Extracorporeal Membrane Oxygenation—Hemostatic Complications

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Abstract

The use of extracorporeal membrane oxygenation (ECMO) support for cardiac and respiratory failure has increased in recent years. Improvements in ECMO oxygenator and pump technologies have aided this increase in utilization. Additionally, reports of successful outcomes in supporting patients with respiratory failure during the 2009 H1N1 pandemic and reports of ECMO during cardiopulmonary resuscitation have led to increased uptake of ECMO. Patients requiring ECMO are a heterogenous group of critically ill patients with cardiac and respiratory failure. Bleeding and thrombotic complications remain a leading cause of morbidity and mortality in patients on ECMO. In this review, we describe the mechanisms and management of hemostatic, thrombotic and hemolytic complications during ECMO support.

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0887-7963/© 2014 Elsevier Inc. All rights reserved.
The first case report of successful extracorporeal membrane oxygenation (ECMO) for respiratory failure was published by Hill and colleagues [1] in 1972. Since that time, there has been considerable interest in its role as supportive therapy for patients with life-threatening cardiac and/or respiratory failure. The role of ECMO in the neonatal population has been clearly established [2–4], and a growing acceptance of ECMO in the adult population has occurred despite a lack of convincing randomized controlled trial evidence to support its use [5–8]. This expanding role has occurred in the context of advances in membrane oxygenator and pump technology, the 2009 H1N1 influenza pandemic and interest in the use of temporary mechanical circulatory support, particularly in patients in refractory cardiac arrest [7–15]. Hemostatic complications, both bleeding and thrombosis, remain the leading causes of morbidity and mortality in patients treated with ECMO [11,16–19]. Hematologists and transfusion specialists are increasingly being asked to help navigate the complexities of thrombotic and hemorrhagic risks that occur when blood is exposed to the extracorporeal circuit. Here, we review the current literature around the utility of ECMO with special focus on hemostatic complications commonly found in patients receiving ECMO support and include some suggested strategies to manage such hemostatic complications.

**Mode of ECMO Support**

The mode of ECMO is defined by the location of the access and return cannulae. ECMO involves accessing deoxygenated venous blood from the systemic circulation, pressurizing it using a pump, passing it through a membrane oxygenator and then returning it to either the venous side of the circulation (the right atrium) in venovenous ECMO (VV ECMO or respiratory ECMO), or to the arterial circulation (typically the aorta) in venoarterial ECMO (VA ECMO or cardiac ECMO). Pumpless arteriovenous configurations exist but tend to provide more carbon dioxide ($\text{CO}_2$) removal than oxygenation (extracorporeal $\text{CO}_2$ removal). They provide minimal oxygenation support and no cardiovascular support and will not be specifically addressed in this discussion.

**VV ECMO**

**Indications**

VV ECMO is currently indicated for potentially reversible cardiogenic shock (bridge to recovery), or as a bridge to more definitive long-term cardiovascular support in patients who are suitable for ventricular assist device (VAD) or heart transplantation. Where the suitability or need for long-term support is unclear, VA ECMO may be used as a bridge to decision. Venoarterial ECMO as an adjunct to cardiopulmonary resuscitation (ECMO-CPR, or E-CPR) is emerging as a viable option in select patients who are refractory to conventional CPR [13–15].

**VA ECMO**

VA ECMO is used to support patients with inadequate cardiac output and patients with combined cardiac and respiratory failure. VA ECMO can be either central or peripheral. The decision to use central or peripheral ECMO can be institution or patient specific.

**Central VA ECMO**

Cannulae are inserted directly via a sternotomy—with venous access into the right atrium and arterial return into the proximal aorta. This ensures oxygenation of the arterial supply to the coronary and the cerebral circulations (the most proximal branches of the aorta). Central VA ECMO can support patients with both cardiac and respiratory failure (Fig 2).

**Peripheral VA ECMO**

Cannulae are inserted into the cavae via the femoral or jugular vein approach. The return cannula is classically placed in the distal aorta via the femoral artery. Insertion may be percutaneous or open. A distal perfusion cannula is recommended to supply the limb distal to the return cannula (Fig 3). More recently, the subclavian artery has been described as an alternative return site.

**Membrane Oxygenators**

Improvements in membrane oxygenators have facilitated the increased use of ECMO support in recent years. Current oxygenators consist of multiple polymethylpentene hollow microfibers that are permeable to gas but not liquid. They provide a very efficient surface for gas exchange with no direct blood–gas interaction. In contrast to previous generations of oxygenators designed for short-term use in cardiopulmonary bypass, they have a low priming volume and a low resistance to blood flow that has enabled the use of centrifugal rather than roller blood pumps. In addition, they are resistant to plasma leak (as occurs in microporous gas exchange membranes), allow the potential for thromboreistant coatings and have been associated with reduced clotting factor and platelet transfusion requirements [10,23–27].

**Blood Pumps**

Both displacement (roller) and rotary (centrifugal and diagonal) pumps have been used for ECMO as well as cardiopulmonary bypass (CPB). With the advent of lower resistance oxygenators, centrifugal pumps have been employed more widely. They have the advantages
of small priming volumes, reduced hemolysis (particularly with newer magnetically suspended rotors), allowing thromboresistant coating and enabling circuit modifications to exclude bridges and reservoirs to minimize circuit volume (and hence size of blood: ECMO interface) and connections (that create sites of turbulent flow and potential thrombus generation) [28].

![VENO-VENOUS ECMO Diagram](image)

**Fig 1.** VV ECMO. Cavoatrial configuration of VV ECMO shown using bifemoral approach. Access cannula is shown percutaneously inserted via left femoral vein. Blood passes via pump to oxygenator and is returned to right atrium via cannula inserted percutaneously from right femoral vein cannula. VV ECMO provides respiratory support only. Schematic representation of blood flow in circuit demonstrating that the degree of oxygenation support provided by VV ECMO will depend on the proportion of the venous return captured.

![VENO-ARTERIAL ECMO Diagram](image)

**Fig 2.** Central VA ECMO. Central VA ECMO configuration. Access cannula is in right atrium. Blood passes via pump to oxygenator and is returned into ascending aorta. Direction of flow in aorta is antegrade. Cannulation is performed at sternotomy. VA ECMO provides cardiac and respiratory support.
Common Hemostatic Complications Seen During ECMO

Both bleeding and clotting complications can occur during ECMO support, often coexist in the same patient and are associated with significant morbidity and mortality. Balancing the relative risks of bleeding and thrombosis can be difficult as many factors related to the patient's illness, the extracorporeal support and the balance of proinflammatory and anti-inflammatory pathways will differ between patients. The common thrombotic bleeding and hemolytic complications as reported to the Extracorporeal Life Support Organisation (ELSO) Registry are detailed in Tables 1 and 2.

Thrombosis

Thrombosis is one of the most common and feared complications of ECMO support [19,17,25]. The true incidence of thromboembolic complications of ECMO is unknown, and autopsy studies would suggest that clinical evaluation underestimates its occurrence [18].

In the most recent annual ELSO report, clots were reported to occur in the oxygenator in nearly 13% of patients. Additional clots in other parts of the circuit were more common in patients on ECMO for cardiac support than those on for respiratory support. Central nervous system infarction was reported to occur in up to 3.5% of patients.

Mechanisms

ECMO necessitates contact between blood and nonendothelial surfaces and results in coagulation and fibrinolytic pathway activation and a complement-mediated inflammatory response. Although it developed from CPB, there are several differences in the nature of blood activation in ECMO patients that reduces the extent of these responses:

- Absence of surgical stimulus and minimal air–blood interface without an open surgical field
- Less complex circuitry with reduced circuit volume (nonendothelial surface area) and fewer connections (sites of turbulent flow)
- Less blood exposed to circuit per unit time

Table 1

<table>
<thead>
<tr>
<th>Complications</th>
<th>Pediatric 1 mo–18 y</th>
<th>Adult &gt;18 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complication</td>
<td>Reported (%)</td>
<td>Survived (%)</td>
</tr>
<tr>
<td>Clots: oxygenator</td>
<td>10.4</td>
<td>51</td>
</tr>
<tr>
<td>Clots: bridge</td>
<td>4.0</td>
<td>55</td>
</tr>
<tr>
<td>Clots: bladder</td>
<td>5.6</td>
<td>54</td>
</tr>
<tr>
<td>Clots: other</td>
<td>11.6</td>
<td>54</td>
</tr>
<tr>
<td>CNS: infarction</td>
<td>4.0</td>
<td>34</td>
</tr>
<tr>
<td>GI hemorrhage</td>
<td>4.0</td>
<td>27</td>
</tr>
<tr>
<td>Cannula site bleeding</td>
<td>17.5</td>
<td>53</td>
</tr>
<tr>
<td>Surgical site bleeding</td>
<td>13.4</td>
<td>46</td>
</tr>
<tr>
<td>Hemolysis (PfHg &gt; 0.5 g/L)</td>
<td>9.8</td>
<td>44</td>
</tr>
<tr>
<td>DIC</td>
<td>5.4</td>
<td>27</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>1.9</td>
<td>43</td>
</tr>
<tr>
<td>Pulmonary hemorrhage</td>
<td>8.2</td>
<td>31</td>
</tr>
</tbody>
</table>

Total numbers are cumulative ECMO runs.

Abbreviations: CNS, central nervous system; GI, gastrointestinal.

Survived = survival to discharge or transfer based on number of runs. Percentage survival describes patients with that complication who survived. Because patients who died may have had more than one complication, numbers will not total 100%.

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Counterbalancing this is the increased duration of support [19,29,30]. Furthermore, patients requiring ECMO often have additional noncircuit-related reasons for activation of platelets and inflammatory pathways related to their underlying illness.

Configuration-Related Thrombosis

Minimizing the size and complexity of the ECMO circuit can reduce the total nonendothelial surface area and the sites of turbulent flow that may promote thrombosis.

In patients on VA ECMO with little or no native cardiac function, stasis within the pulmonary circulation and within the heart itself can lead to thrombus generation. In addition to anticoagulation strategies, it is important to maintain flow through the heart wherever possible (for example, using inotropes and adjusting ECMO flow to optimize native cardiac function).

Thrombus Deposition in the Circuit and Oxygenator

Thrombus deposition in the membrane oxygenator as well as elsewhere in the circuit is common and can lead to oxygenator failure and thromboembolism. The circuit and oxygenator can be monitored by visual observation (e.g., using torch). Monitoring clot burden using daily D-dimer estimation can predict developing oxygenator failure. Although D-dimers can be elevated for many reasons in patients receiving ECMO support, a sudden rise can signify incipient failure of the oxygenator and is a predictor that a circuit change is likely within the next few days [31]. Adequate function of the oxygenator is assessed by monitoring the postoxygenator pressure drop as well as postoxygenator gas exchange. We routinely use D-dimer estimation as part of our circuit assessment as elective circuit change is preferable to sudden failure of the membrane oxygenator.

Pump Thrombosis

The other important cause of hemolysis in a patient on ECMO is pump thrombosis. This is a relatively rare but clinically important syndrome caused by a thrombus at the pump head. It is associated with a noisy pump, frank intravascular hemolysis, and hemoglobinuria. It can develop quickly and is associated with pump failure. It is not possible to see clot at the pump head during operation of ECMO, unlike clot in the oxygenator (which can be seen with a torch). It is very important to diagnose and treat expeditiously as it can lead to pump stoppage. The treatment is circuit exchange with ongoing adequate anticoagulation.

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is a rare, transient prothrombotic condition caused by circulating heparin-platelet factor 4 complex antibodies [32]. Since exposure of ECMO patients to unfractionated heparin is almost universal, the complication of HIT is important to consider. Although data are lacking on the incidence of HIT in this setting, one would expect its incidence to be similar to that seen in other critically ill patients. The issues around diagnosis and treatment have been extensively published elsewhere [33–35]. Specific points regarding treatment of confirmed or suspected HIT in patients on ECMO include removing all exposure to heparin which may include the ECMO circuit. It is important to realize that many modern ECMO circuit components are heparin bonded (Bioline and Safeline, Maquet Cardiopulmonary AG, Hirrlingen, Germany) in an effort to ameliorate the immune response to circuit components [36–38]. The heparin in these systems is covalently bonded to albumin in the coating. It is prudent (but not often practical) to consider removal of any catheters or circuit components with heparin bonding if possible. Thus, if platelet recovery does not occur after withdrawal of heparin, it is possible that ongoing exposure from the heparin bonding is a factor [39].

Options for alternative anticoagulation in this setting include direct thrombin inhibitors (argatroban and bivalirudin) as well as fondaparinux and danaparoid [40–45]. Of course, none of these drugs have an available antidote. The direct thrombin inhibitor lepirudin is approved for use in HIT and is described for this use in ECMO patients with HIT [46,47]; however, the production of the drug was discontinued in 2011 for financial reasons. Bivalirudin may be very useful in this patient population owing to its enzymatic clearance (80% enzymatic 20% renal) and short half-life (25 minutes) [48]. However, there is a risk of thrombosis in areas of stasis due to the unique pharmacology of bivalirudin which is well described in the cardiopulmonary bypass setting [49]. The 2012 American College of Chest Physicians HIT guidelines did not provide guidance for patients on ECMO support likely due to the paucity of clinical evidence in this group. However, they recommend bivalirudin for patients with acute HIT who require urgent cardiac surgery over other nonheparin anticoagulants and over heparin plus antiplatelet agents (grade 2C) and bivalirudin (grade 2B) or argatroban (grade 2C) for patients with HIT requiring acute percutaneous coronary interventions [50].

Table 2

Complications in patients requiring ECMO for cardiac support adapted from ELSO registry data 2014

<table>
<thead>
<tr>
<th>Complication</th>
<th>Total no.</th>
<th>Pediatric (1 mo–1 y) Survived*</th>
<th>Pediatric (1-16 y) Survived*</th>
<th>Adult (&gt;16 y) Survived*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clots: oxygenator</td>
<td>7.9</td>
<td>42</td>
<td>7.4</td>
<td>50</td>
</tr>
<tr>
<td>Clots: bridge</td>
<td>3.1</td>
<td>38</td>
<td>2.5</td>
<td>51</td>
</tr>
<tr>
<td>Clots: bladder</td>
<td>4.1</td>
<td>40</td>
<td>2.1</td>
<td>49</td>
</tr>
<tr>
<td>Clots: other</td>
<td>9.9</td>
<td>43</td>
<td>10</td>
<td>55</td>
</tr>
<tr>
<td>CNS: infarction</td>
<td>4.4</td>
<td>33</td>
<td>4.4</td>
<td>39</td>
</tr>
<tr>
<td>CNS: hemorrhage</td>
<td>6.0</td>
<td>30</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>Gl hemorrhage</td>
<td>1.9</td>
<td>14</td>
<td>2.7</td>
<td>30</td>
</tr>
<tr>
<td>Cannula site bleeding</td>
<td>12.3</td>
<td>40</td>
<td>18.4</td>
<td>54</td>
</tr>
<tr>
<td>Surgical site bleeding</td>
<td>32.6</td>
<td>40</td>
<td>28.4</td>
<td>48</td>
</tr>
<tr>
<td>Hemolytic (PfHg &gt; 0.5 g/L)</td>
<td>9.8</td>
<td>33</td>
<td>8.4</td>
<td>44</td>
</tr>
<tr>
<td>DIC</td>
<td>3.3</td>
<td>24</td>
<td>3.9</td>
<td>35</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>5.2</td>
<td>36</td>
<td>5.2</td>
<td>49</td>
</tr>
<tr>
<td>Pulmonary hemorrhage</td>
<td>5.1</td>
<td>24</td>
<td>6</td>
<td>38</td>
</tr>
</tbody>
</table>

Total numbers are cumulative ECMO runs. Abbreviations: CNS, central nervous system; GI, gastrointestinal.

* Survived = survival to discharge or transfer based on number of runs. Percentage survival describes patients with that complication who survived. As patients who died may have had more than one complication, numbers will not total 100%.

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Management of Thrombosis

Strategies for Anticoagulation

The aim of pharmacologic anticoagulation is to counterbalance the effects of exposure to the nonendothelial surface of the ECMO circuit. Ideally, this would inhibit activation of platelets, coagulation, and inflammatory pathways without increasing the risk of bleeding. Critically ill patients requiring ECMO may have additional indications for anticoagulation in the context of their underlying disease that must also be considered. Unfortunately, the ideal pharmacologic anticoagulant remains elusive.

Unfractionated heparin is the current international standard for anticoagulation during ECMO. It is inexpensive, widely available, titratable, and potentially reversible. Although other agents have been used, the overwhelming majority of international experience and data on ECMO are with heparin anticoagulation. However, there is no consensus on heparin monitoring or therapeutic targets and considerable inter-institutional variability exists [19,17,29,51–54]. The Extracorporeal Life Support Organisation has also released a specific anticoagulation guideline [55].

In addition to systemic anticoagulation, bioactive coatings of circuit components have been developed using heparin, phosphorylcholine, and polymethoxethyl acrylate in an attempt to ameliorate the inflammatory and coagulation response to circuit exposure. These are now in widespread use [23,29,56–58].

Monitoring of Anticoagulation

Activated partial thromboplastin time (aPTT), activated clotting time, anti–factor Xa (anti-Xa) levels, thromboelastography (including rotational thromboelastography), absolute heparin dose, and/or a combination of some or all of the above are used in different centers [19,23,17,29,51,53–55].

The ideal strategy for monitoring anticoagulation is unknown. There have been several recent reviews of the issues surrounding anticoagulation monitoring on ECMO [54,55].

Activated Clotting Time

Activated clotting time is a whole-blood clotting test used primarily in CPB settings but also used extensively during ECMO, particularly in pediatrics. It has a poorer relationship with aPTT at the lower levels of heparin used in ECMO compared with cardiac surgery. It is affected by heparin but also by other factors including thrombocytopenia, platelet dysfunction, antiplatelet medications, hypothermia, age, and hypofibrinogenemia [19]. Where it is used, the target suggested is usually 180 to 220 seconds [54,55].

Activated Partial Thromboplastin Time

Activated partial thromboplastin time has been the mainstay of laboratory-based heparin monitoring in the adult ECLS population. Therapeutic targets range is generally 1.5 to 2.5 times increase in baseline aPTT.

Anti–factor Xa

Anti–factor Xa activity has been described more recently with typical target ranges quoted as 0.3 to 0.7 IU/mL. Anti-Xa has the advantage of being a measure of heparin effect as distinct from heparin concentration. It is important to note that AT levels will influence the assay and results may be inaccurate if the laboratory adds exogenous AT to the specimen [51].

Antithrombin

Antithrombin (AT) is a serpin (serine protease inhibitor) present in serum that inactivates thrombin and activated factor X. The anticoagulant effect of heparin requires AT [59]. Neonates have lower levels of AT than older children and adults. Acquired deficiency in AT may occur in patients on ECMO [51,60]. Heparin use prior to ECMO, hemodilution, and consumptive coagulopathy may contribute. Although AT levels decrease initially with ECMO support, a recent pediatric study showed increasing levels over time in patients on ECMO regardless of whether supplementation was used [51]. Small studies in pediatric and neonatal ECMO populations point to no increase in bleeding risk [61] or even reduced bleeding when AT supplementation is used [62].

The use of pentasaccharides for anticoagulation also includes warfarin (a prototype vitamin K antagonist). The use of AT monitoring or therapeutic targets and considerable inter-institutional variability exists [19,17,29,51–54]. The Extracorporeal Life Support Organisation has also released a specific anticoagulation guideline [55].

In light of ongoing uncertainty in the strategies for anticoagulation and anticoagulation monitoring in patients on ECMO, a randomized pilot study is currently in progress in Australia (ACTRN12611300138707) (in patients without an additional indication for therapeutic anticoagulation) comparing an anticoagulation strategy of “standard” systemic heparin (aPTT target 50–70 seconds), and lower-dose heparin (12 000 units/24 h—adjusted for body weight and aiming for an aPTT < 45 seconds) and examining a range of anticoagulation tests. This has been designed to establish the feasibility of a larger randomized controlled trial to define the safest anticoagulation practice.

Bleeding

Bleeding is the Achilles heel of ECMO support. It is the leading contributor to mortality in ECMO patients in most large series and registry data [66,67]. Increase in blood product usage is independently associated with patient outcomes in both adults and pediatric case series [16,68].

Reported blood product usage in various series differs between centers and likely describes the rate of surgical procedures, transfusion triggers, practices around ECMO support, and other variables [69]. The reported requirement for blood products in the modern era has fallen compared with earlier reports [70].

This may have occurred due to improvements in ECMO technology including bioactive coatings. Despite this, it is sobering to note, however, that the main cause of mortality in the large H1N1 series reported in Australia and New Zealand in 2009 was hemorrhage. This accounted for 71% of deaths (10/64 people requiring ECMO), with intracranial hemorrhage being the cause of death in 6 of the 10 patients who died [71]. Bleeding can be seen with minor procedures and can be disproportionate to the trauma (which may be minor) and also the degree of coagulation disturbance by routine testing.

Mechanisms

The causes of bleeding in patients on ECMO and other forms of mechanical support are poorly understood and likely multifactorial. Hemositas is a complex process, and there are many cellular interactions...
leading to adequate hemostasis that may be disturbed in patients receiving ECMO support. The groups of critically ill patients requiring ECMO are among the sickest of the intensive care unit (ICU) patient population. They frequently have multiorgan failure and may have had CPR or sepsis preceding their ECMO commencement. It is hardly surprising then that we grapple with disorders of hemostasis and thrombosis. We take critically ill patients who already have an imbalance of their procoagulant and anticoagulant pathways and commence them on support with a system causing platelet activation, inflammation, and consumption of clotting factors, utilizing large bore arterial and venous access to do so.

**Thrombocytopenia**

Thrombocytopenia is common in critically ill patients. It occurs in 20% to 50% of ICU patients, and if moderate or severe, it is consistently associated with increased bleeding and increase in mortality [72–74]. Data on the proportion of patients receiving ECMO who have thrombocytopenia and the degree of platelet drop are lacking.

As in any setting of thrombocytopenia, it is important to try and identify the cause and treat appropriately. Required thresholds for prophylactic platelet transfusion in ICU patients are generally at a platelet level above the recommended 10 to 20 × 10^9/L recommended for non-ICU patients with chemotherapy-associated thrombocytopenia given the requirements for invasive procedures and risk of bleeding [75]. Greinacher and Selleng [76] have commented that bleeding in a critically ill patient with a platelet count greater than 30 × 10^9/L points to the likelihood of an additional disturbance of hemostasis. They recommend platelet transfusion in patients who are bleeding with either primary or secondary platelet abnormalities regardless of the level of platelets. Although this is not specific to patients on ECMO, these patients are often critically ill along with the additional potential effects of a mechanical device on their platelets and in the absence of other evidence to guide practice, using this approach in ECMO patients seems to be reasonable. There is no known level of platelet count beyond which risk of bleeding increases in ECMO patients, and this risk will also depend on the patient’s condition, for example, postoperative. Many centers describe targeting a platelet count greater than 100 × 10^9/L [64] (Table 3). Research to support this practice is lacking and urgently required.

**Disseminated Intravascular Coagulation**

One of the causes of excessive bleeding in patients receiving ECMO is disseminated intravascular coagulation (DIC). This may be a feature of the severity of illness or of the underlying disorder causing the need for ECMO. In addition, extracorporeal support is associated with a DIC-like consumptive coagulopathy due to tissue injury and contact activation in the artificial membrane [77]. Disseminated intravascular coagulation is an acquired disorder seen in a wide variety of conditions. It is characterized by widespread activation of coagulation resulting in fibrin deposition and microthrombi formation in small and mized-sized vessels. The platelet and coagulation factor consumption associated with DIC can lead to severe bleeding and, conversely, thrombosis [78]. There is no single diagnostic test that characterizes DIC, but the association of thrombocytopenia with low levels of coagulation factors (which, in turn, cause prolongation of the PT and aPTT) is suggestive [79]. Low (or dropping) fibrinogen levels are suggestive. D-Dimers are frequently elevated in patients on ECMO support so less useful in this setting. Low levels of anticoagulant proteins in plasma are evidence of ongoing activation of coagulation. Low levels of protein C and AT are found in 40% to 60% of critically ill patients and in 90% of patients with DIC, in addition to low levels of tissue factor pathway inhibitor [79–81]. Scoring systems that combine some of these tests and improve the sensitivity and specificity of the diagnosis of DIC have been proposed [82].

**Hyperfibrinolysis**

Fibrinogen is fundamental to clot integrity. Excessive fibrinolysis leading to bleeding is known as hyperfibrinolysis [83]. This should be suspected if bleeding is associated with very high levels of D-dimer and relatively normal platelet levels. Activation of fibrinolysis may be either a primary plasmin-mediated process or a secondary process occurring in the setting of thrombin-mediated activation. Both are commonly seen in extracorporeal support [84] and can be associated with significant bleeding in patients on ECMO. Clot deposition within the circuit including the membrane oxygenator can lead to excessive fibrinolysis characterized by steep increases in D-dimer and generalized coagulopathy-type bleeding, for example, mucous membranes. Replacing the circuit can often help to reverse this process.

Bleeding due to fibrinolysis may respond to antifibrinolytics [85]. Amicar (ε-aminocaproic acid) and tranexamic acid infusions have been described in this setting in pediatric and neonatal patients receiving ECMO [86–88]. Topical tranexamic acid may be useful for mucosal bleeding.

**Acquired von Willebrand Syndrome**

Acquired von Willebrand syndrome (AVWS) is a condition in which structural or functional defects in von Willebrand factor (VWF) activity occur secondarily to a variety of clinical causes (cardiovascular diseases, lymphoproliferative disorders, autoimmune conditions). It was first described as a clinical entity (Heyde syndrome) in patients with severe aortic stenosis associated with angiodyplasia-related gastrointestinal bleeding [89].

Clinically, this syndrome resembles type 2 von Willebrand disease (VWD) in which there is a qualitative defect in VWF. This presents with mucocutaneous bleeding as well as excessive bleeding in response to surgery or trauma.

**Diagnosis of AVWS**

Difficulty arises in diagnosing AVWS because there is no single diagnostic test. A panel of laboratory tests is required, as is used in the diagnosis of hereditary VWD. Tests include coagulation screen, FVIII level, VWF antigen (VWF:Ag), collagen binding assay, ristocetin cofactor assay (VWF:RCo), and multimer analysis. Expected abnormalities in the AVWS include decreased VWF:Ag/VWF:RCo or

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Transfusion thresholds in ECMO patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Question</strong></td>
<td><strong>Responses</strong></td>
</tr>
<tr>
<td>What is the low hematocrit threshold (%) you use for packed red blood cell transfusion in a typical ECMO patient?</td>
<td>Pediatric only programs (n = 81), median (range) [35 (25-45)] Adult-only and mixed adult and pediatric programs (n = 40), median (range) [30 (20-40)] [P \text{ &lt; .001}]</td>
</tr>
<tr>
<td>What is your typical low fibrinogen threshold (mg/dL) for platelet transfusion in an otherwise uncomplicated ECMO patient?</td>
<td>100 000 [50 000-200 000] 100 000 [20 000-100 000] [P \text{ = .34}]</td>
</tr>
<tr>
<td>What is your typical low platelet count (cells/µL) for platelet transfusion in an otherwise uncomplicated ECMO patient?</td>
<td>[100 000 \text{(50 000-200 000)}]</td>
</tr>
<tr>
<td>What is your typical low fibrinogen threshold (mg/dL) for which you would administer fresh-frozen plasma or cryoprecipitate?</td>
<td>[150 \text{(60-200)}] [145 \text{(50-200)}] [P \text{ = .33}]</td>
</tr>
</tbody>
</table>

Responses to 2010/2011 survey of ELSO units. Adapted from Benneba et al [64] with permission from Wolters Kluwer Health.

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collagen binding assay ratio and loss of high-molecular-weight VWF multimers (Fig 4).

Acquired von Willebrand syndrome is well described in high-shear situations (e.g., high-velocity flow associated with aortic stenosis) [90,91]. It has been also reported in continuous flow left VADs and hypothesized to be due to high shear. Nonpulsatile or low pulsatile circulation in patients with these continuous flow devices may also be a factor [92,93]. This is associated with higher bleeding rates and reversed on removal of the pump [94,95]. Not surprisingly, there is interest in this syndrome in patients receiving ECMO [96–100]. In one study [101], AVWS was seen in 31 of 32 patients on ECMO (and none of the 19 controls evaluated).

The significance of the testing abnormalities to suggest an AVWS due to ECMO requires ongoing investigation. At this stage, it appears to be a risk factor for bleeding, but this should be confirmed in further studies.

Altered blood flow associated with ECMO can also potentially affect platelet activation, by either increasing the interaction of VWF with its primary receptor, glycoprotein (GP)Ibα of the GPIb-IX-V complex at elevated shear rates, or through changes in expression of platelet surface receptors such as GP Ib or the collagen receptor, GPVI, through VWF-dependent or VWF-independent pathways. In this regard, exposure of healthy platelets to elevated shear stress ex vivo induces metalloproteinase-mediated ectodomain shedding of platelet GPVI, and the shed soluble GPVI is elevated in plasma from patients with single- vessel coronary stenosis [102]. Plasma-soluble GPVI is also elevated in patients with coronary disease, immune thrombocytopenia, or disseminated intravascular coagulation, and experimentally, shedding is induced by platelet activation, antiplatelet antibodies, or coagulation (FXa dependent) [110]. However, to date, changes in platelet receptor expression or shedding have not been analyzed in the setting of ECMO.

Treatment of AVWS. Treatment will depend on the cause of the AVWS. If associated with ECMO, it is likely due to high shear and thus makes sense to try and reduce the pump speed and improve access to minimize any turbulent flow. The condition is likely to reverse on removal of ECMO, so consideration should be given to whether weaning of ECMO is possible.

Plasmapheresis, desmopressin, and intravenous immune globulin have all been reported for treatment of antibody-mediated AVWS [104]. They are very unlikely to be useful in patients with ECMO-related AVWS. Desmopressin has been shown to be less useful in patients with cardiovascular causes of AVWS in the International Society on Thrombosis and Haemostasis registry [105]. Tiede et al [106] suggest withdrawal of antiocoagulants in patients with cardiovascular causes of AVWS. The role of VWF concentrates is uncertain in this setting.

Antifibrinolytic drugs (oral, topical, or intravenous) have also been reported as treatment options for patients with AVWS [104]. Other topical therapies are likely to be beneficial for local bleeding.

Management of Bleeding

Bleeding in patients receiving ECMO support can be catastrophic and out of proportion to the degree of coagulation abnormalities and may occur after no or minor trauma. Management includes preventative strategies to prevent bleeding. Cessation of anticoagulation if significant bleeding occurs as well as transfusion support, antifibrinolytics, and local measures and surgical control where required. There is a lack of evidence to guide transfusion triggers in the setting of ECMO support, but established triggers used in other critically ill patients, including massive hemorrhage, are available [107]. A suggested approach to prevent and manage bleeding is presented in Table 4. Figure 5 demonstrates simple local measures that can be used to minimize bleeding risk.

Use of Recombinant Factor VIIa

Recombinant factor VIIa (rFVIIa) has been proposed as a general hemorrhagic agent with much enthusiasm for its use in varied clinical settings including in patients receiving ECMO. Despite multiple randomized

**Fig 4.** VWF multimers. VWF multimer analysis. Loss of high-molecular-weight multimers of VWF in a patient on ECMO, which normalizes postdecannulation. VWF multimer pattern in the patient on ECMO is similar to that of a control sample of a patient with type 2B VWD, relative to a healthy control.
studies of its use in varied clinical settings, meta-analyses have shown that its effects on transfusion requirements are modest at best (average ~1 unit packed red cells) and that this is counterbalanced by a significant increase in the rate of arterial thrombosis [108,109]. Revision of Canadian National Advisory transfusion guidelines suggest that off-label use of rFVIIa for bleeding not associated with hemophilia remains unproven and should be restricted to clinical trials [110]. Multiple case reports and small case series have reported its use in patients on ECMO with bleeding complications [111,112]. Significant clotting within the ECMO circuit is a risk in this setting. Thus, in light of the paucity of clinical evidence associated with the use of rFVIIa, it cannot be recommended for patients on ECMO based on current data [113–115].

**Surgery in Patients on ECMO Support**

Patients receiving ECMO frequently require surgery, for example, cardiac or thoracic surgery, associated with a high risk of bleeding. Many surgeons can be naturally reticent about operating on a group of patients with such a high risk of bleeding [116]. However, with modern tip-to-tip heparin-bonded circuits, it is possible to run ECMO without any anticoagulation for prolonged lengths of time, and excessive bleeding even in the setting of surgery or massive trauma does not have to be a given [117,118]. The risk benefit of continuing anticoagulation in a postsurgical patient needs to be carefully considered, and ideally, anticoagulation should not commence until postsurgical bleeding has resolved.

**Hemolysis**

**Mechanisms**

Hemolysis is a common complication of any form of mechanical circulatory support including ECMO. In one meta-analysis of adult and pediatric ECMO complications, it affected 18% of patients [67]. Hemolysis in patients on ECMO is most likely to be due to a complication of the mechanical support but can be due to the underlying condition. Intravascular hemolysis is characterized by an increase in plasma-free hemoglobin (PFHb) and is associated with significant complications including renal failure and multiorgan failure [119,120]. The ELSO registry defines hemolysis complicating ECMO support as PFHb > 0.5 g/L. Hemoglobininemia and hemoglobinuria can be seen if hemolysis is severe. The PFHb is sensitive to phlebotomy technique, and handling both of which can contribute to an artifactually raised measurement. Importantly, if elevated, it is a sign that there is likely to be a circuit or patient problem leading to the hemolysis.
Patient and Circuit-Related Factors Causing Hemolysis. Hemolysis in mechanical circulatory support can be due to a number of factors. Red cell damage is thought to be due to an increase in shear stress [121]. The pressure drop across the membrane oxygenator is also directly associated with hemolysis [122]. Most centers use centrifugal pumps for ECMO support. Hemolysis is less likely with centrifugal pumps than with the older-style roller pumps [123].

Centrifugal pumps can be associated with generation of high negative pressures if the blood flow is obstructed or decreased. This will be manifest as kinking or chattering in the lines and falling pump outputs. The negative pressures generated at the pump head can intermittently be as large as ~700 mmHg. This negative pressure can cause a suction effect, with cavitation of blood causing blood trauma and hemolysis [124,125]. This problem can be erroneously addressed by increasing the pump speed (revolutions per minute) in a misguided attempt to increase pump flow. The correct approach is to decrease the revolutions per minute while dealing with the issue leading to the access insufficiency. High pump speed is also related to the development of technical-related hemolysis in the setting of ECMO support and should be monitored at least twice per day. Other markers of hemolysis may also be present (increased Lactate dehydrogenase (LDH), unconjugated bilirubin, reduced haptoglobin) but are less sensitive.

Summary and Future Directions

Patients requiring ECMO represent a heterogeneous group of critically ill patients with many different underlying conditions unified only by their requirement for this level of cardiorespiratory support. There is a variety of potential circuit and patient factors that contribute to disturbances in coagulation (Fig 6). They provide many challenges in managing and preventing bleeding and clotting complications. In order for ECMO to become more established, we require ongoing quality research to describe the impact of ECMO support on clotting and hemostasis. Only then can we hope to develop robust guidelines for treatment of bleeding, management of anticoagulation, and optimal monitoring strategies in order to improve survival.

References


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