Mediators in Cardiac surgery

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Key Questions....

• What are the factors contributing to the Mediator Response following Cardiac surgery?

• Does the mediator response impact on outcome following Cardiac surgery?

• What are the current strategies to reduce the mediator response?

• Are there any specific therapeutic strategies?
Initiating Factors

• **Contact Activation**
  – Exposure of blood to the ‘foreign’ surfaces of CPB circuit
  – Primary activation of complement and coagulation systems

• **Ischaemia-Reperfusion Injury**
  – Aortic clamping and unclamping
  – Demonstrable Injury to vital organs

• **Other Factors**
  – Protamine
  – Endotoxin - Controversial role
Complement System

Classical Pathway

Lectin Pathway

Alternative Pathway
Complement System

• **Key effector arm of the immune system**
  – Over 30 separate components
  – Proteolytic cleavage cascade
  – Contributes to innate and adaptive immune responses

• **Activation of Complements**
  – CPB Circuit [e.g. direct adsorption of C3 to CPB circuit]
  – Protamine reversal of Heparin [activates classical pathway]
  – Ischemia-reperfusion injury

• **Role of Complement Activation post Cardiac Surgery**
  – Postoperative C3a levels predict risk of organ dysfunction
  – C3a levels predicts likelihood of MODS in children
  – Improving CPB circuit Biocompatibility reduces Complement Activation
    • may decrease postoperative morbidity, particularly in high risk patients.
Activation of Complement

Cytokine Balance

**INITIATING FACTORS**
- Contact Activation
- Endotoxin
- Ischaemia Reperfusion Injury
- Endothelial injury

↑ TNFα  
↑ IL-1β  
↑ IL-6  
↑ IL-8  
↑ TGF-β  
↑ IL-10  
↑ TNF-sr 1 + 2  
↑ IL-1ra
Importance of Cytokines

• Patients that develop SIRS following cardiac surgery
  – demonstrate significant elevations in cytokine concentrations


• SIRS non-survivors demonstrate dramatically higher levels of IL-8 and IL-18 concentrations compared to survivors


• Correlation between serum concentrations of IL-6 and morbidity following pediatric cardiac surgery


• Early increases in serum sTNF Receptor-p55 levels predicts increased mortality in high-risk patients.

Coagulation – Inflammation Axis

- ↑ Proinflammatory mediators
- ↑ Tissue factor expression
- ↑ Thrombin production
- Heparin-Protamine Complex

Coagulation – Inflammation

- ↑ Fibrinolysis

Endothelial Injury

Homeostasis

- Increased PAI-1
- Increased TAFIa
- Reduced Protein C

PAI-1 = plasminogen activator inhibitor-1; TAFIa = thrombin activatable fibrinolysis inhibitor.
The Neutrophil-Endothelial Interaction

Endothelial Injury
Importance of Neutrophils

- **CPB causes Pulmonary neutrophil sequestration**
  - evidence of severe histological lung injury

- **Inhibition of neutrophil CD11/CD18 improves myocardial function**

- **Blockade of neutrophil adhesion decreases pulmonary injury after CPB**

- **Strategies to deplete circulating leukocytes**
  - can attenuate organ injury
  - may improve patient outcome following CPB
Clinical Impact of Mediator Response to Cardiac surgery
Beneficial Effects

- Immune System Priming
- Prevention of Infection
- Improved Wound Healing

Deleterious Effects

- Cardiovascular
- Pulmonary
- Neurologic
- Renal
- Hepatic
- Hemostatic
'Pump Lung' - ARDS
Acute Respiratory Distress Syndrome

• Incidence
  – ALI seen in up to 12% patients
  – 1–3% ARDS following CPB
  – ARDS risk and severity linked to CPB duration.


• ARDS post Cardiac Sx increases morbidity and mortality.


• Role of Inflammatory Response
  – Correlation between mediator levels and Lung Injury severity


  – Attenuation of the inflammatory response may reduce post-CPB ALI.
    • Mechanical mediator removal
    • Leukocyte depletion during CPB
    • Blockade of neutrophil adhesion
    • Inhibition of complement activation
Cardiac Dysfunction

- 10% incidence major cardiovascular complications post CABG
  - cardiac death
  - heart failure

- Pro-Inflammatory Cytokines Response implicated in:
  - Left ventricular wall motion abnormalities [IL-6, IL-8]
  - Myocardial Stunning, Ischemia and Dysfunction [IL-6, IL-8]
  - Cardiac myocyte adrenergic refractoriness [TNFα, IL-1β, IL-6]
  - Suppression of myocardial performance in the elderly [TNFα]
Neurologic Injury

- Postoperative neurological/cognitive dysfunction
  - 69% of patients immediately postoperatively
  - persists for at least one month in 36%

- Endothelial dysfunction central to neurologic injury post-CPB.

- Attenuation of the Inflammatory Response.
  - Experimental selectin adhesion molecule blockade reduces cerebral injury
  - Aprotinin decreases the incidence of stroke post-CPB
  - Heparin coated circuits may reduce neurologic dysfunction in humans
Minimizing the impact of mediator response
Minimize Initiating Factors

• **Reduce Contact Activation**
  – Improve Circuit Biocompatibility
  – Avoid / Reduce exposure to Circuit

• **Minimize Ischemia-Reperfusion Injury**
  – Reduce CPB / Aortic Clamp time

• **Minimize Endotoxemia**
  – Selective digestive decontamination
  – Enteral Nutrition and Immunonutrition
  – Maintenance of Splanchnic Perfusion

• **Minimize 'Second Hit' Potential**
  – Maintenance of hemodynamic stability
  – Infection control strategies
  – Adequate resuscitation
  – Minimize Blood Transfusion / Leukodepletion
  – Protective mechanical ventilation
Beneficial Effects of Leukocyte Depletion of Transfused Blood on Postoperative Complications in Patients Undergoing Cardiac Surgery

A Randomized Clinical Trial

Leo M.G. van de Watering, MD; Jo Hermans, PhD; Jos G.A. Houbiers, PhD; Pieter J. van den Broek, MD; Hens Bouter, MD; Fred Boer, MD; Mark S. Harvey, PhD; Hans A. Huysmans, MD; Anneke Brand, MD

- 900 adult patients undergoing CABG and/or Heart valve surgery

- Randomized to transfusion with:
  - Freshly leukocyte depleted PRBC [n = 305]
  - Stored leukocyte depleted PRBC [n = 303]
  - Non leukocyte depleted (without Buffy Coat) PRBC [n = 306]

- Leukodepletion
  - Reduced 60 day mortality
  - Reduced death from MODS
  - Reduced postoperative infection [Patients received > 3U PRBC]
Heparin-Coated Circuits for High-Risk Patients: A Multicenter, Prospective, Randomized Trial

Marco Ranucci, MD, Alessandro Mazzucco, MD, Renzo Pessotto, MD, Giovanni Grillone, MD, Valter Casati, MD, Lorenzo Porreca, MD, Roberto Maugeri, MD, Marco Meli, MD, Paolo Magagna, MD, Silvia Cirri, MD, Pierpaolo Giomarelli, MD, Roberto Lorusso, MD, and Annette de Jong, CCP

- 886 high risk patients
  - Duraflo II HCCs [n = 442] vs. conventional circuits [n = 444].

- HCC's
  - decreased duration of ICU and hospital stay,
  - reduced incidence of poor outcome [prolonged ICU or death].

- Subgroup analysis
  - less renal dysfunction in diabetic patients,
  - less lung dysfunction in COPD patients with COPD
  - Less lung dysfunction in Mitral Valve Surgery.

A Prospective, Randomized Study of Goal-Oriented Hemodynamic Therapy in Cardiac Surgical Patients

Pekka Pölönen, MD*, Esko Ruokonen, MD, PhD*, Mikko Hipeläinen, MD, PhD†, Mikko Pöyhönen, MD, PhD*, and Jukka Takala, MD, PhD*

Critical Care Research Program, *Departments of Anesthesia and Intensive Care, and †Surgery, Kuopio University Hospital, Kuopio, Finland

- Evaluated optimization of early postoperative cardiovascular function
  - 403 elective cardiac surgical patients
  - Randomly assigned to Control vs Protocol Groups.

- Haemodynamic optimization
  - preload augmentation and dobutamine
  - aimed to normalize mixed SvO₂ and lactate concentration for 8h postop

- Findings
  - reduced length of hospital stay (6 vs 7 days, P < 0.05)
  - reduced organ dysfunction at the time of discharge
  - reduced overall morbidity at hospital discharge (1.1% vs 6.1%, P < 0.01)
**OPCAB, Inflammation and Outcome**

- **OPCAB reduces Organ Injury** [Puskas et al, J Thorac Cardiovasc Surg 2003;]
  - OPCAB [n = 98] vs. conventional CABG with CPB [n = 99].
  - Reduced myocardial and pulmonary injury
  - Reduced transfusion requirements and coagulation system dysfunction
  - Reduced length of hospital stay.

  - Multi-centre, prospective, controlled, randomised trial
  - Predominantly single or double vessel disease
  - OPCAB [n = 142] vs. conventional CABG with CPB [n = 139].
  - Similar graft patency at one year postoperatively

- **OPCAB reduces mediator response**
  - Decreases Cytokine concentrations
  - Attenuates the cellular inflammatory response
  - Attenuates complement activation [C3a, C5a]
  - Decreases reactive oxygen species induced injury
  - Minimizes endotoxemia
Mechanical ventilation affects inflammatory mediators in patients undergoing cardiopulmonary bypass for cardiac surgery: A randomized clinical trial

Enrico Zupancich, MD, a,†‡ Domenico Paparella, MD, b,‡ Franco Turani, MD, a, c Christopher Munch, MD, a Alessandra Rossi, MD, a Simone Massaccesi, MD, a and V. Marco Ranieri, MD b

• 40 patients post elective CABG
• Groups
  • Low Vt (8 ml/Kg); High PEEP (10 cm H2O)
  • High Vt (10 – 12 ml/Kg); Low PEEP (2 – 3 cm H2O)
• Outcome
  • Favourable postoperative Cytokine [IL-6, IL-8] Profile
Therapeutic Strategies to reduce mediator Response
Stress doses of hydrocortisone reduce severe systemic inflammatory response syndrome and improve early outcome in a risk group of patients after cardiac surgery

Erich Kilger, MD; Florian Weis; Josef Briegel, MD; Lorenz Frey, MD; Alwin E. Goetz, MD; Daniel Reuter, MD; Andreas Nagy; Albert Schuetz, MD; Peter Lamm, MD; Anette Knoll; Klaus Peter, MD

- 91 CPB patients at high risk for severe SIRS
  - Hydrocortisone [n = 43] vs. standard therapy [n = 48]
  - 100 mg given prior to induction
  - Then 10 mg/hr for 24 hrs followed by 5 mg/hr for 24 hrs,
  - Three doses 20 mg/day followed by three doses 10 mg/day [One week]

- Hydrocortisone
  - Decreased indices of inflammation
  - Decreased Organ Dysfunction
    - Cardiovascular [Inotrope/Vasopressor Support]
    - Respiratory [Duration Ventilation; P/F Ratio]
    - Hemostatic
  - Decreased ICU and Hospital stay.
  - Study not powered to detect overall differences in mortality

Crit Care Med 2003; 31:1068–1074
**Table 2.** Primary Study End Point and Components of the Primary Study End Point in the Dexamethasone and Placebo Groups

<table>
<thead>
<tr>
<th></th>
<th>No. (%) of Patients</th>
<th></th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dexamethasone (n = 2235)</td>
<td>Placebo (n = 2247)</td>
<td></td>
</tr>
<tr>
<td>Primary study end point&lt;sup&gt;a&lt;/sup&gt;</td>
<td>157 (7.0)</td>
<td>191 (8.5)</td>
<td>0.83 (0.67-1.01)</td>
</tr>
<tr>
<td>Components of the primary study end point</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>31 (1.4)</td>
<td>34 (1.5)</td>
<td>0.92 (0.57-1.49)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>35 (1.6)</td>
<td>39 (1.7)</td>
<td>0.90 (0.57-1.42)</td>
</tr>
<tr>
<td>Stroke</td>
<td>29 (1.3)</td>
<td>32 (1.4)</td>
<td>0.91 (0.55-1.50)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>28 (1.3)</td>
<td>40 (1.8)</td>
<td>0.70 (0.44-1.14)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>67 (3.0)</td>
<td>97 (4.3)</td>
<td>0.69 (0.51-0.94)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Primary study end point was a composite of death, myocardial infarction, stroke, renal failure, or respiratory failure, within 30 days after surgery.
Table 3. Secondary End Points in the Dexamethasone and Placebo Groups

<table>
<thead>
<tr>
<th>Secondary End Points</th>
<th>Dexamethasone (n = 2235)</th>
<th>Placebo (n = 2247)</th>
<th>Relative Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of postoperative mechanical ventilation, h</td>
<td>Median (IQR)</td>
<td>NA</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Length of stay in the ICU, h</td>
<td>7.0 (4.7-10.0)</td>
<td>12.0 (19.0-25.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Length of hospital stay, d</td>
<td>13 (7-13)</td>
<td>9 (7-13)</td>
<td>.009</td>
</tr>
</tbody>
</table>
Steroids In Cardiac Surgery Trial (SIRS Trial)

- McMaster University-Hamilton Health Sciences
- ClinicalTrials.gov identifier: NCT00427388
- Intra-operative IV Methylprednisolone 2 doses
- Phase III; Planned 10000 patients; Commenced Jun 07
Beneficial effects of C1 esterase inhibitor in ST-elevation myocardial infarction in patients who underwent surgical reperfusion: a randomised double-blind study

Khalil Fattouch*, Giuseppe Bianco, Giuseppe Speziale, Roberta Sampognaro, Carlo Lavalle, Francesco Guccione, Pietro Dioguardi, Giovanni Ruvolo

* p=0.02
p=0.03
p=0.02

p=0.002
p=0.001

Serum Cl-INH level (mg/dl)

C4a (value ng/ml ± SD)

Group C1-INH
Group Placebo

Placebo-group
C1-INH
Beneficial effects of C1 esterase inhibitor in ST-elevation myocardial infarction in patients who underwent surgical reperfusion: a randomised double-blind study*

Khalil Fattouch*, Giuseppe Bianco, Giuseppe Speziale, Roberta Sampognaro, Carlo Lavalle, Francesco Guccione, Pietro Dioguardi, Giovanni Ruvolo
Recombinant, single-chain, anti-C5 monoclonal Ab

3099 adult patients undergoing CABG ± Valve surgery
- Pexelizumab (2.0 mg/kg bolus + 0.05 mg/kg/hour for 24h; n = 1553)
- Placebo (n = 1546)

Primary Outcome [30 Day Death or MI in CABG only patients]
- Pexelizumab – 134 (9.8%) of 1373 patients
- Placebo – 161 (11.8%) of 1359 patients (P = .07)

30 Day Outcome in patients for CABG ± Valve [Death or MI]
- Pexelizumab – 178 (11.5%) of 1547 patients
- Placebo – 215 (14.0%) of 1535 patients (P = .03).

JAMA. 2004;291:2319-2327
### Results

#### Day 30 Outcomes

<table>
<thead>
<tr>
<th>Population</th>
<th>Outcome</th>
<th>Placebo No./Total (%)</th>
<th>Pexelizumab No./Total (%)</th>
<th>Favors Pexelizumab</th>
<th>Risk Reduction, %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG Surgery Only</td>
<td>Death or MI</td>
<td>161/1359 (11.8)</td>
<td>134/1373 (9.8)</td>
<td>-</td>
<td>18</td>
<td>.07</td>
</tr>
<tr>
<td></td>
<td>MI</td>
<td>141/1368 (10.3)</td>
<td>111/1378 (8.1)</td>
<td>-</td>
<td>22</td>
<td>.04</td>
</tr>
<tr>
<td></td>
<td>Death</td>
<td>39/1359 (2.9)</td>
<td>32/1373 (2.3)</td>
<td>-</td>
<td>19</td>
<td>.36</td>
</tr>
<tr>
<td>All Participants</td>
<td>Death or MI</td>
<td>215/1535 (14.0)</td>
<td>178/1547 (11.5)</td>
<td>-</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MI</td>
<td>185/1546 (12.0)</td>
<td>152/1553 (9.8)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Death</td>
<td>52/1535 (3.4)</td>
<td>39/1547 (2.5)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PRIMO-CABG II (4254 patients) also negative for Primary Outcome of Death or MI by Day 30
• 564 high risk CPB patients
  – Placebo versus TP10 bolus (1, 3, 5, 10 mg/Kg)

• TP10 inhibited complement activation

• No difference in primary composite outcome
  – Composite of death, MI, IABP support (>24h) and prolonged intubation

• Sex difference in effect
  – TP10 reduced combination of Death+MI in males (P = 0.026)
• 297 high risk female patients
  – Urgent surgery, CABG+Valve, reoperations, reduced LVEF
  – Placebo versus TP10 bolus (5 mg/Kg)

• TP10 inhibited complement activation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>TP10</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death outcome</td>
<td>25 (17)</td>
<td>31 (21)</td>
<td>0.255</td>
</tr>
<tr>
<td>MI (%)</td>
<td>4 (3)</td>
<td>1 (1)</td>
<td>0.210</td>
</tr>
<tr>
<td>Intensive care unit LOS (days)</td>
<td>3.09±3.04</td>
<td>3.42±3.72</td>
<td>0.405</td>
</tr>
<tr>
<td>Hospital LOS (days)</td>
<td>8.66±7.00</td>
<td>9.58±8.83</td>
<td>0.346</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>45 (31)</td>
<td>48 (31)</td>
<td>0.352</td>
</tr>
</tbody>
</table>
Effect of remote ischaemic preconditioning on myocardial injury in patients undergoing coronary artery bypass graft surgery: a randomised controlled trial

Derek J Hausenloy, Peter K Mwamure, Vinod Venugopal, Joanne Harris, Matthew Barnard, Ernie Grundy, Elizabeth Ashley, Sanjeev Vichare, Carmelo Di Salvo, Shyam Kolvekar, Martin Hayward, Bruce Keogh, Raymond J MacAllister, Derek M Yellon

• 57 low risk CABG pts

• Non-invasive RIPC technique
  - Three 5-min cycles
  - Right Upper limb ischemia

• Findings
  - Reduced Troponin T
  - No data regarding organ function

Lancet. 2007 Aug 18;370(9587):575-9
• 162 low risk CABG/CPB pts

• Non-invasive RIPC technique
  - Three 5-min cycles
  - Right Upper limb ischemia

• Findings
  - No effect on Troponin I
  - No effect on Heart/Lung/Renal

Circulation. 2010;122:S53-S59
Effect of Early Use of Low-Dose Pravastatin on Major Adverse Cardiac Events in Patients With Acute Myocardial Infarction

— The OACIS-LIPID Study —

Hiroshi Sato, MD; Kunihiro Kinjo, MD; Hiroshi Ito, MD*; Atsushi Hirayama, MD**;
Shinsuke Nanto, MD†; Masatake Fukunami, MD‡; Masami Nishino, MD†;
Young-Jae Lim, MD‡‡; Yoshiyuki Kijima, MD§; Yukihiro Koretsune, MD§§;
Daisaku Nakatani, MD; Hiroya Mizuno, MD; Masahiko Shimizu, MD;
Masatsugu Hori, MD; for the Osaka Acute Coronary Insufficiency Study (OACIS)-LIPID Study Investigators

Arrhythmia/Electrophysiology

Randomized Trial of Atorvastatin for Reduction of Postoperative Atrial Fibrillation in Patients Undergoing Cardiac Surgery

Results of the ARMYDA-3 (Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery) Study

Giuseppe Patti, MD; Massimo Chello, MD; Dario Candura, MD; Vincenzo Pasceri, MD;
Andrea D’Ambrosio, MD; Elvio Covino, MD; Germano Di Sciascio, MD

(Circulation. 2006;114:1455-1461.)
The future - Personalized therapy?
Profiling Inflammatory Indices

- **Preoperative**
  - Low Anti-endotoxin core antibody (EndoCAb) levels
    - predictor of adverse postoperative outcome
    - Predictor of post-op cognitive dysfunction especially in older patients.
  - High C-reactive protein levels
    - predicts a greater likelihood of septic complications
    - predicts need for catecholamine therapy
    - longer duration of respiratory support
    - increased duration of ICU stay

- **Postoperative**
  - High sTNF receptor-p55 levels
    - predicts cytokinemia and systemic inflammatory response post-CPB
    - predicts mortality in high-risk patients
Genetic Predisposition???

• TNF gene polymorphisms
  • predict prolonged mechanical ventilation post CABG

• IL-10 gene polymorphisms
  • Haplotypes predicts complicated course

• Apolipoprotein E-epsilon 4 allele
  • predicts predisposition to neurologic injury

• Factor V Leiden haplotype
  • decreases blood loss and transfusion in cardiac surgery patients
    [Donahue BS et al. Circulation. 2003;107(7):1003-8]

• ACE insertion (I)/deletion (D) polymorphism
  • ACE DD genotype predicted increased mortality after CABG
    [Volzke H et al, Chest. 2002; 122(1):31-6]
Summary

• An uncontrolled mediator response post CPB is BAD
  – Contribution to pathogenesis of organ dysfunction clear

• Therapeutic strategies should be focused on high risk patients
  – subset most likely to suffer deleterious consequences
  – hence most likely to experience benefit.

• Strategies to minimize insult of Cardiac surgery have utility

• Specific targeting of mediator response has proved disappointing
  – Anti-complement strategies [Pexelizumab; TP10]
  – Ischemic Preconditioning etc

• Steroids demonstrate some promise
  – Definitive large scale trial awaited