Cardioplegia – What Type and How Much?

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Congenital Skills and Decision Making
AATS
Saturday, May 4, 2013
• No disclosures
• Steady improvement
• Credited to better...
  – ICU practices
  – Management of cardiopulmonary bypass
  – Myocardial protection

• Contribution of myocardial protection?
Good to study – Hard to translate

Amenable to large animal models

– Myocardial performance precisely measured
– Early outcomes evaluated
– Correlation with myocardial samples

BUT...

– Late outcomes difficult to measure
  • Rarely >6 hours
  • Very rarely days-years after arrest
– Typically healthy hearts
  ? Pathologic models
  ? Cyanotic models
  ? Neonatal models
We know a lot about:

Normal adult hearts within a few hours of arrest

We need to know about:

‘Abnormal’ hearts in neonates/infants for minutes/hours/days/weeks....

Objective:

What type and how much?
Discussion Outline

1. What do we know from RCT’s?
2. How has #1 been translated into current practice?
Literature search

“Cardioplegia”
- 4,054 entries

Limit to “all children 0-18 yrs”
- 330

Limit to English text and Humans
- 224

Limit to “Randomized”
- 23

Manual review
- 11 studies (2 double dips)
Rapid review of RCT’s
ANTEGRADE COLD BLOOD CARDIOPLEGIA IS NOT DEMONSTRABLY ADVANTAGEOUS OVER COLD CRYSTALLOID CARDIOPLEGIA IN SURGERY FOR CONGENITAL HEART DISEASE

• Design
  – n= 138
  – Cold blood vs crystalloid (Plegisol)

• Outcomes
  – Inotropes, function, complications, LOS, 30d survival
  – Cold blood: less intraop inotropes
  – All others: No Δ

• Conclusion
  – AXC predicts outcomes more than cardioplegia
Clinical Evaluation of Leukocyte-Depleted Blood Cardioplegia for Pediatric Open Heart Operation

• Design
  – n=50
  – Cold blood cardioplegia +/-Leukocyte depletion

• Outcomes
  – Leukocyte depletion:
    • Less inflammation markers
    • Less peak CK
    • Less catecholamines

• Conclusion
  – Leukocyte depletion associated with clinical benefit

Hayashi, Ann Thor Surg 2000
Cold Blood Versus Cold Crystalloid Cardioplegia for Repair of Ventricular Septal Defects in Pediatric Heart Surgery: A Randomized Controlled Trial

• Design
  – n=40 (~24m, not cyanotic)
  – Crystalloid (St Thomas) vs cold blood

• Outcomes
  – Cold blood
    • Less drop in ATP at reperfusion (effect greater in infants)
    • Less TnI release up to 48 hrs (effect greatest in infants)

• Conclusion
  – Cold blood has protective effect greatest in infants
Cardioprotective effects and the mechanisms of terminal warm blood cardioplegia in pediatric cardiac surgery

Yoshiya Toyoda, MD$^{a,b}$

- **Design**
  - n=103 (50% cyanotic, mean 5.5yrs)
  - Cold blood vs cold blood/hot shot

- **Outcomes**
  - Hot shot:
    - more spontaneous defib
    - Higher lactate extraction
    - Lower troponin T and fatty acid binding protein @18hrs

- **Conclusion**
  - Hot shot enhances protection with cold blood
The myocardial protective effects of a moderate-potassium adenosine–lidocaine cardioplegia in pediatric cardiac surgery

Zhen-Xiao Jin, MD, PhD, Sheng-Li Zhang, MD, Xi-Ming Wang, MD, Sheng-Hui Bi, MD, Mei Xin, MD, Jing-Jun Zhou, PhD, Qin Cui, MD, PhD, Wei-Xun Duan, MD, PhD, Hong-Bing Wang, MD, and Ding-Hua Yi, MD, PhD

• Design
  – n=134
  – Hi K+ (20mM)
  – Hi K+ (20mM) & adenosine/lidocaine
  – Lo K+ (10mM) & adenosine/lidocaine

• Outcomes
  – Lo K+/ADO/Lido higher BP and lower troponin

• Conclusion
  – Better myopreservation with Lo K+/ADO/Lido
Blood Cardioplegia Provides Superior Protection in Infant Cardiac Surgery

Kerstin Åmark, MD, Håkan Berggren, MD, PhD, Kerstin Björk, CCP, Annica Ekroth, CCP, Rolf Ekroth, MD, PhD, Krister Nilsson, MD, PhD, and Jan Sunnegårdh, MD, PhD

• Design
  – n=30 AVSD
  – Cold blood vs crystalloid (plegisol)

• Outcomes
  – Better after cold blood cardioplegia:
    • Coronary sinus lactate, lactate release, O_2 extraction
    • Cardiac index, LV fxn

• Conclusion
  – Transient benefit w/ blood
• Design
  – n=30
  – Crystalloid vs Blood

• Outcomes
  – Crystalloid
    • Uptake: Glutamate/leucine/beta hydroxybutyrate
    • Release: Lactate
  – Blood
    • Update: free fatty acids

• Conclusion
  – Different substrate metabolism
Design
- n=103
- Crystalloid (St Thomas) vs cold blood vs cold blood/hot shot

Outcomes at reperfusion + 20min
- All groups: No Δ ATP, ATP/ADP, glutamate, troponin
- Cyanotic patients - Cold blood/hot shot:
  - less deficit vs crystalloid
  - Higher myocardial free amino acids (ASP, ALA, GLU, TAU)

Conclusion
- Older, non-cyanotic, short AXC: no Δ
- Cold blood/hot shot benefit: cyanotic/young/long AXC

Modi, JTCVS 2004 – EJCTS 2006
• Design
  – n=47
  – Mild hypothermia and cold crystalloid cardioplegia vs
  – Normothermia and intermittent warm blood cardioplegia

• Outcomes
  – [ATP]: different time profiles, no Δ at end of case
  – Neuro at 4 yrs: no Δ

• Conclusion
  – Normothermia/iWBC is not inferior
• Design
  – n=68
  – Cold blood
    • Hi K+ (20mM) vs Lo K+ (10mM)

• Outcomes
  – No Δ inotropes, ICU time, hospital LOS
  – Lo K+
    • Less long term ventilation
    • Lower troponins at 1,3,6 hrs

• Conclusion
  – Better myopreservation with Lo K+
What do we know from RCT’s?

– Difficult to see consistent pattern
– Publication bias may be present in selection of studies

– Wide variety of testable variables
– precludes RCT as practical tool to identify optimum management

– Alternatives:
  • Observational trials
  • More animal studies with
    – Pathological models
    – Cyanosis
    – Neonates
    – Longer followup
  • Aggregate clinical wisdom
Aggregate clinical wisdom

....Somehow, we have improved....

• Large populations can recognize complex patterns

• Large populations = aggregate
• Recognition of complex patterns = wisdom
Iowa Electronic Markets: Predictive Accuracy Through Time

Average absolute error in predicting two-party vote shares, 1988-2000
Assessment of cardioplegia efficacy

![Graph showing the relationship between myocardial performance and surgeon's estimate of efficacy. The x-axis represents the surgeon's estimate of efficacy, and the y-axis represents myocardial performance. The data points form a scatter plot with a trend line indicating a positive correlation.](image)
Aggregate clinical wisdom

• Have we ‘figured it out’ as a group?

• Let’s see what we do in clinical practice
What do we do?

• Working group facilitated by CHSS
  – Yasuhiro Kotani
  – James Tweddell
  – Peter Gruber
  – Christian Pizarro
  – Erle H. Austin III
  – Ronald K Woods
  – Colleen Gruenwald

• Survey sent to 122 surgeons in North America
• 56/122 (46%) responses
Age stratification

• Neonates: <30d undergoing a complex repair
  – Truncus Arteriosus
• Infants: 1-6 months undergoing a complex repair
  – Tetralogy of Fallot
• Children: 6 months-6 years complex repair
  – Mitral valve repair
• Adolescents: 6 years-18 years complex repair
  – Mitral valve replacement
Type of Cardioplegia by Age

Number

Neonates
Infants
Children
Adolescents

Blood-based cardioplegia
Crystalloid cardioplegia
Type of Cardioplegia by Solution

- del Nido
- Custodiol
- St. Thomas
- Customized
- Microplegia

Number

Blood-based

Crystalloid
Type of Solution by Age

Neonates
- del Nido
- Custodiol
- St. Thomas/Plegisol/Baxter
- Customized
- Microplegia

Infants
- del Nido
- Custodiol
- St. Thomas/Plegisol/Baxter
- Customized
- Microplegia

Children
- del Nido
- Custodiol
- St. Thomas/Plegisol/Baxter
- Customized
- Microplegia

Adolescents
- del Nido
- Custodiol
- St. Thomas/Plegisol/Baxter
- Customized
- Microplegia
Dilution ratio (Crystalloid:Blood) by Age

Number

Neonates  Infants  Children  Adolescents

- microplegia
- 1:1
- 1:2
- 1:3
- 1:4
- >1:4
Dilution ratio (Crystalloid:Blood) by Solution

- del Nido
- Custodiol
- St. Thomas
- Customized
- Microplegia

Legend:
- microplegia (<1:60)
- 1:1
- 1:2
- 1:3
- 1:4
- ≥4:1
Cardioplegia Temperature by Age

Number

Neonates  Infants  Children  Adolescents
<5  5 - 10  11 - 20  21-30

Legend:
- Green: <5
- Blue: 5 - 10
- Light Blue: 11 - 20
- Pink: 21-30
Cardioplegia Temperature by Solution

- del Nido: 6.1 ± 2.6
- Custodiol: 5.0 ± 0
- St. Thomas: 7.6 ± 6.6
- Customized: 6.1 ± 1.8
- Microplegia: 10.0 ± 4.4

Number

- <5
- 5 - 10
- 11 - 20
- 21-30

AVE
Systemic Cooling Temperature by Age

Neonates
Infants
Children
Adolescents

Number

<18  20-18  25-21  30-26  35-31  36>

0  10  20  30  40  50  60
Systemic temperature by Solution

<table>
<thead>
<tr>
<th>Solution</th>
<th>Number</th>
<th>Systemic Temperature (°C ± Standard Deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>del Nido</td>
<td>26.9 ± 4.9</td>
<td></td>
</tr>
<tr>
<td>Custodiol</td>
<td>27.3 ± 3.6</td>
<td></td>
</tr>
<tr>
<td>St. Thomas</td>
<td>26.6 ± 5.9</td>
<td></td>
</tr>
<tr>
<td>Customized</td>
<td>26.5 ± 4.8</td>
<td></td>
</tr>
<tr>
<td>Microplegia</td>
<td>27.3 ± 8.3</td>
<td></td>
</tr>
<tr>
<td>AVE</td>
<td></td>
<td>27.3 ± 8.3</td>
</tr>
</tbody>
</table>

Legend:
- <18
- 20-18
- 25-21
- 30-26
- 35-31
- 36+
Use of Topical Cooling by Age

- **Neonates**
  - Yes: 35
  - No: 25

- **Infants**
  - Yes: 30
  - No: 30

- **Children**
  - Yes: 40
  - No: 20

- **Adolescents**
  - Yes: 50
  - No: 50
Use of Topical Cooling by Solution

- **del Nido**
  - Yes: 15
  - No: 5

- **Custodiol**
  - Yes: 2
  - No: 3

- **St. Thomas**
  - Yes: 4
  - No: 1

- **Customized**
  - Yes: 20
  - No: 0

- **Microplegia**
  - Yes: 2
  - No: 3

Legend:
- Blue: Yes
- Red: No
Use of “Hot Shot” by Age

- Neonates
- Infants
- Children
- Adolescents

Number

- Yes
- No
Use of “Hot Shot” by Solution

- del Nido
- Custodiol
- St. Thomas
- Customized
- Microplegia

Number

- a
- b

Yes  No
Induction Dose by Age

Neonates
Infants
Children
Adolescents

ml/Kg

5 10 15 20 25 30 35 40
### Induction Dose by Solution

<table>
<thead>
<tr>
<th>Solution</th>
<th>Dose (mL/Kg)</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>del Nido</td>
<td>23.1 ± 6.6</td>
<td></td>
</tr>
<tr>
<td>Custodiol</td>
<td>30.0 ± 0</td>
<td></td>
</tr>
<tr>
<td>St. Thomas</td>
<td>25.1 ± 8.5</td>
<td></td>
</tr>
<tr>
<td>Customized</td>
<td>27.4 ± 9.5</td>
<td></td>
</tr>
<tr>
<td>Microplegia</td>
<td>20 ± 10</td>
<td></td>
</tr>
<tr>
<td>AVE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The diagram shows the distribution of induction doses for different solutions, with a focus on del Nido, Custodiol, St. Thomas, Customized, and Microplegia.
Maintenance Dose by Age

- **Neonates**
- **Infants**
- **Children**
- **Adolescents**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dose (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>25</td>
</tr>
</tbody>
</table>

Legend:
- Red: 5 mL
- Pink: 10 mL
- Cyan: 15 mL
- Blue: 20 mL
- Dark Blue: 25 mL
Maintenance Dose by Solution

- del Nido: 11.2 ± 4.2 mL
- Custodiol: 13.8 ± 2.5 mL
- St. Thomas: 15.0 ± 3.8 mL
- Customized: 15.0 ± 4.5 mL
- Microplegia: 8.3 ± 2.9 mL

AVE: 13.8 ± 2.5 mL
Time Interval between doses by Age

- **Neonates**: Continuous
- **Infants**: 10-15, 20-25, 30-35, 40-45, 50-55, 60, Single dose
- **Children**: 10-15, 20-25, 30-35, 40-45, 50-55, 60, Single dose
- **Adolescents**: 10-15, 20-25, 30-35, 40-45, 50-55, 60, Single dose
Type of Solution and Time Interval between Dose

<table>
<thead>
<tr>
<th>Type of Solution</th>
<th>Time Interval between Dose (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood-based cardioplegia</td>
<td>44.5 ± 17.2</td>
</tr>
<tr>
<td>Crystalloid cardioplegia</td>
<td>40.0 ± 14.1</td>
</tr>
<tr>
<td>Custodiol</td>
<td>28.9 ± 17.6</td>
</tr>
<tr>
<td>Customized Microplegia</td>
<td>25.3 ± 13.4</td>
</tr>
<tr>
<td>St. Thomas/Plegisol</td>
<td>23.3 ± 7.6</td>
</tr>
</tbody>
</table>

AVE = 44.5 ± 17.2

*4/22

*2/3

*2/18
<table>
<thead>
<tr>
<th>No.</th>
<th>Solution</th>
<th>Blood vs. Crystalloid</th>
<th>Dilution</th>
<th>CP temperature</th>
<th>Systemic temperature*</th>
<th>Topical Cooling</th>
<th>Hot Shot</th>
<th>Route</th>
<th>Initial dose</th>
<th>Maintenance dose</th>
<th>age</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>del Nido</td>
<td>Blood</td>
<td>1:4</td>
<td>&lt;5</td>
<td>32</td>
<td>No</td>
<td>No</td>
<td>Ante</td>
<td>20</td>
<td>10</td>
<td>Only neonates</td>
</tr>
<tr>
<td>2</td>
<td>del Nido</td>
<td>Blood</td>
<td>1:4</td>
<td>5</td>
<td>30</td>
<td>Yes</td>
<td>No</td>
<td>Ante</td>
<td>30</td>
<td>10</td>
<td>Except adolescents</td>
</tr>
<tr>
<td>3</td>
<td>del Nido</td>
<td>Blood</td>
<td>4:1</td>
<td>15</td>
<td>22</td>
<td>No</td>
<td>No</td>
<td>Ante</td>
<td>20</td>
<td>10</td>
<td>All</td>
</tr>
<tr>
<td>4</td>
<td>del Nido</td>
<td>Blood</td>
<td>1:1</td>
<td>&lt;5</td>
<td>30</td>
<td>Yes</td>
<td>No</td>
<td>Ante</td>
<td>30</td>
<td>5</td>
<td>All</td>
</tr>
<tr>
<td>5</td>
<td>St. Thomas</td>
<td>Crystalloid</td>
<td>n/a</td>
<td>&lt;5</td>
<td>25</td>
<td>No</td>
<td>No</td>
<td>Ante</td>
<td>15</td>
<td>10</td>
<td>Only neonates</td>
</tr>
<tr>
<td>6</td>
<td>St. Thomas</td>
<td>Crystalloid</td>
<td>n/a</td>
<td>&lt;5</td>
<td>18</td>
<td>No</td>
<td>No</td>
<td>Ante</td>
<td>20</td>
<td>n/a</td>
<td>Only neonates</td>
</tr>
<tr>
<td>7</td>
<td>Customized</td>
<td>Blood</td>
<td>1:4</td>
<td>6</td>
<td>28</td>
<td>No</td>
<td>No</td>
<td>Ante</td>
<td>10</td>
<td>10</td>
<td>Only neonates</td>
</tr>
<tr>
<td>8</td>
<td>Customized</td>
<td>Crystalloid</td>
<td>n/a</td>
<td>&lt;5</td>
<td>18</td>
<td>No</td>
<td>No</td>
<td>Ante</td>
<td>30</td>
<td>n/a</td>
<td>Only neonates</td>
</tr>
</tbody>
</table>

* Based on neonates
Summary of data

- Most use blood-based cardioplegia
- Age not important
- Large proportion use del Nido or Customized
- del Nido and Custodial ass’d w/ longer intervals
- ~20% use single dose regardless of duration

- Wide variety of solutions, less variety in technique
- Greatest variability: time interval between doses
Inferences

• *If* current myopreservation is clinically satisfactory for all surgeons, ....

...*then* a large proportion of surgeons can safely extend intervals between cardioplegia doses –
...*then* there is little difference between solutions
...*then* there is equipoise to test different regimens in a prospective fashion
What type and how much?

We may be forced to rely on aggregate clinical wisdom

Integrating basic science, large animal studies, observational clinical studies, and occasional RCT’s