

Bleeding and Thrombotic Complications in the Use of Extracorporeal Membrane Oxygenation

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Abstract

Extracorporeal membrane oxygenation (ECMO) has been used for >40 years to support lung and heart failure; however, bleeding and thrombosis remain serious complications. The known etiologies of bleeding include heparin effect or overdose, coagulopathy, thrombocytopenia, platelet dysfunction, acquired von Willebrand syndrome, and hyperfibrinolysis. Bleeding sites may include cannula insertion sites, recent surgical incisions, vascular access sites, lung, gastrointestinal tract, mouth, nose, thoracic cavity, abdominal cavity, and brain. Massive bleeding in the brain, the most feared bleeding complication, can be rapidly fatal because it occurs in a rigid closed space, is difficult to drain, and cannot be stopped with direct pressure to the bleeding site. Pulmonary hemorrhage may cause irreversible lung damage. Management should be swift and precise to prevent fatal bleeding. In contrast, etiologies of thrombosis include high fibrinogen and factor VIII levels, heparin resistance, and platelet activation. Achieving the optimal anticoagulation balance to prevent bleeding and thrombosis in ECMO patients is extremely complex. Experts in hemostasis should be a part of an institutional ECMO team and continuously available for immediate management.

Keywords

- ▶ extracorporeal membrane oxygenation
- ▶ ECMO
- ▶ hyperfibrinolysis
- ▶ heparin
- ▶ hemolysis
- ▶ acquired von Willebrand syndrome
- ▶ bivalirudin

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) refers to a group of therapies deployed with increasing frequency in patients with isolated cardiac or respiratory failure or combined cardiorespiratory failure. It is often a therapy of last resort, applied when conventional therapies have failed and a patient is either dying or likely to die. Extracorporeal cardiopulmonary resuscitation, or the initiation of ECMO during active (but unsuccessful) resuscitation, represents a specific application to rescue dying patients in hospitals, and in some locations, in a prehospital setting. In the years since the first

successful ECMO cases, our aggregate experience managing patients and technical improvements in ECMO equipment to make it less immunologically provocative and less destructive to cellular blood elements, has led clinicians to consider ECMO in a wider range of patients, thereby shrinking the types of patients previously excluded from this therapy. This general tendency, coupled to the fact that the majority of ECMO patients are critically ill, with underlying coagulation states that range from normal to markedly abnormal, means that the risk of bleeding and thrombotic complications in ECMO remains elevated and demands expectant and continuous management from experts in coagulation and transfusion medicine.

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The primary physiologic objectives of ECMO are maintenance of cellular tissue oxygenation and CO₂ removal. ECMO can be used in isolated disorders of gas exchange (e.g., acute respiratory distress syndrome, status asthmaticus), isolated disorders of circulation (e.g., dilated cardiomyopathy, septic shock), or mixed disorders with features of both (e.g., viral pneumonia with myocarditis). When the primary pathology is impaired gas exchange—oxygenation, ventilation, or both—most clinicians will place a patient on venovenous (VV) ECMO. In this mode, deoxygenated blood is removed via a large vein, passed through an artificial lung which “breathes” a high FiO₂ and facilitates efficient CO₂ removal, and is returned with a higher O₂ concentration to the same or different vein. If heart function is impaired or tissue metabolic demands exceed the heart and circulatory systems’ abilities to meet the needs of critical end organs, clinicians will employ venoarterial (VA) ECMO, which returns the oxygenated blood to the aorta, thereby taking over not only gas exchange functions but the heart’s blood pumping or distribution role as well. What ECMO mode a patient needs can also change during the course of ECMO. Occasionally, a patient in severe septic shock caused by a bacterial pneumonia may initially require central VA ECMO (cannulated in the right atrium and aortic root via median sternotomy) to achieve adequate O₂ delivery but may then need VV ECMO once the shock resolves to support the patient until her/his lung function returns.

ECMO evolved directly from attempts to maintain circulation and gas exchange in patients while operating on their nonbeating hearts. In 1971, ECMO was first used successfully to save the life of an injured motorcyclist who developed posttraumatic acute respiratory distress syndrome.¹ In 1976, Bartlett et al cannulated and successfully supported a newborn (aptly named Esperanza) dying of persistent pulmonary hypertension on VA ECMO for 3 days.² These tentative first steps were followed by a flurry of ECMO trials that led to different outcomes in different populations. The results with adults were abysmal and led to the abandonment of ECMO in adult disease from the late 1970s to 2010, while smaller, more selective trials in newborns and children led to more encouraging outcomes and cemented pediatrics as the incubator of advances in ECMO for the ensuing 30 years. Only with worldwide H1N1 influenza epidemic and the experiences in a small number of centers with adult ECMO expertise did adult ECMO become resurgent as a viable therapy.

As alluded to earlier, the indications for placing a patient on ECMO are in flux. Previously, most clinicians would cannulate patients only with known diagnoses, certain prognoses, likely favorable outcome for the individual patient, no significant comorbidities, no genetic abnormalities (except trisomy 21), and only brief (<7 days) prior mechanical ventilation. Today, the range of respiratory conditions treated with ECMO is broad. (See ► **Table 1** for a sample of both isolated respiratory diseases as well as multisystem diseases with respiratory involvement.) Isolated cardiac diseases and multisystem illness with cardiovascular involvement that may be treated with ECMO have also grown in the past several years. (See ► **Table 2** for a representative list.) In the

current era of “ECMO 2.0,”³ indications have expanded and contraindications have contracted. Cardiac patients with single ventricle lesions and patients awaiting transplant are now considered viable candidates, and respiratory patients with prior prolonged ventilation, active cancer, or irreversible disease awaiting lung transplant can be supported for prolonged periods on ECMO. There are few absolute contraindications for ECMO. The absence of an immune system (e.g., bone marrow transplant candidate postablation but pre-engraftment), significant internal (especially intracranial) bleeding that precludes anticoagulation, and noncandidacy for destination therapy (e.g., organ transplant, or long-term mechanical circulatory support) represent conditions that would require significant mitigating circumstances for most clinicians to cannulate. ECMO support in the setting of acute liver failure is also relatively contraindicated because of the severe, uncorrectable coagulopathy and the risk of associated bleeding and intracranial hypertension. Some centers have nevertheless attempted to use ECMO together with continuous VV hemodialysis or molecular adsorbent recycling system to bridge patients to liver transplantation, albeit with varying success. The smallest infants to be cannulated weigh between 1,500 and 1,800 g, though ability to cannulate depend on vessel size more than body weight. Although 6 Fr arterial cannulas exist, they clot easily due to high resistance; therefore, 8 Fr cannulas are preferred.⁴

Advances in ECMO equipment design and manufacture have made circuits less likely to activate coagulation and innate immune responses and have also spurred changes in ECMO practice. Newer armored double-lumen VV catheters allow for single vessel cannulation, reduce recirculation of oxygenated blood through the ECMO circuit, and have permitted ECMO patients to undergo extubation and active rehabilitation. Current hollow fiber oxygenators and tubing coated with biocompatible films (composed of combinations of heparin, albumin, and other molecules) are sturdier and more biologically inert, and have replaced the previous generation of uncoated membranes, and tubes and have enabled longer ECMO runs, reduced blood product consumption, decreased surface-triggered inflammation, and made serial circuit changes more routine and less traumatic to the patient. Moreover, current centrifugal pump technology reduces heat and mechanical stress on blood, leading to less intravascular hemolysis.

Certain areas of the current ECMO circuits remain problematic from a coagulation standpoint. Adaptors, connectors, and access points in most circuits are hard plastic and uncoated and reduce the internal diameter of the circuit, presenting a procoagulant, proinflammatory surface with surrounding turbulent flow and areas of stasis. These sites almost always develop thrombi. Finally, the hemofilter and smaller bore tubing used for blood flow to and from it, lack a biocompatible coating, and are a source of clot formation within the ECMO circuit. The filter membrane is a large, porous surface area which causes turbulent flow and contact activation of coagulation cascade and requires routine changes to prevent clot accumulation.

Table 1 ECMO for respiratory disease

Isolated respiratory disease	Multisystem disease with respiratory involvement
Pneumonia (all etiologies)	Congenital diaphragmatic hernia
ARDS/ALI (multiple causes)	Meconium aspiration syndrome with PPHN
Status asthmaticus	Neonatal sepsis with PPHN
Sickle cell acute chest syndrome	Pulmonary embolism
Air leak syndromes	Primary pulmonary hypertension
Interstitial lung disease	Severe sepsis with respiratory failure
Foreign body obstruction	Posttraumatic ARDS
Mediastinal mass	Lymphoma with pulmonary infiltration
Pulmonary hemorrhage	Soft tissue tumor with pulmonary metastases

Abbreviations: ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; PPHN, persistent pulmonary hypertension of the newborn.

Taken together, these advances—increased experience, broader indications, fewer contraindications, and improved technology—imply that today's and tomorrow's ECMO patients may have an underlying coagulation state that ranges from normal to grossly altered, increasing the difficulty in optimizing anticoagulation while avoiding the dual complications of bleeding and thrombosis. A 1-year-old patient cannulated for respiratory syncytial virus pneumonia

Table 2 ECMO treatment of cardiac diseases

Isolated cardiac diseases	Multisystem diseases with cardiac involvement
Myocarditis/dilated cardiomyopathy	Septic shock with biventricular heart failure
Malignant dysrhythmias	PPHN with right heart failure (CDH, sepsis, MAS)
Postbypass myocardial failure	Bacterial endocarditis
Transplant rejection	Pericardial disease, including tamponade
E-CPR	E-CPR
Left- or right-sided obstructive disease	Pulmonary embolism with right heart failure
Systemic to pulmonary shunt obstruction	Primary pulmonary hypertension
Valvular disease	

Abbreviations: CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation; E-CPR, extracorporeal cardiopulmonary resuscitation; MAS, meconium aspiration syndrome; PPHN, persistent pulmonary hypertension of the newborn.

and respiratory failure may have a normal prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, antithrombin activity, and platelet count and respond normally to the usual doses of heparin. By the same token, a 17-month-old patient with pneumococcal septic shock, purpura fulminans with a platelet count of 40,000/mm³, fibrinogen of 100 mg/dL, PT >40 seconds, and severe hemolysis and bleeding may need to undergo aggressive correction of underlying factor deficiencies, therapeutic plasma exchange (TPE) to reverse a microangiopathic process, and ginger initiation of anticoagulation until deficiencies are corrected and the risk of bleeding is reduced. Until the risk of bleeding and thrombosis is eliminated in ECMO patients (an unlikely prospect), the best centers will continue to rely on the expertise of clinicians who can monitor and adjust anticoagulation and identify and treat disorders and imbalances as these appear in patients on long ECMO runs.

Priming an Extracorporeal Membrane Oxygenation Circuit

Under optimal conditions, preparing an ECMO circuit for patient use requires three distinct steps: (1) building the circuit, (2) priming the circuit with a crystalloid solution, and (3) priming the circuit with blood. Building the circuit can be as easy as pulling a specified, preconfigured circuit (with tubing, pump head, oxygenator, sensor ports, sampling/infusion sites) from a box and installing it on the pump, oxygenator rack, and cart, or it can be assembled from scratch with the component elements. In ECMO centers with high patient volumes, once the circuits are built, they are crystalloid primed with the expectation that they will be used within 30 to 60 days, the recommended duration of the crystalloid prime.⁵ This crystalloid prepriming actually speeds the blood priming process once a decision has been made to cannulate. Crystalloid primes vary in composition but are usually isotonic solutions (0.9% normal saline or lactated Ringers). Some centers add 25% albumin to this prime, but others do not (the practice is a holdover from a time when circuits lacked biocompatible coatings). Centers with lower ECMO patient volumes will usually crystalloid prime their circuits immediately prior to blood priming. This approach lengthens the priming process just prior to cannulation but avoids having to discard a circuit if no cannulation occurs 30 to 60 days after crystalloid priming the new circuit.

In an emergency, such as during active cardiopulmonary resuscitation, a patient (particularly one >30 kg) can be cannulated for VA ECMO with a crystalloid-primed circuit. Doing so creates complications to be handled during and after cannulation (dilutional anemia, dilutional coagulopathy, dilutional thrombocytopenia, and hypocalcemic cardiac arrest), but may be the fastest way to restore circulation.⁶

Usually, however, there is sufficient time to blood prime a circuit, and in the case of VV ECMO, "balance" it. The composition of the blood prime varies from center to center, but the goals of blood priming are threefold: (1) dilute red blood cells (RBCs) from the blood bank to a more physiologic hematocrit; (2) prevent/minimize a dilutional coagulopathy;

and (3) ensure approximately physiologic pH and critical electrolyte concentrations (particularly ionized calcium and potassium). In our center, we mix two units of RBCs, one unit of fresh frozen plasma (some centers use albumin or no colloid) and include calcium (either gluconate or chloride) and sodium bicarbonate (to adjust the pH and/or decrease the potassium concentration if the RBCs are old) in a single bag. This blood mixture is introduced into the circuit and the crystalloid prime is expelled. If there is adequate time or if the patient is destined for VV ECMO (because the patient's endogenous heart function is required for circulation), the blood is warmed and point-of-care testing of pH, ionized calcium, and potassium concentrations is undertaken to prevent the cardiac effects of sudden introduction of cold blood, hypocalcemia, or hyperkalemia. If there is even more time before placing the patient on the ECMO circuit, the hematocrit may be increased by ultrafiltration of the blood prime.

Bleeding and Thrombosis

During ECMO, bleeding and thrombosis are common problems. Thrombosis *in vivo* is not commonly seen clinically, but clot formation in the circuit is common despite seemingly adequate anticoagulation. For small infants such as newborns, catheter-induced venous or arterial thrombosis is occasionally seen. Obviously, if the patient has other thrombotic risks such as factor V Leiden, congenital antithrombin, protein C or protein S deficiency, or antiphospholipid antibodies, the risk of thrombosis may be higher, but there are no systematic studies documenting an increased risk in the ECMO setting. Clot formation in the cannula or circuit, including pump and oxygenator, may first be detected by increasing D-dimer and increased plasma-free hemoglobin concentrations. If there are clots in arterial cannula, there is a risk of thromboembolism. Microthromboembolism in skin capillaries may cause visible cutaneous lesions but otherwise is clinically silent.

Bleeding, on the contrary, is always "in vivo." Bleeding may occur at the cannula or catheter insertion sites, recent surgical incisions, nose, mouth, urinary tract, abdominal or

thoracic cavities, lungs and airways, gastrointestinal (GI) tract, and calvarium. The etiology of bleeding is multifactorial. High blood pressure⁷ or low CO₂⁸ is associated with intracranial bleeding. Gastritis or peptic ulcer may cause GI bleeding. Hematological etiologies include, but are not limited to, over anticoagulation, deficiency of coagulation factors including factor XIII, thrombocytopenia, acquired von Willebrand syndrome (AVWS), platelet function defects, hyperfibrinolysis, and heparin-like substances. Intravascular hemolysis may contribute to both bleeding and clot formation.

Monitoring Hemostasis and Anticoagulation during ECMO

Unfractionated heparin (hereafter noted as heparin) is the most commonly used anticoagulant drug. When heparin-induced thrombocytopenia (HIT) or some form of heparin resistance is developed, a direct thrombin inhibitor such as bivalirudin or argatroban may be used. When heparin is used as an anticoagulant, then hemostatic balance and anticoagulation are usually monitored by activated clotting time (ACT), aPTT, PT, fibrinogen, anti-FXa assay, and platelet count. Combination of monitoring methods and the desired target ranges may vary among hospitals. Although ACT has been used for decades, its utility in monitoring coagulation and heparin effect for ECMO has been criticized. The correlation of ACT with aPTT or anti-FXa, all employed as measurements of the anticoagulation effects of heparin, is poor.⁹ Therefore, heparin effect cannot be accurately monitored by ACT alone.^{10,11} ▶ **Table 3** shows a monitoring panel which is used at the Texas Children's Hospital. The debate is still ongoing as to which test is best to monitor heparin therapy. Anti-FXa values best represent the overall heparin anticoagulant activity and have some similarity with anti-FIIa inhibition. High bilirubin and plasma-free hemoglobin concentrations interfere with the anti-FXa assay, but the underlying coagulable state does not affect anti-FXa results.¹² There are different anti-FXa assay kits with and without addition of exogenous antithrombin to the assay system. To

Table 3 Monitoring hemostasis parameters at the Texas Children's Hospital⁵⁵

Test	Desired target/range	Purpose
PT	<16.0–17.0 s	To assess underlying coagulable state
aPTT with Dade Hepzyme	<38.0 s	
Fibrinogen	>200 mg/dL	
aPTT	70–90 s	To monitor heparin effect
D-dimer	Not established	To monitor fibrin formation and fibrinolysis in the circuit and patient's circulation
Platelet count	>100,000/mm ³⁵⁵	To monitor clot firmness
Anti-FXa	0.2–0.5 units/mL	To monitor heparin activity
Antithrombin	>80–100%	To maximize heparin therapy

Abbreviations: aPTT, activated partial thromboplastin time; PT, prothrombin time. Source: Reproduced with permission from Teruya and Burgman.⁴⁷

monitor *in vivo* heparin anticoagulant activity, the amount of heparin–antithrombin complex needs to be measured since heparin alone does not show any anticoagulant effect. For these reasons, anti-FXa assay kits without exogenous antithrombin are more clinically relevant.¹³ While there is no consensus regarding the superiority of the anti-FXa level or the aPTT for monitoring unfractionated heparin therapy from the clinical standpoint, it is known that aPTT is affected by other factors such as high factor VIII, high C-reactive protein,¹⁴ and lupus anticoagulant. Although not documented specifically in the ECMO setting, aPTT and anti-FXa values are frequently discordant and a disproportionate prolongation of aPTT is the more common discordant pattern.¹⁵

Viscoelastometry (ROTEM or TEG) may be used during ECMO; however, it has not replaced conventional coagulation assays using plasma. The utility of viscoelastometry is to monitor overall primary and secondary (or platelet and coagulation) hemostasis and fibrinolysis. However, the clotting time is prolonged in the presence of “strong” lupus anticoagulant¹⁶ and sensitivity to hyperfibrinolysis is low. In addition, low von Willebrand factor (VWF) levels, a cause of potential bleeding, cannot be detected due to the absence of shear force in the assay system¹⁷ unless factor VIII level is decreased.

Heparin

The main target of heparin anticoagulant action is the inhibition of factor Xa and factor IIa. The heparin molecule forms a complex with antithrombin and binds abovementioned factors, thereby inactivating them (anti-factor Xa and anti-factor IIa effects) or it binds heparin cofactor II and the complex binds and inactivates activated factor IIa (anti-FIIa effect only). Heparin also indirectly promotes anticoagulation by triggering release of tissue factor pathway inhibitor (TFPI), free and total, from the endothelial cells, increasing levels by two- to fourfold. Heparin overdose is the one of commonest causes of bleeding during ECMO.¹⁸ TFPI is released from endothelium with a half-life in circulation of 60 to 120 minutes. The main sites of TFPI clearance *in vivo* are the liver and kidney. The factor VII–tissue factor complex activates factor X to factor Xa. TFPI binds activated factor Xa and inactivates it. Furthermore, the TFPI inhibits the process of factor X activation by factor VIIa–tissue factor complex, meaning that any additional factor Xa is generated via factor IXa not the factor VIIa–tissue factor complex.

Congenital severe TFPI deficit has not been reported; however, low levels of circulating TFPI or decreased heparin-releasable TFPI was reported to be associated with venous and arterial thromboses.^{19,20} In opposite, increased levels of circulating TFPI due to mutations in factor V can cause persistent bleeding.^{21,22} Pediatric patients showed more sustained increase of TFPI after heparin infusion, which may increase the risk of bleeding due to over anticoagulation.²³ Continuous release and accumulation of TFPI in the bloodstream may be another etiology of bleeding during heparin therapy.

There is a wide variation of heparin response among patients. Usually, heparin infusion is started at 20 to 25 units/kg/h to reach the target of anti-FXa level within 0.2 to 0.5 units/mL; however, sometimes the infusion rate should be increased up to 50 to 60 units/kg/h to achieve this goal. Since heparin as negatively charged macromolecule is avidly binding to many proteins in the circulating blood other than antithrombin and heparin cofactor II, its bioavailability depends on individual patients and comorbid conditions.

Alternative Anticoagulant—Bivalirudin

Since bivalirudin is indicated for use as an anticoagulant in unstable angina undergoing percutaneous transluminal coronary angioplasty, its use for ECMO heparin resistance or HIT is off-label but occurs. Heparin resistance is defined as clot formation despite adequate heparin infusion or inability to reach target anticoagulation with heparin dose >70 units/kg/h.²⁴ In HIT, which is diagnosed by clinical and laboratory testing (e.g., heparin platelet factor 4 antibody assay and serotonin release assay), heparin needs to be discontinued to allow the platelet count to recover. Bivalirudin is often used as an alternative to heparin in patients with HIT or heparin resistance who need acute anticoagulation.²⁵ Bivalirudin has much better bioavailability than heparin, since it specifically binds to circulating and clot-bound thrombin without forming a complex with antithrombin or heparin cofactor II. While it typically exhibits predictable and dose-dependent anticoagulant effect, bivalirudin resistance may exist without clear etiology.²⁶

Recommendations for bivalirudin dosing on ECMO vary somewhat. Nagle et al²⁷ reported a median bivalirudin loading dose of 0.1 mg/kg and maintenance dose ranges from 0.045 to 0.48 mg/kg/h among 13 pediatric patients on ECMO. In contrast, Pieri et al²⁸ used a lower dose for 20 adult patients on ECMO; 0.028 to 0.05 mg/kg/h with hemofiltration and 0 to 0.041 mg/kg/h without hemofiltration for a target aPTT of 45 to 60 seconds. Since bivalirudin is metabolized in the kidney as well as proteolytically cleaved, the dose should be reduced during renal dysfunction.²⁹ While bivalirudin has been used in neonates, pharmacokinetic data in newborns are scarce: only 4 newborns were included in pilot study among 16 infants <6 months old.³⁰

The major drawback to bivalirudin use as an anticoagulant is the lack of antidote in the case of overdose or bleeding. Although the half-life is relatively short at 25 minutes compared with unfractionated heparin, once major bleeding occurs, there is no effective treatment to manage bleeding. Although recombinant factor VIIa may be helpful as had been shown *in vitro*³¹ and *in vivo*,³² the risk–benefit analysis must include the possible loss of the ECMO circuit due to thrombosis. Another inconvenience to anticoagulation with bivalirudin stems from the inability to monitor a patient's underlying coagulable state, since bivalirudin cannot be removed or inactivated from *in vitro* specimens. When heparin is used for anticoagulation, PT and aPTT with Dade Hepzyme (Siemens, Newark, DE) treatment can disclose the underlying coagulable state since most PT reagents contain a

heparin neutralizer and aPTT with Hepzyme removes heparin from the specimen. A final downside to bivalirudin use is its invalidation of those test results using PT- or aPTT-based assays, such as one-stage clotting-based coagulation factor, protein C (if not chromogenic), protein S (if based on aPTT), or lupus anticoagulant assays.³³

The aPTT is most often used to monitor the anticoagulant effect of bivalirudin. There are reports of using plasma-diluted thrombin time as a better monitoring method.^{34,35} While the target aPTT for bivalirudin anticoagulation is usually either 60 to 80 or 70 to 90 seconds, there are no standardized aPTT reagents, somewhat unlike the case for PT and standardization via the international normalized ratio.

Costs related to anticoagulation also differ depending on the agent employed. Bivalirudin is more expensive than heparin, but bivalirudin use eliminates the need to monitor anti-FXa and antithrombin activity. Moreover, clinicians at many institutions administer either antithrombin concentrate or recombinant antithrombin to maintain a minimum antithrombin activity, leading to additional costs for heparin anticoagulation. ►Table 4 shows a comparison between heparin and bivalirudin.

Coagulopathy

Once ECMO is initiated, dilutional coagulopathy and dilutional thrombocytopenia immediately develop if the ECMO circuit is primed with only crystalloid solutions or RBCs. If ECMO circuit is primed with RBCs and plasma, dilutional coagulopathy is not severe; however, dilutional thrombocytopenia occurs. Therefore, transfusion of platelets and plasma, if not primed with plasma, is required to correct dilutional thrombocytopenia and coagulopathy. Some evidence suggests even if the heparin anti-FXa activity is within the target range, there is still significant activation of coagulation, detected by elevated markers such as thrombin-antithrombin complex and prothrombin fragment 1.2 during ECMO.³⁶ This shows an additional limitation of anticoagulation by heparin.

Due to the continuous thrombin formation and fibrinogen consumption, fibrinogen levels may decrease. Low fibrinogen levels should be corrected by cryoprecipitate transfusion or fibrinogen concentrate infusion. Fibrinogen concentrations should be maintained >150 mg/dL.³⁷ If there is bleeding or a concern for bleeding, a higher fibrinogen target such as 200 or 250 mg/dL may be used. As it is an acute phase reactant, however, fibrinogen levels may be elevated in the setting of severe pneumonia or sepsis, potentially increasing the risk of thrombosis.

There are also reports of decreases in factor XIII levels during ECMO.³⁸ Factor XIII levels <30% could potentiate bleeding risk for patients not treated with anticoagulants. However, the appropriate factor XIII level to maintain adequate hemostasis in ECMO patients anticoagulated with heparin is not established. Once factor XIII level is <70% in patients on ECMO, administration of factor XIII has been suggested and is effective in minimizing bleeding. Therefore, factor XIII (purified from plasma or recombinant) may be administered if bleeding persists when the factor XIII level is decreased.

Thrombocytopenia/Platelet Dysfunction

Thrombocytopenia commonly occurs during ECMO. A constant shear force caused by the ECMO pump is also implicated in acquired platelet dysfunction. Moreover, accurate assessment of platelet function cannot be performed in the presence of thrombocytopenia, further complicating evaluation of a patient's bleeding or thrombotic potential. The platelet impairment can occur in already 15 minutes after starting ECMO and last throughout ECMO until it is discontinued.³⁹ The mechanism of platelet dysfunction may be related to reduced glycoprotein (GP)Ib α and GPVI levels.⁴⁰ Of note, GPIb α is a receptor for VWF and GPVI is a receptor for collagen. Minimal target platelet count varies from 50,000/mm³ to 100,000/mm³ across hospitals. However, if the patient is prone to bleeding, the target platelet count could be increased to 150,000/mm³ or above once platelet dysfunction is suspected.

Table 4 Comparison between heparin and bivalirudin

	Heparin	Bivalirudin
Half life	90 min	25 min
Clearance	Reticuloendothelial system, kidney	Kidney, liver
Mode of action	Anti-FXa and anti-FIIa by making a complex with antithrombin Anti-FIIa by making a complex with heparin cofactor II Anti-FXa releasing tissue factor pathway inhibitor	Anti-FIIa
Thrombin inhibition	Only circulating thrombin	Circulating thrombin and clot bound thrombin ⁵⁶
Antidote	Protamine	None
Monitoring method	aPTT, anti-FXa	aPTT, dilute thrombin time

Abbreviations: aPTT, activated partial thromboplastin time; FIIa, factor IIa; FXa, factor Xa.

Hyperfibrinolysis

During ECMO, the activation of fibrinolytic system is mainly due to the release of tissue plasminogen activator (tPA) from endothelial cells. Elevated tPA and plasmin–antiplasmin complex levels have been associated with decreased plasminogen activator inhibitor 1 level during neonatal ECMO.⁴¹ While infusion of antifibrinolytic agents did not change the incidence of intracranial bleeding in neonates, it reduced the rate of surgical bleeding.⁴² Infusion of antifibrinolytic drugs such as aminocaproic acid or tranexamic acid can be used in the setting of acute bleeding to stabilize primary thrombi without evidence of hyperfibrinolysis, especially if decannulation or discontinuation of heparin is not a therapeutic option.

Acquired von Willebrand Syndrome

AVWS is observed virtually in every patient on ventricular assist device (VAD). It is also seen in most patients on ECMO.^{40,43} Though common, it is underrecognized as an entity complicating ECMO.⁴⁴

There are various etiologies of AVWS. High shear forces associated with ECMO cause the loss of large VWF multimers. Development of AVWS can occur within 24 hours after ECMO initiation.⁴⁵ Laboratory findings include decreased VWF activity–to–VWF antigen ratio and large multimers loss while VWF activity and antigen are normal or increased.^{43,46} The diagnosis of AVWS in the setting of ECMO is based on decreased VWF activity–to–VWF antigen ratio and decreased large multimer bands of VWF multimer study (► **Fig. 1**). The VWF activity–to–VWF antigen ratio correlates with the percentage of high molecular multimer bands.⁴⁷ Ristocetin cofactor activity may be normal or slightly decreased in patients on ECMO.⁴⁸

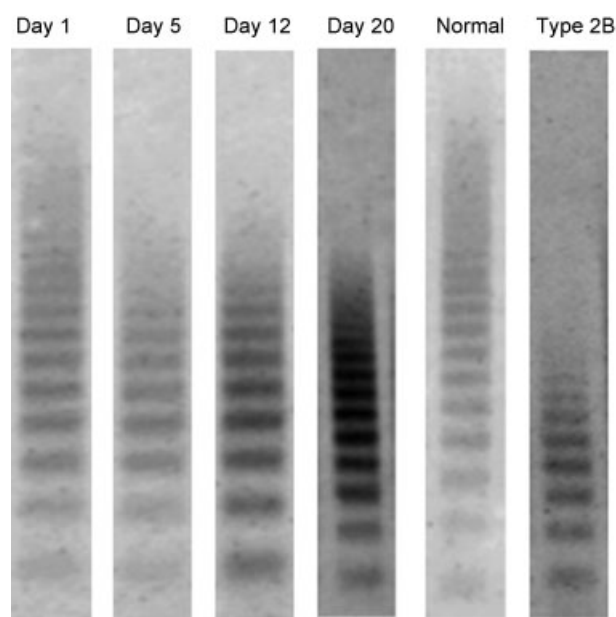


Fig. 1 Multimer pattern of von Willebrand factor during ECMO. ECMO, extracorporeal membrane oxygenation. (Reproduced with permission from Teruya and Burgman.⁴⁷)

AVWS may be managed with cryoprecipitate transfusion or VWF concentrate infusion, for example, Humate-P as used in our facility. While concentrations of large VWF multimers in cryoprecipitate are normal, some VWF concentrates have a borderline level of large VWF multimers, due to partial loss during the processing and purification. Nevertheless, because of the continuous persistence of high shear force, as a cause of AVWS, in patients on ECMO or VAD, efficacy of cryoprecipitate or VWF concentrate is temporary. Therefore, some clinicians give small doses repeatedly rather than large infusions less frequently. Of note, cryoprecipitate also contains other acute phase coagulation factors such as fibrinogen and factor VIII. If the levels of these factors are already elevated in patient's plasma, additional transfusion of them with cryoprecipitate may increase the risk of thrombosis. Likewise, VWF concentrates contain substantial amounts of factor VIII, which may increase the risk of thrombosis if factor VIII is already increased. Recently, recombinant VWF (Vonvendi) has become available in the United States. Since it does not contain factor VIII, it may be a preferable treatment for AVWS when the factor VIII level is increased to avoid thrombosis. VWF in patients on mechanical circulatory support is a double-edged sword: absence of large multimers leads to bleeding, but replacement therapy or excess endogenous VWF promotes thrombosis.⁴⁹ The optimal dose and frequency of VWF replacement in patients on ECMO have not been established.

Hemolysis

Another cause of deranged hemostasis is ongoing intravascular hemolysis that may lead to damage of renal function. Elevated free hemoglobin in plasma (≥ 50 mg/dL) enhances in vitro VWF-mediated platelet adhesion. It also augments microthrombi formation on fibrinogen, fibrin, extracellular matrix, and collagen at high shear stress.⁵⁰ It also induces dysregulation of nitric oxide which suppresses platelet function.⁵¹ In addition, free hemoglobin in plasma competes for the VWF A2 domain with ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13),⁵² which in turn can worsen the tendency to form thrombus. Once clots start to grow in the ECMO circuit, they continue to consume coagulation factors and platelets, causing consumptive coagulopathy and increasing the risk of bleeding. Intravascular hemolysis may be an early sign of thrombus formation in the circuit or cannula position. For these reasons, free hemoglobin level in plasma should be routinely monitored every day during ECMO. Pump flow adjustment to reduce shear stress on RBCs may help if flow rate is supranormal, but low pump flow can also lead to localized stasis and precipitate more clot formation. Thrombus formation in the circuit is not the only cause of hemolysis. RBC breakdown can also be induced by high shear force within the circuit itself; therefore, changing the oxygenator or the whole circuit could be attempted first. If free hemoglobin concentration exceeds 150 mg/dL, TPE with fresh frozen plasma as replacement fluid should be performed to lower temporarily hemoglobin concentrations to prevent thrombosis formation and preserve renal function while

searching for the origin of hemolysis. If free hemoglobin concentration in plasma is too high, monitoring anticoagulation becomes difficult because high concentrations interfere with the colorimetric anti-FXa assay. Elevated plasma-free hemoglobin is associated with higher mortality.^{53,54}

Summary and Conclusion

Dealing with bleeding and thrombosis is a current problem for patients on ECMO. The etiology of bleeding and thrombosis is multifactorial, including, but is not limited to,

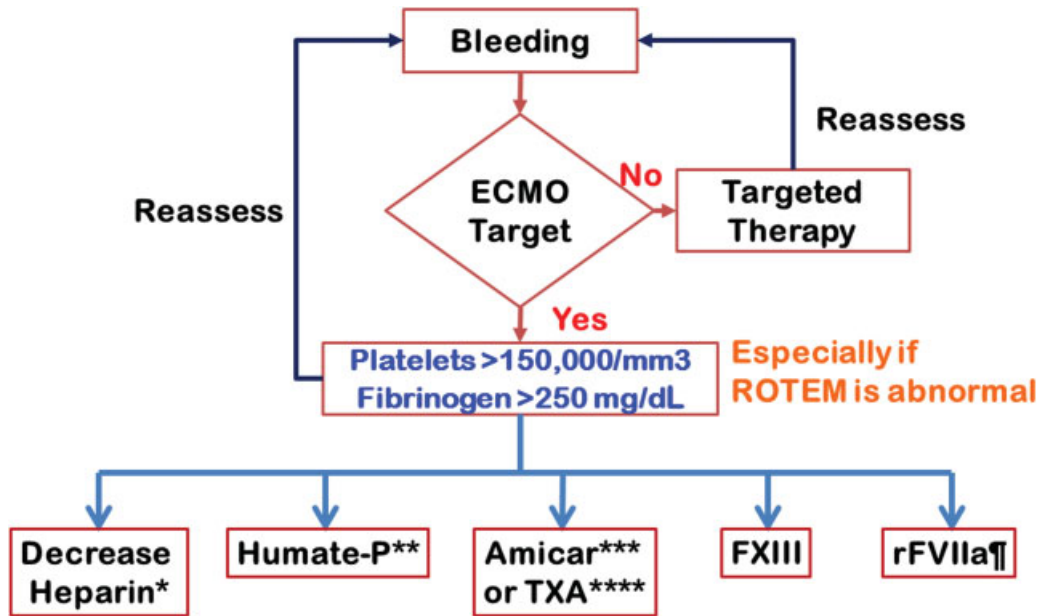


Fig. 2 Algorithm-based management based on using Humate-P as the VWF concentrate. Note that the use of different VWF concentrates may require use of different amounts. *Anti-FXa 0.1 to 0.2 units/mL or hold heparin up to 12 hours; **20 to 30 units/kg; ***10 to 30 mg/kg/h until bleeding improved; ****10 mg/kg bolus, 1 mg/kg/h; and †Usage of rFVIIa increases significantly the risk of thrombosis and clotting the circuit. ECMO, extracorporeal membrane oxygenation; FXa, factor Xa; FXIII, factor XIII; rFVIIa, recombinant factor VIIa; VWF, von Willebrand factor. (Reproduced with permission from Teruya and Burgman.⁴⁷)

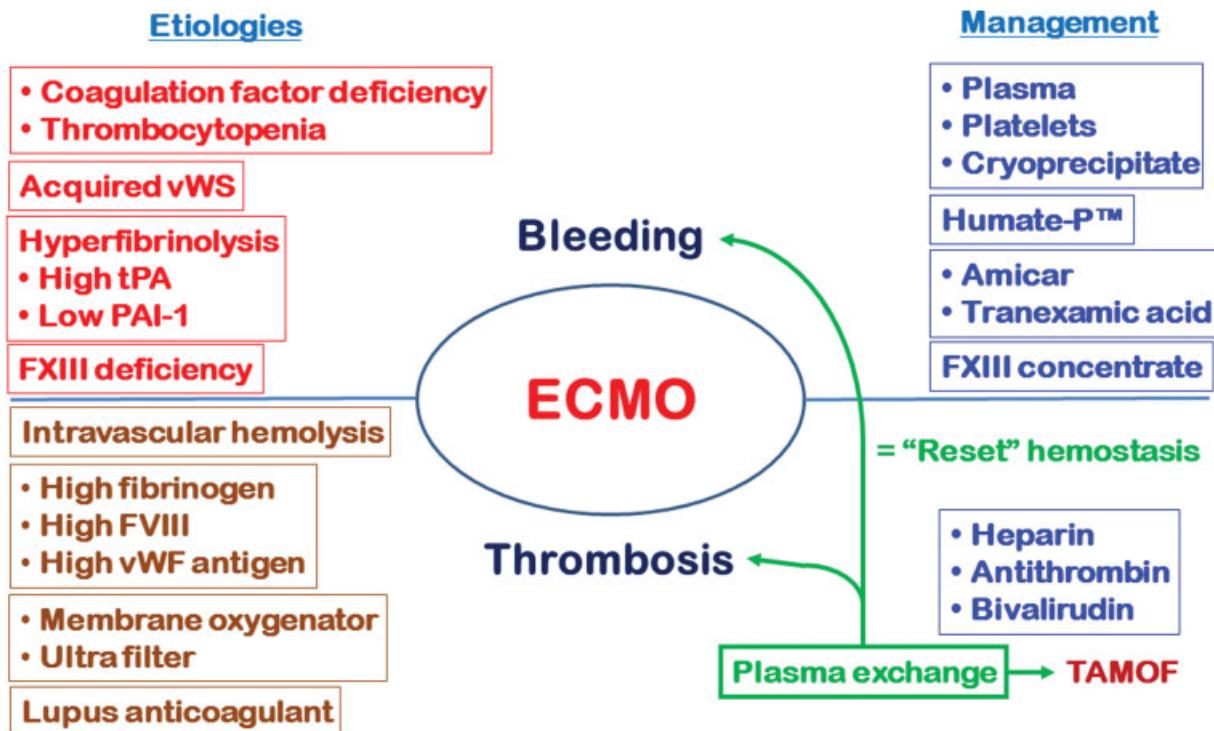


Fig. 3 Bleeding and thrombosis during ECMO: etiology and management. ECMO, extracorporeal membrane oxygenation; FVIII, factor VIII; FXIII, factor XIII; PAI-1, plasminogen activator inhibitor 1; TAMOF, thrombocytopenia-associated multiorgan failure; tPA, tissue plasminogen activator; VWF, von Willebrand factor; vWS, von Willebrand syndrome. (Reproduced with permission from Teruya and Burgman.⁴⁷)

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consumptive coagulation factor deficiency, excessive activation of fibrinolysis, thrombocytopenia, platelet dysfunction, and AVWS. Intravascular hemolysis also plays a significant role for hemostatic derangement. Regular monitoring and targeted management with the help of clinicians who are expert in coagulation and its complications are required to prevent major often fatal bleeding in the brain or lung and clot formation in the circuit. ► **Figs. 2 and 3** summarize the etiology of these complications and their management, as practiced at our institution.

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