Chapter 3

ECMO Biocompatibility: Surface Coatings, Anticoagulation, and Coagulation Monitoring

Timothy M. Maul, M Patricia Massicotte and Peter D. Wearden

Additional information is available at the end of the chapter

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Abstract

The interaction between the patient and the ECMO (extracorporeal membrane oxygenation) circuit initiates a significant coagulation and inflammatory response due to the large surface area of foreign material contained within the circuit. This response can be blunted with the appropriate mix of biocompatible materials and anticoagulation therapy. The use of anticoagulants, in turn, requires appropriate laboratory testing to determine whether the patient is appropriately anticoagulated. Physicians must balance the risks of bleeding with the risks of thrombosis; the proper interpretation of these tests is often shrouded in mystery. It is the purpose of this chapter to help demystify the coagulation system, anticoagulants, biocompatible surfaces, and coagulation testing so that ECMO practitioners can make informed decisions about their patients and to spur coordinated efforts for future research to improve our understanding of these complex processes.

Keywords: anticoagulation, coagulation testing, surface coatings, ACT, aPTT, TEG, heparin, direct thrombin inhibitors

1. Introduction

The ECMO circuit, as a whole, represents one of the largest surface areas and volumes for blood contact in any medical device. The oxygenator surface area ranges from 0.8–2.5m^2 with a volume of 75–250 mL depending on the manufacturer and size (pediatric to adult). In addition, there typically is an associated 250–500 cm of polyvinyl chloride (PVC) tubing to connect the pumps, oxygenators, and equipment to the patient, which creates an additional

0.05–0.15 m^2 surface area and 70–250 mL volume depending on length and diameter of the tubing. When blood comes into contact with any foreign surface, a series of reactions begin to occur within milliseconds that impact the coagulation and inflammatory systems, and essentially lead to the rejection of the material by the host organism. Therefore, in order to utilize ECMO in a clinical setting, these processes are required to be modulated through systemic anticoagulation or the utilization of materials and coatings designed to disguise the materials from the body. This currently represents one of the greatest challenges to the utilization of ECMO in patients, particularly in the long-term application for lung recovery and/or lung transplantation. According to the Extracorporeal Life Support (ELSO) registry, which is a self-reported database of ECMO patients and their associated diagnoses, equipment utilized, outcomes and complications, there are approximately 0.5 thrombotic events and 0.5 bleeding events per patient run [1]. Although survival statistics for ECMO patients are population-specific, the occurrence of these two adverse events often results in a 20–30% reduction in overall survival. Therefore, it is of utmost importance that ECMO practitioners create a better understanding of the complex processes involved in an effort to better utilize current technology. Further, it is of even greater importance that device manufacturers and researchers continue to work on new drugs, materials, and surfaces in an effort to modulate activation of coagulation and inflammation. The purpose of this chapter will be to provide an overview of the processes and principles of coagulation and anticoagulation in the setting of ECMO as a necessary foundation for understanding this problem.

2. Cell-based model of coagulation

Since 2001, the way that coagulation has been understood has undergone some fundamental changes. The traditional coagulation cascade has been replaced with the cell-based model of coagulation [2]. In this model, there are essentially three phases to the clotting cascade: initiation, propagation, and amplification. In each of the three phases, the impact of tissue factor (TF) bearing cells and platelets has been placed at the forefront and these are the platforms upon which much of the conversion of coagulation factors from their inactive to active forms occurs. The cell-based model provides a more accurate picture of the way that an enzymatic cascade works and allows for a clearer picture of the cross-talk between the inflammatory and coagulation systems which must be appreciated by clinicians for a true understanding of the hemostatic picture in ECMO patients. While the details of the cell-based model are beyond the scope of this chapter, an overview of the model along with the drugs that interact with the coagulation proteins is provided for visual reference (**Figure 1**)

3. Surface activation

The primary concern for most clinicians in ECMO is the prevention of thrombus formation on the surface of the ECMO circuit. Thrombi are composed of platelets, red cells, and fibrin meshes that are adherent to the surface. It is important to understand that cells cannot adhere directly

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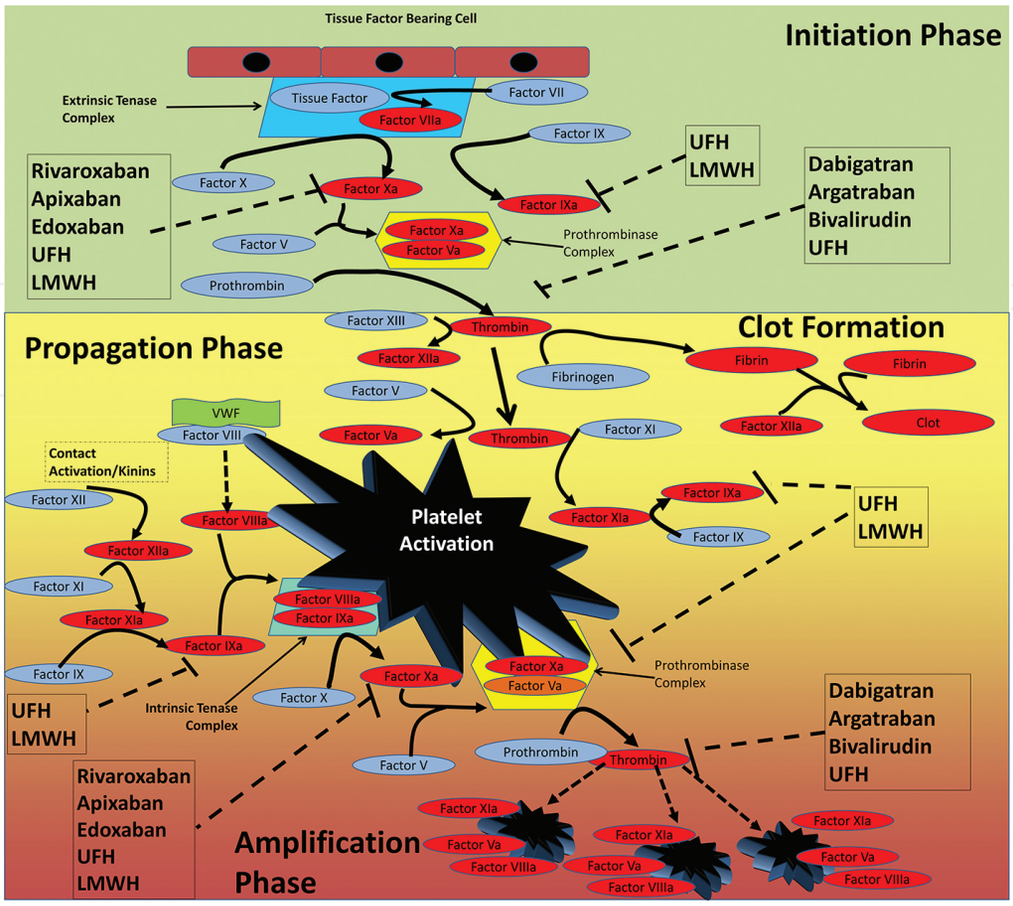

Figure 1. In the cell-based model of coagulation, three phases of coagulation take place on the surface of cellular elements of the blood. While platelets take center stage, the impact of TF-bearing cells cannot be overlooked because multiple cell types can express TF, including endothelial cells, monocytes, and macrophages. Inactive forms of the coagulation factors are presented in blue ovals while activated versions are presented in red ovals. Coagulation complexes are enclosed in parallelograms or hexagons. Drugs that interact with the coagulation cascade are identified and point to the specific factors they inhibit. Image adapted from Ahrens et al. [3].

to polymers, but rather require a receptor binding to a protein coating on the surface. Therefore, the first step in the coagulation and inflammatory response to the ECMO circuit is the adsorption (covalent or ionic reactions) of plasma proteins. This adsorption is based on stochastic processes driven by the thermodynamic reaction kinetics between the surface chemistry of the foreign material and the concentration of proteins available in the plasma [4]. For the ECMO circuit, these surfaces typically include PVC, silicone, polycarbonate, polymethylpentene, and/or polypropylene. Each of these materials is hydrophobic, with some being more hydrophobic than others depending on the side chain composition of the main polymer. The adsorptive process is also dynamic where proteins continually compete, adsorb, and desorb from the surface depending on both time and the changing concentrations of plasma [5]. Another important feature of this adsorptive process is that it often leads to a conformational change in the natural 3-D protein structure (**Figure 2**). In simple terms, the proteins may alter their shape to place their hydrophobic components near the hydrophobic polymer surface so as to exclude the water along a favourable thermodynamic gradient. This change in 3-D

structure can subsequently expose other hidden areas of the proteins to the aqueous environment and lead to hydrolysis (the breaking of bonds due to reaction with water) or provide ligands for receptors on the cellular elements (platelets and leukocytes) that will enable adhesions and subsequent cellular activation. The primary proteins of interest to prevent adsorption include fibrinogen and complement protein C3. Adsorption of fibrinogen is associated with platelet consumption [6]. C3 adsorption and subsequent autohydrolysis initiates the alternative complement system leads to the production of C5, which has been shown to significantly influence the homing of leukocytes to the intestine and lung tissues and promote the systemic inflammatory response syndrome and its deleterious effects [7].

Coagulation and inflammatory systems are interrelated such that activation of one will often result in cross-over activation of the other. Thus, it should be evident that the first step in mitigation of the deleterious effects of ECMO should be on the creation of biologically inert surfaces or masking of the surfaces from the coagulation and inflammatory proteins within the plasma. However, despite over 50 years of research, a perfectly biocompatible surface has not yet been created.

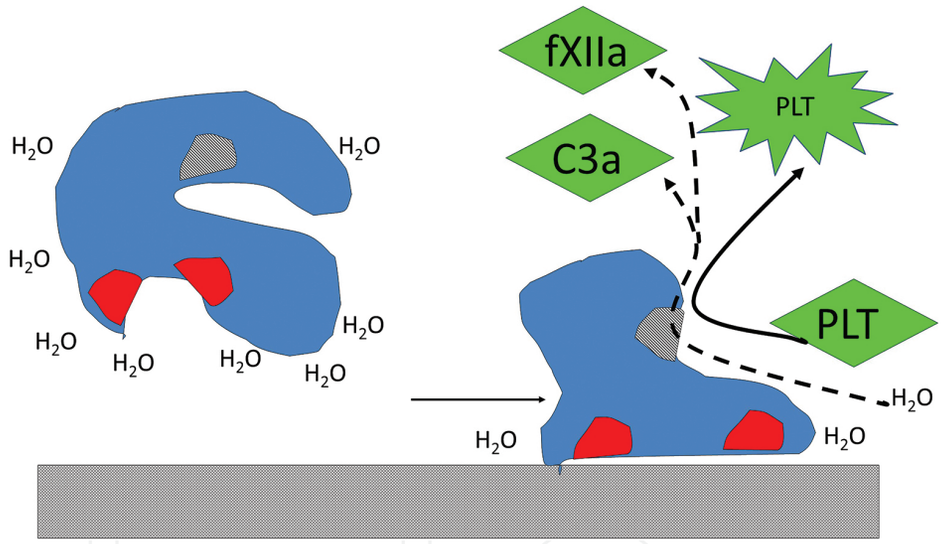

Figure 2. Representative image of the conformational change made by a protein in contact with a hydrophobic surface. The red zones are hydrophobic and are hidden from the surrounding aqueous solution until the protein comes near the hydrophobic surface. Upon approach, the thermodynamics favors a conformational change to exclude the water molecules and allow the hydrophobic patches to contact the hydrophobic surface, thereby inducing a conformation change that uncovers an active area of the protein (cross-hatched area). This area can react with the aqueous medium to initiate autohydrolysis and create the active forms of compliment or coagulation proteins (through intermediate steps such as bradykinins) or can provide the signal to activate platelets.

4. Surface coatings

In an effort to control the adsorption of plasma proteins to the ECMO circuit, the concept of pre-coating or surface modification has been in existence since nearly the beginning of

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extracorporeal circuit utilization. This section will examine the various coating technologies and their application to extracorporeal Technology. A table outlining the key points of each of the coatings discussed is provided (**Table 1**). One overarching theme from the research studies involving these and other novel coatings is that the strongest evidence for their implementation comes from in vitro short-term blood studies, and nearly all clinical studies have been performed in cardiopulmonary bypass settings. The clinical evidence for efficacy or changes in patient outcomes is often conflicting and most clinical studies have Class IIb recommendations to support them, and blinded, randomized trials are almost impossible to perform [8]. However, there is no evidence that coated circuits do any harm and their utility may be in those unusual clinical cases where protocol deviation is necessary or other factors that are not controlled may be influenced. These clinical scenarios are rare, thus creating challenges for adequate sample size in studies including only these unusual patients.

Manufacturer	Coating name	Coating technology
Medtronic	Carmeda	Covalently bonded heparin (anticoagulant)
	Trilium	Covalently bonded heparin (anticoagulant), sulfate and sulfonate groups (negative charge), polyethylene oxide (hydrophillic)
Maquet	Bioline	Covalently bonded recombinant human albumin (passivation) and heparin (anticoagulant)
	Safeline	Covalently bonded synthetic albumin (passivation)
	Softline	Amphyphilic polymer coating (reduced surface tension)
Terumo	X-Coating	Poly 2-methoxylacrylate (reduced cellular and protein adhesion)
Sorin	Smart-X	Tribloc Copolymer (Polycaprolactone-Polydimethylsiloxane-Polycaprolactone) integrated into plastic (reduced cellular and protein adhesion)
	P.h.i.s.i.o.	Phosphorylcholine (reduced cellular and protein adhesion)

Table 1. Listing of manufacturers and their coating products.

4.1. Albumin

One of the first proteins to be used for pre-coating blood-contacting surfaces was albumin [9]. Prior to the introduction of ionic or covalently bound surfaces, albumin was added to the circuit prime of adult circuits to increase the oncotic pressure of the priming solutions. In pediatrics, it was often used as a precursor to the addition of packed red cells. The purpose of the albumin pre-coat was to provide a base layer of protein that would delay or mitigate the biological response to the heavily hydrophobic surfaces [9, 10]. Adsorbed albumin both increases the hydrophilicity of the surface and provides a competitive protein that the fibrinogen must displace. Albumin covalently linked to surfaces (e.g., Safeline® by Maquet) ensures its retention and prevents displacement. Research on this coating technique has demonstrated short-term reductions in the concentration of fibrinogen and platelets on the surface and some evidence that it reduces complement activation [11].

4.2. Heparin

The most widely used anticoagulant in cardiopulmonary bypass and ECMO has been unfractionated heparin (UFH). The use of UFH has contributed significantly to the advancement of cardiac surgery and improved outcomes in these patients and will be discussed in detail in subsequent sections. Because UFH was such a successful systemic anticoagulant, a natural extension would be to immobilize it to a blood-contacting surface to provide local anticoagulant effects and potentially decrease some of the side effects of systemic anticoagulation, particularly in post-operative cardiac surgery patients where surgeons desire blood coagulation at the site of the incision but not in the extracorporeal circuit. Immobilization can be accomplished through covalent linkage to the surface, polymerization on the surface, or ionic interactions with the surface.

End-point covalent linkage of heparin to polymer surfaces was first made commercially available as Carmeda Bioactive Surface™ (Carmeda, Switzerland), available on Medtronic tubing and oxygenators. The process for linkage is relatively straightforward and applicable to a variety of biological compounds. The process begins adding a layer of an amide (NH_3) containing material to the surface. This amide surface is then easily reacted with the end of the polysaccharide chain of heparin. The covalent linkage of heparin has been demonstrated to be reproducible and stable, with the heparin reactivity present several hours after the initial exposure to the blood [12]. Other manufacturers have made similar heparin coatings (e.g., Rheoparin (Medos) and Bioline (Maquet)) using composite covalent and/or cross-linking techniques. The largest challenge with these methods is that the active site of heparin may be involved in the binding area and thus not available for interaction with antithrombin. In addition to covalent linkage, ionic linkage has also been demonstrated, most notably in the Duraflo (Baxter) products. However, the difference between ionic and covalent linkage is the retention of the heparin molecule after blood contact in the covalent bonding versus leaching of the heparin in the ionic linkage [13, 14].

Overall, the use of a heparin coating has been seen as a success in the medical community, and nearly 300 papers on heparin-coated circuits have been published. Most in vitro or animal models demonstrate benefits of heparin coating including reduced soluble thrombin production, platelet binding, and D-dimer production [12, 15–19, 20]. With respect to inflammation, most studies demonstrate reduced inflammatory response, particularly in the interleukins, alternative complement pathway and polymorphonuclear cells, compared to controls and other coating systems [12, 20–25, 26]. Meta-analyses of the benefits of heparin coating have consistently found improvements in transfusion requirements, arrhythmias, ventilator times, and lengths of stay in the hospital or ICUs when using heparin-coated circuits for cardiopulmonary bypass [17, 27, 28, 29]. One important aspect of many of these studies has been that many have focused on short-term impacts of heparin coatings. These studies also indicate that it does no harm to the patient, and therefore it may be worthwhile to utilize this technology in the absence of large studies containing a heterogeneous patient cohort. However, some studies have been published that demonstrate no appreciable systemic benefits to heparin coating during cardiopulmonary bypass [30] or for ECMO beyond 6 hours, for reasons that have never truly been elucidated [19]. Practitioners are cautioned to interpret these studies

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carefully because of their short-term nature and the significant effects of the air-blood interface found during cardiopulmonary bypass (CPB). In a statement which is reflected in the anticoagulation guidelines from the Extracorporeal Life Support Organization, "ECMO patients are highly complex and the additional time on support cannot be ignored as a key factor in their outcomes" [31].

4.3. Polymer surfaces

In addition to the biologic molecules of heparin and albumin, there are several other surfaces that have been developed with the aim of increasing hydrophilicity or surface charge similar to that of the endothelial cells lining mammalian blood vessels. These are typically polymers including phosphorylcholine, poly 2-methoxyethylacrylate, polyethylene oxide, and triblock surface-modifying additives. Each will be discussed in terms of relative chemistry, and studies examining their effectiveness at blunting the coagulation and/or inflammatory response.

4.3.1. Phosphorylcholine (PC)

Phospholipids make up the bulk of the cell membrane in mammalian cells and provide the ability to separate the plasma and cytosolic solutions, both of which are aqueous environments. Phosphorylcholine (PC) is a zwitterionic phospholipid compound with no overall charge that is found on the plasma leaflet of the red cell membrane. This compound has been previously demonstrated to be non-thrombogenic, as opposed to its cytoplasmic counterpart, phosphatidylserine, which has been shown to be pro-thrombogenic [32]. It has been successfully used in stent coating technology, and has also been used to coat PVC and polypropylene and polymethylpentene oxygenators for cardiopulmonary bypass and ECMO uses under the brand name P.h.i.s.i.o. from Sorin. The effects of PC on PVC have been shown to reduce fibrinogen binding and subsequent platelet binding through GPIIb receptors [32]. PC-coated circuits perform similar to heparin-coated circuits [33] in clinical studies with evidence of improved platelet retention and reduced postoperative transfusion requirements, but no effects on overall outcomes [34]. Further, PC coating may increase immune cell (T-Cell) response through an IL-8 mechanism [35].

4.3.2. Polyethylene oxide (PEO)

Polyethylene oxide (PEO) is a water-soluble, non-toxic, and non-immunogenic polymer that has been shown to reduce protein and bacterial adhesion in a variety of surfaces [36]. Its utility in blood-contacting materials was originally designed for increasing the hydrophilicity of the silicone polymers that made up the early membrane oxygenators. Silicone, while relatively biocompatible and an ideal biomaterial for many applications, is very hydrophobic, and increased hydrophobicity leads to increased protein adhesion, particularly fibrinogen adsorption [37]. A challenge with silicone coating is that production of functional groups for attachment is not as easy as with other polymers. However, it is possible with the use of mercury lamps to create radicals and oxidation by O_2 plasmas to create alcohol groups. Alternative preparations begin with incorporating hydromethylsilicone in the polymerization process and the subsequent use of platinum catalysts can create the functional groups for coating attach-

ment. Coating of PEO to the surface of silicone rubber has been demonstrated to increase water contact angles (increased hydrophilicity) and reduce both fibrinogen and albumin adhesion by 90% [36]. These reductions are dependent on a number of factors, including the molecular weight of the PEO and the functional structure of the PEO (single, monofunctional chains or bi-functional, loop structured PEO). Like most coating technologies, this coating is not a pure monolayer and gaps do exist. The use of PEO is commercially available as part of the Trillium package on Medtronic tubing. Studies using the Trillium surface have shown reductions in inflammatory markers and reduced bleeding events [38–40], but also increased stroke rates [38] from cardiopulmonary bypass. Like most CPB studies, these are small, single-center studies with variable sample collection, and no long-term studies have been performed.

4.3.3. Poly 2-methoxyethylacrylate

Poly 2-methoxyethylacrylate (PMEA) is a polymer coating generated on polypropylene and PVC surfaces through plasma charge preparation of a surface. Allowing 2-methoxyacrylate to react with the surface provides a weakly hydrophilic surface that has improved biocompatibility characteristics. PMEA was originally developed for plasma separation devices to permit non-hemolytic dry priming of the devices [41]. However, it was soon realized that this coating provided significant reduction in platelet and leukocyte activation and adhesion, and coagulation and complement activation [42]. Numerous laboratory studies have been undertaken to understand why this particular polymer has such effects, including variations of the polymer to include hydroxyl, phenyl, ethyl, and other groups. In all cases, the PMEA adsorbed fewer proteins and the protein conformation changes differed very little from the native surface [42, 43]. This coating is currently marketed under the SMARTx brand from Sorin. Clinical and in vitro studies using cardiopulmonary bypass circuits with this coating technology (available as the X Coating from Terumo) have had mixed results. Like other coatings, PMEA-coated systems have improved markers of inflammation and some clinical outcomes over non-coated systems [44, 45]. However, several studies have demonstrated increases in ventilator times, chest tube output, and inflammatory markers of PMEA compared to other coatings [39, 46, 47], while others studies found little or no difference between PMEA and heparin-coated surfaces [44, 48].

4.3.4. Surface-modifying additives

Another technique for producing more biocompatible surfaces is the use of surface-modifying additives (SMAs) that can either be blended with the base polymer resins during manufacturing and subsequently rise to the surface, or they can be coated onto a device's blood-contacting surfaces. One such SMA, a polycaprolactone-polysiloxane-polycaprolactone triblock copolymer, has been incorporated into the polyvinylchloride base resin and coated onto a polypropylene membrane [49]. The incorporation into the bulk resin yields significant surface modification and in initial in vitro tests demonstrated large reductions in thrombin and complement generation on SMA surfaces compared to uncoated surfaces. Clinical studies of the SMA coating have provided some evidence for a change in physiologic response, typically increased blood pressure and anti-inflammatory IL-10, reduced platelet and blood

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loss [50–52], and reduced use of inotropes [50, 51, 52]. Interestingly, terminal complement complex and complement protein C3 have been found to be no different in the SMA and control (uncoated) circuits in several studies [50, 53], and there is no difference in the generation of high-intensity transient signals in transcranial Doppler between SMA and non-coated circuits [52].

5. Anticoagulants

The need for systemic anticoagulation has been understood since the earliest extracorporeal circuits were developed in the laboratories in the 1800s. It wasn't until the discovery of the heparin molecule in the early 1900s that safe anticoagulation could be achieved for the purposes of moving and storage of blood outside of the body. As a result, heparin is the most widely used anticoagulant for ECLS owing to its long history, cheap production costs and reversibility with the fish-based enzyme, protamine. In addition to heparin, there are other classes of anticoagulants, including direct thrombin inhibitors. These have been utilized in extracorporeal circuits, particularly when heparin is not recommended to be used, such as patients with a heparin allergy (i.e., heparin-induced thrombocytopenia) or protamine allergy. Each of the anticoagulants will be discussed in terms of their mechanisms of action, cofactors required, dosing for ECMO, and case studies or clinical trials related to their use in ECMO. **Table 2** at the end of this section provides relevant dosing for pediatric and adult patients along with responses to bleeding for each drug.

5.1. Heparins

Heparin is a natural anticoagulant produced by the basal and mast cells in the body. Its discovery in 1916 was instrumental in the progress of blood-contacting devices because it could effectively halt the coagulation process which was a consistent problem for blood-contacting materials at the time. Heparin is a variable length carbohydrate in the glycosaminoglycan family, with molecular weights ranging from 3 to 30kDa. The primary mechanism of action of heparin is its ability to interact with another naturally occurring anticoagulant, antithrombin (AT, discussed below) and increase its ability to bind and inhibit the enzymatic activity of thrombin (Factor IIa) and Factor Xa by over 2,000-fold [54]. Only heparins containing 15 or more saccharide chains are capable of binding and inhibiting thrombin and FXa; heparins with 5–15 saccharide chains can only bind and inhibit FXa. Of note, the heparin/AT complex can only bind to soluble thrombin or FXa due to the large size of the AT molecule. Thrombin or FXa already complexed within an adherent clot cannot be affected by the presence of heparin and will continue their enzymatic processes unimpeded.

Pharmaceutical preparation of heparin is derived from the mucosal tissues of farm animals including pigs and cows, although most current preparations are derived from pigs due an increased incidence of heparin-induced thrombocytopenia (HIT) with bovine-derived heparin [55]. As such, the derivation of heparin from these tissues is unfractionated, containing all the molecular weights. Low molecular weight heparin can be derived through a size fractionation

or chemo-enzymatic process. Heparin can be given intravenously or subcutaneously, and has a relatively short half-life of 60–90 minutes (unfractionated) to 4–5 hours (low molecular weight) [56]. As such, unfractionated heparin (UFH) is typically administered continuously intravenously while low molecular weight heparin (LMWH) is administered once or twice daily subcutaneously.

Drug	Clearance	Dose (mg/kg/hr)		Monitoring		Bleeding
		Child	Adult	Child	Adult	Child & Adult
UFH	Renal	15–28 IU/kg/hr	10–18 IU/kg/hr	aPTT 1.5–2X (<100 sec) ACT 180–220 sec Anti-Xa 0.3-0.6 IU/mL	PTT 40–60 ACT 180–220 sec	Protamine 1.5 mg/100 IU UFH (reversal)
LMWH	Renal	1.2 subcutaneous q 12hrs	1mg/kg subcutaneous q 12hrs	Anti-Xa 0.5–1 IU/mL		Protamine 1.5 mg/100 IU LMWH (partial reversal)
Argatroban	Hepatic	Infusion: 0.045 Adjust 0.06–0.015 Hepatic compromise 0.012 In HIT: 0.006-0.6;	Infusion: 0.12 In HIT: 0.012	PTT 1.5–3X (<100 sec) ACT 160–200	PTT 40–120 ACT 170–200	FVIIa** 30–90 μg/kg
Bivalirudin	Proteolysis: 75% Renal: 25%	Bolus 0.125–0.25 Infusion Primary: 0.125–0.2 Tx UFH: 0.1–0.8	Infusion:0.08–0.2 Adjust 0.03	PTT 50-70 ACT160–200	PTT 40–120 ACT 200–220	
Aspirin	Liver	1–5 mg/kg/d Max 91 mg		TEG MA and α depression TEG AA Inhibition 70%		Platelet Transfusion
Clopidogrel	Liver	0.2 mg/kg/d	1 mg/kg/d	TEG MA and α depression		Platelet Transfusion
Dypyridamole	Liver	1.5 mg/kg/d		TEG MA and α depression TEG ADP net G 4–8		Platelet Transfusion

Note: **Based on <10 case reports.

Table 2. Dosing guides for anticoagulants for mechanical circulatory support.

Heparin is cleared through two mechanisms. Low doses of heparin are rapidly cleared through a reticuloendothelial process, whereas higher doses which saturate these processes are cleared

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through the kidneys in a much slower fashion [57]. Additionally, heparin effects can be rapidly reversed through administration of a reversal agent, protamine sulfate, which is negatively charged and binds with UFH or LMWH to form a stable ionic pair preventing binding to AT3. The ionic complex goes on to be broken down through the reticuloendothelial system.

The ease of production, rapid onset, relatively linear dosing and ease of reversal has made heparin the standard anticoagulant for cardiopulmonary bypass and subsequently ECMO for the past 50+ years. For cardiopulmonary bypass, a loading dose of 300–350 units/kg is administered, which results in an activated clotting time >400 seconds (see ACT below), and the standard perfusion target of ACT>400 sec for the duration of surgery is easily met with additional bolus dosing as necessary. For ECMO, loading doses of 30–100 units/kg have been used for initiation and then a continuous infusion between 10 and 30units/kg/hr is administered according to a specified coagulation test target protocol [58].

5.1.1. Heparin-induced thrombocytopenia

In addition to binding to AT to mediate its anticoagulant effect, heparin can also interact with platelet factor 4 (PF4) to form very large (>670kDa), stable complexes. These complexes are more common with UFH than LMWH and can trigger pre-existing PF4/heparin-intolerant B cells [59]. The chances of a B cell reaction leading to proliferation and antibody production may increase in some patients with repeated exposure to exogenous UFH, leading to a condition called heparin-induced thrombocytopenia (HIT). HIT is characterized by a sudden and severe drop in platelet count, diffuse thromboses resulting in petechiae, and subsequent increases in risk for stroke, pulmonary embolism, or myocardial infarction. HIT occurs in approximately 2.5% of the general population, with higher incidences in patients with repeated heparin exposure. HIT is formally diagnosed through either an immunoassay to identify antibodies against the heparin-platelet factor 4 complex or the gold standard functional assays that measure the platelet activating capacity of this complex [55]. Patients who are found to be HIT positive can no longer receive heparin without serious risk for stroke or sudden death. Alternative anticoagulants are typically used (see direct thrombin inhibitors below). High dose IV gamma globulins or plasmapheresis can also be employed to reduce the presence of the heparin antibodies and mitigate the effects of HIT [60, 61].

5.1.2. Antithrombin

Antithrombin (AT) is a 58 kDa serine protease inhibitor produced by the liver. Because a majority of the coagulation cascade proteins are themselves serine proteases, AT can target many of them; including kallikrein, plasmin, FXIIa, FXIa, FXa, FIXa, FVIIa, and FIIa. In the presence of heparin, AT activity against FIIa, FIXa, and Fxa is increased. AT inhibition of FIIa is accelerated 2,000–4,000, and only 500–1,000-fold against FXa [62]. With sufficient calcium and heparin, AT inhibition of FIXa can increase over 1 million fold [63].

In patients on heparin therapy with no known genetic deficiency in AT production, the apparent heparin resistance (i.e., increasing heparin dosing with no effect) can often be attributed to low AT levels in the plasma. AT levels also change developmentally, with

approximately half as much AT at birth that rises towards adult levels around 6 months of age [64]. The drop in AT levels can occur for a variety of reasons in the setting of ECMO. First and foremost, for pediatric patients, there is a high likelihood of factor dilution when connecting to the ECMO circuit (average ECMO circuits range from 270 −700 mL and are primed with packed red cells and/or crystalloid). Second, the activation of the coagulation cascade as a result of the additional foreign surface, inflammatory response to the hypoxic state, and the surgical procedure can cause significant amounts of AT to complex with the activated blood elements in equimolar and extremely stable complexes [65] as well as to complex with any immobilized heparin on the surface of the ECMO circuit [66].

Administration of AT on ECMO is routinely performed, and there are reports of patients who have received only AT as their sole anticoagulant [58]. There are relatively few studies that have examined the effects of AT administration on ECMO patients. Most are severely underpowered, lacking sufficient events for efficacy analysis. However, those that are published do indicate that AT increases heparin levels in the blood and reduces the heparin dose in ECMO patients, and that AT can be safely administered to patients on ECMO without increased risk of bleeding [67–69, 70]. There have been reports of increased failure rates of ECMO circuits in patients receiving AT, but this may be due primarily to sub-therapeutic heparin effect (for which AT is being given) [68]. However, it is the lack of true efficacy (reduced bleeding or thrombosis events) in these studies that continues to raise questions about the utility of this costly therapy in ECMO patients.

5.2. Direct thrombin inhibitors

In the setting of conditions that limit the use of heparin, such as HIT, direct thrombin inhibitors (DTIs) can be used. These drugs specifically target FIIa and have the advantage that they do not require cofactors like AT to function; nor are they neutralized by PF4 like heparin [71]. Furthermore, they are small molecules and can bind to FIIa that is currently enmeshed in a clot as well as FIIa in the plasma (i.e., soluble and insoluble thrombin). The primary disadvantage to their use in ECMO is the relative lack of experience using these drugs along with the differing clearance mechanisms that may make one DTI preferable to another in the setting of multiple organ failure. There is also no antidote, unlike heparin which can be specifically reversed with protamine. Each of the various DTIs that have been used with ECMO will be discussed, along with specific mechanisms of action and dosing that have been documented in ECMO patients.

5.2.1. Argatroban

Argatroban is a small site-directed DTI first discovered in 1981 and became the first oral DTI available in the market for patients with HIT. The primary interaction is a reversible binding between a hydrophobic portion of the argatroban molecule and the hydrophobic pockets near the active site of the thrombin molecule [72]. Although primarily given intravenously, the main advantage that argatroban has over other DTIs like Bivalirudin is that it is a very small molecule (~500 Da). The half-life of argatroban is ~50 minutes, and it is cleared solely through hepatic mechanisms, making it suitable for use in patients with acute renal failure. Anticoagulation

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monitoring is typically performed through the activated thromboplastin time (aPTT) test because argatroban can lead to false increases in the international normalised ratio (INR) level [71].

Of all the DTIs, argatroban has seen the greatest clinical use in the settings of cardiopulmonary bypass and ECMO for patients with confirmed or suspected HIT [71, 73, 74]. Dosing for argatroban in these therapies ranges from 0.1–250 μg/kg loading dose depending on the setting (CPB vs PCI), patient age (neonates may require a smaller bolus because their thrombin generation is lower than adults [75]), and physician experience, or 10–30 μg in an extracorporeal circuit. The loading dose is followed by 0.1–24 μg/kg/min continuous infusion [71, 74]. Target aPTTs are typically 1.5–2 times baseline or 45–65 seconds [71] or activated clotting times (ACTs) of 250–300 seconds [74]. Patients receiving argatroban during ECMO have experienced similar thrombotic complications as those on traditional heparin therapy (including circuit thrombosis, disseminated intravascular coagulation, and diffuse thrombotic disease) [71]. Although the case series are small, rates of complications hover around 25%, which is lower than the combined bleeding and thrombotic complications reported by ELSO for their registry (~40–50%). Larger, randomized control studies should be performed to determine whether the use of argatroban is associated with significantly reduced complications in the extracorporeal setting or if these small case series are simply a result of higher anticoagulation vigilance in the setting of a higher risk patient.

5.2.2. Bivalirudin

Bivalirudin is a synthetic version of the leech-derived anticoagulant hirudin. It is a slightly larger molecule than argatroban (~2,000 Da) requiring that it be delivered intravenously. Bivalirudin has two thrombin binding sites, one in the catalytic pocket of thrombin and the other on fibrin-binding exosite. After binding to thrombin, a portion is cleaved off that will restore some thrombin activity. The remainder of the drug is cleared through renal mechanisms, making it suitable for use in patients with acute liver dysfunction where argatroban may be unsuitable [72]. Because of the partial enzymatic cleavage, the half-life of bivalirudin is shorter (~30 min), which makes it attractive for short-term procedures like percutaneous coronary intervention and cardiopulmonary bypass [71]. However, the challenge with using bivalirudin is that the drug is degraded with stasis of blood flow and therefore may cause unexpected clotting in the reservoir of the cardiopulmonary bypass machine or in any area of stasis in the ECMO circuit. Recommendations have been made by experts that left heart volume should be reduced as much as possible to prevent the occurrence of a "cardiac reservoir" and possible thrombosis [76]. For other extracorporeal therapies where there is no reservoir (ECMO or VADs), bivalirudin may be preferable over argatroban for patients who are in liver failure. Dosing for bivalirudin has been reported at 0.15–0.5 mg/kg bolus followed by 0.12–0.25 mg/kg/hr. The target ACTs and aPTTs are similar to that of argatroban at >200 seconds and 1.5–2 times baseline, respectively [71].

In the setting of ECMO, small case reports and single-center retrospective reviews have been generated describing the use of bivalirudin over heparin [77–79, 80]. One such report from Ranucci et al. [80] described the reduced use of platelet and plasma donor products in patients

receiving bivalirudin for postcardiotomy ECMO compared to patients receiving UFH. Another small case-controlled study from Pieri et al. [81] demonstrated less variation in aPTT but no difference in bleeding and thrombotic complications versus UFH. The consensus from these reports has primarily been that bivalirudin use in the extracorporeal setting is feasible provided the patients are closely monitored.

5.3. Factor Xa inhibitors

Another alternative to heparins is to use Factor Xa Inhibitors, which can either bind directly to FXa to prevent interaction or can catalyze inhibitory reactions via AT3 (similar to the action of UFH). The primary advantage to these drugs is that they can inhibit free and platelet-bound FXa and can be dosed infrequently due to long half-lives, and can be administered with intermittent subcutaneous injections. Several oral FXa inhibitors have been approved by the FDA for treatment of venous thromboembolism (VTE) and atrial fibrillation (AF). These

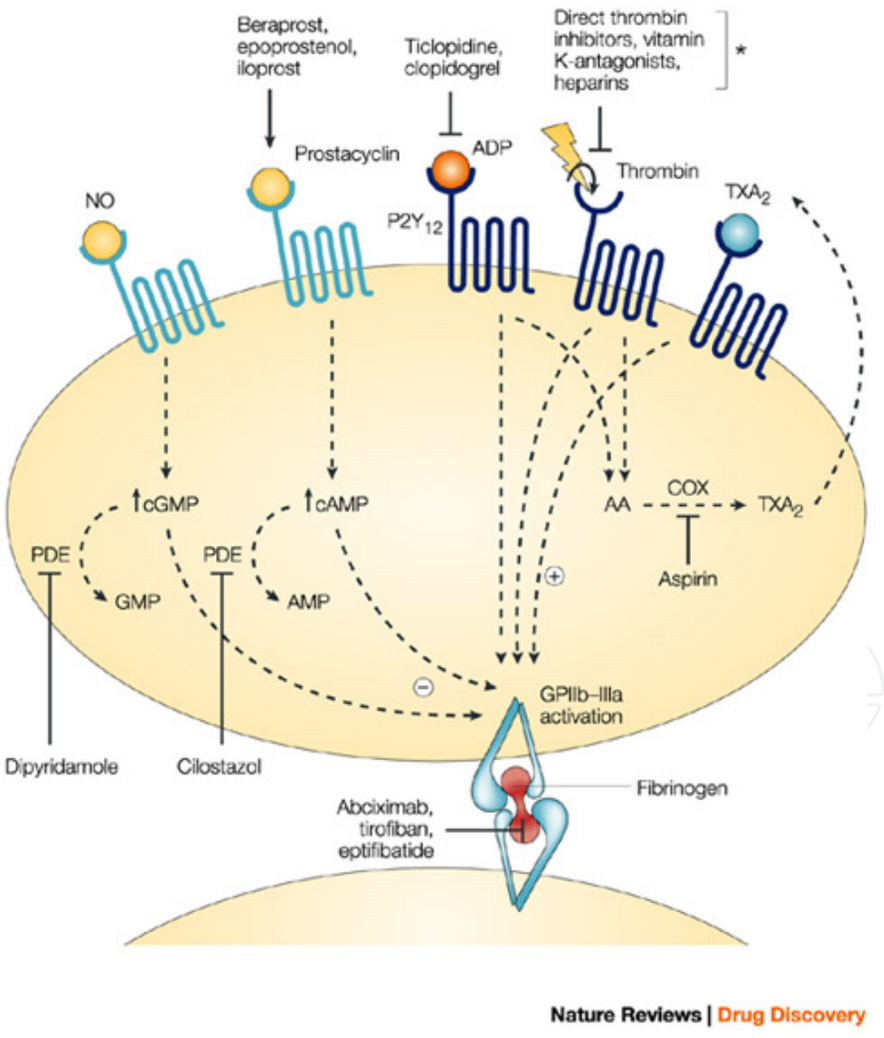

Figure 3. Regulatory pathways of platelets including their stimuli and pharmacologic inhibitors. Reprinted with permission from Macmillian Publishers Lt: Nature Reviews Drug Discovery, Copyright 2003 [85].

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include rivaroxaban, dabigatran, edoxiban, and apixaban. Dosing is typically once per day, and monitoring is performed performed through an anti-FXa assay or through aPTT [82]. There are no data currently on the use of these agents in the acute care setting, but it may become a possible choice for patients on long-term ECMO who are extubated and awaiting lung transplantation. A major caveat for this drug is that it has no antidote and in the case of worsening renal function, the drug will not be cleared efficiently and dialysis does not appear to alter plasma levels [83]. However, a recent study on a double-blind placebo trial of a general FXa-antidote (andexanet) is promising [84].

5.4. Anti-platelet agents

Platelet activation and deposition occur rapidly in the setting of extracorporeal circulation and have been a primary focus of coating technologies developed for extracorporeal therapies (see above). The deposition of fibrinogen to the artificial surfaces provides ample binding and activation signals to the platelet through their GIIb/IIIa receptors [85, 86]. Further, the altered shear stress environments are also known to activate platelets [87, 88] to form aggregates with other cells, including monocytes and other platelets via von Willebrand factor (vWF) and p-selectin mechanisms under inflammatory conditions related to mechanical circulatory support devices [89, 90]. Pharmacologic intervention into platelet activation and adhesion has only been recently explored in the laboratory and a few small case studies, but most studies show a potentially beneficial effect. Anti-platelet agents (**Figure 3**) have a long history in other forms of mechanical circulatory support such as the implantable ventricular assist devices [91–93], stents [94], and mechanical heart valves [95]. Anti-platelet therapy incorporation into ECMO anti-coagulation treatment has been successfully applied in La Pitie Hospital and reported previously [96, 97].

5.4.1. Nitric oxide

Nitric oxide (NO) is a natural inhibitor of platelet activity through cGMP mechanisms similar to those of dipyridamole [85]. Recently, efforts have begun to be explored in the laboratory to incorporate NO-releasing polymers in the ECMO circuit [98] and to provide NO in the sweep gas [99, 100, 101]. The reasoning for its use in the setting of extracorporeal life support is that the half-life is so short (2–6 sec) that only a local effect occurs [102]. This is the goal of the coated circuits where the anticoagulation activity is sequestered to the artificial surfaces and does not act systemically. In vitro and animal studies of the use of NO on ECMO circuits have demonstrated a significant improvement in platelet functionality and retention of platelets with minimal generation of the undesirable side effects of nitric oxide infusion, specifically methemoglobin [100, 101, 102]. The primary downsides to this type of therapy are the lack of current devices, which can accurately dose nitric oxide through the membrane, and the high cost of nitric oxide therapy. Materials that release nitric oxide have a finite lifespan (several hours up to 1 week) and regeneration of the NO production has yet to be realized. Future developments as companies and other research enter this space may provide unique solutions to these problems, making NO a viable adjunct to the anticoagulation regimen.

5.4.2. Clopidogrel

Clopidogrel is a specific inhibitor of ADP receptors on platelets that is often used as part of dual antiplatelet therapies in patients undergoing percutaneous coronary intervention (PCI) for stent placement or balloon angioplasty. It has been used in ventricular assist device patients in an effort to reduce pump thrombosis [103, 104]. Small subsets of patients receiving clopidogrel in addition to other anticoagulants while on ECMO have also been reported [105, 106]. Outcomes from patients receiving clopidogrel on mechanical circulatory support devices are similar to those receiving traditional anticoagulants alone. Transfusion requirements tend to be increased, with slightly more units of red cells and/or FFP required, but no ultimate effect on outcome has been noted.

5.4.3. Aspirin

Aspirin (acetylsalicylic acid) is an irreversible cyclooxygenase (COX) inhibitor in platelets that affects the COX-1 variant in a greater fashion than the COX-2 variant [107]. This effectively blocks the production of thromboxane from the platelet, which is a potent stimulator of surrounding platelets. Aspirin therapy has been recommended alone or as an adjunctive therapy in a variety of cardiovascular diseases, such as the prevention of primary or secondary myocardial infarctions and strokes [108–110], management of stents and mechanical valves [111–113], and the prevention of embolic phenomenon on ventricular assist devices [91, 93, 103, 114, 115]. The use of aspirin on ECMO technology has been reported in some small case series [116] and as part of the regular treatment of ECMO at La Pitie [96]. Because it is an irreversible inhibitor, there has always been concern for bleeding events post-ECMO until new platelets are produced by the body in the absence of aspirin. Interestingly, in contrast to the other anti-platelet agents mentioned here, the use of aspirin has been shown to reduce the need for transfusions [116]. In the same study, the use of aspirin was shown to dramatically reduce platelet binding to the surfaces of oxygenators through scanning electron microscopy imaging. Given the limited impairment of aspirin on the platelet systems (decreased thromboxane production to limit activation) and the apparent lack of adverse events in these small studies, and its routine use in ventricular assist devices, a multi-center trial of aspirin as adjunctive therapy in the ECMO setting may be warranted.

5.4.4. Dipyridamole

Dipyridamole is a phosphodiesterase inhibitor that prevents the breakdown of cAMP, which is a key component in the prevention of signal transduction in platelet activation [117]. Like aspirin therapy, it has been extensively used in the realms of synthetic vascular graft, stent and valve therapies [111, 118] as well as ventricular assist devices, particularly in the development of the Berlin Heart protocols [91, 104, 114, 119]. The use of dipyridamole in the setting of ECMO has been reported in single-center studies aimed at demonstrating safety [96]. Interestingly, there have also been attempts at producing dipyridamole conjugated surfaces for applications in synthetic grafts [120]. The chemistry is quite similar to what would be required for use in ECMO devices and could be readily translated.

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5.4.5. GPIIb/IIIa inhibitors

GPIIb/IIIa inhibitors are drugs specifically targeted to the GPIIb/IIIa receptor on the surface of platelets permitting their adhesion to fibrinogen. These types of drugs are commonly used in the settings of percutaneous coronary interventions (PCI), but almost never used in the setting of extracorporeal mechanical circulatory assist, particularly ECMO. There is one small case report (N=18) on the rescue of PCI patients in cardiogenic shock using VA-ECMO [105]. The authors reported successful outcomes for most of the patients (65%) with a small subset (5 patients) who received GPIIb/IIIa inhibitors. Compared to the other antiplatelet agents used, those with the GPIIb/IIIa treatment had much higher transfusion requirements than those receiving only heparin. The authors attributed this to a consumptive coagulopathy that was set up by the use of the additional agents; although no increase in mortality was seen.

5.5. Antifibrinolytics

Cannula and surgical site bleeding are common complications in ECMO patients, particularly in cardiac ECMO where the patient may have an open chest or undergone significant vascular repair. According to the ELSO registry 7–21% of patients will experience one of these complications during their ECMO run [1]. The numbers vary based on patient age and reason for ECMO. Often this bleeding can occur in the face of reasonable anticoagulation parameters or even when anticoagulants are withheld. The reasons for this can be attributed to one or a combination of issues including low platelet counts, deranged hemostasis associated with consumptive coagulopathy where the circuit may be consuming most of the patient's coagulation factors and increasing the risk for bleeding, and fibrinolysis. Patients who are at risk for increased bleeding (e.g., planned surgical procedures) while on ECMO have often been treated with an antifibrinolytic drugs (e.g., aminocaproic acid or tranexemic acid) in an effort to reduce the chances for existing clots to break down and keep surgical sites intact. Evidence from the literature in these patients suggests that the use of antifibrinolytics decreases surgical site bleeding, but does not impact intracranial hemorrhage [121, 122]. There is some concern that using antifibrinolytics may decrease circuit lifespan because as thrombus is deposited on the interior surfaces, it cannot be remodelled in a normal fashion and continues to build to the point of requiring a component change. Some studies have found the use of antifibrinolytic drugs increases the change-out rates of ECMO circuits by approximately three-fold, while others have found no relationship [123]. Administration is typically done as a loading dose (e.g., 100 mg/kg aminocaproic acid) followed by 72 hours of continuous infusion at a lower dose (e.g., 25–30 mg/kg aminocaproic acid) [121, 122]. Additional vigilance should be provided to the patient and ECMO circuit during a period of treatment to be aware of additional thrombosis and address it appropriately.

6. Coagulation testing

As a consequence of the use of systemic anticoagulants, there exists a need for laboratory testing of the blood to determine whether acceptable levels of anticoagulation have been

reached. There have been two tests specifically developed to address the needs of coagulation testing as a result of heparin, the Heparin Activity Assay and the Activated Clotting Time, while others that have been in existence for the monitoring of hereditary bleeding disorders, pro-thrombin time and activated partial thromboplastin time, have been accepted for use in these instances. Another, relatively recent class of testing, thromboelastography or thromboelastometry, has been developed to provide a more global view of hemostasis with the purpose of identifying specific points where deficiencies might exist and interventions could be possible. Each of the tests will be discussed in terms of technical advantages and disadvantages as well as application to ECMO coagulation monitoring. **Table 3** at the end of this section provides an overview of the tests discussed.

6.1. Activated clotting time (ACT)

The ACT is a point-of-care whole blood test that was developed during the early adoption of cardiopulmonary bypass because perfusionists needed a way to rapidly determine in the OR setting whether a sufficient dose of heparin had been given to ensure that bypass could be conducted safely. The stimulating agents of the ACT (Celite or kaolin, silica, calcium and phospholipid) are in high concentration and designed to elicit a strong coagulation response and induce clot formation within 800 seconds even at high heparin concentration. Thus, the ACT was developed as essentially a binary coagulation test in the face of heparin and its linearity is primarily associated with higher concentrations of heparin that are seen during cardiopulmonary bypass (350–400 IU/kg). From the mid-1970s to the mid-2000s, most ECMO centers have used the traditional ACT as their gold standard test for determining heparin administration. However, after 2000, another form of the ACT became available. The low-range ACT (ACT-LR), which was designed for use in PCI settings where lower heparin dosing was the norm (150–200 IU/kg) and where the traditional ACT was not reproducibly linear, has become frequently used by ECMO practitioners. In fact, over 90% of hospitals use the ACT (traditional or ACT-LR) as part of their routine coagulation testing on ECMO [58]. Furthermore, a number of manufacturers began to alter their test procedures to reduce the size of the machine and the amount of blood required to run the test. Some ACT machines are based on mechanical methods of larger volumes (2mL) of blood to detect clot formation in real-time, while others use very small volumes (100 μL) in an optical-mechanical system in accelerated time, and still others use electrochemical resistance changes in even smaller volumes (10 μL) in real-time to determine clot formation. Despite these differences, clinicians have traditionally clung to relatively narrow ranges (180–220 seconds) to determine heparin doses [58]; with different machines having ACTs which may not correlate with each other. This has created significant confusion in the ECMO community and spurred several practitioners to look for alternatives to this long-standing tradition of ACT-based heparin management on ECMO.

6.2. Activated partial thromboplastin time (aPTT)

The aPTT is a well-established, validated laboratory test for the monitoring of a patient's coagulation status that is used for all patients where bleeding is a concern, not just those on ECMO. It is a laboratory-based test of plasma, thus eliminating the effects of platelets and other

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cellular elements from the test process, and is performed on citrated blood which removes the cofactor calcium from the coagulation cascade during collection. This effectively arrests the clotting cascade at the levels of factor IX and X and below, preventing further progression through the common pathway until exogenous calcium is added. Similar to the ACT, the initiating agent is silica, which represents blood activation by a foreign substance, or the intrinsic pathway. However, the amounts of silica and phospholipids and the lack of other exogenous factors make the aPTT reagents a milder pro-coagulant and particularly useful for low-dose heparin monitoring. Recently, the aPTT has begun to find favor amongst clinicians for monitoring heparin therapy on ECMO because it has a better correlation to the heparin doses in adults [124–127], and is now typically measured on the modern ECMO patient [31]. The trend in lower heparin dosing and use of the aPTT have been shown to reduce patient bleeding events, and thereby decrease mortality [126]. aPTT goals for most patients are 1.5–2.5 times age-normal values., which is important for the neonatal patient who will have prolonged aPTT times due to the nature of the development of their coagulation system [64, 75].

6.3. Thromboelastography

Thromboelastography (or thrombelastometry) is a real-time image of the coagulation of whole blood in the presence of a stimulating agent (typically kaolin and calcium). Two main manufacturers have abbreviated their tests as TEG and ROTEM, respectively. The advantages of this test are that it provides several pieces of information related to different aspects of the coagulation cascade (**Figure 4**), instead of just a single endpoint of "thrombus formed" that is found in the PT/INR, ACT, and aPTT tests. Addition of the enzyme heparinase to the test

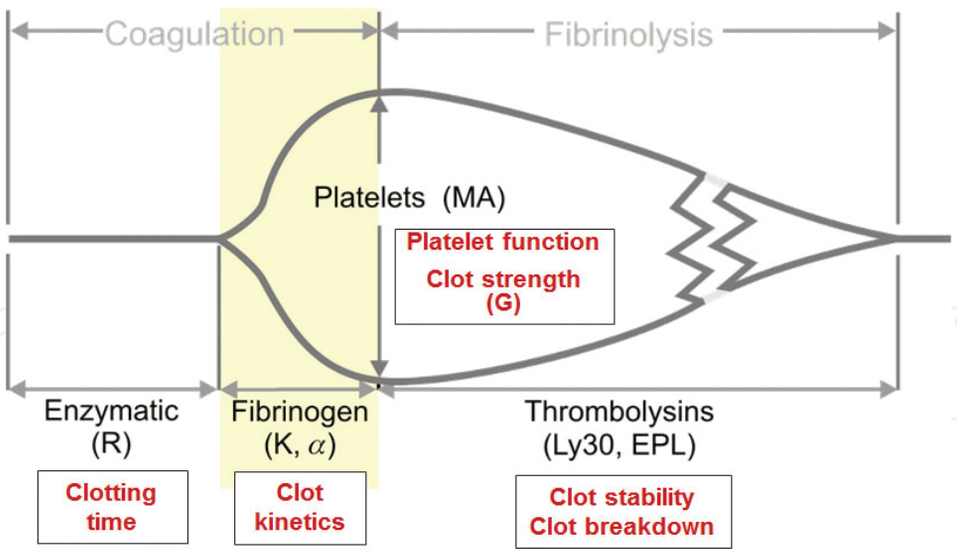

Figure 4. Overview of the TEG tracing. The initial phase of the curve (R time) represents the time from initiation to the beginning of clot formation via the enzymatic activation of coagulation factors through thrombin. The parameters K and α represent the clot kinetics as fibrinogen cross-links begin to form. The MA is the ultimate clot strength and is composed of 80% platelet concentration and function plus 20% fibrinogen concentration and function. The fibrinolysis cascade is represented by the Ly30 and EPL parameters. TEG® Hemostasis Analyzer tracing images are used by permission of Haemonetics Corporation. TEG® and Thromboelastograph® are registered trademarks of Haemonetics Corporation in the US, other countries, or both.

sample can also give a clinician a glimpse of the patients' underlying hemostasis independent of the presence of heparin anticoagulation, and reveal a coagulopathy that may be masked by the presence of being on an anticoagulant. The use of heparinase may also highlight that there is some underlying liver dysfunction in the presence of little or no heparin through the release of so-called heparanoids, which are small heparin-like molecules like chondroitin sulfate that may affect the TEG test and show an altered curve in the presence of heparinase [128–131] Thromboelastography has been used by several authors to manage anticoagulation in ECMO patients [58, 132–138]. The primary finding from these studies is that thromboelastography detects platelet dysfunction and can help guide specific factor therapy. Only one study showed that the thromboelastography results could actually predict bleeding [133]. The ultimate utility of the test is to provide additional insight into the underlying coagulation cascade, and pinpoint areas of concern when used in conjunction with the other coagulation tests [139, 140].

6.4. Prothrombin time (PT)

The prothrombin time is a laboratory test to assay the formation of a clot from the addition of tissue factor, phospholipids, and calcium to patient plasma. The key difference between the PT and the aPTT is the activating agent being tissue factor, which is believed to activate the clotting cascade through the extrinsic pathway associated with cellular or tissue injury. Although the traditional description of the clotting cascade being a waterfall cascade divided into the separate intrinsic and extrinsic pathways that converge at the common pathway is no longer technically valid, it is conceptually useful for teaching and some interpretation of coagulation tests [141]. The PT test is very sensitive to particular reagents used because the source of tissue factor and phospholipids was extraction from brain and other organs. As such, it is necessary to normalize patient results in the face of changing lot numbers or manufacturers by creating comparative assays on normal patients with no known liver dysfunction or oral anticoagulant use (e.g., warfarin). The World Health Organization (WHO) provides an international reference preparation of thromboplastin for calibration to create the international sensitivity index (ISI) for a given preparation, and this is what is currently used in most facilities [142]. For patients receiving heparin, the PT/INR is useful for determining the effects of disease on the liver-independent of lower doses of heparin. Patients who are septic typically exhibit an elevated INR due to derangement of the clotting cascade from multiple areas associated with sepsis and/or liver dysfunction [143]. Thus, the goal INR for a patient on ECMO receiving heparin therapy should be less than 1.5. For other anticoagulants, such the vitamin K antagonists (e.g., warfarin), DTIs, or the newer oral Factor Xa inhibitors, the PT/INR would be expected to be in the range of 2–3 or higher [144].

6.5. Anti-Xa assay

The anti-Xa assay is a chromogenic laboratory assay for determining the effective heparin concentration in patient plasma. It is typically conducted by combining patient plasma (containing UFH or LMWH) with an exogenous amount of factor Xa followed by a chromogenic reaction for unbound factor Xa. Thus, more the color change, the less the heparin/AT complex interacted with factor Xa, and therefore the lower the drug level. The test is highly

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sensitive to the relationship between heparin and AT; meaning that even with high levels of UFH or LMWH, an AT deficiency will have more unbound factor Xa and read as a low heparin level. Most importantly, this test does not measure thrombosis generation or the impact of heparin (UFH or LMWH) or oral Xa inhibitors on the ultimate generation of thrombin [145]. While the test is valuable in helping clinicians achieve stable heparin drug levels and eliminate inconsistency in the aPTT testing [146], patients on ECMO may have a complex underlying derangement in the balance of their clotting factors. It is important to keep in mind that the coagulation system is a series of enzymatic reactions, and having more substrate should naturally require more inhibitor to control the balance. For example, an increased presence of fibrinogen (i.e., hyperfibrinogenemia >500 mg/dL) or thrombin may tip the coagulation cascade towards pro-thrombotic requiring additional anti-Xa levels (i.e., more heparin) to modulate hemostasis. The expected range of anti-Xa levels on UFH therapy (0.3–0.8 IU/mL), however, should be accompanied by further coagulation testing to determine the actual effect. Xa levels of 0.3–0.8 IU/mL *normally* correlate with an aPTT of 90–110 seconds [147]. Because the aPTT is dependent upon the reagents used, individual ranges must be established at each institution in accordance with the College of American Pathologists' recommendations [148]. Even within the same institution, individual patients on ECMO may have variations in their underlying coagulation system or treatment that impacts the correlations between heparin levels and their coagulation tests [126].

6.6. Anti-thrombin (AT)

The AT assay can be performed in a quantitative (immunologic) or qualitative (functional) methodology, with the latter being preferred in most clinical labs because it can be done in a simple chromogenic assay similar to the methodology for anti-Xa testing. In the qualitative chromogenic assay, plasma is incubated with an excess amount of heparin in the presence of FIIa (thrombin) followed by a chromogen for unbound FIIa. The values are reported as a percentage of standard normal adult plasma (100%). Standard cut-off values for AT replacement while on heparin therapy are typically ≥ 60%. Replacement can be accomplished through the use of fresh frozen plasma, which can raise AT levels approximately 20% for every 20ml/kg given. Alternatively, there are pharmacologic interventions using either pooled human donor AT or a recombinant AT. Routine testing to drive the administration of AT on ECMO has been performed at a number of centers and is gaining popularity despite a paucity of safety and efficacy data [58].

6.7. D-dimer

The D-dimer protein is the cleaved product of the fibrinolysis process. The D-dimer test is commercially available as an immunologic test for the specific D domain on cross-linked fibrin, although available kits may not test for the exact same epitope. As such, the presence of D-dimers in the blood indicates the formation of thrombin and subsequent conversion of fibrinogen to fibrin and its polymerization to form a clot has previously occurred and is in the process of resolving. D-dimer levels are typically elevated in patients who are experiencing DIC because of sepsis, DVTs, pulmonary embolism, or other thrombotic disorders [149]. In the

setting of ECMO, D-dimer may be a useful surrogate for the presence of thrombus in the interior of the oxygenator and signal the need for circuit change due to consumptive coagulopathy [150, 151].

	ACT++	ACT-LR	aPTT	PT	TEG	Anti-Xa	AT	D-dimer
Anticoagulant to be monitored	Moderate-high heparin dose (1-6 IU/mL)	Low-moderate heparin dose (0-2.5 IU/mL)	Low heparin dose (0–1.5 IU/mL), DTIs	Vitamin K inhibitors DTIs Anti-Xa agents	Low heparin dose (0–1.5 IU/mL) DTIs Anti-platelet agents	UFH, LMWH., oral anti-Xa drugs	Substrate availability for UFH and LMWH	Fibrinolysis end products
Used in	CPB	ECMO	ECMO & VAD	ECMO & VAD	ECMO & VAD	ECMO & VAD	ECMO & VAD	ECMO & VAD
Test kit	silica, kaolin, phospholipid	Lower conc. silica, kaolin, phospholipid	Glass, kaolin, phospholipid	Tissue factor, calcium	Kaolin and Calcium; Optional heparinase and platelet agonists for platelet mapping	Excess FXa Colorimetric Assay	Chromo-genic substrate	Latex Agglutination
Blood components Tested	Whole blood	Whole Blood	Citrated plasma	Citrated Plasma	Citrated whole blood	Citrated plasma	Citrated Plasma	Citrated Plasma
End point	Clot detection	Clot Detection	Thrombus detection	Thrombus detection	Clot Detection and breakdown	Bound FXa	Available AT	Available Fibrin split products

The tests range in sensitivity to hemostatic factors from left (least sensitive) to right (most sensitive) Note that only the ACT+, ACT-LR, aPTT, PT, and TEG measure coagulation as an endpoint.

Table 3. Table of the laboratory tests used for monitoring anticoagulation, their intended targets, test details, and endpoints.

7. Conclusion

The history of anticoagulation and biocompatibility is a relatively short, but important part of the development of mechanical circulatory assist devices. The use of surface coatings and

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systemic anticoagulation is at this point in clinical care considered a necessity for the successful application of ECMO in the clinical setting. Although heparin continues to be the primary anticoagulant of choice for patients on mechanical circulatory support, particularly ECMO, the continued use of direct thrombin inhibitors may signal an end to the heparin era. The philosophy adopted by the authors here is that it is important to start with a normal underlying coagulation and inflammatory system prior to the introduction of systemic drugs designed to alter the normal set point of this complex biological system. Furthermore, patients with altered hemostatic systems may require "reset" or adjusted laboratory parameters in order to achieve hemostasis. Many clinicians have often utilized plasmapheresis or plasma exchange to accomplish this, although the use of these techniques expressly for the purpose of resetting the hemostatic system in the ECMO setting is controversial and has not been adequately studied or validated in a multi-center clinical trial. At best, it is considered to be a reasonably safe adjuvant therapy to ECMO. Furthermore, the lack of a sufficient single coagulation test to accurately assess the hemostatic status of an ECMO patient has resulted in the utilization of a host of tests with the hopes that they agree and that we have achieved a safe, stable anticoagulation profile. However, future efforts may obviate the need for a systemic anticoagulant by providing a surface or material that is truly biologically inert.

Author details

Timothy M. Maul[1,2*], M Patricia Massicotte[3] and Peter D. Wearden[1]

*Address all correspondence to: timothy.maul@nemours.org

1 Nemours Children's Hospital, Orlando, Florida, USA

2 University of Pittsburgh, Pittsburgh, Pennsylvania, USA

3 University of Alberta, Edmonton, Alberta, Virginia, USA

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