Neuroprotective Strategies in Neonates, Infants and Children

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"As we know, there are known knowns; there are things we know we know. We also know there are known unknowns; that is to say we know there are some things we do not know. But there are also unknown unknowns -- the ones we don't know we don't know."
Newborn Brains Are Vulnerable
Neuro development delay is the most common morbidity for children with complex CHD who require surgery as neonates or infants.

- The incidence of long term neurologic deficit 25-75%
- 50% required remedial academic services
Neonates demonstrate

- Abnormal muscular tone
- Feeding difficulty
- Major milestone delay
- Abnormal speech

Children demonstrate

- Low academic achievement score
- Learning disability
- Behavioral problems
- Poor social skills

Currently the holy grail of congenital heart surgery is to prevent early and late central nervous system injury.
Etiology of CNS Morbidity in CHD

Preoperative Factors

Abnormal uterine blood flow → abnormal fetal brain
  • TVG; red blood to the lungs; not brain
  • HLHS small ascending aorta; less blood to brain

Abnormal cerebral vascular resistance
  • Left heart obstruction ↓ CVR
  • Right heart obstruction ↑ CVR
1. Microcephaly

- Low head circumference is a marker for abnormal brain development
- Incidence 10-55% in patients with CHD
- Strongly correlated with late CNS morbidity
- Highly correlated with low brain volume (MRI)
- More complex CHD, higher incidence of microcephaly
- Microcephaly highly correlated with small ascending aorta
  - Worse with aortic atresia/HLHS

Shillingford AJ. Pediatr Cardiol 2005:25:81
2. Periventricular Leukomalacia

- White matter injury in vascular watershed area adjacent to lateral ventricles
- Injury is hypoxia/ischemia and hypoglycemia
- Highly associated with decreased CBF
- Associated in term patients with CHD and prematurity
- Seen preoperatively in 16-27% of patients with CHD
- Seen postoperatively in 50-75% of patients with CHD
3. Periventricular Leukomalacia (cont’d)

- Cells injured are premyelinating oligo dendrocytes (OD)
- OD peak prevalence at 23-32 wks gestation
- OD persists up to 35-36 wks gestation
- PVL increased with hypoxia and hypoglycemia
- CHD pts highly susceptible to PVL
Etiology of CNS Morbidity in CHD

Preoperative Factors

4. Prematurity less than 37 weeks
   - Highly associated with CNS injury pre- and postoperatively
   - CNS injury worse in association with CHD
   - Avoid operating before 37 weeks
   - Avoid delivery before 39 to 40 weeks

∞ Full-term is 280 days = 40 weeks
5. **Open operculum**

- The operculum is where the frontal, temporal, and parietal convolutions merge and remain closed.
- Open operculum is highly associated with CHD and PVL.
- Open operculum can be bilateral or unilateral
  - Absence of the corpus callosum – bilateral open operculum
- Operculum controls oral-motor coordination, taste and speech
Preoperative Markers for CNS Injury

- Need for ventilation and intubation
  - Can decrease cerebral blood flow
- Potential for paradoxical cerebral embolus
  - Air
  - Intravenous access
  - Balloon atrial septostomy
Strategy

- Full-term and in pre-term infants with CHD, preoperative white matter brain injury (PVL) has now been well documented and is related to impaired brain development.

- In the operating room and postoperatively, our goal as surgeons and perfusionists is to employ protective strategies that prevent further neurologic injury.
“In pediatric heart surgery, you cannot be too gentle and you cannot be too accurate.”

Dwight McGoon, M.D.
## ACC/AHA Level of Evidence System

### Size of Treatment Effect

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Benefit &gt;&gt;&gt; Risk</td>
</tr>
<tr>
<td>IIa</td>
<td>Benefit ➔ Risk</td>
</tr>
<tr>
<td>IIb</td>
<td>Benefit ➔ Risk</td>
</tr>
<tr>
<td>III</td>
<td>No Benefit or Class III Harm</td>
</tr>
</tbody>
</table>

### Level A
- Multiple populations evaluated*
- Data derived from multiple randomized clinical trials or meta-analyses

#### Recommendation
- Procedure or treatment is useful/effective
- Sufficient evidence from multiple randomized trials or meta-analyses

### Level B
- Limited populations evaluated*
- Data derived from a single randomized trial or nonrandomized studies

#### Recommendation
- Procedure or treatment is useful/effective
- Evidence from single randomized trial or nonrandomized studies

### Level C
- Very limited populations evaluated*
- Only consensus opinion of experts, case studies, or standard of care

#### Recommendation
- Procedure or treatment is useful/effective
- Only expert opinion, case studies, or standard of care

### Procedure/Treatment
- **Class I:** Benefit >>> Risk
  - Procedure/Treatment SHOULD be performed/administered

- **Class IIa:** Benefit ➔ Risk
  - Additional studies with focused objectives needed
  - It is REASONABLE to perform procedure/administer treatment

- **Class IIb:** Benefit ➔ Risk
  - Additional studies with broad objectives needed; additional registry data would be helpful
  - Procedure/Treatment MAY BE CONSIDERED

- **Class III:** No Benefit or Class III Harm
  - Procedure/Test
  - Treatment
  - Class III: No benefit
  - Class III: Harm

#### Evidence

- Recommendation’s usefulness/efficacy less well established
- Greater conflicting evidence from multiple randomized trials or meta-analyses

#### Procedure or Treatment

- Recommendation that procedure or treatment is not useful/effective and may be harmful
- Sufficient evidence from multiple randomized trials or meta-analyses

#### Harmful to Patients

- Recommendation that procedure or treatment is not useful/effective and may be harmful
- Evidence from single randomized trial or nonrandomized studies

- Only expert opinion, case studies, or standard of care
Near Infrared Spectroscopy
• “Normal” NIRS in deceased patients
• Multiple variables impact impact rSOi$_2$
  - CPB, CBF, Arterial O$_2$ SAT, PACO$_2$ and CMRO$_2$
• Not associated with improved outcomes
• Low NIRS not correlated with clinical or MRI findings
  (exception: McQuillen; Stroke 2007;38:736)
• Best used as trend monitor
  - Fall of 20% below baseline ? significance

Score class III-B
NIRS Detection of Aortic Cannula Malposition

Figure 1
Cerebral oxygen saturation. An abrupt decrease in regional cerebral saturation index (rSO$_2$i) occurred at the onset of CPB (Time A). After repositioning of the aortic cannula, rSO$_2$i recovered to baseline levels.

Figure 2
Aortic cannula position.

From Gottlieb EA. et al. Ped Anes 2006:16:787
Transcutaneous Doppler

Score class III-B
Transcutaneous Doppler

• Pulse wave ultrasound at 2 MHZ frequency
• Measures real time cerebral blood flow velocity
• Peak and mean flow recorded
• Monitor MCA at Zygoma-Tragus angle
• Peak velocity drop
• Multiple variables impact peak velocity
  ❖ Less than 60%  moderate impairment
  ❖ Less than 80%  severe impairment
• Can access emboli and altered brain perfusion

Problem: No correlation between velocity changes and early or late neurologic outcomes.
TCD Pre-Bypass
TCD During CPB: Cooling

<table>
<thead>
<tr>
<th>Mean</th>
<th>Peak</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>30.4</td>
<td>33.9</td>
<td>78</td>
</tr>
</tbody>
</table>

CM/s

65 1 25% 10 115 45% Mute Upper 2
Depth Gain Power Sample Scale Zero Volume Env Probe
TCP During RCP

### Table

<table>
<thead>
<tr>
<th>Mean</th>
<th>Peak</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.8</td>
<td>31.6</td>
<td>108</td>
</tr>
</tbody>
</table>

### Graph

- cm/s
- 30
- 20
- 10
- 0
- -10
- -20
- -30

### Controls

- Depth
- Gain
- Power
- Sample
- Scale
- Zero
- Volume
- Env
- Probe

- Mute
- Upper
Electro Encephalogram Monitoring

- Bulky
- Signal affected by
  - electrocautery
  - patient temperatures
  - CPB flow
  - anesthetic agents
Electro Encephalogram Monitoring

- Will detect
  - anesthetic depth
  - electrical silence with DHCA
  - postop epilepiform activity
- Postop EEG slowing is common with no associated adverse outcome
- Normothermic isoelectric EEG > 50 seconds duration is associated with adverse neurologic outcomes
  
  Score class III-C

Pediatric Perfusion Characteristics

- Smaller circulating volume
- Higher $O_2$ consumption
- Reactive pulmonary bed
- Intra- and extracardiac shunting
- Poor tolerance to micro emboli
- Altered thermoregulation
- Aortopulmonary collaterals
Body metabolism decreases linearly

Brain metabolism decreases exponentially
  - CMRO$_2$ decreases to 85-90% of baseline but never to zero

Q$_{10}$ is ratio of metabolic rates in a chemical reaction at two temperatures separated by 10°C
  - Adults Q$_{10}$ = 2.4-2.8
  - Children Q$_{10}$ = 3.7

Children → greater metabolic rate decrease with hypothermia

Hypothermia provides better organ protection in children
BODY and BRAIN

Probability of "safe" circulatory arrest

Duration of total circulatory arrest (min)

- 37°C: 4 min
- 28°C: 30 min
- 18°C: 40 - 50 min

PCPB
Hypothermia

Brain, Blood Flow and Blood Pressure
Brain Physiology

Temperature During Cooling

• Brain $O_2$ consumption decreases 50% for each 10°C drop
• Brain temperature is 2° - 3° lower than Naso pharyngeal
### Brain Physiology

**Adults Normothermia**

<table>
<thead>
<tr>
<th></th>
<th>O2 Consumption</th>
<th>O2 Extraction</th>
<th>Glucose Extraction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cc/min/100gr</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Brain</td>
<td>160</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Kidney</td>
<td>400</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>Heart</td>
<td>640</td>
<td>50</td>
<td>2</td>
</tr>
</tbody>
</table>
Brain Physiology

Adult Brain  Normothermia

• Brain receives 15% of cardiac output
• Brain receives 20% of total body $O_2$
• Brain receives 25% of total body glucose
• Brain extracts 50% of oxygen delivered
• Brain extracts 10% of glucose delivered
Temperature and Cerebral Blood Flow

The Supply Curve
Hypothermia effect on CMRO₂
CMRO₂ and Temperature

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>CMRO₂ (ml/100 g/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>1.48</td>
</tr>
<tr>
<td>32</td>
<td>0.823</td>
</tr>
<tr>
<td>30</td>
<td>0.654</td>
</tr>
<tr>
<td>28</td>
<td>0.513</td>
</tr>
<tr>
<td>25</td>
<td>0.362</td>
</tr>
<tr>
<td>20</td>
<td>0.201</td>
</tr>
<tr>
<td>18</td>
<td>0.159</td>
</tr>
<tr>
<td>15</td>
<td>0.112</td>
</tr>
</tbody>
</table>
Oxygen Demand Curve

- Hypothermia
- Normothermia

$CMRO_2$ (mL/100 g per minute) vs. Temperature (°C)

Data points showing the relationship between $CMRO_2$ and temperature, differentiated between hypothermia and normothermia.
<table>
<thead>
<tr>
<th></th>
<th>Normal CBF</th>
<th>Normal CMRO2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30-40 cc/100 gr/min</td>
<td>1.5-3 cc/100gr/min</td>
</tr>
<tr>
<td>Supply/Need</td>
<td>10-20:1</td>
<td>0.16 cc/100gr/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuronal cell death</td>
<td>CBF &lt; 10 cc/100 gr/min</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>37° C</td>
<td>18° C</td>
</tr>
<tr>
<td></td>
<td>15 cc /100 gr/min</td>
<td>0.16 cc/100gr/min</td>
</tr>
<tr>
<td></td>
<td>10-20:1</td>
<td>90:1</td>
</tr>
</tbody>
</table>

**Neuronal cell death**

**CBF < 10 cc/100 gr/min**
Blood Pressure and Cerebral Blood Flow
CBF (ml/100 g/min)

MAP (mm Hg)

25°C
R = 0.74
p < 0.002

20° C
Systolic

Blood pressure (mm Hg)

Cerebral blood flow (ISI)

Autoregulation

normothermia

PCPB
Hypothermia: Brain and Blood Flow

Summary

• CBF is independent of mean arterial pressure above 25°C
• CBF autoregulation is lost below 22°C
• CBF becomes dependent on MAP below 22°C
• CBF decreases as temperature decreases
• Brain metabolism decreases as temperature decreases
• Brain metabolism is never zero
Hypothermic Brain Injury

Risk

• Temperature and blood pressure
• Duration of cooling
• Blood gas management
• Aortopulmonary collaterals
Blood Gas Strategy

Fundamentals

- PH Strategy may be important below 25°C
- Hypothermia increases CO₂ solubility
- Equation shifts rightward
  - \( H^+ + HCO_3^- \rightarrow H_2CO_3 \leftarrow \rightarrow CO_2 + H_2O \)
- As you cool, H+ ↓ PH ↑
- HB curve shifts to left
- Oxygen more tightly bound
To keep chemical neutrality imidazole ring of histidine is a buffer.

\[
\text{Alpha} = \frac{\text{I}}{\text{H I}} = 0.55
\]

- Alpha remains constant as temperature decreases
- CO₂ in blood slowly decreases as temperature decreases
- Lower cerebral blood flow
- \( \text{Ph}_i \) is normal

Alkaline Strategy

- \( \text{HB-O}_2 \) – curve shifts to left: less \( \text{O}_2 \) release to tissues
Blood Gas Strategy

PH Stat

• Add CO$_2$ with cooling to keep PH 7.4
• Ph$_i$ drops H+ OH – imbalance
• PCO$_2$ rises as you cool
• Cerebral blood flow increases
• Acid Strategy HB curve shifts to the right
• Better O$_2$ delivery
• Preserves cytochrome 3-a
Advantages of PH Stat (cont’d)

• High CO$_2$ inhibits PD Hg enase
  ✓ Less lactate production

• ICU and ventilator time is less

• Better neuro protection especially at low temperature

• Better neuro protection with MAPCAS

• Better myocardial performance
  ✓ High CO$_2$ coronary dilatation
  ✓ High cardiac index first 18 hours
  ✓ Lower troponin levels

Duplessis. JTCVS 1997;114:9917
Brain Metabolism and Hypothermia

Hypothermia ↓ CMRO$_2$ exponentially

Supply/Demand Ratio ↑

- Alpha Stat 30:1
- pH Stat 60:1
Hypothermic Brain Injury

pH Strategy

- Moderate hypothermia – either method
- Deep hypothermia – adding CO$_2$ may improve cold perfusate to deep brain structures
- Large aorto-pulmonary collaterals may benefit with pH stat during cooling
Methods of Cerebral Perfusion

- Mild-Moderate Hypothermia and Continuous CPB
- Deep Hypothermia and intermittent CPB
- Deep Hypothermia and Circulatory Arrest and No CPB (DHCA)
- Regional Cerebral Perfusion
Cerebral Protection

Perfusion Strategies

- Hypothermia 14° - 18° C
- Slow cooling 20 – 35 minutes
- Ice packs and cooling blanket
- Cold reperfusion 3 – 5 minutes
- Avoid excessive rewarming beyond 35° - 36° C
Cerebral Protection

Pharmacologic Strategies

• Alpha blockade
• Isoflurorane
• Solumedrol
• Mannitol
• MUF
Cerebral Protection

Temperature Monitoring

- Nasopharangeal
- Bladder
Regional Cerebral Perfusion (RCP)

Pigula et al JTCVS 2000;119:331-9
Regional Cerebral Perfusion

• Optimal flow
  ✓ 30-50 cc/kg/min
  ✓ guided by NIRS and TCD

• Cool to 18°C

• Right arm mean BP 30 mmHg

• PH Stat at all phases

• Pump flow 150 cc/kg/min

• Hct: 30-35%

• Slow cooling ≥ 20 min

• Surface cooling

• Regitine (if available)
Cardiopulmonary Bypass Strategy
Higher Hematocrit

147 subjects randomized to lower and higher hematocrit strategy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lower Hct</th>
<th>Higher Hct</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest Cl</td>
<td>2.8 ± 1.1</td>
<td>3.1 ± 1.1</td>
<td>.02</td>
</tr>
<tr>
<td>Lactate 1 hr post-CPB</td>
<td>3.3 ± 1.9</td>
<td>2.7 ± 1.3</td>
<td>.03</td>
</tr>
<tr>
<td>Resistance (% change from preop to post day 1)</td>
<td>-38.2 ± 16.5</td>
<td>28.4 ± 20.3</td>
<td>.006</td>
</tr>
</tbody>
</table>

Jonas RA, Wypij D, Roth SJ, Bellinger DC, et al. The influence of hemodilution on outcome after hypothermic cardiopulmonary bypass: Results of a Randomized Trial in infants. JTCVS. 2003 December;126:1765-1774
Regional Cerebral Perfusion Optimal Flow

- Keep NIRS > 90%
- Keep TCD ± 10% baseline
Hypothermia: Blood Flow/Pressure in the Brain

- Monitor BP during low flow bypass.
- Monitor BP during regional cerebral perfusion.
- Keep right arm BP ~ 30 mmHg
DHCA

- Cool slowly, ≥ 20 min
- Hyperoxygenation prior to arrest
- Limit time ≤ 45-50 min
- Topical cooling (Head packed in ice)
- Intermittent cerebral perfusion only if longer than 50 min
- Try to avoid DHCA
Hypothermia: the Brain and CBF

Remember

- DH with low flow bypass
  - CBF is normalized during rewarming
- DHCA alone
  - CBF does not return to normal and may remain low for hours
- Why?
  - Low CBF is a function of low metabolic demand secondary to DHCA
  - Low CBF from “no reflow” secondary to high CVR
Postoperative Measures

- Cerebral autoregulation is not normal postoperatively
- Keep systolic BP normal
- Avoid decrease in cerebral blood flow
  - Avoid hypocarbia
  - Avoid alkalosis
- Aggressive treatment of hypoxia and hyperthermia
The effects of concentration of work show themselves in our results, which depend so greatly on such details as perfection of anesthesia, scrupulous technique, ample expenditure of time, painstaking closure . . . which so many operators regard as trivialities.

Harvey Cushing, JAMA 1915
Cardinal Glennon
SSM Cardinal Glennon Children’s Medical Center