Transcranial Doppler Identification of Neurologic Injury during Pediatric Extracorporeal Membrane Oxygenation Therapy

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Background: We used transcranial Doppler to examine changes in cerebral blood flow velocity in children treated with extracorporeal membrane oxygenation. We examined the association between those changes and radiologic, electroencephalographic, and clinical evidence of neurologic injury. *Methods:* This was a retrospective review and prospective observational study of patients 18 years old and younger at a single university children's hospital. Transcranial Doppler studies were obtained every other day during the first 7 days of extracorporeal membrane oxygenation, and 1 additional study following decannulation, in conjunction with serial neurologic examinations, brain imaging, and 6- to 12-month follow-up. *Results:* The study included 27 patients, the majority (26) receiving veno-arterial extracorporeal membrane oxygenation. Transcranial Doppler velocities during extracorporeal membrane oxygenation were significantly lower than published values for age-matched healthy and critically ill children across different cerebral arteries. Neonates younger than 10 days had higher velocities than expected. Blood flow velocity increased after extracorporeal membrane oxygenation decannulation and was comparable with age-matched critically ill children. There was no significant association between velocity measurements of individual arteries and acute neurologic injury as defined by either abnormal neurologic examination, seizures during admission, or poor pediatric cerebral performance category. However, case analysis identified several patients with regional and global increases in velocities that corresponded to neurologic injury including stroke and seizures. *Conclusions:* Cerebral blood flow velocities during extracorporeal membrane oxygenation deviate from age-specific normal values in all major cerebral vessels and across different age groups. Global or regional elevations and asymmetries in flow velocity may suggest

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impending neurologic injury. **Key Words:** Cerebral blood flow—ECMO—transcranial Doppler—pediatric.

Introduction

Extracorporeal membrane oxygenation (ECMO) is a rescue therapy providing cardiorespiratory support for critically ill children. ECMO is associated with a risk of acute neurologic complications including intracranial hemorrhage, stroke, and brain death.[1-4] Recognition of new, acute neurologic injury in patients supported by ECMO is limited by the need for sedation and neuromuscular blockade during treatment. Transport for central nervous system (CNS) imaging studies (computed tomography [CT], magnetic resonance imaging [MRI]) is often impractical. Bedside head ultrasound is used routinely in neonates, but has limited ability to detect insults other than intracranial hemorrhage[5,6] and is typically limited to children less than 1 year.

We have previously shown that continuous electroencephalography (EEG) monitoring detects seizures in 23% of non-neonates treated with ECMO.[7] Other reported approaches to the detection of neurologic injury during ECMO include transcranial Doppler (TCD),[8] near-infrared spectroscopy,[9,10] and serum biomarkers.[11,12] Each of these approaches evaluates a separate component of neurologic function or physiology, including neurophysiology and seizures (EEG), cerebral blood flow (CBF; i.e., TCD), and cerebral autoregulation (near-infrared spectroscopy).

CBF is altered during ECMO owing to non-pulsatile flow in venoarterial (VA) ECMO, cannulation of the carotid artery, and unilateral ligation of the internal jugular vein. Pre-cannulation events leading to ECMO often result in brain injury, which can also lead to hyperemia or loss of cerebral autoregulation. Understanding changes in CBF may help both to identify new vascular injury during ECMO and to optimize cerebral perfusion.

TCD is a noninvasive test that uses ultrasonography to measure CBF velocities in the anterior and posterior circulation. TCD has been used in adult and pediatric traumatic brain injury,[13-16] neonatal hypoxic-ischemic encephalopathy,[17] sickle cell disease,[18] and stroke[19] to assess autoregulation, to predict mortality, and to provide a target for goal-directed therapy. In contrast, there are limited data on the use of TCD to detect neurologic injury during ECMO. One study suggested that abnormal TCD velocity (TCDV) in pediatric ECMO may occur before neurologic injury, including intracranial hemorrhage, increased intracranial pressure, or ischemia.[8] Currently, normal values are described for healthy neonatal and pediatric populations,[20,21] and critically ill children,[22] but no data exist for children treated with ECMO.

As a first step toward establishing parameters for normal TCDV in children supported by ECMO, we used TCD to obtain serial measurements during ECMO and after decannulation. The objectives of this study were to characterize changes in TCDV during ECMO, and to determine whether TCD can identify neurologic injury as assessed by neuroimaging, EEG, and neurodevelopmental outcome.

Methodology

This was a combined retrospective and prospective observational study including all pediatric patients, newborn to 18 years of age, undergoing ECMO therapy in the neonatal, cardiac, and pediatric intensive care units in a single tertiary care pediatric center. The local institutional review board approved the study. Patients whose guardians did not provide consent, and those in whom TCD windows could not be obtained, were excluded. Data gathered included demographic (age, gestational age, weight, sex), clinical (primary diagnosis, need for cardiopulmonary resuscitation [CPR] or vasopressors), ECMO data (duration, site, type, complications), and laboratory values (blood gases, sodium, lactate, glucose, hematocrit, SvO_2). At the time of each TCD study, we collected vitals, laboratory data, and ECMO parameters.

Prospective Study Arm

Subjects were enrolled between October 2013 and December 2014. Parents or guardians were approached for study consent after ECMO cannulation. The study protocol involved TCDs performed every other day during the first week on ECMO, and 1 additional comparison TCD after decannulation from ECMO, for a maximum of 5 total studies. When available, TCDs outside the study protocol ordered by physicians caring for the patient were also included in the analysis. Trained technicians performed all studies. Velocities from bilateral anterior (ACA), middle (MCA), and posterior (PCA) cerebral arteries and the internal carotid artery (ICA) were measured. Resistive and pulsatility indices were calculated for each artery. Physicians caring for the patient were blinded to the results, and all analysis occurred after patient decannulation.

Retrospective Study Arm

To increase the sample size, patients placed onto ECMO before October 2013 who also received TCDs as part of their care were included in the study. Ten of 39 patients on ECMO (26%) admitted between May 2011 and August