Early Neurological Pupil Index Assessment to Predict Outcome in Cardiac Arrest Patients Undergoing Extracorporeal Membrane Oxygenation

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Hypoxic-ischemic brain injury is the main cause of death or disability in patients resuscitated from cardiac arrest (CA).[1] Veno-arterial extracorporeal membrane oxygenation (VA ECMO) may be used as a mechanical support for refractory CA or post-CA cardiogenic shock. However, the potential benefit of this resource-intensive treatment should be balanced against the risk of futility. In a recent multicenter study,[2] absence of pupillary reactivity detected using automated pupillometry (AP) showed to accurately predict hypoxic-ischemic brain injury outcome at 24–48 hours from CA. However, no data on the role of AP on admission (*i.e.,* earliest timing for prognostication) in ECMO patients (*i.e.,* the sickest population) are currently available. This *post hoc* analysis aimed to assess the accuracy of early AP for outcome prediction in CA patients undergoing ECMO.

Materials and Methods

An international prospective multicentric cohort[2] enrolled adult (>18 years) comatose (Glasgow Coma Scale ≤ 6) patients with CA admitted to 10 European Intensive Care Units (ICU) from January 2015 to March 2017. In this study, a neurologic pupil index (NPi, ranging from 0, absent pupillary function, to 5, normal pupillary function) ≤2 at 24–48 h after CA predicted poor neurologic outcome (PNO, defined as a cerebral performance category 3–5 at 3 months) with 100% specificity.[2] In this study, we evaluated whether NPi on hospital admission could predict PNO in the subset of patients treated with VA ECMO, either for refractory CA (*i.e.,* extracorporeal cardiopulmonary resuscitation[ECPR]) or for cardiogenic shock occurring after the return of spontaneous circulation (POST-ROSC). The secondary outcome was to assess whether the accuracy of NPi was similar in these two subgroups. Discrete variables were expressed as count (percentage) and continuous variables as mean ± SD or median [25th to 75th percentiles]. The Kolmogorov-Smirnov test was used, and histograms and normal-quantile plots were examined to verify the normality of distribution of continuous variables. Demographics, clinical, and values between groups were assessed using the χ^2 test, Fisher's exact test, Student's *t*-test, or Mann-Whitney *U* test, as appropriate. For the entire cohort and for each subgroup, we calculated sensitivity and specificity of NPi ≤ 2 on admission to predict PNO. All statistical tests were two-tailed, and a $p < 0.05$ was considered as statistically significant. Data were analyzed using IBM SPSS Statistics for Macintosh 25 (Armonk, NY).

Results

On 456 eligible patients, 66 (14%) from four centers were treated with VA ECMO; 37 (56%) were in the ECPR group and 29 (44%) in the POST-ROSC group. The median age was 57 [47–66] years and 48 (73%) were males; PNO was reported in 43 (65%) patients, 26 (70%) in the ECPR and 17 (59%) in the POST-ROSC group (*i.e.*, ECMO was implemented within 6 hours from ICU admission in all). Baseline characteristics of the patients according to neurologic outcome are shown in Table 1. Patients with PNO had a longer time to ROSC and had less commonly an initial shockable rhythm. NPi on admission was similar in patients with PNO and good neurologic outcome (3.6 [1.8–4.2] *vs.* 3.9 [3.6–4.2]; $p = 0.14$). Fifteen patients showed a NPi ≤ 2 on admission; of those, 13 (87%) had PNO. NPi ≤ 2 on admission showed a sensitivity of 30% and a specificity of 91% to predict PNO. NPi ≤ 2 on day 1 and 2, was observed in 11/66 (17%) and 3/49 (6%) patients, respectively, all of them presenting PNO. As shown in Table 2, NPi on admission was similar between patients with good neurologic outcome and PNO in both subgroups; however, in the POST-ROSC group, all patients with NPI ≤2 had PNO (Figure 1); sensitivity and specificity were 35% and 100%, respectively. Conversely, in the group of patients treated with ECPR, two of nine patients with NPi ≤ 2 on admission had a good neurologic recovery.

Discussion

In this study, NPi on admission showed a sensitivity of 30% and a specificity of 91% to predict PNO in CA patients

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Table 1. Characteristics of the Study Patients, According to the Neurologic Outcome at 3 Months

	Good Neurologic Outcome (*n* = 23)	Poor Neurologic Outcome (*n* = 43)	*p*
Age, years	53 (36–64)	59 (48–69)	0.09
Male gender, n (%)	16 (70)	32 (74)	0.77
Bystander CPR, n (%)	20 (87)	29 (67)	0.14
Time to ROSC, min	20 (17–38)	55 (20–75)	<0.01
Shockable rhythm, n (%)	20 (87)	27 (63)	0.04
Cardiac origin, n (%)	16 (70)	32 (74)	0.77
ECPR, n (%)	11 (48)	26 (61)	0.44
Lactate at admission, mmol/L	4.6 (2.7–10.5)	8.2 (3.1–11.8)	0.28
NPi on admission	3.9 (3.6–4.2)	3.6 (1.8–4.2)	0.14
NPi ≤ 2 on admission	2 (9)	13 (30)	0.07

Values are shown as number (percentage) or median (25th–75th percentile).

CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; NPi, neurologic pupil index; ROSC, return of spontaneous circulation.

Table 2. Pupillary Response Values, According to ECMO Indication

	ECPR (n = 37)		POST-ROSC (n = 29)	
	GNO (n = 11)	PNO (n = 26)	GNO (n = 12)	PNO (n = 17)
NPi on admission, value	3.6 (3.1–3.9)	3.5 (1.9–4.1)	4.2 (3.9–4.4)	3.6 (1.6–4.3)
NPi ≤ 2 on admission	2 (18)	7 (27)	–	6 (35)*

Values are shown as number (percentage) or median (25th–75th percentile).

ECPR, extracorporeal cardiopulmonary resuscitation; GNO, good neurologic outcome; NPi, neurologic pupil index; PNO, poor neurologic outcome; ROSC, return of spontaneous circulation.

undergoing ECMO. The highest specificity was observed in the subgroup of patients in whom ECMO was implemented within few hours after ICU admission for post-CA cardiogenic shock (POST-ROSC). In the group of patients undergoing ECPR, two out of nine patients with NPi ≤ 2 on admission had a good neurologic recovery thereafter. As such, the decision to implement ECMO, in particular for those requiring ECPR, should not rely only on pupillometry assessment on admission.

One single center study reported that abnormal NPi values (<3, at any time from 24 to 72 hours after ECMO initiation) were 100% specific to predict 90 days mortality, with 0% false positives.[3] Moreover, repeated NPi measurements identified patients' trajectories, with those having persistently abnormal NPi values or those showing initially normal and then decreasing to abnormal values had the highest mortality rates. However, the NPi assessment in this study occurred later than in our report, as we specifically focused on NPi on admission; moreover, we did not focus on mortality but on neurologic outcome, which is a more relevant outcome in CA patients.

One possible explanation of the false positive prediction of low NPi values on admission could be related to the early neuronal dysfunction occurring during the anoxic injury in some cerebral areas sensitive to hypoxia, such as in the brainstem or the retina,[3,4] which could result in fixed mydriasis. However, in these patients, the return of spontaneous circulation and brain reperfusion could result in some neuronal recovery, with pupils becoming reflective to light stimulation. As the time to recovery of pupillary function is variable among patients in the first hours after resuscitation,[5] this might result in misclassification of neurologic outcome using NPi on admission. The differences among subgroups might be secondary to a prolonged resuscitation time to implement ECPR, which would result in a more severe initial injury and, potentially, in a slower pupillary recovery after reperfusion.

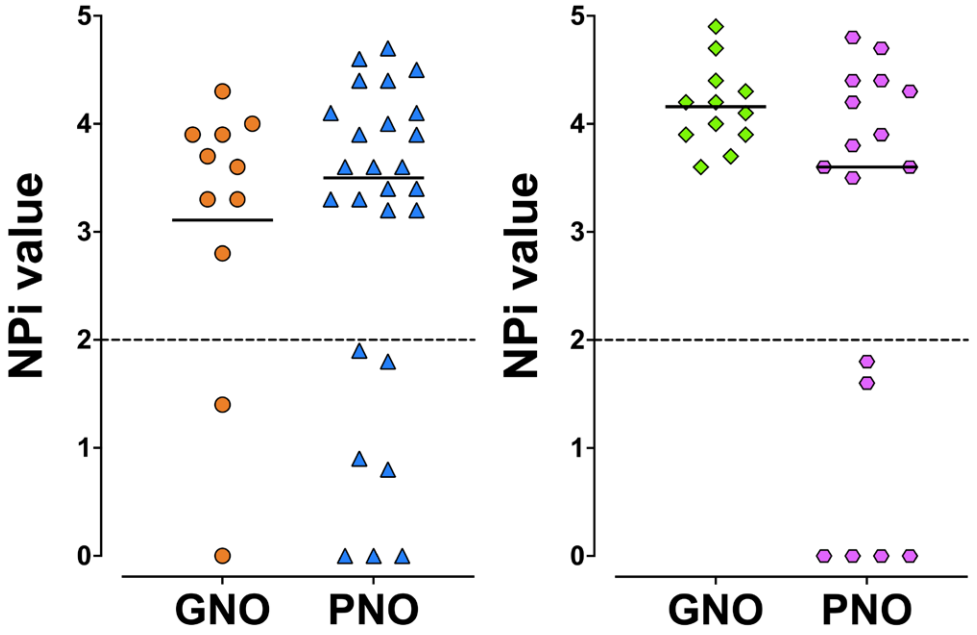

Figure 1. NPi values according to the neurologic outcome at 3 months (ECPR group on the left panel, POST-ROSC group on the right panel). GNO defined as a cerebral performance category 1–2 at 3 months; PNO defined as a cerebral performance category 3–5 at 3 months. ECPR, extracorporeal cardiopulmonary resuscitation; GNO, good neurologic outcome; NPi, neurologic pupil index; PNO, poor neurologic outcome; ROSC, return of spontaneous circulation.

Our study presents several limitations; first, this is a *post hoc* analysis and the sample size was not specifically calculated; as such, the study may be underpowered to adequately assess the specificity of NPi in different subgroups. Second, although all centers followed ERC-ESICM guidelines for postresuscitation care,[6] the criteria for withdrawal of life support therapies were not consistent.

In conclusion, this *post hoc* analysis indicated that NPi on admission might help to identify ECMO patients at high risk of PNO, in particular those treated with post-CA cardiogenic shock, but a risk of false prediction should be considered. As such, neurologic prognosis should include a combination of different predictors, as such as electroencephalography, evoked potentials, or biomarkers.[7]

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