Inflammatory effects of ECMO/ECLS

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FRANCE
COI disclosure to this presentation

• Speaker at some Medtronic and Sorin-Liva Nova conferences
Introduction

• Purpose limited to adults

• ECMO is mainly indicated for
  – Lung failure: ARDS
  – Cardiac failure: ECLS (post-cardiotomy) or CPR

• Systemic inflammatory response (SIRS) is already present before ECMO or ECLS start

• **What is the contribution of ECMO, as assisted circulation, to SIRS?**
Measures to Control Blood Activation During Assisted Circulation

Christophe Baufreton, MD, PhD, Matthias Kirsch, MD, and Daniel Y. Loisance, MD

- Immediate postop. period
- Prolonged MCS

- Circulatory shock
- Biomaterial independent factors
- Acute blood/biomaterial interaction
- Time
- IR
- Rehabilitated patient
- Chronic biomaterial modifications
- Infection
**Extracorporeal Life Support for Severe Acute Respiratory Distress Syndrome in Adults**

*Hemmilä M Ann Surg 2004;240:595*

<table>
<thead>
<tr>
<th>Most frequent complications (&gt;20% of patients)</th>
<th>Frequency</th>
<th>Univariate p value for mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cannula problems</td>
<td>21.1%</td>
<td>NS</td>
</tr>
<tr>
<td>• Oxygenator failure</td>
<td>20.8%</td>
<td>NS</td>
</tr>
<tr>
<td>• Clots in circuit</td>
<td>20.7%</td>
<td>NS</td>
</tr>
<tr>
<td>Hemorrhagic complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cannulation site bleeding</td>
<td>31.4%</td>
<td>0.03</td>
</tr>
<tr>
<td>• Surgical site bleeding</td>
<td>26.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Culture-proven new infection</td>
<td>38%</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Is ECMO a particular case of VAD?

- ECMO/ECLS has been part of the rationale to develop the minimally extracorporeal circulation (MECC) concept that results in near-OPCAB effects (Mazzei V. Circulation 2007;116:1761-7.)
- Different settings: VAD-like patients (organ failure) but MECC-like perfusion
- Different settings for baseline SIRS
- Beating and working heart: Veno-Venous (VV) for ARDS
- Beating but non working heart: Veno-Arterial (VA) for ECLS/CPR
The experience of CPB

- CPB-induced SIRS has been extensively assessed but needs to be continued because of changes in patients therapy
- SIRS is strongly associated to hemostasis disturbances
- The resulting blood activation may have early and late phases and may be prolonged as long as 1 month after surgery
- Very complex physiopathology but may be classified as dependent or independent of blood contact with biomaterials
Post CPB SIRS

CONTACT BLOOD / MATERIALS

- Contact phase
- Complement
- Platelets - Neutrophiles
- Monocytes (cytokines)

BIOMATERIAL INDEPENDENT FACTORS

- Air - Blood contact
- Tissue pathway activation
- Hypothermia
- Ischemia - reperfusion
- Pulsatility
- Endotoxin release
- Heparin – protamine
- Hemodilution

CELLULAR AND PLASMACIC ACTIVATION
There is no current national standardized protocol that has been elucidated for the control of anticoagulation for patients on ECMO, and further study is required in this area.
Hemolysate-mediated platelet aggregation: an additional risk mechanism contributing to thrombosis of continuous flow ventricular assist devices

Phat L Tran,1*, Maria-Grazia Pietropaolo,2† Lorenzo Valerio,2 William Brengle,1 Raymond K Wong,1 Toshinobu Kazui,1 Zain I Khalpey,1 Alberto Redaelli,2 Jawaad Sheriff,3 Danny Bluestein3 and Marvin J Slepian1,3

Figure 4. Prothrombotic activity of RBC hemolysate. A) Platelet aggregation effectiveness of RBC hemolysate in comparison to that of LDH and pHb (at levels observed in cVAD patients); RBC-hemo demonstrated at least a 7-fold increase in aggregation when compared to pHb and 15-fold when compared to LDH and control (PRP alone). *p-value <0.05. B) Scanning electron microscope (SEM) of RBC. C) SEM of non-activated platelets. D) SEM of RBC-hemo-induced platelet aggregation. n-samples = 4, *p-value <0.05.
Increased prothrombotic state lasting as long as one month after on-pump and off-pump coronary surgery

Alessandro Parolari, MD, PhD, Luciana Mussoni, PhD, Marta Frigerio, PhD, Moreno Naliato, MD, Francesco Alamanni, MD, Andrea Galanti, MD, Giuseppe Fiore, MD, Fabrizio Veglia, PhD, Elena Tremoli, PhD, Paolo Biglioli, MD, and Marina Camera, Biol Sci, PhD.
Contact of blood with biomaterials (BM)

- Constant
- Initiated very early after CPB start
- Involves fibrinogen, platelets and complement cascades
- BM-dependent blood activation

![Diagram showing blood coagulation pathways](image)
Oxygenator is the most important artificial surface in contact with blood.

Figure 1: Typical hollow fiber design with a direct gas to blood interface through an open pore.

Figure 2: Gas exchange by diffusion through a semi-permeable membrane.

Polypropylene
Silicone

Diffusion membrane
Poly-methyl pentene

Avoid areas of blood stagnation and limit shear stress.
Biocompatibility
Surface treatment by heparin-coating

- Heparin
  - Covalently-bonded using Endpoint Attachment process that ensures bioactivity
- Non-leaching
- Negative charge
  - Heparin
  - Hydrophilicity
  - Hydrophilic priming layer

Preliminary support to reduce safely anticoagulation during CPB within dedicated protocols
Heparin-coating provides thromboresistance and reduce SIRS resulting from blood contact with the artificial surface.
BM-independent blood activation

- Less important in ECMO/ECLS than in CPB
- May vary among different clinical settings
- VA: postcardiotomy with previous CPB including BMI-BA
- VV: ARDS without CPB
Once installed, ECMO has only 3 components.

- **Patient**
- **Oxygénateur**
- **Pompe**
Biocompatibility of a closed vs open perfusion system

Systemic Blood Activation With Open and Closed Venous Reservoirs

Jacques P. A. M. Schönberger, MD, PhD, Peter A. M. Everts, EKP, and Johannes J. Hoffmann, PhD

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- Reduced activation of
  - Complement
  - Neutrophils
  - Platelets
  - Fibrinolysis
- Reduced hemolysis and postop. Bleeding
- Improves endotoxin clearance

Tissue pathway and pericardial cavity
Tissue factor expressed by monocytes

HEPARIN-COATED CIRCUITS
AND REDUCED ANTICOAGULATION
Cell deposits on arterial filters

Electron microscopy (x 350)

Heparin-coated ECC
Full heparinization
300 IU/Kg  ACT > 400 s.

Heparin-coated ECC
Reduced heparinization
200 IU/Kg  ACT > 300 s.
Cell deposits on arterial filters

Electron microscopy (x 7500)

Markers for Endothelial Activation During Open Heart Surgery

Hilde Eikemo, MS, Olav F. M. Sellevold, MD, PhD, and Vibeke Videm, MD, PhD

Departments of Immunology and Transfusion Medicine, and Anesthesia and Intensive Care, St. Elisabeth Heart Center, University Hospital of Trondheim, and Department of Laboratory Medicine, Children’s and Women’s Health, Norwegian University of Science and Technology, Trondheim, Norway

Conclusions. Endothelial cells were activated during cardiopulmonary bypass. The soluble adhesion molecules sICAM-1, sVCAM-1, and sE-selectin displayed different kinetics, rendering it difficult to determine a simple expression for the degree of endothelial cell activation. Clinically, sVCAM-1 seemed to be the best-suited marker for endothelial cell activation, because it was only associated with aortic cross-clamping and heparin and protamine doses, and it also showed the largest numerical changes.

The highest heparin dose, the highest endothelial activation

Fig 1. Concentrations of sVCAM-1, sICAM-1, and sE-selectin (median ± 95% confidence interval) in sera from patients undergoing open heart surgery (n = 21). Sampling times: T1 = before anesthesia, T2 = after retransfusion of blood from the heart-lung machine, and T3 = the first postoperative morning. The p values refer to differences between subsequent time points.
Pulsatility and gut perfusion

- Not an issue in VV-ECMO because working-beating heart
- Of clinical relevance in VA-ECLS but to which extent since beating function of heart is maintained?
- Pulsatility: oscillatory energy transmitted laterally to tissues
- Pulse trace? not a reliable marker
- Energy Equivalent Pressure: \( EEP = \frac{\int fpdt}{\int fdt} \) Shepard 1966
  - EEP>15-20 mm Hg: pulsatile; EEP<15 mm Hg: non pulsatile
- Lack of skills to measure it in clinical practice
**Surplus Hemodynamic Energy**

- Exists only if some pulsatility is created in pressure or flow
- SHE=0 with 100% non-pulsatile flow
- Maintains peripheral perfusion by keeping capillary beds open and tissue fluid moving
- Capillary collapse: anaerobic metabolism

\[
\text{SHE (ergs/cm}^3\text{)} = 1332\left[\left(\frac{\int fpdt}{\int fdt}\right) - \text{MAP}\right]
\]
Arterial pumps and pulsatility
Transcranial Doppler examination

- Conventional roller pump
- Centrifugal pump

Ripple
Index of pulsatility

No pulsatility
Impact of arterial pumps on SIRS

Inflammatory Response to Cardiopulmonary Bypass Using Roller or Centrifugal Pumps

Christophe Baufreton, MD, PhD; Liliane Intrator, MD; Piet G. M. Jansen, MD, PhD; Henk te Velthuis, PhD; Paul Le Besneraís, MD; Alexander Vonk, MD; Jean-Pierre Farcet, MD; Charles R. H. Wildevuur, MD, PhD; and Daniel Y. Loisance, MD

Gut Perfusion
Pulsatile flow and normothermia

% Change in gastric mucosal
laser Doppler blood flow

Pulsatile flow
28°C P vs NP
* p=0.04
37°C P vs NP
** p=0.03

Temperature
P 28°C vs 37°C
§ p=0.03
NP 28°C vs 37°C
§§ p<0.04

The lowest temperature and pulsatility
The highest gut damage

on cpb  release of  off cpb  x-clamp
Endotoxinemia during CABG
Role of pulsatile perfusion

Features of endotoxin

• Biphasic release: after start CPB (C3a) and during aortic cross clamp time (Jansen N. 1992)
• Factors of endotoxin release during CPB (Jansen P. 1994)
  – Vasoconstricting drugs
  – Duration of aortic cross clamping
  – Hypo-oncotic hemodilution
• Intestinal permeability during CPB is associated to endotoxinemia (Oudemans-van Straaten H. 1996)
• Circulating endothelin and endotoxin are correlated, but it is unknown which one is the trigger (te Velthuis H. 1996)
Plasma Concentrations of Inflammatory Cytokines Rise Rapidly during ECMO-related SIRS due to the Release of Pre-formed Stores in the Intestine


Conclusions—TNF-α and IL-8 concentrations rose faster in plasma than in the peripheral tissues during ECMO, indicating that rising plasma levels of these cytokines immediately following the initiation of ECMO may not reflect increasing tissue synthesis of these cytokines. Mobilization of preformed cellular stores of inflammatory cytokines such as in mucosal mast cells may play an important pathophysiological role in ECMO-related SIRS.
Pulsatility in resistance arteries in vitro protects vascular function from oxidative stress and inflammation.
Gastrointestinal bleeding rates in recipients of nonpulsatile and pulsatile left ventricular assist devices

Sheri Crow, MD, MS, a Ranjit John, MD, b Andrew Boyle, MD, c Sara Shumway, MD, b Kenneth Liao, MD, PhD, b Monica Colvin-Adams, MD, c Carol Toninato, RN, b Emil Missov, MD, c Marc Pritzker, MD, c Cindy Martin, MD, c Daniel Garry, MD, PhD, c William Thomas, PhD, d and Lyle Joyce, MD, PhD b

Objective: Pulsatile and nonpulsatile left ventricular assist devices are effective in managing congestive heart failure. Despite early evidence for clinical efficacy, the long-term impact of nonpulsatile flow on end-organ function remains to be determined. Our goal was to compare rates of gastrointestinal bleeding in nonpulsatile and pulsatile device recipients.

Methods: In a retrospective review of 101 left ventricular assist device recipients (55 nonpulsatile, 46 pulsatile) from October 31, 2003, to June 1, 2007, at a single center, gastrointestinal bleeding was defined as guaiac-positive stool with hemoglobin drop requiring transfusion of at least 2 units of packed red blood cells. To assess bleeding risk outside the initial postoperative course, any patients with a device in place for 15 days or less was excluded.

Results: Twelve nonpulsatile and 3 pulsatile left ventricular assist device recipients had gastrointestinal bleeding 16 days or longer after device implantation. The event rates were 63 events/100 patient-years for nonpulsatile devices and 6.8 events/100 patient-years for pulsatile devices (P = .0004). This difference persisted for bleeding occurring 31 days or longer after device implantation, with 46.5 events/100 patient-years for nonpulsatile devices versus 4.7 events/100 patient-years for pulsatile devices (P = .0028). Mortalities were similar between groups (15% nonpulsatile vs 17% pulsatile, P = .6965).

Conclusion: Patients with nonpulsatile left ventricular assist devices appear to have a higher rate of gastrointestinal bleeding events than do pulsatile left ventricular assist device recipients. Further prospective evaluation is needed to determine potential etiologies and strategies for reducing gastrointestinal bleeding in this population.
Off-pump coronary artery bypass surgery versus standard linear or pulsatile cardiopulmonary bypass: endothelial activation and inflammatory response

Francesco Onorati a,∗, Antonino S. Rubino a, Sergio Nucera a, Daniela Foti b, Vincenzo Sica d, Francesco Santini c, Elio Gulletta b, Attilio Renzulli a
Pulsatile perfusion with intra-aortic balloon pumping ameliorates whole body response to cardiopulmonary bypass in the elderly*

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Objective: The growing life expectancy has led the elderly to be increasingly referred to coronary artery bypass grafting. Preexisting comorbidities may benefit from theoretical advantages of pulsatile perfusion during cardiopulmonary bypass (CPB).

Design: Prospective randomized trial.

Setting: Cardiac surgery unit in a university hospital.

Patients: Eighty consecutive patients older than 70 years.

Interventions: Elective coronary artery bypass grafting on CPB, randomizing to conventional linear CPB (40 patients, group A) or intra-aortic balloon pump (IABP)-induced pulsatile CPB (40 patients, group B).

Measurements and Main Results: We evaluated hemodynamic response by pulmonary artery flotation catheter, metabolic/splanchnic response by lactate and transaminase, bilirubin, amylase, and renal function (creatinine clearance, creatinine, incidence of renal insufficiency and failure), respiratory response by $\text{Pao}_2/\text{FiO}_2$, respiratory compliance, scoring of chest radiograph, intubation time, and need for noninvasive positive-pressure ventilation, hematologic response by chest drainage, hemocoagulative and fibrinolytic cascades, and transfusions. IABP-related complications were recorded. Two minor IABP-related complications (2.5%) were registered. Hemodynamics was comparable, except for a slightly better cardiac index and indexed systemic vascular resistances at the end of CPB and at intensive therapy unit (ITU) admission ($p < 0.05$). Transaminases, bilirubin, amylase, proved lower in group B ($p < 0.05$ from ITU admission to 48 hours). Creatinine clearance, serum creatinine, and lactate were better in group B ($p < 0.05$), and acute renal insufficiency was accordingly lower ($p = 0.02$). Respiratory response demonstrated better $\text{Pao}_2/\text{FiO}_2$ and respiratory compliance from aortic declamping to 48 hours, with better scoring of chest radiograph ($p < 0.05$ from ITU admission to 48 hours), lower noninvasive positive-pressure ventilation ($p = 0.002$) and intubation time ($p = 0.031$) in group B. Lower chest drainage ($p < 0.05$ at first and second day), transfusions ($p < 0.05$), activated partial thromboplastin time, international normalized ratio, white blood cells, and D-dimer ($p < 0.05$ from ITU admission to 48 hours), together with higher platelets, fibrinogen, and antithrombin III ($p < 0.05$ from ITU admission to 48 hours) were demonstrated in the pulsated group.

Clinical benefit on:

- Gut, kidney, lung function
- Hemostasis and need for transfusion
Perspectives and developments

• New surface modification, new oxygenator?

• IABPC: but limited in time because of limb malperfusion

• Endotoxin removal

• Blood purification (cytokine and free-hemoglobion adsorber)

• Platelet anesthesia?

• Corticosteroids
**Prophylactic corticosteroids for cardiopulmonary bypass in adults.**


### Summary of Findings for the Main Comparison

#### Primary endpoints

<table>
<thead>
<tr>
<th>Comparison outcome</th>
<th>Number of studies</th>
<th>Participants</th>
<th>Peto OR (Fixed) [95% CI]</th>
<th>Heterogeneity (I²%)</th>
<th>Mantel-Haenszel OR (random) [95% CI]</th>
<th>Heterogeneity (I²%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>49</td>
<td>3213</td>
<td>1.06 [0.58, 1.95]</td>
<td>1</td>
<td>1.00 [0.55, 1.82]</td>
<td>0</td>
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<tr>
<td>Myocardial complications</td>
<td>26</td>
<td>2103</td>
<td>0.95 [0.57, 1.60]</td>
<td>4</td>
<td>0.95 [0.55, 1.64]</td>
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<td>Pulmonary complications</td>
<td>21</td>
<td>1340</td>
<td>0.83 [0.49, 1.40]</td>
<td>5</td>
<td>0.90 [0.51, 1.58]</td>
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</table>

#### Secondary endpoints

<table>
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<tr>
<th>Comparison outcome</th>
<th>Number of studies</th>
<th>Participants</th>
<th>Peto OR (Fixed) [95% CI]</th>
<th>Heterogeneity (I²%)</th>
<th>Mantel-Haenszel OR (random) [95% CI]</th>
<th>Heterogeneity (I²%)</th>
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<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>17</td>
<td>1399</td>
<td>0.60 [0.46, 0.78]</td>
<td>11</td>
<td>0.61 [0.45, 0.82]</td>
<td>10</td>
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<tr>
<td>Infections</td>
<td>16</td>
<td>1517</td>
<td>0.86 [0.56, 1.31]</td>
<td>0</td>
<td>0.88 [0.57, 1.36]</td>
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<tr>
<td>Gastro-intestinal complications</td>
<td>4</td>
<td>304</td>
<td>2.84 [0.40, 20.36]</td>
<td>36</td>
<td>1.86 [0.30, 11.68]</td>
<td>0</td>
</tr>
<tr>
<td>Re-thoracotomy</td>
<td>9</td>
<td>866</td>
<td>1.12 [0.47, 2.65]</td>
<td>34</td>
<td>1.28 [0.51, 3.22]</td>
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<td>Neurological complications</td>
<td>14</td>
<td>1171</td>
<td>0.70 [0.33, 1.48]</td>
<td>16</td>
<td>0.87 [0.38, 1.96]</td>
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<tr>
<td>Renal failure</td>
<td>13</td>
<td>825</td>
<td>1.00 [0.45, 2.19]</td>
<td>26</td>
<td>1.02 [0.44, 2.36]</td>
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<tr>
<td>Inotrope y/n</td>
<td>17</td>
<td>1237</td>
<td>0.91 [0.67, 1.23]</td>
<td>49</td>
<td>0.92 [0.58, 1.45]</td>
<td>39</td>
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<tr>
<td>Bloodtransfusion y/n</td>
<td>6</td>
<td>535</td>
<td>0.87 [0.54, 1.39]</td>
<td>0</td>
<td>0.87 [0.54, 1.40]</td>
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</tr>
</tbody>
</table>
Extracorporeal life support for cardiogenic shock: influence of concomitant intra-aortic balloon counterpulsation

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Abstract

**OBJECTIVES:** Intra-aortic balloon counterpulsation (IABP) during extracorporeal life support (ECLS) for cardiogenic shock may improve pulsatility and coronary perfusion, thereby promoting recovery of cardiac function. However, the risks and benefits of IABP during ECLS in real clinical settings have not been evaluated. This study aims to evaluate the effect of IABP on the early outcome of ECLS for cardiogenic shock.

**METHODS:** We evaluated 253 adult patients (aged 58.8 ± 15.3 [mean ± standard deviation] years, 154 males) undergoing ECLS for cardiogenic shock from January 2005 to August 2012. Of them, 60 patients underwent concomitant IABP (IABP group) and 193 underwent ECLS only (control group). In-hospital outcomes were compared using the inverse probability of treatment weighting based on propensity scores.

**RESULTS:** The indications for ECLS were low cardiac output after cardiac surgery in 118 patients (46.6%), heart failure in 71 (28.1%), acute myocardial infarction in 49 (19.4%) and others in 15 (5.9%). Successful ECLS weaning rate was significantly higher in the IABP group than in the control group (61.7 vs 42.0%, \(P = 0.008\)); however, there was no significant difference in in-hospital mortality between the two groups (68.6 vs 72.0%, \(P = 0.58\)). After adjustment for propensity of treatment assignment conditional on baseline characteristics, the IABP group showed a decreased risk of weaning failure (odds ratio [OR] 0.51; 95% confidence interval [CI] 0.28–0.92, \(P = 0.024\)) but with a similar risk of in-hospital mortality (OR 0.85; 95% CI 0.46–1.60, \(P = 0.62\)) compared with the control group.

**CONCLUSIONS:** The use of IABP during ECLS increased a successful ECLS weaning rate, but was not translated into improved survival. Studies on larger populations may verify the survival effect of IABP during ECLS.
Conclusion

- Knowledge is limited, and is mainly derived from CPB
- An intermediate step between VAD and CPB?
- VV-ECMO different from VA-ECLS
- Lack of pulsatile flow and hemostasis disturbances are major determinants of outcome