Anticoagulation and Antithrombin in Veno-venous Extracorporeal Membrane Oxygenation

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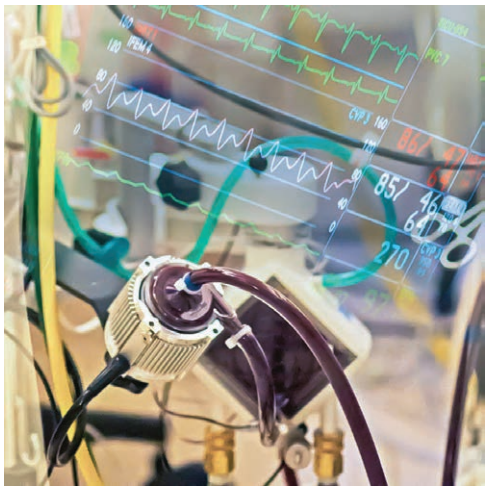
Extracorporeal membrane oxygenation is effective therapy for combined respiratory and cardiac failure (veno-arterial extracorporeal membrane oxygenation) or respiratory failure alone (veno-venous extracorporeal membrane oxygenation) providing days and weeks of support. However, extracorporeal membrane oxygenation is also associated with serious sequelae including mortality (overall survival 55%) and morbidity both highly related to hemostatic abnormalities. Morbidity includes major bleeding (50%), intracranial hemorrhage (6%), and thrombosis (12%),[1–3] with ischemic stroke being the most feared (12%).[1,3] Thrombosis results from activation of *in vivo* physiologic pathways (hemostasis, fibrinolysis, platelets, complement, and inflammation)[4] as a result of blood interaction with the foreign materials within extracorporeal membrane oxygenation circuit components and shear stress caused by the circuit pump. Cellular damage as reflected by elevated plasma-free hemoglobin, circulating microparticles (platelets, endothelial cells), and biomarkers of activation of coagulation, complement, inflammation, and platelets increases the risk of thrombosis. Often, thrombosis in extracorporeal membrane oxygenation components (circuit, oxygenator, and/or pump) necessitates equipment replacement during ongoing therapy to prevent malfunction and thrombus embolization. However, compounding the challenge is increased bleeding risk due to a number of factors including underlying illnesses, decreased levels of von Willebrand factor due to degradation, and unknown optimal anticoagulation strategies, as reflected by variable dosing and laboratory monitoring. Modulation of hemostasis using anticoagulation therapy is necessary to prevent thrombosis, but must do so without increasing bleeding.



"[T]he best management for extracorporeal membrane oxygenation, including the anticoagulation agent and laboratory monitoring tests, remains elusive..."

In the current issue of Anesthesiology, Protti *et al.* determined current practice in veno-venous extracorporeal membrane oxygenation by surveying 50 countries with 273 unique responses (Extracorporeal Life Support Centers).[5] Ninety-seven percent of centers prescribed heparin as the anticoagulant of choice,[5] consistent with previous publications. Although most centers use heparin for extracorporeal membrane oxygenation, bleeding, variable pharmacodynamics,[6] and patient drug resistance[6] are problematic, necessitating monitoring. Inhibition of factor Xa and thrombin is blocked by platelet binding and fibrin and endothelial surfaces, respectively, resulting in heparin resistance. Heparin also binds to proteins (platelet factor 4, vitronectin, and histidine-rich glycoproteins). The concentrations vary between individuals and disease states causing drug neutralization and heparin resistance. Finally, heparin lacks a linear dose and anticoagulant response necessitating monitoring.[6] Recognition that heparin acts by binding to and activating the enzyme inhibitor, antithrombin, is important in understanding heparin's mechanism of action, but also the controversy about antithrombin replacement during extracorporeal membrane oxygenation. Adding to the variability of heparin response, only a fraction of heparin molecules containing a specific pentasaccharide sequence have high affinity for antithrombin. The heparin-antithrombin complex subsequently increases inhibition of activated coagulation factors, especially factor Xa and thrombin by 300-fold.[6]

The major challenge is identifying the "best way" to monitor heparin effect with optimal patient outcomes. Lack of

Image: J. P. Rathmell.

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evidence-based guidance on appropriate monitoring tests is again illustrated by Protti *et al.* by variable laboratory testing between centers.[5] Laboratory monitoring of heparin was divided among centers included partial thromboplastin time (PTT), activated clotting time, and anti–factor Xa activity in 41.8%, 30.0%, and 22.7%, respectively. Notably, each test has limitations, which must be recognized by the clinician. Traditionally, the PTT has been the monitoring test of choice for heparin. Different laboratory test systems (reagents and analyzers), high concentrations of nonspecific acute phase reactants (*e.g.,* factor VIII or fibrinogen), antiphospholipid antibody, acquired antithrombin deficiency, or coagulopathy will result in a PTT that will not prolong as expected in the presence of heparin. Despite recommendations to establish a therapeutic PTT range to correspond to a heparin concentration of 0.2 to 0.4 U/ml (protamine titration) or 0.35 to 0.7 U/ml (chromogenic testing) to standardize for differences in reagents, this approach is not utilized in many centers.[6] PTT is measured on plasma devoid of cells and doesn't reflect *in vivo* hemostasis. Similarly, the activated clotting time—although traditionally used—has variability depending on the reagent used and clot detection technique. Additional limiting factors for the activated clotting time include hypothermia, platelet count, hemodilution, and glycoprotein IIb/IIIa inhibitors (*e.g.,* abciximab, tirofiban, and eptifibatide). Anti-Xa monitoring, which measures heparin concentration and activity in the *ex vivo* test sample, is demonstrated to decrease transfusion requirements thrombosis and bleeding and circuit changes.[7] Complicating the clinician's test choice for patient management is the lack of correlation of PTT, activated clotting time, and anti-Xa concentration.[8] Discussions continue among experts as to the appropriate monitoring tests whether PTT, anti-Xa, or measuring global hemostasis using thromboelastography are more reflective of *in vivo* clinical state.

Although the best management for extracorporeal membrane oxygenation, including the anticoagulation agent and laboratory monitoring tests, remains elusive; clinicians are seeking guidance as to which laboratory parameters optimize patient outcomes. Retrospective clinical studies in extracorporeal membrane oxygenation and non–extracorporeal membrane oxygenation adults and children have demonstrated that use of an anti-Xa monitoring strategy may improve patient outcomes, including survival.[7]

In this study, Protti *et al.*[5] report that 49% of centers measured antithrombin concentration with routine supplementation in 38.1% if the target was not reached (51%), or if antithrombin was lower than 70% (49%). Not surprisingly, due to the cost of antithrombin, multivariate analyses demonstrated antithrombin supplementation was associated with national income and less likely to be prescribed in lower income countries. Supplementation was not dependent on the size of the clinical center. Many extracorporeal membrane oxygenation patients consume antithrombin, which can result in heparin resistance depending on the *in vivo* antithrombin concentration. Furthermore, in neonates, developmental hemostasis results in physiologic antithrombin concentrations, which are about 30% of adult values until 6 weeks of age, and can be much lower in ill infants. Heparin use in extracorporeal membrane oxygenation in ill neonates is complicated as upwards of 40 $U \cdot kg^{-1} \cdot h^{-1}$ of heparin is often required. Evidence-based guidance on use of antithrombin supplementation in children, and adults, on extracorporeal membrane oxygenation is conflicting, with some retrospective pediatric studies demonstrating decreased thrombotic events with supplementation,[7,9] but not in others.[10,11] Thus, the benefit of antithrombin replacement in extracorporeal membrane oxygenation patients has not been established, with costs as much as $3.50 (USD) per unit and some patients being replaced with more than 500 units per administration, which could be on a daily basis or more.

Extracorporeal membrane oxygenation has extended life in patients with cardiopulmonary illness refractory to medical therapy, however there remains few prospective clinical studies guiding management, particularly evaluating anticoagulation. The financial cost of extracorporeal membrane oxygenation is significant and additional untested therapies further increase the cost (antithrombin supplementation). Management currently varies internationally, as demonstrated by Protti *et al.*[5] with patient outcomes continually suboptimal. Limitations of this study include study design (survey where reported data is unvalidated); that only selective Extracorporeal Life Support Organization centers were included; and finally, that the data are dependent upon those centers that elected to report data.

Urgent large prospective international studies are required to provide evidence-based guidelines for management. Before designing these studies, outcome events must have more refined, clinically relevant definitions. Extracorporeal Life Support Organization is uniquely poised to play a major role in this initiative to definitively establish safe and efficacious management for extracorporeal membrane oxygenation patients.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article. Dr. Massicotte is a member of the National Institutes of Health/National Heart, Lung, and Blood Institute (Bethesda, Maryland) expert panel to define patient outcomes.

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References

1. Dalton HJ, Reeder R, Garcia-Filion P, Holubkov R, Berg RA, Zuppa A, Moler FW, Shanley T, Pollack MM, Newth C, Berger J, Wessel D, Carcillo J, Bell

M, Heidemann S, Meert KL, Harrison R, Doctor A, Tamburro RF, Dean JM, Jenkins T, Nicholson C; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network: Factors associated with bleeding and thrombosis in children receiving extracorporeal membrane oxygenation. Am J Respir Crit Care Med 2017; 196:762–71

2. 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
3. Murphy DA, Hockings LE, Andrews RK, Aubron C, Gardiner EE, Pellegrino VA, Davis AK: Extracorporeal membrane oxygenation-hemostatic complications. Transfus Med Rev 2015; 29:90–101
4. Ekdahl KN, Teramura Y, Hamad OA, Asif S, Duehrkop C, Fromell K, Gustafson E, Hong J, Kozarcanin H, Magnusson PU, Huber-Lang M, Garred P, Nilsson B: Dangerous liaisons: Complement, coagulation, and kallikrein/kinin cross-talk act as a linchpin in the events leading to thromboinflammation. Immunol Rev 2016; 274:245–69
5. Protti A, Iapichino GE, Di Nardo M, Panigada M, Gattinoni L: Anticoagulation management and antithrombin supplementation practice during veno-venous extracorporeal membrane oxygenation: A worldwide survey. Anesthesiology 2020; 132:562–70
6. Hirsh J: Heparin. N Engl J Med 1991; 324:1565–74
7. Niebler RA, Parker H, Hoffman GM: Impact of anticoagulation and circuit technology on complications during extracorporeal membrane oxygenation. ASAIO J 2019; 65:270–6
8. Delmas C, Jacquemin A, Vardon-Bounes F, Georges B, Guerrero F, Hernandez N, Marcheix B, Seguin T, Minville V, Conil JM, Silva S: Anticoagulation monitoring under ECMO support: A comparative study between the activated coagulation time and the anti-Xa activity assay. J Intensive Care Med 2018:885066618776937
9. Stansfield BK, Wise L, Ham PB 3rd, Patel P, Parman M, Jin C, Mathur S, Harshfield G, Bhatia J: Outcomes following routine antithrombin III replacement during neonatal extracorporeal membrane oxygenation. J Pediatr Surg 2017; 52:609–13
10. Byrnes JW, Swearingen CJ, Prodhan P, Fiser R, Dyamenahalli U: Antithrombin III supplementation on extracorporeal membrane oxygenation: Impact on heparin dose and circuit life. ASAIO J 2014; 60:57–62
11. Niebler RA, Christensen M, Berens R, Wellner H, Mikhailov T, Tweddell JS: Antithrombin replacement during extracorporeal membrane oxygenation. Artif Organs 2011; 35:1024–8