ECMO in COVID-19: Is There a Role for Bivalirudin?

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Off-label use of bivaluridin will be discussed
What’s Different with COVID-19?

- Klok, F.A. *et al.* → 3 Dutch Hospitals
  - 184 COVID-19 Positive, 13% mortality
  - 31% thrombotic complications
- Tang *et al.* → Wuhan China
  - Mortality 11.5% → Non-survivors

↑ D-Dimer
↑ FDP
↑ PT
↑ aPTT
COVID-19 → Pro-Thrombotic
Micro-thrombi → exacerbate/precipitate hypoxemic respiratory failure

Excessive Coagulopathy?
NOT yet confirmed
Hemostatic Δ’s → COVID specific?
ALL hospitalized pts → ↑VTE

- https://academy.isth.org/isth/#!*menu=8*browseby=8*sortby=2*media=1*label=19868
- 10.1161/CIRCULATIONAHA.120.047549
ECMO Anticoagulation Plan
Anticoagulation for ECMO
Rational Simplified
Coagulation Cascade

Extrinsic activation
Vessel injury
Factor VII

Intrinsic activation
Surface contact
Factor XII
Factor XI
Factor VIII
Factor IXa
Factor X

“Tenase Complex”

Exposed proteins

Collagen binds to kininogen & prekallikrein

Prothrombin
Factor V
Factor Xa

Thrombin

Fibrinogen
Fibrin

Factor
Exposed proteins
Impact of Thrombin

Purpose of Anticoagulation

Contact Phase

Blood + ECMO Circuit

Thrombin Generation
Ideal Anticoagulant Features

- Effective
- Titratable
- Reversible

Ideal
Heparin Mechanism of Action

Intrinsic activation:
- Surface contact
  - Factor XII
  - Factor XI

Extrinsic activation:
- Vessel injury
  - Factor VII
  - Factor VIII
  - Factor IXa
  - Factor X

Heparin

Antithrombin III

**Prothrombin**

**Thrombin**

**Fibrinogen** → **Fibrin**
Limitations of Heparin

• Relatively long half-life

• Unpredictable dose response
  • $\uparrow$ dose adjustment & lab frequency

• Heparin Resistance $\Rightarrow$ $\downarrow$ AT-III Levels

• HIT

• COVID $\Rightarrow$ thrombosis despite aPTT 60-80 sec
What Else Can Be Considered?
What Else Can Be Considered?

DTI Based Anticoagulation
Direct Thrombin Inhibitors
Direct Thrombin Inhibitors

• **Bivalirudin:**
  • Synthetic, bivalent inhibitor of thrombin
  • Directly attach free & fibrin-bound thrombin
  • Immediate onset + short half-life ~25 min
  • Clearance ⇒ 80% by blood proteases
DTI’s Mechanism of Action

Bivalirudin

Intrinsic activation
- Surface contact
  - Factor XII
  - Factor XI
- Factor VIII
  - Factor IXa
  - Factor X

Extrinsic activation
- Vessel injury
  - Factor VII

Prothrombin

Thrombin

Fibrinogen → Fibrin
Advantages Over Heparin

- Inhibition of fibrin (clot)-bound thrombin
- More predictable anticoagulant response
  - Independent of AT-III
  - No effect on platelet factor 4
- Reported in literature… thus far modest evidence

Safe in HIT

Published Evidence

Case Report ➔ Pappalar et al.
- 71F post cardiotomy
- HIT +
- ACT 180 - 220 s

DOI:10.1186/cc10556
DOI:10.1177/0267659109106773
Published Evidence

Retrospective \(\rightarrow\) Ranucci et al.
- 21 post cardiotomy VA
  - 8 consecutive heparin
  - 13 consecutive bival

\(\downarrow\) aPTT variations  \(\downarrow\) total cost  \(\downarrow\) blood loss  \(\downarrow\) transfusion

DOI:10.1186/cc10556
DOI:10.1177/0267659109106773
Published Evidence

Case Control → Pieri et al.
- 5 VV & 5 VA → aPTT
- Compared vs heparin
  - ↓ Dose correction
  - ↓ Supratherapeutic aPTT
Published Evidence

**Systematic Review** → Sanfilippo et al.
- 8 publications (5 case reports)
- 58 patients → 24 peds
  - 18 received heparin as control

- Infusion → 0.1 – 0.5 mg/kg/h
- Monitoring → aPTT 45 – 88 s
  → ACT 180-220
  → TEG in 1 study
Published Evidence

Retrospective → Netley *et al.*
- 8 ARDS & 3 ECLS
- Described dosing protocol
- ALL therapeutic within 24 hours

Retrospective → Berei *et al.*
- 44 shock → 92% VA
- No Δ thrombotic events or mortality
- Suggested bival as viable alternative
Published Evidence

Retrospective → Walker et al.
- 12 ARDS + 2 post-cardiotomy
- ↑ infusion rates with CRRT

Review → Goswami et al.
- Bival in pediatric cardiac surgery
- Circumvents problems with heparin
- Comes with unique challenges

DOI: 10.5492/wjccm.v8.i6.87
DOI: 10.1097/MAT.0000000000000780
PMID: 30250342
DOI: 10.1053/j.jvca.2012.07.019
DOI: 10.1097/MAT.0000000000000691
When to Use Bivalirudin?

- Alternative first line
- HIT
- Heparin resistance
  - Congenital & acquired AT-3 deficiency
- Refractory fibrin &/or clot

Superior anticoagulant
Mayo Clinic Bival Guideline

Based Upon:
- Conservative Dosing
- Ranucci + Pieri
- HIT

Improvements:
- 26 adult ECMO pts
- Renal dose table
- Added “low flow”

Enhancements:
- 122 adult ECMO pts
- Fine-tuned dosing table
- “Unique Scenarios”
  - APS, PLEX, HIT

1st Generation → 2016

2nd Generation → 2018

3rd Generation → 2020

Mayo Total Bival Pts → 208 Adult + 87 Peds
Mayo Clinic Bival Guideline

- Algorithm based dosing
Mayo Clinic Bival Guideline

- **Algorithm based dosing**

**Table 1:** Initial Dose Based Upon Estimated Renal Function

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Bivalirudin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10</td>
<td>0.02 mg/kg/hr &amp; discuss with pharmacy</td>
</tr>
<tr>
<td>CRRT</td>
<td>0.04 mg/kg/hr</td>
</tr>
<tr>
<td>10 - 29</td>
<td>0.07 mg/kg/hr</td>
</tr>
<tr>
<td>30 - 60</td>
<td>0.1 mg/kg/hr</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>0.15 mg/kg/hr</td>
</tr>
</tbody>
</table>

Adult Extracorporeal Life Support (ECLS) and ECMO Direct Thrombin Inhibitor (DTI) Anticoagulation Guideline, 2020
Mayo Clinic Bival Guideline

• Algorithm based dosing

<table>
<thead>
<tr>
<th>APTT sec</th>
<th>Rate Change</th>
<th>Repeat aPTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>More than 20 sec low</td>
<td>Increase 20%, no bolus</td>
<td>6 hour</td>
</tr>
<tr>
<td>10-20 sec low</td>
<td>Increase 10%, no bolus</td>
<td>6 hour</td>
</tr>
<tr>
<td>Target Limits</td>
<td>No change</td>
<td>12 hour</td>
</tr>
<tr>
<td>10-20 sec high</td>
<td>Decrease 10%</td>
<td>6 hour</td>
</tr>
<tr>
<td>More than 20 sec high</td>
<td>HOLD 1 hr, Decrease 20%</td>
<td>6 hour</td>
</tr>
</tbody>
</table>
Mayo Clinic Experience

• Bival guideline compliant vs non-compliant…
  • Time to goal aPTT $\rightarrow \downarrow 80$
  • Number of dose adjustments $\rightarrow \downarrow 60$

• Outcomes:
  • Pre- COVID $\rightarrow \downarrow$ mortality & complications
Mayo Clinic COVID Experience

- 1 VV pt → Bival + ASA 81 mg → no complications

aPTT on Bivalirudin 0.25 mg/kg/h
Implementation Considerations

- Know when NOT to use bivalirudin
- Carefully consider titration schedule
- Develop plan for dialysis start/stop/pauses
- Be aware of nuances of drug dosing
  - Non-linear dose response curves
  - PT/INR interference
  - Hemorrhage management

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PT/INR Interference
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Hemorrhage management

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Implementation Considerations

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  - Be aware of nuances of drug dosing
- Plan for “low flow” states ➔ stasis = thrombosis

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Take Home Points

• ECMO + COVID-19 has unique features
  • ↑ thromboembolic complications & ↓ circuit life

• Controlling thrombin generation/activity is critical
  • Systemic anticoagulation → essential

• Heparin most common but NOT the only option
  • DTI’s → Bivalirudin may be superior