

10 ECMO ANTICOAGULATION GUIDELINES

10.1 Introduction

Unfractionated heparin is used as a systemic anticoagulant in ECMO. The activated clotting time (ACT) has been the standard point of care test in our unit to titrate and dose infusions of heparin during ECMO. The anticoagulant effect of heparin is dependent on an adequate antithrombin level.

Anticoagulation strategies vary according to patient diagnosis and status of clotting versus bleeding (e.g. disseminated intravascular coagulation, post-cardiotomy with significant bleeding) and circuit considerations. The principle aim is to achieve sufficient anticoagulation in order to minimize circuit interventions associated with clotting and at the same time minimize the risk for bleeding in the patient.

10.2 Initiating ECMO

Prior to cannulation, recommended baseline blood investigations should include: FBC, PT/PTT, Fibrinogen level and ACT where possible.

Heparin is given at various time points during the initiation process:

- Circuit prime: 1 unit of heparin per ml of circuit prime
- Cannulation dose: **50 units/kg heparin bolus is the recommended dose during cannulation.** Lower or higher doses (25-100 units/kg) may be required depending on the clinical situation. Read-back the intended dose to the surgeon before giving the heparin bolus, and ALWAYS use units/kg in communicating the heparin dose.

Repeat ACT 5-10 min after heparin bolus. Consider repeating heparin bolus (25-50u/kg) if the ACT < 250 sec in discussion with cannulating surgeon.

Following cannulation (i.e. flow established), repeat ACT hourly until ACT < 250s and start heparin infusion (see below), guided by the patient's clinical status (e.g. bleeding risk). The presence of clinically significant bleeding may necessitate starting the heparin infusion at a more conservative dose. ACT targets should be discussed with the cannulating surgeon at initiation and whenever there are significant clinical/ circuit concerns.

- In all patients: start heparin infusion at 10 units/kg/hour
(Note: neonates and infants < 6 months of age, may require higher starting infusion rates)

10.3 During ECMO run

Heparin is given as a continuous infusion during the ECMO run, and the rate is titrated accordingly to the goals and guidelines of heparin infusion during ECMO. This is to be reviewed on a daily basis.

10.3.1 Goals and Guidelines of heparin infusion during ECMO

- Perform ACT Q1-2 hourly for the 1st 24 hours of ECMO run, or more frequently if indicated.
- Maintain ACT 180-220s (suggested range for VA ECMO) with heparin infusion rate 10-40 units/kg/h. Lower ACTs may be targeted in VV ECMO (160-180) or in situations where there is clinically significant bleeding.

- If ACT is below 20% of desired range, a bolus of 10-25 units/kg of heparin may be necessary in the absence of significant bleeding/ bleeding risk (see section on “Titration of heparin infusion”)
- In stable patients on ECMO > 24 hours post initiation, ACT monitoring frequency may be decreased to 2-4 hourly as guided by their clinical status and transfusion requirements.
- Inform ICU consultant if ACT < 140 or > 260.

10.3.2 ECMO Coagulation Tests

ECMO Coagulation Tests are used in conjunction with the ACT to monitor anticoagulation.

Coagulation Test	Therapeutic goals
aPTT	60-80s
Fibrinogen	>1.5 g/L

These tests are ordered in the ECMO Daily Management Orders (see Section 11.2.1).

The following additional tests may be obtained in conjunction with a review by the Haematology team, if heparin requirement is ≤ 10 or ≥ 40 units/kg/hr. See also Table 1 for additional lab tests commonly utilized in ECMO.

- Anti-Xa levels to measure heparin effect may be done if clinically indicated (target 0.3-0.7). **Please order as Anti-Xa (UFH) and NOT Anti-Xa (LMWH)**
- Where Antithrombin III deficiency is suspected, Antithrombin III levels may be requested (turnaround time > 3 days) and replacement with FFP 20ml/kg may be considered
- Platelet aggregation studies
- Von Willebrand panel: Factor VIII activity, von Willebrand antigen, Ristocetin-cofactor

10.3.3 Blood product support

Haematological indices are monitored as patients are at risk of bleeding, have frequent blood sampling and often receive blood products to maintain haemoglobin and other haematological targets on ECMO.

Sample targets while on ECMO are stated below:

- Haemoglobin > 10-12g/dL
- Platelets > 80, 000 (recognizing that platelet function may be impaired on ECMO)
- Fibrinogen > 1.5 g/L
- INR < 1.5. Consider optimizing nutritional sources with the physicians or Vitamin K supplementation in young infants or patients with liver dysfunction

10.3.4 Titration of Heparin Infusion

The heparin infusion is titrated to the ACT level, keeping in the range of 180-220 seconds, unless otherwise stated.

If the ACT is <180s:

- if ACT is 160-180: increase heparin infusion by 10%
- if ACT is 140-160: increase heparin infusion by 20%

- if ACT < 140: consider heparin bolus 10-25units/kg & increase heparin infusion by 20%. Inform ICU consultant.

If the ACT is >220s:

- if ACT 220-240: decrease heparin by 10%
- if ACT 240-260: decrease heparin by 20%
- if ACT > 260: inform ICU consultant

In the case of bleeding or thrombosis, the ACT goals may be different.

Antithrombin III deficiency may cause a degree of heparin resistance, requiring higher doses of heparin or the supplementation of antithrombin with antithrombin concentrate or FFP in order to maintain ACT targets. If heparin infusion exceeds 30 units/kg/h in children (> 10kg) or 40 units/kg/h in neonates (< 10kg), consider antithrombin deficiency. In such cases, consider FFP infusion 20mL/kg to replenish antithrombin stores.

Factors other than Heparin dose that may modify the ACT include the following:

- Administration of platelets have a profound effect on the ACT and decrease the ACT abruptly. Prior to platelet administration, an ACT should be drawn and heparin infusion may need to be increased by 10-20% before platelets are administered, depending on the ACT level.
- Administration of Fresh Frozen Plasma (FFP) & Cryoprecipitate may also have a transient effect on the ACT and can increase or decrease the ACT.
- Patients with impaired liver function and/or abnormal INRs may have changes in their ACTs unrelated to the doses of heparin.
- Changes in temperature targeted therapy or in diuretic therapy may also affect the steady state of the ACT.

10.4 Bleeding

10.4.1 Definition

- Thoracotomy or haemothorax: drainage > 4 mL/kg/hour for 4 hours
- GI, oral, or nasal bleeding w/ ↓ Hb despite intervention
- Catheter or cannula site bleeding w/ ↓ Hb despite intervention
- New or worsening cranial bleed

Major:

- Hb drop of 2 g/dL over 24 hrs
- >20ml/kg blood loss over 24 hrs
- Retroperitoneal, pulmonary or CNS bleed
- Any bleeding requiring surgical intervention

Minor:

- 10-20ml/kg of bleeding over 24 hrs
- ≤ 10ml/kg PRBC transfusion per day

In situations where there is excessive bleeding, particularly in post-cardiotomy patients, holding the heparin infusion temporarily may be warranted after discussion with ICU consultant and cannulating surgeon. The circuit must be closely monitored for development of thrombotic complications.

Targeting lower ACTs while there is clinically significant bleeding may be necessary till the bleeding is well controlled.

In these situations, consider:

- Accepting lower ACT targets (160-180s or lower if clinically indicated)
- Keep Hb > 12g/dL, Platelets $\geq 120 \times 10^9/L$, Normal INR, Fibrinogen > 1.5g/L
- Consider activation of the massive transfusion protocol if > 20mL/kg of PRBC or > 40mL/kg of fluid bolus has been transfused and primary cause of instability is from uncontrolled bleeding
- Frequent re-evaluation and frequency of lab monitoring (Q4-8hourly) and return to routine laboratory monitoring when bleeding subsides
- Consider performing ROTEM (see section on “Thromboelastometry”) if bleeding does not subside after 4 hours of intervention.

In addition, the agents discussed below may be considered on a case by case basis.

10.4.2 Anti-fibrinolytic Agents

Tranexamic acid

Loading dose: 10mg/kg IV over 1 hour, followed by 10mg/kg/dose Q8H

Infusion dose: 1-10 mg/kg/hr IV infusion

10.4.3 Other Haemostatic Adjuncts:

Activated Factor VII

Activated Factor VII may be considered for patients with severe refractory haemorrhage only after the optimization of coagulation factors, fibrinogen and platelets. The cannulating surgeon must be informed prior and preparations made to manage acute circuit thrombosis, including the preparation of a standby circuit may need to be discussed.

Dose: 30-90mcg/kg IV

Prothrombin Complex Concentrate

4-factor prothrombin complex concentrate (Octaplex) contains Factors II, VII, IX and X. It can be considered for use when there is bleeding associated with liver dysfunction or a high INR. There is a risk of acute circuit thrombosis similar to when activated Factor VII is used, and the 2 agents should preferably not be used together.

Dose: Depends on the INR prior to infusion.

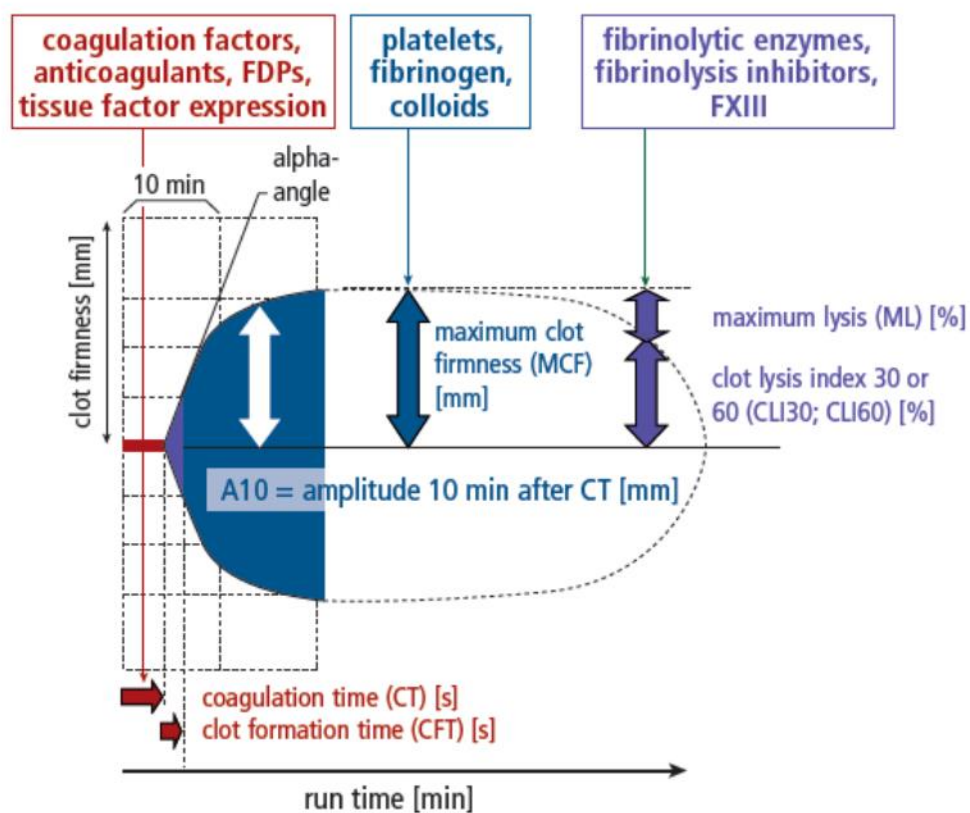
Patient weight	Pre-treatment INR < 3	Pre-treatment INR > 3
<10 kg	10 ml	20 ml
10-25 kg	20 ml	30 ml
25-50kg	30 ml	40 ml
Each ml = 25 IU, e.g. 40mL=1000 IU/FIX)		

10.4.4 Thromboelastometry

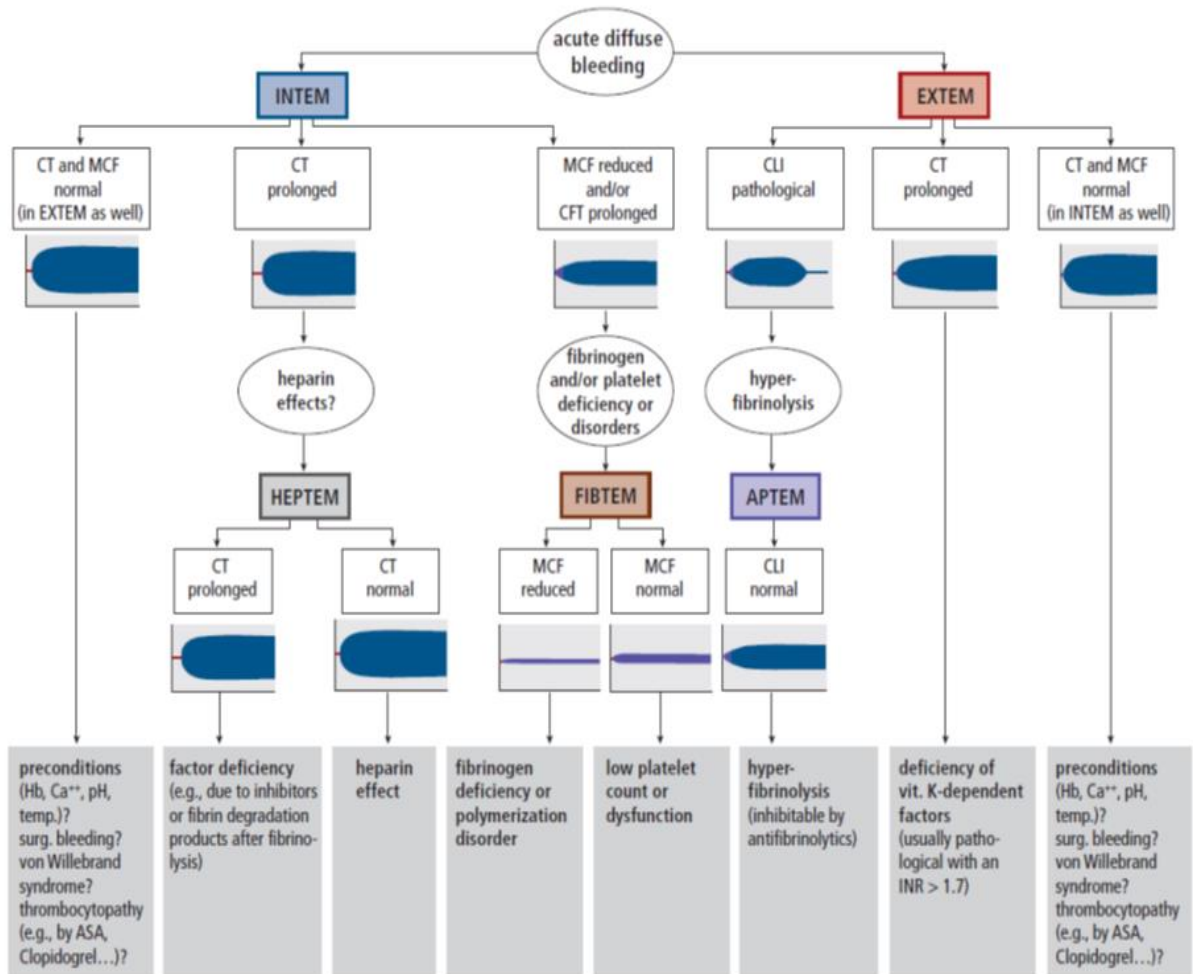
In the event that bleeding is not well controlled, ROTEM (Rotational Thromboelastometry) may be used to guide therapy. This is a whole blood POCT of the viscoelastic properties of clot formation that measures the integrity of the coagulation cascade from the time of fibrin formation to fibrinolysis and importantly includes the contribution of platelets. ROTEM provides information relating to multiple phases of coagulation in whole blood, which is extremely relevant to ECLS patients since there may be more than one reason for coagulation abnormalities.

Contact the anaesthetist on call to arrange for this blood test to be done in OT.

ROTEM Tracing, Parameters and Influences



ROTEM Diagnostic Algorithm



Reference: Essener Runde algorithm Hämostaseologie 2013; 33: 51–61

Reference ranges:

ROTEM® parameter	InTEM CT (s)	InTEM CFT (s)	InTEM ALP (°)	InTEM A10 (mm)	InTEM MCF (mm)	ExTEM CT (s)	ExTEM CFT (s)	ExTEM ALP (°)	ExTEM A10 (mm)	ExTEM MCF (mm)	ExTEM CLI60 (%)
Median	184	63	77	55	61	55	95	72	53	60	No data
Reference ranges in adults ⁵	137–246	40–100	71–82	44–68	52–72	42–74	46–148	63–81	43–65	49–71	
0–3 months (n=51)											
Median	184	44	81	62	66	48	57	78	60	62	87
Reference range	105–285	27–88	74–85	50–72	54–73	38–65	30–105	69–84	51–72	54–74	71–94
4–12 months (n=55)											
Median	172	60	78	59	63	53	72	76	57	60	86
Reference range	76–239	37–100	73–83	47–70	52–73	37–77	44–146	68–82	46–68	46–71	71–95
13–24 months (n=54)											
Median	161	61	78	59	64	55	75	75	56	60	88
Reference range	99–207	42–112	70–82	45–67	50–72	37–73	46–139	64–81	41–68	46–72	77–94
2–5 yr (n=70)											
Median	170	60	78	59	63	56	72	75	58	61	86
Reference range	99–239	40–94	72–82	49–68	53–73	46–97	41–109	69–82	49–68	52–70	74–93
6–10 yr (n=79)											
Median	168	64	77	57	62	57	77	74	56	60	87
Reference range	97–212	48–93	72–80	49–66	53–69	43–74	49–114	67–80	49–65	53–68	70–97
11–16 yr (n=50)											
Median	171	68	77	56	62	59	81	74	57	62	88
Reference range	128–206	45–106	70–81	48–67	54–71	44–91	53–115	67–80	49–67	53–72	76–94

Reference: *British Journal of Anaesthesia*, Sep 2010, Page 1 of 9

Table 1: Laboratory tests utilized in ECMO

	Laboratory Test	
1.	Activated clotting time (ACT)	<ul style="list-style-type: none"> - time in seconds in which whole blood clots in response to a fibrin activating reagent - influenced by factors other than heparin, such as thrombocytopenia, hypofibrinogenemia etc.
2.	Activated partial thromboplastin time (aPTT)	<ul style="list-style-type: none"> - assesses intrinsic and final common pathways of coagulation - influenced by coagulation factors, heparin, and antithrombin levels - performs less reliably in neonatal and pediatric patients compared to adults
3.	Anti-factor Xa assay	<ul style="list-style-type: none"> - measures the anticoagulation activity of UFH - more specific and less dependent on levels of coagulation factors besides common pathway factors
4.	Thromboelastometry (ROTEM)	<ul style="list-style-type: none"> - whole blood point of care test of the viscoelastic properties of clot formation that measures integrity of the coagulation cascade from fibrin formation to fibrinolysis; importantly includes the contribution of platelets - can be done with and without an agent that inactivates heparin, so the anticoagulant effect of heparin can be separated from other factors
5.	Antithrombin (AT) III assay	<ul style="list-style-type: none"> - acquired AT deficiency may contribute to heparin resistance (in infants and children with escalating UNFH requirements, or clinically sub-therapeutic anticoagulation) - target levels ranging from >50% to >100% - treated by giving fresh frozen plasma, cryoprecipitate, or recombinant AT3 concentrates

ECLS Anticoagulation and Blood product administration protocol

Standard protocol

Cannulation - Heparin loading dose - 50units/kg

Post-Cannulation – Commence Heparin infusion at 10units/kg/hr when ACT < 250 sec

Ongoing management- Heparin infusion 10-40 units/kg/hr

Target levels

ACT 180-220 sec (Hourly)

Platelets $\geq 80 \times 10^9/L$

Hb ≥ 10 g/dL

Fibrinogen > 1.5g/L

INR < 1.5

DAILY Lab Monitoring

Heparin dosing

If Heparin is ≥ 40 units/kg/hr,
Consider antithrombin deficiency
Give FFP 20mls/kg

Recheck ACT

ACT > 220

Decrease heparin as follows:

ACT 220-240:
decrease heparin by **10%**

ACT 240-260:
decrease heparin by **20%**

ACT > 260: inform ICU consultant

ACT < 180

Increase heparin as follows:

ACT 160-180: increase heparin infusion by **10%**

ACT 140-160: increase heparin by **20%**

ACT < 140: **consider heparin bolus 10-25 units/kg**, increase heparin by 20% & inform ICU consultant

ACT 180-220

Continue Current heparin infusion dose.

Daily clinical management should continue to be documented by the ICU Consultant on the ECMO order sheet.

Any variations to the above Protocol should be discussed with the ECMO CICU/NICU Consultant

ECLS Anticoagulation and Blood product administration protocol

Bleeding protocol

Target levels

ACT 160-180 sec (Hourly)
Platelets $\geq 120 \times 10^9/L$ Fibrinogen $> 1.5 \text{ g/L}$
Hb $\geq 12 \text{ g/dL}$ INR normal

If Patient is bleeding $\geq 4\text{mls/kg/hr}$ for ≥ 4 hours.

1. Consider decreasing heparin infusion
2. Maintain Plt, Hb, fibrinogen levels as above. Check aPTT
3. Notify ICU Consultant and Cardiac Surgery Fellow/Consultant.

Blood Products

PRBC –10-15ml/kg before rechecking Hb)

Platelet - 10ml/kg/ $4U/m^2$ of paediatric apheresed platelets (APP)

FFP give 10-20mls/kg

Cryoprecipitate give 5mls/kg

Review HOURLY

Has bleeding reduced?

Yes

Continue to monitor ACTs hourly and assess blood loss.

If remains minimal then increase Heparin infusion as necessary to maintain ACT range set.

No

Bleeding continues – unchanged.

Repeat FBC, fibrinogen and PT/PTT, ensure target levels are met.
Perform **ROTEM** to determine specific deficiency (consider consulting Paediatric Anaesthesia re interpretation)

Liaise with ICU consultant and Cardiac Surgery Consultant to discuss

- surgical re-exploration
- temporarily ceasing heparin
- tranexamic acid or other adjuncts

Review HOURLY

Has bleeding reduced?