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Anticoagulation in neonatal ECMO

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ABSTRACT

Despite advances made in technology and neonatal intensive care, the rate of hemorrhagic and thrombotic complications remains unacceptably high in patients undergoing extracorporeal membrane oxygenation (ECMO) and these complications negatively impact morbidity and mortality. Management of anticoagulation in neonates who have a developing hemostatic system is vastly different from adults and poses unique challenges. Variation in practice among ECMO centers regarding anticoagulation monitoring and titration reflects the lack of high-quality evidence. Novel anticoagulants may offer alternative options, though their impact on outcomes is yet to be demonstrated. In this chapter, we review the hemostatic alterations that occur during ECMO with a focus on current approaches and limitations to anticoagulation titration in neonates on ECMO.

Introduction

The evolution of ECMO component technology and supportive care have improved survival for critically ill neonates, children, and adults with otherwise fatal acute cardiac or respiratory failure.[1] The ECMO circuit is complex and intricate, allowing oxygenation of the blood to occur through an artificial lung (membrane oxygenator) that permits blood to bypass the lungs (venovenous mode) or heart and lungs (venoarterial mode).[2]

Exposure of blood to the large nonendothelial surface of the ECMO circuit initiates coagulation, activates platelets and induces inflammation.[3] Anticoagulation, generally with unfractionated heparin (UFH), is necessary to prevent thrombus formation and maintain circuit function. Titrating the intensity of anticoagulation in neonates on ECMO remains a major challenge, and hemorrhagic and thrombotic complications remain major causes of morbidity and mortality in this population.

Extracorporeal life support organization (ELSO) reported summary statistics of 5839 neonates who underwent extracorporeal life support (ECMO) in the years 2009–2015.[4] Of this cohort, survival to discharge was 68% in patients with respiratory failure and 45% in those with cardiac failure. Intracranial hemorrhage occurred in 11% of the cohort, with an additional 7% with surgical site bleeding and 2% with gastrointestinal hemorrhage. The prevalence of ischemic stroke was 3%. Similarly, in 1001 neonates on ECMO from pediatric centers within the Collaborative Pediatric Critical Care Research networks, bleeding complications occurred in 33% of patients and thrombotic complications occurred in 29%; both bleeding and thrombosis were associated with decreased survival.[5]

Optimization of anticoagulation management in neonates undergoing ECMO remains an unmet need. While most centers have developed institutional guidelines for anticoagulation management, there is tremendous variation in

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practice from center to center due to the lack of high-quality evidence. Recent increased attention and ongoing investigation directed at reducing thrombotic and hemorrhagic complications may influence future practice.[6] Aspects relevant to the anticoagulation of neonates will be reviewed in this article.

Hemostatic alterations that occur during ECMO

The pathophysiologic changes that occur upon exposure to the ECMO circuit are complex and multifactorial (Fig.). Detailed understanding of these changes is important when trying to optimize anticoagulation on ECMO.

Initiation of ECMO results in significant hemodilution, which is exaggerated in neonates due to their blood volume relative to the circuit blood volume.[3] This can have profound effect on the overall concentration of clotting factors, the levels of which are already much lower in neonates compared to adults due to their developing hemostatic system. The subsequent dilutional coagulopathy results in reduced thrombin generation, heparin resistance [due to low levels of antithrombin III (AT III)] and an increased bleeding tendency. Upon initiation of ECMO, plasma proteins, including albumin, factor XII and fibrinogen, are immediately adsorbed onto the foreign surface. This causes activation of factor XII to XIIa that initiates the "intrinsic" or "contact factor" pathway and leads to thrombin generation. This thrombin generation results in amplification of coagulation, activation of platelets, and activation of the fibrinolytic pathway.

Circulating platelets also adhere to the artificial surface and become activated.[7] Repeated platelet activation though the circuit leads to decreased platelet aggregation over time due to degranulation and receptor down-regulation. Thus, while this process of platelet activation and consumption is prothrombotic in the circuit, it results in platelet dysfunction and thrombocytopenia, likely contributing to the bleeding risk in the patient.

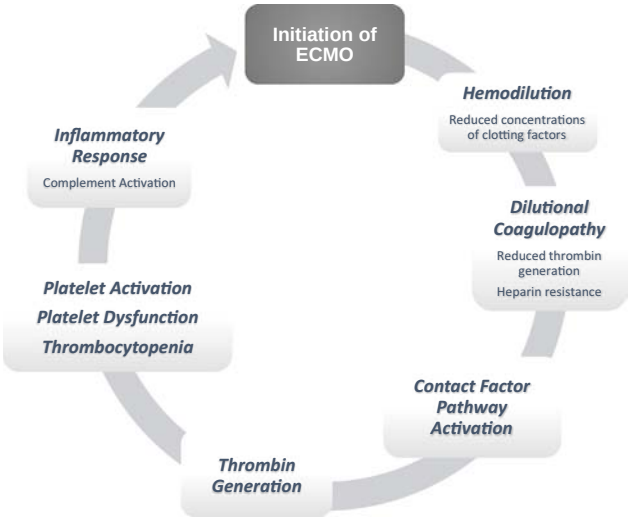

Fig – Hemostatic alterations during ECMO. Alterations of hemostasis as a result of each of these steps may lead to hemorrhagic and/or thrombotic complications. Anticoagulation is necessary to prevent the circuit from clotting.

Activation of a complex inflammatory response also occurs upon initiation of ECMO. The complement system is activated through the alternative pathway releasing anaphylatoxins C3a and C5a.[8] Pro-inflammatory cytokines (i.e., interleukin-6, interleukin-8, and tumor necrosis factor-α) are stimulated, and these cytokines activate leukocytes which can impair endothelial integrity leading to possible hemostatic and thrombotic complications.[9,10]

Developmental hemostasis

Developmental hemostasis poses an additional unique challenge to managing anticoagulation in neonates on ECM0.[11] Compared to older children, neonates have decreased concentrations of vitamin K dependent coagulation factors and AT III, reduced thrombin generation and reduced clot lysis.[12] In a healthy infant, the overall balance of hemostasis is maintained; however, ill neonates are at increased risk of both hemorrhagic and thrombotic events given the developmentally immature hemostatic system. Preterm infants are at additional risk of hemorrhagic complications due to reductions in platelet aggregation as well as platelet hyporeactivity.[7] The primary effect of this still developing coagulation system in a neonate on ECMO includes (1) increased susceptibility to dilutional coagulopathy with further impaired thrombin generation and (2) relative heparin resistance due to low AT III concentrations which may lead to increased bleeding and/or clotting.

Anticoagulation

Anticoagulation using UFH has been the standard of care since ECMO inception in 1976.[13] UFH exerts it anticoagulant effect by binding to the endogenous anticoagulant AT III to accelerate the inactivation of thrombin and factor Xa.[14] In addition, the administration of UFH causes a release of tissue factor pathway inhibitor which is a potent inhibitor of the extrinsic coagulation system.[15]

Benefits of UFH include widespread clinician familiarity, low-cost, short half-life, and reversibility.[16] However, there is considerable variation between patients in response to a fixed dose of heparin, particularly in neonates, which makes it challenging to standardize dosing and titration. This is partly related to the binding of heparin to various non-specific plasma proteins, which can result in a lack of anticoagulant effect.[17] Many of the plasma proteins that bind heparin are acute phase reactants and may explain the heparin resistance that is frequently encountered in critically ill children. Low plasma concentrations of AT III, which are physiologically normal in neonates, may also contribute to heparin resistance.

Dosing and monitoring of UFH

Although most pediatric centers have developed institutional guidelines for anticoagulation-based their experience, published literature, and ELSO guidelines, a survey of ELSO-