Epidemiology of Stroke in Pediatric Cardiac Surgical Patients Supported With Extracorporeal Membrane Oxygenation

David K. Werho, MD, Sara K. Pasquali, MD, MHS, Sunkyung Yu, MS, Janet Donohue, MPH, Gail M. Annich, MD, Ravi R. Thiagarajan, MBBS, MPH, Jennifer C. Hirsch-Romano, MD, MS, and Michael Gaies, MD, MPH, on behalf of the ELSO Member Centers

University of Michigan Congenital Heart Center, C.S. Mott Children's Hospital, Ann Arbor, Michigan; Department of Critical Care Medicine, Toronto Hospital for Sick Children, Toronto, Ontario, Canada; and Department of Cardiology, Boston Children's Hospital, Boston, Massachusetts

Background. **Stroke is a common complication of extracorporeal membrane oxygenation (ECMO), and pediatric cardiac surgical patients may be at higher risk. Epidemiology and risk factors for stroke in these patients are not well characterized.**

Methods. **We analyzed pediatric (<18 years) cardiac ECMO cases in the Extracorporeal Life Support Organization Registry from 2002 to 2013. Cardiac surgical patients were identified, and procedures were stratified according to The Society of Thoracic Surgeons morbidity categories. The primary outcome was any stroke (hemorrhagic or infarction) identified by neuroimaging. Risk factors were identified through multivariable logistic regression.**

Results. **We analyzed 3,517 cardiac surgical patients; 81% with cyanotic disease, and 57% in high-risk categories from The Society of Thoracic Surgeons (categories 4 and 5). Overall, 12% experienced stroke while receiving ECMO, and those with stroke had greater in-hospital mortality (72% versus 51%; $p < 0.0001$). In multivariable analysis, neonatal status (adjusted odds ratio, 1.8; 95% confidence interval, 1.3 to 2.4), lower weight-for-age z score (adjusted odds ratio, 1.1 for each 1-point decrease; 95% confidence interval, 1.04 to 1.25), and longer ECMO duration (upper quartile [≥167 hours] adjusted odds ratio, 1.4; 95% confidence interval, 1.1 to 1.8) were independently associated with increased stroke risk, whereas cyanotic disease, The Society of Thoracic Surgeons category, and bypass time were not.**

Conclusions. **This multicenter analysis demonstrates that pediatric cardiac surgical patients on ECMO are at high risk of stroke; younger or underweight patients and those with longer ECMO duration are at greatest risk, independent of procedural complexity. Future study is necessary to determine how anticoagulation or other clinical practices can be modified to reduce stroke incidence.**

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Cardiothoracic surgeons increasingly use extracorporeal membrane oxygenation (ECMO) to support patients with postcardiotomy myocardial depression after congenital cardiac repairs and in those with cardiomyopathy [1, 2]. Although ECMO remains a final option to salvage patients in need of temporary cardiopulmonary support after surgery, treatment can be limited by complications [3–6]. Extracorporeal membrane oxygenation exposure incites both bleeding and clotting cascades, and necessitates systemic anticoagulation during therapy, which places patients at high risk for both hemorrhagic and ischemic strokes [7]. Stroke remains a common and potentially devastating complication of ECMO, with reported rates of intracranial hemorrhage or cerebral infarction in 7.6% and 5.8% of pediatric patients on ECMO, respectively [4].

Stroke occurs frequently after congenital cardiac surgery even in patients without the need for ECMO [8, 9]. Thus, pediatric patients undergoing cardiac surgery who then require ECMO support postoperatively may be at extremely high risk for stroke. Procoagulant factors related to cardiopulmonary bypass and ECMO circuits, decreased cardiac output preceding cannulation, and other factors likely increase the risk of stroke and may exacerbate neurologic injury in this population [10]. We previously reported higher frequencies of hemorrhagic stroke in cardiac surgical patients compared with other cardiac ECMO patients [6].

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Address correspondence to Dr Werho, University of Michigan Congenital Heart Center, C.S. Mott Children's Hospital, 1540 E Hospital Dr, Ann Arbor, MI 48109; e-mail: dwerho@med.umich.edu.

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Despite the scope of this problem, the epidemiology of and risk factors for stroke in pediatric cardiac surgical patients requiring ECMO remain unknown. Filling this knowledge gap is a necessary step to inform future efforts to reduce the frequency of stroke for these children. We aimed to examine the incidence of stroke in this population using a multiinstitutional database and to identify patient, procedural, and clinical variables that could be targeted in future research and quality improvement efforts to improve outcomes for children requiring ECMO support after cardiac surgery. We hypothesized that cannulation techniques, thromboses in the ECMO circuit, and pump flows would be associated with risk of stroke.

Material and Methods

Data Source

The Extracorporeal Life Support Organization (ELSO) maintains a registry of ECMO data from more than 350 international ECMO centers and currently houses information from greater than 58,000 ECMO runs since 1990. Each participating ECMO center collects and voluntarily reports standardized data on all patients undergoing ECMO including patient characteristics, details of the ECMO run, complications, and outcomes. Centers submit a cardiac addendum for patients who required ECMO for cardiac support with data on the underlying cardiac lesion, surgical information (if applicable), and physiologic data. The ELSO Registry data is deidentified before release; thus our study was deemed exempt after review by the University of Michigan Hospital and Health Systems Institutional Review Board.

Study Patients

Under ELSO data sponsorship, registry data were queried on the initial ECMO run during a hospitalization from all children (<18 years at ECMO onset) who underwent cannulation for venoarterial ECMO for cardiac support between January 1, 2002, and April 30, 2013 (n = 6,692). We identified the cohort with primary cardiac disease using codes available in the database, which include a combination of International Classification of Diseases, 9th Revision diagnostic codes, Current Procedural Terminology codes, and ELSO cardiac addendum procedure codes. Patients were included in the analysis if they had an ECMO run within 6 months after a cardiothoracic surgical procedure during the same hospitalization, including those on ECMO preoperatively who continued on ECMO postoperatively. Patients who had preoperative ECMO only were not considered to be at the same risk for ECMO complications as a postoperative patient, and therefore were excluded for a separate analysis. Extracorporeal membrane oxygenation for pulmonary support (n = 683) or extracorporeal cardiopulmonary resuscitation (n = 1,717) were not included because the surgical data necessary for our analysis are not collected for these patients. Records with missing, implausible, or out-of-range values were also excluded (n = 1,979).

Data Collection

The primary outcome variable was any stroke (hemorrhagic or ischemic). Stroke in the ELSO database is defined as a positive finding identified by cranial ultrasound or computed tomography. Information on indications for neuroimaging and data on the clinical manifestations of stroke are not collected. Surgical procedures were classified into The Society of Thoracic Surgeons (STS) morbidity categories. The STS morbidity categories empirically group operations by associated morbidity risk [11]. Examples of low-morbidity procedures include atrial septal defect repair, bidirectional Glenn palliation, or coarctation repair (categories 1, 2, and 3, respectively), whereas an interrupted arch repair (category 4) or Norwood procedure (category 5) represent high-morbidity operations. Each cardiac diagnosis was classified as cyanotic or acyanotic after review by the primary authors, who are both pediatric cardiologists (D.K.W., M.G.).

Variables in the database considered to be biologically plausible risk factors for stroke were collected, including patient characteristics (race, age, weight-for-age, presence of structural heart disease, cyanotic heart lesions, presence of any known genetic anomalies, pre-ECMO mechanical support including ventricular assist device [VAD] or aortic balloon pump), ECMO factors (duration, high flow [relative to weight], low flow [independent from weight], more than two cannulas, left atrial cannulation, neck cannulation, circuit component thrombosis), and surgical factors (STS morbidity category, cardiopulmonary bypass time). Data on staffing, neurologic monitoring, and anticoagulation therapy are not collected in the database; therefore, these clinical practices could not be analyzed for association with stroke rates.

Statistical Analysis

Incidences of stroke were reported as the cumulative incidence proportion. Variables with greater than 10% missing data or those with a zero frequency were not included in the analysis. Univariate comparisons of the characteristics selected were made between patients with and without stroke using the χ^2 test for categorical variables and Wilcoxon rank sum or Student's t tests for continuous variables. Continuous variables were also evaluated categorically using quartiles, and flow exposure variables were analyzed as upper or lower quartile versus normal. Risk factors found to be associated with stroke in univariate analyses at a probability value of less than 0.15 were included in multivariable logistic regression to determine independence of the association. Multicollinearity for variables included in the multivariable analysis was examined using variance inflation factor, which is an indication of multicollinearity if greater than 10. Variance inflation factors for all variables in the model were less than 1.5, which was acceptable for inclusion. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC), with statistical significance set at probability values less than 0.05 using two-sided tests.

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