The Vasoplegic Syndrome Following Cardiopulmonary Bypass

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Pharmacy Grand Rounds
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Objectives

• Review the pathology and consequences of the cardiac vasoplegic syndrome

• Determine the role of salvage therapies for catecholamine-refractory cardiac vasoplegia

• Develop a treatment strategy for a vasoplegic patient following cardiopulmonary bypass
Intraoperative hypotension

↑ baroreceptor stimulation

Aortic cross clamp release

↓ vasopressin

Reperfusion syndrome

↑ nitric oxide

Smooth muscle hyperpolarization

↓ nitric oxide

↑ baroreceptor stimulation

SIRS

↑ nitric oxide

Protamine reversal

Exposure of blood to CPB circuit

Complement activation

Blood transfusion

The Cardiac Vasoplegic Syndrome

• Incidence, ~5 to 45%

• Vasodilatory shock
  • Good cardiac function
  • Good circulatory volume
  • Requires vasopressors

• Hypoperfusion
  • Multi-organ failure
  • Death

Cardiac Vasoplegia

- High or normal cardiac output
- Adequate fluid resuscitation
- Hypotension (↓↓ SVR)
Based on the physiologic changes during cardiopulmonary bypass, what would be your first line therapy for cardiac vasoplegia?

A. Catecholamines (i.e. norepinephrine)
B. Vasopressin
C. Methylene blue
D. Hydroxocobalamin (vitamin B12)
E. Ascorbic acid (vitamin C)
1st Line: Vasopressors

• Catecholamines
• Vasopressin
• Vasopressor-refractory
  • Incidence unknown
  • Consequences of high vasopressor rates
  • Strong predictor of mortality
• Salvage therapies
  • Methylene blue
  • Hydroxocobalamin
  • Ascorbic acid
↑ nitric oxide

Smooth muscle hyperpolarization

↓ vasopressin

Reperfusion syndrome

↑ baroreceptor stimulation

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Intraoperative hypotension

Methylene Blue

↑ SVR
↑ BP

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↑ nitric oxide

MB: Methylene Blue or Magic Bullet?

<table>
<thead>
<tr>
<th>Design</th>
<th>Multicenter, randomized, placebo-controlled (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>• MAP &lt; 50 mmHg&lt;br&gt;• CVP &lt; 5 mmHg&lt;br&gt;• PCWP &lt; 10 mmHg&lt;br&gt;• CI &gt; 2.5 L/min/m²&lt;br&gt;• SVR &lt; 800 dyn/s/cm⁻⁵&lt;br&gt;• “vasopressor need”</td>
</tr>
<tr>
<td>Exclusion</td>
<td>• None reported</td>
</tr>
<tr>
<td>Intervention</td>
<td>• Methylene blue 1.5 mg/kg bolus (n = 28)&lt;br&gt;• Placebo (n = 28)</td>
</tr>
</tbody>
</table>

MAP = mean arterial pressure  
CVP = central venous pressure  
PCWP = pulmonary capillary wedge pressure  
CI = cardiac index

The Magic Bullet?

- Baseline norepinephrine rate ~ 0.7 mcg/kg/min
Bolus Only

**Leyh et al. 2003**
- Retrospective cohort study (n = 54)
- Baseline norepinephrine ≥ 0.5 mcg/kg/min
- Bolus methylene blue 2 mg/kg
- ↓norepinephrine, ↑SVR at 1, 6, and 12 hours
- ↑ALT/AST
- In-hospital mortality, 6% (n = 3)

**Mazzeffi et al. 2017**
- Retrospective cohort study (n = 88)
- Baseline N 12.5 mcg/min, V 0.09 units/min, E 7.4 mcg/min
- Bolus methylene blue 1-2 mg/kg
- ↓norepinephrine, ↑MAP
- ↑MAP, only variable associated with response

N = norepinephrine  
E = epinephrine  
V = vasopressin  
ALT = alanine aminotransferase  
AST = aspartate aminotransferase

Why Just One Dose?

- Retrospective cohort (n = 3608)
- Bolus 2 mg/kg then 0.5 mg/kg/h (n = 118)

## Have We Been Doing it Wrong?

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR (n = 48)</th>
<th>ICU (n = 70)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event</td>
<td>34 (71%)</td>
<td>53 (76%)</td>
<td>0.554</td>
</tr>
<tr>
<td>Transfusion</td>
<td>44 (92%)</td>
<td>58 (83%)</td>
<td>0.170</td>
</tr>
<tr>
<td>Length of stay (d)</td>
<td>12 (10, 19)</td>
<td>12 (6, 21)</td>
<td>0.447</td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (4%)</td>
<td>4 (6%)</td>
<td>0.707</td>
</tr>
<tr>
<td>Renal failure</td>
<td>5 (10%)</td>
<td>20 (29%)</td>
<td>0.018</td>
</tr>
<tr>
<td>Reoperation</td>
<td>10 (21%)</td>
<td>21 (30%)</td>
<td>0.266</td>
</tr>
<tr>
<td>Sternal infection</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>0.219</td>
</tr>
<tr>
<td>Prolonged MV</td>
<td>11 (23%)</td>
<td>16 (23%)</td>
<td>0.994</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>5 (10%)</td>
<td>20 (29%)</td>
<td>0.018</td>
</tr>
</tbody>
</table>
Limitations

- Low incidence of refractory vasoplegia
- No report of hemodynamic parameters
- Unknown amount of methylene blue received
- No description of vasopressor and hemodynamic behavior in early vs. late recipients
Methylene Blue

- Fluid and tissue discoloration
- Maximum dosage
- Serotonin Syndrome
- Hemolytic anemia
- ↓ Oximetry measurements

Intraoperative hypotension

↑ baroreceptor stimulation

Protamine reversal

↑ nitric oxide

Smooth muscle hyperpolarization

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Aortic cross clamp release

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Hydroxocobalamin

↑ SVR

↑ BP

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↑ SIRS

Protamine reversal

The Trendsetters

- 71 year-old male undergoing dual-valve repair, single-vessel coronary bypass, PFO closure

**Anesthesia Induction**
- N 0.07 mcg/kg/min

**CPB Initiated**
- MAP 30-45 mmHg
- N 0.1 mcg/kg/min
- V 0.033 units/min

**70 min of CPB**
- ↓MAP with cardioplegia doses
- 5 grams IV hydroxocobalamin

**Post-op Day 1**
- Extubated
- Off pressors

**After B12**
- MAP > 60 mmHg
- ↓N, V off
- ↓hypotension from cardioplegia

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PFO = patent foramen ovale
N = norepinephrine
V = vasopressin

**And The Followers…**

<table>
<thead>
<tr>
<th>Case</th>
<th>Surgery</th>
<th>Pressor Requirements</th>
<th>Other Interventions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AVR, MVR</td>
<td>N ? V 0.1 units/min</td>
<td>MB 1 mg/kg + 0.5 mg/kg</td>
<td>Pressors weaned POD 2, extubated POD 3</td>
</tr>
<tr>
<td>2</td>
<td>LVAD implantation</td>
<td>N 0.25 mcg/kg/min V 0.04 units/min</td>
<td>MB 1 mg/kg x 2</td>
<td>Pressors weaned on ICU arrival</td>
</tr>
<tr>
<td>3</td>
<td>Aortic aneurysm repair</td>
<td>N 0.45 mcg/kg/min V 0.04 units/min</td>
<td>MB 0.375 mg/kg + 0.75 mg/kg</td>
<td>Discharged ICU on POD 17</td>
</tr>
<tr>
<td>4</td>
<td>TVR, PFO closure</td>
<td>N 0.2 mcg/kg/min</td>
<td>None</td>
<td>Discharged ICU on POD 12</td>
</tr>
<tr>
<td>5</td>
<td>AVR, MVR, TVR</td>
<td>N 0.2 mcg/kg/min E 0.1 mcg/kg/min V 0.06 units/min</td>
<td>MB 3.3 mg/kg total ECMO</td>
<td>Pressors weaned POD 4</td>
</tr>
</tbody>
</table>

AVR = aortic valve replacement  
MVR = mitral valve replacement  
TVR = tricuspid valve replacement  
LVAD = left ventricular assist device  
ECMO = extra corporeal membrane oxygenation

Hemodialysis alarm interference
Cost, Cost, Cost
Sustained overt ↑MAP
Hydroxocobalamin
Colorimetric analysis interference
Chromaturia
Making The Case: Ascorbic Acid

L-tyrosine → Ascorbic Acid → L-DOPA → Dopamine

Epinephrine

Norepinephrine

### Ascorbic Acid in Cardiac Surgery

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/ Sex</th>
<th>Surgery</th>
<th>CPB time (m)</th>
<th>Pressors at Vitamin C initiation</th>
<th>Shock co-therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22/ M</td>
<td>Septal myectomy</td>
<td>55</td>
<td>N 0.1 mcg/kg/min E 0.02 mcg/kg/min V 0.04 units/min</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>18/ M</td>
<td>LVAD exchange</td>
<td>85</td>
<td>N 0.12 mcg/kg/min E 0.08 mcg/kg/min V 0.04 units/min</td>
<td>Hydrocortisone</td>
</tr>
<tr>
<td>3</td>
<td>67/ M</td>
<td>AVR, MVR, TVR</td>
<td>196</td>
<td>N 0.3 mcg/kg/min E 0.08 mcg/kg/min V 0.04 units/min</td>
<td>Hydrocortisone, methylene blue, VA ECMO</td>
</tr>
</tbody>
</table>

Wieruszewski et al. *Unpublished data, under peer review.*
Vasopressor Requirements (mcg/kg/min)

Total Vaspressors*

Norepinephrine

Time From Vitamin C Initiation (h)

Case 1
Case 2
Case 3

* Norepinephrine equivalents
N 0.1 mcg/kg/min = E 0.1 mcg/kg/min = V 0.04 units/min

Wieruszewski et al. Unpublished data, under peer review.
Limitations to Current Vasoplegia Data

- Inconsistent definitions of vasoplegia including the “vasopressor-refractory” cases
- Heterogeneous outcome variables
- Ideal dosing schema not truly known
- No comparison of salvage therapies
- Salvage therapy vs. first line?
- Scant reporting of adverse events
In The Meantime…

- Standardized vasoplegia definition
  - Particularly concerning need for vasopressors
  - Proposal: vasopressin then when norepinephrine > 0.1 mcg/kg/min
  - Consider methylene blue or ascorbic acid
  - Hydroxocobalamin as last resort

- Consider methylene blue administration in the operating theatre when coming off pump
Who May Benefit From OR Administration

- Left ventricular assist device
- Heart failure, especially known reduced ejection fraction
- Multiple comorbidities (including pre-existing dialysis dependence)
- Previous sternotomy and bypass exposure
- Extended durations of CPB and aortic cross clamp timing
- Not isolated vessel bypass cases
Future Directions for Vasoplegia Research

• Identification of patients at highest risk of vasopressor-refractory vasoplegia

• Elucidation of optimal administration timing
  • Perioperative or intensive care unit

• Taking advantage of all mechanisms of CPB resulting vasoplegia
  • Identification of novel agents
The cardiopulmonary bypass circuit does which of the following?

A. Invokes a SIRS-like immune response
B. Results in vasopressin deficiency
C. Increases nitric oxide synthesis
D. All of the above
Ascorbic acid is proposed to

A. Inhibit nitric oxide synthesis
B. Increase endogenous catecholamine synthesis
C. Agonize the angiotensin-renin system
D. All of the above
Conclusion

• The cardiac vasoplegia syndrome is a significant contributor of morbidity and mortality in cardiac surgical patients

• Salvage therapies are necessary in some vasoplegia cases, though data supporting their use is sparse

• Future research should focus on optimal timing of initiation of salvage therapies
“The ultimate objective of my work in this field has been to be able to operate inside the heart under direct vision.”

John H. Gibbon, Jr., M.D., 1954
The Vasoplegic Syndrome Following Cardiopulmonary Bypass

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## Procurement Costs

<table>
<thead>
<tr>
<th>Example Treatment</th>
<th>Procurement Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylene blue 1 mg/kg, then 1mg/kg x 6h, 80kg patient</td>
<td>~$43</td>
</tr>
<tr>
<td>Hydroxocobalamin 5 grams once</td>
<td>~$770</td>
</tr>
<tr>
<td>Ascorbic acid 1.5 gm q6h x 4 days</td>
<td>~$82</td>
</tr>
</tbody>
</table>
## Risk of Serotonin Toxicity

<table>
<thead>
<tr>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Drug 3</th>
<th>Drug 4</th>
<th>Drug 5</th>
<th>Drug 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>Milnacipran</td>
<td>Clomipramine</td>
<td>Cocaine</td>
<td>Ondansetron</td>
<td>Fentanyl</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Venlafaxine</td>
<td>Desipramine</td>
<td>Ecstasy</td>
<td>Palonosetron</td>
<td>Buspirone</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Bupropion</td>
<td>Doxepin</td>
<td>LSD</td>
<td>Metoclopramidine</td>
<td>Sumatriptan</td>
</tr>
<tr>
<td>Fuvoxamine</td>
<td>Vilazodone</td>
<td>Imipramine</td>
<td>Tramadol</td>
<td>Dexfenfluramine</td>
<td>Rizatriptan</td>
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<tr>
<td>Paroxetine</td>
<td>Trazodone</td>
<td>Maprotiline</td>
<td>Meperidine</td>
<td>Carbamazepine</td>
<td>Naratriptan</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Nefazodone</td>
<td>Nortriptyline</td>
<td>St. John’s Wort</td>
<td>Sibutramine</td>
<td>Almotriptan</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>Amitriptyline</td>
<td>Protriptyline</td>
<td>Dolasetron</td>
<td>Dextromethorphan</td>
<td>Zolmitraptan</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Amoxapine</td>
<td>Trimipramine</td>
<td>Granisetron</td>
<td>Cyclobenzaprine</td>
<td>Pentazocine</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>Fenfluramine</td>
<td>Phentermine</td>
<td>Valproate</td>
<td>Dextroamphetamine</td>
<td>Methamphetamine</td>
</tr>
<tr>
<td>Levodopa</td>
<td>Cardidopa</td>
<td>Lithium</td>
<td>Phencelzine</td>
<td>Tranylcypromine</td>
<td>Isocarboxazid</td>
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<tr>
<td>Moclobemide</td>
<td>Safinamide</td>
<td>Selegilene</td>
<td>Rasagiline</td>
<td>Linezolid</td>
<td>Tedizolid</td>
</tr>
</tbody>
</table>
VANCS Trial 2017

- Vasopressin 0.01 to 0.06 units/min vs. norepinephrine 10 to 60 mcg/min to maintain MAP ≥ 65 mmHg
- V ↓ primary endpoint (mortality + severe complications)
  - Driven by renal failure (36% v. 10%, p <0.0001)
- V ↓ time on pressors, ICU, and hospital stay
- V ↓ atrial arrhythmias (82% v. 64%, p = 0.0004)
- No differences in adverse events

Hajjar et al. Anesthesiology 2017;126:85-93.