Scientific Update of Coagulation and Anticoagulation during ECMO

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Texas Children’s Hospital
Disclosure
Conflict of Interest in the Past 12 months.
Nothing is related to this presentation.

<table>
<thead>
<tr>
<th>Research Support/P.I.</th>
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<tbody>
<tr>
<td>Employee</td>
<td>No relevant conflicts of interest to declare</td>
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<td>Consultant</td>
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<td>Major Stockholder</td>
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<td>Scientific Advisory Board</td>
<td>No relevant conflicts of interest to declare</td>
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I am not an Intensivist. I am a Transfusion Medicine and Coagulation physician.
Bleeding and Clotting on ECMO

- Retrospective chart review (from 12/2005 to 12/2014) that identified 30 patients who died while receiving or within 24 hours of the discontinuation of ECMO, and also had an autopsy performed.

- Thirty patients [age 0.46 years (0.08-3.41), males 16 (53.3%)] were identified and of these, 29 patients (97%) were noted to have hemorrhage in at least one organ system on autopsy. Thrombosis was identified in 17 (57%) of the patients.
<table>
<thead>
<tr>
<th>Test</th>
<th>Desired Target / Range</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>&lt;16.0-17.0 sec</td>
<td>To assess underlying coagulable state</td>
</tr>
<tr>
<td>PTT hepzyme</td>
<td>&lt;38.0 sec</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>&gt;200 mg/dL</td>
<td></td>
</tr>
<tr>
<td>PTT</td>
<td>70-90 sec</td>
<td>To monitor heparin effect</td>
</tr>
<tr>
<td>D-dimer</td>
<td>Normal</td>
<td>To monitor fibrin formation and fibrinolysis in the circuit and patient’s circulation</td>
</tr>
<tr>
<td></td>
<td>&lt;0.4 µg/mL</td>
<td></td>
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<tr>
<td>Platelet count</td>
<td>&gt;100,000/mm3</td>
<td></td>
</tr>
<tr>
<td>Anti-Xa</td>
<td>0.2-0.5 units/mL</td>
<td>To monitor heparin activity</td>
</tr>
<tr>
<td>Antithrombin</td>
<td>80-100%</td>
<td>To maximize heparin efficacy</td>
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</table>
Note

- ECMO coagulation panel is performed 2-4 times a day depending on the stability of coagulation.
- All tests including antithrombin and anti-Xa are available 24/7 within a turn-around time of <1 hour (average 30-45 min).
- ROTEM™ is performed once a day.
- A plasma free hemoglobin level measurement is performed once a day.
- von Willebrand panel (factor VIII, vWF antigen, vWF activity, and vWF multimer study) every week.
- Lupus anticoagulant assay may be performed if suspected.
## Monitoring Methods for Unfractionated Heparin

<table>
<thead>
<tr>
<th>Lab test</th>
<th>Advantages</th>
<th>Disadvantages</th>
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</table>
| **Anti–Xa** (by Rotachrom™, Diagnostica Stago) | ✦ Relatively easy to perform  
✦ Overall anti-Xa action with the patient’s own antithrombin | ✦ Affected by bilirubin and free hemoglobin  
✦ Not available for all hospitals |

Evaluation of heparin assay for coagulation management in newborns on ECMO.  
# PTT vs ACT

<table>
<thead>
<tr>
<th>Lab test</th>
<th>Advantages</th>
<th>Disadvantages</th>
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</table>
| **PTT**  | ✦ Global test for intrinsic coagulation factors  
✦ Readily available  
✦ By removing heparin with Hepzyme, baseline PTT can be measured  
✦ Evaluates heparin's overall activity | ✦ Affected by lupus anticoagulant, bilirubin, plasma hemoglobin, CRP, etc.  
✦ Not precise to monitor heparin effect |
| **ACT**  | ✦ Uses fresh whole blood  
✦ Can be performed at bedside | ✦ Affected by coagulation factors, heparin, lupus anticoagulant, and many others |

ACT is not used to monitor heparin effect except bedside surgery for CDH or plasma exchange without using ACD as anticoagulant.
Effect of Bilirubin on PTT and Anti-Xa Assay
Effect of Free Hemoglobin on PTT and Anti-Xa Assay

PTT

Anti-Xa

hgb, mg/dL

0 100 200

hgb, mg/dL

0 100 200

Hep-0.6

Hep-0.3

Hep-0.0
Effect of Free Hemoglobin and Bilirubin on PTT and Anti-Xa Assay
Age-Based Difference in Activation Markers of Coagulation and Fibrinolysis in Extracorporeal Membrane Oxygenation

Shilpa G. Hundalani, MBBS1,2; Kim T. Nguyen, MLS (ASCP)3; Esther Soundar, MD3; Vadim Kostousov, MD3; Lisa Bomgaars, MD2,4; Alicia Moise, MD1,2; Shiu-Ki R. Hui, MD, FCAP3; Jun Teruya, MD, DSc, FCAP2,3,5

Ped Crit Care Med, 2014;15:e198-205
PAI-1 Activity (normal: <5 ng/mL)

PAI-1 Antigen (normal: 1-25 ng/mL)
tPA (normal: 2-12 ng/mL)
Plasmin-Antiplasmin Complex (μg/L)

Day 1 n=34
Day 5 n=29
Day 12 n=10
Day 20 n=5
Off Day 12 n=3
Plausible Mechanism of Hyperfibrinolysis in ECMO Based on the Evidence in CPB

- Artificial surface leads to activation of contact system; increase bradykinin and factor FXIIa.
- Bradykinin stimulates endothelial cells to secrete tPA.
- Cardiopulmonary bypass (CPB) stimulates 5-fold increase in tPA activity.
- Increased tPA and increased fibrin leads to a 10 to 30 fold rise in plasmin generation during CPB.
Intravascular Hemolysis

- Monitored by plasma hemoglobin level
  - Normal <30 mg/dL
- Due to high shear force caused by clots, position of cannula, or high viscosity.
- Causes renal damage.
- Decreases nitric oxide and competes with ADAMTS13 binding site in vWF A2 domain → more thrombosis.
- Consider plasma exchange to remove plasma hemoglobin if >150 mg/dL.
Free hemoglobin increases von Willebrand factor-mediated platelet adhesion in vitro: implications on circulatory devices

Qi Da1, Miho Teruya2, Prasenjit Guchhait3, Jun Teruya4, John S. Olson5, and Miguel A. Cruz1,*
Blood August 25 2015

- Platelets accumulated on extracellular matrix, vWF, fibrin(ogen), or collagen surface at 180 s using buffer or 500 mg/dL of free Hb (p<0.001).
- Increasing doses of heparin did not block the increment of platelet adhesion to fibrin(ogen) induced by free Hb (500 mg/dL).
PathophysiologicaMechanism of Acquired von Willebrand Syndrome (AVWS)

1. Autoantibody against VWF
2. Adsorption of VWF
3. Increased shear stress
4. Decreased synthesis: this may be the only condition that may have type 1 AVWS.
5. Increased proteolytic degradation of VWF
6. Unknown mechanism

With the exception of mechanism #4, vWF is synthesized in normal or even increased in most patients with AVWS.
Diagnosis of Acquired von Willebrand Syndrome Associated with ECMO

- Factor VIII – normal to increase
- vWF antigen – normal to increase
- vWF activity (ristocetin cofactor activity) – normal or increase, occasionally decrease
- vWF activity/antigen ratio – low
- vWF multimer analysis – missing large multimer bands
Example of Acquired von Willebrand Syndrome

<p>| | |</p>
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<tbody>
<tr>
<td>Factor VIII</td>
<td>224%</td>
</tr>
<tr>
<td>vWF antigen</td>
<td>266%</td>
</tr>
<tr>
<td>vWF activity</td>
<td>143%</td>
</tr>
<tr>
<td>vWF activity/antigen</td>
<td>0.5</td>
</tr>
<tr>
<td>Multimer study</td>
<td>Missing large multimer bands*</td>
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High molecular weight multimers 10%
Intermediate molecular weight multimers 56%
Low molecular weight multimers 34%
VWF:RCo / Ag Over ECMO Duration

Systemic Variance of Days:
\[ p = 0.032 \]

\[ p = 0.044 \]
Extracorporeal Membrane Oxygenation Induces Short-Term Loss of High-Molecular-Weight von Willebrand Factor Multimers

Helmuth Tauber, MD,* Helmut Ott, MD,† Werner Streif, MD,‡ Guenter Weigel, MD,† Lorin Loacker, MD,† Josef Fritz, Dipl.Ing.,§ Anneliese Heinz, MD,¶ and Corinna Velik-Salchner, MD*

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www.anesthesia-analgesia.org
Management of AVWS

- Cryoprecipitate (1-2 units/10 kg)
- Humate-P™ (15-25 units/kg)

- Caution – both cryoprecipitate and Humate-P™ contain factor VIII. When factor VIII is elevated, it is further increased, causing thrombosis.
- Because the cause of AVWS is ongoing, it requires more often with a lower dose.
Indications of Plasma Exchange for ECMO Patients

- Plasma hemoglobin >150 mg/dL.
- Acquired von Willebrand syndrome (confirmed or suspected), which cannot be managed by Humate-P™ or cryoprecipitate due to a high factor VIII or high fibrinogen.
- Elevated bilirubin level that heparin anti-Xa cannot be measured.
- In the setting of TAMOF (thrombocytopenia-associated multiple organ failure), min 5 days, max 14 days everyday. Monitor OFI (organ failure index) for efficacy.
- FFP should be used as replacement fluid in order to prevent dilutional coagulopathy.
Algorithm-Based Management

- **Bleeding**
  - Yes
    - ECMO Target
      - Platelets >150,000/mm³
      - Fibrinogen >250 mg/dL
        - Yes: Heparin
        - No: Reassess Especially if ROTEM is abnormal
  - No: Targeted Therapy
    - Yes: Humate-P
    - No: Amicar
    - Reassess

**Reassess**
Algorithm-Based Management

Heparin

Humate-P

15-25 units/kg

Anti-Xa 0.1-0.2 units/mL or hold heparin up to 12 hours

Amicar

10-30 mg/kg/hour until bleeding improved

rFVIIa
Heparin-like effect in postcardiotomy extracorporeal membrane oxygenation patients

Marco Ranucci, Ekaterina Baryshnikova, Giuseppe Isgrò, Concetta Carlucci, Mauro Cotza, Giovanni Carboni and Andrea Ballotta
Figure 2: Reaction times (R-time) on thromboelastography (TEG) with and without heparinase during the first 12 days on extracorporeal membrane oxygenation (ECMO). Data refer to the whole patient population and are mean values of the different tests done on the same day. *P < 0.05; **P < 0.01.
Identification of acquired coagulation disorders and effects of target-controlled coagulation factor substitution on the incidence and severity of spontaneous intracranial bleeding during veno-venous ECMO therapy

J Kalbhenn,¹ N Wittau,² A Schmutz,¹ B Zieger³ and R Schmidt⁴
Incidence of Acquired Coagulation Disorders in the First 7 Days of ECMO
# Factor XIII Level during ECMO

<table>
<thead>
<tr>
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<th>Median</th>
<th>IQR (1\textsuperscript{st}, 3\textsuperscript{rd})</th>
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<tbody>
<tr>
<td>Normal Plasma</td>
<td>83.6%</td>
<td>80.7, 85.1</td>
</tr>
<tr>
<td>Day 1</td>
<td>59.6%</td>
<td>46.7, 61.6</td>
</tr>
<tr>
<td>Day 5</td>
<td>50.9%</td>
<td>42.3, 57.1</td>
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\[ p < 0.001 \]
Etiologies of Bleeding and Thrombosis and Management during ECMO

**Etiologies**
- Coagulation factor deficiency
- Thrombocytopenia
- Acquired VWS
- Hyperfibrinolysis
  - High tPA
  - Low PAI-1
- Intravascular hemolysis
  - High fibrinogen
  - High FVIII
  - High vWF antigen
- Membrane oxygenator
- Ultra filter
- Lupus anticoagulant

**Management**
- Plasma
- Platelets
- Cryoprecipitate
- Humate-P™
- Amicar™
- Tranexamic acid
- Heparin
- Antithrombin

ECMO

Bleeding

Thrombosis

Plasma exchange

TAMOF

= “Reset” hemostasis
Role of Transfusion Medicine and Coagulation

• Regularly included in the ECMO team.
• ECMO rounds every day and write a progress note.
• Manage bleeding, thrombosis, and anticoagulation by appropriate and timely blood component therapy and/or medication.
• Decision making for plasma exchange.
• Available for consults 24/7.
• QA meeting to monitor the quality of our support.
Future Directions

• How to monitor hyperfibrinolysis; easy and quick turn around time.
• Monitor factor XIII level.
  – Reasons of decreased factor XIII and efficacy of administration of FXIII concentrate or recombinant FXIII for bleeding have not been studied.
• Monitor heparin-like inhibitors. Is it myth or reality?
• New anticoagulant: Factor XII inhibitor – FXII is activated by negatively charged surface, but low FXII does not cause any bleeding. [A FXIIa inhibitory antibody provides thromboprotection in extracorporeal circulation without increasing bleeding risk. Sci Transl Med. 2014;6:222ra17.]
Acknowledgement
People who made a significant contribution

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Oral presentations at AABB 2010
Poster presentation at ECLS 2010

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Thank you.

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