup>16</sup> a 100% specificity on a cut-off value of NPi <2.4 was found with a sensitivity of 44%. Overall, 26% of the patients in our study were classified with poor outcome; this number was 59% in the study by Oddo et al.<sup>3</sup> and 45% in the study by Obling et al.<sup>16</sup> Furthermore, the proportion of poor outcome patients increased to 29% on day 3, which may explain the increased sensitivity. In general, a test is required to have a high specificity in prognostication of OCHA patients because clinicians must avoid WLST in patients with plausible changes of survival (self-fulfilling prophecies).

Although sedatives can alter pupil function, quantitative pupillometry assesses pupil reaction for light better than standard pupil assessment especially in small pupils.<sup>3</sup> Calculation of NPi is less likely affected by sedatives<sup>18–20</sup> but further studies are warranted to clarify which NPi value (lowest/highest) that should be used in prognostication of OHCA patients.<sup>3</sup>

#### 4.1 | Strengths and limitations

This planned sub-study was conducted in two ICUs, adding to the external validity of our results. During the study period, the automated pupillometry results were not used for clinical decision making in the ICUs, which eliminates the risk of a self-fulfilling prophecy. A major limitation of this study is the relatively small sample size and that NPi was not available for all patient at all time points. Patients with good outcome may be discharged from the ICU before day 3 and may explain the increased proportion of poor outcome patients on day 3. This commencement of this sub-study was delayed compared to the main TTH48 trial because of the handheld device NeurOptics® NPi100™ and training of the intensive care nurses. Nevertheless, we do not see this as a limitation of this substudy. We believe our study contributes to the urgent question on how to secure timely and accurate neurological prognostication in comatose OHCA patients in the ICU.

## 5 | CONCLUSION

Quantitative pupillometry measured by NPi was not different in the two TTM study groups, but overall, significantly associated with good versus poor neurological outcomes at 6 months. NPi has a promising diagnostic accuracy, but larger studies are warranted to clarify the optimal cut-off value and time points. Our results suggest that quantitative pupillometry may be a useful parameter to include in a multimodal assessment of comatose ICU patients after OHCA.

## ACKNOWLEDGMENTS

We wish to thank the staff at the ICUs at Stavanger University Hospital and Aarhus University Hospital.

## CONFLICT OF INTEREST

Sansuthan Paramanathan, Anders Morten Grejs, Eldar Søreide, Anni Nørgaard Jeppesen, Åse Johanne Reinertsen and Hans Kirkegaard declare no conflicts of interest. Christophe H. V. Duez received funding from the following private foundations: The Viggo and Helene Bruun foundation, the Lily Bentline Lunds foundation of 1st of June 1978, the Director Jacob Madsen & wife Olga Madsen foundation, and the Grocer A. V. Lykfeldt and wife foundation. The foundations had no influence on study design, data collection, analysis, or data interpretation.

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#### SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

**How to cite this article:** Paramanathan S, Grejs AM, Sørreide E, et al. Quantitative pupillometry in comatose out-of-hospital cardiac arrest patients: A post-hoc analysis of the TTH48 trial. *Acta Anaesthesiol Scand*. 2022;66(7):880-886. doi:[10.1111/aas.14078](https://doi.org/10.1111/aas.14078)