OBSERVATIONAL STUDY

OPEN

Association of Sepsis With Neurologic Outcomes of Adult Patients Treated With Venoarterial Extracorporeal Membrane Oxygnenation

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OBJECTIVES: Neurologic outcomes of patients under venoarterial extracorporeal membrane oxygenation (VA-ECMO) may be worsened by secondary insults of systemic origin. We aimed to assess whether sepsis, commonly observed during ECMO support, is associated with brain injury and outcomes.

DESIGN: Single-center cohort study of the "exposed-non-exposed" type on consecutive adult patients treated by VA-ECMO.

SETTING: Medical ICU of a university hospital, France, 2013–2020.

PATIENTS: Patients with sepsis at the time of VA-ECMO cannulation ("sepsis" group) were compared with patients without sepsis ("no sepsis" group). The primary outcome measure was poor functional outcome at 90 days, defined by a score greater than or equal to 4 on the modified Rankin scale (mRS), indicating severe disability or death.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: A total of 196 patients were included ("sepsis," $n = 128$; "no sepsis," $n = 68$), of whom 87 (44.4%) had presented cardiac arrest before VA-ECMO cannulation. A poor functional outcome (mRS ≥ 4) was observed in 99 of 128 patients (77.3%) of the "sepsis" group and 46 of 68 patients (67.6%) of the "no sepsis" group (adjusted logistic regression odds ratio (OR) 1.21, 95% CI, 0.58–2.47; inverse probability of treatment weighting (IPTW) OR 1.24; 95% CI, 0.79–1.95). Subsequent analyses performed according to pre-ECMO cardiac arrest status suggested that sepsis was independently associated with poorer functional outcomes in the subgroup of patients who had experienced pre-ECMO cardiac arrest (adjusted logistic regression OR 3.44; 95% CI, 1.06–11.40; IPTW OR 3.52; 95% CI, 1.68–7.73), whereas no such association was observed in patients without pre-ECMO cardiac arrest (adjusted logistic regression OR 0.69; 95% CI, 0.27–1.69; IPTW OR 0.76; 95% CI, 0.42–1.35). Compared with the "no sepsis" group, "sepsis" patients presented a significant increase in S100 calcium-binding protein beta concentrations at day 1 (0.94 µg/L vs. 0.52 µg/L, $p = 0.03$), and more frequent EEG alterations (i.e., severe slowing, discontinuous background, and a lower prevalence of sleep patterns), suggesting brain injury.

CONCLUSION: We observed a detrimental role of sepsis on neurologic outcomes in the subgroup of patients who had experienced pre-ECMO cardiac arrest, but not in other patients.

KEYWORDS: brain injury; extracorporeal membrane oxygenation; neuron-specific enolase; S100 calcium-binding protein beta; sepsis

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is increasingly used in refractory cardiogenic shock or refractory cardiac arrest (1). In cardiogenic shock patients, survival rates are over 40% at hospital discharge (1, 2). In patients requiring VA-ECMO during

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KEY POINTS

Question: Is sepsis associated with poorer functional outcomes in adult patients treated with venoarterial extracorporeal membrane oxygenation (VA-ECMO)?

Findings: In this cohort study, we observed a detrimental role of sepsis on neurologic outcomes in the subgroup of patients who had experienced pre-ECMO cardiac arrest, but not in other patients. Compared with non septic patients, patients with sepsis had higher serum concentrations of S100 calcium-binding protein beta and more frequent EEG alterations, suggesting brain injury.

Meaning: Sepsis at time of VA-ECMO initiation is an independent risk factor of poor functional outcome in patients who had experienced pre-ECMO cardiac arrest, but not in other patients.

cardiopulmonary resuscitation (extracorporeal cardiopulmonary resuscitation, ECPR), a survival rate with an acceptable neurologic prognosis is observed in less than 30% of cases (3, 4).

Neurologic complications are frequent, reported in 15% of adult patients during VA-ECMO, and associated with excess mortality and a poor functional prognosis in survivors (5, 6).

VA-ECMO is applied in conditions of refractory cardiac arrest or refractory circulatory failure, putting the brain at high risk of injury, notably of hypoxic and/or ischemic origin. Furthermore, neurologic outcomes of patients under venoarterial ECMO (VA-ECMO) may be worsened by secondary insults of systemic origin. In recent studies, hyperoxia under VA-ECMO was associated with a higher risk of developing ischemic brain injury (7). Recently, higher Pao_2 levels and greater decreases between pre-ECMO $Paco_2$ and postcannulation $Paco_2$ were associated with a higher risk of cerebrovascular complications and poorer outcomes (8). In this regard, avoiding hyperoxia and important $Paco_2$ drops at time of ECMO cannulation may reduce secondary brain injury and help improve neurologic outcomes.

Sepsis is associated with neurologic complications, both in the acute phase and in the long term (9–11).

The neurologic consequences of sepsis have been studied in the general intensive care setting, but not among VA-ECMO patients (12, 13). Different noninvasive tools may help clinicians identify brain injury and assist with prognostication during VA-ECMO support (14). These tools include a clinical evaluation using automated pupillometry (15), serum neuronal/glial injury biomarkers (16), spot or continuous EEG (17, 18), and neuroimaging in selected cases (19).

We hypothesized that in patients undergoing VA-ECMO therapy, the presence of early-onset sepsis within the first 48 hours following cannulation may play a role in causing additional cerebral dysfunction and injury. This, in turn, could result in subsequent compromised functional outcomes when compared with patients who did not encounter early-onset sepsis.

MATERIALS AND METHODS

Patients

This single-center retrospective "exposed-unexposed" cohort study was from 2013 to 2020 in the medical and surgical ICUs of the Bichat-Claude Bernard University Hospital, Paris, France. The local ethics committee reviewed and approved the study (institutional review board 00006477). The procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975.

All patients admitted to one of the units requiring VA-ECMO for refractory cardiogenic shock or cardiac arrest were eligible for inclusion. Exclusion criteria were: 1) age under 18 years, 2) moribund patients, that is, with early death within the first 24 hours following ECMO initiation, and 3) patients who had no EEG during ICU stay.

Clinical Parameters

Data recorded at admission were age, gender, Charlson comorbidity index (20), body mass index, a history of brain injury, Simplified Acute Physiology Score (SAPS) II (21), and the reason for ICU admission (i.e., postcardiac surgery or a cardiogenic shock of medical origin). Data recorded at VA-ECMO initiation included pre-ECMO cardiopulmonary resuscitation, Sepsis-related Organ Failure Assessment (SOFA) score (22), site of VA-ECMO cannulation, use of catecholamines, renal replacement therapy, and invasive mechanical ventilation. A standardized neurologic evaluation performed

by one of the investigators at the time of EEG recording included the presence of ongoing sedation, Glasgow Coma Scale score (23), and Richmond Agitation-Sedation Scale score (24).

Sepsis Definitions

We defined two groups at the time of VA-ECMO cannulation: A "sepsis" group and a "no sepsis" group. The "sepsis" group was defined by: 1) a suspected or documented infection requiring antibiotic treatment within 48 hours of VA-ECMO cannulation, and 2) at least one organ failure, defined by a SOFA score greater than or equal to 2. Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be identified as an acute change in total SOFA score greater than or equal to 2 points consequent to the infection. Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain mean arterial pressure greater than or equal to 65 mm Hg and having a serum lactate level greater than 2 mmol/L (18 mg/dL) despite adequate volume resuscitation (25). The "no sepsis" group was defined by the absence of the two aforementioned criteria.

EEG Protocol

Electroencephalographic recordings consisted of a 30-minutes standard EEG, recorded after ECMO initiation between day 1 and day 3. EEG was recorded using 21 electrodes placed according to the international 10–20 system and interpreted by independent neurophysiologists, blinded to the patient's condition and outcomes. EEG interpretation focuses on the continuous or discontinuous background activity, the background rhythm, the auditory and nociceptive reactivity, and the presence or the absence of sleep transients. We used critical EEG terminology to interpret EEGs (26). Discontinuous background activity was defined when 10–49% of the record consisted of periods of lower voltage, that is, attenuation (> 10 μV) or suppression (< 10 μV). As defined above, burst suppression was defined as greater than or equal to 50% of the record consisting of attenuation or suppression. EEG reactivity was tested at the bedside according to a standardized protocol for each patient, in line with a recent international consensus (27). The stimulus protocol consisted of auditory (clapping, calling out the patient's name) and noxious (pinching, nail bed pressure) stimuli, repeated twice at the beginning and twice at the end of the EEG recording. EEG reactivity was defined as reproducible, diffuse, and transient changes in EEG activity (i.e., amplitude and/or frequency) in response to stimulation. Severe background abnormalities were defined by the presence of a discontinuous and/or unreactive background. Sleep transients were characterized by a combination of spindles (defined by an oscillation frequency from 12 to 16 Hz symmetrical, central-midline maximal, with a duration of at least 500 ms).

Blood Biomarkers

Blood samples were collected on days 1 and 3 after VA-ECMO initiation, allowed to clot 30 min at room temperature, centrifuged at 3000 rpm at 20°C, and stored in aliquots at 80°C until assayed. Neuron-specific enolase (NSE) and S100 calcium-binding protein beta (S100β) concentrations in sera were measured in batches at the end of the study and were therefore not used for prognostication during hospitalization. Samples presenting visible hemolysis were excluded. A quantitative assessment of NSE concentrations was obtained using time-resolved amplified cryptate emission technology on a Kryptor KC+ analyzer (BRAHMS, Hennigsdorf, Germany). S100β was measured using an immunometric method on a Roche Cobas analyzer (Roche Diagnostic, Meylan, France).

Neuroimaging

All radiologic reports of neuroimaging studies performed during ECMO support were reviewed for study purposes. Patients were described according to five types of a priori-defined lesion patterns: 1) cerebral ischemia, 2) cerebral hemorrhage, 3) brain death, 4) diffuse anoxic injury, and 5) diffuse cerebral edema.

Outcomes

The primary outcome measure was poor functional outcome at 90 days, defined by a score greater than or equal to 4 (indicating severe disability or death) on the mRS. Functional outcomes evaluated during follow-up consultations were retrieved from medical records and scored using the simplified mRS questionnaire.

Secondary outcome measures included NSE and S100β blood concentrations, EEG parameters (i.e., background rhythm, reactivity, continuity, and presence/absence of sleep patterns) measured within 72 hours after VA-ECMO cannulation, duration of VA-ECMO and ICU stays, and mortality at 90 days.

Statistical Analysis

Qualitative and quantitative data were described as counts (percent) and median (interquartile range). Data were compared between the "sepsis" and "no sepsis" groups with the Chi-square (with Yates' continuity correction when needed) and Wilcoxon tests for qualitative and quantitative variables, respectively. S100β and NSE concentrations on day 1 and day 3 were visualized using Boxplots, and concentrations were compared between the "sepsis" and the "no sepsis" groups using Wilcoxon tests adjusted for multiple comparisons (18).

We then investigated the effect of sepsis on poor neurologic outcomes (modified Rankin Scale [mRS] ≥ 4 and mortality at 90 days) both in crude and multivariate logistic regression analyses. As an interaction between sepsis and pre-ECMO cardiac arrest was observed, all subsequent analyses were performed according to pre-ECMO cardiac arrest (yes/no) status. EEG parameters were described and compared by sepsis group distinctly among patients with or without pre-ECMO cardiac arrest. A propensity score for sepsis was calculated by logistic regression including the following variables: age, gender, and SAPS II. These variables were chosen as they might be associated with a different risk of sepsis in VA-ECMO patients. Overlapping of propensity score distributions among "sepsis" and "no sepsis" patients was checked graphically. To better control for selection and confusion bias due to a potential disequilibrium between sepsis and no sepsis patients, inverse probability of treatment weighting (IPTW) based on the propensity score was used to assess the association between sepsis and poor neurologic outcomes. All *p* values are two-sided and a *p* value less than 0.05 was considered significant. Statistics were performed using R software (R for Statistical Computing).

RESULTS

Patients' Characteristics at ICU Admission

Over the study period, 217 patients requiring VA-ECMO were admitted to the ICU. A study flowchart is provided in **Figure S1** (http://links.lww.com/CCX/B303), and 196 patients (age 57 yr [47; 64], predominantly males [73%]) were included (**Table 1**). Charlson score, SAPS II, and SOFA score at ICU admission were 2 (1; 3), 61 (47; 78), and 11 (9; 13), respectively. Patients were admitted to the ICU for acute medical conditions in 67.3 % (*n* = 132) and postoperatively in 32.7% (*n* = 64). Eighty-seven (44.4%) patients had received cardiopulmonary resuscitation (CPR) before VA-ECMO initiation (postcardiac arrest shock, *n* = 56, 28.6%; extracorporeal cardiopulmonary resuscitation [ECPR], *n* = 31, 15.8%), with a no-flow duration of 0 (0; 0) minutes, and a low flow duration of 18 (5; 50) minutes.

Patients' Characteristics at Inclusion

The SOFA score at inclusion was 10 (12; 14). All patients were under invasive mechanical ventilation, 169 (86.7%) patients received a continuous infusion of sedative and opioid drugs (Richmond Agitation-Sedation Scale of -5 [–5; –4]), and 49 (25.1%) patients received neuromuscular blocking agents. Overall, 128 (65.3%) patients with sepsis criteria formed the "sepsis" group, including 80 of 120 patients in septic shock (66.7%), and 68 patients without sepsis formed the "no sepsis" group. In the "sepsis" group, the infection was documented in 69 of 128 (53.9%) patients. Main infections included pneumonia (*n* = 40/69, 58%), bloodstream infections (*n* = 15/69, 21.7%), skin and soft-tissue infections (*n* = 11/69, 15.9%), and abdominal infections (*n* = 3/69, 4.3%). The most common pathogens consisted of Gram-positive cocci in 47 of 69 patients (68.1%), Gram-negative bacilli in 28 of 69 patients (55.1%), and nonfermenting gram-negative bacilli in 6 of 69 patients (8.7%). The initial antibiotic therapy included beta-lactams in 121 of 128 patients (94.5%), and fluoroquinolones in 5 of 128 patients (3.9%).

Outcomes

A poor functional outcome was observed in 99 of 128 (77.3%) patients of the "sepsis" group and 46 of 68 (67.6%) of the "no sepsis" group (crude odds ratio [OR] 1.63; 95% CI, 0.84–3.14; adjusted logistic regression OR 1.21; 95% CI, 0.58–2.47; IPTW OR 1.24; 95% CI, 0.79–1.95). Subsequent analyses performed according to pre-ECMO cardiac arrest status suggested that sepsis was independently associated with poorer

TABLE 1.
Patients' Characteristics

	Missing, *n*	All (*n* = 196)	Sepsis (*n* = 128)	No Sepsis (*n* = 68)	*p*
Epidemiology					
Age, yr, median (IQR)	0	57 (47, 64)	57 (49, 65)	55 (44, 62)	0.55
Male gender, *n* (%)	0	143 (73)	104 (81)	39 (57)	< 0.001
Body mass index (kg/m^2), median (IQR)	28	26.3 (23.3, 30.7)	26.5 (23.7, 30.2)	25.3 (22.7, 31.2)	0.20
Comorbidities	0				
Cardiac disease, *n* (%)		124 (63)	79 (62)	45 (66)	0.54
Chronic obstructive pulmonary disease/asthma, *n* (%)		41 (21)	28 (22)	13 (19)	0.65
Diabetes, *n* (%)		57 (29)	39 (31)	18 (27)	0.56
Chronic renal failure, *n* (%)		28 (14)	21 (16)	7 (10)	0.24
Cirrhosis, *n* (%)		4 (2)	3 (2)	1 (2)	0.68
Neurologic comorbidities, *n* (%)		29 (15)	19 (15)	10 (15)	0.98
Modified Rankin Scale before ICU admission ≤ 2, *n* (%)		190 (97)	123 (96)	67 (99)	0.041
Charlson score ≥ 2, *n* (%)		103 (53)	72 (56)	31 (46)	0.16
ICU admission characteristics					
Acute medical condition, *n* (%)	0	132 (67)	88 (69)	44 (65)	0.57
ECPR		31 (16)	26 (20)	5 (7)	
Other medical cardiogenic shocks		91 (51)	62 (49)	39 (58)	
Postcardiotomy shock, *n (%)*	0	64 (33)	40 (31)	24 (35)	
Richmond Agitation-Sedation Scale, median (IQR)	3	−5 (−5, −4)	−5 (−5, −4)	−4.5 (−5, -4)	0.051
Simplified Acute Physiology Score II, median (IQR)	0	61 (47, 78)	64 (53, 82)	52 (41, 68)	0.010
Sepsis-related Organ Failure Assessment score, median (IQR)	0	11 (9, 13)	12 (9, 14)	10 (8, 13)	0.20
Pre-extracorporeal membraneoxygenation cardiac arrest, *n* (%)	0				0.054
No		109 (56)	66 (52)	43 (63)	
Postcardiac arrest shock		56 (29)	36 (28)	20 (29)	
ECPR		31 (16)	26 (20)	5 (7)	
Temperature in °C, median (IQR)	6	36.7 (36.2, 37.0)	36.6 (36.1, 37.0)	36.8 (36.4, 37.0)	0.41
Biological data, median (IQR)					
pH	3	7.40 (7.34, 7.47)	7.40 (7.34, 7.43)	7.42 (7.35, 7.47)	0.097
HCO_3^-, mmol/L	3	23 (20, 25)	22 (19, 24)	25 (22, 27)	0.007
$PaCO_2$, mm Hg	0	37 (33, 42)	37 (33, 41)	39 (34, 43)	0.14
PaO_2, mm Hg	0	113 (82, 163)	113 (82, 153)	116 (84, 192)	0.72
Lactates, mmol/L	4	2.2 (1.4, 3.9)	2.5 (1.5, 4.4)	2.0 (1.2, 2.7)	0.013
Na, mmol/L	0	142 (139, 145)	142 (140, 145)	142 (137, 143)	0.24

ECPR = extracorporeal cardiopulmonary resuscitation, IQR = interquartile range.

functional outcomes in the "pre-ECMO cardiac arrest" subgroup (adjusted logistic regression OR 3.44; 95% CI, 1.06–11.40; IPTW OR 3.52; 95% CI, 1.68–7.73), whereas no such association was observed in patients without pre-ECMO cardiac arrest (adjusted logistic regression OR 0.69; 95% CI, 0.27–1.69; IPTW OR 0.76; 95% CI, 0.42–1.35) (**Table 2**).

The probability density function of the propensity score for sepsis is summarized in **Figure S2** (http://links.lww.com/CCX/B303) and illustrates a mild overlap between "sepsis" and "no sepsis" patients. After weighing, no significant imbalance was observed (**Fig. S3**, http://links.lww.com/CCX/B303). Overall, we found no significant difference between "sepsis" and "no sepsis" patients, in terms of Rankin score greater than or equal to 4, with an adjusted weighted OR of 1.21 (95% CI, 0.58–2.47) and an IPT weighted OR of 1.24 (95% CI, 0.79–1.95).

The serum S100β protein concentration measured on day 1 was statistically higher in the "sepsis" group (0.94 µg/L vs. 0.52 µg/L, $p = 0.03$), compared with the "no sepsis" group (**Fig. 1**), whereas concentrations measured at further time points were similar. NSE concentrations measured on day 1 and day 3 were comparable between "sepsis" and "no sepsis" patients (**Table S1**, http://links.lww.com/CCX/B303).

EEG characteristics are presented in **Table S2** (http://links.lww.com/CCX/B303). "Sepsis" patients had lower maximal background frequencies, more frequent discontinuous EEG backgrounds, and less frequent sleep transient patterns, as compared with "no sepsis" patients. Pre-ECMO cardiac arrest patients with sepsis had the worst EEG patterns with respect to discontinuous background alterations, unreactive background, and sleep transients (Table S2, http://links.lww.com/CCX/B303).

At 90 days, 122 patients (62.2%) were dead. We observed no statistically significant difference in mortality rates in univariate analysis between the "sepsis" and the "no sepsis" groups (85/128 [66.4%] vs. 37/68 [54.4%]; OR 1.66; 95% CI, 0.91–3.03). Subsequent analyses performed according to pre-ECMO cardiac arrest status are presented in **Table S3** (http://links.lww.com/CCX/B303).

Overall, 110 of 196 patients had brain imaging during ECMO support, 65 in the "sepsis" group and 45 in the "no sepsis" group. There was no significant difference between the two groups for the five types of lesions described (**Table S4**, http://links.lww.com/CCX/B303).

DISCUSSION

In adults treated with VA-ECMO, sepsis at the time of VA-ECMO cannulation was associated with significant neurobiological and neurophysiologic changes

TABLE 2.
Association of sepsis with neurologic outcome, multivariate analyses

	No Pre-ECMO Cardiac Arrest ($n = 109$)			Pre-ECMO Cardiac Arrest ($n = 87$)			Interaction[a]
	Sepsis ($n = 66$)	No Sepsis ($n = 43$)	OR[b] (95% CI)	Sepsis ($n = 62$)	No Sepsis ($n = 25$)	OR[b] (95% CI)	*p*
Poor functional outcome at 90 days (modified Rankin Scale ≥ 4)							
n (%)	45 (68)	30 (70)		54 (87)	16 (64)		
Unadjusted			0.93 (0.40–2.12)			3.80 (1.14–11.75)	0.046
Adjusted[c]			0.69 (0.27–1.69)			3.44 (1.06––11.40)	0.038
Inverse probability of treatment weighted			0.76 (0.42–1.35)			3.52 (1.68–7.73)	0.001

ECMO = venoarterial extracorporeal membrane oxygenation, OR = odds ratio.

[a]Test of interaction between sepsis and pre-ECMO cardiac arrest in the association with poor functional outcome at 90 days.

[b]OR of the association between sepsis (yes vs. no) with poor with poor functional outcome at 90 days (yes vs. no).

[c]Adjusted on age, gender, Simplified Acute Physiology Score II.

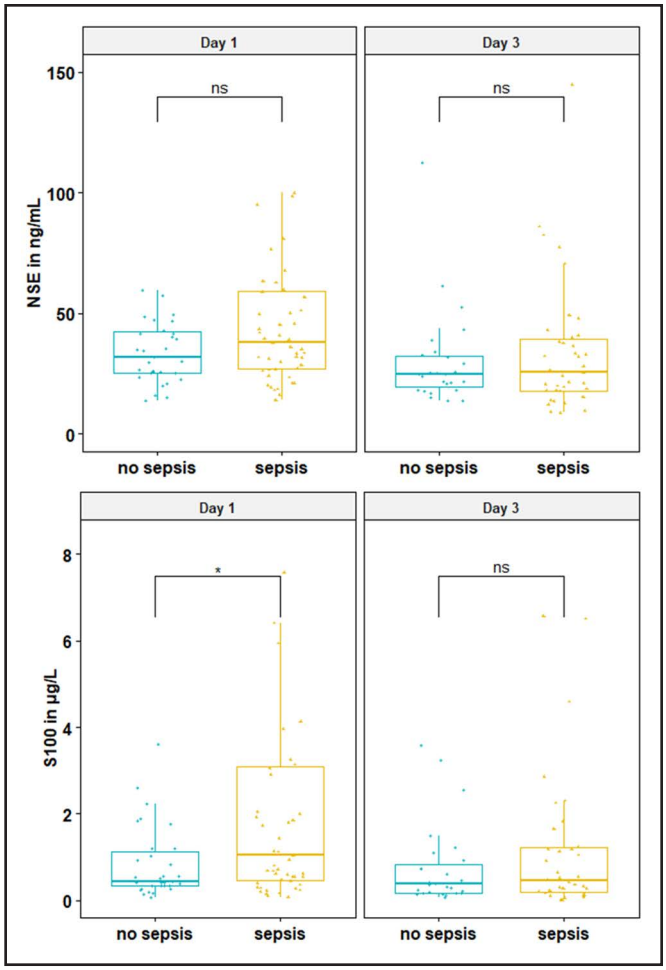

Figure 1. S100 calcium-binding protein beta (S100β) and neuron-specific enolase (NSE) serum concentrations in the "sepsis" and "no sepsis" groups. NS = not significant. *$p < 0.05$.

suggesting brain injury. Specifically, we observed an early increase in serum levels of S100β protein, and electrophysiology alterations suggestive of severe encephalopathy, including diffuse slowing, discontinuous background activity, and absence of sleep transients. These results suggest that sepsis represents a relevant cause of secondary insult of systemic origin in adult patients treated with VA-ECMO, which should be systematically investigated and treated. However, the impact of these early changes on outcomes remains uncertain. Indeed, we observed a detrimental role of sepsis on neurologic outcomes in the subgroup of patients who had experienced pre-ECMO cardiac arrest, but not in other patients.

In our study, sepsis was associated with early changes in S100β serum concentrations, a well-known blood marker of glial injury. Our results are in line with the rapid kinetics of the S100β protein, which can be detected in the first hours after brain injury (28). S100β is associated with poor outcomes in various conditions, including cardiac arrest (29), traumatic brain injury (30), and stroke (31). S100β has also been associated with neurologic complications and worse outcomes in the ECMO population (32, 33). A systematic review and meta-analysis suggest that serum levels of S100β protein may be a useful diagnostic and prognostic biomarker of sepsis-associated encephalopathy (34). Elevated S100β levels observed in our study likely reflect early blood-brain barrier alterations associated with sepsis and associated astrocyte injury. NSE is a marker of neuronal injury, with slower kinetics than S100β, with peak concentrations being observed 24–48 hours after injury. Elevated NSE is associated with poor outcomes in brain-injured and nonbrain-injured patients.

Recent studies suggested an association between NSE levels and outcomes in cardiac arrest patients (35), stroke patients (36), VA-ECMO patients (16), and sepsis-associated encephalopathy (37). The absence of a significant association between NSE levels and sepsis in our study may be confounded by several factors, including cerebral hypoxia before ECMO cannulation, and hemolysis. Furthermore, NSE and S100β are not specific to neurons and astrocytes, respectively. Therefore, it is not clear to what extent non-neurologic organ injury might have contributed to elevated serum concentrations in this setting.

In our study, patients with sepsis had severe EEG alterations, as compared with patients without sepsis. Specifically, we observed severe lower maximal background frequencies, more frequent discontinuous EEG backgrounds, and less frequent sleep transient patterns in sepsis patients as compared with their counterparts. These patterns have been associated with poor prognoses in patients under VA-ECMO, irrespective of sepsis at the time of cannulation (17, 38, 39). Our study confirms that sepsis is a significant risk factor for developing such severe neurophysiologic alterations at the early phase of VA-ECMO support.

Previous studies investigating EEG alterations in sepsis identified that a slower background rhythm in the delta or theta frequencies was observed in 50% of patients and that the absence of reactivity was an independent predictor of mortality (9).

In our study, we also aimed to assess the association of sepsis with patient-centered outcomes. We observed

no significant difference in Rankin scores at day 90 between the "sepsis" and "no sepsis" groups in crude and adjusted analyses. However, we observed a detrimental role of sepsis on neurologic outcomes in the subgroup of patients who had experienced pre-ECMO cardiac arrest. Although this remains speculative, it is likely that such patients, who experienced severe hypoxic brain injury, may be more sensitive to secondary insults of systemic origin, including sepsis.

We observed no significant difference in any of the secondary outcomes, including mortality at day 90, ECMO duration, and ICU length of stay. It should be noted that although our study likely represents the largest cohort evaluating neurobiochemical and neurophysiologic alterations at the early phase of ECMO support, it is likely underpowered to detect an independent association between sepsis and these secondary outcomes. Indeed, our cohort is heterogeneous with respect to ECMO indications, and VA-ECMO is associated with a myriad of complications that may impact survival and functional recovery, irrespective of early-onset complications.

Our study also highlights the value of early multimodal non-invasive monitoring in VA-ECMO patients to identify possible factors of poor neurologic prognosis and aid in decision-making.

This study has several limitations. First, this is a single-center study with an inherent bias in patient recruitment. The external validity of the results deserves to be evaluated in further studies. Furthermore, there is a lack of standardized cutoff values for NSE and S100β, leading to variations in their clinical interpretation across different studies and institutions. However, we used the same method for all measurements in our study. A lack of power and heterogeneity of indications for ECMO support possibly limits the interpretation of the primary and secondary outcome measures. Analyzing larger specific subgroups (i.e., ECPR, medical, and postoperative patients) would probably be helpful in future prospective multicenter studies to better understand the detrimental role of sepsis on neurologic outcomes.

CONCLUSIONS

Sepsis at the time of VA-ECMO cannulation is associated with acute neurobiochemical and neurophysiologic alterations in the form of an early rise in serum S100β protein concentrations and severe EEG changes. We observed a detrimental role of sepsis on neurologic outcomes in the subgroup of patients who had experienced pre-ECMO cardiac arrest, but not in other patients.

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Drs. Tridon, Peoc'h, Bachelet, Eloy, and Sonneville were involved in study conception. Drs. Tridon, Ortuno, and Vellieux were involved in data collection. Drs. Bachelet and Eloy were involved in statistical analysis. Drs. Tridon, Peoc'h, and Sonneville were involved in writing of the article. All co-authors substantially contributed to the writing of this article and approved the final version of the article before submission.

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The dataset analyzed during the study is available from the corresponding author upon reasonable request.

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