

REVIEW

ECMO and anticoagulation: a comprehensive review

M.M.G. Mulder¹, I. Fawzy², M.D. Lancé³

¹Department of Intensive Care, Maastricht University Medical Centre+, Maastricht, the Netherlands

²Department of Medical Intensive Care, Hamad Medical Corporation, Doha, Qatar

³Department of Anaesthesiology, ICU & Perioperative Medicine, Hamad Medical Corporation, Doha, Qatar

Correspondence

M.D. Lancé - mlance@hamad.qa

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Abstract

Since the last decade extracorporeal membrane oxygenation (ECMO) therapy has been widely accepted as the treatment of life-threatening cardiac and pulmonary failure. Maintaining homeostasis of the haemostatic system remains a major challenge. The choice of anticoagulants to inhibit continuous activation of coagulation by the non-endothelialised systems is still restricted. The most widely used agent is intravenous unfractionated heparin. Although one might expect monitoring of the anticoagulant level to be straightforward, the number of bleeding or thrombotic complications is still too high.

In this review, we report the impact of an extracorporeal circuit on the coagulation system and its complications. We describe the strategies for anticoagulation and possibilities of monitoring their effects. Finally, we give a view of the future developments in this specific field.

Introduction

Currently used extracorporeal circuits such as renal replacement therapy and extracorporeal membrane oxygenation (ECMO) – also called extracorporeal life support (ECLS) – belong to the standard therapy in the critically ill patient. These are prolonged forms of cardiopulmonary bypass (CPB), which derives from cardiac surgery where this method is used to maintain cardiac and respiratory function during cardiac surgery. However, there are several major differences between the techniques of which the duration of their use seems to be the most important. While CPB is commonly used for several hours, ECMO application lasts for up to several weeks.^[1] The indication for ECMO covers different situations of heart failure and pulmonary failure which have been established for adults during the last decade. Particularly the use of venovenous (VV) ECMO for respiratory support has increased since the H1N1 pandemic in 2009 and reached a peak in 2012.^[2] On the other hand, the incidence of

venoarterial (VA) ECMO for circulatory support has shown a tremendous increase since 2013. Nevertheless, mortality levels during ECMO use remain high at 58% for VV-ECMO and 66% for VA-ECMO.^[3]

As with any other artificial system, ECMO exposes the blood to a huge endothelial-free, foreign surface, which stimulates inflammation and coagulation, leading to a pro-thrombotic state. Many attempts have been made with anticoagulant medication to counteract coagulation activity, the most common practice being the use of unfractionated heparin (UFH) as a continuous infusion.

From a technical viewpoint, the development of modern hollow fibre oxygenators, biocompatible coatings for the tubing and oxygenators may decrease activation of coagulation. In addition, attempts to reduce the size of the system and thus the surface and applying high blood flow with a low chance of blood stasis are important developments.^[4]

Nevertheless, the underlying disease also influences the haemostatic capacity. Due to this continuous activation, the coagulation eventually leads to exhaustion of platelets and coagulation factors, which could turn haemostasis into a bleeding tendency. This phenomenon is known from sepsis as slow disseminated intravascular coagulation (DIC).^[5] On the other hand, it is known that inflammatory processes such as sepsis or autoimmune diseases, but also pregnancy and trauma, shift the haemostatic system to a hypercoagulable state which could result in thrombosis.

The aim of the current paper is to give an overview of the changes in the coagulation system, the current practice of anticoagulation, and its monitoring possibilities in the adult ECMO population. Finally, we review the haemostatic complications, such as thrombosis and bleeding, and future perspectives in this field.

Changes in the coagulation system

Shortly after blood comes into contact with the artificial surface of the CPB circuit, blood proteins, mainly albumin and fibrinogen, will stick to it. Over time, thrombospondin, fibronectin, von Willebrand factor (vWF) and even immunoglobulin E bind to the surface material.^[6] This protein layer serves as an anchor for platelets. Furthermore, platelets interact with vWF, which is activated by the high shear stress and aberrant flow pattern. Activated platelets bind via the GPIIb/IIIa receptors to the fibrinogen deposit. These activated platelets initiate coagulation by exposing tissue factor and coupling to factor VIIa (FVIIa). This is the initiation of coagulation as we understand it today, leading to activation of FX and finally resulting in a thrombin burst and conversion of fibrinogen to soluble fibrin, which will be transferred to an insoluble fibrin network by FXIIIa. Besides the coagulation system, the fibrinolytic system will be triggered to keep clot formation localised. This is reflected by the increasing D-dimer levels, which slowly rise over time.

During a short-term two-hour contact with the CPB circuit nearly all the coagulation factors show reduced levels, except for FIX, which remains stable. Interestingly FVIII and vWF increase 24 hours after weaning from the circuit.^[7,8]

On the other hand, the contact activation system consisting of FXII, FXI, high-molecular-weight kallikrein (HMWK) and prekallikrein (PK), are activated by the foreign surface. FXII attaches to this surface and is converted to FXIIa, which cleaves PK to release kallikrein. In turn, kallikrein splits bradykinin from HMWK. This system will activate coagulation by the intrinsic coagulation cascade, the immune response by the complement system and an inflammatory reaction by the kallikrein system, which also activates the fibrinolytic system.^[9] This crosstalk of coagulation and inflammation could cause vascular leakage and vasoplegic syndrome, which clinically can be seen as hypotension not responding to vasoactive drugs.

Next to the pro-thrombotic state due to platelet and contact activation, the pro-inflammatory response, as described above, induces leukocyte, neutrophil, and monocyte involvement within the first 30 minutes after initiation, peaks within hours and then tapers down. The cells attach to the surface of the circuit and release their cytokines, including TNF-alpha and interleukin 6. The endothelial cells are again triggered to stimulate tissue factor (TF) generation and consequently contribute to thrombin formation via the FVII mediated extrinsic pathway.^[1]

Inevitably, some of the erythrocytes undergo haemolysis by extracorporeal circulation, resulting in free haemoglobin. In turn, free haemoglobin enhances the platelet-vWF interaction and promotes coagulation.^[10]

Continuous activation of the coagulation system during ECMO therapy leads to consumption of coagulation factors and platelets. Indeed, many authors report a sustained drop in the platelet count of between 25-40% without signs of heparin-

induced thrombocytopenia.^[11] Nonetheless, the low platelet count is not related to the duration of ECMO treatment but more to the pre-existing disease and platelet count before cannulation.^[12] Of note, the platelet count does not necessarily correspond with platelet function.

Several papers have described deteriorated platelet function, due to ADP-receptor dysfunction in patients who were on CPB. Nevertheless, normal platelet function will be restored after discontinuation of the support.

During ECMO application, platelets lose some of their receptors such as glycoprotein Ib (GPIb) and glycoprotein VI (GPVI), which are responsible for interaction with vWF (GPIb) and collagen (GPVI). While GPIb together with the reduced amount of large molecule vWF explain the acquired vWF syndrome, the reduction of collagen receptor activity contributes to the bleeding tendency in general. However, the relevance of acquired vWF syndrome which is mainly related to long-term use such as assist device implantation, is unclear. The association of acquired vWF syndrome with bleeding seems more clear in assist devices, which have different flow characteristics. Kalbhenn and co-workers showed in their cohort of 49 patients that 88% developed FXIII deficiency during the first seven days of VV-ECMO, while 80% developed vWF deficiency. Thrombocytopenia could be seen in only 55% and hypofibrinogenaemia in 40% of their patients.^[13] This is in agreement with Tauber and co-workers, who showed a loss of the high-molecular-weight vWF within the first 24 hours after ECMO initiation, which was accompanied by a drop in FVIII naturally protected from clearance by vWF. However, both factors increased to normal after cessation of the ECMO treatment independently of the indication, the route (VV-VA) or the kind of system used.^[14]

Independent of the decrease in these pro-haemostatic factors, the natural anticoagulant antithrombin (AT) decreases in the first days in about 50% of the cases, but it then returns to normal in the following period.^[11,15] The initial decrease might be explained by the infusion of UFH which binds to AT as a co-factor to inhibit coagulation. On the other hand, AT deficiency is associated with heparin resistance and a pro-thrombotic state, which might cause thrombotic complications in the first days of ECMO therapy.

The levels of other natural anticoagulants, including protein C and protein S, are less well described during ECMO treatment. Currently, one can only reason from studies during CPB where the level of activated protein C increases during and after bypass. The early onset of this reaction has been related to improved haemodynamic stability. There are no reports on levels of protein S, the co-factor of protein C, during or after CPB or EMCO.

Interestingly, one contributor of the endothelial layer to anticoagulation - the glycocalyx - is disturbed by CPB. Koning et al. reported a decrease in the glycocalyx density after initiation of

CPB which sustained until the postoperative period. In contrast, patients undergoing cardiac surgery without CPB treatment (known as off-pump procedures) did not show signs of altered glycocalyx.^[16] In ECMO therapy, a decrease in the glycocalyx density might contribute to the heparin-like effect which is described in patients on ECMO, even though these patients were not on heparin infusion. In more than half of the cases, the laboratory parameters show signs of heparinisation in terms of prolonged activated partial thromboplastin time (aPTT) and R-time in the thromboelastography (TEG). However, this report deals with post cardiac surgery patients in whom remaining heparin effects cannot be excluded completely.^[17]

Incidence of haemostatic complications

The most common complications associated with ECMO are bleeding and thrombosis. Haemorrhage can be associated with an intervention (catheter placement) or with a previous operation. Thrombosis occurs mainly in VA-ECMO after cardiac surgery, due to a huge wound and long operation time combined with massive disturbance of the haemostatic system. On the other hand, exhaustion of the coagulation system and a continuous low level of fibrinolysis can lead to coagulopathic haemorrhage, which is present in 20-33% of the ECMO runs.^[18] One contributor to this problem is chronic loss of small amounts of blood which needs replenishment with red blood cells (RBCs). However, this blood loss will be associated with a loss of coagulation factors and platelets. As a result, coagulation tests will show prolonged aPTT and ACT leading to the findings being misinterpreted as a heparin overdose, inducing a reduction of UFH which could end up in acute clotting of the system. Only direct testing of coagulation factor levels or viscoelastic testing is able to distinguish depletion of coagulation factors from heparin effect.

Substantial bleeding occurs in more than 30% of the patients on ECMO. Nevertheless, the majority of the cases are non-life threatening (e.g. epistaxis or gastrointestinal bleeding). Of these bleeding events, 5-19% are reported to be life-threatening intracranial haemorrhages.^[13] Transfusion of blood products is needed in about 56% according to a recent study.^[19]

Several authors have identified factors associated with bleeding. The most important factors are surgery prior to ECMO treatment, higher APACHE III score and coagulation abnormalities, while blood group 0 could also be associated with intensified bleeding.^[19,20] RBC transfusion is frequently needed. The threshold to administer RBCs is suggested to be between 8 and 10 g/dl, but RBC trigger studies have not been performed in ECMO patients.^[18]

Likewise, thrombosis can be found in the ECMO system, but also during and more frequently after weaning from the device, presenting as deep vein thrombosis (DVT). Already in 2006, Rastan and co-workers suggested in an autopsy study that the true incidence of thromboembolic complications

might be highly underestimated and contribute to morbidity and mortality.^[21] It seems that the incidence of thrombosis is inversely related to the level of anticoagulation with the highest incidence in patients without anticoagulation.^[22] Acute thrombosis of the oxygenator or tubing occurs in 35% of the cases, and must be followed by changing the system.^[23] In contrast, a DVT will frequently be undiagnosed, even during continuous heparin infusion with an adequate aPTT target. In a study by Cooper and co-workers, the authors describe a nearly 20% incidence of DVT after decannulation of which only one patient showed symptoms.^[24] In other retrospective analysis on 63 patients the incidence of venous thrombosis was 46%, while a small case series on 10 patients reported an incidence of upper extremity DVT of 80%.^[25,26]

Anticoagulation practice

To prevent thrombosis in the patient and in particular in the ECMO system, but also to minimise bleeding risks, adequate anticoagulation strategies are indispensable (*table 1*). Up to the present day, UFH remains the main anticoagulant used for

Table 1. Anticoagulants used in ECMO

Drug	Advantages	Disadvantages
Unfractionated heparin	Well known Mechanism known Easy to antagonise (protamine) Easy to monitor (aPTT/ACT)	Non-linear, variable effect Possible HIT induction
Low-molecular-weight heparin	Easy to administer Lower risk of HIT induction	Accumulation in renal impairment Can only be partially antagonised Not easy to monitor (aXa levels)
Direct thrombin inhibitors	Independent of AT levels Good dose response No HIT induction	No antagonist Lesser coagulation inhibition in areas of stasis
- Bivalirudin	Mainly renal clearance	Ceiling effect in aPTT
- Argatroban	Mainly hepatic clearance	Could interfere with INR measurement
Antiplatelet drugs	Inhibit coagulation at starting point Might reduce platelet consumption	No sufficient anti-coagulation No sufficient evidence

ACT = activated clotting time; aPTT = activated partial thromboplastin time; AT = antithrombin; HIT = heparin-induced thrombocytopenia; INR = international normalised ratio; VET = viscoelastic test.

ECMO because of its rapid onset and the easy neutralisation with protamine. This was recently confirmed in a large survey where 96% of the responding centres reported UFH as their anticoagulant of choice.^[18] Nevertheless, UFH administration around ECMO entails some caveats. Besides its unpredictable clinical effect, the use of UFH could cause what is known as

heparin-induced thrombocytopenia (HIT) a life and limb threatening situation occurring in 5% of the patients in which an immediate stop of UFH infusion and switch to alternative anticoagulation strategies is required (e.g. direct thrombin inhibitors [DTIs]). However, the true incidence of HIT seems to be overestimated. In a publication by Glick et al. concerning a cohort of 119 patients undergoing ECMO treatment, the authors reported a clinical suspicion of 19%, with laboratory testing confirming HIT in only one patient.^[27]

Regarding the predictability of heparin effects, the negative charged long chains of the high-molecular-weight heparins are also found in UFH. Those chains bind easily to proteins and cellular structures, which explains the unpredictable inter-individual clinical effects reflected in the aPTT. As indicated above, heparin is not a uniform agent but more a mixture of glycosaminoglycans of different sizes and molecule masses. The primary anticoagulant function is based on heparin's 1000-fold amplifying effect on the protein antithrombin (AT), due to the formation of a heparin-AT complex, which is a direct inhibitor of factor IIa (thrombin) and factor Xa. Further, factor Xa, IXa, and XIIa are inhibited in the same AT-dependent manner but at a much lower level. Immediately after AT is connected to one of the coagulation factors, heparin is dissociated from the complex and available for new AT enhancement. However, the mechanism of action depends on the size of the heparin molecules. The larger they are (such as in UFH), the stronger the interaction with FIIa and FXa. In contrast, the low-molecular-weight heparins (LMWH) bind more effectively to FXa.^[28] Although uncommon, there are publications on the use of LMWH to prevent clotting of the ECMO system.^[29]

Because of the described AT drop in the first few days after ECMO initiation, many attempts have been made to monitor and replace AT. However, none of the investigations showed benefit of AT replacement in terms of better haemostasis control. The only advantage might be a lower amount of heparin administration.^[30] Moreover, 'heparin resistance', which might be the target of AT therapy, is not completely attributable to low AT levels, but also depends on high platelet counts, previous heparin use, age above 65 and low haemoglobin levels.^[31]

A minority of ECMO centres use parenteral direct thrombin inhibitors (DTI) instead of UFH as their first choice. Mainly argatroban and bivalirudin are used upon indication (e.g. HIT). The main advantage of DTIs is that they bind directly and reversibly to thrombin, independent of AT levels, and they do not induce antibodies against platelets. In contrast to heparin's antagonist protamine, there is no antidote available for argatroban and bivalirudin. The effects of both agents are mainly controlled by their short half-lives of 40 minutes and 30 minutes, respectively. While the synthetic arginine derivate argatroban is cleared by the liver, the clearance of the hirudin analogue bivalirudin relies on renal function. This is clinically relevant, because in case of impaired hepatic or kidney function,

the half-life times will be prolonged resulting in overwhelming anticoagulation and bleeding. In a small retrospective study, Ranucci and co-workers showed that a bivalirudin-based protocol could be safely applied with lesser bleeding and a lower incidence of bleeding complications.^[32]

Similarly Sanfilippo et al. showed in a recent meta-analysis in 58 patients that bivalirudin could be safely used. However, these authors mentioned that the dosing protocols and monitoring regimens are highly diverse between the cases.^[33]

From a theoretical point of view, platelet inhibition might be useful and it could help in reducing activation of the coagulation, because platelets are the main initiators of coagulation. This could block the consumption of coagulation factors and platelets while enhancing the level of anticoagulation. However, only some smaller studies and case reports are described using this approach with various drugs.^[30]

The same holds true for alternative agents including citrate, nafamostat mesilate and FXII inhibitors, which are applied in experimental settings. Citrate anticoagulation is used during renal replacement therapy (RRT), as well as in cases of ECMO combined with RRT as an additional local anticoagulant. There are no studies describing citrate use for ECMO as a sole substance. A quite unknown synthetic serine proteinase inhibitor, nafamostat mesilate, was thought to inhibit coagulation, fibrinolysis and platelet activation with lower bleeding complications. In a published retrospective study comparing nafamostat with heparin, the authors failed to demonstrate this. In contrast, this drug was correlated with more bleeding and no significant difference on the incidence of thrombosis.^[34]

Finally, there are institutions which prefer not to use specific therapeutic anticoagulation, but prescribe a low-dose prophylactic LMWH without monitoring or adjusting because of the ECMO use.^[35] However, this is mainly the practice in cases of increased bleeding risk, e.g. after major surgery. Keeping in mind that insufficient anticoagulation is associated with higher thrombosis and intra-device clotting risk, a no-anticoagulation strategy cannot be advised as general practice in ECMO.^[36]

Monitoring coagulation during ECMO

Interestingly, most of the literature about ECMO covers a wide range of monitoring opportunities to guide and prevent inadequate dosing of the anticoagulants (*table 2*).

Traditionally, the effect of UFH on coagulation is assessed by aPTT which reflects the classical interpretation of the intrinsic pathway starting with FXII. A prolongation could be due to an acquired or inherited factor deficiency in this chain (FXII, FXI, FVIII, FIX, FX, FII and FI) but in some cases could also be due to other reasons, such as lupus anticoagulant or, of course, a drug effect. After its introduction by Rapaport and co-workers in 1961 it came clear that the assay reflects the intrinsic pathway

Table 2. Monitoring coagulation

	Advantages	Disadvantages
Standard coagulation tests		
aPTT (sec)	Well known Monitoring UFH Easy to interpret	Inter-laboratory variance (could be excluded by using ratio) Time consuming
ACT (sec)	Bedside method Easy to use Immediate results	Relatively insensitive to low doses of UFH Different devices with different reference ranges
Anti Xa assay (IU/ml)	Sensitive to UFH	Time consuming Needs calibration Free haemoglobin & bilirubin could be underestimated
VETs (ROTEM/TEG)	Inhibit coagulation at starting point Might reduce platelet consumption	Poor specificity and sensitivity regarding therapy adjustment
Fibrinogen mg/l	Consumption marker	Increased in inflammatory situations Time consuming
D-dimer (mg/l)	Prognostic value for oxygenator failure	Time consuming Expensive
AT (%)	Heparin resistance (partial) Pro-coagulatory marker	Heparin resistance not completely relying on AT
Haemoglobin (g/dl)	Easy and fast	Not very relevant for coagulation
Platelet count 10 ⁹ /l	Easy and fast	No proven threshold Platelet count does not reflect platelet function

ACT = activated clotting time; aPTT = activated partial thromboplastin time; AT = antithrombin; ROTEM = rotational thromboelastometry; UFH = unfractionated heparin; TEG = thromboelastography; VET = viscoelastic test.

of coagulation.^[37] Principally this test seems ideal to monitor heparin therapy and in fact it is the current gold standard. However, several disadvantages for this aPTT assay are described. The most important factor seems to be the variability between different laboratories, which is due to the different commercially available reagents, and the use of different devices across the institutions. Also, some diseases interfere with the measurement, e.g. antiphospholipid antibodies (lupus antibodies) prolong the aPTT in most commercial assays while the patient shows a thrombophilic profile. Moreover, in patients with FXII deficiency, the aPTT will be prolonged without a change in haemostatic competence.

A way to exclude some uncertainties is to calculate the aPTT ratio, which is the measured value divided by the local reference value, which will not detect the effect of antiphospholipid antibodies. However, patient response to UFH is not easily predictable because of its binding to plasma proteins. On the other hand, in this test the sample needs spinning to produce plasma which is time consuming and renders it unfit for monitoring during cardiac surgery to guide CPB.

In this setting, the activated clotting time (ACT) is the

established 'bedside' whole blood test. Comparable to the aPTT, the ACT relies on contact activation. Depending on the device there are different activators available (kaolin, celite, glass beads or ellagic acid). Equally to the aPTT, the values may differ, implying similar assay problems as with the aPTT. Likewise, the ACT is also sometimes reported as a ratio (measured value/reference value). In contrast to the aPTT, the ACT is quite insensitive to low UFH dosages which are frequently used in ECMO settings.

Regarding accuracy, the anti-Xa assay seems to be the most reliable. This assay measures the inhibition of activated FX (FXa), the common pathway of the coagulation cascade. However, it is also time consuming and needs separate calibration for each type of heparin (UFH and each of the LMWHs). Similar to the aPTT, the anti-Xa assay underestimates the presence of UFH in case of free haemoglobin or bilirubin in the plasma.^[38]

Because of their ability to reflect all aspects of haemostasis, viscoelastic tests (VETs) such as thromboelastography (TEG) or thromboelastometry (ROTEM) could be more informative than standard tests. Use of VETs is currently recommended in the Extracorporeal Life Support Organisation (ELSO) guidelines.^[39] Basically, these tests are based on activators of the classical coagulation cascades (extrinsic-tissue factor/intrinsic-kaolin, ellagic acid), but they also to some degree reflect platelet function as well as the breakdown of the clots, termed fibrinolysis. By adding inhibitors of heparin (heparinase) one can also confirm the effect of that drug by comparing one sample with and one without heparinase.

Although each assay has advantages and disadvantages, there is no consensus in the literature as to which of them is preferable in monitoring coagulation during ECMO therapy. Equipoise is reflected in the ELSO guideline, in which no uniform recommendation is given.^[39] Most of the studies compare two tests in small, inhomogeneous cohorts. Activated PTT does not correlate well with ACT nor with anti-FXa. The same holds true the other way round. The explanation for this might be the variability between patients, thrombocytopenia and anaemia. The latter could influence the whole blood test more than the plasma tests, because they are independent of a cellular contribution. Even though viscoelastic tests might be a more accurate reflection of the in vivo conditions than other laboratory tests, the predictive value of the R-time, as the most cited parameter of the VETs, is low, with poor sensitivity and specificity for aPTT.^[40] Therefore, many authors recommend a combination of these tests to increase the chance of being in the heparin target range. In recent studies about 11% of the ECMO centres utilised the anti-FXa to guide their heparin regimens and about 42% used the aPTT or the ACT while about 9% used the TEG or a combination of tests.^[18,40,41]

About 90-95% of the ECMO centres routinely monitor AT levels, targeting a value above 70%. When AT is below this target, AT substitution will be initiated. Although the heparin

dose can be reduced following AT, there is no correlation with reduction in complications (bleeding or thrombosis).

Assessment of platelet function during ECMO by modern point of care devices such as impedance aggregometry seems interesting. However, results depend on the platelet count, which hampers usefulness, as more than 50% of all ECMO patients show thrombocytopenia.^[42]

Due to the consumption of coagulation factors, the fibrinogen level frequently decreases during ECMO therapy, requiring daily monitoring. For the same reason a whole blood count and particularly a platelet count is of interest, since both low haemoglobin but also low platelet count are associated with higher rates of coagulation abnormalities leading to sustained bleeding.

The assessment of D-dimers, as a marker for ongoing thrombosis and thrombolysis, could be of use in determining the urgency of changing the oxygenator. In a small study on 13 patients, the authors noticed a rise of D-dimers as a precursor of oxygenator failure. In another study, the same group suggested to monitor this parameter if there was suspicion of oxygenator malfunction. Nevertheless, an exchange of the oxygenator seems indicated if the oxygen transfer is impeded.^[43,44]

While single coagulation tests do not correlate well with the clinical phenotype, a combination of different tests spread over the treatment period might improve treatment. This was shown in a recent meta-analysis where the prevalence of complications was lowest if an aPTT or strategy guided by combined test results was applied while the highest rate of complications was seen if there was no monitoring.^[22]

In this light, many authors propose to combine, for example, the ACT with TEG/ROTEM. On the other hand, performing an assessment of AT and D-dimers on a regular basis to estimate the risk of thrombosis is also recommended, such as Ranucci and co-workers who combined ACT with TEG to improve the positive predictive value from 50% and lower for each single value to more than 70% in terms of being in target range for heparin.^[40]

Similar to other medical challenges, a systematic approach with an evidence-based algorithm seems advisable during ECMO runs also checking other organ systems, such as renal and liver function.

Clinical approach

Before starting anticoagulation one should be familiar with the ECMO system. It is important to note whether the system is fully or partially coated. Next step is to create a system with a tubing long enough for practical purposes but short enough to reduce the contact surface. Both factors determine the prothrombotic activity of the system. Obviously, also the expected speed of the pump plays a major role. If the blood flow exceeds 2-2.5 l/min, the chance of thrombosis will decrease. On the other hand, one should consider technical modifications, such as building a

shunt into the system, to enable a high flow.

In the next step the patient's comorbidities and current bleeding status should be considered; for example after major surgery or trauma the treatment could be started without anticoagulation and initiated after 24 hours. This is common practice after cardiac surgery if heparin during the operation is not antagonised. On the other hand, the patient's medication is important. If this already includes an anticoagulant or an antiplatelet drug, the start with intravenous anticoagulants should be carefully monitored and increased stepwise.

While this seems obvious, the underlying disease could also interfere with the haemostatic system. In some pro-thrombotic situations such as sepsis, autoimmune diseases or after child birth, the frequency of monitoring should be increased in the beginning of the ECMO run to adjust the dosage of anticoagulants. In cases with an increased bleeding tendency or potential bleeding in vital organs such as the brain, or during cerebrovascular accident or DIC it is wise to withhold anticoagulation until the risk is controlled.

In most centres, the choice of agent is straightforward and will be UFH, because of the long experience and ease of use. It is difficult to determine the target of anticoagulation. Most centres target a certain aPTT/ACT level and adjust it according to the bleeding risk. This might be feasible, because thrombotic events could be more disastrous than bleeding situations.

In the beginning, monitoring of the anticoagulation should be done frequently, but intensity could be reduced after reaching a stable situation (*table 3*). For example, monitoring of the aPTT in the starting period should be done every 2-4 hours until the target is reached and stable. In addition, daily assessment of INR, fibrinogen, AT and whole blood count should be done according to a protocol. If available, viscoelastic tests could be added to reflect the fibrinolysis (*table 3*).

Future perspectives

There are many possible future improvements in coagulation strategies for ECMO therapy which could reduce haemolysis and activation of the coagulation and immune system. From a technical viewpoint, minimising the circuit causes less surface

Table 3. Suggested monitoring in UFH-treated patients (stable conditions)

Once daily	Twice daily	Thrice daily
Fibrinogen	Haemoglobin	aPTT combined with:
MA-TEG/MCF-ROTEM	Platelet count	ACT or
Lysis index		R-time TEG/CT-ROTEM
D-dimer		
AT%		

ACT = activated clotting time; aPTT = activated partial thromboplastin time; AT = antithrombin; MA-TEG = maximum amplitude thromboelastography; MCF-ROTEM: maximal clot firmness rotational thromboelastometry, R-time TEG: time to start amplification of clotting in thromboelastography, CT-ROTEM: clotting time in rotational thromboelastometry.

blood contact and consequently decreased activation of the intrinsic coagulation cascade. The use of inner tube heparin coatings is already generally accepted, while attempts to use novel inhibitors of the FXII pathway could stabilise the contact activation system even more. Further improvement of inner circuit surface characteristics could stabilise flow patterns, which results in both less turbulence and less shear stress. This could possibly contribute to less platelet activation, less blood cell damage, and therefore decreased incidence of coagulation abnormalities. In terms of controlling the inflammatory aspects, studies should give more insights into the pathological mechanisms. This should be followed by tailored inhibition of the responsible mediators.

For practical purposes, it is important to clearly define the targets of the anticoagulation therapy (e.g. aPTT, ACT) associated with reduction of bleeding and thrombosis, after which a standardised strategy including choice of drug and methods for monitoring and dosing regimen to achieve this goal should be applied.

Conclusion

In the past 10 years, ECMO was established as a life-saving therapy in critically ill adult patients. Contact with the non-endothelialised surface of the extracorporeal circuit activates both the coagulation and the immune system, which could lead to overwhelming clotting in the system but also in the patient. Therefore, therapeutic anticoagulation is widely accepted. While the most frequent anticoagulant for this purpose remains UFH, the optimal test for monitoring is still a matter of debate. The main problem seems to be the target of monitoring, which can be aimed at clinical endpoints or at laboratory values. Currently, a combination of both targets seems best which results in setting the laboratory target and adjusting it according to the bleeding risk. However, defining standards for daily practice is urgently needed.

Meanwhile new technical developments could improve the circuits and their biocompatibility. Finally, studies should elucidate the interaction of coagulation and inflammation to use the ECMO techniques with minimal impact on critically ill patients.

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