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Complications during extracorporeal membrane oxygenation: why collaboration is key

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Anticoagulation during extracorporeal membrane oxygenation (ECMO) and complications of hemorrhage and thrombosis are difficult issues, daunting to the most seasoned ECMO clinicians, and difficult to study due to heterogeneity of ECMO indications, patient ages, pre-existing comorbidities, etc. As shown in a recent survey of members of the Extracorporeal Life Support Organization (ELSO), there is wide variability in the way anticoagulation is monitored and achieved during ECMO (1). First, among ECMO centers, monitoring ranges from minimalist to very involved approaches: activated clotting time (ACT)-only to multiple-test monitoring, including antithrombin levels, anti-factor Xa activity or thromboelastography. Second, a number of products are being used that have not been rigorously studied in ECMO, including antifibrinolytics, direct thrombin inhibitors, serine protease inhibitors, antiplatelet agents, etc (1). Third, there are no accepted or validated definitions for hemorrhage, thrombosis or disseminated intravascular coagulation (DIC) during ECMO. These terms are being used widely in the literature but will oftentimes be defined differently, making it impossible to compare results among studies. For example, DIC during extracorporeal support cannot be defined using validated scores such as the DIC score of the International Society on Thrombosis and Haemostasis (2). In the absence of ECMO-specific, validated scores, DIC is therefore defined variably or reported without a clear definition, e.g., a composite of thrombocytopenia unresponsive to transfusion, prolonged activated clotting time despite lower heparin infusion rates, prothrombin time higher than three times normal, and evidence of clinical bleeding from surgical and/or other sites, vs d-dimer >10,000 units/L and fibrinogen <150 mg/dL, vs no definition provided (3–6). Similarly variable definitions are used for hemorrhagic complications (6–9).

In this issue of *Pediatric Critical Care Medicine*, Dalton et al present a retrospective analysis of all neonatal and pediatric ECMO-related hemorrhagic and thrombotic complications in eight centers that were part of the second funding cycle of The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Collaborative Pediatric Critical Care Research Network (CPCCRN), using data extracted from the ELSO Registry at each of the centers (10). Patients were separated by presence or absence of a diagnosis of congenital diaphragmatic hernia (CDH), given the known higher rate of overall complications in neonates with CDH on ECMO (7). In this highly selected

group of children's hospitals with large intensive care units and ECMO programs, the authors found that hemorrhagic and thrombotic complications were frequent in both the CDH and non-CDH populations: 45% and 60%, respectively, in 263 CDH patients, and 38% and 31%, respectively, in 1,773 non-CDH patients. After adjusting for potential confounders, such as indication for ECMO, ECMO mode or ECMO duration, hemorrhage and thrombosis were associated with decreased survival (10).

The authors used the results of this study as baseline preparatory data for a now ongoing prospective observational study of hemorrhagic and thrombotic complications in newborns and children on ECMO, conducted at CPCCRN centers. Studies of such complications have been mostly limited to single-center reports spanning several years, and inevitably influenced by local practices, patient selection, and historical bias. This ongoing CPCCRN study will be the first to systematically address hemorrhagic and thrombotic complications during ECMO in multiple centers, using strict data definitions, with detailed dynamic data on the timing of abnormal laboratory results, interventions related to anticoagulation and blood product administration, and onset of complications, and adequate sample size and power. There are several similar projects ongoing in North America, such as the Registry of ECMO Anticoagulation in Pediatrics (REAP) initiated by the Pediatric Critical Care Blood Research Network (BloodNet), a subgroup of Pediatric Acute Lung Injury and Sepsis Investigators, and a Canadian - U.S. collaborative funded by the Extracorporeal Life Support Organization, between the Stollery Children's Hospital, University of Alberta, Edmonton, Canada, and the C.S. Mott Children's Hospital at the University of Michigan, Ann Arbor, MI. The most important task of investigators pursuing this line of research will be to establish strong collaborations to ensure adequate sample size, diversity of centers that allows generalizability, and standardized data collection forms and definitions. Also, basic science and industry partnerships will be needed to further elucidate the complicated and poorly-understood pathophysiology of coagulation during ECMO. Translational studies will be needed to better inform the use of pharmacologic and blood product therapies in ECMO patients, especially in view of the fast-paced development of new, more biocompatible, circuit-blood interfaces.

This study has the limitations of a retrospective review and lack of standardization of hemorrhagic and thrombotic outcomes definitions. Some of the findings in the study, e.g., lower survival rate from 2010 to 2011 in pediatric ECMO patients, are difficult to interpret due to the inability to adjust for confounders such as severity of illness. There are no data on dosing of unfractionated heparin infusions, on the use of direct thrombin inhibitors, the use of blood products, or the type(s) of tests used to monitor anticoagulation. Lastly, there are no data that could help assess for selection bias such as pre-existing comorbid conditions, and no data on missingness (e.g., for rarely-measured laboratory values such as free plasma hemoglobin).

The findings of the Dalton et al study point to the important and common problem of hemorrhagic and thrombotic complications in ECMO patients, and provide a first step for more rigorously conducted prospective studies. Future studies will need to tackle the myriad issues surrounding coagulation disturbances and anticoagulation during ECMO, such as circuit-blood interactions (e.g., inflammatory response, activation of coagulation), adequacy

of tests to assess the status of the coagulation system (e.g., global vs partial measures of coagulation, measures of drug activity such as anti-factor Xa), outcome measures (e.g., bleeding score, thromboembolic burden score), pharmacokinetics and pharmacodynamics of anticoagulant medications, all of these taking into account the influence of age and developmental hemostasis, pre-existing diagnoses, and presence of new or progressive multisystem organ failure (11).

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