Published in final edited form as:

Pediatr Crit Care Med. 2018 November ; 19(11): 1089–1090. doi:10.1097/PCC.0000000000001728.

Extracorporeal membrane oxygenation and hemolysis – still a challenge

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Keywords

extracorporeal membrane oxygenation; hemolysis; cell-free plasma hemoglobin; pediatric; mortality

Hemolysis is a well-known complication of extracorporeal membrane oxygenation (ECMO) increasingly identified as a risk factor for circuit-related morbidities and mortality. The production of cell-free plasma hemoglobin (FPH) during hemolysis has been associated with organ dysfunction such as acute kidney injury, which has been reported in up to 74% of pediatric patients undergoing ECMO [1]. Reports vary as to the level of hemolysis that should be considered problematic. Lou et al. described a cohort of 207 pediatric patients where only those with severe hemolysis (FPH>100mg/dL) had an almost six-fold higher risk of ICU and in-hospital mortality [2]. In adults FPH>50mg/dL has been identified as independent predictor of mortality [3], and The Extracorporeal Life Support Organization (ELSO) guidelines suggest that FPH levels >50mg/dL should be investigated.

In this issue of Pediatric Critical Care Medicine, Okochi et al. present a single-center retrospective study in 96 neonates, infants, and children undergoing ECMO where hemolysis, defined as FPH > 30mg/dL, was found in 26% (25/96) of the cohort and conferred an increased risk of in-hospital mortality (OR 10.0; 95% CI 3.4–32; p<0.001) [4]. Although the authors chose a hemolysis cutoff lower than that reported in the literature, their finding is interesting because it suggests that even low levels of FPH can be associated with mortality.

Research involving ECMO is notoriously difficult to do because of the heterogeneity of both the population of patients requiring ECMO as well as the clinical practices and experience of the institutions where this therapy is offered. This is even more difficult in the pediatric population because of the relatively small number of patients that require ECMO at any one institution and the resulting inadequate sample sizes. Thus, the volume and quality of literature related to ECMO is unfortunately limited. There have been efforts to create consensus guidelines and international consortiums such as ELSO, yet the majority of

studies are still retrospective in nature, either single-center or database, which have many limitations related to data quality.

This challenge is evident in studies such as that presented by Okochi et al. where the authors had to exclude patients who underwent ECMO support for <24hrs or who lacked complete medical records because of practical considerations [4]. Yet, this time frame could potentially be very significant and important to include if one were to understand the natural time course and evolution of hemolysis on ECMO and its effects on outcomes. The onset of hemolysis in the cohort described by Okochi et al. occurred within the first 7 days of ECMO in 21/25 (84%) of their patients [4]. Lou et al. reported that 71–85% of patients who developed hemolysis did so within 48hr of ECMO initiation [2]. There could potentially be a time-dependent effect on hemolysis related to factors such as initial exposure and inflammatory response to the circuit or management and stabilization of inlet pressures upon initiation of ECMO.

ECMO as a therapy is itself complex and adds to the heterogeneity of factors that have to be accounted for in any ECMO study. There is a body of evidence that mechanical issues such as the use of centrifugal pumps, use of hemoconcentrators or CRRT, high inlet pressures, inadequate venous return, small cannula size, etc. can have affects on the degree of ECMO-related hemolysis [2, 5, 6]. Interestingly, the multivariable analysis performed by Okochi et al. identified both hemoconcentrator use and peri-cannulation INR>3.5 as risk factors associated with hemolysis on ECMO [4] and not factors such as age, ECMO type, oxygenator type, venous pressures, time to therapeutic anticoagulation, or anti-Xa levels. They also noted that patients in their cohort with hemolysis also had a greater degree of coagulopathy and thrombocytopenia. This suggests that these patients may have already had existing organ dysfunction, baseline inflammation, and higher susceptibility to hemolysis. Indeed, in clinical practice, hemolysis is often seen during ECMO support without an identifiable mechanical cause. However, this particular cohort lacks a control group or baseline pre-cannulation FPH levels, so it remains unclear whether the level of observed hemolysis is truly ECMO-mediated.

The results of the study by Okochi et al. in combination with existing literature emphasizes the fact that there are a multitude of factors related to both the patient and the mechanical circuit that can influence the development of hemolysis. This heterogeneity highlights the need for a larger multi-center prospective study with clear definitions of hemolysis and elevated FPH that is designed to be able to answer some of these questions. Despite the efforts of Okochi et al. to adjust for patient risk factors by categorizing patient groups based on ECMO indication (i.e. cardiac, ECPR, respiratory), it still remains unclear whether FPH on ECMO is merely an index of severity of illness or an independent risk factor for outcome. There was also a lack of discussion of the cause of mortality, in particular the number of patients who were withdrawn from support, which adds limitations to the use of this particular outcome measure. These issues have obvious implications for design and development of treatment strategies targeting FPH during extracorporeal therapies, and future prospective studies should adjust more specifically for risk factors that may have an impact on circuit related hemolysis such as disease severity, underlying hemolytic and

inflammatory conditions, age, etc. and include control groups such as patients with severe sepsis and organ dysfunction that are not receiving ECMO.

Nevertheless, studies involving cardiopulmonary bypass suggest that targeting FPH may improve organ dysfunction [7, 8]. Hemolysis is now being recognized as problematic and FPH has been suggested to have bioactive properties with roles in nitric oxide regulation and oxidative stress and injury [9, 10]. One factor that may be more relevant to outcomes than a peak level of FPH is its duration of elevation, an analysis that is currently lacking in the literature. Thus, FPH is an attractive target for the development of interventions to ameliorate its effects. It seems, then, that it may be time for more dedicated studies that target the production of FPH as well as its bioactive effects.

Acknowledgments

Copyright form disclosure: Dr. Bayir's institution received funding from the National Institutes of Health (NIH), and they received support for article research from the NIH.

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