Heparin Resistance: Battling Back

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Objectives

• Describe the pathophysiology of heparin resistance

• Identify a patient with heparin resistance

• To distinguish potential strategies for management
Heparin Resistance Definition

- Unusually high amounts of heparin to achieve a therapeutic aPTT
  - >35,000 units per 24 hours
  - 70 kg patient = 21 units/kg/hr
  - 100 kg patient = 15 units/kg/hr

- Inability to maintain therapeutic ACTs with rising doses of heparin on bypass

aPTT = Activated partial thromboplastin time
ACT = Activated clotting time

CHEST 2012; 141(2)(Suppl):e24S-e43S
Arch Intern Med. 1994;154:49-56
Have you cared for a patient with “heparin resistance”?

1. Yes
2. No
Mechanisms of Resistance

- Antithrombin deficiency
- Elevation of factor VIII and/or fibrinogen (laboratory limitations)
- Elevation in heparin binding proteins
- Increased heparin clearance
Activated Partial Thromboplastin Time

• Abbreviation: aPTT

• Uses
  • Monitoring heparin
  • Screening for coagulation factor deficiencies (or elevations)
  • Detection of coagulation inhibitors (e.g. lupus anticoagulant)

• Components
  • Intrinsic pathway: factor XII, XI, IX, VIII and contact factors (PK & HMWK)
  • Common pathway: Factor X, V, II, and fibrinogen (factor I)
  • Phospholipid (partial thromboplastin) and ionic calcium, and activator (e.g. silica)

PK = prekallikrein
HMWK = high-molecular-weight kininogen
Anti-Xa Assay

- Common name: heparin level

- Uses
  - Monitoring heparin concentration
  - Monitoring patients with prolonged baseline aPTT (e.g. Lupus anticoagulant)

- Components
  - Inactivated factor Xa + heparin/antithrombin complex
  - Addition of antithrombin III to sample

- Therapeutic Range
  - Heparin 0.3 – 0.7 IU/mL
  - Low molecular weight heparin 0.5 – 2 IU/mL depending on dosing

Circulation. 2005; 112:e53-e60
Mayo Medical Laboratory
Antithrombin

- Abbreviation: ATIII
- Uses
  - Diagnosis of antithrombin deficiency (acquired or congenital)
- Components
  - Plasma antithrombin
- Laboratory normal range
  - 80 – 130%
- Deficiencies
  - Hereditary deficiencies ~1:2,000 to 1:3,000
  - Minor deficiencies ~ 1:350 to 1:650
Activated Clotting Time

• **Abbreviation:** ACT

• **Uses**
  - Monitoring high-dose heparin (commonly point-of-care)

• **Components**
  - Whole blood with intrinsic activator
  - Affected by patient platelet counts and function

• **Therapeutic Ranges**
  - Bypass: 300 – 500 seconds (depending on the case)
  - PCI: 250 – 350 seconds
  - ELS: 180 – 220 seconds

PCI = percutaneous coronary intervention
ELS = extracorporeal life support

Circulation. 2005; 112:e53-e60
Which of these patients have heparin resistance?

1. Patient A:
   - 54 yoM admitted for bilateral DVT on heparin at 28 units/kg/hr with an aPTT of 37 secs

2. Patient B:
   - 63 yoF with recurrent small PE while on enoxaparin 1mg/kg twice daily

3. Patient C:
   - 72 yoM admitted for ACS on a heparin nomogram who required a dose increase the past 6 aPTT checks whose aPTT is not yet therapeutic

4. All of the above
Which of these patients have heparin resistance?

1. Patient A: 54 yoM admitted for bilateral DVT
2. Patient B: 63 yoF with recurrent small PE
3. Patient C: 72 yoM admitted for ACS on a heparin nomogram
4. All of the above
Identification of Heparin Resistance

• Incidence largely unknown on the floor
  • Up to 22% of all bypass patients

• Depends on the clinical situation and laboratory monitoring

• Consider heparin resistance investigation around 25 units/kg/hr
<table>
<thead>
<tr>
<th>Variable</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (IQR)</td>
<td>47.8 (30-57)</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>58</td>
</tr>
<tr>
<td>Weight, Kg (IQR)</td>
<td>75 (64-99.8)</td>
</tr>
<tr>
<td>BMI (IQR)</td>
<td>26 (20.8-32.6)</td>
</tr>
<tr>
<td>Heparin indication, n (%)</td>
<td></td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Extracorporeal life support</td>
<td>14 (42.4)</td>
</tr>
<tr>
<td>Left ventricular assist device</td>
<td>4 (12.1)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>14 (42.4)</td>
</tr>
<tr>
<td>ICU patients at time of intervention, n</td>
<td>30 (90.9)</td>
</tr>
<tr>
<td>Heparin duration, days (IQR)</td>
<td>7 (4-11)</td>
</tr>
<tr>
<td>Heparin max dose, units/kg/hr (IQR)</td>
<td>27.0 (23.0-29.0)</td>
</tr>
</tbody>
</table>
Treat the Problem

• ATIII deficiencies
• Elevation of other factor
• Elevation in heparin binding proteins
• Increased heparin clearance

Supplement

Change Monitoring

Change anticoagulation strategy
Acquired Antithrombin Deficiencies

- Sepsis
  - Decreased acute phase reaction
- Liver disease
  - Decreased production
- Malnutrition
  - Decreased production
- Nephrotic syndrome
  - Increased elimination
- Heparin consumption

Lab Hematol. 2003;9:125-131
Semin Thromb Haemost 1998;24:19-25
Thromb Haemost 1997;77:197-211
Antithrombin III Supplementation

• Fresh frozen plasma (FFP) vs. ATIII
  • Sabbagh et al 1984 first reported 1 units of ATIII per mL of FFP
  • FFP is inferior to recombinant ATIII
    • Safe and consistent
    • No transfusion related reactions

• Dose?
  • Units = [(desired ATIII – level) * weight] / 1.4
  • 500 to 1,000 units per dose (1 to 2 vials)

• Outcomes

Ann Thorac Surg 1984;37:446-8
Semin Thromb Haemost 1998;24:19-25
<table>
<thead>
<tr>
<th>Antithrombin level</th>
<th>Clinical Situation</th>
<th>Supplement?</th>
</tr>
</thead>
<tbody>
<tr>
<td>80% or greater</td>
<td>Any</td>
<td>Administration unlikely to help heparin requirement</td>
</tr>
<tr>
<td>60% to 80%</td>
<td>ECMO, Bypass, PCI</td>
<td>Possible benefit of decreasing heparin dose. Consider increased heparin dose first</td>
</tr>
<tr>
<td></td>
<td>VTE, other heparin indications</td>
<td>Consider heparin dose increase over ATIII supplementation</td>
</tr>
<tr>
<td>40% to 60%</td>
<td>ECMO, Bypass, PCI</td>
<td>Supplemental likely beneficial</td>
</tr>
<tr>
<td></td>
<td>VTE, other heparin indications</td>
<td>Supplementation will likely reduce heparin requirements</td>
</tr>
<tr>
<td>&lt; 40%</td>
<td>All</td>
<td>ATIII would likely reduce heparin requirements</td>
</tr>
</tbody>
</table>
60 yoF admitted for sepsis who was found to have a DVT on day 2 of admission. The patient is now day 4 of admission. What acquired ATIII deficiencies is this patient NOT at risk for having?

1. Sepsis
2. Malnutrition
3. Heparin consumption
Laboratory Limitation

- Anti-Xa and aPTT provide different information
- Levine et al. 1994
  - VTE patient with heparin doses >35,000 units/day
  - Anti-Xa vs aPTT

<table>
<thead>
<tr>
<th>Variable</th>
<th>Anti-Xa (n=65)</th>
<th>aPTT (n=66)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median heparin dose, U/hour</td>
<td>1675</td>
<td>1900</td>
<td>NA</td>
</tr>
<tr>
<td>Thrombus, n</td>
<td>4 (6.15%)</td>
<td>4 (6.1%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Bleeding, n</td>
<td>1 (1.54%)</td>
<td>4 (6.1%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Factor VII levels, U/mL</td>
<td>2.39</td>
<td>1.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>ATIII levels, U/mL</td>
<td>0.92</td>
<td>0.98</td>
<td>NA</td>
</tr>
</tbody>
</table>
Low Molecular Weight Heparin Alternative

• Krajewski et al. 2015 case report
  • VTE cancer patient
  • Required 66,000 units/day of heparin

• Enoxaparin 1.5mg/kg twice daily was used
  • Anti-Xa levels confirmed dosing
  • No adverse events reported for patient

• LMWH may be a safe option
  • Consider for VTE patients without ATIII deficiencies
## aPTT vs Anti-Xa vs ATIII

<table>
<thead>
<tr>
<th>Patient</th>
<th>Heparin Dose</th>
<th>aPTT</th>
<th>Anti-Xa</th>
<th>ATIII</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>20 units/kg/hr</td>
<td>50</td>
<td>0.2</td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>24 units/kg/hr</td>
<td>45</td>
<td>0.4</td>
<td>77%</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>27 units/kg/hr</td>
<td>48</td>
<td>0.6</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>22 units/kg/hr</td>
<td>62</td>
<td>0.8</td>
<td>37%</td>
<td></td>
</tr>
</tbody>
</table>
Monitoring Change for Heparin Resistance

• Anti-Xa is more specific than aPTT
  • May miss other coagulation issues
• Most cost effective treatment option

• Available data is for patients with VTE
• No critically ill patients included in this strategy
Anticoagulation Therapy Change

- Best for mixed reason for resistance or when ATIII or anti-Xa not indicated
- Switch to an IV direct thrombin inhibitor
  - aPTT 2.5 to 3.5x baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Result (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of ATIII, n</td>
<td>15 (57.7%)</td>
</tr>
<tr>
<td><strong>Median time to therapeutic, hr (IQR)</strong></td>
<td><strong>19.5 (5.5-35.8)</strong></td>
</tr>
<tr>
<td>Dose of ATIII, median units/kg (IQR)</td>
<td>26 (17-39)</td>
</tr>
<tr>
<td>Median ATIII level while on heparin (IQR)</td>
<td>55.0 (45-61)</td>
</tr>
<tr>
<td>Use of Direct thrombin inhibitor, n</td>
<td>21 (63.6%)</td>
</tr>
<tr>
<td><strong>Median time to therapeutic, hr (IQR)</strong></td>
<td><strong>9 (4-16.1)</strong></td>
</tr>
</tbody>
</table>
Bivalirudin in ECMO Anticoagulation

• Ranucci et al 2011 *Bivalirudin vs heparin for ECMO anticoagulation*

![Graph showing comparison between Heparin and Bivalirudin in ECMO anticoagulation.](image)

- **Total Bleeding**: P=0.015
- **pRBCs**: P=0.067
- **FFP**: P=0.02
- **Plts**: P=0.008
- **ATIII**: P=0.048

Argatroban in Heparin Resistance

- Treichl et al. 2015 *Effects of argatroban in critically ill patients with heparin resistance*
- Retrospective analysis of 20 patients
- Argatroban if heparin failed to achieve aPTT 45 to 55 seconds in 2 days

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT on heparin</td>
<td>38.5 seconds</td>
</tr>
<tr>
<td>aPTT on argatroban</td>
<td>48.3 seconds</td>
</tr>
<tr>
<td>ATIII level</td>
<td>77 +/- 15</td>
</tr>
<tr>
<td>Heparin median dose</td>
<td>1,000 units/hr</td>
</tr>
<tr>
<td>Argatroban median dose</td>
<td>0.27 +/- 0.16 mcg/kg/min</td>
</tr>
</tbody>
</table>
Direct Thrombin Inhibitors

- Bivalirudin and argatroban have been used in critically ill patients
- Use for mixed heparin resistance mechanisms
- Reduces ATIII supplementation and may reduce bleeding
- Allows quick achievement of therapeutic anticoagulation
- No reversal agent currently available
Potential for the future

• Novel agents have no current available data for heparin resistance
• Pharmacologically novel agents should be unaffected by heparin resistance
• Potential safe and cost effective alternative for non-critically ill patients
  • Critically ill patients often have variable organ function/elimination
What beneficial outcomes have direct thrombin inhibitors shown in heparin resistance?

1. Reduced red blood cell requirements
2. Achievement of therapeutic anticoagulation in less than 24 hours
3. Decreased mortality
4. Reduced thrombosis rate
Treat the Problem

• ATIII deficiencies
• Elevation of factor
• Elevation in heparin binding proteins
• Increased heparin clearance

Supplement
Monitoring change
Change anticoagulation strategy
Suspect heparin resistance (25 units/kg/hr)

Determine reason
Monitor aPTT, anti-Xa, and ATIII

ATIII deficiency?

No
Laboratory limitation
Monitor anti-Xa instead of aPTT

Yes
Supplement 1 vial (~500 units)
Monitor for repeat

Change in agent required

or

Direct thrombin inhibitor

aPTT 2.5-3.5x baseline
Questions & Discussion
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