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Incidence and predictors of ischemic cerebrovascular stroke among patients on extracorporeal membrane oxygenation support☆,☆☆,★,★★

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ABSTRACT

Introduction: There are scant data on the predictors of ischemic cerebrovascular stroke occurring during extracorporeal membrane oxygenation (ECMO). We investigated the incidence and predictors of ischemic stroke in subjects receiving ECMO support.

Methods: A retrospective chart review was conducted on consecutive adult subjects (>18 years of age) who received ECMO at Tampa General Hospital from 2007 to 2014 with the main outcome variable being the onset of radiologically confirmed ischemic stroke during ECMO support. We examined various risk factors for ischemic stroke including patients' demographics, clinical and laboratory variables, ECMO characteristics, type and amount of transfused blood products, and the indications necessitating ECMO support. To identify independent risk factors of ischemic stroke during ECMO and adjust for confounding variables, a multivariate logistic regression analysis was used.

Results: A total of 171 subjects received ECMO (mean age was 51 years, and 74.9% were male) for cardiac or pulmonary indications. Ten subjects (5.8%) developed ischemic stroke during ECMO. Cases with ischemic stroke had a higher mean pre-ECMO lactic acid level (10.6 ± 6.5 vs 6.3 ± 5.2 mmol/L, $P = .039$) and a higher frequency of pre-ECMO lactic acid level > 10 mmol/L (71.4% vs 24.8%, $P = .019$). Multivariate analysis identified that a pre-ECMO lactic acid greater than 10 mmol/L (odds ratio, 7.586; 95% CI, 1.396-41.223; $P = .019$) is an independent predictor of ischemic stroke occurring during ECMO support.

Conclusion: Ischemic stroke is not uncommon in subjects receiving ECMO support with independent risk factor being a pre-ECMO lactic acid greater than 10 mmol/L.

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1. Introduction

Extracorporeal membrane oxygenation (ECMO) is being increasingly used to support the critically ill patient who is expected to die. It is usually administered to provide adequate tissue oxygen delivery in patients with severe cardiac and/or respiratory failure as bridge to recovery or bridge to transplantation. A multidisciplinary team approach is crucial in establishing an ECMO program that involves the collaboration of a critical mass of trained staff including cardiothoracic and vascular surgeons, intensivists, cardiologists, highly skilled nurses, and respiratory therapists. These personnel should be aware of the ECMO indications, selection criteria, complications, and outcome for optimal results. Also, trained critical care staff is mandatory during transportation of the hemodynamically unstable patient in need of ECMO support to minimize the risk of death.

The in-hospital ECMO mortality can be as high as 60% to 75% [1–3], which is improving over the years.

According to the Extracorporeal Life Support Organization registry report, survival to discharge for adult respiratory failure and cardiac support was 55% and 39%, respectively [4]. The high mortality and high incidence of complications provoke the awareness of determinants

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of poor outcomes for its prevention or reduction. Among these complications are acute neurological injuries which include ischemic and hemorrhagic stroke, seizure, and brain death. An ischemic stroke can be small related to microemboli of clot or air, and larger strokes are due to thromboembolism [5]. The incidence of stroke is underreported because of difficulty obtaining brain imaging in critically ill patients receiving ECMO for the fear of clinical deterioration during transport. Moreover, many patients with neurological injuries are at risk of death and may die before brain imaging [6–8].

Recent literature suggests that ECMO cases complicated with ischemic stroke have a higher morbidity rate of 14.6% (as defined by discharge to long-term care facility) compared with those without cerebrovascular complications who have a 6.8% morbidity rate ($P < .0001$) [9]. There are insufficient data regarding the predictors of ischemic stroke in patients receiving ECMO support except in the pediatric population [7,10]. In a meta-analysis of adults who received ECMO support following cardiopulmonary resuscitation (CPR), it was found that the neurologic sequelae, although suspected to be high, are "poorly described in the literature" [11]. Risk factors for intracranial hemorrhage in patients receiving ECMO support are different from those of ischemic stroke and include low platelet count, low fibrinogen level, prematurity, and the need for anticoagulation to prevent circuit clotting [12,13]. Most ECMO studies in adults combined ischemic and hemorrhagic stroke in a common risk factor analysis. The aim of this study was to determine the incidence and independent predictors of ischemic cerebrovascular stroke occurring during ECMO support.

2. Methods

2.1. Patient information and data collection

This is a post hoc analysis conducted on consecutive adult subjects (>18 years of age) who received ECMO support at Tampa General Hospital from January 2007 to November 2014. The Institutional Review Board at the University of South Florida approved the study and waived the need for patient consent (no. Pro0000580). A retrospective chart review was performed with collection of variables including those that may be risk factors for ischemic stroke such as age; sex; body mass index; diabetes mellitus; hypertension; history of atrial fibrillation; the occurrence of cardiac arrest; performance of CPR before ECMO; the use of venoarterial ECMO; the sites of ECMO cannulation (whether central or peripheral); pre-ECMO cardiac surgery; transfusion of various blood products including red blood cells, platelets, and fresh frozen plasma; and various laboratory variables. The main outcome variable was the onset of ischemic stroke during ECMO support, and we aim to determine the incidence and independent predictors for its occurrence.

2.2. Study definitions

Cerebral infarction was confirmed by computed tomography or magnetic resonance imaging of the brain showing features of ischemic stroke. Cases with alteration of mental status, cases with brain death, and cases with focal neurological deficits without radiological confirmation were excluded from the analysis. Because risk factors for ischemic and hemorrhagic stroke are different, we have excluded cases with hemorrhagic stroke from this analysis. Ischemic stroke cases were included only if they occurred during ECMO support. In studying the effect of transfusion of blood products on the development of ischemic stroke, we used the number of various blood products that were given during ECMO support but not those administered before or after ECMO. Detailed functional outcome data for those who developed an ischemic stroke were not obtained, so we were unable to determine neurological morbidity.

2.3. Clinical management

The ECMO pumps used during the study period were the BioMedicus BP80 (Medtronic, Inc, Minneapolis, MN) and the Thoratec Centrimag pump (Thoratec, Pleasanton, CA). The BioMedicus BP80 (Medtronic) was the main pump used during our study period. The Thoratec Centrimag pump (Thoratec) was infrequently used because of the significantly higher cost. The later pump characteristically requires lower revolutions per minute compared with the former. Anticoagulation during ECMO support was achieved mainly by heparin intravenous infusion at a dose of 30 to 60 U/(kg h) to maintain an activated partial thromboplastin time (aPTT) between 50 and 70 seconds or activated clotting time (ACT) range of 180 to 220 seconds, and only few cases were on warfarin with a target international normalized ratio (INR) between 2 and 3. The oxygenator and tubings were checked for clot formation on regular basis. Inotropic support was maintained for cases of circulatory failure to facilitate left ventricular emptying. If patients with left ventricular dysfunction became hemodynamically stable, inotropes were gradually weaned. The mixed venous oxygen saturation was maintained more than 70%, and the pump flow was reduced gradually to 500 mL/min. Extracorporeal membrane oxygenation support was withdrawn either with continued stability of the patient's hemodynamics [14] or if its continuation was deemed futile. Extracorporeal membrane oxygenation support was considered futile in case of brain damage or absence of heart or lung recovery in those who are not a ventricular assist device or transplant candidates.

2.4. Statistical analysis

Primary analysis compared those with and without ischemic stroke. Continuous variables were expressed as mean ± standard deviation and compared using Student t test for normally distributed variables and Wilcoxon rank sum test for nonnormally distributed variables. Categorical variables were described as counts and percentages and were compared using the χ^2 test or the Mantel-Haenszel estimate of the common odds ratio for nonnormally distributed variables. Normal distribution of variables was tested by a histogram of the sample data to a normal probability curve and quantile-quantile plot. Univariate analysis was used to compare differences between those with and without ischemic stroke. To examine independent risk factor for ischemic stroke during ECMO support, we used a multivariate logistic regression model with backward stepwise elimination. The variables used in the model were either those achieving statistical significance at $P < .05$ upon univariate analysis or variables that are considered clinically relevant. A P value less than .05 was considered statistically significant. Data were analyzed using IBM SPSS 21.0 statistical software (IBM SPSS Version 21.0., Armonk, NY).

3. Results

A total of 171 patients received ECMO support for either cardiac or pulmonary indications after a joint decision of the intensivist, cardiologist, and cardiothoracic surgeon. The mean age of the study subjects was 51±15.6 years, and 74.9% were males. Eighty percent of the cases received venoarterial ECMO, and 20% received venovenous ECMO. The indications for ECMO implantation were cardiogenic shock (42.4%), post cardiac surgery (13.3%), cardiac arrest (9.1%), post cardiac transplant (7.9%), massive pulmonary embolism (3.7%), respiratory failure (12.1%), and post lung transplant (9.7%) (Table 1). In-hospital mortality was 67% (115/171). Ten subjects (5.8%) developed radiologically confirmed ischemic stroke during ECMO support. There was no significant difference between subjects with and without ischemic stroke according to the indication for ECMO implantation or site of cannulation whether central ($P = .291$), axillary ($P = .394$), subclavian ($P = .310$), or common femoral artery ($P = .257$). Activated partial thromboplastin time, ACT, and INR were regularly collected according to local protocol; thus, data preceding the stroke are available. The majority of subjects