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Searching for the Brain's Canary in the Coal Mine

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Vast changes in the epidemiology of pediatric extracorporeal life support (or extracorporeal membrane oxygenation, ECMO) have occurred over recent years. Use of ECMO has more than doubled from 200 cases per year during 1993 – 2004 to 450 cases per year during 2004 – 2008 in institutions reporting to the Extracorporeal Life Support Organization (ELSO) registry.(1) Numbers have increased, in part, as candidacy for ECMO has broadened to include children with previous contraindications including septic shock, hemorrhage, malignancy, chronic respiratory failure, and extracorporeal cardiopulmonary resuscitation (E-CPR).(1,2) ECMO runs, once limited to days, are now frequently measured in weeks. (3,4) The impact of these practice changes on the significant inherent risks for children requiring ECMO is not fully known.

Despite advances in ECMO technology and management, ECMO support is associated with high unadjusted mortality rates, 51% for cardiac cases and 43% for respiratory cases. (1) Neurologic complications during ECMO, including ischemic and hemorrhagic stroke and seizures, occur in 12% to 22% of children, a frequency relatively unchanged over time and likely underdiagnosed. Although long term outcomes are rarely reported, neurological complications are associated with increased mortality and short-term unfavorable neurodevelopmental outcomes, with younger children and those cannulated in the setting of E-CPR at highest risk.(5–7)

The status quo for detection of neurological insults in children supported by ECMO is inadequate, with a recent review noting a lack of consensus regarding neurosurveillance of children on ECMO.(8) Neuromonitoring strategies for children on ECMO include physical exam, serial brain ultrasound, electroencephalogram, brain computed tomography, Doppler ultrasound, and near-infrared spectroscopy. Each modality has its own limitations and none approach a gold standard, risking late detection and more profound brain insult and

disability. New approaches are needed to aid clinicians in earlier identification of ECMO-related morbidity and tailoring of management strategies.

Bembea and colleagues describe a promising approach using blood biomarkers for neurosurveillance and outcome prognostication of ECMO patients in this month's issue of *Critical Care Medicine*.⁽¹⁰⁾ Recognizing that neurologic complications are a large driver of patient outcome, they tested six blood-based biomarkers, each with its own track record in neurocritical care and representative of cellular damage, inflammation, and neurodevelopmental processes: Glial fibrillary acidic protein (GFAP) and S100b are released by damaged astrocytes; Injured neurons spill neuron specific enolase (NSE) and intercellular adhesion molecule-5 (ICAM-5); monocyte chemoattractant protein 1/chemokine (C-C) motif ligand 2 (MCP1/CCL2) is associated with inflammation; and brain derived neurotrophic factor (BDNF) plays a role in neurodevelopment and synaptogenesis.

Samples were prospectively collected daily from 80 neonatal and pediatric patients undergoing venous-venous and venous-arterial ECMO and from 28 critically ill 'control' patients considered for but not requiring ECMO at a single institution. Comparison of the baseline biomarker levels in non-ECMO and non-E-CPR ECMO groups yielded mixed results - GFAP, ICAM-5 and S100b were the same between groups, whereas BDNF and NSE concentrations were higher in controls and MCP1/CC2 levels were higher in non-ECPR ECMO patients. Individually, peak blood levels of GFAP, MCP1/CCL2, NSE and S100b were increased in children on ECMO with unfavorable outcome versus children with favorable outcome, with area under the curve (AUC) ranging from 0.66 to 0.71. They found a slight improvement in outcome prognostication accuracy using a combination of peak GFAP and NSE (AUC = 0.73). Similar results were obtained when the same four biomarkers were evaluated for an association with mortality, with the combination of NSE and MCP1/CCL2 generating the largest AUC of 0.71. A significant association between any abnormal neuroimaging results and increased levels of both peak GFAP and ICAM-5 was noted in the study cohort; however, among a subgroup of 62 infants who underwent daily head ultrasounds, no association was observed between infants with abnormal brain ultrasounds and either functional outcome or mortality.

The benefits of peering directly into a patient's molecular physiology can be outshined by the inherent complexity of what is illuminated. Individual limitations exist for each studied biomarker. The authors note that control patients were both more likely to have elevated BDNF levels and significantly more likely to have a favorable outcome compared to non-ECPR ECMO patients.⁽⁹⁾ BDNF is involved in synaptogenesis and has neuroprotective properties, raising the question whether elevated levels are truly ominous.⁽¹⁰⁾ NSE levels are affected by hemolysis and S100b undergoes renal clearance, both important considerations for patients on ECMO, though no adjustments were made regarding these confounders.^(11,12) Different biomarker profiles may exist by age and disease, something that was not explored in this study population consisting of ages 1 day to 17 years.⁽¹³⁾ The reported AUCs of 0.71 for and 0.73 for mortality and unfavorable outcome, respectively, are significant but arguably not sufficiently robust to allow the studied biomarkers an independent place at the forefront of clinical decision-making without further characterization or combination with other prognostication markers.

Critical care clinicians face the difficult and sometimes urgent challenge of reconciling ECMO's increasing potential with a lack of established tools for prognostication. The magnitude of this task is amplified by the high costs and resource intensity of ECMO, the gravity of illness that ECMO is designed to support and the ever-present risks of ECMO-related morbidity and mortality. Validated, reliable biomarkers can provide incomparable insight to a patient's disease. In the same way cardiac troponin revolutionized decision-making surrounding management of myocardial infarction, a brain injury biomarker can be envisioned guiding multiple aspects of ECMO-related care.(14) Possible eventual uses for ECMO biomarkers include early diagnosis of evolving brain insults and need for additional neuromonitoring, neuroimaging, or for decision-making (i.e., ECMO eligibility, emergent decannulation), and for prognostication.

Mortality and neurologic morbidity represent final common pathways for a number of physiologic derangements that occur in patients supported on ECMO. Bembea and other groups' work argue for prospective validation of brain-focused biomarkers, but single biomarkers alone may not be enough. Accordingly, the prognostic strength of biomarkers will likely be truly realized when these physiologically-relevant signals are paired with other established markers of organ injury and considered alongside the results of comprehensive neurodiagnostics, including imaging and EEG.

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