

Neurological Pupil index for Early Prognostication After Venoarterial Extracorporeal Membrane Oxygenation

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BACKGROUND: Venoarterial extracorporeal membrane oxygenation therapy (VA-ECMO) after refractory cardiogenic shock or cardiac arrest has significant morbidity and mortality. Early outcome prediction is crucial in this setting, but data on neuroprognostication are limited. We examined the prognostic value of clinical neurologic examination, using an automated device for the quantitative measurement of pupillary light reactivity.

METHODS: An observational cohort of sedated, mechanically ventilated VA-ECMO patients was analyzed during the early phase after ECMO insertion (first 72 h). Using the NPi-200 automated infrared pupillometer, pupillary light reactivity was assessed repeatedly (every 12 h) by calculating the Neurological Pupil index (NPi). Trends of NPi over time were correlated to 90-day mortality, and the prognostic performance of the NPi, alone and in combination with the 12-h PREDICT VA-ECMO score, was evaluated.

RESULTS: One hundred consecutive patients were studied (51 with refractory cardiogenic shock and 49 with refractory cardiac arrest; 12-h PREDICT VA-ECMO, 40%; observed 90-day survival, 43%). Nonsurvivors ($n = 57$) had significantly lower NPi than did survivors at all time points (all $P < .01$). Abnormal NPi (< 3 , at any time from 24 to 72 h) was 100% specific for 90-day mortality, with 0% false positives. Adding the 12-h PREDICT VA-ECMO score to the NPi provided the best prognostic performance (specificity, 100% [95% CI, 92%-100%]; sensitivity, 60% [95% CI, 46%-72%]; area under the receiver operating characteristic curve, 0.82).

CONCLUSIONS: Quantitative NPi alone had excellent ability to predict a poor outcome from day 1 after VA-ECMO insertion, with no false positives. Combining NPi and 12-h PREDICT-VA ECMO score increased the sensitivity of outcome prediction, while maintaining 100% specificity.

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KEY WORDS: extracorporeal membrane oxygenation; Neurological Pupil index; outcome; prognostication; pupillometry

ABBREVIATIONS: CPC = Glasgow-Pittsburgh Cerebral Performance Categories; ECMO = extracorporeal membrane oxygenation; IQR = interquartile range; NPi = Neurological Pupil index; r-CA = refractory cardiac arrest; r-CS = refractory cardiogenic shock; VA-ECMO = venoarterial extracorporeal membrane oxygenation; WLST = withdrawal of life-sustaining treatment

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Venoarterial extracorporeal membrane oxygenation (VA-ECMO) therapy is increasingly used as a life-saving support measure in patients with refractory cardiac arrest (r-CA) or refractory cardiogenic shock (r-CS).^{1,2} Despite increasing progress in patient treatment, VA-ECMO for r-CS or r-CA still results in substantial morbidity and mortality, and acute neurologic complications are frequent.³ VA-ECMO-associated neurologic injury may be the consequence of the primary brain injury itself (hypoxic-ischemic brain injury, diffuse cerebral edema), patient comorbidities, or initial disease severity, or it may be intrinsic to the technique (cerebral thromboembolism, hemorrhagic stroke).^{2,4,5} In this setting, early prognostication is an essential step to the treatment of patients receiving VA-ECMO.⁶ Prognostic scores based on general demographic and physiologic variables have been developed,⁷⁻⁹ including the recent 12-h PREDICT VA-ECMO score.¹⁰ However, more specific early neuroprognostication tools have not been extensively studied. Preliminary studies evaluated the role of EEG,¹¹ brain CT imaging,¹² and other noninvasive neuromonitoring tools.¹³ Serum biomarkers of neuronal injury, such as neuron-specific enolase, offer the advantage of providing quantitative measurement; however, prognostic accuracy and precise cutoffs for poor outcome prediction vary among studies.¹⁴⁻¹⁶ Therefore, it is uncertain whether current recommendations on neuroprognostication in postresuscitation care^{17,18} are applicable to patients receiving VA-ECMO. Additional clinical study is needed to better identify optimal neuromonitoring tools that may guide early prognostication in patients receiving

VA-ECMO^{6,14} and accurately orient clinical decision-making.

Automated infrared pupillometry is a novel noninvasive neuromonitoring tool for early neuroprognostication in critically ill patients.¹⁹ Assessment of the standard neurologic examination, particularly of the pupillary light reflex, is central for the prognostication of brain-injured patients.²⁰ Automated infrared pupillometry complements traditional qualitative neurologic examination, by providing a series of quantitative variables derived from the automated analysis of the pupillary response to a standardized calibrated light stimulus. Pupillometry variables include the percentage pupillary light constriction, constriction velocity, pupil dilation, and latency.²¹ Using specific pupillometers, such variables can be integrated to automatically compute the Neurological Pupil index (NPI), a scalar index (from 0 to 5) that is derived from a proprietary mathematical algorithm.^{22,23} Reduced NPI was shown to be highly specific to predict a poor outcome in patients with coma after cardiac arrest²⁴ and other acute brain conditions.²⁵ No clinical study, however, has specifically evaluated the prognostic value of the NPI in patients receiving VA-ECMO.

The objective of this study was to examine the value of the quantitative NPI for early outcome prognostication in patients with VA-ECMO. Using repeated NPI assessments obtained at the acute phase of injury (from ECMO insertion up to 72 h), we analyzed early NPI trends, aiming to identify potential correlations with 90-day patient outcome, and further examined the prognostic value of the NPI, alone or in combination with other known composite prognostic scores.

Patients and Methods

Patients and Setting

Patients included consecutive adult (≥ 18 years old), comatose (Glasgow Coma Score < 6) subjects admitted from June 2016 to June 2019 to the Department of Adult Intensive Care Medicine, CHUV-Lausanne University Hospital (Lausanne, Switzerland) and who underwent VA-ECMO because of r-CS or r-CA. Approval for this observational cohort study was obtained from the local ethics committee, with a waiver of patient consent because all procedures were part of standard patient care.

ECMO Implantation and Management

VA-ECMO insertion was performed by expert cardiac surgeons, generally using peripheral vascular sites, either in the operating room or in the ICU. The VA-ECMO Maquet Cardiohelp system (Getinge Group) or the CentriMag adult circuit (Levitronix) was used. Patients were mechanically ventilated and sedated according to a

written standardized local algorithm, including midazolam (0.05-0.15 mg/kg/h) and/or propofol (2-4 mg/kg/h), targeted to keep the Richmond Agitation-Sedation Scale score between -4 and -5 . Analgesia consisted of a continuous infusion of fentanyl (0.7-1.5 $\mu\text{g}/\text{kg}/\text{h}$). Hemodynamic support was aimed at maintaining normovolemia (with the use of isotonic crystalloids) and mean arterial pressure > 65 mm Hg, and VA-ECMO flow was adjusted to ensure adequate tissue perfusion (central venous oxygen saturation [ScvO_2] $> 65\%$, blood arterial lactate < 2.5 mM, urinary output > 0.5 mL/kg/h). Neuromuscular blocking agents were given as needed. Ventilatory parameters and artificial lung settings were targeted to normoxia (PaO_2 , 80-100 mm Hg), normocapnia (PaCO_2 , 38-42 mm Hg). All patients received therapeutic anticoagulation with continuous infusion of unfractionated heparin, aiming at achieving anti-Xa at 0.3 to 0.4 IU/mL.

Patients with r-CA were treated with targeted temperature management at 35°C to 36°C ; all other patients were kept at normothermic levels, setting ECMO temperature at 37°C .

Automated Infrared Pupillometry

The NPi-200 automated infrared pupillometer (NeuroOptics) has an infrared camera that integrates a calibrated light stimulation of standardized intensity (1,000 lx) and duration (3.2 s), thereby allowing rapid and precise (0.05-mm limit) quantitative measurement of the pupil size and of a series of dynamic pupillary variables (including the percentage pupillary constriction, latency, constriction velocity, and dilation velocity). On the basis of these measured variables, the NPi-200 pupillometer computes the Neurological Pupil index (NPi), a scalar index derived from a proprietary algorithm. Compared with directly measured variables, the NPi is minimally influenced by pharmacologic agents, in particular sedatives and analgesics.^{22,23} The NPi ranges from 0 (no pupillary response) to 5 (full pupillary response), with a 0.1 decimal precision: normal NPi values range between 3 and 5, while an NPi value below 3 is defined as abnormal.^{22,23}

Pupillary measurements were performed on both eyes by the nurse in charge of the patient, as part of standard care. Patients were excluded if they had ocular disease or abnormalities that could have altered pupillary assessment, based on previous history and verification through medical records. Brain CT scanning was not performed systematically.

Demographic Variables and General Prognostic Scores

The following variables were collected: age, sex, ECMO indication (r-CS or r-CA), cumulative dose of sedatives and fentanyl during the first 72 h, APACHE II (Acute Physiology, Age, and Chronic Health Evaluation II) score, SOFA (Sepsis-Related Organ Failure Assessment) score, VA-ECMO duration, and ICU length of stay. The 12-h PREDICT VA-ECMO score was calculated automatically via a website,²⁶ using repeated arterial blood pH, lactate, and standard bicarbonate (SBC) at 1, 6, and 12 h from VA-ECMO insertion, as previously described.¹⁰

Outcome Assessment

Outcome was assessed at 3 months with the Glasgow-Pittsburgh Cerebral Performance Categories (CPC), by way of a structured telephone interview. The CPC scores were further categorized as good outcome (CPC 1-2) vs poor outcome (CPC 3-4-5).²⁷

The cause of death was categorized as nonneurologic when due to extracerebral causes (shock, multiorgan failure) vs neurologic in

cases of severe cerebral injury (based on neuroimaging and electrophysiologic assessment) leading to withdrawal of life-sustaining treatment (WLST) or brain death, in line with previous studies.²⁸ Decisions regarding WLST were made on the basis of the use of a multimodal neuroprognostication approach, including clinical examination (Glasgow Coma Scale motor response, brainstem reflexes), EEG, somatosensory evoked potentials, and neuron-specific enolase. This was based on a written protocol and in line with current recommendations.^{17,18} WLST was considered if at least two modalities (among clinical, electrophysiologic, and biochemical prognosticators) showed unfavorable prognostic signs, and after multidisciplinary discussion. Pupillometry data were not considered for patient treatment and for decisions regarding continuation or withdrawal of life support.

Data Processing and Analysis

Individual NPi trends were obtained at predetermined time points, starting at time 0 (defined as a maximum of 2 h from ECMO insertion), and then every 12 h, up to 72 h. For each time point, the lowest NPi value measured from both eyes during each time interval was retained for the analysis. An abnormal NPi was defined as a value between 0 and 3. The cutoff of NPi < 3 was defined before the study, based on previous reports.^{22,23}

Using the complete 72-h NPi data set, each patient was categorized into one of the following groups, according to the individual NPi trend over time:

- Group 1: NPi always abnormal (all 72-h NPi measurements < 3)
- Group 2: NPi initially normal (first 24-h NPi measurements \geq 3) and then decreasing to abnormal values (< 3) from 24 to 72 h
- Group 3: NPi initially abnormal (first 24-h NPi measurements < 3) and then returning to normal values (\geq 3) from 24 to 72 h
- Group 4: NPi always normal (all 72-h NPi measurements \geq 3)

Outcome at 3 months was analyzed for each patient subgroup.

Data are presented as median and interquartile range (IQR). Univariate comparisons were analyzed with nonparametric Wilcoxon and Fisher exact tests. For prognostication models, sensitivity, specificity, positive predictive value, negative predictive value (with binomial 95% CIs), and the area under the receiver operating characteristic (AUROC) curve are reported. The ROC curve comparisons were analyzed using the DeLong test. Statistical analysis was conducted with STATA 15 (StataCorp). Significance was set at $P < .05$.

Results

A total of 100 consecutive patients (51 r-CS, 49 r-CA; age, 59 [IQR, 49-66] years; median VA-ECMO duration, 4 days) were studied (Table 1). The PREDICT VA-ECMO score was 40 (IQR, 19-54) (estimated predicted survival), while the observed 90-day survival was 43% (58% for r-CS, 29% for r-CA).

Patient Outcome According to Individual NPi Trends Over Time

Using the CPC scores at 3 months, patient outcome was assessed as a function of individual patient NPi trends over time. Outcome data for each patient subgroup are given in detail in Table 2, and the NPi evolution over time for each NPi trend category is shown in Figure 1. All patients with repeatedly abnormal NPi (group 1; n = 21 patients) died,

irrespective of VA-ECMO indication. Group 2 patients, with an abnormal NPi starting after 24 h (n = 7), also had 100% mortality, irrespective of r-CS or r-CA. In contrast, all patients in whom NPi improved over time and returned to normal after 24 h (group 3; n = 5) survived, and most (three of five) had good outcome at 3 months. Additional signs of good prognosis (reactive EEG, serum neuron-specific enolase levels < 50 μ g/L) were found in all five of these patients. Finally, most patients (57%) with persistently normal NPi (group 4; n = 67 patients) survived and the majority had a favorable neurologic recovery at 3 months.

Prognostic Accuracy of Quantitative NPi in Patients Receiving VA-ECMO

As shown in Table 3, an abnormal NPi < 3, at any time from 24 to 72 h after VA-ECMO insertion, had

TABLE 1] Demographic and Clinical Data

Variable	Total (n = 100)	Survivors (n = 43)	Nonsurvivors (n = 57)	P Value
Age, y	59 (49-66)	56 (40-64)	61 (51-67)	.18
Sex, female/male, No.	28/72	14/29	14/43	.29
VA-ECMO indication, No. (%)				
Refractory cardiogenic shock	51 (51)	29 (58)	22 (42)	...
Refractory cardiac arrest	49 (49)	14 (29)	35 (71)	.003
APACHE II score ^a	28 (21-36)	23 (17-28)	33 (26-38)	< .001
SOFA score ^b	14 (12-16)	13 (11-15)	15 (14-16)	< .001
12-h PREDICT VA-ECMO score	40 (19-54)	51 (40-60)	26 (9-41)	< .001
ICU length of stay, d	9 (3-22)	20 (9-35)	4 (2-15)	< .001
ECMO duration, d	4 (2-7)	4 (3-8)	4 (1-7)	.17

Data are presented as median (interquartile range) unless indicated otherwise. 12-h PREDICT VA-ECMO score = survival probability score at 12 h¹⁰; APACHE II = Acute Physiology, Age, and Chronic Health Evaluation II; SOFA = Sepsis-Related Organ Failure Assessment; VA-ECMO = venoarterial extracorporeal membrane oxygenation.

^aOn admission.

^bOn day 1.

100% specificity (95% CI, 92%-100%) for 90-day mortality in our patient population, with a sensitivity of 53% (95% CI, 39%-66%). Of note, the 12-h PREDICT VA-ECMO score had comparable specificity but much lower sensitivity (23%; 95% CI, 13%-36%). The combination of an abnormal NPi < 3 with the 12-h PREDICT VA-ECMO score yielded the highest sensitivity (60%; 95% CI, 46%-72%), while at the same time maintaining 100% specificity (Table 3). Comparisons of the AUROC curves revealed that the combination of NPi with the 12-h PREDICT VA-ECMO score yielded significantly higher prognostic performance than the NPi alone (AUROC, 0.82 vs. 0.74; $P = .035$; Fig 2).

An NPi value of 0 at the time of VA-ECMO insertion (n = 9 patients) was 100% predictive of mortality. Ten patients died within 48 h, of whom seven had an NPi value of 0.

No significant correlation was found between NPi values and the average daily cumulative dose of sedatives (midazolam and propofol; Spearman $P = .83$ on day 1, $P = .41$ on day 2, and $P = .63$ on day 3) and fentanyl ($P = .23$ on day 1, $P = .08$ on day 2, and $P = .24$ on day 3).

Cause of Death as a Function of NPi Values

Neurologic death was more frequent among nonsurvivors with an abnormal NPi (19 of 28; 67%) than nonsurvivors with normal NPi (11 of 29; 38%; $P = .023$; Fig 3), in whom death was more frequently due to systemic complications (cardiac, hemorrhagic, infectious). Time to death was shorter in patients with neurologic vs nonneurologic cause of death (6 vs 15 days).

Discussion

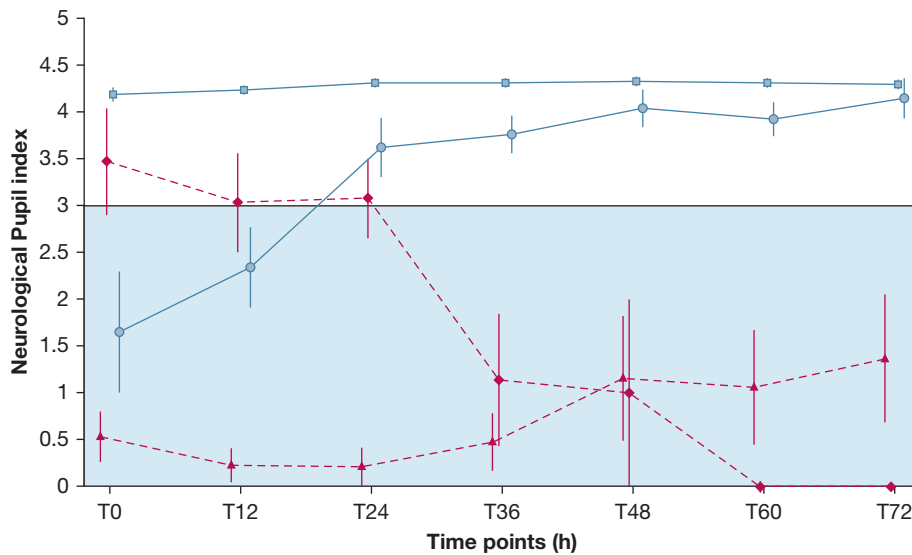
This is the first clinical study testing the role of automated infrared pupillometry as a neuromonitoring tool for the early prediction of outcome in patients

TABLE 2] Ninety-Day Neurologic Outcome^a for Each Patient Subgroup, Defined According to Individual Trends of the Neurological Pupil index During the First 72 Hours From VA-ECMO Insertion

Patient Group	VA-ECMO Indication	No.	CPC 1	CPC 2	CPC 3	CPC 5
Group 1: NPi always < 3	r-CS/r-CA	21	21 (3/18)
Group 2: NPi ≥ 3 from 0 to 24 h, then < 3 from 24 to 72 h	r-CS/r-CA	7	7 (3/4)
Group 3: NPi < 3 from 0 to 24 h, then ≥ 3 from 24 to 72 h	r-CS/r-CA	5	1 (0/1)	2 (0/2)	2 (0/2)	...
Group 4: NPi always ≥ 3	r-CS/r-CA	67	6 (5/1)	17 (14/3)	15 (8/7)	29 (16/13)

CPC 1-3 and 5 = Glasgow-Pittsburgh Cerebral Performance Categories 1-3 and 5; r-CA = refractory cardiac arrest; r-CS = refractory cardiogenic shock. See Table 1 legend for expansion of other abbreviation.

^aCPC 1 and 2, good outcome; CPC 3 and 5, poor outcome.



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Figure 1 – Individual evolution of Neurological Pupil index (NPi) at the early venoarterial extracorporeal membrane oxygenation phase, and 3-month outcome. Group 1, NPi always pathologic (< 3 ; $n = 21$ patients, red triangles); group 2, NPi normal (≥ 3) at 0 to 24 h and then pathologic at 24 to 72 h ($n = 7$ patients, red diamonds); group 3, NPi pathologic at 0 to 24 h and then normal at 24 to 72 h ($n = 5$ patients, blue circles); group 4, NPi always normal ($n = 67$ patients, blue squares). The blue area designates abnormal NPi data (NPi < 3).

receiving VA-ECMO. The first finding of this study was that NPi < 3 alone, at any time between 24 and 72 h from VA-ECMO insertion, was 100% specific for 90-day mortality, irrespective of VA-ECMO indication (r-CS or r-CA). The addition of the 12-h PREDICT VA-ECMO score to abnormal NPi provided the best prognostic performance, with a specificity of 100%, a sensitivity of 60%, and an area under the ROC curve of 0.82, which was significantly better than when using the NPi alone (AUROC, 0.74; $P = .035$ for comparison with the AUROC of the combination of NPi with PREDICT VA-ECMO score). Finally, mortality occurred despite the lack of abnormal NPi; however, normal NPi among nonsurvivors more likely correlated with nonneurologic death (ie, late systemic complications of VA-ECMO), while death with an abnormal NPi was predominantly due to early death because of cerebral damage, thereby further reinforcing the value of the NPi in predicting the neurologic trajectories of patients receiving VA-ECMO.

Altogether, pending further larger confirmatory studies, our data indicate that the Neurological Pupil index may be a valuable tool for the early neuroprognostication of outcome in patients who undergo VA-ECMO support following r-CS or r-CA.

Early Neuroprognostication in Patients With VA-ECMO

VA-ECMO for r-CS or r-CA has substantial morbidity and mortality,³ and therefore early prognostication is crucial to orient clinical decisions and intensity of care.²⁹ Several prognostic scores, based on general demographic and systemic physiologic variables, have been proposed, such as the ENCOURAGE (Prediction of Cardiogenic Shock Outcome for AMI [acute myocardial infarction] Patients Salvaged by VA-ECMO) score,³⁰ the modified SAVE (Survival after Venoarterial ECMO) score,⁷ and the recently reported 12-h PREDICT VA-ECMO score.¹⁰ The role of neurospecific prognostic tools (eg, EEG,

TABLE 3] Prognostic Accuracy of the Various Tests to Predict 90-Day Mortality

	NPi < 3		12-h PREDICT VA-ECMO Score		NPi < 3 + PREDICT VA-ECMO Score	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Sensitivity	53%	39%-66%	23%	13%-36%	60%	46%-72%
Specificity	100%	92%-100%	100%	92%-100%	100%	92%-100%
Positive predictive value	100%	...	100%	...	100%	...
Negative predictive value	61%	55%-68%	49%	46%-53%	63%	58%-72%

Neurological Pupil index (NPi) < 3 at any time between 24 and 72 h from VA-ECMO insertion. See Table 1 legend for expansion of other abbreviation.

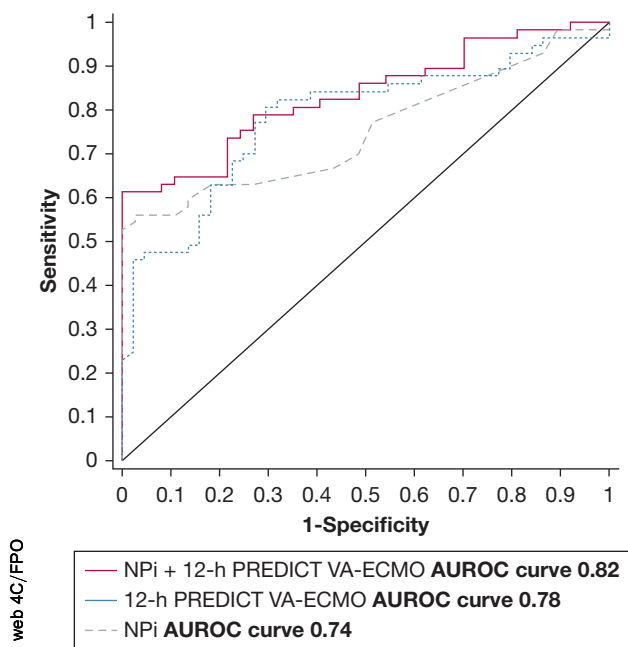


Figure 2 – Prognostic performance of Neurological Pupil index (NPI) and 12-h PREDICT venoarterial extracorporeal membrane oxygenation (VA-ECMO) score, each alone or in combination. Shown is the area under the receiver operating characteristic (AUROC) curves for the prediction of 90-day mortality, using the combination of NPI with 12-h PREDICT VA-ECMO score (AUROC curve, 0.82) in comparison with the 12-h PREDICT VA-ECMO score alone (AUROC curve, 0.78; $P = .18$) and the NPI alone (AUROC curve, 0.74; $P = .035$).

serum biomarkers of brain injury, neuroimaging) is only beginning to be evaluated,^{11,12,15,16} and therefore the value of multimodal neuroprognostication algorithms, as recommended in other settings,^{17,18,31} requires further clinical investigation in patients with VA-ECMO.

Quantitative Pupillometry and Outcome

Previous studies reported high accuracy of automated infrared pupillometry in predicting poor outcome, using

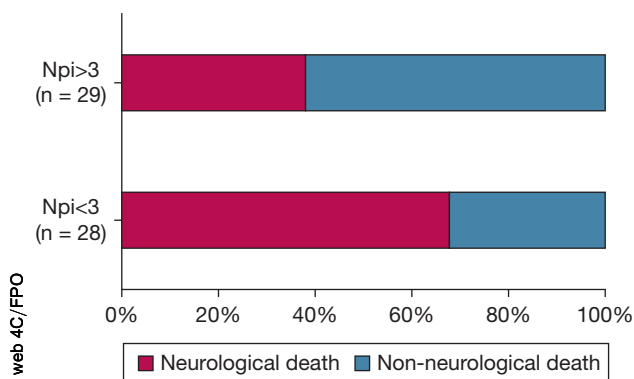


Figure 3 – Cause of death as a function of Neurological Pupil index (NPI). Main cause of death (categorized as neurologic vs nonneurologic) in nonsurvivors of venoarterial extracorporeal membrane oxygenation according to the NPI (normal vs abnormal).

quantitative pupillary constriction³²⁻³⁵ and NPI analysis, in cardiac arrest^{36,37} and other forms of acute brain injury.^{25,38-40} A large multicenter study found high specificity of reduced NPI to predict poor 3-month outcome in comatose cardiac arrest patients.²⁴

Here, we confirmed the value of the NPI for the early prognostication of VA-ECMO. Analysis of NPI trends was very informative, indicating potential evolution of quantitative pupillary light reactivity over time, especially after 24 h from ECMO insertion. “Very early” prognostication may not be advisable before 24 h, as previously shown by others,²⁴ except when NPI was equal to 0, in which mortality was 100% irrespective of the time. Indeed, all nine patients in whom NPI was 0 at time 0 (ie, within a maximum of 2 h from ECMO insertion) died. These very preliminary findings suggest that quantitative NPI, when showing absent pupillary response ($NPI = 0$), is a very strong indicator of poor outcome, and warrant additional studies to evaluate the role of NPI in emergency cardiopulmonary resuscitation, for example, to potentially refine optimal candidates for VA-ECMO in refractory cardiac arrest.

Prognostic Value of the Neurological Pupil index

The NPI, using a cutoff below 3 at any time between 24 and 72 h from ECMO insertion, was strongly predictive of poor outcome at 3 months, with a positive predictive value of 100%. Therefore, the NPI alone provides optimal prediction of poor outcome, with zero false positives, which is ideal to avoid self-fulfilling prophecy and unwanted withdrawal of care. The sensitivity for outcome prediction was higher for the NPI in comparison with the 12-h PREDICT VA-ECMO score (53% vs. 23%). The combination of the NPI with the 12-h PREDICT VA-ECMO score yielded the best sensitivity, while keeping equal specificity: these data imply that when NPI is normal the addition of the 12-h PREDICT VA-ECMO score optimizes prognostic accuracy (highest specificity and sensitivity), with an area under the ROC curve of 0.82, comparable to available composite prognostic scores,^{7,10,30} and significantly higher than that of NPI alone ($P = .035$).

Study Limitations

This was a single-center study, and therefore additional larger confirmatory studies are needed. The patient cohort consisted of a mixed population of patients with r-CS and patients with r-CA; however, we showed that the prognostic value of the NPI was not influenced by VA-ECMO indication. The NPI assessment may be

influenced by the ambient light^{41,42}; although measurement of the NPi at the bedside was preceded by specific education and instruction about device technology and use, we did not specifically control for ambient light. In this regard, however, quantitative pupillometry has very low interrater variability,^{43,44} and uses a standardized light stimulus and an automated pupillary index. Automatic NPi is less influenced by sedation-analgesia,²¹ except when high-dose opioids (especially remifentanyl) are used.^{45,46} Patients included in the study, however, had no high-dose opioids and we found no significant association between NPi and sedatives or opioids during the NPi assessment. High-dose epinephrine, given at the early resuscitation phase (especially for r-CA), may also potentially decrease pupillary light response²¹: this may explain overall lower NPi data in the entire cohort in the first 24 h, and—at least in part—potentially explain reduced prognostic accuracy of the NPi at very early time points. Regarding the effect of neuromuscular blocking agents (which were given to many patients included in this study, especially during the first 24 h) on pupillary reactivity, this seems negligible based on previous reports.⁴⁷

A prognostic cutoff value of 3 was used for the NPi, based on previous published data and referenced normative values.^{22,23} Using a lower NPi cutoff, for example, ≤ 2 as in other reports,²⁴ did not add

specificity, and reduced sensitivity (data not shown). Despite the high accuracy in predicting a poor outcome, the overall sensitivity of NPi was modest (50%-60%), which is in line with what has been reported for other neuroprognostication tools.¹⁷ Normal NPi therefore does not imply 3-month survival. However, when looking at the cause of death, a normal NPi was significantly associated with a nonneurologic death, because of systemic (mainly cardiac, hemorrhagic diathesis, infections) rather than cerebral complications

Finally, although pupillometry data were not used for clinical decision-making, we cannot exclude some degree of self-fulfilling prophecy, inherent to this type of prognostic study.

Conclusions

After VA-ECMO for r-CS or r-CA, an abnormal NPi < 3 from 24 h after ECMO insertion was 100% specific for an unfavorable 90-day outcome, with no false positives. The addition of the 12-h PREDICT VA-ECMO score to NPi assessment increased the sensitivity of outcome prediction, while maintaining 100% specificity, and had the best prognostic performance for outcome prediction. Pending further confirmation by a larger, multicenter study, our findings suggest that automated infrared pupillometry may be a valuable tool for the early neuroprognostication of patients treated with VA-ECMO.

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