Anticoagulation Management During ECLS

Extracorporeal Life Support Symposium
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Disclosures

I have no relevant financial relationships or commercial interests to disclose for this presentation.

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Objectives

• Describe the pathology of Extracorporeal Life Support (ECLS) necessitating anticoagulation therapy

• Summarize appropriate monitoring parameters for anticoagulation and thrombosis for patients requiring ECLS

• Identify the available anticoagulants used during ECLS therapy
Balancing Act

Clotting

- Contact with non-biologic surface
- Inflammation
- Platelet activation

Bleeding

- Consumptive Coagulopathy
- Thrombocytopenia
- Fibrinolysis

What’s The Gold Standard?

Number of Publications

Year


Thrombosis and Hemostasis

Liver failure

Hypothermia

Fibrinolysis

Hemolysis

Acidosis

Hypocalcemia

TF = Tissue Factor
## Activated Clotting Time (ACT)

### Mechanism
- Functional whole blood test
- Blood mixed with activator (i.e. kaolin)

### Advantages
- Point of Care (POC)
- Most historical use in ECLS
- Can be used to monitor heparin and direct thrombin inhibitors (DTI)

### Disadvantages
- Influenced by numerous factors (i.e. hypothermia, thrombocytopenia, hemodilution)
- High vs Low cartridges leading to mismanagement

### Typical Goal
- ELSO recommendation: 180-220 seconds
- Data available for lower goal

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ELSO Anticoagulation Guidelines: elsonet.org/resources/guidelines
Partial Thromboplastin Time (PTT)

**Mechanism**
- Measures intrinsic and common coagulation pathways
- Blood mixed with surface activator and phospholipid which results in clotting time

**Advantages**
- Widely available
- More specific to anticoagulation than ACT
- Can be used to monitor heparin and Direct Thrombin Inhibitor (DTI)

**Disadvantages**
- Therapeutic range depends on reagent used
- Confounding patient attributes (hemophilia, antiphospholipid antibodies, etc.)

**Typical Goal**
- Dependent on institutional goal established

Establishing Therapeutic Range

Therapeutic aPTT

![Graph showing the relationship between Anti-Xa (IU/ml) and aPTT (s). The therapeutic range is indicated by a horizontal line at 80 seconds.]
Anti-Xa

**Mechanism**
- Chromogenic assay that approximates the effect of heparin on hemostasis
- Two types of test available with or without exogenous antithrombin

**Advantages**
- More specific to heparin

**Disadvantages**
- Influenced by hemolysis, hyperbilirubinemia, vitamin K deficiency and hyperlipidemia, etc.
- Too specific? Monitoring one component of heparin activity
- Cannot be used to monitor DTIs

**Typical Goal**
- ELSO recommendation: 0.3-0.7 IU/ml

Moyniha K et al. *Perfusion* 2017;32(8): 675—685
ELSO Anticoagulation Guidelines: elsonet.org/resources/guidelines
# Thromboelastometry (ROTEM)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Significance</th>
<th>Coagulation Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>Time until the initial clot formation</td>
<td>Measured activity of coagulation factors</td>
</tr>
<tr>
<td>CFT</td>
<td>Measures the speed at which fibrin build-up and cross-linking takes place</td>
<td>Represents the activity of fibrinogen</td>
</tr>
<tr>
<td>MCF</td>
<td>Maximal viscoelastic strength of clot</td>
<td>Measures overall platelet and fibrin function</td>
</tr>
<tr>
<td>ML</td>
<td>Measure the decrease in fibrin clot 30 minutes post MA</td>
<td>Rate of fibrinolysis</td>
</tr>
</tbody>
</table>

Thromboelastometry (ROTEM)

**Mechanism**
- POC test of viscoelastic properties of clot formation
- Activator placed in cup with whole blood with rotating plastic pin immersed in blood clot formation changes torque to trace clot formation

**Advantages**
- Measures integrity of coagulation cascade to the time of fibrin formation and clot lysis
- Allows for underlying assessment of coagulation in presence of heparin
- Able to evaluate hyperfibrinolysis

**Disadvantages**
- Not widely available
- No establish way to monitor anticoagulation

**Typical Goal**
- Variable depending on clinical scenario

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# Heparin

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Half Life</th>
<th>Metabolism</th>
<th>Reversible</th>
</tr>
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<tbody>
<tr>
<td>Catalyst for Antithrombin</td>
<td>60-90min</td>
<td>Reticuloendothelial system</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Weitz JI* *NEJM* 1997;337:688-699.
Antithrombin

Mechanism
- Co-factor needed for heparin to have effect

Advantages
- Decrease doses of heparin

Disadvantages
- Majority of evidence in pediatric population
- No consensus on dosing
- Question of how to adjust anticoagulation

Typical Goal
- ELSO recommendation: No specific recommendation

# Heparin

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Heparin Induced Thrombocytopenia Prevalence of 0.36%!

Kimmoun A et al *Intensive Care Med* 2018;44:1460-1469
### Direct Thrombin Inhibitors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Half Life</th>
<th>Metabolism</th>
<th>Reversible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argatroban</td>
<td>DTI</td>
<td>50 minutes</td>
<td>65% Hepatic 25% Renal</td>
<td>No</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>DTI</td>
<td>25 minutes</td>
<td>80% Enzymatic 20% Renal</td>
<td>No</td>
</tr>
</tbody>
</table>

## Literature

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
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</table>
| Ranucci M, et al. 2011 (N=21; 12 adults, 9 children) | • All VA ECMO  
• 8 heparin vs. 13 bivalirudin cases | • Bivalirudin group remained in ACT and aPTT goal ranges longer  
• Fewer blood products required by bivalirudin group | • Bivalirudin is safe and effective in the setting of ECMO  
• May result in fewer bleeding complications |
| Pieri M, et al. 2013 (N=20 adults) | • 50% VA ECMO  
• 10 heparin vs. 10 bivalirudin cases | • Bivalirudin group experienced less aPTT variations  
• No significant differences noted for major or minor bleeding or thrombosis events | • Bivalirudin is an alternative to heparin in ECMO  
• Trends towards less bleeding and thrombosis |
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<td>Berei T, et al. 2017</td>
<td>• 92% VA ECMO</td>
<td>• No difference in thrombosis at 96 hours, throughout ECMO run, or hospitalization (7 Heparin vs. 10 Bivalirudin)</td>
<td>• Bivalirudin supported as an alternative to heparin, but not demonstrated to be superior</td>
</tr>
<tr>
<td>(N=72 adults)</td>
<td>• At least 96 hours of continuous anticoagulation with a single agent</td>
<td>• No difference in major or minor bleeding events or percent of time in therapeutic range</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 28 heparin vs. 44 bivalirudin cases</td>
<td></td>
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## Additional Agents

<table>
<thead>
<tr>
<th>Aspirin</th>
<th>Enoxaparin</th>
<th>Novel Oral Anticoagulants (NOAC)</th>
</tr>
</thead>
</table>
| • Minimal evidence  
  • Continue if patient has indication | • Minimal evidence  
  • Renal clearance and prolonged half life limit use | • No evidence  
  • Recommend against using |

Bein T et al. *ASAIO* 2011;57:164-8  
Krueger K et al. *Artificial Organs* 2017;2(41): 186-92
Expect the Unexpected
ELSO Recommendations

- Monitoring
  - Each institution should develop an approach to monitoring anticoagulation that works best for their patients

- Anticoagulant of choice
  - No official recommendation of what agent to use
    - Heparin 50-100 unit/kg bolus followed by continuous infusion titrated to goal
    - Bivalirudin continuous infusion titrated to goal
  - No official recommendation on the use of antithrombin

ELSO Anticoagulation Guidelines: elsonet.org/resources/guidelines
Conclusion

• Know your institution's laboratory practices and what is available to you
• Understand the limitations around each assay
• Developing a standardized protocol can simplify and improve the application of ECLS
• Use available information as a guide
• More is not always better
Thank You

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