The Acute Coagulopathy of Trauma is due to Impaired Initial Thrombin Generation but not Clot Formation or Clot Strength

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Acute Coagulopathy of Trauma (ACOT)

- Hemorrhage accounts for 40% of all trauma deaths

- An acute coagulopathy is identified in 1 in 4 trauma patients on admission
  - Four-fold increase in mortality

Acute Coagulopathy of Trauma (ACOT)

- Biphasic
- Disseminated Intravascular Coagulation (DIC)
- Activated Protein C

Cannon, WB. Gray, H. *Am J Physiol* 1914

Hardaway, JW. Neimes, R *Ann Surg* 1962

Simmons, R. Collins, J *Ann Surg* 1969

Brohi, D. Cohen, MJ *J Trauma* 2008
Proposed Mechanisms

Disseminated Intravascular Coagulation

- Tissue Hypoperfusion
  - ↑ Thrombomodulin
    - Thrombomodulin/Thrombin Complex
      - Platelet Activation/Aggregation
        - TAFI Activation
          - Hypercoagulability
            - Clotting Factor Consumption
              - Hypocoagulability
            - Endothelial TPA Release
              - Fibrinolysis

Activated Protein C Pathway

- Tissue Injury
  - ↑ Thrombomodulin
    - thrombomodulin/Thrombin Complex
      - Protein C Activation
        - Factors V and VIII Inactivation
          - PAI-1 Consumption
            - ACOT

Clotting Factor Depletion vs. No Depletion
Cell-Based Model of Coagulation

- Plasma-based tests (INR, PTT)

- Viscoelastic hemostatic assays (TEG, RoTEM)
  - comprehensive test

Thrombelastography

R: Reaction Time
SP: Split Point
Delta: (R-SP)
K: Clot Formation Time
MA: Maximum Amplitude
G: Clot Strength
EPL: Percent Lysis

Platelet-Fibrin Interaction
Fibrinolysis

Thrombin Generation
Fibrinogen
Platelets
Purpose

To determine the mechanism of ACOT in a clinically relevant model of trauma/hemorrhagic shock
Methods

- Adult Male Sprague-Dawley Rats
- Trauma/Hemorrhagic Shock
- Statistical Analysis: ANOVA with post-hoc Fisher’s Test
Clinical Relevance

• Tissue Injury + Hemorrhagic Shock
  • Laparotomy
  • ~50% of Total Blood Volume Removed
    – Class IV Shock

• Hb: 14.1 ± 1.5 → 7.4 ± 0.7 g/dL

• Mean Δ in BD: 13.95 mEq/L
Thrombin Generation is Impaired Following T/HS

<table>
<thead>
<tr>
<th>Delta</th>
<th>Baseline</th>
<th>Shock</th>
<th>Post-Resuscitation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.07 (±0.03)</td>
<td>0.32 (±0.11)*</td>
<td>0.27 (±0.05)*</td>
</tr>
</tbody>
</table>

* p < 0.001 from baseline
# p < 0.05 from shock
# TEG Results in T/HS Model

<table>
<thead>
<tr>
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<th>Baseline</th>
<th>Shock</th>
<th>Post-Resuscitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzymatic Activity (R)</td>
<td>0.78 (±0.14)</td>
<td>1.62 (±0.10)*</td>
<td>1.97 (±0.10)*,#</td>
</tr>
<tr>
<td>Split Point (SP)</td>
<td>0.72 (±0.13)</td>
<td>1.30 (±0.11)*</td>
<td>1.70 (±0.12)*,#</td>
</tr>
<tr>
<td>Thrombin Generation (Delta)</td>
<td>0.07 (±0.03)</td>
<td>0.32 (±0.11)*</td>
<td>0.27 (±0.05)*</td>
</tr>
<tr>
<td>Clot Formation (K)</td>
<td>0.87 (±0.07)</td>
<td>0.80 (±0.00)</td>
<td>0.83 (±0.03)</td>
</tr>
<tr>
<td>Fibrin Cross-linking (Angle)</td>
<td>81.8 (±1.42)</td>
<td>82.65 (±0.46)</td>
<td>82.07 (±0.35)</td>
</tr>
<tr>
<td>Platelet Contribution (MA)</td>
<td>70.67 (±2.91)</td>
<td>73.93 (±0.81)</td>
<td>70.63 (±0.75)</td>
</tr>
<tr>
<td>Clot Strength (G)</td>
<td>12.75 (±3.48)</td>
<td>13.68 (±1.59)</td>
<td>12.22 (±1.06)</td>
</tr>
<tr>
<td>Percent Lysis (EPL)</td>
<td>0.15 (±0.13)</td>
<td>1.03 (±0.66)</td>
<td>1.40 (±1.15)</td>
</tr>
</tbody>
</table>

* p < 0.001 from baseline
# p < 0.05 from shock
TEG Supports Activated Protein C Mechanism

Clotting Factor Dysfunction
Impaired Thrombin Generation

DIC

Kouerinis, I, et al.
Conclusion

• ACOT is due to impaired thrombin generation…but not clot formation or clot strength

• Persistence of hemostatic potential suggests no consumption of coagulation factors

These data best support the activated-protein C hypothesis
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