Indian Journal of Thoracic and Cardiovascular Surgery (April 2021) 37 (Suppl 2):S241–S247
https://doi.org/10.1007/s12055-021-01176-3

REVIEW ARTICLE

Anticoagulation in ECMO patients: an overview

Gaurav Kumar[1] · Ashish Maskey[2]

Received: 16 December 2019 / Revised: 3 March 2021 / Accepted: 5 March 2021 / Published online: 23 March 2021

Abstract

Extracorporeal membrane oxygenation (ECMO) is a form of cardiorespiratory support, and is being increasingly used to support refractory heart and respiratory failure. It involves draining blood from the vascular system, which is then circulated outside the body by a mechanical pump and then later reinfused back into the circulation. The blood that is circulated outside the body comes in contact with a large surface area of non-endothelial biosurface. This exposure leads to a pro-thrombotic state, and hence anticoagulation is required. Unfractionated heparin is the most commonly used anticoagulation in most ECMO centers, but it does require close monitoring. Despite the advances made, hemostasis remains a challenge for physicians who manage patients on ECMO.

Keywords Extracorporeal membrane oxygenation · Extracorporeal life support · Anticoagulation

Interactions between hemostasis and ECMO biomaterial surfaces

In humans, the healthy endothelium has protective mechanisms to resist spontaneous thrombosis. During extracorporeal membrane oxygenation (ECMO), blood is exposed to a large surface area of foreign non-endothelial biomaterial surfaces (pump, membrane oxygenator, and tubings), which do not have such endothelium-like protective mechanisms to resist thrombosis. Therefore, when blood is exposed to such a surface, this leads to a pro-thrombotic state.

The initial step is the adsorption of proteins to the ECMO biomaterial surface. Fibrinogen is one of the first proteins adsorbed on the surface. Soon after, other proteins like fibronectin and von Willebrand factor (vWF) (which is activated by high shear stress and aberrant flow pattern in ECMO) [1] get adsorbed to the biomaterial surface. Later, fibrinogen is replaced with protein-like factor (F) XII, high molecular weight kininogen, prekallikrein, and FXI [2], which have a higher affinity for the biomaterial surface. This biomaterial surface–bound FXII undergoes conformational changes to become auto-activated, which triggers thrombin generation via the intrinsic pathway of coagulation [3]. In addition, the classical and the alternative pathway of the complement system is also activated [4]. Once the complement system is activated, it amplifies the thrombin generation and serves as a potent leukocyte chemoattractant and activator.

The adsorbed protein layer not only initiates the intrinsic coagulation pathway but also mediates platelet adhesion [5]. Glycoprotein IIb/IIIa (GPIIb/IIIa) (also known as integrin $\alpha_{IIb}\beta_3$) is the most important platelet surface glycoprotein that is found on the surface of the platelets, which is a receptor for fibrinogen and vWF. Platelets, even in a quiescent state, are capable of binding to fibrinogen that is adsorbed to artificial surfaces [6]. Other proteins like fibronectin and vWF that are in the protein layer also mediate platelet adhesion [7]. This interaction between GPIIb/IIIa and fibrinogen deposit, and other proteins leads to adhesion and activation of the platelets. Also, thrombin that is generated as a result of intrinsic coagulation pathway activation also activates the platelets. Once the platelets get activated, they release thromboxane A_2 and adenosine diphosphate, which activate nearby platelets, thus further amplifying platelet adsorption, adhesion, and activation [8]leading to the formation of platelet-thrombin complex [9]. In brief, platelet and leukocyte activation, coagulation, and complement systems are closely linked processes that are initiated after exposure to the artificial biomaterial surface,

✉ Gaurav Kumar
k8gaurav@gmail.com

Ashish Maskey
ashish.maskey@uky.edu

[1] Department of Pulmonary Critical Care and Sleep Medicine, University of Kentucky, 740 S. Limestone, Second Floor, Wing C, Room 211, Lexington, KY 40536, USA

[2] Department of Pulmonary Critical Care and Sleep Medicine, Kentucky Clinic, University of Kentucky, 740 S. Limestone, 5th Floor L543, Lexington, KY 40536, USA

thereby leading to a pro-thrombotic and a pro-inflammatory state.

Fibrinolysis is another essential hemostatic mechanism of the coagulation cascade and it is suggested that this arm of the hemostatic cascade is also triggered during ECMO. The precise role of the fibrinolytic system is not yet elucidated [10].

In ECMO, the coagulation hemostasis is also affected by other factors, like red blood cell (RBC) hemolysis, acquired vWF deficiency, thrombocytopenia, and platelet dysfunction due to concomitant uremia. Factors that cause RBC hemolysis in the ECMO [11] setting are excessive mechanical shear stress (applied to RBC due to flow and pressure gradients) [12] and thrombosis (locally impaired flow conditions that may lead to mechanical stress) [13]. Free hemoglobin that is released after hemolysis interacts with vascular-derived nitric oxide (NO) and eventually leads to its depletion. NO depletion also leads to further impaired platelet activity by reducing the activity of guanylate cyclase [14] and endothelial function, adding to defective thromboregulation.

vWF is a plasma glycoprotein that binds to FVIII (via D′/D3 domain) and platelet surface $GP1_b$ receptor (via A1 domain), and thereby also plays a crucial role in the hemostasis. Most of vWF is synthesized by the endothelial cells, which is stored in Weibel-Palade bodies in the endothelial cells as ultra-large vWF. Ultra-large vWF is the most thrombogenic form of vWF [15] as it has the highest binding potential to platelets and collagen. vWF is degraded in blood by the ADAMSTS13 enzyme, thereby maintaining an appropriate level of vWF needed for hemostasis. When the A_2 domain on the vWF partially unfolds, it exposes the buried cleavage site for the ADAMSTS13 enzyme, thus breaking vWF into its inactive form. Shear stress that is produced by ECMO leads to unfolding and elongation of vWF, thereby exposing the A2 domain and becomes more susceptible to cleavage by ADAMSTS13 causing depletion of vWF. This depletion of vWF in patients on ECMO leads to acquired vWF syndrome, with a resultant aggravation of bleeding tendency.

Hemostatic complications in ECMO

The most common complication of ECMO is bleeding, and its incidence varies from 10 to 30%. Incidence for major thrombosis is about 8% [16], and this could be due to differences in the anticoagulation practices in different institutions. Bleeding can occur at the surgical site, cannula insertion site, intrathoracic, intra-abdominal, retroperitoneal, pulmonary, or intracranial (3.6% intra-cerebral hemorrhage in veno-venous ECMO patients [17] and 1.5% in veno-arterial ECMO patients [18]). Thrombotic complications include clots in the circuit [19], oxygenator [20], ischemic stroke, limb ischemia, right ventricular thrombus [21], left ventricular thrombus [22], and pulmonary embolism [23]. Oxygenator thrombosis should be suspected when there is a decrease in the post-oxygenator partial pressure of oxygen (PaO_2), an increasing transmembrane pressure gradient, or a need to steadily increase the sweep gas flow rate to manage. Careful evaluation of anticoagulation parameters should be undertaken and it should be optimized, but if this does not help, then the oxygenator will need replacement.

Goal of anticoagulation in ECMO

Interaction of blood and the biomaterial surface of the ECMO circuits leads to a hypercoagulable state, thereby making the patient and the ECMO circuit prone to thrombosis. Hence, anticoagulation is required to prevent thrombosis of the cannula, oxygenator, and the circuit tubing while balancing the bleeding risks in the patients [24].

Most commonly, unfractionated heparin (UFH) or direct thrombin inhibitors (DTIs)—bivalirudin and argatroban—are used. UFH is the most preferred anticoagulant used at most centers, because of its rapid onset and easy reversal with protamine.

Anticoagulation with UFH

UFH exerts its anticoagulation effects *indirectly* by binding to its cofactor antithrombin (AT) and not to coagulation factors directly. Binding of UFH to AT induces a conformational change in AT, which potentiates the anticoagulant activity of AT. Then, this activated AT inactivates anticoagulants like thrombin (but not fibrin-bound thrombin), factor IXa, X, XIa, and XIIa [25]. Of these, thrombin is most sensitive to inhibition by AT. By inactivating thrombin, it blocks the conversion of fibrinogen to fibrin, and thereby prevents the formation of clots and prolongs the clotting time of blood. UFH onset of action is immediate when administered by the intravenous route. UFH is metabolized by the reticuloendothelial system and by the kidneys [26].

The Extracorporeal Life Support Organization (ELSO) recommends an initial UFH bolus of 50–100 units per kilogram body weight at the time of cannulation for ECMO, and then UFH is continued as a continuous infusion. However, the bolus dose can be adjusted based on other pertinent clinical situations, like pre-existing bleeding disorders or recent surgery. Also, ELSO recommends UFH infusion dose between 7.5 and 20 units/kg/h. The infusion rate of UFH is adjusted based on results of laboratory testing like activated partial thromboplastin time (aPTT), anti-factor Xa (anti-Xa) activity levels, activated clotting time (ACT), or viscoelastic tests. As noted above, ELSO recommends a wide range of UHF infusion rates and does not recommend a particular laboratory test for UFH monitoring, but instead encourages each ECMO

center to develop their protocol that best suits their patient population.

Monitoring tests for UFH

1. ACT: ACT measurement uses whole blood (rather than plasma) and hence provides a global functional test of hemostasis, incorporating the effects of RBC and platelets. Note should be made that the ACT testing is not a specific test for assessing heparin activity [27]. Hypothermia, anemia, hypofibrinogenemia, thrombocytopenia, GP IIb/IIIa antagonists, and hemodilution can alter its results. The ACT is the most commonly utilized test to monitor UFH in ECMO, as ACT testing is most commonly available at point-of-care test at most institutions, which allows for a shorter time between sampling and results [27].
2. aPTT: It is a plasma-based test that assesses the intrinsic and common pathways of coagulation. The normal range for the aPTT varies by laboratory and reagent/instrument combination, and local institutional ranges should be established [28]. In most laboratories, the normal range is approximately 25 to 35 s. The aPTT is most often tested in the laboratory and is measured in plasma, and hence the results are not influenced by the platelet count or hematocrit. This might be the reason that aPTT, when compared to ACT assays, correlates better to heparin concentrations during ECMO support [29]. aPTT is a sensitive test for laboratory monitoring for UFH when plasma UFH concentration is between 0.1 and 1 U/ml, but it may not be helpful when the plasma UFH concentration is >1 U/ml. This is because a higher concentration of UFH prolongs the aPTT beyond the linear monitoring range, but instead ACT could be used for laboratory monitoring when UFH concentration is in the range of 1–5 U/ml.
3. Anti-Xa: This is a functional assay of UFH ability to catalyze AT inhibition of Xa. Since this is a chromogenic assay, the results can be affected by hyperlipidemia, hyperbilirubinemia, and high plasma-free hemoglobin [30]. The American College of Chest Physicians and the College of American Pathologists have agreed that heparin levels based on protamine sulfate titration of 0.2 to 0.4 IU/ml are equivalent to chromogenic heparin anti-factor Xa activity levels of 0.3 to 0.7 IU/ml. Anti-Xa level is a measure of "heparin effect" and does not include other coagulation parameters, which might be clinically significant [31].
4. Viscoelastic tests: Thromboelastography (TEG) and thromboelastometry are performed on whole blood and quantitatively measure the ability of whole blood to form a clot [32]. The test detects and quantifies dynamic changes of the viscoelastic properties of a blood sample during clotting under low shear stress. This provides a comprehensive assessment of blood coagulability, including coagulation cascade, platelet function, and fibrinolysis. One of the advantages of viscoelastic tests is that it can analyze fibrinogen function and can indicate the need for cryoprecipitate or fibrinogen concentrate.

Limitations of UFH

Use of UFH has its limitations; UFH cannot neutralize fibrin-bound thrombin, and monitoring for heparin-induced thrombocytopenia (HIT) is needed. UFH also binds non-specifically to a variety of other plasma proteins (platelet factor 4, fibrinogen, FVIII, histidine-rich glycoprotein [33], vitronectin, fibronectin, and lipoproteins). These non-specific interactions can limit the amount of UFH available to bind to AT [34] thereby creating an unpredictable anticoagulant response which requires frequent dose adjustments and anticoagulant monitoring [35].

Acquired AT deficiency

Acquired AT deficiency can occur during ECMO and can result in an ineffective anticoagulation with UFH, also known as *heparin resistance*. AT is an endogenous anticoagulant (protease inhibitor of thrombin and factor Xa) [36] and is produced in the liver. In patients who are on ECMO, and therefore have prolonged exposure to UFH, AT is consumed at a higher rate than what can be produced by the liver. AT levels are measured by functional assay (which measures AT ability to inhibit thrombin in the presence of UFH) and are expressed as a percentage, and normal values range from 80 to 120% [37]. The functional assay can measure both qualitative and quantitative defects in AT. It is assumed that a low level of AT decreases the anticoagulant effects of UFH. Currently, there are no guidelines established on target, timing, and rate of AT supplementation in ECMO, and hence, there exists a heterogeneity among different ECMO centers about AT supplementation. Generally, AT levels are corrected to keep them within the normal range (80–120%) [38, 39]. AT could be supplemented by transfusing fresh frozen plasma (FFP), purified human-derived AT concentrate, or recombinant form of human AT (rHAT). One IU of AT corresponds to the activity of AT in 1 ml of human plasma, and there is a 1.4% increase above baseline activity level per IU/kg of AT given. Therefore, about two units of FFP are required to achieve a dose of 500 IU, whereas one vial of purified human-derived AT concentrate (10 ml) contains about 500 IU AT [40, 41] and rHAT contains approximately 1750 IU per 10 ml. Hence, purified human-derived AT concentrate and rHAT provide lesser volume but are also safer, when compared to FFP, in

terms of infectious disease transmission. However, the additional cost of AT concentrate should also be considered.

HIT

Platelet factor 4 (PF4), when bound to exogenous UFH, triggers the formation of antibodies (HIT antibodies) to the UFH-PF4 complex, as this complex is immunogenic. When immunoglobulin G (specific to the UFH-PF4 complex) binds to the FC receptor on the platelets while being attached to the UFH-PF4 complex, it leads to platelet activation which then releases prothrombotic substances. Activated platelets also release more prostaglandin 4, which is stored in the alpha granules within the platelets, thus amplifying the process [42]. Thus, a prothrombotic state is created and leads to both arterial and venous thrombi with subsequent thrombocytopenia. In a meta-analysis [43], 83% of patients were suspected of having HIT, but only 17% were confirmed to have HIT. Diagnosis of HIT is based on a high index of suspicion as there are other causes of thrombocytopenia in a patient who is on ECMO—platelet consumption in the oxygenator membrane, sepsis, drug-induced, including HIT. A scoring system is devised, 4T, to access the pre-test probability of HIT. The presence of HIT can be evaluated by immunoassay (UFP-PF4 antibody by ELISA) and functional assay (serotonin release assay, heparin-induced platelet activation). When HIT is suspected or confirmed, UFH is changed to alternative anticoagulants.

Other coagulopathy issues that need to be addressed are thrombocytopenia (shear force caused by ECMO pump), platelet dysfunction (reduced glycoprotein (GP) Ibα and GPVI levels), hyperfibrinolysis, and acquired von Willebrand syndrome. Also, intravascular hemolysis is observed, which results in elevated free hemoglobin, which in turn causes dysregulation of NO.

Direct thrombin (factor IIa) inhibitors (DTIs)

As the name implies, DTIs are a group of anticoagulants that bind directly to active sites on thrombin (free and bound to fibrin unlike UFH which binds to only free thrombin) to exert their anticoagulation effect. They also provide more consistent and predictable anticoagulation as they do not bind to other plasma proteins. Besides, they do not cause HIT. Their primary limitation is that they do not have a pharmacologic antidote.

Currently, three parenteral DTIs are available—bivalirudin, argatroban, and desirudin. The role of desirudin in ECMO is under investigation.

Bivalirudin is a synthetic analog of hirudin, which binds reversibly to thrombin. It is mostly metabolized by proteolytic cleavage and by the liver, and about 20% of bivalirudin is cleared by the kidneys [44]. Therefore, renal dysfunction is an important consideration when using bivalirudin for ECMO as it can prolong its half-life. It is administered via intravenous infusion, and its onset of action is within 2 to 4 min. In patients with normal renal function, its half-life is about 25 min. There are a few case reports and retrospective studies to support its use in ECMO patients (both VV and VA). Also, currently, there is no common consensus about the dosing for bivalirudin for patients on ECMO. In published reports, few authors reported that they started anticoagulation with an initial bolus [45, 46] (ranging from 0.04 to 2.5 mg/kg) followed by a continuous infusion whereas few authors started the anticoagulation without the initial bolus [47–50]. The maintenance infusion dosing ranged from 0.025 to 2.5 mg/kg/h in order to maintain the therapeutic targets. Patients who have renal dysfunction, those who are on continuous renal replacement therapy (CRRT), and those who are on bivalirudin need to be carefully monitored, where the initial bolus dose or the maintenance infusion rates might need to be reduced [46]. The preferred way of monitoring in most reports is aPTT, which is measured first after 2 h and then later at a 4-h interval. Although there have been no prospective reports comparing bivalirudin to UFH, from the few studies, bivalirudin appears to be a safe alternative to UFH [48–50].

Bivalirudin is known to exhibit dose-dependent and predictable anticoagulation. However, in a few cases, resistance to anticoagulation (similar to UFH) with bivalirudin has been reported. There is often a delayed presentation. Initially, adequate anticoagulation is achieved, and an unexplained, gradual increase in bivalirudin dose is required to achieve therapeutic aPTT levels. When therapeutic aPTT is achieved, a note is made of a significant increase in international normalized ratio (INR) [51, 52]. This indicates a "*resistance phenomenon*." Though the etiology of this resistance remains unclear, this may be associated with elevated factor VIII and fibrinogen. A similar resistance phenomenon has also been reported with the use of argatroban [53].

Low flow states create a unique set of circumstances, where blood can stagnate in the cardiac chambers, and bivalirudin is metabolized rapidly due to rapid local cleavage by the proteolytic enzymes, and this predisposes to spontaneous thrombosis [54]. Low flow states can, at times, occur during weaning trials, where circuit flows are decreased [55].

Argatroban is a synthetic analog that binds irreversibly to thrombin to exert its anticoagulant effect. It is metabolized in the liver, and hence its half-life is extended in patients with liver dysfunction [56]. It is also administered intravenously, with the onset of action of 30 min and its half-life is 45 min (in patients with normal liver function). Dose adjustment is not required for patients who have renal dysfunction or require CRRT. Mostly, argatroban has been reported to be used in patients who have developed or suspected to have HIT [57, 58]. In the published literature, most commonly, a lower dose of argatroban infusion is used ranging from 0.1 to 0.3 μg/kg/

min as bleeding has been noted with the use of higher infusion rate at 2 μg/kg/min [59]. Similar to other DTIs, argatroban is also monitored by using aPTT.

Anticoagulation practice

Currently, there are no standardized protocols for anticoagulation for patients requiring ECMO, and there is heterogeneity in anticoagulation practice and monitoring. Based on a recent cross-sectional survey of ECMO centers, UFH is the most preferred anticoagulation, which is titrated based on ACT, aPTT, or anti-Xa test results [60]. There are no established protocols that are universally accepted for monitoring of anticoagulation in ECMO patients. In an absence of well-established protocols and heterogeneity, in practice, ELSO recommends that each ECMO center should formulate an algorithm that works best for them (considering the expertise, costs, clinical outcomes, and availability of anticoagulants and related products).

Anticoagulation in ECMO remains a challenge despite numerous advances in anticoagulation and biomaterial surface to improve hemocompatibility. Each institution should have a multi-disciplinary team that helps address this complex hemostasis to optimize patient care.

Funding None.

Declarations

Informed consent Not required being a review article.

Ethics committee approval Not required being a review article.

Animal and human rights statement None.

Conflict of interest The authors declare no competing interests.

References

1. Besser MW, Klein AA. The coagulopathy of cardiopulmonary bypass. Crit Rev Clin Lab Sci. 2010;47:197–212.
2. Turbill P, Beugeling T, Poot AA. Proteins involved in the Vroman effect during exposure of human blood plasma to glass and polyethylene. Biomaterials. 1996;17:1279–87.
3. Sperling C, Fischer M, Maitz MF, Werner C. Blood coagulation on biomaterials requires the combination of distinct activation processes. Biomaterials. 2009;30:4447–56.
4. Wiegner R, Chakraborty S, Huber-Lang M. Complement-coagulation crosstalk on cellular and artificial surfaces. Immunobiology. 2016;221:1073–9.
5. Xu LC, Bauer JW, Siedlecki CA. Proteins, platelets, and blood coagulation at biomaterial interfaces. Colloids Sur B: Biointerfaces. 2014;124:49–68.
6. Savage B, Ruggeri ZM. Selective recognition of adhesive sites in surface-bound fibrinogen by glycoprotein IIb-IIIa on nonactivated platelets. J Biol Chem. 1991;266:11227–33.
7. Tsai WB, Grunkemeier JM, McFarland CD, Horbett TA. Platelet adhesion to polystyrene-based surfaces preadsorbed with plasmas selectively depleted in fibrinogen, fibronectin, vitronectin, or von Willebrand's factor. J Biomed Mater Res. 2002;60:348–59.
8. Gremmel T, Frelinger AL 3rd, Michelson AD. Platelet physiology. Semin Thromb Hemost. 2016;42:191–204.
9. Stegner D, Nieswandt B. Platelet receptor signaling in thrombus formation. J Mol Med (Berl). 2011;89:109–21.
10. Doyle AJ, Hunt BJ. Current understanding of how extracorporeal membrane oxygenators activate haemostasis and other blood components. Front Med (Lausanne). 2018;5:352.
11. Lou S, MacLaren G, Best D, Delzoppo C, Butt W. Hemolysis in pediatric patients receiving centrifugal-pump extracorporeal membrane oxygenation: prevalence, risk factors, and outcomes. Crit Care Med. 2014;42:1213–20.
12. Williams DC, Turi JL, Hornik CP, et al. Circuit oxygenator contributes to extracorporeal membrane oxygenation-induced hemolysis. ASAIO J. 2015;61:190–5.
13. Lehle K, Philipp A, Zeman F, et al. Technical-induced hemolysis in patients with respiratory failure supported with veno-venous ECMO–prevalence and risk factors. PLoS One. 2015;10:e0143527.
14. Marcus AJ, Broekman MJ. Cell-free hemoglobin as an oxygen carrier removes nitric oxide, resulting in defective thromboregulation. Circulation. 1996;93:208–9.
15. Reininger AJ. Function of von Willebrand factor in haemostasis and thrombosis. Haemophilia. 2008;14:11–26.
16. Sy E, Sklar MC, Lequier L, Fan E, Kanji HD. Anticoagulation practices and the prevalence of major bleeding, thromboembolic events, and mortality in venoarterial extracorporeal membrane oxygenation: a systematic review and meta-analysis. J Crit Care. 2017;39:87–96.
17. Lorusso R, Gelsomino S, Parise O, et al. Neurologic injury in adults supported with veno-venous extracorporeal membrane oxygenation for respiratory failure: findings from the Extracorporeal Life Support Organization database. Crit Care Med. 2017;45:1389–97.
18. Lorusso R, Barili F, Mauro MD, et al. In-hospital neurologic complications in adult patients undergoing venoarterial extracorporeal membrane oxygenation: results from the Extracorporeal Life Support Organization registry. Crit Care Med. 2016;44:e964–72.
19. Lubnow M, Philipp A, Foltan M, et al. Technical complications during veno-venous extracorporeal membrane oxygenation and their relevance predicting a system-exchange–retrospective analysis of 265 cases. PLoS One. 2014;9:e112316.
20. Dalton HJ, Garcia-Filion P, Holubkov R, et al. Association of bleeding and thrombosis with outcome in extracorporeal life support. Pediatr Crit Care Med. 2015;16:167–74.
21. Bhat AG, Golchin A, Pasupula DK, Hernandez-Montfort JA. Right sided intracardiac thrombosis during veno-arterial extracorporeal membrane oxygenation: a case report and literature review. Case Rep Crit Care. 2019;2019:8594681.
22. Weber C, Deppe AC, Sabashnikov A, et al. Left ventricular thrombus formation in patients undergoing femoral veno-arterial extracorporeal membrane oxygenation. Perfusion. 2018;33:283–8.
23. Parzy G, Daviet F, Persico N, Rambaud R, Scemama U, Adda M, Guervilly C, Hraiech S, Chaumoitre K, Roch A, Papazian L, Forel JM. Prevalence and risk factors for thrombotic complications following venovenous extracorporeal membrane oxygenation: a CT scan study: a CT scan study. Crit Care Med. 2020;48:192–9.

24. Marasco SF, Lukas G, McDonald M, McMillan J, Ihle B. Review of ECMO (extra corporeal membrane oxygenation) support in critically ill adult patients. Heart Lung Circ. 2008;17:S41–7.
25. Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126:188S–203S.
26. Hirsh J, Raschke R, Warkentin TE, Dalen JE, Deykin D, Poller L. Heparin: mechanism of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety. Chest. 1995;108:258S–75S.
27. Horton S, Augustin S. Activated clotting time (ACT). Methods Mol Biol. 2013;992:155–67.
28. Baglin T, Barrowcliffe TW, Cohen A, Greaves M. Guidelines on the use and monitoring of heparin. Br J Haematol. 2006;133:19–34.
29. Koster A, Ljajikj E, Faraoni D. Traditional and non-traditional anticoagulation management during extracorporeal membrane oxygenation. Ann Cardiothorac Surg. 2019;8:129–36.
30. Ranucci M, Cotza M, Isgrò G, Carboni G, Ballotta A, Baryshnikova E. Anti-factor Xa–based anticoagulation during extracorporeal membrane oxygenation: potential problems and possible solutions. InSeminars in thrombosis and hemostasis 2020 Jun (Vol. 46, no. 04, pp. 419-427). Thieme Medical Publishers.
31. Colman E, Yin EB, Laine G, et al. Evaluation of a heparin monitoring protocol for extracorporeal membrane oxygenation and review of the literature. J Thorac Dis. 2019;11:3325–35.
32. Shaydakov ME, Blebea J. Thromboelastography (TEG). StatPearls. 2019 Jan 2. https://www.ncbi.nlm.nih.gov/books/NBK537061. Accessed 2 March 2021.
33. Anderson JAM, Saenko EL. Heparin resistance. Br J Anaesth. 2002;88:467–9.
34. Cosmi B, Fredenburgh JC, Rischke J, Hirsh J, Young E, Weitz JI. Effect of nonspecific binding to plasma proteins on the antithrombin activities of unfractionated heparin, low-molecular-weight heparin, and dermatan sulfate. Circulation. 1997;95:118–24.
35. Lee CJ, Ansell JE. Direct thrombin inhibitors. Br J Clin Pharmacol. 2011;72:581–92.
36. Hepner M, Karlaftis V. Antithrombin. Methods Mol Biol. 2013;992:355–64.
37. Finley A, Greenberg C. Heparin sensitivity and resistance: management during cardiopulmonary bypass. Anesth Analg. 2013;116:1210–22.
38. Panigada M, Spinelli E, Cucino A, et al. Antithrombin supplementation during extracorporeal membrane oxygenation: study protocol for a pilot randomized clinical trial. Trials. 2019;20:349.
39. Schwartz RS, Bauer KA, Rosenberg RD, Kavanaugh EJ, Davies DC, Bogdanoff DA. Clinical experience with antithrombin III concentrate in treatment of congenital and acquired deficiency of antithrombin. Am J Med. 1989;87:S53–60.
40. Levy J, Clark E, Lin R, Lowry S. 284: Integrated safety analysis of recombinant human antithrombin administration in patients with heparin resistance requiring cardiac surgery and cardiopulmonary bypass. Crit Care Med. 2012;40:1–328.
41. Spiess BD. Treating heparin resistance with antithrombin or fresh frozen plasma. Ann Thorac Surg. 2008;85:2153–60.
42. Nicolas D, Reed M. Heparin induced thrombocytopenia. InStatPearls.2018. https://pubmed.ncbi.nlm.nih.gov/29493955 . Accessed 2 March 2021.
43. Choi JH, Luc JG, Weber MP, et al. Heparin-induced thrombocytopenia during extracorporeal life support: incidence, management and outcomes. Ann Cardiothorac Surg. 2019;8:19–31.
44. Robson R, White H, Aylward P, Frampton C. Bivalirudin pharmacokinetics and pharmacodynamics: effect of renal function, dose, and gender. Clin Pharmacol Ther. 2002;71:433–9.
45. Pappalardo F, Maj G, Scandroglio A, Sampietro F, Zangrillo A, Koster A. Bioline heparin-coated ECMO with bivalirudin anticoagulation in a patient with acute heparin-induced thrombocytopenia: the immune reaction appeared to continue unabated. Perfusion. 2009;24:135–7.
46. Walker EA, Roberts AJ, Louie EL, Dager WE. Bivalirudin dosing requirements in adult patients on extracorporeal life support with or without continuous renal replacement therapy. ASAIO J. 2019;65:134–8.
47. Jyoti A, Maheshwari A, Daniel E, Motihar A, Bhathiwal RS, Sharma D. Bivalirudin in venovenous extracorporeal membrane oxygenation. J Extra Corpor Technol. 2014;46:94–7.
48. Pieri M, Agracheva N, Bonaveglio E, et al. Bivalirudin versus heparin as an anticoagulant during extracorporeal membrane oxygenation: a case-control study. J Cardiothorac Vasc Anesth. 2013;27:30–4.
49. Berei TJ, Lillyblad MP, Wilson KJ, Garberich RF, Hryniewicz KM. Evaluation of systemic heparin versus bivalirudin in adult patients supported by extracorporeal membrane oxygenation. ASAIO J. 2018;64:623–9.
50. Ranucci M, Ballotta A, Kandil H, et al. Bivalirudin-based versus conventional heparin anticoagulation for postcardiotomy extracorporeal membrane oxygenation. Crit Care. 2011;15:R275.
51. Cardinale M, Ha M, Liu MH, Reardon DP. Direct thrombin inhibitor resistance and possible mechanisms. Hosp Pharm. 2016;51:922–7.
52. Kennedy DM, Alaniz C. Apparent argatroban resistance in a patient with elevated factor VIII levels. Ann Pharmacother. 2013;47:e29.
53. Poyant JO, Gleason AM. Early identification of argatroban resistance and the consideration of factor VIII. J Pharm Pract. 2019;897190019885232.
54. Ranucci M. Bivalirudin and post-cardiotomy ECMO: a word of caution. Crit Care. 2012;16:427.
55. Burstein B, Wieruszewski PM, Zhao YJ, Smischney N. Anticoagulation with direct thrombin inhibitors during extracorporeal membrane oxygenation. World J Crit Care Med. 2019;8:87–98.
56. Swan SK, Hursting MJ. The pharmacokinetics and pharmacodynamics of argatroban: effects of age, gender, and hepatic or renal dysfunction. Pharmacotherapy. 2000;20:318–29.
57. Menk M, Briem P, Weiss B, et al. Efficacy and safety of argatroban in patients with acute respiratory distress syndrome and extracorporeal lung support. Ann Intensive Care. 2017;7:82.
58. Rougé A, Pelen F, Durand M, Schwebel C. Argatroban for an alternative anticoagulant in HIT during ECMO. J Intensive Care. 2017;5:39.
59. Beiderlinden M, Treschan T, Görlinger K, Peters J. Argatroban in extracorporeal membrane oxygenation. Artif Organs. 2007;31:461–5.
60. Esper SA, Welsby IJ, Subramaniam K, et al. Adult extracorporeal membrane oxygenation: an international survey of transfusion and anticoagulation techniques. Vox Sang. 2017;112:443–52.

Editorial Comments:

Anti-coagulation on ECMO is a challenging subject as no ideal anti-coagulant without side-effects is available. However, for the practical management of patients on ECMO, ELSO has recommended to keep Heparin infusion usually between 20 to 40 international units/kg/hour as continuous infusion keeping ACT (Activated Clotting Time) between 180-200 seconds. Most units give Heparin 75 units/kg as stat dose at the time of cannulation and follow it up with continuous infusion once the ACT levels start falling to 300 seconds. ACT was chosen as it is available as a point of care test that can be done bedside. It has been our practice to aim for ACTs 160-180 while on veno venous ECMO and 180- 200 while on VA ECMO. In exceptional situations, the infusion rate of Heparin can fluctuate. Examples include states of Disseminated intra-vascular coagulation, pre-surgery and post-surgery, possible deficiency of Anti thrombin 3, Heparin induced thrombocytopenia etc. Additional investigations like Factor Xa levels, thrombo-elastogram will be needed if the requirement of Heparin is disproportionate to the measured levels of ACT. As the half life of Heparin tends to last for 6 hours, Heparin infusion should be stopped for atleast 6 hours or longer prior to an intended surgical procedure. Heparin infusion can be restarted once there is cessation of active bleeding in post surgical state. As long as the ECMO flows remain high, the risk of clotting can be kept low, even without heparinization for few hours to days. Elevated pre-oxygenator pressures and increasing delta pressure are some of the indications for clot accumulation in the membrane oxygenator. The life of the oxygenator will be decided by keeping all the available evidence, including the fall in post-oxygenator blood gas oxygenation. Usually, Heparin reversal medications are not used while on ECMO. Fresh frozen plasma and Cryo precipitate, platelet transfusions can be used as per the need to stop bleeding. In exceptional circumstances of torrential non-surgical bleeding, Novo seven has been used with the understanding it can result in widespread clotting. The above recommendations are made as best practice guidelines with the understanding that clots/bleeds can't be eliminated completely.

Reference:

1. https://www.elso.org/portals/0/files/elsoanticoagulationguideline8-2014-table-contents.pdf