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Modifiable Risk factors and mortality from ischemic and hemorrhagic strokes in patients receiving veno-arterial extracorporeal membrane oxygenation: Results from the Extracorporeal Life Support Organization Registry

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Abstract

Objectives: Although acute brain injury (ABI) is common in patients receiving extracorporeal membrane oxygenation (ECMO), little is known regarding the mechanism and predictors of ischemic and hemorrhagic stroke. We aimed to determine the risk factors and outcomes of each ischemic and hemorrhagic stroke in patients with venoarterial (VA)-ECMO support.

Design: Retrospective analysis.

Setting: Data reported to the Extracorporeal Life Support Organization by 310 extracorporeal membrane oxygenation centers from 2013 to 2017.

Patients: Patients more than 18 years old supported with a single run of VA-ECMO.

Interventions: None.

Measurements and Main Results: Of 10,342 V-A ECMO patients, 401 (3.9%) experienced ischemic stroke and 229 (2.2%) experienced hemorrhagic stroke. Reported ABI during V-A

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ECMO decreased from 10% to 6% in 5 years. Overall in-hospital mortality was 56%, but rates were higher when ischemic stroke and hemorrhagic stroke were present (76% and 86%, respectively). In multivariable analysis, lower pre-ECMO pH (adjusted odds ratio [aOR], 0.21; 95% CI, 0.09–0.49; $p<0.001$), higher PO₂ on first day of ECMO (aOR, 1.01; 95% CI, 1.00–1.02; $p=0.009$), higher rates of ECMO circuit mechanical failure (aOR, 1.33; 95% CI, 1.02–1.74; $p=0.03$), and renal replacement therapy (aOR, 1.49; 95% CI, 1.14–1.94; $p=0.004$) were independently associated with ischemic stroke. Female sex (aOR, 1.61; 95% CI, 1.16–2.22; $p=0.004$), ECMO duration (aOR, 1.01; 95% CI, 1.00–1.03; $p=0.02$), renal replacement therapy (aOR, 1.81; 95% CI, 1.30–2.52; $p<0.001$), and hemolysis (aOR, 1.87; 95% CI, 1.11–3.16; $p=0.02$) were independently associated with hemorrhagic stroke.

Conclusions: Despite a decrease in the incidence of ABI in recent years, mortality rates remain high when ischemic and hemorrhagic strokes are present. Future research is necessary on understanding the timing of associated risk factors to promote prevention and management strategy.

Introduction

Extracorporeal membrane oxygenation (ECMO) is a life-saving procedure that provides cardiopulmonary as well as circulatory support. The use of ECMO has increased exponentially in recent years¹. Prior analysis of the Extracorporeal Life Support Organization (ELSO) registry for years 1992–2013 showed that the presence of neurologic complications increases the risk of poor functional outcome and mortality from ECMO^{2,3}. In that study, 15% of adults with veno-arterial ECMO (V-A ECMO) support^{2,3} experienced neurologic complications, and among those, mortality ranged from 68% to 89%, depending on the number of complications^{2,3}. However, risk factors and predictors for ischemic and hemorrhagic stroke were not specifically addressed; instead, study authors analyzed all types of neurologic complications as one outcome variable. A recent comprehensive review of neurocritical care for patients receiving ECMO identified a large knowledge gap in the prevalence, mechanism, timing, and management of ECMO-related acute brain injury (ABI) defined as ischemic stroke, hemorrhagic stroke, and brain death⁴. The mechanisms of ischemic and hemorrhagic stroke likely differ in this population and have been understudied in ECMO-treated patients. Understanding these mechanisms may provide crucial information regarding how to prevent such complications and how to develop appropriate management strategies.

The aim of this study was to identify modifiable and non-modifiable risk factors of ischemic and hemorrhagic stroke in patients receiving V-A ECMO support and determine the outcomes associated with each based on information in a large registry database. We hypothesized that ischemic stroke and hemorrhagic stroke have different pre-ECMO and on-ECMO risk factors, and that these factors will impact outcome.

Materials and Methods

Study Design and Population

The ELSO registry is a voluntary international database that collects information on use, indications, complications, and outcomes of ECMO support in adults and children from 310 member centers worldwide⁵. Records stored in the registry include patient demographics, clinical characteristics, pre-ECMO conditions, hemodynamic and laboratory values collected before and during ECMO, complications that occur during ECMO support, including neurologic complications, and outcome data such as survival to hospital discharge. Diagnosis and medical history are reported according to the International Classification of Diseases (ICD) 9th edition (ICD-9) codes and ICD-10.

We carried out a retrospective analysis of the ELSO registry database for years 2013 through 2017. We included only patients 18 years and older who received one run of V-A ECMO support for either cardiac or respiratory failure. We excluded patients who underwent multiple runs to avoid complexity and bias in the analysis resulting from severe illness, as the morbidity during the inter-ECMO periods could introduce major confounders. Patients with veno-venous ECMO (V-V ECMO) also were excluded as the risk factors and mechanism of ABI between the V-V and V-A ECMO patients are different.

Data Collection and Definitions

For all included patients, we extracted the following information from the ELSO registry database: pre-ECMO demographic information; pre-ECMO clinical variables; cardiac diagnosis; pulmonary diagnosis; laboratory values; on-ECMO clinical variables, including hemodynamic data and other supportive cardiac devices; and ECMO-associated morbidity and mortality, including neurologic complications.

For ECMO indications, we selected three major categories—cardiac arrhythmia, postcardiotomy shock, and cardiac arrest. We combined the independent variable of “cardiopulmonary bypass” and the ICD code of “postcardiotomy shock” into one variable of “postcardiotomy shock” to capture all patients who had cardiogenic shock after cardiac surgery. Similarly, “pre-ECLS (extracorporeal life support) cardiac arrest” and “cardiac arrest” variables were combined. We did not include patients with the ELSO defined-extracorporeal cardiopulmonary resuscitation (ECPR). We created “additional mechanical support device” as a variable that included left (L) ventricular assist device (VAD), right (R) VAD, BiVAD, intra-aortic balloon pump, and percutaneous VAD. The “ECMO circuit mechanical failure” variable included oxygenator failure, cracks in pigtail connectors, clots in the hemofilter, clots in the circuit component, circuit change, cannula problems, air in the circuit, pump failure, and tubing rupture. The pre-ECLS hemodynamics and arterial blood gas (ABG) values were measured no more than 6 hours before ECLS; if the database contained multiple values, we chose those closest to the time of cannulation. Twenty-four-hour ABG values were drawn between 18 and 30 hours after ECLS start time. Renal replacement therapy occurred during ECMO support.

Neurologic complications included ischemic stroke, hemorrhagic stroke, brain death, and seizure. In the ELSO database, ischemic stroke is defined as central nervous system (CNS)

infarction determined by ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI). Hemorrhagic stroke is defined as intra- or extra-parenchymal CNS hemorrhage determined by ultrasound, CT, or MRI. The ELSO database has two seizure variables: those determined by clinical assessment and those confirmed by electroencephalogram. We combined these two variables as “seizure” for the analysis. The brain death definition followed the Canadian Neurocritical Care and American Academy of Neurology Guidelines^{6,7}. However, those guidelines do not include ECMO patients. The ELSO describes one method of apnea test in which patients are placed on continuous positive airway pressure while the sweep gas flow rate is set to a maximum of 1.0 L/min. If the PaCO₂ does not rise above 60 mmHg or change by 20 mmHg, the sweep flow can be incrementally lowered to as low as 0.1 L/min while still maintaining adequate oxygenation⁸. Although new neurologic variables, including “CNS diffuse ischemia,” “intraventricular hemorrhage,” and “neurosurgical intervention performed,” recently have been added to the ELSO database addendum, these were not available in 2013–2017. Additionally, subtypes of hemorrhagic stroke such as intracerebral hemorrhage, subarachnoid hemorrhage, and subdural hematoma were not available. This study was approved by the local institutional review board.

Statistical Analysis

Demographic and clinical variables in subjects with and without each type of neurologic injury (ischemic stroke, hemorrhagic stroke, and brain death) were compared by unpaired t-test, chi-square test, or Mann-Whitney U test as appropriate. Results are expressed as the mean with standard deviation for quantitative variables and as proportions for categorical findings. Ordinal or categorical data are reported as numbers and percentages. A *p* value <0.05 was considered statistically significant. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using logistic regression. We carefully selected clinically relevant variables that have biologically plausible associations or causality for inclusion in multivariable logistic regression analysis to identify factors that predicted each ischemic and hemorrhagic stroke. All analyses were carried out in STATA 14.2/MP (StataCorp, LLP, College Station, TX, USA).

Results

A total of 10,342 patients (median age 57 years, 67% male) who received V-A ECMO support in 2013–2017 were included in the study. The use of V-A ECMO increased over time from 1187 in 2013 to 2844 in 2017, representing a 2.4-fold increase in 5 years (Table 1). Of the 10,342 patients 813 (7.9%) had at least one type of ABI, including ischemic stroke, hemorrhagic stroke, or brain death (Fig. 1). Overall, 401 (3.9%) patients had ischemic stroke and 229 (2.2%) had hemorrhagic stroke. The rates of ECMO-associated ischemic stroke remained stable over 5 years (*p*=0.70). In contrast, the rates of hemorrhagic stroke and brain death decreased over time (*p*=0.003 and *p*=0.001, respectively; Tables 1 and 2, Supplemental Table 1). Overall, ABI during V-A ECMO decreased from 10% in 2013 to 6% in 2017 (Fig. 1). The mortality for all 10,342 patients was 56% over 5 years, a rate that increased to 76% in the presence of ischemic stroke and 86% in the presence of hemorrhagic stroke. Overall mortality was similar over time with a decreasing trend (from 58% to 55%,

$p=0.29$) during the study period (Supplemental Figure 1). A brain death diagnosis was reported in 266 (2.6%) of the patients. However, of those, only 28 (11%) were documented as having had ischemic strokes and 22 (8%) as having had hemorrhagic strokes. In contrast, 81% of patients with brain death had no associated neurologic diagnosis reported.

Among the 401 patients who had ischemic strokes, the median age was 57 and 68% were male. Patients who are white and whose ECMO indications were cardiac arrest and postcardiotomy shock, or who exhibited a lower pH, lower pCO_2 , lower serum HCO_3 , and higher mean arterial pressure (MAP) pre-ECLS were more likely than others to have ischemic stroke. Furthermore, additional mechanical support devices, higher PO_2 on ECMO, longer ECMO duration, and higher rates of ECMO complications, including ECMO circuit mechanical failure, renal replacement therapy, hemolysis, cardiac arrhythmias (not pre-ECMO), gastrointestinal hemorrhage, disseminated intravascular coagulation, and seizure, were associated with ischemic stroke (Table 1).

For the 229 patients with hemorrhagic stroke (median age 55, 57% male), younger age, female sex, white race, lower pre-ECMO pH, lower pre-ECMO PO_2 , and higher pre-ECMO HCO_3 values were identified as risk factors. A longer duration of ECMO support and higher rates of ECMO complications, including renal replacement therapy, hypoglycemia, hemolysis, cardiac arrhythmia (not pre-ECMO), gastrointestinal hemorrhage, disseminated intravascular coagulation, and seizure were risk factors for ECMO-associated hemorrhagic stroke (Table 2).

Significant risk factors for brain death were age, cardiac arrhythmia, and cardiac arrest as the indication for ECMO, pre- and on-ECMO severity of metabolic acidosis, and ECMO complications, including renal replacement therapy, cardiac arrhythmia (on-ECMO), disseminated intravascular coagulation, and seizures (Supplemental Table 1).

PO_2 at 24 hours of ECMO was higher among those who experienced ischemic stroke than among those who did not (167 vs. 145 mmHg, $p=0.006$; Supplemental Fig. 2). Similarly, PO_2 was higher among those with hemorrhagic stroke (163 vs. 146 mmHg, $p=0.27$) and those with brain death (184 vs. 145 mmHg, $p<0.001$; Supplemental Fig. 2).

In multivariable analysis, lower pre-ECMO pH, a higher PO_2 value in first 24 hours of ECMO support, higher rates of ECMO circuit mechanical failure, and renal replacement therapy were all independent risk factors for ischemic stroke (Table 3). For hemorrhagic stroke, female sex, ECMO duration, renal replacement therapy, and hemolysis were independent risk factors (Table 4).

Discussion

Incidence of Brain Injury and Mortality

Our analysis of data from 10,342 V-A ECMO patients in the ELSO registry showed that the reported incidence of ABI decreased between 2013 and 2017. In-hospital mortality with ABI was high, 76% for ischemic stroke and 86% for hemorrhagic stroke, similar to percentages reported previously^{3,4,9}. Rates of ischemic stroke (3.9%) and hemorrhagic stroke (2.2%)

were lower than previously published rates, which have ranged from 7% to 33%^{4,9–19} and 7% to 16%^{4,9,10,13,18,19}, respectively. In addition, although a CT study can detect hemorrhage with high sensitivity, it has low sensitivity for the detection of early cerebral ischemia and posterior fossa infarcts. In another study that reported neurologic injury in 87 adults treated with ECMO, although stroke was rarely diagnosed clinically, 9 of 10 brains studied at autopsy exhibited hypoxic-ischemic injury and hemorrhagic lesions²⁰. Such results suggest that the true prevalence of ABI is likely higher than that reported previously and in our current study²¹. Because ABI is associated with the immediate consequence of high mortality, early detection and prevention is critical. Recent observational studies, in which all ECMO patients received early routine CT scans, reported an incidence of 16.4% for hemorrhagic strokes in those treated with V-V ECMO²² and 10% in ECPR patients treated with V-A ECMO²³. Systematic neurologic monitoring, including sedation cessation protocols with electroencephalography, Transcranial Doppler (TCD) ultrasound, somatosensory evoked potentials, and CT brain studies increased the detection of ABI during ECMO support in a prospectively followed cohort^{9,24,25}. Given the high mortality associated with ABI, the results from our study underscore the importance of standardizing neurologic monitoring for diagnosis, and instituting prevention strategies that address the associated conditions that we found.

Ischemic Stroke

Our study provides evidence of modifiable risk factors that correlate with ECMO-associated stroke. We included clinically relevant variables for ischemic stroke in our multivariable analysis model and identified 4 independent risk factors: modifiable risk factors including hyperoxia at 24 hours of ECMO support and ECMO circuit mechanical failure; and non-modifiable risk factors including lower pre-ECMO pH and renal replacement therapy. It is important to remember that the ELSO registry did not differentiate hypoxic ischemic brain injury (HIBI) from ischemic stroke, hence limiting our ability to interpret the data. Despite this limitation, we may speculate that a higher rate of renal replacement therapy in the ischemic stroke group is partly, if not mostly, caused by multi-organ failure from the lack of adequate perfusion. This lack of adequate perfusion would include cerebral perfusion, resulting in HIBI. Similarly, a lower pre-ECMO pH was independently associated with ischemic stroke, again suggesting that inadequate pre-ECMO systemic perfusion leads to ischemic insult of the brain during the pre- or peri-cannulation time. Further analyses of ischemic stroke and HIBI are needed with more granular data to better understand the types of ABI.

When thromboembolism is a cause of ischemic stroke, there is a biologic and mechanistic plausibility for “ECMO circuit mechanical failure” being a strong modifiable risk factor. For example, arterial-sided oxygenator clots have been associated with TCD microembolic signal (MES), and TCD MES resolves when the circuit is switched out²⁵. In a similar cohort undergoing coronary artery bypass grafting (CABG), TCD MES was associated with neurologic deficits²⁶. However, no TCD studies used MRI correlation, which is the gold standard in assessing cerebral infarcts. Prospective studies are warranted to establish a causal relation between embolic ischemic stroke and ECMO circuit arterial-sided clot⁹, as this represents a potentially modifiable risk factor for ischemic stroke.

Hyperoxia

It is well established that after cardiac arrest and acute stroke, early hyperoxia resulting in oxidative stress with free radical formation and neurotoxicity is a predictor of poor neurologic function^{27,28}. However, the effect of hyperoxia on ECMO patients is unclear. In pediatric studies that have examined this specific question, moderate hyperoxia in the first 48 hours was an independent risk factor for increased mortality [$PO_2 > 193$ mmHg in 93 patients with V-A ECMO²⁹; >200 mmHg in 87% of V-A ECMO patients³⁰]; however, evidence is limited in the adult population. In a prior analysis of the ELSO registry from 2010 through 2015, hyperoxia, defined as a $PO_2 > 100$ mmHg at 24 hours, was associated with increased mortality in patients treated with V-V ECMO and ECPR, but not V-A ECMO. However, neurologic injury was not analyzed as an outcome³¹. Our study suggests that hyperoxia within 24 hours of ECMO is associated with ABI, which is a modifiable risk factor. Clearly, additional research is needed to determine if targeting early normoxia in this population improves neurologic outcomes.

Hemorrhagic Stroke

Intracerebral hemorrhage appears to be the most common type of hemorrhagic stroke in patients treated with ECMO, followed by subarachnoid hemorrhage and subdural hematoma^{22,32}. All of these subtypes have different risk factors, a subject which to date is understudied. Similar to ischemic stroke, the timing and mechanisms of hemorrhagic stroke are not well characterized. Risk factors for ECMO-associated hemorrhagic stroke reported in prior studies included the use of antithrombotic therapy^{33,34}, thrombocytopenia^{32,35}, central cannulation³⁵, longer ECMO duration³⁶, bloodstream infection³⁴, and renal failure^{4,33,37}. In our study, female sex was an independent risk factor for hemorrhagic stroke as was renal replacement therapy, and longer ECMO duration (5 vs. 4 days), although the effect of duration was small, with an aOR of only 1.01. These are all non-modifiable risk factors. Interestingly, patients with hemorrhagic stroke were 1.9 times more likely than those without hemorrhagic stroke to have significant hemolysis (plasma hemoglobin >50 mg/dL). One interpretation could be that non-pulsatile mechanical circulatory support devices such as LVAD and ECMO cause endothelial cell dysfunction with subsequent acquired von Willebrand syndrome (Factor VIII deficiency), a known risk factor for bleeding^{34,38}. However, hemolysis and subclinical pump thrombosis, (which would cause the elevations in plasma free hemoglobin that we observed) are known risk factors for *ischemic infarct* in the LVAD population³⁹, not hemorrhagic stroke. Notably, hemolysis is associated with significant thrombocytopenia, acute renal failure, dialysis, and hence, and a longer ECMO duration⁴⁰. Therefore, it is possible that statistical associations of hemorrhagic stroke with renal replacement therapy and hemolysis represent ongoing ECMO complications associated with a longer ECMO support time and anticoagulation exposure, leading to an increased risk of hemorrhagic transformation of acute ischemic stroke. Based on the data, we suggest that patients treated with long runs of ECMO who have ongoing hemolysis and require dialysis need more intense, protocolized neurologic monitoring⁹ to detect hemorrhagic stroke early. In this setting, though, decreasing anticoagulation intensity represents a double-edged sword, trading less risk for hemorrhage extension at the risk of ECMO thrombosis.

Strengths and Limitations

Strengths of our study include a large sample size and high statistical power. However, the study had limitations as well. As mentioned above, the ELSO registry is a voluntarily reported database with varying degree of missing data for each variable and without central or local adjudication of neurologic diagnosis. Uncertainty exists for each type of brain injury diagnosis included in the analysis. Of 266 brain deaths, only 19% were coded as strokes (28 ischemic and 22 hemorrhagic), whereas 81% provided no underlying neurologic diagnosis. Although this can be conceived as a limitation, this is likely due to earlier termination of ECMO in patients with brain death (ECMO duration: 70 vs. 107 hours for no brain death), resulting in under-diagnosis of acute brain injury. The incidence of brain injury in the ELSO registry likely is an underestimation. Moreover, the fact that hemorrhagic stroke imaging was not available is problematic as the pathophysiology differs for lobar and deep ICH, at least in the non-ECMO population. Also, despite independent statistical associations in our multivariable logistic regression models, we were unable to develop any “predictors” for each type of stroke owing to the retrospective study design and uncertainty regarding the timing of strokes and CT scans. Some of the univariate associations may be significant by chance, as multiple comparisons were performed. Also, it is important to emphasize that interpretation of our study results should take into account the clinical significance by looking at the actual treatment effect and should not be solely based on statistical significance, which may be simply due to the large sample size. Therefore, we made an effort to address this limitation by carefully selecting clinically meaningful variables that have biologically plausible associations or causality for inclusion in the final models. The ELSO registry is the largest international repository of ECMO data, offering a distinctive opportunity to evaluate the incidence, trend, mortality, and independent risk factors of each ischemic and hemorrhagic stroke in a large number of patients. Lastly, ABI reported from the ELSO registry is an underestimation of true incidence. A meta-analysis of studies in which patients underwent systematic MRI after CABG showed a 27% cerebral infarct rate⁴¹ and a systematic review of ECMO studies reported 13% of neurologic complications⁴², suggesting that ECMO patients may have just as many, if not more, ABIs. As the use of ECMO is increasing exponentially, future research should be directed toward developing neurologic monitoring and management strategies for early recognition and targeted management.

Conclusions

Despite a decrease in the incidence of ABI in recent years, mortality rates remain high in patients with ischemic and hemorrhagic strokes. Understanding the associated modifiable risk factors may aid in prevention of ABI occurrence by targeting early normoxia and managing ECMO circuit mechanical failure aggressively.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
The incidence of acute brain injury in patients treated with venoarterial extracorporeal membrane oxygenation, 2013–2017. Data were collected from the Extracorporeal Life Support Organization registry.

Table 1.

Baseline demographics and extracorporeal membrane oxygenation variables in patients who experienced ischemic stroke while treated with venoarterial extracorporeal membrane oxygenation

Variable	No Ischemic Stroke (n=9,941)	Ischemic Stroke (n=401)	p
Age, * yrs	57 (46–66)	57 (44–64)	0.08
Weight, * kg	82 (70–99)	84 (71–100)	0.22
Male *	6,398 (67)	270 (68)	0.69
Race			
White	5,691 (59)	262 (67)	0.002
Asian	1,174 (12)	42 (11)	
Black	870 (9)	40 (10)	
Hispanic	472 (5)	16 (4)	
Others	1,487 (15)	44 (11)	
Year of ECLS			
2013	1,134 (11)	53 (13)	0.70
2014	1,537 (15)	61 (15)	
2015	2,044 (21)	87 (22)	
2016	2,483 (25)	99 (25)	
2017	2,743 (28)	101 (25)	
ECMO indications/diagnosis			
Cardiac arrhythmia	385 (4)	19 (5)	0.38
Postcardiotomy shock	1,846 (19)	94 (23)	0.01
Cardiac arrest *	2,914 (32)	159 (40)	<0.001
Additional mechanical support device	2,677 (27)	141 (35)	<0.001
Pre-ECMO ABG			
pH *	7.27 (7.16–7.37)	7.25 (7.11–7.33)	<0.001
CO ₂ , * mmHg	41 (33–52)	44 (35–56)	0.03
PO ₂ , * mmHg	90 (61–187)	86 (5–186)	0.48
HCO ₃ , * mmol/L	19.3 (15.3–23.0)	19.3 (15.3–22.0)	0.048

Variable	No Ischemic Stroke (n=9,941)	Ischemic Stroke (n=401)	p
Pre-ECMO mean blood pressure, * mmHg	60 (50–72)	61 (51–72)	0.002
Mixed venous oxygen saturation *	60 (48–73)	63 (50–73)	0.69
Cardiac index, L/min/m ²	1.9 (1.5–2.4)	1.8 (1.5–2.4)	0.65
ABG at 24 hrs			
pH *	7.42 (7.37–7.46)	7.41 (7.37–7.45)	0.52
CO ₂ *	38 (34–42)	3.8 (33–42)	0.15
PO ₂ *	145 (92–253)	167 (97–309)	0.006
HCO ₃ *, mmol/L	24.0 (21.2–27.0)	24.0 (21.3–27.0)	0.78
Days on ECMO support *	4.3 (2.0–7.5)	5.6 (3.2–9.4)	<0.001
ECMO complications			
ECMO circuit mechanical failure	3,708 (37)	203 (51)	<0.001
Renal replacement therapy	2,768 (28)	186 (46)	<0.001
Glucose < 40 mg/L	156 (2)	10 (2)	0.15
Hemolysis (plasma hemoglobin >50 mg/dL)	389 (4)	26 (7)	0.01
Cardiac arrhythmia	1,238 (12)	78 (19)	<0.001
Gastrointestinal hemorrhage	393 (4)	33 (8)	<0.001
Disseminated intravascular coagulation	250 (3)	17 (4)	0.03
Seizure	131 (1)	22 (5)	<0.001

All data are presented as n (%) for categorical variables and median (interquartile range) for continuous variables.

ABG = arterial blood gas; ECLS = extracorporeal life support; ECMO = extracorporeal membrane oxygenation.

Bold text indicates statistical significance.

* Missing values for some variables resulted in different denominators for the following variables: age (10,103), weight (n=9,584), sex (n=9,939), race (n=10,088), cardiac arrest (n=9,626), pH (n=7,231), CO₂ (n=7,220), O₂ (n=7,198), HCO₃ (n=6,887), pre-ECMO mean blood pressure (n=3,173), mixed venous oxygen saturation (n=1,551), cardiac index (n=1,054), 24 hour pH (n=8,116), 24 hour CO₂ (8,146), 24 hour O₂ (n=8,143), 24 hour HCO₃ (n=7,882) days on ECMO support (n=10,186).

Table 2.

Baseline demographics and extracorporeal membrane oxygenation variables in patients who experienced hemorrhagic stroke while treated with venoarterial extracorporeal membrane oxygenation

Variables	No Hemorrhagic Stroke (n=10,113)	Hemorrhagic Stroke (n=229)	p
Age, * yrs	57 (46–66)	55 (42–64)	0.01
Weight, * kg	82 (70–99)	81 (66–96)	0.07
Male *	6,540 (67)	128 (57)	0.001
Race			
White	5,815 (59)	138 (61)	0.03
Asian	1,189 (12)	27 (12)	
Black	891 (9)	19 (8)	
Hispanic	472 (5)	16 (7)	
Others	1,494 (15)	27 (12)	
Year of ECLS			
2013	1,147 (11)	40 (17)	0.003
2014	1,551 (15)	47 (21)	
2015	2,092 (21)	39 (17)	
2016	2,529 (25)	53 (23)	
2017	2,794 (28)	50 (22)	
ECMO indications/diagnosis			
Cardiac arrhythmia	393 (4)	11 (5)	0.48
Postcardiotomy shock	1,901 (19)	39 (17)	0.50
Cardiac arrest *	2,996 (32)	77 (34)	0.45
Additional mechanical support device	2,755 (27)	63 (28)	0.93
Pre-ECMO ABG			
pH *	7.27 (7.16–7.37)	7.24 (7.11–7.33)	0.02
CO ₂ , * mmHg	42 (33–52)	42 (32–54)	0.71
PO ₂ , * mmHg	90 (61–188)	81 (55–16)	0.03
HCO ₃ , * mmol/L	19.4 (15.8–23.0)	18.5 (14.5–22.5)	0.04

Variables	No Hemorrhagic Stroke (n=10,113)	Hemorrhagic Stroke (n=229)	p
Pre-ECMO mean blood pressure, * mmHg	60 (50–72)	59.5 (47–68)	0.64
Mixed venous oxygen saturation *	60 (48–73)	60 (43–67)	0.31
Cardiac index, L/min/m ²	1.9 (1.5–2.4)	1.7 (1.3–2.3)	0.25
ABG at 24 hrs			
pH *	7.42 (7.37–7.46)	7.41 (7.37–7.45)	0.41
CO ₂ *	38 (33–42)	38 (43–47)	0.32
PO ₂ *	146 (92–255)	163 (84–312)	0.27
HCO ₃ *, mmol/L	24.0 (21.2–27.0)	24.0 (21.7–27.0)	0.51
Days on ECMO support *	4.4 (2.1–7.6)	5.2 (2.7–9.6)	<0.001
ECMO complications			
ECMO circuit mechanical failure	3,810 (38)	101 (44)	0.05
Renal replacement therapy	2,849 (28)	105 (46)	<0.001
Glucose < 40 mg/L	158 (2)	8 (3)	0.02
Hemolysis (plasma hemoglobin >50 mg/dL)	392 (4)	23 (10)	<0.001
Cardiac arrhythmia	1,275 (13)	41 (18)	0.02
Gastrointestinal hemorrhage	406 (4)	20 (9)	<0.001
Disseminated intravascular coagulation	256 (3)	11 (5)	0.03
Seizure	143 (1)	10 (4)	<0.001

All data are presented as n (%) for categorical variables and median (interquartile range) for continuous variables.

ABG = arterial blood gas; ECLS = extracorporeal life support; ECMO = extracorporeal membrane oxygenation.

Bold text indicates statistical significance.

* Missing values for some variables resulted in different denominators for the following variables: age (10,103), weight (n=9,584), sex (n=9,939), race (n=10,088), cardiac arrest (n=9,626), pH (n=7,231), CO₂ (n=7,220), O₂ (n=7,198), HCO₃ (n=6,887), pre-ECMO mean blood pressure (n=3,173), mixed venous oxygen saturation (n=1,551), cardiac index (n=1,054), 24 hour pH (n=8,116), 24 hour CO₂ (8,146), 24 hour O₂ (n=8,143), 24 hour HCO₃ (n=7,882) days on ECMO support (n=10,186).

Table 3.

Multivariable analysis of each type of ischemic stroke in patients treated with venoarterial extracorporeal membrane oxygenation

Parameter	aOR	95% CI	<i>p</i>
Age	1.00	0.99–1.01	0.53
Male Sex	1.11	0.83–1.46	0.49
Cardiopulmonary bypass	1.26	0.92–1.72	0.18
Pre-ECMO cardiac arrest	1.14	0.86–1.51	0.37
pH, pre-ECMO	0.21	0.09–0.49	<0.001
pO ₂ (/10 mmHg), pre-ECMO	1.01	1–1.02	0.30
pH at 24 hrs	2.65	0.58–12.09	0.21
pO ₂ (/10 mmHg) at 24 hrs	1.01	1–1.02	0.009
Days on ECMO support	1.01	0.99–1.02	0.35
ECMO circuit mechanical failure	1.33	1.02–1.74	0.03
Renal replacement therapy	1.49	1.14–1.94	0.004
Hemolysis (plasma hemoglobin >50 mg/dL)	1.33	0.82–2.16	0.25
Cardiac arrhythmia	1.20	0.86–1.67	0.29
Gastrointestinal hemorrhage	1.35	0.82–2.23	0.24
Disseminated intravascular coagulation	1.15	0.59–2.25	0.69

aOR = adjusted odds ratio; CI = confidence interval; ECMO = extracorporeal membrane oxygenation. Bold text indicates statistical significance.

Table 4.

Multivariable analysis of hemorrhagic stroke in patients treated with venoarterial extracorporeal membrane oxygenation

Parameter	aOR	95% CI	P-value
Age	0.99	0.98–1.00	0.23
Male Sex	0.62	0.45–0.86	0.004
Postcardiotomy shock	1.02	0.67–1.55	0.94
Cardiac arrest	1.07	0.75–1.52	0.71
pH, pre-ECMO	0.39	0.13–1.10	0.08
PO ₂ , pre-ECMO	0.99	0.98–1.01	0.47
pH at 24 hrs	0.76	0.13–4.37	0.76
PO ₂ at 24 hrs	1.01	1.00–1.02	0.22
Days on ECMO support	1.01	1.00–1.03	0.02
ECMO circuit mechanical failure	1.19	0.85–1.65	0.31
Renal replacement therapy	1.81	1.30–2.52	<0.001
Hemolysis (plasma hemoglobin >50 mg/dL)	1.87	1.11–3.16	0.02
Cardiac arrhythmia	1.11	0.73–1.68	0.62
Gastrointestinal hemorrhage	1.39	0.77–2.50	0.27
Disseminated intravascular coagulation	0.84	0.35–1.99	0.68

aOR = adjusted odds ratio; CI = confidence interval; ECMO = extracorporeal membrane oxygenation. Bold text indicates statistical significance.