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Editorial on “Neurologic injury in adults supported with veno-venous extracorporeal membrane oxygenation for respiratory failure: findings from the Extracorporeal Life Support Organization database”

Nicolas Persico^{1,2}, Jeremy Bourenne³, Antoine Roch^{1,2}

¹Aix-Marseille Univ, APHM, Hôpital Nord, Réanimation des Détresses Respiratoires et Infections Sévères, Marseille, France; ²Emergency Department, APHM, CHU Nord, Marseille, France; ³APHM, CHU Timone, Réanimation, Marseille, France

Correspondence to: Prof. Antoine Roch, Emergency Department, APHM, CHU Nord, Chemin des Bourrelly, Marseille 13015, France.

Email: antoine.roch@ap-hm.fr.

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The technique of extracorporeal membrane oxygenation (ECMO) for patients with severe acute respiratory distress syndrome (ARDS) involves placing them on a veno-venous (VV) or veno-arterial (VA) life support circuit with a membrane oxygenator to temporarily take over the gas exchange and, sometimes, cardiac function (1). Over the last two decades, the technique has progressed significantly, and several studies have reported encouraging survival rates using mainly VV-ECMO in adults with ARDS (2-8). In the CESAR trial, an ECMO-based management protocol for selected ARDS patients transferred to a referral center was shown to improve 6-month disability-free survival (9). However, due to recent advances in the management of ARDS (10,11), ECMO remains a salvage therapy in a limited number of patients with life-threatening hypoxemia or respiratory acidosis (12).

Among potential complications occurring under ECMO, severe central nervous system (CNS) disorders such as stroke and intracranial hemorrhage (ICH) significantly affect prognosis and risk-benefit ratio of ECMO. Therefore, their risk factors should be better known and taken into account in the decision regarding whether to treat patients with ECMO. Recently, a French consensus conference precized that the risk-benefit ratio of ECMO

in ARDS should be considered unfavorable in cases of hemorrhagic or potentially hemorrhagic intracranial lesions and in case of coma following cardiac arrest (12). Neurological complications are among the most frequent under ECMO. In a cohort of 4,522 adult patients supported with VA-ECMO and included in the Extracorporeal Life Support Organization (ELSO) registry (13), CNS complications occurred in 15.1% of patients, and included brain death in 7.9%, cerebral infarction in 3.6%, seizures in 1.8%, and cerebral hemorrhage in 1.8%. Because VV-ECMO does not access the arterial circulation compared to VA-ECMO, risks and factors associated with CNS injury may be different. However, patients supported with VV-ECMO for respiratory failure often require prolonged ECMO support and complications such as damage to blood elements, hemolysis, thrombopenia and infections may increase the risk of all complications. Furthermore, the use of anticoagulation to prevent thrombosis can increase the risk of bleeding complications, including ICH (14). Some studies have investigated CNS complications in patients treated with VV-ECMO. Gray *et al.* (15), studied 353 adults supported with VV-ECMO and reported ICH or stroke in 10% of the cases. In the CESAR Trial (9), neurologic injury was observed in 4% of the ECMO cases. In 68 patients

treated with VV-ECMO during the 2009 H1N1 pandemic, 6 (9%) patients suffered from ICH. More recently, Luyt *et al.* (16) showed a 13% occurrence rate of CNS complications in a single-center experience of 135 adult VV-ECMO patients. Finally, in the largest study published to date (17), all patients receiving ECMO were selected from the US Nationwide Inpatient Sample between 2001 and 2011. Of 23,951 patients, 8,397 adults were included in this study. 10.9% suffered neurologic complications of seizure (4.1%), stroke (4.1%), or ICH (3.6%). Patients with ICH had a mortality rate of 59.7% *vs.* 50.0% in patients without ICH ($P<0.0001$). In this study, it was nevertheless not possible to distinguish between patients receiving VA and VV-ECMO, no definition of CNS complications was used and no data were available to determine risk factors of neurologic disorders.

In this sense, Lorusso *et al.* (18) recently published the results of an observational study which described neurological complications and their risk factors in a large cohort of patients treated with VV-ECMO. The authors used multicenter data from about 350 centers reported to the ELSO's data registry. Data from the standardized ELSO form were extracted on all adults who underwent single-run of VV-ECMO for respiratory failure during the January 1, 1992, through December 31, 2015 period. According to the ELSO's form, neurologic injury was categorized as brain death, ICH, stroke, and seizures reported during the ECMO run. ICH and stroke were defined based on their presence on CT scan. Univariate and then multivariable logistic regression with the forward stepwise method was used to identify covariates associated with neurologic injury. In the initial model, all variables with P value of less than 0.2 at univariate analysis were tested. To note, the model validation was performed using bootstrap method and conditional specification (Markov Chain Monte Carlo) was used to address missing values. The study cohort contained 4,988 adults with a median age of 46 years (interquartile range, 32–58). Four hundred and twenty-six neurologic complications occurred in 356 patients (7.1%) and included 290 (5.8%) with one, 62 (1.2%) with two, and four (0.1%) with three neurologic complications. Among the 426 neurologic events reported, there were 181 ICHs (42.5%), 100 brain deaths (23.5%), 85 strokes (19.9%), and 60 seizures. Although the rate of neurologic complications initially declined from 1992 to 2003, it remained constant in the recent time [2004–2015]. The in-hospital mortality was 75.8% for patients with neurologic complications, compared to 37.8% in patients without these complications

($P<0.001$). Mortality was 79.6% in patients with ICH, 68.2% in patients with stroke, and 50% in patients with seizures. Demographic as well as pre-ECMO support data in patients with or without neurological complications were similar regarding diagnostic category, ventilator and blood gas results. However, to note, patients with complications had received more narcotics and neuromuscular blockers, whereas no severity score was provided to evaluate the influence of pre-ECMO severity on the occurrence of neurological complications (19). Univariate analysis showed that patients with neurologic injury commonly experienced higher rates of acute renal insufficiency requiring or not hemofiltration, need for inotropic support during ECMO, systemic hypertension during ECMO requiring the use of vasodilators, cardiac arrhythmias, blood-proven infection, pneumothorax requiring treatment, pulmonary hemorrhage, pH less than 7.2 during ECMO support, and hyperbilirubinemia events (14.1%). Multivariate analysis showed that pre-ECMO cardiac arrest [odds ratio (OR), 3.127; 95% CI, 1.788–5.469], hyperbilirubinemia during ECMO (OR, 2.370; 95% CI, 1.446–3.886), and use of continuous VV hemofiltration (OR, 2.331; 95% CI, 1.280–4.426) were independent predictors of neurologic injury during VV-ECMO.

The limitations of this study are mainly related to its retrospective design and to incomplete data collection. Therefore, data on severity, site, exact timing, and functional impact of neurologic injury were not available for analysis. Although ICH and stroke were diagnosed on CT-scan, neurologic events reported to the registry were not adjudicated. The expected wide variability in center practices for management of anticoagulation and blood transfusions could not be investigated. Finally, long-term prognosis and sequelae from CNS injury were not evaluated.

Several important results must be emphasized. First, this study confirms a lower risk of CNS injury (7.1%) under VV than under VA-ECMO (15%) (13). The results of this study also confirm that cerebral bleeding is the most frequent form of neurologic injury during VV-ECMO and is associated with a very high probability of death. Factors likely associated with ICH occurrence notably include the underlying coagulopathy or anticoagulation use (20) suggesting that anticoagulation management is critical for prevention of neurologic injury during VV-ECMO. In the study by Lorusso *et al.* (18), 13.5% of patients with neurological complications had presented pre-ECMO cardiac arrest *vs.* 6.3% of patients without CNS

complications. Although the impact of pre-ECMO cardiac arrest on mortality was not studied, this result confirms that the indication of ECMO should be challenged in these patients. The reported increased risk of CNS injury in case of hyperbilirubinemia may be explained by increased coagulopathy due to hepatic dysfunction but also to hyperbilirubinemia as a marker of hemolysis. This is a limitation from this study since hyperbilirubinemia could be induced by very different mechanisms. This point should be further evaluated future studies. Finally, one major finding is the lack of decrease in CNS complications in the last 10 years despite continuous technical improvements. This result shows that the mechanisms of CNS complications are only partially understood and should be further investigated.

For the practice, the results of the study by Lorusso *et al.* (18) will help clinicians in paying attention to the risk of CNS complication occurring under VV-ECMO, notably in patients who have presented pre-ECMO cardiac arrest, and who present with hepatic or kidney dysfunction requiring hemofiltration. In those patients, a close monitoring of coagulation and anticoagulation should be performed.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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