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Challenges with Navigating the Precarious Hemostatic Balance during Extracorporeal Life Support: Implications for Coagulation and Transfusion Management

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ABSTRACT

For the past four decades, extracorporeal life support (ECLS) has been used to treat critically ill adult and pediatric patients with cardiac and/or respiratory failure, and there are increasingly numbers of centers worldwide performing ECLS for numerous indications. Despite the progress with advancing the technology, hemorrhagic and thrombotic complications are frequently reported and associated with worse outcomes, but the exact cause is often elusive or multifactorial. As a result of the interaction between blood and an artificial circuit, anticoagulation is necessary and there is resultant activation of coagulation, fibrinolysis, as well as, an increased inflammatory response. While unfractionated heparin (UFH) remains the mainstay anticoagulant used during ECLS, there is a paucity of published data to develop a universal anticoagulation guideline and centers are forced to create individualized protocols to guide anticoagulation management while lacking expertise. From an international survey, centers often use a combination of tests, which in turn result in discordant results and confused management. Studies are urgently needed to investigate optimization of current anticoagulation strategies with UFH, as well as, use of alternative anticoagulants and non-thrombogenic biomaterials.

Blood transfusion during extracorporeal support typically occurs for several reasons, which includes circuit priming, restoration of oxygen carrying capacity, maintenance of a hemostatic balance, and treatment of hemorrhagic complications. As a result, the majority of patients will have been exposed to at least one blood product during extracorporeal support and transfusion utilization is high. ECLS Centers have adopted transfusion thresholds based upon practice rather than evidence as there have been no prospective studies investigating the efficacy of red cell (RBC) transfusion in patients receiving extracorporeal support. In addition, RBC transfusion has been associated with increased mortality in ECLS in several retrospective studies. Additional studies are needed to establish evidence based thresholds for transfusion support and diagnostics to guide transfusion therapy to assess efficacy of transfusion in this population, as well as, exploration of alternatives to transfusion.

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Extracorporeal life support (ECLS), also referred to as extracorporeal membrane oxygenation (ECMO), has been used to treat critically ill adult and pediatric patients with cardiac and/or respiratory failure for over four decades. The first successful use of ECLS was published in a trauma patient who developed acute respiratory distress syndrome in

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1972, followed by use in cardiogenic shock in 1973, and in meconium aspiration syndrome in 1975 [1]. Since these first descriptions, ECLS has been demonstrated to be a life-saving therapy, indications for ECLS have expanded to now include cardiopulmonary resuscitation (ECPR), and ECLS centers have grown worldwide [2-4]. The Extracorporeal Life Support Organization (ELSO) supports a registry by which member institutions can submit limited data such as technical details of extracorporeal support, complications and outcome of an ECLS run with the purpose to provide data to improve quality of care to ECLS patients; the complications are grouped into mechanical, hemorrhagic, neurologic, renal, cardiovascular, pulmonary, infectious, metabolic, and limb categories. As of the last ELSO Registry International Summary published January 2016, there were 298 international centers performing over 6000 ECLS cases in 2015 [5]. From the report, the cumulative number of patients treated with ECLS was 73 596 with 70% surviving ECLS, but only 58% surviving to discharge or transfer; however, survival is dependent upon the age and indication (cardiac versus respiratory) for ECLS. Recently, investigators from the University of Michigan, recognized as the center who has treated the largest number of patients worldwide, published their updated experience with 2000 ECLS patients [1]. The authors report that survival was better in the first 1000 patients as compared to those treated after 1998, 74% versus 55% ($P < .01$), with the exception of pediatric respiratory patients. While the exact reason for this decrease is unclear, the authors suggest that it may be secondary to the severity of illness of patients being initiated on ECLS in present times. In addition, the authors compare complication incidences in the cohorts treated from 1972–1998 and 1998–2010 and note that there have not been significant improvements in complications, including both hemorrhagic and thrombotic events. Moreover, in their second group of 1000 patients, the incidence of hemolysis and circuit clots increased.

Acquired Coagulation Changes and Anticoagulation Management during ECLS

Hemostatic complications, both bleeding and thrombosis are common, often coexist in the same patient, and remain the leading causes of morbidity and mortality in patients treated with ECLS. Recently, Murphy et al. summarized the hemostatic complications occurring during ECLS from data from the ELSO registry and these data have been updated to include the most recent ELSO International Report in Tables 1 and 2 [6]. The reasons for hemorrhagic and thrombotic complications include both circuit, as well as, systemic patient factors (Fig 1). Exposure of blood to the artificial, non-endothelialized surface of an extracorporeal circuit results in initiation of coagulation, cellular activation, and increased inflammation, which disrupts normal homeostasis in an already acutely ill patient [7-13]. In addition, sheer stresses and turbulence generated during ECLS further contribute to this activation, and to platelet or fibrin deposition during high or low sheer force, respectively. Moreover, fibrinogen and other coagulation factors are absorbed onto the artificial surface over the first 24 hours of ECLS [14]. Platelets acquire both quantitative and qualitative defects during ECLS. Specifically, sheer stress results in exposed collagen and release of von Willebrand factor (VWF), which results in subsequent platelet adhesion via GPIb and expression of GPIIb/IIIa receptors, and may be exacerbated by release of free hemoglobin [15]. As a result, platelets further bind to the absorbed fibrinogen and platelet counts fall to less than 40% of normal within the first few hours of ECLS [16]. Impaired platelet aggregation has also been reported during ECLS [17-20]. Last, high sheer rates result in uncoiling of VWF making it susceptible to cleavage by ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin motif) thereby resulting in loss of high molecular weight multimers and decreased binding of VWF, which characterizes the acquired von Willebrand syndrome (AVWS) [21,22].

Nevertheless, anticoagulation is necessary to not only maintain the patency of the circuit and components, but also, to reduce thrombotic complications whilst minimizing the risk of bleeding. Unfractionated heparin (UFH) remains the most widely utilized anticoagulant during ECLS; a recent international cross-sectional survey with 119 of 121 ELSO-reporting centers responding found that only 8% of the time had a non-UFH anticoagulant been used in the preceding six months, and if an alternative anticoagulant was used, a direct thrombin inhibitor, most commonly, argatroban was used [23]. However, it remains unclear if UFH is the optimal anticoagulant during ECLS and what the optimal anticoagulation monitoring strategy is during ECLS. From the international survey, 97% of centers utilize the activated clotting time (ACT) to monitor UFH anticoagulation; however, most centers also monitor the activated partial thromboplastin time (APTT) (94%) and anti-factor Xa (65%) at some frequency [23]. However, often results of two or all three tests are discordant due to the poor correlation between assays and heparin dose [24-29]. In addition, some centers (47%) have added viscoelastic testing with thromboelastography (TEG®) or thromboelastometry (ROTEM®) to their testing repertoire creating even more uncertainty to the significance of results [11,23]. A recent publication has discussed the ideal characteristics of a laboratory test to monitor anticoagulants. The characteristics identified include that the test should have good precision, be well standardized and readily available, inexpensive, and, most importantly, have a well-defined relationship with a clinical outcome, in this case, thrombosis and bleeding [30]. Currently, no single laboratory test has all of these ideal characteristics to monitor UFH. Only recently, have there been publications examining associations with any monitoring test with clinical outcomes. In a large retrospective study of 604 pediatric veno-arterial ECMO patients, the only significant predictor of survival was heparin dose when the impact of ACT, heparin dose, age, weight, diagnosis, and previous surgery on survival were assessed; there was 56% probability of survival for each increase of 10 units/kg/hr. up to a max of 70 units/kg/hr [31]. However, even though ACT was not a significant predictor of survival, the heparin infusion rate was guided by ACT results and additional investigation is needed to understand the relationship between heparin dose and survival. Additionally, a retrospective review of 47 pediatric ECLS patients treated at a single center with a lab based APTT protocol compared to historical ACT managed controls demonstrated a significant decrease in the prevalence of bleeding when patients were managed with APTT; however, there was a reciprocal increase in the prevalence of clotting but no association with survival suggesting subclinical thrombosis without long term consequences [32]. Most recently, publications have examined anti-factor Xa monitoring with clinical outcomes in ECLS. In 2011, a tertiary care, academic children's hospital altered their anticoagulation protocol using the anti-factor Xa assay without exogenous antithrombin (AT) to guide heparin titration and goal ACT ranges were adjusted to maintain an anti-factor Xa 0.3–0.7 IU/mL. Following implementation, the authors demonstrated significant decreases in the incidence of cannula and surgical site bleeding at the expense of increased oxygenator clots. The authors also demonstrated increased circuit life, decreased transfusion volumes of red cells (RBC), fresh frozen plasma (FFP), platelets, and cryoprecipitate, and, most importantly, increased survival to hospital discharge (43% to 55%, $P = .06$) following implementation [33]. Another center has also published their experience with anti-factor Xa monitoring without exogenous AT during ECLS. In a cohort of 22 patients managed with anti-factor Xa compared to 10 ACT managed controls, patients managed with the revised protocol had almost 20 fewer blood draws per day, more results within the goal range (91% compared to 78%, $P < .01$), and less bleeding (27% compared to 50% in the ACT managed controls) [34]. In regards to viscoelastic testing, with the exception of case reports and series, only one publication has examined association of TEG® with hemorrhage defined as total transfusion of greater than 2 mL/kg/hr [11]. In a cohort of 30 neonatal ECLS patients, no single TEG® parameter (R time, K time, alpha angle, maximum amplitude) was consistently able to separate those with higher transfusion volumes over 8 days of ECLS. However, a prospective randomized study of anticoagulation monitoring with