Solving the Clot Problem in Cardiopulmonary Life Support Devices

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The Problem

ARDS
TOF
Noah et al, JAMA 2011

Two Solutions or one..

- Over 58,000 patients have been supported with ECMO
- Over 18,000 children/yr are supported with cardiopulmonary bypass (CPB) circuit.


ECMO saves lives

ECMO has an overall survival of 62% & Congenital Cardiopulmonary Bypass heart surgery has a survival >95%.

Dalton, Peds Crit Care Med, 2015

Improves Neurologically Intact Survival

Shin et al, Crit Care Med, 2011

Everything is getting smaller.

800 Pounds
22 Pounds

Increased Utilization

ECMO utilization for Adults increased 433% from 2001 to 2011.

What is the catch?

ECMO thrombosis rate 30 to 40% & CPB heart surgery is >11%.
Manlihot, Circulation, 2011

Aye, the rub...

Dalton, Peds Crit Care Med, 2015

The Catch 22

Dalton, Peds Crit Care Med, 2015

Contact Activation

Longo et al, Harrisons Principles of Internal Medicine, 18th Ed.

Improve the pump?

**Improve the oxygenator?**

- Hollow-fiber vs. silicone membrane vs. bubble oxygenators
- SEM of silicone hollow fiber oxygenator after 7 days.


**Coat the Circuit**

- **B-thromboglobulin**


**Protocols for Anticoagulation**

<table>
<thead>
<tr>
<th>Table 1: Anticoagulation Laboratory Protocol</th>
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<tbody>
<tr>
<td>Condition</td>
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<tr>
<td>-----------</td>
</tr>
<tr>
<td>Stable</td>
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<tr>
<td>Bleeding or clotting</td>
</tr>
<tr>
<td>Heparin dose decreasing</td>
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<tr>
<td>Heparin dose increasing</td>
</tr>
</tbody>
</table>

Northrup, Peds Crit Care Med, 2014

**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

Oliver WC et al, Semin in Cardiothorac and Vasc Anesth, 2009

**Thromboelastograms**

- Normal
- Anticoagulants/hemophilia
- Platelet Blockers
- Fibrinolysis

Romlin BS et al, Anesth & Analges, 2010

**Anti-thrombin III & Anti Xa**

- Byrnes, ASAIO, 2014 & O’Meara, ASAIO, 2015
Fellowship Research Hypothesis

- Thus, there is a compelling need to model and further study the mechanisms that promote these complications.

- Our initial 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
  - Platelet Function

- Meyer et al, PCCM, 2012

Mean Free Plasma Hemoglobin

- All four ECMO systems created free plasma hemoglobin at a similar rate. (p=0.491).
- Meyer et al, PCCM, 2012

Materials and Methods

- Adult Swine Blood
- Flow: 300 mL/min
- Flow Cytometry Measurements at
  - 0 minutes
  - 120 minutes
  - 240 minutes
  - 360 minutes
- Meyer et al, PCCM, 2012

Results

- Mean free plasma hemoglobin
  - All four ECMO systems created free plasma hemoglobin at similar rates. (p=0.491)
  - Meyer et al, PCCM, 2012
What is a microparticle?

Reininger et al, Blood, 2006

To wash or not wash....


MP Clot Mechanisms

Brio et al, JTH, 2003

Prothrombotic Microparticles


Porcine Study Conclusions

Meyer et al, ASAIO, 2015

KL2-K23 Research Approach

• Specific Aim 1: Define the thrombotic potential of (PMPs & MoMPs) generated in an in vitro model of pediatric cardiopulmonary bypass (CPB) using human blood.

• Specific Aim 2: Define the thrombotic potential of PMPs and MoMPs in blood samples from pediatric patients supported by CPB.

NIH/NHLBI: 1K23HL124336-01A1, 2015-2019

Pro-thrombotic Microparticles Generated by Pediatric Cardiopulmonary Bypass
Preliminary Results

Aim 1: Pediatric Model

- An pediatric CPB circuit circulated human blood, from normal healthy human volunteers at 0.3, 0.5, and 0.7 L/min.
- Components: Roller Pump, KIDS D100, 8Fr arterial catheter & 12 Fr Venous catheter
- An aliquot of static blood controls was maintained in a similar test environment without ECLS circuitry.
- Each circuit & control was normalized for hematocrit, pH, calcium, dextrose, and an ACT of 180 to 220.

Military Health System Research Symposium

Best in Show Poster
1500 entries, 1000 displayed in three sessions, picked overall winner.
Conclusions & Lessons Learned

Conclusions:
- Ex-vivo extracorporeal circulation led to an increase in pro-thrombotic PS.
- Plasma Free Hemoglobin rose in pump samples consistent with increased shear accumulation.
- Decrease in ProCoag PPL clotting time a measure of phosphatidylserine contribution to clot formation.
- There was a trend to decreasing ADP aggregation but no change in AA aggregation using TEG with PlateletMapping.
- Multiplate showed decreases in aggregation over time.
- Platelet activation by CD62P increased.

Aim 2: Patients/Populations

- Inclusion (target goal 50 children and adults)
  - Age 0 to 6 years & 18 to 99 years old
  - Will undergo CPB surgery to repair heart defect
  - Moderate (Risk Adjustment for Congenital Heart Surgery Score 2-3) to severe surgical complexity (RACHS 4-5)*
- Exclusion
  - Age >7 years or under <3 kg
  - Determined to be nonviable or uncertain
  - Mild surgical complexity (RACHS 1)
  - On ECMO/Mechanical circulation
  - Known inherited bleeding disorder

UTHSCSA IRB (#20140224H) and UHS Research Approved
Aim 2 Clinical Study

Call Study Staff if:
- Central line is being removed.
- Clot suspected requiring ultrasound.
- At start of oral anti-coagulant.
- At post-op day 28.
- At discharge/declared non-viable/expired.

We may repeat a:
- Blood Draw* AND Ultrasound

Post-op Course

Blood Draw*:
- At 20 to 24 hours from arrival in ICU, fill 2 tubes, and record time.
  1) 4.5 mL light blue
  2) 2.5 mL green

Ultrasound:
- We may order a venous ultrasound on all four extremities and central line to detect the presence of clots.

ICU Post-op Day 1

Blood Draw*:
- Upon arrival in ICU, fill 2 tubes, and record time:
  1) 4.5 mL light blue
  2) 2.5 mL green

ICU Post-op Day 0

Blood Draw*:
- For each TIME POINT, fill 2 tubes:
  1) 4.5 mL light blue
  2) 2.5 mL green

Time Points:
1) START of Bypass
2) At 60 minutes of Bypass
3) END of Bypass, not needed if bypass time ≤ 60 mins.

Populations

Children
- Birth ≤ 7 yrs. old
- ≤ 33 kg birth weight.
- OR
Adults
- 16 to 74 yrs. old
- AND Consented for cardiopulmonary bypass surgery.

Aim 2: Study Progress - May 2016

Clinical Data
- 13 children with congenital heart disease with CPB Surgery
  - Age range: 6 days to 5 years
  - Single Ventricle: 6
  - Double Ventricle: 7
  - REDCap Database
  - Adult Enrollment
  - Working with Cardiology and CV Surgery to start soon.

Aim 2: Conclusions

- PMP rose during the operation and the quickly cleared from circulation when patient removed from the pump.
- Platelet aggregation fell during OR and then recovered in PICU.
- Arachidonic Acid aggregation began impaired.
- Increased numbers of ballooning and PS expressing platelets.

Aim 2: Study Progress

Aim 2: Aggregation (n=9)

CPB ADP Aggregation (Mean ± SE, n=9)

CPB AA Aggregation (Mean ± SE, n=9)

Aim 2: Study Progress

CPB013 Confocal Zoomed

47 minutes of CPB

CPB013-C, OR END (60X, 5.8x zoom)
Future Directions

- **Ex-vivo Model**
  - Define the effect of platelet activation and PMP release in different circuit configurations (e.g., centrifugal vs. roller)
  - Define effectiveness of different therapeutic interventions (e.g., phosphatidylerine inhibitors or Anti-XIIa)
  - Define the platelet protein, mRNA, and mitochondria DNA
  - Determine the effect that pump-generated plasma has on coagulation function of endothelial cells using CAT*

- **Clinical Studies**
  - Expand to the adult population
  - Expand to the LVAD population (Jared Cohen, MD)
  - Collect HUVECs from newborns with congenital heart surgery and model coagulation in the lab.

*Geenen et al, Thrombosis Haemost, 2012

Collaborations (Cody Lab)

- EMILIN2 (also known as the Elastin Microfibril Interface Located Protein2) gene, located on Chromosome 18p, has a significant role in platelet aggregation.
- Identification of a gene and its downstream products that control platelet aggregation may help to identify populations at increased risk for heart attack or stroke.
- FUNDED by pilot project IIMS/CTSA at UTHSCSA

Grants

- **Completed**
  - Morrison Trust Meyer (PI) 10/1/2014 to 9/30/2015
  - Pro-thrombotic Blood Cell-Derived Microparticles Generated by CPB
    - KL2 Scholar, Mentored research and career development in Clinical & Translational Science Science
  - Microparticles Generated by Pediatric Cardiopulmonary Bypass
  - NIH/NCATS UL1TR001120 Clark (PI) 7/1/2015 to 6/30/2016
  - School of Medicine and the IIMS Clinical Investigator Kickstarter (CLIK) Pilot
  - Cardiopulmonary Bypass Surgery Related Coagulation Complications: The Role of Platelet Function and Platelet-derived Microparticles
- **Current/Awarded**
  - DOD/CCRP B-027/B028/B029-2017 Cap (PI) 10/1/2016 to 9/30/2019
    - Define the interaction of anti-coagulants and cell-based therapies with biomaterial surfaces in a laboratory ECMO model
    - Define operating parameters in a clinically relevant ex-vivo ECMO model
    - Evaluation of the platelet protein, mRNA, and mitochondria DNA signatures generated in an in vitro model of ECMO
  - AHA/Grant-In-Aid 16GRNT3098009 Meyer (PI) 7/1/2016 to 6/2018
    - Southwest Affiliate Grant-In-Aid: Coagulation Complications of Cardiopulmonary Bypass (C-3PO Study)
  - NIH/NHLBI 5K23HL124336-01A1 Meyer (PI) 8/1/2015 to 4/30/2019
    - Mentored Patient-Oriented Research Career Development Award
  - Pro-thrombotic Microparticles Generated by Pediatric Cardiopulmonary Bypass
  - NIH/NCATS UL1TR001120 Clark (PI) 10/1/2016 to 9/30/2017
  - EMILIN2 genetic variation effects on platelet aggregation and thrombosis

Collaborations (Aune Lab)

- Children with a hematological malignancy have an increased relative risk of a venous thromboembolism, despite having an overall survival that exceeds 85%.
- The incidence of VTE also increases:
  - adolescence
  - chemotherapy
  - necessary central venous catheter.
- However, the coagulation derangement measured at the onset of VTE did not predict VTE occurrence.

**Event:** Pediatric Grand Rounds University of TX Health Science Center at San Antonio

**Topic:** Children with a hematological malignancy have an increased relative risk of a venous thromboembolism, despite having an overall survival that exceeds 85%.

**Speakers:**
- Andrew Meyer, MD, MS
  - Principal Investigator
- Robin Tragus, RN
  - Clinical Research Nurse Supervisor
- Andrew Cap, MD, PhD
  - PCCU Medical Director and Safety Coordinator
- Brian Bryant
  - Blood Bank Manager
- Thomas Clark, MD
  - Director, Cardiothoracic Surgery
- Jon Gelfond, MD, PhD
  - PCCU Medical Director
- Steve Winters
  - Director, Biostatistics
- Ron Bryant
  - Blood Bank Manager
- Diana Taeed, MD
  - Task Area Manager, Cardiothoracic Surgery
- Andrew Cap, MD, PhD
  - PCCU Medical Director
- Ron Bryant
  - Blood Bank Manager
- Erik Delgren
  - Admin Assistant
- Michael Scherer, MBA
  - Business Manager
- David Darlington, PhD
  - Research Chemist

**Summary:**
- The incidence of VTE also increases in children with hematological malignancy: adolescence, chemotherapy, and necessity of a central venous catheter.
- However, the coagulation derangement measured at the onset of VTE did not predict VTE occurrence.
THANK YOU