Neuroprotective Strategies – What Do We Really Need to Know

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Baylor College of Medicine

No disclosures
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Texas Heart® Institute

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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."
“If you do not know where you want to go, it doesn't matter which path you take.”

Lewis Carroll
Newborn Brains Are Vulnerable
Introduction

- New intraparenchymal brain injury on MRI is seen in 36-73% of neonates undergoing surgery with CPB
  - White matter injury (WMI) introduction
  - Ischemic infarction
  - Hemorrhagic infarction

*Stroke 2007;38:736;JTCVS 2006;131:190;Circulation 2002;106[suppl I] I-109*

- Preoperative MRI injury is seen in 20-40% of neonates

*Sherlock RL et al. Stroke 2008 Nov 6. [Epub ahead of print]*
Etiology of Neonatal Brain Injury in CHD

- **Preoperative Brain Injury**
  - Diminished in utero blood flow and brain growth

  *JTCVS 2004;128:841*

- **Brain Immaturity in CHD**
  - Delayed structural maturation
  - Delayed myelination and intracellular maturation
  - Diminished in utero blood flow and brain growth

  *N Eng J Med 2007;357; Licht et al JTCVS 2008*

- **Intra- and Postoperative Brain Injury**
  - Prolonged low brain regional oxygen saturation
  - Prolonged DHCA, low flow ACP

  *Stroke 2007;38:736;
  JTCVS 2006;131:190*
Etiology of CNS Morbidity in CHD

- 21-69% incidence of long-term neurodevelopment problems after infant congenital heart surgery
- Recent emphasis has shifted away from cardiopulmonary bypass
- Should “patient” factors be emphasized?
  - Prenatal, genetic, socioeconomic, perioperative

Wernovsky, Cardiol Young 2006;16:92
“PVL was found in 50% of neonates after cardiac surgery but rarely in older infants. Hypoxemia & hypotension in the early postop period, particularly diastolic hypotension, may be important risk factors for PVL.”
TCH Heart Center

20th – Clinic, echo lab

19th – Administrative offices

18th – CVICU, CVOR, Cath Lab, Holding area, Cath Recovery area

17th – Family waiting area, offices

15th – In-patient unit, step-down
**Cardiovascular Anesthesia Complications**

**by Volume**

- **Cases without Complications**: 2,310 (97%)
- **Cases with Complications**: 75 (3%)

Only 3% of total pediatric cardiovascular anesthesia cases in 2011 could be categorized as complicated cases. Of this 3%, 45% were airway or respiratory complications, 22% were cardiac, 13% were medication-related and 9% were categorized as other.

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**Developmental Outcomes**

Children treated for congenital heart disease have been found to be at greater risk and have higher rates of motor delays, language and visual difficulties, and attention and behavioral problems. The recently developed Cardiac Developmental Outcomes Program at Texas Children’s Hospital supports patients with congenital heart disease who have survived surgery during the first month of life by providing developmental assessments and coordinating any appropriate care needed.

Our experts in cardiology, critical care, developmental pediatrics, clinical psychology, nursing and other professions work together to screen children for issues at identified developmental milestones. These thorough assessments can recognize subtle but significant delays where early intervention can make a difference.

The program provides family-centered care, where the child’s parents or caregivers are directly consulted and involved in assessments and interventions in their child’s best interest for developmental progress. The Cardiac Developmental Outcomes Program is focused on a patient’s medical, social and developmental health in order to help them reach their maximum potential.

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**Neurodevelopmental Outcomes Research**

Led by Dean Andropoulos, M.D., Chief of Anesthesiology at Texas Children’s Hospital and Professor of Anesthesiology and Pediatrics at Baylor College of Medicine, a multidisciplinary team from Pediatric Cardiovascular Anesthesiology, Congenital Heart Surgery, Pediatric Cardiology, Pediatric Intensive Care, Pediatric Radiology, Pediatric Neurology and Developmental Pediatrics has enrolled a cohort of 97 neonates undergoing complex cardiac surgery for long-term follow-up of neurological events and neurodevelopmental outcomes.

Two major papers were written about this study and will soon be published in *Annals of Thoracic Surgery*. The first won the J. Maxwell Chamberlain Award for the best paper in Congenital Heart Surgery at the 2012 Society of Thoracic Surgeons’ Annual Meeting. This study found that the 20 patients with transposition of the great arteries undergoing the arterial switch operation had a mean cognitive score on the Bayley Scales of Infant Development III of 104.8 ± 15.6, significantly above the reference population mean normal value.

In addition, for the very first time, these Texas Children’s Hospital investigators demonstrated an association between preoperative MRI brain injury and later neurodevelopmental outcomes.

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TCH philosophy

- Optimize intraoperative brain protection/minimize potential for CPB and hemodynamic induced brain injury
  - Anesthesia/Surgery/Perfusion
  - Individualized CPB strategy – This is usually the debate
  - Technique/Accuracy
  - Intraop is the one period in continuum of care over which surgeon exerts most control
- Deliver appropriate CBF vs. work against the clock

- Our approach is to focus on appropriate O2 delivery/CBF

- Recognizing individual variability requires varying technique

- Individualize perfusion to brain (RCP) requires brain monitoring
“In pediatric heart surgery, you cannot be too gentle and you cannot be too accurate.”

Charles D. Fraser, Jr., M.D.
Neonatal Brain Protection in Cardiac Surgery and the Role of Intraoperative Neuromonitoring

Muhammad S. Khan, MD,¹ and Charles D. Fraser Jr, MD, FACS¹

Abstract
Improving mortality rates in children undergoing surgery for congenital heart disease has enabled a shift in focus to improving morbidity, particularly with respect to neurological complications. Various factors have been implicated in influencing neurological outcomes. We share our experience in formulating a customized cardiopulmonary bypass (CPB) protocol based on currently available evidence. Theoretical advantages of intraoperative neuromonitoring during CPB, specifically use of near-infrared spectroscopy, will be discussed in the context of methodologies to monitor cerebral perfusion during surgery.

Keywords
near-infrared spectroscopy, cardiopulmonary bypass, antegrade cerebral perfusion, deep hypothermic circulatory arrest

Submitted September 12, 2011; Accepted September 15, 2011.
Presented at the Fourth Annual Symposium of the Walter Sisulu Paediatric Cardiac Centre for Africa, Johannesburg, South Africa; March 23-24, 2011.
Heterogeneity

- Pathology
- Pressure-Volume curve
- Pressure autoregulation
- Metabolic regulation/ CBF coupling
- CO2 reactivity
- O2 reactivity
Near-infrared spectroscopy (NIRS)

- Measures % hemoglobin saturation in the blood vessels of the frontal cerebral cortex
- Cerebral $O_2$, Cerebral Blood Volume
- Correlates very well with jugular venous $SO_2$ (as measured directly from jugular bulb venous blood gases)
NIRS Principles

Skin

Skull

SomaSensor

Light Emitting Diode

Surface Photodetector

Cerebral Cortex

Deep Photodetector

Image from www.somantics.com
BiFrontal NIRS Probes
NIRS Detection of Aortic Cannula Malposition

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

Figure 2
Aortic cannula position.

Neonatal Coarctation
TCD Anatomy in the Neonate

MCA-ACA Bifurcation
TCD Pre-Bypass
<table>
<thead>
<tr>
<th>Table 1. Core Practices of the CPB Strategy in Texas Children’s Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full CPB flow of 150 mL/kg per min at all possible times</td>
</tr>
<tr>
<td>Minimize or eliminate low-flow CPB</td>
</tr>
<tr>
<td>Minimize or eliminate DHCA (exception TAPVR)</td>
</tr>
<tr>
<td>ACP for aortic arch reconstruction</td>
</tr>
<tr>
<td>“Adequate” ACP flow rate guided by NIRS and TCD</td>
</tr>
<tr>
<td>pH-stat management during all phases of CPB</td>
</tr>
<tr>
<td>Hematocrit of 30%-35% on CPB</td>
</tr>
<tr>
<td>Slow deep cooling over no &lt;20 minutes to deep hypothermia</td>
</tr>
</tbody>
</table>

Abbreviations: CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; TAPVR, total anomalous pulmonary venous return; ACP, antegrade cerebral perfusion; NIRS, near-infrared spectroscopy; TCD, transcranial Doppler.
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 CI</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
Core Practices – TCH

- pH stat management all phases of CPB
  
  duPlessis, JTCVS 1997;114:991

- Higher hematocrit 30-35% on CPB

  Jonas, JTCVS 2003;126:1765

- Slow cooling over no less than 20 minutes to deep hypothermia

  Bellinger, Circulation 2003;78:II358
CPB Setup

- Surgeon's headcam
- ABG/lab station
- Blood pumps
- Anesthetic vaporizer
- Patient monitor
- Perfusionist
- Pump monitors

Texas Children's Hospital | Surgery
Regional Cerebral Perfusion

- Designed to avoid or minimize DHCA
- Cannulation sites
  - Right innominate artery
  - Right carotid artery
- Cannulation materials
  - PTFE graft
  - Small flexible cannula
Regional Cerebral Perfusion (RCP)

Pigula et al  JTCVS 2000;119:331-9
Surgical Field During RCP

- Aortic Cannula
- 3.5 mm PTFE shunt
- Native Aorta
- Neoaorta Homograft Patch
What flow rate during RCP?

- 4-day old for Norwood procedure. Flow is directed to the right carotid, with the great vessels snared for 90 minutes. How are flow rates chosen?

- Right radial mean pressure 30 mmHg
- Left radial, mean pressure 20 mmHg
- 20 cc/kg/min, alpha stat
- 40 cc/kg/min, alpha stat
- 60 cc/kg/min, pH stat

Slide information courtesy of Ken Brady, MD
Selective Perfusion and Autoregulation

Pressure autoregulation in the brain is dependent on a parallel systemic blood flow for the push and pull of excessive and inadequate CBF.

Slide information courtesy of Ken Brady, MD
Selective Perfusion and Autoregulation in the Piglet

Large increases in SVR narrow the difference between the upper and lower limits of CBF pressure autoregulation.

Slide information courtesy of Ken Brady, MD
### Best laid plans of Piglets and Men...

<table>
<thead>
<tr>
<th></th>
<th>Brain Wt (g)</th>
<th>Body Wt (kg)</th>
<th>P\textsubscript{a}CO\textsubscript{2}</th>
<th>CBF (cc/100g/min)</th>
<th>CBF (cc/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piglet</td>
<td>60</td>
<td>3</td>
<td>α-stat</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Piglet</td>
<td>60</td>
<td>3</td>
<td>pH-stat</td>
<td>60</td>
<td>12</td>
</tr>
<tr>
<td>Human Infant</td>
<td>450</td>
<td>3</td>
<td>α-stat</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Human Infant</td>
<td>450</td>
<td>3</td>
<td>pH-stat</td>
<td>20</td>
<td>30</td>
</tr>
</tbody>
</table>

*Slide information courtesy of Ken Brady, MD*
ABP and CPB flow during RCP

- Piglets managed with alpha-stat or pH-stat have similar flow-pressure relationships during selective perfusion:

- Explained by small brain size

Slide information courtesy of Ken Brady, MD

ABP and CPB flow during RCP

- Human infants under alpha-stat have similar ABP-flow relationships to the piglet.
- Human infants under pH-stat require higher flow to maintain ABP during RCP.
- Explained by large human brain.

Slide information courtesy of Ken Brady, MD
TCD Pre-CPB

Mean: 20.0
Peak: 38.5
HR: 145

cm/s

65 1 25% 10 115 45% Mute Upper 2 PW

Depth Gain Power Sample Scale Zero Volume Env Probe
TCD During CPB: Cooling
TCP During RCP
NIRS Pre-Bypass
150 cc/kg/min
NIRS During Bypass
 Pediatric \%SO₂

11/29/06 09:49:18

System Signal OK

L  87

Baseline \%SO₂ ↑ 19%

R  91

Baseline \%SO₂ ↑ 20%

Baseline Menu Event Mark Alarm Suspend Options Menu
75 cc/kg/min
30 cc/kg/min
Monitoring for RCP
IAA Repair

NIRS (Abdomen)  NIRS (Head)
TCD  Bypass Flow rate

CBFV (cm/s); Cerebral SO2%; Abdominal SO2%

OR Times

CPB Flow (cc/min)
A Case for Neuromonitoring

- Baseline TCD and cerebral oximetry with NIRS at 18°
- Initiate SACP
- Titrate flows to achieve baseline TCD flow velocities and cerebral oximetry

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Novel cerebral physiologic monitoring to guide low-flow cerebral perfusion during neonatal aortic arch reconstruction

Dean B. Andropoulos, MD
Stephen A. Stayer, MD
E. Dean McKenzie, MD
Charles D. Fraser, Jr, MD, FACS

Results:

- \( n = 34 \)
- Range of RLFP rate – 24 to 94 ml/kg/min
- 13 patients – ScO\(_2\) of 95 during RLFP
- Radial BP – no correlation with RLFP flow
A Case for Neuromonitoring

Wide inter-subject variability of flow rates to achieve baseline flow
**MRI Results with RCP strategy**

**Neurodevelopmental Outcomes After Regional Cerebral Perfusion With Neuromonitoring for Neonatal Aortic Arch Reconstruction**

Dean B. Andropoulos, MD, R. Blaine Easley, MD, Ken Brady, MD, E. Dean McKenzie, MD, Jeffrey S. Heinle, MD, Heather A. Dickerson, MD, Lara S. Shekerdemian, MBChB, Marcie Meador, RN, MS, Carol Eisenman, RN, Jill V. Hunter, MBBS, Marie Turcich, MS, Robert G. Voigt, MD, and Charles D. Fraser, Jr, MD

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### Table 4. Brain Magnetic Resonance Imaging Data (N = 57)

<table>
<thead>
<tr>
<th>MRI Findings</th>
<th>Single Ventricle (n = 47)</th>
<th>Two Ventricle (n = 10)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative brain injury&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14 (30)</td>
<td>2 (20)</td>
<td>0.708</td>
</tr>
<tr>
<td>New 7-day postoperative brain injury&lt;sup&gt;a&lt;/sup&gt;</td>
<td>21 (45)</td>
<td>2 (20)</td>
<td>0.178</td>
</tr>
</tbody>
</table>

<sup>a</sup> Brain injury definition: total number of patients with any or all of white matter injury, intraparenchymal infarction, or intraparenchymal or intraventricular hemorrhage added together.
### Neurodevelopmental Outcomes After Regional Cerebral Perfusion With Neuromonitoring for Neonatal Aortic Arch Reconstruction

Dean B. Andropoulos, MD, R. Blaine Easley, MD, Ken Brady, MD, E. Dean McKenzie, MD, Jeffrey S. Heinle, MD, Heather A. Dickerson, MD, Lara S. Shekerdemian, MBChB, Marcie Meador, RN, MS, Carol Eisenman, RN, Jill V. Hunter, MBBS, Marie Turcich, MS, Robert G. Voigt, MD, and Charles D. Fraser, Jr, MD

**Table 6. Best Subsets Multivariable Regression Final Model (N = 35)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cognitive Score</th>
<th>Language Score</th>
<th>Motor Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient (95% CI)</td>
<td>p Value</td>
<td>Coefficient (95% CI)</td>
</tr>
<tr>
<td>RCP time</td>
<td>0.28 (0.08 to 0.48)</td>
<td>0.007</td>
<td>NA</td>
</tr>
<tr>
<td>DHCA time</td>
<td>-0.83 (-1.28 to -0.37)</td>
<td>&lt;0.001</td>
<td>NA</td>
</tr>
<tr>
<td>CPB time</td>
<td>NA</td>
<td>NA</td>
<td>0.08 (0.01 to 0.15)</td>
</tr>
<tr>
<td>Aprotinin use</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ICU length of stay</td>
<td>-0.14 (-0.27 to -0.01)</td>
<td>0.045</td>
<td>NA</td>
</tr>
<tr>
<td>Anesthetics, first 12 months</td>
<td>General, total number</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Fentanyl equivalents</td>
<td>NA</td>
<td>0.029 (0.01 to 0.050)</td>
</tr>
<tr>
<td></td>
<td>Benzodiazepine equivalents</td>
<td>-3.87 (-7.72 to -0.02)</td>
<td>0.049</td>
</tr>
<tr>
<td></td>
<td>Chromosome anomaly</td>
<td>-13.50 (-23.41 to -3.59)</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>Maternal intelligence quotient</td>
<td>0.45 (0.20 to 0.69)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI = confidence interval; CPB = cardiopulmonary bypass; DHCA = deep hypothermic circulatory arrest; ICU = length of stay; NA = not applicable; RCP = regional cerebral perfusion.
Core Practices – TCH

- “Adequate” ACP flow guided by NIRS and TCD
  - ACP flows of 30 ml/kg/min or less will not provide any CBF to some patients
    

- Explanation for lack of outcome difference DHCA vs. ACP – “Apples to Apples”
  
  Visconti, Ann Thorac Surg 2006;82:2207
Changing Expectations for Neurological Outcomes After the Neonatal Arterial Switch Operation

DB Andropoulos, RB Easley, KM Brady, ED McKenzie, JS Heinle, HA Dickerson, LS Shekerdemian, MR Meador, CA Eisenman, JV Hunter, M Turcich, RG Voigt, CD Fraser

Texas Children’s Hospital/Baylor College of Medicine
Houston, Texas

J. Maxwell Chamberlain Paper for Congenital Heart Surgery
STS 48th Annual Meeting, Fort Lauderdale, Florida
January 30, 2012
Introduction

- Survival for the neonatal arterial switch operation (ASO) for dextrotransposition of the great arteries (D-tGA) continues to improve

- TCH: 179 neonatal ASO 2001-2011
  - No 30-day in hospital mortality
  - ASO performed regardless of coronary anatomy
  - 800g to 4200g patient weights
  - 17% with complex associated anomalies
    - Taussig-Bing Anomaly
    - Aortic arch obstruction

Andropoulos et al, presented Jan 2012 STS 48th Annual Mtg Changing Expectations for Neurological Outcomes After the Neonatal Arterial Switch Operation
Neurodevelopmental outcomes have assumed greater importance

Many ASO neonates have neurodevelopmental problems

65% of 16 year olds in Boston Circulatory Arrest Study required special education services

- Circulation 2011;124:1361

Expectations for neurodevelopmental assessment, follow-up, and long term outcomes are changing

Andropoulos et al, presented Jan 2012 STS 48th Annual Mtg Changing Expectations for Neurological Outcomes After the Neonatal Arterial Switch Operation
Study Purpose

- TCH protocol to maximize oxygen delivery to the brain: high flow CPB and neuromonitoring
  - Team collaboration since 1997
  - Low incidence of MRI brain injury and EEG seizures
- Study Aim: determine if early improved neurological status translates into better long term outcomes for ASO patients
- Secondary Aim: determine associations with neurodevelopmental outcomes

Andropoulos et al, presented Jan 2012 STS 48th Annual Mtg Changing Expectations for Neurological Outcomes After the Neonatal Arterial Switch Operation
Methods

- Prospective observational cohort study
- Neonates (<30 days) undergoing ASO compared to non-ASO patients
- Exclusion criteria:
  - < 35 weeks gestational age
  - Recognizable dysmorphic syndrome
  - Preoperative CPR

Andropoulos et al, presented Jan 2012 STS 48th Annual Mtg Changing Expectations for Neurological Outcomes After the Neonatal Arterial Switch Operation
Methods (cont’d)

- CPB technique:
  - Full flow CPB 150 ml/kg/min except during DHCA or RCP
  - ASO and other 2-ventricle repairs at 25-28°C
  - DHCA or RCP at 18°C, cooling over ≥ 20 minutes
- pH stat blood gas management

Andropoulos et al, presented Jan 2012 STS 48th Annual Mtg Changing Expectations for Neurological Outcomes After the Neonatal Arterial Switch Operation
Methods (cont’d)

- CPB Technique:
- Hematocrit 30-35%
- Conventional ultrafiltration, no modified UF
- MAP 30-35 mm Hg; α-blockade
- Methylprednisolone 20 mg/kg CPB prime
- Aprotinin or ε-aminocaproic acid

Andropoulos et al, presented Jan 2012 STS 48th Annual Mtg Changing Expectations for Neurological Outcomes After the Neonatal Arterial Switch Operation
Methods (cont’d)

- Standardized anesthetic and ICU sedation
- NIRS to monitor rSO2c
  - Attempt to increase rSO2c if < 50%
- Brain MRI pre- and postoperatively

Andropoulos et al, presented Jan 2012 STS 48th Annual Mtg Changing Expectations for Neurological Outcomes After the Neonatal Arterial Switch Operation
Methods (cont’d)

- Bayley Scales of Infant Development III at 12 months
- 3 major domains:
  - Cognitive Score
  - Language Score
  - Motor Score
- Scores scaled to 100 mean ± 15 SD
- Widely utilized standard test validated in broad range of patients

Andropoulos et al, presented Jan 2012 STS 48th Annual Mtg Changing Expectations for Neurological Outcomes After the Neonatal Arterial Switch Operation
Statistical Analysis

- Primary comparison: ASO vs. non-ASO patients
- Primary outcome: 12 month BSID III Cognitive, Language, Motor scores
- 2 sided T test, chi-square, Fisher exact test
- Univariate regression for the 3 primary outcomes
- Multivariate regression for entire group for factors with p<0.1; included ASO status

Andropoulos et al, presented Jan 2012 STS 48th Annual Mtg Changing Expectations for Neurological Outcomes After the Neonatal Arterial Switch Operation
Results

- 93 neonates enrolled 2005-2010
- No 30 day in hospital mortality in ASO patients (0/30)
- 2/63 (3%) 30 day mortality for non-ASO patients
  - 8 later deaths
  - All deaths HLHS patients
- 56/83 survivors returned for 12 month neurodevelopmental assessment (67%)

Andropoulos et al, presented Jan 2012 STS 48th Annual Mtg Changing Expectations for Neurological Outcomes After the Neonatal Arterial Switch Operation
Results (Cont’d)

- **ASO group, n = 30**
  - 28 ASO
    - 7 with VSD
    - 21 IVS
  - 2 ASO, VSD, aortic arch repair

- **Non-ASO group, n = 63**
  - 42 Stage I palliation for HLHS
  - 12 VSD, aortic arch repair
  - 7 Truncus repair
  - 1 VSD/TAPVR
  - 1 TOF

*Andropoulos et al, presented Jan 2012 STS 48th Annual Mtg Changing Expectations for Neurological Outcomes After the Neonatal Arterial Switch Operation*
### Brain MRI Data

<table>
<thead>
<tr>
<th>MRI Findings</th>
<th>ASO Patients, n=30</th>
<th>Non-ASO Patients, n=63</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative MRI brain injury, n(%)</td>
<td>10 (33)</td>
<td>18 (28)</td>
<td>0.642</td>
</tr>
<tr>
<td>NEW 7-day Postoperative MRI brain injury, n(%)</td>
<td>13 (43)</td>
<td>27 (43)</td>
<td>0.980</td>
</tr>
</tbody>
</table>

**White matter injury and/or infarction, and/or hemorrhage**

**24% incidence of new WMI**

**70% of WMI classified as minimal**

_Andropoulos et al, presented Jan 2012 STS 48th Annual Mtg Changing Expectations for Neurological Outcomes After the Neonatal Arterial Switch Operation_
Minimal WMI

Andropoulos et al, presented Jan 2012 STS 48th Annual Mtg Changing Expectations for Neurological Outcomes After the Neonatal Arterial Switch Operation
### Primary Outcome: 12 Month BSID III

<table>
<thead>
<tr>
<th>Domain</th>
<th>ASO Patients, n=19</th>
<th>Non-ASO Patients, n=37</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive</td>
<td>105.8 ± 14.7</td>
<td>100.1 ± 12.7</td>
<td>0.162</td>
</tr>
<tr>
<td>Language</td>
<td>90.8 ± 13.9</td>
<td>86.3 ± 12.2</td>
<td>0.239</td>
</tr>
<tr>
<td>Motor</td>
<td>93.3 ± 13.8</td>
<td>87.8 ± 14.4</td>
<td>0.172</td>
</tr>
</tbody>
</table>

Andropoulos et al, presented Jan 2012 STS 48th Annual Mtg Changing Expectations for Neurological Outcomes After the Neonatal Arterial Switch Operation
Andropoulos et al, presented Jan 2012 STS 48th Annual Mtg Changing Expectations for Neurological Outcomes After the Neonatal Arterial Switch Operation
Final Multivariable Models

- **Cognitive:**
  - Chromosomal abnormality: $p = 0.012$
  - Low postoperative $rSO_2c$: $p = 0.015$

- **Language:**
  - Preoperative MRI brain injury: $p = 0.032$
  - Additional anesthetics: $p = 0.019$

- **Motor:**
  - Chromosomal abnormality: $p = 0.044$
  - Low preoperative $rSO_2c$: $p = 0.021$
  - Additional anesthetics: $p = 0.040$

**ASO not a factor in final models**

Andropoulos et al, presented Jan 2012 STS 48th Annual Mtg Changing Expectations for Neurological Outcomes After the Neonatal Arterial Switch Operation
Final Multivariable Models

- **Cognitive:**
  - Chromosomal abnormality: $p = 0.012$
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  - Preoperative MRI brain injury: $p = 0.032$
  - Additional anesthetics: $p = 0.019$

- **Motor:**
  - Chromosomal abnormality: $p = 0.044$
  - Low preoperative rSO$_2$ c: $p = 0.021$
  - Additional anesthetics: $p = 0.040$

**ASO not a factor in final models**

Andropoulos et al, presented Jan 2012 STS 48th Annual Mtg Changing Expectations for Neurological Outcomes After the Neonatal Arterial Switch Operation
Final Multivariable Models

- Cognitive:
  - Chromosomal abnormality: $p = 0.012$
  - Low postoperative $rSO_2c$: $p = 0.015$

- Language:
  - Preoperative MRI brain injury: $p = 0.032$
  - Additional anesthetics: $p = 0.019$

- Motor:
  - Chromosomal abnormality: $p = 0.044$
  - Low preoperative $rSO_2c$: $p = 0.021$
  - Additional anesthetics: $p = 0.040$

ASO not a factor in final models

Andropoulos et al, presented Jan 2012 STS 48th Annual Mtg Changing Expectations for Neurological Outcomes After the Neonatal Arterial Switch Operation
Comment

Main study findings:

- 12 month Cognitive outcomes for ASO patients are 0.4 SD above reference norms: mean 105.8
- 12 month Language outcomes 0.6 SD below norms
- 12 month Motor outcomes 0.5 SD below norms

Andropoulos et al, presented Jan 2012 STS 48th Annual Mtg Changing Expectations for Neurological Outcomes After the Neonatal Arterial Switch Operation
The association between low rSO$_2$c and worse neurodevelopmental outcome is a novel finding.

The association between MRI brain injury and worse neurodevelopmental outcome is also a new finding.

Conclusions

- Our ASO neonates have no mortality, and favorable neurodevelopmental outcomes
- Expectations for neurodevelopmental outcomes after ASO are changing
  - Routine neurodevelopmental assessment
- Research should address perioperative monitoring, detection of brain injury, treatment, and long term neurodevelopmental outcomes

Andropoulos et al, presented Jan 2012 STS 48th Annual Mtg Changing Expectations for Neurological Outcomes After the Neonatal Arterial Switch Operation
Methods

- Prospective observational cohort study
- Neonates (<30 days) undergoing RCP for aortic arch reconstruction
- Comparison groups: single vs. two ventricle repairs with RCP
- Anesthetic data, subsequent cardiac surgery, clinical events, chromosome analysis
Methods (cont’d)

- pH stat management, hematocrit 30-35%
- RCP and DHCA at 18°C after ≥ 20 min cooling
- RCP via PTFE graft to innominate artery
- RCP flows adjusted for NIRS rSO2c ≥ 90%, TCD flow velocity ± 10% baseline
- Full flow CPB 150 ml/kg/min except during DHCA or RCP
Methods (cont’d)

- Brain MRI pre- and postoperatively
- Bayley Scales of Infant Development III
  - at 12 months
- 3 major domains:
  - Cognitive Score
  - Language Score
  - Motor Score
- Scores scaled to 100 mean ± 15 SD
- Widely utilized standard test validated in broad range of patients including neurodevelopmental disabilities
Statistical Analysis

- Primary comparison: single ventricle vs. two ventricle repairs
- Primary outcomes: 12 month BSID III Cognitive, Language, Motor scores
- 2 sided T test, chi-square, Fisher exact test
- Best subsets multivariable linear regression on 17 covariates
Results

- 57 neonates enrolled 2005-2010

- Single ventricle group (n = 47)
  - HLHS Stage I palliation = 42
  - DILV, arch obstruction = 2
  - Tricuspid atresia, arch obstruction = 2
  - DORV, mitral atresia, arch obstruction = 1

- Two ventricle group (n = 10)
  - VSD, arch obstruction = 7
  - D-TGA, arch obstruction = 3
## Preoperative Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Single Ventricle (n=47)</th>
<th>Two Ventricle (n=10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight (g)</td>
<td>3091 ± 391</td>
<td>3125 ± 486</td>
<td>0.814</td>
</tr>
<tr>
<td>Gestational Age (Weeks)</td>
<td>38.6 (38.0-39.3)</td>
<td>38.6 (37.0-39.0)</td>
<td>0.666</td>
</tr>
<tr>
<td>Head Circumference (cm)</td>
<td>33.4 ± 1.5</td>
<td>33.7 ± 1.52</td>
<td>0.590</td>
</tr>
<tr>
<td>Age at Surgery (Days)</td>
<td>7 (5-9)</td>
<td>7 (4-10)</td>
<td>0.824</td>
</tr>
<tr>
<td>1 min Apgar Score</td>
<td>8 (8-9)</td>
<td>8 (8-9)</td>
<td>0.831</td>
</tr>
<tr>
<td>5 min Apgar Score</td>
<td>9 (8-9)</td>
<td>9 (8-9)</td>
<td>0.659</td>
</tr>
<tr>
<td>Chrom. abnl (n,%)</td>
<td>7 (15)</td>
<td>4 (40)</td>
<td>0.088</td>
</tr>
<tr>
<td>Mean rSO2c (min)</td>
<td>61.2 (55.9-65.3)</td>
<td>72.9 (64.5-78.6)</td>
<td>0.002*</td>
</tr>
<tr>
<td>rSO2c &lt;45% AUC (%-min)</td>
<td>0 (0-28.6)</td>
<td>0 (0-0)</td>
<td>0.0/298</td>
</tr>
</tbody>
</table>
## Intraoperative Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Single Ventricle (n=47)</th>
<th>Two Ventricle (n=10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPB Time, min</td>
<td>193 (169-234)</td>
<td>155 (144-295)</td>
<td>0.123</td>
</tr>
<tr>
<td>AoXcl Time, min</td>
<td>97 (83-108)</td>
<td>96 (85-176)</td>
<td>0.482</td>
</tr>
<tr>
<td>DHCA Time, min</td>
<td>11 (8-14), n=41</td>
<td>15 (15-16), n=2</td>
<td>0.182</td>
</tr>
<tr>
<td>RCP Time, min</td>
<td>80 ± 20</td>
<td>26 ± 15</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>rSO&lt;sub&gt;2&lt;/sub&gt; c&lt;sub&gt;&lt;45&lt;/sub&gt;% AUC</td>
<td>62 (0-480)</td>
<td>0 (0-1)</td>
<td>0.005*</td>
</tr>
<tr>
<td>rSO&lt;sub&gt;2&lt;/sub&gt; mean</td>
<td>69.6 (64.7-72.7)</td>
<td>77.2 (75.3-83.4)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Fentanyl dose, mcg/kg</td>
<td>195 (157-306)</td>
<td>171 (112-190)</td>
<td>0.116</td>
</tr>
<tr>
<td>Midazolam dose, mg/kg</td>
<td>1.22 (0.83-1.5)</td>
<td>1.07 (0.83-1.30)</td>
<td>0.361</td>
</tr>
<tr>
<td>Isoflurane, MAC-hours</td>
<td>1.25 (0.79-2.00)</td>
<td>1.45 (0.67-2.80)</td>
<td>0.578</td>
</tr>
</tbody>
</table>

**RCP Data for Entire Group:**

Mean RCP Time: 71 ± 28 min (5-121)

Mean RCP flow rate: 56.6 ± 10.6 ml/kg/min (35-81)
## Postoperative Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Single Ventricle (n=47)</th>
<th>Two Ventricle (n=10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rSO$_2$c $&lt;45%$ AUC</td>
<td>257 (4-2003)</td>
<td>0 (0-0)</td>
<td>$&lt;0.001^*$</td>
</tr>
<tr>
<td>rSO$_2$c mean</td>
<td>57.8 ± 6.1</td>
<td>76.1 ± 5.1</td>
<td>$&lt;0.001^*$</td>
</tr>
<tr>
<td>Cardiac arrest, n(%)</td>
<td>2 (4)</td>
<td>0 (0)</td>
<td>0.99</td>
</tr>
<tr>
<td>ECMO, n(%)</td>
<td>2 (4)</td>
<td>0 (0)</td>
<td>0.99</td>
</tr>
<tr>
<td>Mech. Vent. days</td>
<td>4 (4-7)</td>
<td>4 (3-5)</td>
<td>0.262</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>9 (7-16)</td>
<td>8 (7-8)</td>
<td>0.151</td>
</tr>
<tr>
<td>Hospital LOS</td>
<td>34 (24-54)</td>
<td>26 (22-37)</td>
<td>0.123</td>
</tr>
<tr>
<td>Hospital discharge mortality (n,%)</td>
<td>2 (4)</td>
<td>0 (0)</td>
<td>0.99</td>
</tr>
<tr>
<td>Total mortality first 12 months</td>
<td>10 (21)</td>
<td>0</td>
<td>0.183</td>
</tr>
</tbody>
</table>
## Brain MRI Data

<table>
<thead>
<tr>
<th>MRI Findings</th>
<th>Single Ventricle (n=47)</th>
<th>Two Ventricle (n=10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preoperative MRI brain injury, n(%)</strong></td>
<td>14 (30)</td>
<td>2 (20)</td>
<td>0.708</td>
</tr>
<tr>
<td><strong>NEW 7-day Postoperative MRI brain injury, n(%)</strong></td>
<td>21 (45)</td>
<td>2 (20)</td>
<td>0.178</td>
</tr>
</tbody>
</table>

*White matter injury and/or infarction, and/or hemorrhage NO DIFFERENCE in location (L/R), severity, or type of injury SV vs. 2V*
Primary Outcome: 12 Month BSID III (n=35, 74% of survivors)

<table>
<thead>
<tr>
<th>Domain</th>
<th>Single Ventricle</th>
<th>Two Ventricle</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Means for Entire RCP Group:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive:</td>
<td>100.1 ± 14.6 (75-125)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Language:</td>
<td>87.2 ± 15.0 (62-132)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor:</td>
<td>87.9 ± 16.9 (58-121)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Best Subsets Model (n=35)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cognitive</th>
<th>Language</th>
<th>Motor</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCP time</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DHCA time</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPB time</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>ICU LOS</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General anesthetics, first 12 months</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Fentanyl dose</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepine dose</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Chromosome anomaly</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Maternal IQ</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Discussion

- Main study finding: 12 month Cognitive outcomes with RCP at reference population norms
  - Language and motor outcomes 0.8-0.9 SD below norms
- Longer duration of RCP not associated with adverse ND outcomes
- Longer DHCA times associated with worse Cognitive outcomes
- No laterality difference in new postoperative MRI brain injury with RCP
- Anesthetic technique may impact ND outcomes
Limitations

- Small sample size of RCP group limits conclusions
  - 35 patients is largest neurodevelopment follow-up to date
  - Previous largest study (Goldberg 2007, n = 22) had very different RCP protocol
- Not a controlled trial of RCP vs. DHCA
- BSID III is very different than BSID II, limiting comparisons with previous trials
<table>
<thead>
<tr>
<th></th>
<th>Flow Rate cc/kg/min</th>
<th>ABP</th>
<th>Monitoring</th>
<th>$P_aCO_2$</th>
<th>Dev. Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andropoulos</td>
<td>57 ± 10</td>
<td>R. 30-35 mmHg</td>
<td>NIRS, TCD</td>
<td>pH-Stat</td>
<td>Bayley III</td>
</tr>
<tr>
<td>Goldberg</td>
<td>20</td>
<td>NR</td>
<td>NIRS (Flow not adjusted)</td>
<td>α-Stat</td>
<td>Bayley II</td>
</tr>
<tr>
<td>Visconti</td>
<td>30-40</td>
<td>L. 20-25 mmHg</td>
<td>None</td>
<td>pH-Stat</td>
<td>Bayley II</td>
</tr>
</tbody>
</table>

Slide information courtesy of Ken Brady, MD
TCD and NIRS Based Autoregulation Measurement
TCD- monitored autoregulation: Easy to interpret, difficult to keep the signal
NIRS Based Autoregulation (COx) & TCD Based Autoregulation (Mx) during CPB

Brady et al. Stroke 2010
Refine Continuum of Risk → Minimize Additive Injury

Congenital Heart Disease

- Prenatal Dx → Timely Delivery → Early vs Late Intervention → Diligent Follow-up

- Perinatal Monitoring (NIRS, MRI)

- Fetal Intervention
- Brain Monitoring Assessment (MRI)

- Neurodevelopmental Outcomes Clinic (Drs. Penny & Shekerdemian)
TCH MRI Study Patients

Normal Pre- and Postoperative Axial T2-weighted scans: Norwood Stage I patient

JTCVS 2010 March; 139(3): 543–556
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 impatiently regard as trivialities.

*Harvey Cushing, JAMA 1915*
Society of Thoracic Surgeons convened a task force to evaluate publications on infant brain protection

- 1 January 1990-30 July 2010, all infant (human) birth to 12 months
- 7 surgeons, 1 anesthesiologist/intensivist, 1 neurologist
- Oxford Evidence Based Medicine scoring system and American College of Cardiology/American Heart Association level of evidence grade

Protecting the Infant Brain During Cardiac Surgery: A Systematic Review

Jennifer C. Hirsch, MD, MS, Marshall L. Jacobs, MD, Dean Andropoulos, MD, Erle H. Austin, MD, Jeffrey P. Jacobs, MD, Daniel J. Licht, MD, Frank Pigula, MD, James S. Tweddell, MD, and J. William Gaynor, MD

Cardiac Surgery OR Perfusion Strategy

AND

Neuromonitoring

Medications

Neuroprotection/Neuroinjury

Limit Search

527 Manuscripts

Abstracts reviewed and manuscripts excluded that did not reach criteria.

187 Manuscripts

Manuscripts/references reviewed. Manuscripts excluded and added

Final 162 Manuscripts
<table>
<thead>
<tr>
<th>Category</th>
<th>No. of Manuscripts in Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomarkers</td>
<td>17</td>
</tr>
<tr>
<td>Bispectral Indices</td>
<td>1</td>
</tr>
<tr>
<td>EEG</td>
<td>5</td>
</tr>
<tr>
<td>Imaging</td>
<td>9</td>
</tr>
<tr>
<td>Monitoring</td>
<td>10</td>
</tr>
<tr>
<td>Near-infrared spectroscopy</td>
<td>27</td>
</tr>
<tr>
<td>Perfusion</td>
<td>32</td>
</tr>
<tr>
<td>Pharmacology</td>
<td>5</td>
</tr>
<tr>
<td>Postoperative monitoring</td>
<td>11</td>
</tr>
<tr>
<td>Risk factor analysis</td>
<td>33</td>
</tr>
<tr>
<td>Transcranial Doppler</td>
<td>8</td>
</tr>
<tr>
<td>Technique</td>
<td>3</td>
</tr>
<tr>
<td>Temperature/SvO₂</td>
<td>1</td>
</tr>
</tbody>
</table>

EEG = electroencephalogram; SvO₂ = venous oxygen saturation.
# ACC/AHA Level of Evidence System

## Size of Treatment Effect

### 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

<table>
<thead>
<tr>
<th>Estimation of Certainty (Precision) of Treatment Effect</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level A</strong> Multiple populations evaluated*</td>
<td>Recommendation that procedure or treatment is useful/effective</td>
</tr>
<tr>
<td>Data derived from multiple randomized clinical trials or meta-analyses</td>
<td>Sufficient evidence from multiple randomized trials or meta-analyses</td>
</tr>
</tbody>
</table>

| **Level B** Limited populations evaluated* | Recommendation that procedure or treatment is useful/effective |
| Data derived from a single randomized trial or nonrandomized studies | 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 that procedure or treatment is useful/effective |
| Only expert opinion, case studies, or standard of care | Recommendation in favor of treatment or procedure being useful/effective |

<table>
<thead>
<tr>
<th>Procedure/Test</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>COR III: No benefit</td>
<td>Recommended that procedure or treatment is not useful/effective and may be harmful</td>
</tr>
<tr>
<td>Harm</td>
<td>Evidence from single randomized trial or nonrandomized studies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. No benefit</td>
<td>Additional studies with broad objectives needed; additional registry data would be helpful</td>
</tr>
<tr>
<td>3. Helpful</td>
<td>Procedure/Treatment MAY BE CONSIDERED</td>
</tr>
<tr>
<td>4. No Proven Benefit</td>
<td>Procedure/Treatment SHOULD be performed/administered</td>
</tr>
</tbody>
</table>

---

**Notes:**
- Class III no benefit or class III harm are not recommended.
- Level A has the highest level of evidence.
- Level C has the lowest level of evidence.
- Level B is between Level A and Level C.
Median sample size = 43 (3-2481)
Neurologic outcome: 43%
Neuro follow-up after discharge: 29%

Prospective observational cohort: 54%
Case control study: 22%
RCT = 13%
Retrospective observational cohort: 10%

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Final Score</th>
<th>Original Distribution of Scores</th>
<th>Final Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood gas management</td>
<td>3</td>
<td>Class IIB, Level B</td>
<td>Class IIB, Level B (7) Class III (no benefit), Level B (2)</td>
<td>No data to demonstrate superiority of alpha vs pH stat blood gas management at long-term neurodevelopmental testing. It is reasonable to use either strategy.</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>3</td>
<td>Class IIA, Level A</td>
<td>Class I, Level B (2) Class IIA, Level A (3) Class IIA, Level B (4)</td>
<td>Avoiding extreme hemodilution can be beneficial/effective/useful. An exact lower limit for hematocrit has not been well defined but should probably not go below 24%.</td>
</tr>
<tr>
<td>EEG</td>
<td>4</td>
<td>Class III (no benefit), Level C</td>
<td>Class IIB, Level B (4) Class III (no benefit), Level B (2) Class III (no benefit), Level C (3)</td>
<td>No data to show that EEG monitoring is associated with better or worse outcomes. Use of routine EEG monitoring cannot be recommended.</td>
</tr>
<tr>
<td>Cooling</td>
<td>5</td>
<td>Class III (no benefit), Level B</td>
<td>Class III (no benefit), Level B (9)</td>
<td>No data to support any difference in outcomes with any specific cooling strategy or duration. No specific cooling strategy can be recommended.</td>
</tr>
<tr>
<td>Glycemic control</td>
<td>5</td>
<td>Class III (harm), Level B</td>
<td>Class IIA, Level B (1) Class IIB, Level B (3) Class III (no benefit), Level B (4)</td>
<td>There is no evidence of benefit for tight glycemic control; however, there may be harm from hypoglycemia. Tight glycemic control is not indicated.</td>
</tr>
<tr>
<td>S100β</td>
<td>12</td>
<td>Class III (no benefit), Level B</td>
<td>Class III (no benefit), Level A (1) Class III (no benefit), Level B (2) Class III (no benefit), Level C (6)</td>
<td>Measuring S100β has not been demonstrated to identify patients at increased risk of neurologic injury. Measurement of S100β is not indicated.</td>
</tr>
<tr>
<td>Group</td>
<td>No.</td>
<td>Final Score</td>
<td>Original Distribution of Scores</td>
<td>Final Conclusion</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----</td>
<td>----------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Transcranial Doppler (TCD)</td>
<td>15</td>
<td>Class III (no benefit), Level B</td>
<td>Class IIB, Level B (4) Class IIB, Level C (1) Class III (no benefit), Level A (1) Class III (no benefit), Level B (2) Class III (no benefit), Level C (1)</td>
<td>The data concerning TCD is limited in quality. There is no evidence that the use of TCD is associated with improved neurodevelopmental outcomes. TCD monitoring may be considered.</td>
</tr>
<tr>
<td>NIRS</td>
<td>35</td>
<td>Class III (no benefit), Level B</td>
<td>Class IIB, Level B (2) Class IIB, Level C (2) Class III (no benefit), Level B (2) Class III (no benefit), Level C (3)</td>
<td>The data concerning NIRS and neurodevelopmental outcomes are limited in quality. There is no consistent evidence that the use of NIRS is associated with improved neurodevelopmental outcomes. NIRS may be considered as a monitoring methodology.</td>
</tr>
<tr>
<td>DHCA/LFCPB/RCP</td>
<td>44</td>
<td>Class III (no benefit), Level B</td>
<td>Class IIB, Level B (2) Class III (no benefit), Level B (6) Class III (no benefit), Level C (1)</td>
<td>Among the 3 commonly used perfusion strategies employed for neonatal cardiac surgery using cardiopulmonary bypass and deep hypothermia, none is clearly superior. No specific perfusion strategies can be recommended.</td>
</tr>
</tbody>
</table>
STS Task Force Conclusions

- A variety of monitoring and management strategies have evolved intending to protect the brain
- Data supporting these techniques is limited and their effectiveness is uncertain
- Avoiding extreme hemodilution has strongest evidence
- Failure to design proper studies that include orderly observations, rigorous data collection, and meaningful neurological outcomes is the cause
- Future studies on infant brain protection should focus on neurodevelopmental outcomes with long term followup
TCH Conclusions: Intraoperative Neuroprotection

- ACC/AHA and EBM evidence systems primarily applied to large studies in adult cardiovascular medicine

- Small single center studies without careful measurements, and insufficient outcome measures, both short and longer term, severely limit the quality of data for most neuroprotection studies
TCH Conclusions (cont’d)

- This does NOT mean that all of these strategies have no merit, or some will not be shown to be beneficial with properly designed studies
  - Multicenter: for adequate sample size
  - RCT
  - Short and long term neurodevelopmental outcome measures
- RCP with adequate flows and neuromonitoring is effective and safe for intraoperative neuroprotection resulting in good longer term neurodevelopmental outcomes
The rise of statistics and evidence-based medicine
Trials of TBI Therapies

Originally presented by Tony Figaji, at 6th World Congress of Paediatric Cardiology & Cardiac Surgery 2013
Intraop Pulse Oximetry: EBM?

- Cochrane database review
- 23,000 surgical subjects randomized:
  - Pulse oximetry
  - No pulse oximetry
- No difference:
  - Postoperative cognitive dysfunction
  - Cardiovascular complications
  - Neurologic complications
  - Respiratory complications
  - Infectious complications
  - Length of stay
  - Death
  - Intensive care unit admission

Protecting the Brain

- Unavoidable
  - congenital brain anomalies
  - intrauterine accidents

- Avoidable (or at least mutable)
  - post natal, but pre-operative, hemodynamic and iatrogenic insults
    DX, RESUSCITATION, TIMING OF SURGERY, NO AIR, TIMING OF DELIVERY

  - intra-operative insults
    ANESTHESIA, SURGICAL PRECISION, CPB MANAGEMENT

  - post-operative hemodynamic and iatrogenic insults
    CVICU CARE, QUALITY OF REPAIR AND MYOCARDIAL PROTECTION
Protecting the Brain

- Of the multiple mutable factors just mentioned, CPB management is the most controversial.

- It doesn’t really matter whether CPB management represents 50%, or 5%, of the total neurodevelopmental risk to the infant. It does have an incremental effect, and it, along with surgical precision, are what surgeons most directly control.
Protecting the Brain

- The risks of ACP relate to the uncertainties of delivering oxygenated blood to the brain in a reliable way.

- These risks are easily understood:
  - technical factors
  - determining appropriate flows and pressures
  - eliminating gas and particulate embolism

We should be smart enough to figure this out.
Protecting the Brain

- The risks of DHCA are much more challenging. A profoundly unphysiologic state is created: no blood flow to the brain

- Addressing these risks essentially requires neutralizing millions of years of evolution

Are we that smart?