Review Article

# Point-of-Care Thromboelastography, Rotational Thromboelastometry during Extracorporeal Membrane Oxygenation


## Abstract

Extracorporeal membrane oxygenation (ECMO) has been used increasingly for both respiratory and cardiac failure in adult patients. The patients requiring ECMO are at increased risk of developing significant coagulopathy. The exposure of a patient's blood to the artificial surface of the ECMO circuit results in the activation of the coagulation-fibrinolysis system and an inflammatory response. During ECMO, anticoagulation is required to prevent thrombotic complications, and unfractionated heparin (UFH) remains the predominant anticoagulation agent used to minimize the potentially life-threatening complications related to bleeding events or thromboembolic complications. Most centers adjust UFH by activated clotting time (ACT) of 140–180 sec or partial thromboplastin time (PTT) of 40–80 s. In this article, we will review thromboelastometry use during ECMO in ICU.


**Keywords:** *Anticoagulation, extracorporeal membrane oxygenation, point-of-care anticoagulation*


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## Introduction

Extracorporeal membrane oxygenation (ECMO) has been used increasingly for both respiratory and cardiac failure in adult patients.[1] The patients requiring ECMO are at increased risk of developing significant coagulopathy. The exposure of a patient's blood to the artificial surface of the ECMO circuit results in the activation of the coagulation-fibrinolysis system and an inflammatory response.[2] Coagulation and inflammation are also closely linked through networks of both humoral and cellular components, which might lead to disseminated intravascular coagulation.[3] During ECMO, anticoagulation is required to prevent thrombotic complications, and unfractionated heparin (UFH) remains the predominant anticoagulation agent used to minimize the potentially life-threatening complications related to bleeding events or thromboembolic complications. Most centers adjust UFH by activated clotting time (ACT) of 140–180 sec or partial thromboplastin time (PTT) of 40–80 s.[4]

Of course, the ACT is more commonly used because it is a bedside diagnostic test. PTT needs to be done in the laboratory. Moreover, the selection and schedule of diagnostic tests, including platelet count, antithrombin, ACT, activated partial thromboplastin time (aPTT), anti-factor Xa (anti-Xa), prothrombin time, and international normalized ratio must be carefully considered. Maintaining an appropriate balance between preventing thrombosis and the risk of bleeding is challenging because standard diagnostic tests are only partially functional measures of hemostasis. Although coagulation tests are routinely used to guide anticoagulation, they do not always accurately predict the risk for thrombosis or bleeding.

Patients on ECMO exhibit a range of hemostatic changes, including consumption of coagulation factors, thrombocytopenia, altered von Willebrand factor multimers, platelet dysfunction,[5] and reductions in anti-thrombin levels.[6]

Significant bleeding events occur in more than 30% of patients on ECMO, and better anticoagulation control may improve patient outcomes.[7] Thrombotic complications occur in up to 8%–17% of patients on ECMO.[8] Both bleeding and thrombotic complications are associated with increased mortality.[9-11]

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## The Activated Clotting Time

The ACT is a whole blood test used to measure the anticoagulant effect of heparin; the ACT will be done bed site and give us immediate results and adjustment of the UFH. An ACT range of 180–200 s has been recommended for ECMO. However, the result is not always reliable because of multiple factors which can prolong the ACT independent of the UFH dose, including hemodilution, platelet function and number, hypothermia, hypofibrinogenemia, and coagulation factor deficiencies.[12]

## The Activated Partial Thromboplastin Time

The aPTT test is a plasma-based assay of clot formation used to monitor UFH. The therapeutic ranges for ECMO are 60–80 s in the setting of a standard bleeding risk versus targets of 40–60 s in patients at an increased bleeding risk.

The aPTT is a laboratory test and will not be done on-site, and in some diseases, the result needs to be more accurate. Furthermore, in some instances, the target level is not achieved, or if the level exceeds the 80 s, it is a risk of bleeding or thrombosis.[12] Previous studies found little or no correlation between ACT and heparin dose, a moderate correlation between aPTT and heparin amount, and a weak correlation between ACT and aPTT. ACT might be an unreliable tool to monitor UFH during extracorporeal life support (ECLS) in adults.[12]

### Viscoelastic tests

Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are viscoelastic tests of hemostasis in whole blood that has been used to monitor anticoagulation with ECMO.[13] TEG can be done with or without an agent that inactivates heparin, so the anticoagulant effect of heparin can be separated from other factors. TEG can be done at the bedside on fresh blood or in the laboratory in calcium-free blood (adding calcium to the activator).[14]

TEG®/ROTEM parameters inform time to initial fibrin formation, cross-linking of fibrin, clot firmness, platelet function, and fibrinolysis. Paired TEG®/ROTEM samples with and without adding heparinase allow for the underlying assessment of hemostasis in the presence of UFH. As a result, UFH responsiveness can be evaluated with TEG®/ROTEM by examining the difference in R or clotting time between tests with and without heparinase, which may be beneficial when there is a concern for heparin resistance.[15]

In a series of 27 pediatric ECLS patients, TEG® measurements were performed alongside ACT and aPTT.[16] In 171 paired results, aPTT correlated with all TEG® parameters (R time, K time, and α angle), but given that they both measure time to initial fibrin formation, the strongest correlation was between aPTT and TEG® R time ($r = 0.31$).

In contrast, ACT correlated weakly with all TEG® parameters. Similar results have been published comparing ROTEM with conventional coagulation tests.[17]

Regarding patients supported on ECMO, multiple studies have evaluated the safety and feasibility of a TEG-driven strategy to titrate heparin versus the "conventional" approach based on aPTT monitoring, with a trend toward improvement in adverse outcomes. For example, a recent multicenter, randomized, controlled trial was performed involving adult patients with acute respiratory failure treated with venovenous ECMO who were randomized to manage heparin anticoagulation using either a TEG-based protocol (target 16–24 min of the R parameter, TEG group) or a standard of care aPTT-based protocol (target 1.5–2 of aPTT ratio, aPTT group). While underpowered to detect statistically significant differences between the groups ($n = 42$), patients in the aPTT group tended to bleed more compared to the TEG group (15 vs. 10, $P = 0.21$). In addition, heparin dosing was lower in the TEG group compared to the aPTT group (12 IU/kg/h vs. 16 IU/kg/h, respectively, $P = 0.03$), with no increase in thrombotic complications. While a larger trial is needed, the results indicate that a TEG-driven protocol is safe and feasible in adult patients requiring venovenous (VV) ECMO.[18] In a recent pediatric study, a retrospective chart review of patients requiring VV and venoarterial ECMO was performed within a single-center, tertiary-care children's hospital. The study evaluated optimal values for citrated kaolin TEG R time and anti-Xa activity that would minimize both bleeding and thrombotic complications in pediatric and neonatal patients. The study concluded that an anti-Xa activity greater than 0.25 IU/mL (sensitivity 81%, specificity 67%, positive predictive value [PPV] 81%, and negative predictive value [NPV] 58%) and a TEG R time greater than 17.85 min (sensitivity 84%, specificity 68%, PPV 82%, and NPV 59%) might minimize the risk of thrombosis in pediatric and neonatal ECMO patients. An optimal target to reduce the risk of bleeding events could not be identified in this study.[19]

To date, there is a belief that optimal anticoagulation, including the indications for antithrombin supplementation, relies on a comprehensive and standardized evaluation of multiple measures of hemostasis, including aPTT, ant-Xa, TEG®, Activated Thrombine (AT) activity, platelet count, and fibrinogen concentration. Anticoagulation should be titrated based on the overall hemostatic state of the patient, as evidenced by laboratory evaluation. It should be put in context with the clinical hemostatic condition of the patient and their unique risk of bleeding or thrombotic complications.

### Interpretation of the thromboelastography test

*R-time (reaction) (5–10 min)*

- Time of latency from the start of the test to initial fibrin formation (amplitude of 2 mm)
- Initiation phase
- Dependent on clotting factors.

If prolonged R (clotting factors/anticoagulation).

Treatment: Fresh frozen plasma and reverse anticoagulation.

*K-kinetics (1–3 min)*

- Time is taken to achieve a certain level of clot strength (amplitude of 20 mm)
- Amplification phase
- Dependent on fibrinogen.

If K increased, give Cryo.

*Angle (slope of the line between R and K) (50°–70°)*

- Measures the speed at which fibrin build-up and cross-linking take place, hence assesses the rate of clot formation
- "Thrombin burst"/propagation phase
- Dependent on fibrinogen.

If decrease the angle give, Cryo.

*Maximal amplitude*

- Represents the ultimate strength of the fibrin clot, i.e., the overall stability of the clot
- Dependent on platelets (80%) and fibrin (20%) interacting via GPIIb/IIIa

If maximal amplitude (MA) decreases, give platelets and Desmopressin.

*A30 or LY30 = Amplitude at 30 min*

- Percentage decrease in amplitude at 30 min post-MA [Figure 1]
- Fibrinolysis phase.

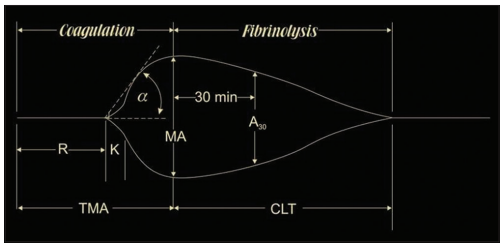


**Figure 1: Normal result TEG test shows all different phases. TMA: Time to maximum amplitude, CLT: Clot lysis time, R: Time reaction, K: Kinetics, MA: Maximal amplitude, A30, or LY30: Amplitude at 30 min**

## Conclusion

TEG is one of the diagnostic tests to measure the effect of the UFH, providing more information than the ACT. No available data in the literature necessitate a deviation from current practice and the recommendation of multiple laboratory tests, including but not limited to anti-Xa, TEG/ROTEM, PTT, and AT levels.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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Case Report

# Extracorporeal Membrane Oxygenation in Diffuse Alveolar Hemorrhage: A Case Report and Review of Anticoagulation Strategies

**Abstract**

Anticoagulation in extracorporeal membrane oxygenation (ECMO) can be one of the obstacles in starting and managing patients with refractory hypoxemia, especially with diffuse alveolar hemorrhage (DAH). In this case report, we describe our experience with a 21-year-old male patient who presented with DAH and refractory hypoxemia secondary to systemic lupus erythematosus and was anticoagulated safely during ECMO to maintain circuit integrity, as a bridge to immunosuppressive therapy until he was decannulated successfully. Thromboelastography played a major role in our case management to guide our anticoagulation intensity.

**Keywords:** *Anticoagulation, diffuse alveolar hemorrhage, extracorporeal membrane oxygenation*

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## Introduction

Anticoagulation in extracorporeal membrane oxygenation (ECMO) can be one of the obstacles in starting and managing patients with refractory hypoxemia, especially with diffuse alveolar hemorrhage (DAH). In this case report, we describe our experience with a 21-year-old male patient who presented with DAH and refractory hypoxemia secondary to systemic lupus erythematosus and was anticoagulated safely during ECMO maintain circuit integrity as a bridge to immunosuppressive therapy until he was decannulated successfully Thromboelastography played a major role in our case management to guide our anticoagulation intensity.

## Case Report

A 21-year-old male patient, known to have systematic lupus erythematous and lupus nephritis, was diagnosed at the age of 16 in 2016 based on a renal biopsy that previously received induction with mycophenolate mofetil and achieved remission, after which the patient had interrupted follow-up and in compliance with medications, to present on September 11, 2022, to the nephrology day clinic complaining of generalized overload features consistent with lupus nephritis and generalized anasarca. The patient was admitted to the hospital under the care of nephrology, receiving diuretics and colloids in addition to the Euro-Lupus Cyclophosphamide Protocol by rheumatology. The patient spent the following nine days in the hospital for completion of rheumatological management, for which he was on room air with a clear chest X-ray. His stay so far was remarkable only for high blood pressure, for which nifedipine 30 mg was started.

The patient's condition deteriorates nine days post-hospital admission. He developed massive hemoptysis and low oxygen saturation of 80% on a 15L nonrebreather oxygen mask, blood pressure of 180/100, and heart rate of 150 beats/min. The intensive care team was involved, and the patient was intubated with a bloody airway. Postintubation chest X-ray revealed new bilateral opacification. Despite frequent suctioning of persistent bloody secretions, the saturation was barely maintained at 80% with the partial pressure of oxygen of 62 mmHg on continuous bagging. Every attempt to attach the patient to a mechanical ventilator resulted in a severe reduction of oxygen saturation, mandating further bagging, suctioning, and frequent administration of muscle paralysis [Figure 1].

After a few hours of observation without improvement and with a refractory hypoxemia state, the decision was



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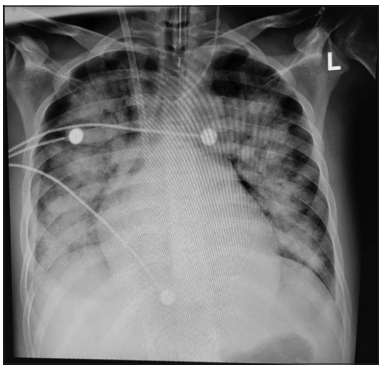


**Figure 1: Chest X-ray**

made to initiate rescue veno-venous extracorporeal membrane oxygenation (ECMO). After full disclosure and obtaining consent, the patient's critical condition made the transportation attempt quite hazardous, necessitating the cannulation to be performed at the site of the general medical floor. Cannulation of the left femoral vein with a 23 Fr access cannula and a suitable internal jugular vein 17 Fr return cannula was done successfully, during which the patient received 5000 units of intravenous heparin.

ECMO was initially set with a flow of 4 L/min, $FiO_2$ of 1.0, and sweep gas at 4 L/min. The patient was kept on PEEP of 10, FiO2 of 0.5, and respiratory rate of 10 with 98% SpO2 improvement post initiation of ECMO. Heparin infusion was started targeting activated clotting time (ACT) of 180–200 s. Post cannulation and initiation of ECMO, return cannula site continuous oozing was observed, ACT result of 160 s. Thromboelastography (TEG) was performed due to the questionable validity of the ACT result, which revealed an elevated R time. Accordingly, the heparin infusion was adjusted, and further titration of anticoagulation was made according to TEG results performed on a 12-h basis. No further hemorrhagic complications were observed, and TEG monitoring to guide anticoagulation continued until the successful liberation of ECMO.

Post stabilization of the patient, sequential bronchoalveolar lavage came positive. The patient developed massive hemoptysis with a new drop of hemoglobin from 80 g/l to 69 g/l, and new bilateral infiltrates in the chest X-ray diffuse alveolar hemorrhage (DAH) causing acute respiratory distress syndrome was made. The patient received immunotherapy as a pulse steroid, rituximab, followed by plasma exchange therapy and broad-spectrum antimicrobial agents initiated for the risk of infection.

The patient's course showed a rapid and remarkable recovery. He was successfully weaned from ECMO after four days, extubated on day 6, and discharged home after 2 weeks. Currently, the patient is following up with rheumatology daycare for completion of the Euro-Lupus Cyclophosphamide Protocol.

## Discussion

Anticoagulation in patients with ECMO is essential to maintain circuit and oxygenator integrity. However, anticoagulation decisions might be challenging in cases of DAH due to the risk of worsening alveolar hemorrhage.[1] DAH is a life-threatening condition that may lead to advanced respiratory failure and may require intubation, mechanical ventilation, and even ECMO support to maintain life and buy time to treat the inciting event, mainly autoimmune diseases like systemic lupus erythematosus.[2,3] Mostly, evidence regarding anticoagulation strategy in ECMO with respiratory failure due to DAH comes from small retrospective studies and case reports suggesting low-intensity anticoagulation (lower than usual target); for example, Abrams *et al.* described four cases with DAH requiring ECMO; in all cases, anticoagulation was instituted with continuous heparin infusion without major complications with a target-activated partial thromboplastin time of 40–60 s (mean, 47.4 ± 11.6 s), and all patients survived to decannulation. However, in one case, anticoagulation was held after the initial bolus due to worsening hemoptysis, and after 36 h, the oxygenator was replaced due to thrombosis, followed by resumption of heparin infusion.[4]

Another case report published by Rawal *et al*. described using heparin infusion in a patient with DAH associated with granulomatosis with polyangiitis using target ACT (140–160). The patient had no bleeding complications during ECMO support with low-intensity anticoagulation.[5] As described in our case presentation, our patient had some oozing from cannulas with near-normal activated partial thromboplastin. TEG was done and provided insight to adjust the heparin infusion and manage our patient. The role of TEG was also mentioned in the literature, especially in cases where bleeding and thrombosis might co-exist and may guide the anticoagulation intensity in ECMO if a hypercoagulable state like COVID-19 is present.[6]

## Conclusion

We describe a strategy of low-intensity anticoagulation in patients with DAH being supported with ECMO with careful monitoring of coagulation profile, ACT, and viscoelastic tests like TEG to have a better view and guide anticoagulation strategy. Further studies are needed to support these results

### Consent

The patient verbally consented according to our research ethical committee protocol.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understand that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

There are no conflicts of interest.

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