Blood Failure:

oxygen debt, coagulopathy, and endothelial damage

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Disclosures

• Cofounder of Stasys Medical Corp.
• NO OTHER CONFLICTS
Hemorrhagic Blood Failure

- Hemorrhage
- Shock
- Endotheliopathy
- Coagulopathy
Hemorrhage creates oxygen debt

All debts must be repayed

Organ Function

How is oxygen debt linked to blood failure?
Electron Transport- electrons roll down hill
Fig. 1. Temporal effects of ischemia and reperfusion on mitochondrial ETC function and respiratory coupling.
ROS and Oxidation


Oxidation can directly alter coagulation

Fibrinogen Oxidation


Oxidative Dysfibrinogenemia of Trauma

Table 2
Fibrinogen methionine sulfoxide content (% of total).

<table>
<thead>
<tr>
<th>Methionine position (chain)</th>
<th>Control (INR ≤ 1.2)</th>
<th>Coagulopathy (INR &gt; 1.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>422 (β)</td>
<td>N=11</td>
<td>Mean 0.22%</td>
</tr>
<tr>
<td>305 (β)</td>
<td>N=11</td>
<td>Mean 1.45%</td>
</tr>
<tr>
<td>314 (β)</td>
<td>N=11</td>
<td>Mean 0.73%</td>
</tr>
<tr>
<td>367 (β)</td>
<td>N=11</td>
<td>Mean 1.67%</td>
</tr>
<tr>
<td>373 (β)</td>
<td>N=11</td>
<td>Mean 0.36%</td>
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<tr>
<td>78 (γ)</td>
<td>N=11</td>
<td>Mean 1.08%</td>
</tr>
<tr>
<td>476 (α)</td>
<td>N=11</td>
<td>Mean 1.83%</td>
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</tbody>
</table>

A. Fibrinogen $\alpha$-M476 Sulfoxide Content

- T test, p=0.047

B. Albumin M553 Sulfoxide Content

- T test, p=0.83

C. Metabolic Shock

- $R=0.56$, $p=0.008$

D. Anatomic Injury

- $R=0.42$, $p=0.046$

Catecholamine surge

Endotheliopathy- Glycocalyx

Tuma et al. Trauma and Endothelial Glycocalyx: the Microcirculation Helmet? SHOCK DOI : 10.1097/SHK.0000000000000635

Kozar et al. Anesth Analg 2011; 112:1289–95
Procoagulant Activation

[a] Quiescent endothelium
- SOD
- Thrombomodulin
- Endothelial cell
- Pericyte
- Basement membrane

[b] Shed glycocalyx and selectins
- Syndecans
- CD44
- E-selectin
- Heparin sulfate
- Chondroitin sulfate
- Hyaluronic acid
- Growth factors

[c] Endothelial microparticles
- Leukocyte
- Platelets
- Microparticles

[d] Circulating endothelial cells
- Redox signaling
- PS
- Pericyte
- Circulating endothelial cell
Endothelium- Barrier Disruption


Endotheliopathy induces TIC

**Plasmin**

Targets

- Fibrinogen
- Fibrin
- Fibronectin
- Laminin
- von Willebrand factor
- Platelet Receptors (GPIIb)
- Factor XIIIa
Trauma-Induced Coagulopathy

Coagulopathy

Coagulopathy

Critical components governing hemostatic transitions:
Thrombin generation
Platelet activation state
Fibrinogen concentration/fibrinolysis
Platelet Function

Credit: David Motto MD, PhD. Bloodworks Northwest, Seattle, WA

Pasterk et al. Scientific Reports (2016) 6:22104
Platelet Microforces
Platelet contractile dysfunction

Unit Odds Ratio for blood product transfusion = 0.97
95%CI= [0.936, 0.996]
What is required to treat blood failure?

- Repay Oxygen Debt
- Restore the Glycocalyx
- Stop Proteolysis
- Replete the Coagulation System
Treatment Limitations

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Crystalloid</th>
<th>PRBC</th>
<th>Plasma</th>
<th>Cryo</th>
<th>TXA</th>
<th>Plts</th>
<th>WB</th>
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</thead>
<tbody>
<tr>
<td><strong>Oxygen Debt</strong></td>
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<td><em>(Oxygen Content and Delivery)</em></td>
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<td><strong>Endotheliopathy</strong></td>
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<tr>
<td><em>(Glycocalyx, proteolysis, barrier fx)</em></td>
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<td><strong>Coagulopathy</strong></td>
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<td><em>(Proteolysis, Factors, platelets)</em></td>
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Acknowledgements

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EPIC FAIL