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Stroke in pediatric ECMO: a target for prevention and improvement

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Stroke is the focus of an original study[1] in the growing population of neonates and children treated with extracorporeal membrane oxygenation (ECMO).[2] Stroke in this population is an important topic given that neurological complications remain the main source of morbidity among survivors treated with ECMO and a major cause of death.[3,4] In the article titled "Stroke in pediatric ECMO patients: analysis of the National Inpatient Sample (NIS) database" Ezetendu et al. compare a representative national sample of pediatric inpatients hospitalized between 2000 and 2017 who were treated with ECMO and who were identified as having a diagnosis of stroke, to a group treated with ECMO who did not have a diagnosis of stroke.[1] During the index hospitalization, 10% of ECMO patients had a diagnosis of stroke, ECMO patients with a stroke had longer lengths of stay compared to the ECMO group without a stroke, and the risk of mortality was greater with a hemorrhagic stroke (or combined hemorrhagic and ischemic stroke) compared to an ischemic stroke or to no stroke at all. The prevalence of the diagnosis of stroke in this sample of ECMO patients increased over the two decades studied. While the increase may be associated with a greater utilization of diagnostic neuroimaging in ECMO patients in the recent decade,[5] their findings warrant much greater attention from the clinical and research communities.

There is a biological rationale for ECMO patients to be at risk of stroke. Patients treated with ECMO have multiple reasons and multiple periods of risk to have a stroke: before being connected to ECMO, during ECMO, during the wean trial and separation from ECMO, and after being separated from ECMO.

Diseases may predispose patients to thrombosis or to stroke before exposure to ECMO (e.g., congenital heart disease, sickle cell disease, Downs syndrome).[6] In this study, ECMO patients with stroke compared to no stroke had a higher frequency of cardiac co-morbid diagnoses coded during the hospitalization, including cardiac arrests, hypertension, congenital heart disease, myocarditis, heart failure, ventricular assist device, cardiomyopathy, and acute kidney injury. These findings are aligned with the knowledge that thrombotic risk in general is increased in children with cardiac disease[7] and from the International Stroke Registry that suggests that the risk of stroke in neonates and children with cardiac disease is high.[8]

ECMO treatment may increase the underlying risk of developing a stroke as ECMO involves connecting the patient to an artificial pump and a membrane with cannulas, in large vessels of the neck or femoral such as the carotid artery and jugular veins or femoral artery and veins, or directly in the right atrium and aorta through the chest. Cannulation using the carotid artery has been found to be associated with increased risk of acute neurologic event in the ELSO registry.[9]

During ECMO, the brain is exposed to changes in systemic arterial and venous pressures, oxygen tension, carbon dioxide, temperature, pH, and hematocrit (which alters viscosity). These changes occur at time when the cerebral vascular reserve may be altered by mechanisms associated with the disease or its treatment (e.g., epinephrine), leaving the brain vulnerable to cerebral ischemia and hemorrhage. Moreover, the effects on the brain may not be visible to front line clinicians without complex neuromonitoring.[10,11] Patients supported with veno-arterial modes are at particular risk of air or particle emboli. Several pathways are triggered by patient-disease factors and patient-artificial surface interactions (cannulas, circuit, pump, membranes) that produce an inflammatory[12] and prothrombotic state that necessitates the use of systemic anticoagulation. ECMO treatment involves exposure to transfusion therapies and often other concurrent extracorporeal interventions such as renal replacement or apharesis therapies, which alter the integrity of blood components (e.g., platelets, red cell) and coagulation factors (e.g., calcium, hypofibrinogenemia). ECMO treatment can last from days to months that prolongs the period of risk.

At the time of weaning from ECMO when supported with veno-arterial ECMO, the assessment of a patient's ability to wean from the technology involves decreasing pump flows or interrupting flow (e.g., called a clamp trial) that may increase clot or fibrin deposition in the cannulas or across the circuit. At the time of the separation from the circuit, the integrity of the vascular structures may be lost from their ligation or the reconstruction (carotid artery, jugular veins, or right atrium and aorta, or the femoral artery and veins) or from the pressure applied for hemostasis. This may increase the risk of thrombosis and of stroke in this later phase of ECMO treatment.

Given these multiple potential mechanisms, it is not surprising that patients treated with ECMO experience a stroke during their hospitalization. Stroke may be an important modifiable factor associated with the outcome of patients supported with ECMO.[13]

This study was not suited to provide information on the temporal nature of the stroke relative to the ECMO treatment. A better understanding of the timing of the occurrence of a stroke

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and the factors involved in the development of stroke may allow for prevention strategies to be applied or may allow for timely reperfusion.[13]

In this study where 74% of the sample was aged less than 1 year and more than half were neonates, the frequency of strokes was higher in the older children aged 1–18 years. This finding deserves more investigation as it is difficult to explain without a greater understanding of the detailed characteristics of each age group. In the future in this type of study, it would be useful to understand with the addition of procedure codes if the vascular strategy at the time of cannulation and at the time of separation from ECMO had an impact on the risk of stroke. The co-morbid diagnoses of cardiac arrest and acute kidney injury are confounders that deserve to be untangled with further study as each may offer different opportunities in the prevention of stroke.

This epidemiological study provides the reader with new information that is pertinent for pediatric intensivists and surgeons, neonatologists, neurologists, cardiologists, nephrologists, who are involved during ECMO treatment, and for pediatric hospitalists and subspecialists whos' patients are treated with ECMO, e.g., respirologists, rheumatologists, hematologists, gastro-enterologists, or oncologists. This study shines a light on a growing number of neonatal and pediatric ECMO patients at risk of stroke: it provides a target for prevention and improvement.

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AUTHOR CONTRIBUTIONS

The author wrote the commentary.

COMPETING INTERESTS

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ADDITIONAL INFORMATION

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