Patterns of ECMO-Related Acute Brain Injury

Subjects: Neurosciences

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Extracorporeal membrane oxygenation (ECMO) is a frequently used mechanical cardiopulmonary support for rescuing critically ill patients for whom conventional medical therapies have failed. However, ECMO is associated with several complications, such as acute kidney injury, hemorrhage, thromboembolism, and acute brain injury (ABI). Among these, ABI, particularly intracranial hemorrhage (ICH) and infarction, is recognized as the primary cause of mortality during ECMO support.

extracorporeal membrane oxygenation | critical illness | acute brain injury

1. Intracranial Hemorrhage

Intracranial hemorrhage (ICH) (including micro- and macro-hemorrhages) was diagnosed in 22/43 (51%) of decedents during autopsy [1], while, in retrospective studies, the prevalence of ICH was similar between VV- and VA-ECMO patients (2–18% vs. 4–19%, respectively) [2][3][4][5][6][7]. Pathologically, ICH occurs more frequently in the frontal neocortex, basal ganglia, cerebellum, and pons [1]. As reported, the most common type of intracranial hemorrhage is subarachnoid hemorrhage (SAH), followed by petechial intraparenchymal hemorrhage [6][8]. However, the ICH timing is not yet well characterized. In one study, 85% of ICH presented on a CT scan shortly after cannulation [6], while, in another study, the median time for ICH detection was 7 days after ECMO initiation (see **Table 1**) [5].

Table 1. Characteristic of each pattern of ECMO-related ABIs.

Patterns Of ABI	Incidence	Intracranial Location	Timing
ICH	VV: 2–18%, VA: 4–19%	frontal neocortex, basal ganglia, cerebellum, pons	shortly after cannulation to 7 days cannulation
Ischemic Stroke	VV: 1.7–2% VA: 3.6–5.3%	frontal neocortex, basal ganglia anterior hypophysis cerebellum	second week of ECMO support
Seizures	VA: 2–6% VV: 1.3%	MCA territory	3.2 h of the initiation of cEEG monitoring
HIBI	VV: 1%	cerebral cortex, cerebellum	peri-ECMO cannulation period

Patterns Of ABI	Incidence	Intracranial Location	Timing
	VA: 13%	brain stem, basal ganglia	
Brain Death	VV: 2% VA: 7.9%	NA	NA

steps are involved. First, the integrity of endothelial cells and the blood–brain barrier is altered; second, the plasma and erythrocytes extravasated, impairing hemostasis [9]. In addition, bloodstream infection is correlated with ICH in patients using a left ventricular assistive device; therefore, it may also play a role in ECMO patients [10][11]. Furthermore, a previous study found that, although the hemorrhagic group had the highest average blood pressure, it had the lowest cerebral tissue oxygenation saturation, suggesting that elevated vascular resistance may lead to poor cerebral perfusion [12]. The risk factors related to ICH include use of anticoagulants and antiplatelet therapy [10], female sex [13], higher pre-cannulation PaCO2 [14], thrombocytopenia, high transfusion requirements [5], a large dual-lumen venovenous cannula [7], ECMO duration [4], bloodstream infections [10], renal failure, and dialysis [15]. Finally, ICH patients are known to have high mortality and morbidity [5].

ECMO: extracorporeal membrane oxygenation; ABI: acute brain injury; VV: venovenous; VA: venoarterial; ICH: intracranial hemorrhage; HIBI: hypoxic-ischemic brain injury; cEEG: continuous electroencephalogram; MCA: middle cerebral artery.

2. Ischemic Stroke

In a mixed VA- and VV-ECMO study, ischemic stroke was observed in 4.1% of patients across all age groups [16]. Although ischemic stroke is more common in VA ECMO (3.6–5.3%), it also occurs in VV ECMO patients (1.7–2%) [2][3][13][15][16]. However, one study reported that the true prevalence is also underestimated, and a rate of 11% was reported recently [17]. The pathology of ischemic stroke, occurring in the frontal neocortex, basal ganglia, anterior hypophysis, and cerebellum [1], is territorial, such that embolism may be the underlying mechanism [18][19]. Moreover, one study claimed that ischemic stroke events during ECMO are located in the left hemisphere in 70% of cases [20].

Although poorly described, cerebral venous sinus thrombosis and emboli from the circuit through the patent foramen ovale are possible etiologies of ischemic stroke [21]. In addition, researchers reported that it tends to occur 1 week after ECMO cannulation, with the only risk factor being platelets >350 giga/L at ECMO initiation [13]. However, other studies have concluded that multiple factors likely contribute to ischemic stroke, including a low brain perfusion state, a dual-lumen venovenous catheter [13][22], hemolysis [23], internal jugular vein cannulation [21], and acute infection or sepsis [24][25], which can lead to thromboembolization. Additionally, in an animal study, hyperthermia was shown to be associated with ischemic cerebral injury in the hemisphere ipsilateral to ligation, leading to elevated cerebral metabolism [26].

3. Seizures

Seizures are abnormal, paroxysmal electroencephalography (EEG) events that vary from background activity [27]. Due to the use of sedative drugs and a lack of EEG monitoring, seizure incidence may also be underestimated at 2–6% in patients undergoing VA ECMO [2][14] and 1.3% in VV ECMO adult patients [28]. Previous studies have claimed that younger pediatric patients have higher occurrence of seizures than older patients [29][30]. Other studies

using continuous EEG and regular sedation reported a much higher seizure rate in patients [31][32][33]. Seizure activity can be subsequently detected in patients with ICH, embolic infarcts, or global cerebral hypoxia/anoxia [34]. However, most ECMO-related seizures are related to neurologic insults, occurring around the time of cannulation [33]. It is noteworthy that, in children and adults under ECMO, severe background abnormalities (burst suppressions, severe slowing or unresponsiveness, or electrographic seizures) result in CT- or MRI-defined brain injury and poor outcomes, including lower IQ and neurodevelopmental delays [35][36][37][38]. Importantly, severely abnormal background activity in the first 24 h after ECMO initiation is associated with death and seizure lateralization related to arterial cannulation position, including the middle cerebral artery (MCA) territory. However, in patients presented with seizures, mostly implicating brain injury, only one-third of patients with ABI had monitored seizures [27]. Moreover, cerebral gas embolism (CGE) may result in the rapid onset of epileptic seizures [39], and cerebral edema is another known risk factor for seizures [40].

4. Hypoxic–Ischemic Brain Injury (HIBI)

As the most common type of ABI in patients who received ECMO at autopsy [8][41], HIBI is reported to have a higher incidence in patients with VA-ECMO over VV-ECMO (13% vs. 1%, $p < 0.001$) [42]. Pathologically, HIBI demonstrates the most diffuse damage in multiple anatomic locations [1], involving the cortex, cerebellum, brain stem, and basal ganglia, with a preponderance in the cerebral cortices (82%) and cerebellum (55%) [8]. Hypoxia from refractory respiratory failure is a possible cause, while CO_2 dysregulation, cerebral vasoconstriction, and North–South syndrome, resulting from hemodynamic changes specific to VA-ECMO, can lead to cerebral ischemia [21]. When it comes to risk factors, HIBI is most likely to occur in patients with hypertension, hyperlactatemia, and low pH (acidosis), and signs of inadequate perfusion. It often presents during the peri-ECMO cannulation period (24 h) before and after ECMO cannulation [8], because ECMO provides adequate perfusion of the brain after successful cannulation.

5. Brain Death

The occurrence of brain death is reportedly different in the two modes of ECMO. Approximately 2% in patients with VV-ECMO and 7.9–13.1% in patients with VA-ECMO [2][43][44]. Contrary to the prevalence of ABI in different populations, the incidence of brain death in pediatric patients increases with age, from 1.3% in those aged 0–30 days, to 4.0% in those aged 31 days to less than 1 year, and finally to 8.4% in those aged 1 year to less than 16 years [45]. Additionally, severe post-anoxic swelling, extensive infarction, or hemorrhage may lead to brain death [2][24]. Traditionally, brain death was defined as irreversible functional loss of the entire brain, including the brainstem [46]. Clinical assessments of brain death include hemodynamic stability (systolic arterial pressure >90 mmHg), adequate core temperature (>36 °C), and without circulating analgesics, sedatives, muscle blocking agents, or severe electrolyte or glucose disturbances [47]. Unfortunately, in the presence of ECMO support, brain death determination is challenging and there are no guidelines for the determination of brain death in ECMO [34].

Moreover, novel monitoring methods such as EEG, plasma biomarker glial fibrillary acidic protein (GFAP), and cerebral angiography may be useful; however, they still require further investigation [48][49][50].

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