Anticoagulation & Extracorporeal Circuit

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Disclosures

• None
Objectives

- A little bit of history
- Present day anticoagulation during ECLS
- Surface Modifications present and future (more future)
1885 Frey&Gruber: First Film Oxygenator
1930 Gibbon & Gibbon: Cardiopulmonary Bypass

The oxygenator consisted of a vertical revolving cylinder that was occupied by a hollow, stationary chamber that was connected to peripheral circuits (A, B, C, D). The diagram illustrates the flow of gas and liquid through the oxygenator, with various components such as the oxygenator itself (E) and the connecting tubes (F). The device was designed to maintain a constant partial pressure of oxygen and carbon dioxide, ensuring optimal conditions for perfusion. The image shows a historical photograph of the oxygenator and its components, highlighting the early development of cardiopulmonary bypass technology. The device was used to simulate physiological functions in patients undergoing surgery or medical procedures that required temporary cessation of circulation.
1968 Ted Kolobow and Warren Zapol
First successful ECLS Patient; Santa Barbara, Ca, 1971.
ARDS Post Trauma
J Donald Hill MD and Maury Bramson BME
1975 Bartlett: First Neonatal Respiratory Case

Esperanza Day 1 of Life for Respiratory Distress Syndrome

Slide Courtesy of RH Bartlett
Dr. McLean’s discovery of heparin was recognized posthumously as he developed a fatal illness and died November 14, 1957.
Anticoagulation During ECLS

- Heparin is old, clumsy and variable but it is what we know.

- We have become expert in using a suboptimal anticoagulant.

- And have added more monitoring tests than we actually know what to do with.
Anticoagulation During ECLS

• Direct thrombin inhibitors have much better utility.

• We have become comfortable in their use.

• They make sense to use with ECLS for both anticoagulant and anti-inflammatory properties.

• They are expensive and unlikely to cover ECLS anticoagulation worldwide.
Mechanism of Action

Thrombin

(fibrinogen) binding site

(catalytic) site

1

2

Apolar site

Heparin-binding site (exosite 2)

Fibrinogen-binding site (exosite 1)

Argatroban

Bivalirudin

Bivalirudin for Alternative Anticoagulation in Extracorporeal Membrane Oxygenation: A Systematic Review

Filippo Sanfilippo, MD, PhD¹,², Sven Asmussen, MD³,⁴, Dirk M. Maybauer, MD, PhD⁴,⁵, Cristina Santonocito, MD¹, John F. Fraser, MD, PhD⁴, Gabor Erdoes, MD⁶, and Marc O. Maybauer, MD, PhD⁴,⁵,⁷
# Guide to Dosing and Management

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>MONITORING**</th>
<th>BLEEDING**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>CHILD</strong></td>
<td><strong>ADULT</strong></td>
<td><strong>CHILD</strong></td>
</tr>
<tr>
<td>Argatroban</td>
<td>0.1-10 ug/kg/min in HIT*; 0.75 ug/kg/min in hepatic compensation</td>
<td>0.2 ug/kg/min*</td>
<td>PTT 1.5-3X (&lt;100 sec)</td>
</tr>
<tr>
<td></td>
<td>Adjust dose by 0.1-0.25 ug/kg/min and adjust re PTT</td>
<td></td>
<td>2 hr post initiation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ACT 160-200</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Esper et al 2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>CASE REPORTS</strong></td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>Bolus 0.125-0.25 mg/kg</td>
<td>Infusion 0.08-0.2 mg/kg/h</td>
<td>PTT 50-70</td>
</tr>
<tr>
<td></td>
<td>Infusion 0.125-0.2 mg/kg/h (if initial drug)</td>
<td>Dose increase up to 0.03 mg/kg/h</td>
<td>2 hr post initiation</td>
</tr>
<tr>
<td></td>
<td>Infusion 0.1-0.8, if tx from UFH</td>
<td></td>
<td>ACT 160-200</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>&lt;10 case reports</strong></td>
</tr>
</tbody>
</table>

*Courtesy of Patti Massicotte*
Monitoring Remains a Debate:

- Monitoring remains challenging with the need for both aPTT (1.5-3.5 x normal) and ACTs (160-<=220) for correlation

- Anti IIa useful to determine amount of inhibition

- Reimplementation of Total Thrombin Time is another consideration

- Direct tests are Ecarin Assay (Bival) and Argatroban levels
Platelet Inhibitors

- Main experience in VADs and shunt patency management with use of arachidonic pathway inhibitors (ASA) and ADPase inhibitors (Dipyridamole)

- Monitoring is indirect through effect on whole blood clot ability (ACT, thromboelastography, thromboelastometry)
Safety of nitric oxide added to the ECMO circuit: a pilot study in children

Roberto Chilletti,1 Steve Horton,2 Andrzej Bednarz,3 Robert Bartlett4 and Warwick Butt1

Abstract
We describe our experience of 30 consecutive children supported with ECMO and receiving 20 ppm of nitric oxide in the oxygenator of the ECMO circuit. Administration of nitric oxide into the ECMO circuit is safe and could potentially mitigate ischaemia reperfusion injury and end-organ dysfunction of children requiring mechanical support.

Keywords
ECMO; nitric oxide; ischaemia reperfusion injury; bleeding; outcome

Sir,

Extracorporeal membrane oxygenation (ECMO) is a standard therapy that is used in many different life-threatening clinical situations, such as acute respiratory failure, but also resuscitation from cardio-respiratory arrest, cardiogenic shock, sepsis and circulatory support following cardiac surgery and respiratory or cardiac transplantation. Many of these situations (especially for veno-arterial ECMO) are associated with patients likely to have a systemic inflammatory response syndrome (SIRS) or a potential reperfusion injury following tissue ischaemia.

Both animal and human studies have shown beneficial effects of administered nitric oxide (NO) on platelet function1 and minimization of SIRS after exposure of blood to extracorporeal circuits. Equally importantly, ischaemia/reperfusion injury can be lensened in many organs, including the brain2 and the heart,3 with the administration of NO or nitric oxide donors prior to or concomitant with reperfusion. A randomized control trial by James et al. showed that the addition of 20 ppm of NO to the oxygenator gas flow during cardiopulmonary bypass (CPB) for children having cardiac surgery for congenital heart disease reduced the incidence of postoperative low cardiac output syndrome.4 This study supported the findings of Chechhia et al. who had previously shown reduced inflammatory response and decreased duration of mechanical ventilation in children with Tetralogy of Fallot undergoing repair on CPB.5 Hence, we hypothesized that adding NO to the fresh gas flow of the oxygenator when ECMO was initiated and then continuing the NO would potentially limit ischaemia/reperfusion injury as well as contact activation of platelets and white blood cells.

NO comes at a concentration of 800 ppm and, in order to have 20 ppm, a total fresh gas flow of at least 3 litres per minute is needed. This is easy to achieve on CPB, with the addition of CO2 and a perfusionist present continuously. This can also be done on ECMO in adults or larger patients, but with small patients, small oxygenators and lower blood flow (500 mls/min or so) there is a possibility that 3 litres per min of gas flow can lead to a high pressure on the gas side of the membrane and, hence, a potential gas to blood leak and gas embolism. In order to avoid this potential problem, we have chosen to use 3 litres per min total gas flow (allows DSIR unit to control NO ppm) and add a combination low-flow and pressure release valve to our ECMO circuit, as shown in Figure 1.

The hospital ethics committee approved the initial study (HREC BD031) which was designed to evaluate

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A Factor Xllla Inhibitory Antibody Provides Thromboprotection in Extracorporeal Circulation Without Increasing Bleeding Risk

Magnus Larsson,1,2* Veronika Rayzman,3* Marc W. Nolte,4* Katrin F. Nickel,1,5,6* Jenny Björkqvist,1,5 Anne Jämsä,1,5 Matthew P. Hardy,3 Marion Fries,4 Stefan Schmidbauer,4 Patricia Hedenqvist,7 Michael Broomé,2,8 Ingo Pragst,4 Gerhard Dickneite,4 Michael J. Wilson,3 Andrew D. Nash,3 Con Panousis,3* Thomas Renné1,5,6*†

Currently used anticoagulants prevent thrombosis but increase bleeding. We show an anticoagulation therapy without bleeding risk based on a plasma protease factor XII function-neutralizing antibody. We screened for antibodies against activated factor XII (FXIIa) using phage display and demonstrated that recombinant fully human antibody 3F7 binds into the FXIIa enzymatic pocket. 3F7 interfered with FXIIa-mediated coagulation, abolished thrombus formation under flow, and blocked experimental thrombosis in mice and rabbits. We adapted an extracorporeal membrane oxygenation (ECMO) cardiopulmonary bypass system used for infant therapy to analyze clinical applicability of 3F7 in rabbits. 3F7 provided thromboprotection as efficiently as heparin, and both drugs prevented fibrin deposition and thrombosis within the extracorporeal circuit. Unlike heparin, 3F7 treatment did not impair the hemostatic capacity and did not increase bleeding from wounds. These data establish that targeting of FXIIa is a safe mode of thromboprotection in bypass systems, and provide a clinically relevant anticoagulation strategy that is not complicated by excess bleeding.
Anticoagulation During ECLS

*IMAGINE* no more heparin, no more AT infusions, no more systemic agents that affect the patient hemostatic response, no more endless debates about the correct way to measure for adequate anticoagulation.
Surface Modifications: The Artificial Endothelium

**IMAGINE** nonthrombogenic circuitry that has longevity, preserves patient hemostatic response and therefore reduces risk to the patient regardless of extracorporeal device.
Current Materials Paradigm

Current Devices

Clotting Cascade
Protein Deposition
Platelet Activation
Fibrin Formation

Strategies
1. Passivated Surfaces
2. Bioactive Surfaces
3. Regenerative Surfaces

How do we get from systemic therapies to surface localized therapies that augment cell responses?
Non-thrombogenic Endothelium

Maintains the delicate balance between thrombosis and anticoagulation
The Challenges with Non-Thrombogenic Circuitry

- Medical Personnel Considerations:
  - Provide oxygenation
  - Control thrombosis/hemostasis
  - Prevent inflammation
  - Balance biochemical responses

- Device Considerations:
  - Maintain blood flow
  - Provide adequate gas transport
  - Prevent clotting surface

- The Challenges with Non-Thrombogenic Circuitry:
  - What do you want the material to do? Function?
    - Prevent platelet adhesion? Infection? Inflammation? Promote re-endothelialization?
    - Remain permanently implanted? How long want it to last?
    - Do you want local or systemic action?
  - How can you incorporate this function into the material?
    - Drug release? Surface morphology?
    - Chemical linkages?
  - What form does the material need to be in?
    - Adhered to a metal substrate? Molded? Extruded?
  - How can you assess whether or not the material has the desired function?
    - Yes? No? Quantitative?
    - Mode of action?
  - Safety considerations
    - What are the unintended consequences?

- Manufacturing Considerations
  - Integrated into current processes
  - Sterilization using current practices
  - Cost

- Incredibly large surface area device
  - huge volume of blood contact
The Challenges with Non-Thrombogenic Circuitry

**Medical Personnel Considerations:**
- Provide oxygenation
- Control the coagulation cascade
- Prevent the inflammation
- Balance biochemical responses

**What do you want the material to do? Function?**
- Remain permanently implanted? How long want it to last? 
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- Maintain blood flow
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- Integrated into current processes
- Sterilization using current practices
- Cost
Classification of Surface Modifications

- Surface Passivation
  - phosphorylcholine
  - albumin

- Biomimetic Surface Functionalization
  - heparin
  - nitric oxide
  - direct thrombin inhibitor

- Endothelialization
  - in vitro preseeding
  - in situ capture
Reduced Platelet Activation and Thrombosis in Extracorporeal Circuits Coated with Nitric Oxide Release Polymers


Roadblock: The Entire Compound Leaches!!!
Effect of varying nitric oxide release to prevent platelet consumption and preserve platelet function in an \textit{in vivo} model of extracorporeal circulation

Amy M Skrzypchak$^1$, Nathan C Lafayette$^1$, Robert H Bartlett$^1$, Zhengrong Zhou$^1$, Megan C Frost$^2$, Mark E Meyerhoff$^2$, Melissa M Reynolds$^3$ and Gail M Annich$^4$
The immobilization of a direct thrombin inhibitor to a polyurethane as a nonthrombogenic surface coating for extracorporeal circulation

Jane Yu, Elizabeth Brisbois, Hitesh Handa, Gail Annich, Mark Meyerhoff, Robert Bartlett and Terry Major

Fig. 2  (A) Structure of argatroban linked to CarboSil®. (B) Immobilization of argatroban to CarboSil® is possible due to the presence of a free amine (NH₂ group) on argatroban and is shown in the synthesis scheme.
Combined Direct Thrombin Inhibitor and NO

The effectiveness of the process is determined by the presence of NO,
which is released at a rate of about $6 \times 10^{-10}$ mol/cm²/min.

**Tygon** tubing (PVC)
**Base layer**—100% PU

**Active layer**
- PU
- 25% DBHD/N₂O₂
- 10 wt% PLGA (1-2 months)

**Top coat**—Argatroban-immobilized PU

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Success!!! Now how do we produce them?

Biomaterials. 2014 August; 35(26): 7271–7285
Can apply to oxygenators and filters.
Classification of Surface Modifications

**Surface Passivation**
- phosphorylcholine
- albumin

**Biomimetic Surface Functionalization**
- heparin
- nitric oxide
- direct thrombin inhibitor

**Endothelialization**
- *in vitro* preseeding
- *in situ* capture
Based on fluorous chemistry, fluorous molecules can be physically adsorbed onto fluorous-containing surfaces. The strong intermolecular interaction between the fluorinated lubricant and the fluorosilane layer locks the lubricant.
Classification of Surface Modifications

Surface Passivation
- phosphorylcholine
- albumin

Biomimetic Surface Functionalization
- heparin
- nitric oxide
- direct thrombin inhibitor

Endothelialization
- *in vitro* preseeding
- *in situ* capture
Introduction

The use of endothelialized biomaterials for tissue engineering and regenerative medicine has developed using polymers such as expanded polytetrafluoroethylene and polyethylene terephthalate (e.g. Dacron®) [1]. However, graft patency was limited for small diameter (<4 mm) situations, such as for coronary bypasses. This early work revealed the desire to implant endothelial cells. The modular scaffolds are then implanted directly or randomly prior to implantation in order to create a rudimentary internal vasculature. (b) Scaffolds for in vitro use of endothelialized biomaterials are cultured or immobilization of pro-angiogenic factors to initiate host endothelial cell in-growth [2]. Unfortunately, attachment to the graft further compromised the pre-seeding approach while unfavorable between canine and human EC and their ability to migrate from the anastomosis, the region where the graft was attached to the patient's vasculature (reviewed in [3]). Limited EC endothelialization via pre-seeding was first attempted in the early 1980's [2].

Endothelialized biomaterials for tissue engineering applications
in vivo

Omar F. Khan¹,² and Michael V. Sefton¹,³
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³ Corresponding author: Sefton, M.V. (michael.sefton@utoronto.ca).

1. Acellular vascular graft
2. Pre-endothelialized vascular graft
3. Acellular scaffold
4. Released soluble factors
5. Vessel infiltration
6. Pre-endothelialized scaffold
7. Vessel outgrowth
8. Modular tissue-engineered construct
9. Perfusion through interconnected void space
10. Endothelialized module with embedded therapeutic cells

VV extracorporeal life support for the Third Millennium: will we need anticoagulation?

Danny Eytan¹, Yuval Bitterman¹, Gail M. Annich²

¹Department of Pediatric Critical Care, Rambam Medical Center, Haifa, Israel; ²Department of Critical Care Medicine, The Hospital for Sick Children University of Toronto, Toronto, Canada

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Table 2 Characteristics of ideal extracorporeal surface modification

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Heparin bonded</th>
<th>PPC</th>
<th>No releasing</th>
<th>No generating</th>
<th>Combination NO and DTI</th>
<th>EDC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cover entire circuit</td>
<td>✓</td>
<td>?</td>
<td>✗</td>
<td>✓</td>
<td>±</td>
<td>✓</td>
</tr>
<tr>
<td>Longevity</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>?</td>
</tr>
<tr>
<td>No systemic anticoagulation</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Normal manufacture</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Prevent thrombosis</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Preserve platelet function</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Reduce inflammation</td>
<td>±</td>
<td>±</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

PPC, phosphorylcholine; EDC, endothelialization; DTI, direct thrombin inhibitor; NO, nitric oxide.
The Future Circuit

- Will require both thrombin inhibitor and platelet inhibitor that do not leach systemically.

- For long term devices customize to the patient an autologous endothelial lined circuit/device.

- More challenges/roadblocks ahead despite believing we have now experienced all unforeseen limitations.
There is no one great mind behind the development of the ideal biocompatible surface. It is rather, a dedicated team of people from across disciplines who bring to the table their abilities and knowledge to allow the team to think beyond a narrow scope and anticipate the challenges.

- 2007 UK Cesar Trial Finishes
- 2008 Switch to Lower Pressure Oxygenators and centrifugal systems with more refined, streamlined circuitry
- 2009 H1N1 Epidemic and Adult ECLS explodes
- 2015 Multiple Worldwide Chapters for ELSO with >200 centers worldwide sharing and collaborating on the experience
- 2018 EOLIA Study
- Present long term ECLS for respiratory failure is a reality
Esperanza with her adoptive mother
Thank You

Questions?