



**ICT 2023**

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Congress on Thrombosis

# Anticoagulation and Bleeding in ECMO

*Ana Rita Rodrigues*  
*MD EDIC*



## Declaration of Conflict Of Interest

- I have no potential conflict of interest to report**

# Introduction

- ECMO
- Anticoagulation and monitoring
- Complications
- Bleeding and management

# ECMO

- Extracorporeal membrane oxygenation:
  - VV or VA
  - Cardiocirculatory and lung support
  - Lifesaving intervention
  - Complex procedure  Potential risks and associated life-threatening adverse events





# Anticoagulation

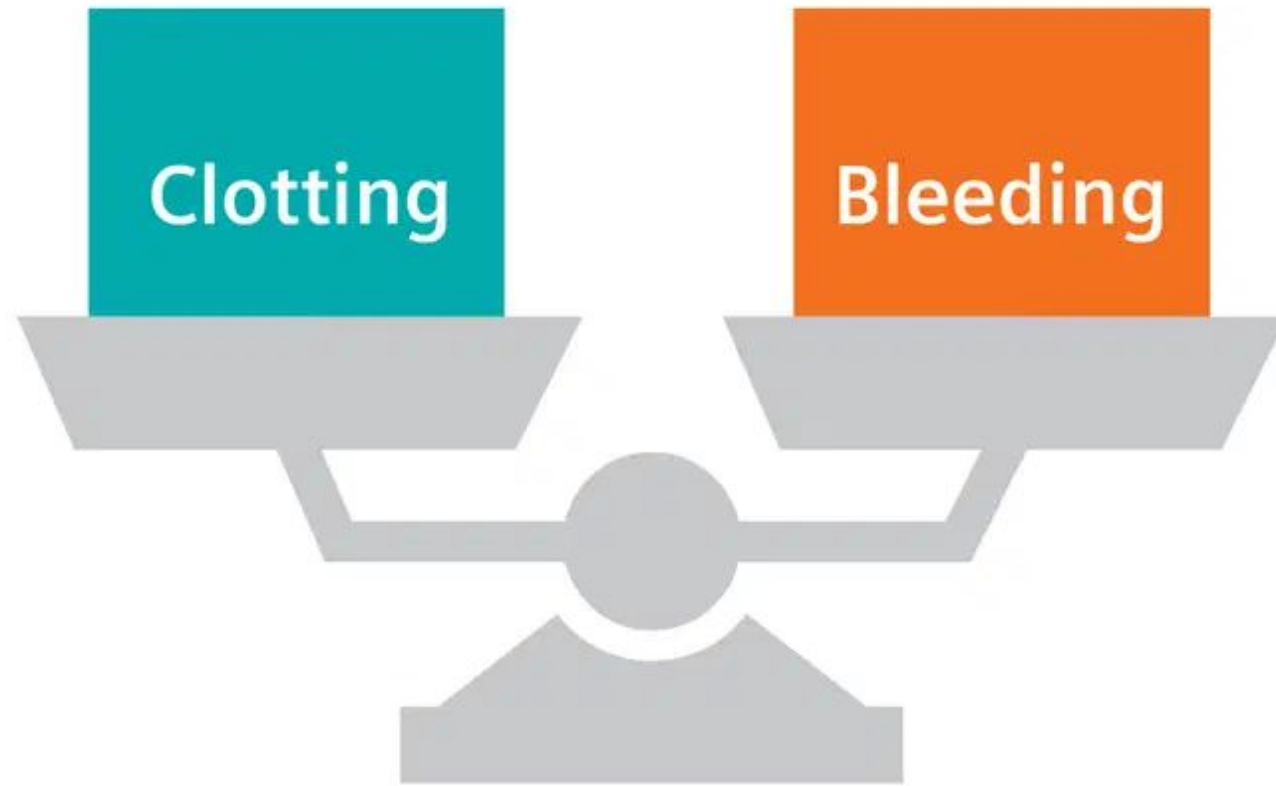
Anticoagulation is needed to prevent circuit thrombosis

Critical condition  
Patient/Circuit interaction  
Inflammatory response



Hemostasis disrupture  
Complex process

January 2022  Guidelines ELSO 2021



# Anticoagulation

## Importance of Anticoagulation in ECMO:

- Prevention of circuit clotting
- Maintaining circuit patency
- Enhancing gas exchange

## Risks and Challenges:

- Bleeding complications
- Heparin-induced thrombocytopenia (HIT)
- Individual patient variability

# Choosing anticoagulants...

## Unfractionated Heparin (UFH):

- Binds antithrombin (AT)
- □ inhibits thrombin (IIa) and Xa
- Half-life 60-90 min
- Advantages:
  - Low cost
  - Antidote (prothamine)
- Disadvantages
  - Binds other proteins, endothelial cells and macrophages (pharmacokinetics, distribution volume)
- Heparin induced thrombocytopenia

## Direct thrombin inhibitors (Bivalirudin):

- Binds thrombin
- Half-life 25 min
- Advantages:
  - No need for antithrombin
  - Short half-life □ fast washout
- Disadvantages
  - No antidote
  - Kidney and liver failure
  - Blood stasis

# Monitoring

- **Tailor made strategy**

Patient individual characteristics  
Inflammation  
Organ dysfunction  
Platelet function  
Haemorrhagic/ thrombotic risk

Optimized anticoagulation strategy

Plasmatic + viscoelastic tests  measure clot/platelet function

# APTT – Activated Partial Thromboplastin Clotting Time

- Plasmatic coagulometric test
- Measures time since factor XII activation until formation of fibrin
- *Standard* test to evaluate UFH anticoagulation
- Widely available
- Also used for DTI
- Target: aPTT > 1.5 - 2.5 x normal (no RCTs in ECMO...)

# APTT – Activated Partial Thromboplastin Clotting Time

- Sample is compared to “normal” controls with linear correlation
- In critical patient often baseline aPTT is  $\neq$  from normal  limits usage
  - Interference with acute phase reagentes, FVIII, Fibrinogen ->> often  $\uparrow\uparrow$  masking anticoagulation effect and shortening aPTT
  - Inhibitors such as lupic anticoagulant  $\uparrow$  aPTT
- High variability with several measurements and dose adjustments

# ACT – Activated Clotting Time

- *Point-of-care*  *bedside*
- Whole blood test:
  - Measures time (seconds) that takes to form the fibrin clot (after adding coagulation factors)
- Does not measure only the anticoagulant effect... but all haemostasis
- Does not measure clot strength/firmness
- Fast results

# ACT – Activated Clotting Time

- Multiple interfering factors □ Platelets (number/function), fibrinogen, factor deficiency, temperature, hemodilution...
- Approved to monitor UFH (cardiac surgery/bypass) ... Poor correlation with ECMO coagulation targets and other monitoring methods
- Primary method to monitor UFH in ECMO
- Not approved for DTI □ can be useful to monitor trends after achieving anticoagulation target

# Anti-Xa Activity

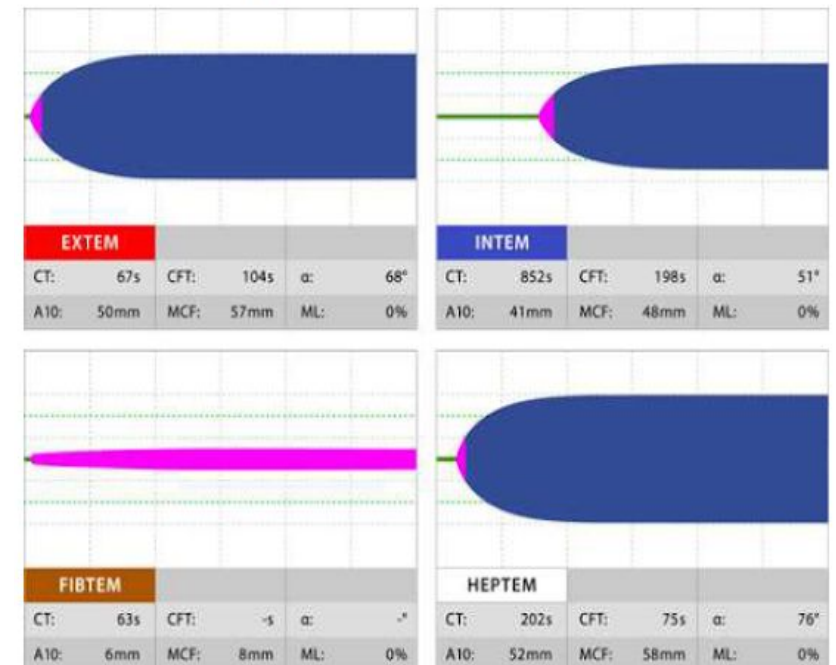
- Plasmatic chromogenic test
- Measures UFH effect by AT catalysis and Fxa inhibition
- Only useful for Xa inhibitors  no use in DTIs
  
- Only measures chemical reaction of UFH-AT
  - Measures heparinization
  
  - No use for platelet function

# VET – Viscoelastic tests (ROTEM, TEG, Quantra)

Point-of-care  Precision medicine - rapid, goal-directed therapy

- Use whole blood sample to measure clot formation and lysis
  - Qualitative test
- Comparing to classical plasma tests:
  - Global analysis of haemostasis
  - Clot formation (CT-clotting time)
  - Clot firmness (clot strength)
  - Amplitude (fibrinogen, platelet function)
  - Stability (fibrinolysis)

## Heparin Effect



## Diluted Thrombin Time (dTT)?

- Plasma test  based on thrombin time
- More sensitive for DTIs than APTT
- Nomogram to correlate dTT to bivalirudin
- Not routinely used, not widely available
- Future?

# Monitoring and targets

**Table 3. Suggested Anticoagulation Monitoring Laboratory Schedule\***

Laboratory Test	Frequency
ACT	Q1h-Q2h
aPTT	Q6h-Q12h
Anti-factor Xa assay	Q6h-Q12h
Platelets	Q6h-Q12h
INR	Q12h-Q24h
Fibrinogen	Q12h-Q24h
CBC	Q12h-Q24h
Antithrombin level	Daily-PRN
Plasma free hemoglobin	Daily
Thromboelastography/ thromboelastometry	Daily-PRN for bleeding or thrombotic complications

**ACT**  
180-200 sec

**APTT**  
1.5 – 2x control  
40-60 sec

**Anti- Xa**  
0.3-0.7IU/mL

A decorative graphic at the top of the slide features a large, light red oval on the left side. From this oval, a trail of smaller, semi-transparent red blood cells extends across the top of the page towards the right. The cells are rendered in various orientations and sizes, creating a sense of movement and depth. The overall color palette is a soft, muted red.

# Complications

# Complic

	Criteria	Points
Thrombocytopenia	Count drop >50% Nadir $\geq 20 \times 10^9/L$	2
	Count drop 30 - 50% Nadir $10 - 19 \times 10^9/L$	1
	Count drop < 30 % Nadir < $10 \times 10^9/L$	0
Timing of the decrease in platelet count	5 to 10 days*	2
	> 10 days or possible start in 5-10 days	1
	<4 days	0
Thrombosis manifestations	Acute thrombosis Cutaneous necrosis Systemic reaction	2
	Recurring thrombosis Other skin lesions Suspicion of thrombosis, no confirmation	1
	Asymptomatic	0
	Other causes of thrombocytopenia	
	Apparently none (absence)	2
	Possible	1
	Confirmed	0

platelet drop

P  
HIT  
Evaluate haemor  
Start alternative  
ELISA (IgG anti-PP

**\*If previous heparin exposure consider:**  
 - 2 points if thrombocytopenia  $\leq 1$  day, exposure less than 30 days ago  
 - 1 point if thrombocytopenia  $\leq 1$  day, exposure 30 to 100 days

# Complications with anticoagulation – Heparin Resistance

- Abnormal or very high dose of heparin needed to achieve anticoagulation target
  - (>35,000 U/day = infusion > ~25 U/kg/h)

Heparin works by binding to antithrombin

□ Heparin + AT → [complex Heparin-AT] → Inhibition Xa (+ IIa )

# Complications with anticoagulation – Heparin Resistance

## investigation & management of heparin resistance

Cause of heparin resistance	anti-Xa level	PTT level	Antithrombin-III level	Treatment
<b>Pseudo-heparin resistance</b> (Increased levels of factor VIII and fibrinogen due to inflammation)	Therapeutic	Low	Normal or moderately low	Dose heparin based on Xa level -or- Transition to low molecular-weight heparin
<b>Genuinely low heparin concentration</b> - Increased heparin clearance - Increased heparin-binding proteins	Sub-therapeutic	Sub-therapeutic	Normal or moderately low	Increase heparin dose -or- Transition to direct thrombin inhibitor
<b>Antithrombin-III deficiency</b>	Sub-therapeutic	Sub-therapeutic	Severely reduced (e.g. <40-50%)	May give antithrombin-III -or- Transition to direct thrombin inhibitor

The Internet Book of Critical Care, by @PulmCrit

- Management: Increase dosage, AT supplementation, monitor with method with no interference with plasma proteins or change drug of choice

# Complications with anticoagulation – Discrepant tests

Anti-Xa (0.3-0.7IU/mL)	aPTT (60-90s)		
	Low	Normal	High
Low	Increase heparin	Increase heparin	Consider low factor + FFP
Normal	Consider hypercoagulable state	No change	Repeat aPTT, consider FFP if still high
High	Low probability <input type="checkbox"/> repeat test	Consider hypercoagulable state, repeat test	Decrease heparin

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# Bleeding

# Bleeding – causes and risk factors

- **Anticoagulation** ☐ predisposes patients to higher risk of bleeding
- **Platelet dysfunction** ☐ ECMO-induced shear stress + exposure to foreign surfaces
  - Hemolysis
- **Invasive procedures** ☐ cannulation, line placement, chest tube insertion
- **Pre-existing coagulopathies** ☐ underlying coagulation disorders or acquired bleeding tendencies

# Bleeding – Clinical implications

## Hemorrhagic complications

- Surgical sites
- Cannulation sites
- GI tract
- Intracranial hemorrhage

## Circuit-related issues

- Circuit dysfunction and clotting with need for circuit change

**Significant morbidity and mortality**

# Transfusion support

If bleeding ...

Full blood count and biochemistry

Standard coagulation test

Blood gases

VET testing

XIII

vWF Ag and Rco

VII in severe bleeding

Transfusion Medicine consultation

# Transfusion support



## Maintain:

- Hb > 7g/dL, >8g/dL if heart disease
- Platelets >50x10<sup>9</sup>/L
- Fibrinogen >200mg/dL or under VET control
- Absence of hyperfibrinolysis
- Temperature >36° and ph>7.2
- Calcium and Magnesium levels
- Haemodynamics

# Conclusion

- Anticoagulation plays a crucial role in ECMO therapy
  - Preventing clotting within the circuit and maintaining optimal gas exchange.
- Balancing clotting and bleeding risks is a complex task
  - Careful monitoring, individualized approaches, and collaboration among healthcare teams.
- Appropriate monitoring and optimized anticoagulation therapy in ECMO
  - Improve patient outcomes and advances the field of extracorporeal support

An aerial photograph of a city, likely Lisbon, Portugal, during sunset. The foreground is dominated by a dense cluster of buildings with red-tiled roofs. In the middle ground, a large body of water is visible, with a suspension bridge spanning across it. The bridge's towers are illuminated, and the sun is setting behind one of them, creating a warm, orange glow. In the background, a hillside features a prominent white monument with a cross on top. The sky is a mix of orange and blue, and the overall scene is peaceful and scenic.

Thank you