Inflammation & Coagulation for SARS-COV-2: Perfusionist’s Perspective

Timothy M. Maul, CCP, FPP, PhD
Perfusionist and Sr. Researcher
Nemours Children’s Hospital

Adjunct Asst. Professor, Biomedical Engineering, University of Pittsburgh

Co-Director ELSO Simulation Group

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Your child. Our promise.
Bleeding and Thrombosis: It has been a problem...it still is a problem

- 43% of deaths, in the ANZ-ECMO series were related to intracerebral hemorrhage
- 75% of Adult ECMO patients have systemic thrombosis at autopsy
- 8/10 patients post Avalon cannula were found to have upper extremity DVT
- ELSO Registry reports 10-12% circuit changes req’d in adult Respiratory ECMO
  - Current COVID-19 Registry data indicating a 20% rate; consistent with other local data

<table>
<thead>
<tr>
<th>Thromboembolic events</th>
<th>Clinical findings</th>
<th>Autopsy findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall venous thrombosis</td>
<td>6 (7.7%)</td>
<td>32 (41.0%)</td>
</tr>
<tr>
<td>Overall arterial embolism</td>
<td>3 (4.8%)</td>
<td>15 (23.8%)</td>
</tr>
<tr>
<td>Left heart thrombus formation</td>
<td>1 (1.3%)</td>
<td>8 (10.2%)</td>
</tr>
</tbody>
</table>
Virchow’s Triad

Intrinsic Hypercoagulability

Blood Flow
(Shear, turbulence, vortices, residence time)

ECMO

Artificial Material Thrombogenicity
Pre-ECMO: Primed to Clot

Aspirin May be Beneficial

Table 3. Changes in Coagulation Parameters, Hemoglobin, and Free Hemoglobin Level Before, During, and After ILA Treatment in Patients Treated with Acetylsalicylic Acid (ASA Group) and in the Matched-Pair Control Group (CON Group)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ASA Before ILA</th>
<th>ASA After Removal of ILA</th>
<th>CON Before ILA</th>
<th>CON After Removal of ILA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count/µl</td>
<td>182 ± 22</td>
<td>203 ± 26</td>
<td>191 ± 15</td>
<td>161 ± 16</td>
</tr>
<tr>
<td>PTT (s)</td>
<td>43 ± 7</td>
<td>44 ± 8</td>
<td>43 ± 7</td>
<td>37 ± 7</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>9.2 ± 2.2</td>
<td>10.2 ± 3.9</td>
<td>9.5 ± 2.0</td>
<td>10.2 ± 1.7</td>
</tr>
<tr>
<td>Free Hb (mg/dl)</td>
<td>71 ± 42</td>
<td>81 ± 57</td>
<td>70 ± 44</td>
<td>80 ± 47</td>
</tr>
</tbody>
</table>

Data are presented as mean values ± SD. T<sub>0</sub> = T<sub>IL</sub> = 24 h, 72 h after initiation of ILA.

Table 4. Acetylsalicylic Acid (ASA), Heparin Application Dosages (Mean Values ± SD), and Demand for Transfusion of Blood Components in Patients Treated with Acetylsalicylic Acid (ASA Group) and in the Matched-Pair Control Group (CON Group; Median and Min-Max Values)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ASA Group</th>
<th>CON Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA total dosage (mg)</td>
<td>687 ± 268</td>
<td>415 ± 84</td>
</tr>
<tr>
<td>Heparin total dosage (IU)</td>
<td>84,700 ± 1,200</td>
<td>144,300 ± 8,800</td>
</tr>
<tr>
<td>Units of RBC transfused</td>
<td>6 ± 2</td>
<td>0 (D-3)</td>
</tr>
<tr>
<td>Units of FFP transfused</td>
<td>0 (D-3)</td>
<td>0 (D-1)</td>
</tr>
</tbody>
</table>

Wolff, E. Master's Thesis, University of Pittsburgh, 2010

Vallet, Critical Care 2003

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Virchow’s Triad

Intrinsic Hypercoagulability

Blood Flow
(shear, turbulence, vortices, residence time)

Artificial Material Thrombogenicity

ECMO
Initial Events in Coagulation: The Surface

- Plasma proteins instantly adsorb (<1 sec) to form a monolayer
  - **Fibrinogen** is the major player and is responsible for most contact activation
  - Hydrophilic materials adsorb less fibrinogen than hydrophobic materials

- Adsorbed proteins can change their conformation to expose “receptor” structures to cells and other enzymes
Blood Contact during ECMO

- Steep increase in the first 2 hrs
- Thereafter, F1+2 & TAT decrease, D-Dimer remains high
- The reason for less contact activation may be a surface replete with proteins/cellular components

Oliver, Sem in CT and Vasc Anesth, 2009
Bonded Circuits: Reduced Platelet Activation/Attachment

**Carmeda®**

Wendel et al., *Perfusion*, 1999

**Safeline® (Albumin) vs. Softline® (Amphiphilic)**

**Phosphorylcholine**

Bonded Circuits: Reduced Inflammation

- **Phosphorylcholine**
  - Reduced peak complement activation

- **Heparin**
  - Alternative Pathway (APW) reduced (C3b(Bp)P-complex)
  - Terminal Compliment Complex (TCC) reduced (SC5b-9)

Bonded Circuits: Caveats to Published Data

- Majority of testing on coatings is done *in vitro* or short-term CPB
  - Effect lasts ~6 hrs

- None of these coatings have been shown to directly affect mortality, length of stay, chest drainage, etc.

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Model</th>
<th>Coating</th>
<th>Pt Size</th>
<th>Surface Area (m²)</th>
<th>Priming Volume (mL)</th>
<th>Range Q (L/min)</th>
<th>ΔP at Q_{max} (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maquet</td>
<td>HLS 7.0</td>
<td>BioLine (heparin/albumin), SoftLine (polymer)</td>
<td>Adult</td>
<td>1.8</td>
<td>273</td>
<td>0.5-7</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>HLS 5.0</td>
<td></td>
<td>Small Adult</td>
<td>1.3</td>
<td>240</td>
<td>0.5-5</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Quadrox</td>
<td></td>
<td>Adult</td>
<td>1.8</td>
<td>250</td>
<td>0.5-7</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>PediQuadrox</td>
<td></td>
<td>Peds</td>
<td>0.8</td>
<td>81</td>
<td>0.2-2.8</td>
<td>38</td>
</tr>
<tr>
<td>Medos</td>
<td>Hilite 800 LT</td>
<td>None</td>
<td>Neo</td>
<td>0.32</td>
<td>55</td>
<td>0.1-0.8</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Hilite 2400 LT</td>
<td></td>
<td>Peds</td>
<td>0.65</td>
<td>95</td>
<td>0.2-2.4</td>
<td>160</td>
</tr>
<tr>
<td></td>
<td>Hilite 7000 LT</td>
<td></td>
<td>Adult</td>
<td>1.9</td>
<td>275</td>
<td>0.5-7</td>
<td>185</td>
</tr>
<tr>
<td>LivaNova</td>
<td>EOS</td>
<td>Phosphorylcholine</td>
<td>Small Adult</td>
<td>1.2</td>
<td>150</td>
<td>0.5-5</td>
<td>330</td>
</tr>
<tr>
<td></td>
<td>TademLung</td>
<td>None</td>
<td>Adult</td>
<td>1.8</td>
<td>160</td>
<td>1-5</td>
<td>N/A</td>
</tr>
<tr>
<td>Abbott</td>
<td>Eurosets</td>
<td>Phosphorylcholine</td>
<td>Adult</td>
<td>1.81</td>
<td>220</td>
<td>0.5-7</td>
<td>250</td>
</tr>
</tbody>
</table>
Virchow’s Triad

- ECMO
- Intrinsic Hypercoagulability
- Blood Flow (Shear, turbulence, vortices, residence time)
- Artificial Material Thrombogenicity
Where Does Stasis Occur on ECMO?

- Areas of non-ideal flow
  - In-line SVO₂ cells
  - Connectors
  - Oxygenator
  - Pigtails
  - Hemofilters
- These sites should be monitored regularly
  - Good indicators for inadequate anticoagulation
  - May need changed if clot becomes significant
- Become more problematic during low flow situations
No Magic Bullet


Taciluzimab, Vitamin C (Hartman et al., ASAIO, 2020)
Leukocyte Activation Coincides with Lung Opacification & Is a Function of Oxygenator Surface

<table>
<thead>
<tr>
<th>Oxygenator Type</th>
<th>24 hr X-ray Score</th>
<th>Days to Subsidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silicone</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Heparinized PMP</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
