Improving ECMO: The effect of the extracorporeal circuit on blood, platelets, and coagulation.

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Disclosures
• I have no financial interests in any product or company.
• I will discuss off-label devices and drugs.

Roadmap
• Perceptions of Extracorporeal Membrane Oxygenation (ECMO)
• Complications of ECMO
• Coagulation Management
• Hemolysis
• Platelet Dysfunction
• Future Directions

CPB vs. ECMO
• Basic Components are membrane oxygenator and blood pump.
• CPB differs that it has an open venous reservoir, cardiotomy suction, requires increased anticoagulation, and usually performed at hypothermic temperatures.

ECMO saves lives
• Overall survival 64%
  – 77% for neonatal respiratory failure
  – 45% for pediatric cardiac failure
  – 32% for adult cardiac failure
• Major complications are still bleeding and thrombosis

Implements Neurologically Intact Survival

Shin et al, Crit Care Med, 2011
Comorbidities and ECLS

Duration of Mechanical Ventilation Prior to ECMO (Zabrocki L et al, Crit Care Med 2011)

Duration of ECMO (Camboni D et al Eur J CT Surgery 2011)

ECMO Complications:
- Thrombosis (30%)
- Berlin Heart % of deaths due to stroke
- Hemolysis (10%)
- Decreased due to new devices
- Still leading cause of renal failure and mortality
- Severe Bleeding (up to 30%)
- Surgical Site Bleeding (6.1-31%)
- Mechanical (overall <5%)
- Oxygenator Failure (5.7-7.2%)
- Pump Malfunction (1.3-1.8%)

Case Report:
- 2.8 kg - term infant with severe respiratory distress
  - Dx: Primary Pulmonary Hypertension
  - Placed on to ECMO
- 132nd hour
  - DIC with 55-60% reductions in platelets and fibrinogen despite transfusions.
  - One third of the membrane is clotted

Extracorporeal Life Support Organization (ELSO) Registry

Thrombosis Complications

Dalton HJ, Data adapted from ELSO Registry January 2012
Contact Activation

- Pathophysiology of RC related Hemostatic System Measurements
  - ACTIVATION
    - Thrombin
    - Platelet activation
    - Factor X activation
    - Factor Va activation
    - Factor VIII activation
    - von Willebrand factor activation
    - Platelet activation
  - CONSUMPTION
    - Thrombin
    - Fibrinolytic
    - Factor Xa
    - Factor Va
    - Factor VIIIa
    - von Willebrand factor
- Oliver WC, Semin in Cardiothorac and Vasc Anesth, 2009

Monitoring Anticoagulation

- Pearson et al, R=0.48, Retrospective review of ACT vs. Heparin concentration in 640 consecutive ECMO patients.
- Urlesberger et al noted heparin concentrations remained steady in term newborns needing ECMO

Thromboelastogram after CPB

- Miller B et al, Anesth & Analges, 2000
- Shore-Lesserson et al, Semin in Cardiothorac and Vasc Anesth, 2005

TEG use during Pediatric CV Surgery

- Romlin BS et al, Anesth & Analges, 2010

Anti-thrombin III

- Avidan MS, J Thorac Cardiovasc Surg. 2005

Case Report

- 2.8- term infant with severe respiratory distress
  - Dx: Primary Pulmonary Hypertension
  - Placed on to ECMO
- Blood Product transfused
  - First 120 hours: 4.4 ± 2.2 ml/hr
  - Final 35 hours: 7.8 ± 3.5 ml/hr
Hemolysis Complications

Ding et al, Cell Bio Int. 2007 & Lawson et al, Pediatric Crit Care Med, 2005

SEM of erythrocytes on roller-head pump for 8 hours.

Which pump is best?

Lawson et al, Pediatric Crit Care Med, 2005

& Moon et al, Artificial Organs, 1996

Which oxygenator is best?


Which system is best?


Perfusion Devices

- According to a 2008 survey of North American active ECMO centers:
  - over 80% routinely used roller pumps for neonatal ECMO.
  - 67% used the classical silicone membrane oxygenators in comparison to the centers using polymethylpentene hollow fiber oxygenators (14%).
- A follow-up survey in 2010 found that the majority of centers had switched to hollow-fiber oxygenators, although centrifugal pump use remains less than roller pumps.
Previous Research

- Our hypothesis was that at low flow rates, the differences are negligible when comparing a centrifugal pump/hollow-fiber oxygenator system to a traditional roller-pump/silicone membrane system.
  - Low Flow Neonatal Environment
  - Hemolysis
  - Platelet Aggregation

Components Tested

- HL20 Maquet
- Rotaflo Maquet
- 0800 Medtronic
- Quadrox D Maquet

Heparin Coated Components/Tubing
- Maquet - Bioline
- Medtronic - Carmeda

Experimental Design

- Four ECMO systems created fPH at a similar rate compared to the static control. (p=0.491).

Mean Free Plasma Hemoglobin

- All four ECMO systems created fPH at a similar rate compared to the static control. (p=0.491).

Case Report

- 2.8-term infant with severe respiratory distress
  - Dx: Primary Pulmonary Hypertension
  - Placed on to ECMO
- TEG at hour 173
  - Platelet count: 78
  - Fibrinogen: 96 mg/dL

Extracorporeal Life Support Organization (ELSO) Registry

<table>
<thead>
<tr>
<th>Site</th>
<th>Neon (%)</th>
<th>Peds (%)</th>
<th>Card 0-30D</th>
<th>Card 31D-6Y</th>
<th>Card 1-16Y</th>
<th>Adults</th>
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</thead>
<tbody>
<tr>
<td>Extracorporeal</td>
<td>27%</td>
<td>48%</td>
<td>60%</td>
<td>58%</td>
<td>59%</td>
<td>53%</td>
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<tr>
<td>Dalton HJ, Data adapted from ELSO Registry January 2012</td>
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ECMO Platelet Dysfunction

SEM of oxygenator membrane after 60 min. of pump time.

Platelet Methods

• Flow Cytometry
  – Microaggregates are associated with impaired neuropsychological functioning.
  – PE anti-CD61 labeled antibody
  – A flow cytometric gate was set acquired cell events in the platelet population

Platelet Aggregation

Mean platelet aggregation percentage plotted as function of time. The percentage of platelet aggregation (anti-CD61) was the same in all ECMO systems after six hours of continuous use (p=0.74).

Limitations

• A limited time period that data was collected
• The use of a mock in vitro study which may not replicate the real neonatal ECMO condition
• The use of porcine blood instead of human blood.
• Further studies are needed using human blood components in a multiple day ECMO experiment and comparative clinical samples to confirm current study findings.

Conclusions

• In a low-flow neonatal environment; state of the art centrifugal pump combined with new fiber type oxygenators appear to be safe in regards to hemolysis and platelet aggregation.
• These results are encouraging as more hospitals begin using state of the art ECMO components for infants and small children.
• Increasing use of similar systems is also occurring in rapid extracorporeal life support systems with CPR (E-CPR), low-prime cardiopulmonary bypass systems, and during interhospital transport of patients.

However...

• Whole blood flow cytometry profile.
• Increase in the number of Platelet-derived Microparticles (PMPs) over time.
What is a microparticle?

Shear Stress Activation

- A: low shear stress, B: high shear stress, C: anti GP Ib
- D: anti-vWF, E: Anti-GP IIB/IIIA, F: RGDS, G: EGTA

MP are procoagulant

MP are inflammatory

PMP in Adult CPB

PMP in Congenital Heart Disease


Horigome et al, JACC, 2002
Specific Aim 1:

- Establish and characterize the generation of platelet-derived microparticles in an in vitro model of Pediatric Cardiopulmonary Bypass.
- Our hypothesis is that an increase in magnitude and duration of shear stress in the CPB circuit will increase the amount of PMPs and
  - Increase platelet activation
  - Increase coagulation
  - Increase in vitro inflammatory markers

Aim 1 Experimental Design

- Adult volunteer human blood to circulate for six hours at 300 ml/min and 600 ml/min.
- Static blood control will also be maintained in a similar test environment, only without extracorporeal circuitry.

Expected Outcomes & Pitfalls

- We expect to see an increase in PMP and
  - Drop in platelet number and fibrinogen
  - Increase in platelet activation, aggregation, and coagulation.
  - Increase in a measured inflammatory response.
- Limitations
  - Flow cytometry can only detect sizes greater than 0.5 micron
  - MP have been shown to degrade with storage and time.

Specific Aim 2:

- Examine the amount of PMPs generated for pediatric patients supported by CPB in relationship to post-operative outcomes.
- Our hypothesis is the PMPs increase as a function of CPB time and correlate with
  - Bleeding
  - Thromboembolism
  - Development of an inflammatory response
  - Post-operative outcomes

Aim 2 Experimental Design

Enrollment
- All patients under 18 yo undergoing CPB surgery or needing CPB support.

After Induction of Anesthesia

After Initiation of CPB

Before reversal of anticoagulation

After chest closure or Arrival in the PICU

12 hours after closure or arrival

24 hours after closure or arrival

36 hours after closure or arrival

After reversal of anticoagulation

Post-operative Outcomes

- Primary Outcomes
  - Mortality
  - Low Cardiac Output Syndrome
  - Acute Renal Failure or Injury (AKI-RF)
  - Kidney Failure
  - Mediastinal Tube Bleeding, >10 ml/kg
  - Thrombosis in circuit or patient
- Secondary Outcomes
  - 30 day post-operative mortality
  - Quantity of blood products transfused
  - Mechanical ventilation days
  - Hospital days

Hoffman et al, Circulation, 2003
**Expected Outcomes & Pitfalls**

- During CPB we expect circulating PMPs to increase after bypass and then normalize in a few hours.
- We expect that a significant increase in PMPs will correlate with post-operative outcomes.
- Future studies will help to correlate these findings to the in vitro model.

**Future Roadmap**

- Understand the pathophysiology of microparticles as a possible therapeutic target.
- Establish a reproducible in vitro model that simulates Pediatric CPB or ECMO support.
- Evaluate device improvements and biopharmaceuticals as effective therapeutics to reduce complications of CPB or ECMO.
- Understand the scope of microparticle generation in other pediatric conditions (e.g. sickle cell, oncology, sepsis, cystic fibrosis).
- Translate these research findings into clinical practice with the overall goal to improve outcomes of pediatric patients.

**Thank you**