Anticoagulation in extracorporeal membrane oxygenation

Judith Ju-Ming Wong[1,2], Joyce Ching Mei Lam[2,3], Yee Hui Mok[1,2], Jan Hau Lee[1,2]

[1]Children's Intensive Care Unit, Department of Paediatric Subspecialties, KK Women's and Children's Hospital, Singapore; [2]Duke-NUS Medical School, Singapore; [3]Paediatric Haematology/Oncology Service, Department of Paediatric Subspecialties, KK Women's and Children's Hospital, Singapore

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Correspondence to: Judith Ju-Ming Wong, MBBCh BAO, MRCPCH. Children's Intensive Care Unit, Department of Paediatric Subspecialties, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899, Singapore. Email: judith.wong.jm@singhealth.com.sg.

Abstract: During extracorporeal membrane oxygenation (ECMO) support, the underlying disease process and contact between blood and non-biological surfaces cause alterations in haemostasis. This results in the activation of coagulation and platelet pathways and consumption of factors which can provoke haemorrhage, thrombosis or both. Currently, despite its limitations, unfractionated heparin (UFH) is the anticoagulant of choice in patients supported on ECMO. However, there is increasing experience with the use of new anticoagulants (bivalirudin, argatroban and lepirudin). Bleeding remains the most common complication and the use of haemostatic adjuncts in ECMO, including antifibrinolytic agents and desmopressin are supported by a weak body of evidence, although there is growing literature to support the cautious use of recombinant activated factor VII in certain situations. Bleeding bundles have been advocated to ensure step-by-step measures are taken to control bleeding. Similarly, advancements in monitoring of anticoagulation may lie in the development of anticoagulation laboratory protocols and algorithms. This review aims to furnish the ECMO provider with an update on advancements in anticoagulation in ECMO.

Keywords: Extracorporeal membrane oxygenation (ECMO); blood coagulation disorders; blood coagulation tests; anticoagulant drugs; pediatric intensive care unit

Introduction

Extracorporeal membrane oxygenation (ECMO) supports patients in refractory cardiac and/or respiratory failure (1). ECMO has evolved over the years with advancements in hardware and expert skills, such that increasingly complex patients are being supported with more complex circuits (e.g., incorporating plasmapheresis, dialysis, molecular adsorbent recirculating system) (2-4). Concurrent supportive care such as nutrition, physiotherapy, mobilization regimes and transportation during ECMO support continue to be developed (5). Experience is increasing with the Extracorporeal Life Support Organization Registry (ELSO) reporting more than 85,000 ECMO runs as of January 2017 (6). Nevertheless, anticoagulation, an essential component of ECMO support, remains an area of ongoing challenge with patients suffering haemostatic imbalance and physicians still struggling to establish the optimal management strategy for anticoagulation on ECMO (7).

Bleeding and thrombotic complications are the most frequent causes of death and morbidity affecting patients on ECMO (8,9). Bleeding (e.g., surgical site bleeding, cannula site bleeding and intracranial haemorrhage) and thrombosis (e.g., circuit clots, oxygenator failure and hemolysis) occurred in 38–70% and 31–44% of patients, respectively (8,9). Both bleeding and thrombosis were associated with decreased survival {relative risk (RR) 0.59
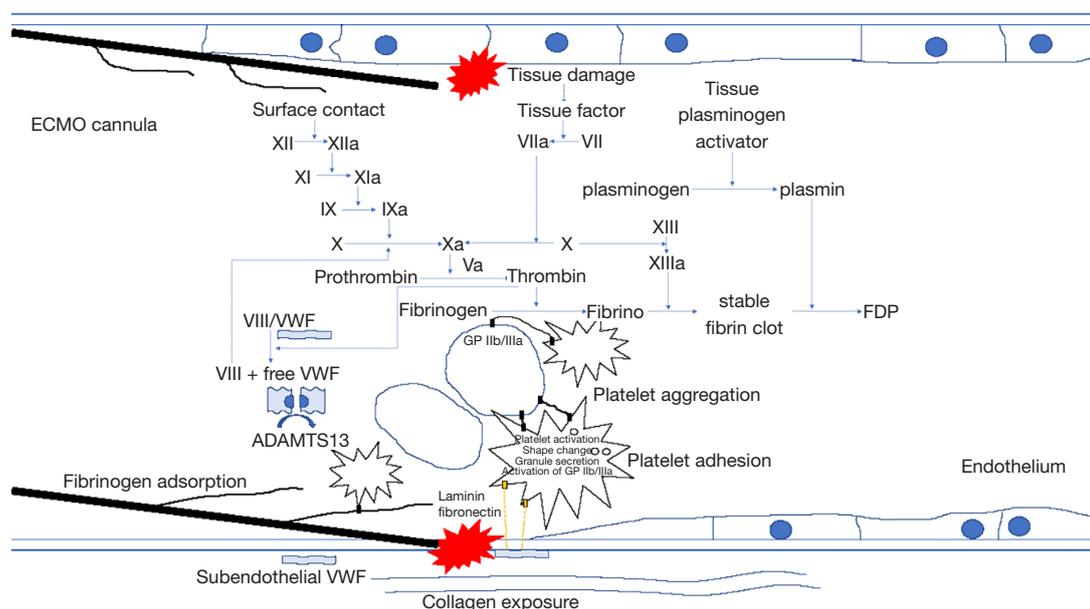
Figure 1 Schematic diagram of pathophysiology of impaired haemostasis on extracorporeal membrane oxygenation. Roman numerals indicate coagulation factors (e.g., X, coagulation factor X); Roman numerals followed by "a" indicate activated coagulation factors (e.g., Xa, activated coagulation factor X). ADAMTS 13, ADintegrin-like and metalloprotease with thrombospondin type 13; ECMO, extracorporeal membrane oxygenation; FDP, fibrin degradation product; VWF, von Willebrand factor; GP IIa/IIIb, glycoprotein IIa/IIIb.

[95% confidence interval (CI): 0.53–0.66] and 0.67 (95% CI: 0.60–0.74), respectively}. Anticoagulation practices vary among centres and may impact bleeding/thrombotic outcomes as well as overall cost of ECMO support (10,11). In addition to describing the fundamental effect of ECMO on coagulation pathways, we will in this review, also present a summary of the medical literature on the newer alternative anticoagulants used in ECMO and new monitoring strategies.

Methods

We reviewed studies on all age groups including neonates, pediatric and adult subjects, and all types of ECMO including cardiac, respiratory and extracorporeal cardiopulmonary resuscitation. Anticoagulation use in ventricular assist devices, Berlin heart devices, and extracorporeal carbon dioxide (CO_2) removal are beyond the scope of this review. In view of the limited medical literature, we included all published studies, including retrospective studies, to comprehensively assess this topic. We summarized the medical literature into the following subheadings: (I) the pathophysiology of impaired haemostasis on ECMO; (II) the use of anticoagulants;

(III) the role of haemostatic adjuncts; (IV) tests of anticoagulation; and (V) future directions.

The pathophysiology of impaired haemostasis on ECMO

During ECMO support, impairments in haemostasis are in part due to exposure of blood to non-biological surfaces of the extracorporeal circuit that activates both the coagulation and inflammatory pathways, and in part due to ongoing disease processes that cause varying degrees of immune dysregulation, endothelial dysfunction and consumption of coagulation factors (12-15). Underlying disease processes (e.g., sepsis, systemic autoimmune syndromes and severe burns) result in a systemic inflammatory response. The widespread cytokine storm [such as interleukin (IL)-6, IL-1, IL-8 and tumour necrosis factor alpha], complement activation and interactions between inflammatory cells and endothelium further impair endothelial integrity (16). Changes in the haemostatic system can be broadly divided into effects on platelets and on the coagulation system.

Platelets are activated upon contact with ECMO circuit surfaces and with high shear stress and turbulence within the circuit (*Figure 1*) (17). Activated platelets amplify coagulation

pathways, aggregate and adhere onto the circuit surfaces and to damaged endothelium, resulting in both thrombosis and consumptive coagulopathy (18). Fibrinogen adsorption onto artificial surfaces also contributes to platelet activation via glycoprotein IIb/IIIa binding (18). Platelet counts are expected to drop within the first few hours of ECMO and patients who remain on ECMO longer often have declining platelet counts over time (19). Platelet function has also been shown to be affected, with impairment of platelet aggregation noted in a time-dependent manner (17,20). Acquired von Willebrand syndrome (AVWS) is a phenomenon that has been recognized to occur during ECMO runs (21-23). AVWS is characterized by loss of high molecular weight multimers of von Willebrand factor (VWF) as a result of high shear stress, and leads to impaired binding of VWF to platelets and to the subendothelial matrix, which is not reversed by repeated platelet transfusions (17,20). A small adult study reported a high prevalence of AVWS in 31/32 (97%) patients on ECMO and 22/32 (69%) had bleeding complications (22). Severe qualitative platelet dysfunction for adenosine diphosphate (ADP)- and arachidonic acid (AA)-mediated aggregation were found on thromboelastography-platelet mapping studies which were associated with severe bleeding and mortality on ECMO (24).

Effects on the coagulation system include contact activation of the intrinsic pathway via exposure of circulating factor XII and prekallikrein to non-biological surfaces, which triggers fibrinolysis and bradykinin release downstream (initiating inflammatory and the renin-angiotensin pathways) (16). Exposure of negatively charged collagen in damaged endothelium also triggers activation of high molecular weight kininogen, prekallikrein and factor XII which form a complex on collagen and further amplifies the intrinsic pathway (16). The extrinsic coagulation pathway is activated via the exposure of subendothelial tissue factor on damaged endothelia to circulating factor VII (16). This is the major pathway responsible for thrombosis and disseminated intravascular coagulation (18).

Acquired antithrombin (AT) deficiency is commonly seen upon initiation of ECMO. Produced in the liver, AT is an endogenous inhibitor of activated clotting factors, including factor Xa and thrombin. AT deficiency that develops during ECMO runs can be attributed to a combination of accelerated consumption and reduced synthesis (25). Heparin acts by potentiating the anticoagulant effects of AT. AT deficiency leads to heparin resistance and potentially thrombosis (26).

Anticoagulant agents

An international cross-sectional survey (n=121 respondents) demonstrated that unfractionated heparin (UFH) was universally used for anticoagulation in ECMO (10). UFH is inexpensive, familiar to most physicians and has an age-related, dose-dependent short half-life (range 1–2 hours) (27). The effect of UFH is mediated via potentiation of the anticoagulant action of AT and induction of tissue factor pathway inhibitor, and results in inhibition of free thrombin, factors XIa, Xa, IXa and the tissue factor/factor VIIa complex (28). However, limitations of UFH include ineffective inhibition of platelet-bound factor Xa, phospholipid-bound factor Va–Xa complex and fibrin-bound thrombin. It also has the potential to cause heparin induced thrombocytopenia (HIT) (29). UFH also has undesirable pharmacokinetic properties; it binds to plasma proteins including acute - phase reactants leading to heparin resistance especially in acutely ill patients (30). Moreover, heparin therapy itself produces a decrease in circulating AT which also leads to heparin resistance (30).

Heparin resistance is a phenomenon whereby high doses of UFH are required to achieve therapeutic activated clotting time (ACT) levels. AT concentrate or fresh frozen plasma is given to replenish AT levels. The clinical benefit of replacing AT routinely is however, controversial. A retrospective study in paediatric ECMO (n=64) aiming to raise the AT levels to 120% (normal 80–120% in children and adults) showed a reduction in the UFH infusion rate of 10.1 unit/kg/hour (95% CI: 7.6–36.6) but no change in thrombosis or bleeding rates (31). Another retrospective paediatric ECMO study (n=40) aiming for 100% AT levels showed that AT replacement was independently associated with increased risk of circuit change compared to the control group [hazard ratio 3.15 (95%CI: 1.21–8.16)] (32). A retrospective neonatal ECMO study (n=162) targeting 100% AT levels in turn, showed that the AT group had less thrombotic/haemorrhagic complications (40.3% *vs.* 66.7%; P<0.001), less transfusions per day (54.7±20.1 *vs.* 67.4±34.9 mL/kg per day, P=0.001) and higher anti-Xa assay levels (0.48±0.16 *vs.* 0.3±0.14; P<0.001) compared to controls (33).

HIT, an immune-mediated side effect of heparin therapy characterized by thrombocytopenia and by a paradoxical prothrombotic state following heparin exposure, occurs in around 0.8–7% of adult patients on ECMO (29,34). Its occurrence is rare in children, being only reported in scattered case reports (35,36). These reports do not evaluate

Table 1 Summary of evidence for alternative anticoagulants in extracorporeal membrane oxygenation

Author	Study design	Results
Bivalirudin		
Ranucci et al. [2011]	Retrospective study (n=21); pediatric and adult ECMO; dose: 0.03–0.05 mg/kg/hour; target: ACT 160–180 s, APTT 50–80 s, TEG r time 12–30 min	ACT and APTT were more stable; PLT and AT were better preserved; less bleeding; lower cost
Nagle et al. [2013]	Retrospective study (n=12); pediatric cardiac and respiratory ECMO; dose: initial bolus 0.1 mg/kg, maintenance 0.045–0.48 mg/kg/hour; target: APTT	Positive correlation r^2=0.267 between dose and APTT (P=0.044)
Pieri et al. [2013]	Retrospective study (n=20); adult ECMO; dose: 0.025 mg/kg/hour; target: APTT 45–60 s	APTT more stable; no difference in bleeding, thrombosis, ECMO duration and mortality
Argatroban		
Mejak et al. [2004]	Case report; newborn Norwood stage I with HIT	Dose: initial bolus 200 µg/kg, maintenance 3–7.5 µg/kg/min; target: APTT 60–80 s
Mejak et al. [2005]	Case report; newborn TGA with suspected HIT	Dose: initial bolus 100 µg/kg, maintenance 12 µg/kg/min
Scott et al. [2006]	Case report; pediatric VV ECMO with HIT	Target: ACT 180 to 200
Beiderlinden et al. [2007]	Case series (n=9); adult VV ECMO with HIT	Dose: one patient received 2 µg/kg/min which resulted in significant bleeding; Subsequently the rest received 0.2 µg/kg/min which was sufficient; target: APTT 50–60 s was achieved within 4hours
Dolch et al. [2010]	Case report; adult ARDS with HIT	Dose: 0.35 µg/kg/min; target: APTT 45–60 s; duration: 95 days
Phillips et al. [2014]	Case report; adult ARDS, obesity, with HIT	Dose: 0.1–0.65 µg/kg/min; target: ACT 170–200 s, APTT 60 s; duration: 7 days
Lepirudin		
Dager et al. [2004]	Case report; pediatric trauma ECMO with HIT	Dose: bolus 0.1 mg/kg, maintenance 0.12 mg/kg/hour; target APTT: 2× normal; duration: 6 days; no unexpected bleeding or thrombosis
Balasubramanian et al. [2005]	Case report; adult respiratory ECMO with HIT	–

ECMO, extracorporeal membrane oxygenation; ACT, activated clotting time; HIT, heparin induced thrombocytopenia; TEG, thromboelastography; APTT, activated partial thromboplastin time; TGA, transposition of great arteries; VV ECMO, veno-venous extracorporeal membrane oxygenation; ARDS, acute respiratory distress syndrome; PLT, platelets; AT, antithrombin III.

outcomes related to HIT, however, extrapolated from other groups of patients who develop HIT, the management involves immediate withdrawal of heparin and switching to alternative anticoagulants to maintain circuit patency and to prevent thrombotic complications (37).

Alternative anticoagulants (e.g., argatroban, bivalirudin and lepirudin [direct thrombin inhibitors (DTI)] are used only by a minority of providers (*Table 1*) (10). Of these, bivalirudin is supported by evidence derived from retrospective adult and pediatric studies (38-40). Unlike UFH, the DTI are not dependent on AT for their anticoagulant effect but directly inhibit both free circulating

and fibrin bound thrombin. The short half-life (25 minutes) of bivalirudin in particular makes it suitable for rapid titration (41). Of note, the doses of bivalirudin would need to be adjusted in patients with renal impairment (42). Bivalirudin is administered as a continuous infusion with the dose ranging between 0.025–0.48 mg/kg/hour. It is usually titrated to target a therapeutic APTT range. A positive correlation was demonstrated between bivalirudin dose and APTT (r^2=0.267; P=0.044) (40). Two retrospective studies compared bivalirudin to UFH and found that bivalirudin resulted in more stable APTT measurements (38,39). The largest study (n=21) which included both adults and

children, showed better preservation of platelet count and AT levels, less bleeding and counterintuitively, lower overall cost despite the higher cost of bivalirudin (38).

Another DTI, argatroban, has a slightly longer half-life (39–51minutes) (43). However, it is metabolized in the liver and hence contraindicated in severe hepatic dysfunction. Case reports and case series in adult, paediatric and neonatal ECMO have reported the use of argatroban in place of UFH in suspected/proven HIT (35,44-48). Some utilized an initial bolus dose of 100–200 µg/kg, while the maintenance dose reported ranged from 0.1–0.65 µg/kg/min. Dose titration was guided by APTT and ACT levels. Lepirudin as an anticoagulant in ECMO has been reported in only a small number of case reports (49,50). Infrequent usage is likely due to the less favourable, longer half-life (1.3 hours) and renal excretion, thus requiring caution and dose adjustment in renal impairment (51).

Regional anticoagulation in ECMO is currently in its developmental infancy. The benefit of regional anticoagulation as opposed to systemic anticoagulation is reduced bleeding since only the extracorporeal circuit is anticoagulated (52). A regional anticoagulant, Nafamostat mesylate, which is a protease inhibitor of the coagulation (thrombin, Xa, and XIIa), fibrinolytic and complement systems has been used as a regional anticoagulant for continuous renal replacement therapy in Japan (53). Its use in ECMO has been reported in a group of 13 patients with bleeding complications from ECMO (54). It was infused into the venous/drainage limb of the ECMO circuit and anticoagulation measured by ACT and APTT were lower in the samples taken from the patient compared to samples taken from the circuit. Citrate, long used for regional anticoagulation in continuous renal replacement therapy is also being evaluated for use in ECMO (clinicaltrials.gov identifier: NCT00968565) (55).

In summary, UFH remains the default anticoagulant used in ECMO. However, UFH is associated with several serious limitations. With increasing experience with the use of newer anticoagulants, these limitations may be overcome. With the current state of evidence, it is uncertain if the use of these new anticoagulants may one day surpass UFH.

The role of haemostatic adjuncts

Bleeding is a common and serious complication of ECMO occurring in up to 60–70% of adults or children put on ECMO (9,56). It includes cannula site bleeding, surgical site bleeding, gastro-intestinal bleeding, hemothorax, hemopericardium and intracranial hemorrhage. The most devastating, are intracranial hemorrhages which are reported to occur in up to 16% pediatric/neonatal ECMO runs and was associated with higher rates of brain death (9). Whereas in adults, the rate of intracranial hemorrhage is around 2% (56). Bleeding is independently associated with higher daily risk of mortality (56). As such, hemostatic adjuncts are employed to minimize this risk of bleeding and reduce transfusion requirements (10). These drugs provide weak haemostatic effects and do not replace transfusion of blood products and replacement of coagulation factors. Haemostatic adjuncts include antifibrinolytics (e.g., tranexamic acid and aminocaproic acid, aprotinin), desmopressin and recombinant factor VIIa (rFVIIa). However, evidence for their use specifically in ECMO is scarce.

Aminocaproic acid and tranexamic acid, derivatives of the amino acid lysine, are competitive inhibitors of plasminogen preventing its conversion to plasmin (57). They also competitively inhibit tissue plasminogen activator and directly inhibit plasmin. In the adult population, both have been used successfully in other types of traumatic, surgical (including cardiac surgery) and post-partum haemorrhage to reduce bleeding and reduce transfusion requirements (56,58,59). In neonatal ECMO, retrospective studies have reported the use of aminocaproic acid to be safe, and effective in reducing the incidence of cannulation site and surgical site bleeding (27,41,42). The efficacy of tranexamic acid in ECMO was reported in a small retrospective cohort (n=10) of neonates with congenital diaphragmatic hernia where the use of tranexamic acid was associated with lower incidence of surgical site bleeding and lower transfusion requirements (43). However, thrombotic complications were reported in the intervention arm. Aprotinin is a non-specific protease inhibitor with a complex mechanism of action (57,60). It interferes with contact factor activation (factor XII), fibrinolysis, renin-angiotensin system, and neutrophil activation—hence having anti-inflammatory, anticoagulation and procoagulation effects. Aprotinin use in the adult cardiac surgery population was associated with increased mortality, renal, cardiovascular and cerebrovascular events, hence, its use is limited (59,61,62). A large, single center retrospective study (n=564) in neonatal ECMO found no increase in mortality in patients on tranexamic acid and aprotinin. However, this study did not report the efficacy on haemostasis (63). Desmopressin, a synthetic vasopressin analogue, induces release of factor VIII and VWF. It produces a small reduction in

postoperative blood loss in adult cardiac surgery especially in patients on aspirin (64). Its use in ECMO has been reported but there are no dedicated studies evaluating its efficacy in this group of patients (51).

rFVIIa was originally developed for the treatment of haemophilia with inhibitors (58). However, its use has expanded to include treatment of any haemorrhage that does not respond to plasma transfusion or other conventional therapy (65). Coagulation is triggered locally at the site of vascular injury as rFVIIa binds to tissue factor, and activates factors IX and X, ultimately leading to thrombin generation and clot formation. Given its local effects at the site of vascular injury, rFVIIa may have a role in achieving haemostasis in patients experiencing refractory postoperative bleeding complications. An international survey reported that more than half of ECMO providers use rFVIIa (10).

Paediatric and adult retrospective ECMO studies demonstrated a reduction in bleeding and transfusion requirements with the use of rFVIIa (66-68). Patients were deemed to be adequately transfused and surgical bleeds were excluded prior to rFVIIa administration. These studies utilised doses ranging from 45–90 μg/kg/dose. An adult ECMO study (n=66) reported that the rate of effective haemostasis was 93.3% (66). The rate of thromboembolic events was 3.3% (1 case) which was not significantly different from the control group. There was also no difference in the need for circuit change, ventilation time, infectious complications or survival between patients who received rFVIIa or not. However, the use of rFVIIa is limited due to the fear that it may cause overt thrombosis in the patient or the circuit as has been reported in small case series (68,69).

Some centres have reported success in the use of bleeding bundles encompassing standard initial steps in the control of bleeding: (I) ensuring correction of acidosis, hypothermia, hypocalcemia; (II) ensuring platelets, coagulation factors and fibrinogen are adequately replaced; (III) use of adjuncts like tranexamic acid, aprotinin, aminocaproic acid and desmopressin; and (IV) excluding surgical bleeding prior to administration of rFVIIa. First dose of rFVIIa was given in the presence of perfusion staff and a fully primed backup circuit ready for the possibility of circuit thrombosis (70).

Specific ECMO data on antifibrinolytic agents are lacking and its use is extrapolated from cardiac surgical data. Data on the use of rFVIIa reveals it to be a double-edged sword as there is a definite thrombotic risk. Moderate sized retrospective studies report its efficacy in reducing bleeding and transfusion. However, the increased thrombotic rate though not statistically significant is worrisome. Importantly, a bleeding bundle to ensure all contributory factors are addressed in a multipronged manner is rational.

Monitoring of anticoagulation in ECMO

Most ECMO programs routinely monitor ACT, full blood counts (FBC), prothrombin and activated partial thromboplastin time (PT and APTT) and fibrinogen (10). Additionally, AT levels 60/119 (50%), anti-factor Xa assay 46/115 (40%) and thromboelastography (TEG) 21/116 (18%) have been used at varying time points or on a "as needed" basis (10). There are limitations with each test and hence, a combination of tests are required for optimal anticoagulation management (71).

ACT remains the preferred choice for monitoring anticoagulation in ECMO (72). Minimum ranges of 140–220 and maximum ranges of 170–240 have been used (10,11). Its main advantages are that it is an inexpensive, point-of-care test, thus allowing for immediate heparin titration. There is also extrapolated experience from its use in cardiopulmonary bypass. There are, however, mechanistic differences between cardiac bypass and ECMO that affects the performance of ACT (72). These factors include higher doses of heparin used in bypass, the relatively prolonged nature of ECMO and its common association with systemic inflammation and multiorgan dysfunction (72). ACT measures the time to fibrin clot formation after adding a contact activator (e.g., glass, celite or kaolin) to whole blood. In the presence of haemodilution, hypothermia, abnormalities in coagulation factors, fibrinogen and platelets, and the use of adjuncts like aprotinin, ACT would not be able to measure the effect of heparin accurately. These co-existing conditions are common in ECMO, and renders ACT inaccurate as a measure of the anticoagulant effect of heparin (73).

APTT, an assessment of the intrinsic pathway, is measured in the laboratory (74). This test involves the addition of platelet poor plasma to the partial thromboplastin reagent. The result reflects the time taken for clot formation as detected by optical or electromechanical methods. Although this method can be affected by a variety of factors (e.g., drugs, hematocrit, acute phase reactants and abnormalities in coagulation factors) it has better correlation with heparin dose than ACT in the neonatal, paediatric and adult population (73-76).

In the anti-Xa assay, known amounts of factor Xa and AT

are added to the sample (77). Heparin forms an inhibitory complex with AT and inactivates factor Xa. Therefore, excess amount of factor Xa remaining in the sample is inversely proportional to the original amount of heparin. This is detected using chromogenic methods. The results are then compared to a standard curve and are provided as a concentration of anti-Xa (units/mL). Hence, anti-Xa assay directly measures UFH activity and is considered the gold standard for monitoring UFH in ECMO. Compared with APTT, anti-Xa has a higher degree of correlation with heparin dose and less variation (73). The accuracy of the anti-Xa assay can however, be affected by hyperbilirubinemia, haemolysis and lipaemia which are not uncommon occurrences in patients on ECMO (78). Moreover, some centers may have limited availability and or turn-around time of anti-Xa assays.

A prospective adult ECMO study (n=22) correlating the clinical anti-thrombotic effect of ACT, APTT and anti-Xa levels, showed that every unit decrease in anti-Xa level was associated with increased odds of developing deep vein thrombosis [OR 7.28 (95% CI: 1.61–32.94)], whereas there was no relationship with ACT and APTT (79). A retrospective study in paediatric ECMO (n=62) showed that patients who did not require a circuit change had higher heparin doses and anti-Xa levels compared to patients who did require it. Each decrease of 0.01 IU/mL anti-Xa level increased the odds of requiring a circuit change [OR 1.105 (95% CI: 1.00–1.10)].

Lastly, other point-of-care tests like TEG, also called thromboelastometry (TEM), provides global information on the dynamics of clot development, stabilization and dissolution (80). Its use is extrapolated from experience in complex major surgery including cardiopulmonary bypass, having shown to be associated with decreased blood product administration and mortality (81,82). A prospective, observational study assessing the use of TEM in adult ECMO showed that reliable and timely information on haemostatic parameters could be obtained during bleeding episodes and guide transfusion decisions (83). However, there is lack of evidence supporting its routine use in ECMO with no published threshold parameters or therapeutic goals.

The currently available anticoagulation assays measure either specific pathways or global haemostasis, and each test may be influenced by a variety of factors. As such, the bedside physician must use this knowledge to make an overall judgement on how to manage a bleeding patient and minimise the thrombotic risk at the same time.

Further advancement is required in the development of anticoagulation management protocols and algorithms. One such protocol which includes monitoring of ACT, FBC, APTT, anti-Xa, AT and TEG, was shown to reduce the occurrence of cannula site bleeding (22% to 12%; P=0.04), surgical site bleeding (38% to 25%; P=0.02) and increase the median ECMO circuit life (3.6 to 4.3 days; P=0.02). (11).

Future directions

UFH anticoagulation is associated with several limitations including heparin resistance, need for AT replacement and HIT. As such, there is growing experience with alternative anticoagulants. These drugs especially bivalirudin which has favourable pharmacokinetic properties are currently being evaluated in randomised trial. A study comparing bivalirudin and UFH in neonatal and pediatric ECMO is underway (clinicaltrials.gov identifier: NCT03318393) (55). Increasing knowledge about the safety and efficacy of these alternative anticoagulants may eventually challenge UFH as the anticoagulant of choice. We also anticipate the emergence of feasibility data on the use of regional anticoagulation in ECMO.

The cause of bleeding in a patient on ECMO is multifactorial, as demonstrated in the various pathways that can be affected. As such, the efficacy of an individual haemostatic agent may be difficult to evaluate in isolation in a research or clinical setting. Over the next few years, we expect more development of evidenced based bleeding bundles/protocols tailored to the capabilities of each ECMO centre.

Knowledge of various anticoagulant tests to map the different haemostatic pathways may soon be combined and incorporated into these bundles/protocols as these seem to translate into improved clinical outcomes. ACT and APTT, being crude measures of anticoagulation and influenced by many concomitant factors in ECMO, may be superseded by a combination of tests like anti-Xa assay, TEG/TEM and platelet mapping. We await trials evaluating anticoagulation monitoring algorithms based on TEG versus conventional algorithms based on ACT or APTT (clinicaltrials.gov identifier: NCT02271126) (55).

Conclusions

Alterations in almost every haemostatic pathway exist in the patient on ECMO producing both bleeding and thrombotic risks. As such, anticoagulation remains one of the most

challenging aspects of ECMO management. Newer anticoagulation agents are being evaluated for use in ECMO and we can expect more data on regional anticoagulation methods in the next few years. Advancement in the form of bleeding bundles and anticoagulation management protocols are also anticipated to emerge.

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Footnote

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