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Chapter

Anticoagulation in Pediatric Extracorporeal Membrane Oxygenation

Jamie Weller, Lakshmi Raman, Ayesha Zia and Ali McMichael

Abstract

Anticoagulation during extracorporeal membrane oxygenation (ECMO) is necessary to prevent catastrophic circuit clotting, but significant morbidity and mortality continue to be attributed to hemorrhagic and thrombotic complications. Due to the inflammatory response from the extracorporeal circuit and developmental hemostasis, anticoagulation can be challenging particularly for pediatric patients. Unfractionated heparin (UFH) is the gold standard anticoagulant used in ECMO, but there is an expanding area of research evaluating other anticoagulants, such as direct thrombin inhibitors. This chapter provides an overview of anticoagulant options for pediatric patients on ECMO as well as describes the various tests used to monitor and titrate anticoagulation.

Keywords: extracorporeal membrane oxygenation, anticoagulation, unfractionated heparin, bivalirudin

1. Introduction

Anticoagulation during extracorporeal membrane oxygenation (ECMO) is necessary to prevent catastrophic circuit clotting, but it contributes to significant morbidity and mortality. The Extracorporeal Life Support Organization (ELSO) international registry shows a 24% increase in the number of patients placed on ECMO and a 55% growth of centers utilizing ECMO from 2009 to 2015 [1]. Although there has been rapid growth in ECMO around the world, pediatric mortality rates have remained static or even increased depending on the reason for cannulation [1]. In a multicenter study, Dalton et al. showed that 19–70% of patients had a bleeding event and 12–43% of pediatric patients had a thrombotic event while anticoagulated on ECMO [2]. With the increase in centers utilizing ECMO, anticoagulation has become an important area of research.

2. Overview of hemostasis

In order to discuss the intricacies of anticoagulation during ECMO, a basic understanding of the mechanisms required for hemostasis and the coagulation cascade is necessary (**Figure 1**). Hemostasis occurs by vascular constriction, platelet plug creation, and clot formation through fibrin [3]. The vasculature surrounding the damaged tissue constricts limiting blood flow to the area. Platelets adhere to the exposed endothelium

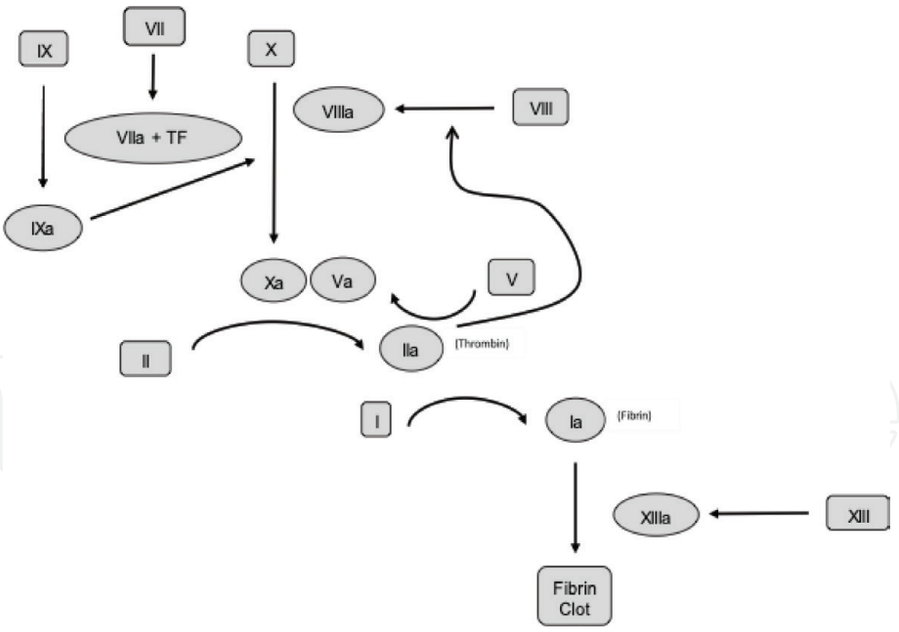

Figure 1.
In vivo concept of coagulation. The clotting system is classified into the initiation, amplification, and propagation phase. TF, tissue factor (thromboplastin); II, prothrombin; I, fibrinogen.

via von Willebrand factor creating a platelet plug to temporize the bleeding. Finally, the clotting cascade is activated by the presence of tissue factor released when blood vessels are damaged [3]. The clotting cascade has been traditionally described as the intrinsic and extrinsic pathways merging to initiate the common pathway, and resulting in the activation of fibrinogen to fibrin to form a stable clot. This classification is pertinent for understanding *in vitro* coagulation tests, but fails to account for the *in vivo* coagulation process [4, 5]. Current evidence suggests that the initial cascade augments the formation of thrombin through multiple feedback loops. The initiation phase is activated with exposure of tissue factor from damaged blood vessels. The initial amount of thrombin produced is insufficient to achieve adequate hemostasis, thus a series of feedback loops prompted by thrombin act to catalyze the factor (F) V and FVIII, eventually accelerating the activity of FXa and FIXa. This second phase is classified as the amplification phase [4]. The propagation phase ensures continued production of thrombin and thus fibrin, by forming sufficient prothrombinase complexes [4].

The hemostatic processes are counterbalanced by antithrombotic factors such as protein C, protein S, thrombomodulin, antithrombin, and tissue factor pathway inhibitor. Clot degradation is initiated by the fibrinolytic factors such as tissue plasminogen activator (tPA), plasminogen, and urokinase plasminogen activator [3]. The extracorporeal circuit interferes with the described mechanisms designed to achieve adequate hemostasis. Immediately upon contact with the foreign ECMO circuit, the coagulation cascade is activated and a complex inflammatory response occurs [6]. Platelets, neutrophils, and leukocytes are activated along with thrombin and plasmin. Platelets adhere to the foreign surface leading to both platelet and factor consumption. Activated neutrophils contribute to the inflammatory response by producing cytokines. In addition, thrombin, FXa, and FVIIa cause complement activation further causing an inflammatory state. The end result is a consumptive state with disequilibrium of coagulation [7–10].

3. Anticoagulation with unfractionated heparin in ECMO

Although anticoagulation during ECMO is necessary to prevent circuit thrombosis and subsequent thromboembolic events in the patient, it continues to be a

	ICH N(%)	Surgical site bleeding N(%)	GI hemorrhage N(%)	Cerebral infarct N(%)
Neonatal cardiac	326(11)	739(26)	35(1)	93(3)
Neonatal respiratory	643(11)	386(7)	89(2)	180(3)
Pediatric cardiac	251(6)	974(25)	79(2)	231(6)
Pediatric respiratory	243(5)	332(10)	135(4)	158(7)

Table 1.
Patient-related hemorrhagic and thrombotic complications extrapolated from the ELSO registry, 2009–2015 [1]. ICH, intracranial hemorrhage; GI, gastrointestinal.

significant risk factor for complications in ECMO patients. The most common bleeding complications during ECMO include intracranial hemorrhage (ICH), surgical site bleeding, and gastrointestinal hemorrhage (**Table 1**). Surgical site bleeding is the most frequent complication and occurs in up to 25% of pediatric cardiac and respiratory ECMO patients [1]. Bleeding events are associated with increased mortality [2]. For example, while ICH is not a frequent complication, the effect is significant with a survival rate of 17–40% compared to 45–68% for those who do not have an ICH [1]. In addition to hemorrhage, thrombotic complications can occur. While not as common as bleeding complications, cerebral infarcts accounted for 3–7% of complications described in the ELSO registry report [1]. Unfractionated heparin continues to be the most widely studied and used anticoagulant for anticoagulation in ECMO, but alternative agents are increasingly being used in pediatric and adult ECMO patients.

3.1 Unfractionated heparin

Unfractionated heparin (UFH) is the gold standard anticoagulant during ECMO and is commonly used in ECMO centers worldwide. Heparin acts as a catalyst to potentiate the action of antithrombin III, inhibiting thrombin and activated coagulation factor X, thus inhibiting the conversion of fibrinogen to fibrin [11]. The half-life of heparin is approximately 1–2 hours in healthy adults, but can vary significantly in pediatric patients. Heparin is metabolized by the reticuloendothelial system in the liver and spleen, and is excreted in the urine [11]. In the pediatric population, developmental hemostasis and the patient's age may affect the pharmacokinetics of heparin [12]. For example, the neonatal population frequently requires additional monitoring and higher bolus and infusion rates to obtain effective anticoagulation [6, 12–14]. Another complication due to unfractionated heparin use is heparin-induced thrombocytopenia that is seen in 1–2% of pediatric patients [11].

For patients with preexisting conditions that preclude them from safe anticoagulation, such as trauma patients with intracranial hemorrhage or patients that develop hemorrhagic complications while on ECMO, successful use of heparin-free ECMO management with or without heparin-bonded circuits has been documented [15–17]. However, the published literature is limited primarily to specific populations and for a limited duration of time.

4. Monitoring during heparin anticoagulation

Close monitoring to ensure anticoagulation is therapeutic is necessary to decrease the risk of hemorrhage or thrombosis during ECMO. The common tests used to monitor heparin during ECMO are activated clotting time (ACT), activated partial thromboplastin time (aPTT), and anti-factor Xa. No single test has been

found to be superior to monitor heparin during ECMO. ECMO centers worldwide vary in their practices on the type of test or combination of tests used to monitor heparin [2, 18].

4.1 Activated clotting time

The activated clotting time (ACT) is a whole blood test used at the bedside that provides immediate results [3, 6]. The ACT measures the time in seconds to form a fibrin clot after the addition of specific coagulation activators, thus it does not solely measure the effect of unfractionated heparin. It is a relatively inexpensive test that has been widely used to monitor heparin during cardiopulmonary bypass, but coagulation factor deficiencies, hemodilution, platelet function, and hypofibrinogenemia may affect the value [3, 19]. Due to these limitations in ACT, Baird and colleagues retrospectively reviewed 600 pediatric ECMO patients and found only a modest correlation between ACT and UFH dose suggesting that ACT may not be an accurate tool for monitoring UFH anticoagulation [20]. Bembea and colleagues found similar results to Baird with only a 42% correlation between target ACTs and anti-factor Xa [21].

4.2 Activated partial thromboplastin time

Activated partial thromboplastin time (aPTT) is a plasma-based test, instead of a whole blood test, which only measures the initial 5% of thrombin generated and without incorporating platelet function or assessing clot strength. The aPTT measures the time from FXII activation to fibrin formation after addition of the PTT reagent and calcium [3, 19]. The therapeutic range for aPTT in adults has been shown to correlate to 1.5–2.5× the patient's baseline aPTT [22]. However, this range has not been validated in pediatric patients and can vary significantly compared to adults. For example, an aPTT that correlates to anti-factor Xa between 0.35 IU/ml and 0.7 IU/ml in a patient less than 1 year old is between 58 and 105 seconds, but in a patient 6–10 years old the anti-factor Xa correlates to an aPTT between 45 and 251 seconds [23]. The results of aPTT can be affected by fibrinogen level, presence of acute phase reactants, and increased levels of FVIII. These variables are often skewed in critically ill patients, which can lead to a high degree of intra- and inter-patient variability [19].

4.3 Anti-factor Xa assay

The anti-Xa assay is a plasma-based test that measures the ability of UFH to catalyze antithrombin's inhibition of factor Xa. Anti-Xa assay differs from ACT and aPTT as it measures the heparin concentration in the patient's blood [24]. Since the anti-Xa assay only measures one specific action of heparin, the value is used as a surrogate to approximate overall function [19]. The anti-Xa value may be affected in patients with elevated plasma-free hemoglobin, hyperbilirubinemia, hypertriglyceridemia, and antithrombin (depending on test reagants). A point of care anti-Xa test is available, but it is currently not widely used. Anti-factor Xa has been shown to have improved correlation to heparin activity as compared to aPTT and ACT [25]. In addition, a retrospective review of 62 pediatric ECMO patients with a mean anti-factor Xa level >0.2 IU/ml was associated with decreased circuit change [26].

Published literature supports the correlation between anti-factor Xa values and UFH dose. Unfortunately, many studies have shown a poor correlation between anti-factor Xa and ACT and/or aPTT. Multiple cardiac studies evaluating patients

requiring cardiopulmonary bypass report disparities between ACT values and anti-Xa as compared to UFH doses [27–30]. ECMO adult studies have shown an improved correlation between aPTT and UFH concentrations, but pediatric studies demonstrate poor correlation to anti-factor Xa levels [31–33].

4.4 Viscoelastic testing

Viscoelastic testing such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are whole blood tests that measure the interaction of clotting factors, fibrinogen, and platelets as well as fibrinolysis (**Figure 2**). By measuring more than clotting factors, viscoelastic tests can give a more global picture of the coagulation system and allow for tailored transfusion management [3, 19]. **Figure 2** shows the standard TEG measurements including reaction time (R), kinetics (K), and maximum amplitude (MA). The R value is the time necessary for the initial clot formation. This value can be affected by the presence of anticoagulants, factor deficiencies, and hypercoagulable states. The K value measures the time for the clot to strengthen and can be affected by platelet count, fibrinogen, and coagulation factors. The maximum amplitude quantifies the final strength of the clot. Overall clot strength can be affected by the amount and function of fibrinogen and platelets [3]. In general, viscoelastic tests can be limited by static flow conditions [19]. While there is limited evidence in trauma, obstetrics, liver transplantation, and hemophilia using viscoelastic testing to help define coagulopathy and decrease overall blood product transfusions, studies are needed to confirm these results in ECMO patients [34]. Furthermore, prospective studies should examine the use of TEG and ROTEM in conjunction with aPTT and/or anti-factor Xa.

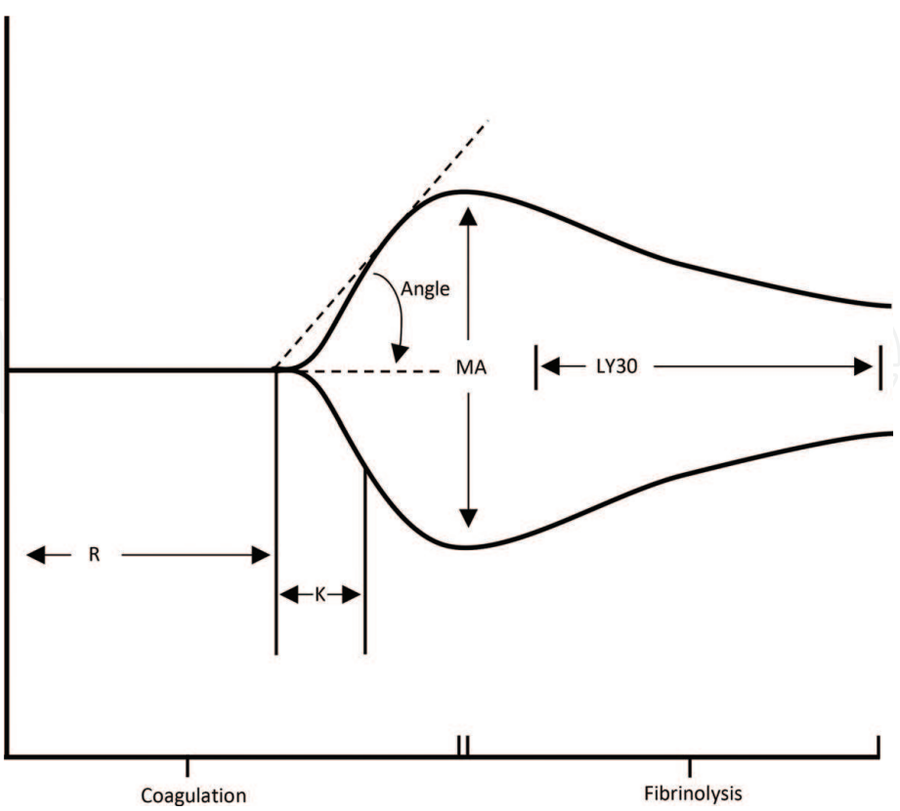

Figure 2.
Thromboelastography (TEG). R, reaction time; K, kinetics; MA, maximum amplitude; LY30, amplitude at 30 minutes.

5. Direct thrombin inhibitors

5.1 Bivalirudin

Alternative agents, such as direct thrombin inhibitors (DTI), have been increasingly used in ECMO centers worldwide. Bivalirudin is a DTI that binds to both circulating and clot-bound thrombin [35]. The basic structure of thrombin consists of the active site, exosite 1, and exosite 2. Exosite 1 is the location where specific substrates, such as fibrin, can bind and orient peptide bonds toward the active site of thrombin [36]. Bivalirudin is a bivalent DTI that blocks thrombin at the active site and exosite 1 [36, 37]. Bivalirudin is primarily metabolized by proteolytic enzymes with 20% renally excreted [36]. With limited evidence to support the safety and therapeutic profile of bivalirudin in patients undergoing ECMO, bivalirudin has primarily been used in patients unresponsive to unfractionated heparin or those who developed heparin-induced thrombocytopenia [38]. In *in vitro* studies, bivalirudin inhibits both soluble and clot-bound thrombin, a unique mechanism of action not known to occur with unfractionated heparin [35]. Two prospective studies assessing clot resolution found that patients anticoagulated with bivalirudin for the treatment of deep vein thrombosis (DVT) had complete or partial clot resolution within 48 hours [39, 40].

5.2 Argatroban

Argatroban is a L-arginine derivative that reversibly binds and inhibits thrombin. Argatroban is a univalent DTI that binds solely to the active site of thrombin. It is metabolized by hepatic CYP3A4/5 oxidases and is excreted primarily in the feces [36, 41, 42]. Menk and colleagues retrospectively reviewed 78 adult patients with acute respiratory distress syndrome (ARDS) on ECMO. The single center study supported that patients anticoagulated with argatroban had no difference in major or minor bleeding and had more goal aPTT values compared to UFH controls [43]. Multiple studies have shown that doses vary widely between adult and pediatric patients anticoagulated with argatroban on ECMO, thus careful monitoring is imperative to ensure optimal anticoagulation [43–45]. A literature analysis reviewed nine articles describing 34 patients anticoagulated with argatroban. Pediatric patients were administered a dose ranging from 0.1 to 12 mcg/kg/min to achieve therapeutic anticoagulation. There was no correlation between the dose of argatroban and the age of the patient [45].

Bivalirudin and argatroban remain the most commonly utilized direct thrombin inhibitors for anticoagulation during ECMO, but small case studies have evaluated the efficacy of lepirudin [46, 47]. Unfortunately, the product is no longer available due to production discontinuation by the manufacturer.

5.3 Direct thrombin inhibitor use in ECMO

Disadvantages of DTIs include limited availability of laboratory monitoring specific to DTIs and lack of antidote. Currently, most centers that use DTIs follow aPTT for monitoring, which as mentioned previously can be affected by several patient variables. Ecarin chromogenic assay and dilute thrombin time are possible superior tests for monitoring, but are currently not widely available [36]. Unlike heparin, which can be reversed with protamine, no antidote exists for DTIs, but recombinant factor VIIa has been shown to be an effective reversal agent [48]. Plasmapheresis has also been shown to be effective in clearing bivalirudin, but limited evidence has been published supporting its use. An advantage of bivalirudin over argatroban is that it can be quickly removed by continuous renal replacement therapy [49].

Evidence of DTIs for ECMO patients is limited to case series or retrospective analyses. To confirm the safety and efficacy of DTIs and superiority (or at least non-inferiority) to heparin, prospective randomized trials of pediatric and adult patients are needed. Two randomized studies are currently enrolling to compare bivalirudin to UFH for pediatric and adult ECMO patients (NCT03318393 and NCT03707418).

6. Nitric oxide

At present, systemic anticoagulation is the primary method to prevent thrombus formation during ECMO, but the use of nitric oxide within the extracorporeal circuit may be used to inhibit platelet adhesion. Nitric oxide (NO) is an endogenous substance released by the endothelial cells. NO temporarily inactivates platelets resulting in decreased function and aggregation [50, 51]. However, the effect of NO only temporarily inhibits platelets and after rapid degradation of NO by hemoproteins, platelets will regain normal function [52]. The utility of NO within ECMO circuits to limit or negate the requirement of systemic anticoagulation remains a promising area of research, but further studies to evaluate the long-term risks of thrombosis are warranted.

7. Conclusion

In summary, while the goal for ECMO anticoagulation is to prevent clinically significant bleeding and clotting, the morbidity and mortality for these complications remain high for pediatric patients. Unfractionated heparin continues to be the most commonly used anticoagulant for ECMO patients in spite of its many disadvantages including altered pharmacokinetics in children and difficulty in lab monitoring. While there is a large variation between lab monitoring of heparin among ECMO centers, combination testing with anti-factor Xa and/or aPTT with viscoelastic tests is potentially superior. DTIs such as bivalirudin and argatroban remain promising alternatives to heparin, but prospective studies are needed to confirm their safety and efficacy.

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