What I’ve Learned About the Brain
As a Pediatric Cardiac Intensivist

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Outline: Part I

- Congenital Heart Disease (CHD) Made Easy
- The Normal Fetal Circulation
- The Transitional Circulation
- The Fields of Pediatric Cardiology and Congenital Heart Surgery mid 1950’s- mid 2010’s
- The Two Most Important Innovations That Changed Everything in My Field
Congenital Heart Disease

• 1:100 Live Births – 40,000 year in USA
• ~ 1/3 require surgery in first months of life ~11,000/year
• Although there are hundreds of specific types of CHD, they may be broadly classified, alone or in combination:
  1. Holes
  2. Narrowings
  3. All Parts are Present, but Arranged Abnormally
  4. Missing Parts

• Without urgent treatment, most of these 11,000/year infants die during the transitional circulation
Fetal Circulation

In a Fetus with a Structurally Normal Heart

• Oxygenated Umbilical Venous Blood From the Placenta travels to Right Atrium Through the Ductus Venosus and is Directed to the Left Atrium.

• This Oxygenated Blood is Preferentially Ejected to the Brain and Coronary Arteries

• Deoxygenated Blood from the upper and lower body is directed to the lower body and through the Umbilical Arteries to the Placenta
Fetal Circulation -> Normal Transitional Circulation Anatomic Changes

- Closure of the ASD
- Closure of the Ductus Arteriosus
- Closure of the Ductus Venosus
Fetal Circulation -> Normal Transitional Circulation: Physiologic Changes

Clamping of Umbilical Cord

Lung Expansion
Fetal Circulation -> Normal Transitional Circulation: Physiologic Changes

Loss of Low Resistance Placenta -
↑ Systemic Vascular Resistance (SVR)

Lung Expansion
↓ Pulmonary Vascular Resistance (PVR)
It Had Been Known Since the 1930s Babies with Critical Congenital Heart Disease Died in the First Few Days-Weeks of Life

Specifically: Closure of the Ductus Arteriosus
Specifically: Closure of the Ductus Arteriosus
All of What We Do in the care of Complex CHD Would Not Have Happened Without Two Major Breakthroughs in the Mid 1970’s:

- Prostaglandin
- “Portable” Echocardiography
Beginning in the Late 1970’s-Early 1980’s Children with Previously Lethal CHD Started to Survive

Many are Now in their 30’s
“Half of What I’m Teaching You is Wrong
The Problem Is:
I Don’t Which Half It Is”
My Second Year of Fellowship: “Truths”
1986 Things I *Knew* Were True

1. A Good Operation “Fixes Everything”
2. Majority of Babies Were Normal Except For Their Heart
3. Seizures Were Not a Bad Prognostic Sign
   • “Baby Twitches”
4. Cardiac Surgeons Were Good Pediatric Neurologists
1985 – 1995: We Learned That, In Reality, All Was *Not* Well

Why Am I Here: A Pediatric Cardiac Intensivist????

- The unique position of the pediatric cardiologist with clinical perspective from ICU, (or even before birth), through young adulthood
  - “How the Blood Goes Around”
- A good operation doesn’t fix everything
- Many kids were having trouble meeting developmental milestones
It Must Be the Surgery!!!
The “Boston Circulatory Arrest Study”  
1988-1992

- NIH Sponsored Randomized Clinical Trial Comparing Neurological Outcomes of Cardiac Surgery Utilizing Deep Hypothermic Circulatory Arrest vs Low-Flow Bypass
- 4 years of enrollment
- Co-PIs: Richard Jonas and Jane Newburger
Transposition (TGA) Planned Arterial Switch
N = 191

Met Eligibility Criteria Parental Consent
180/191 (94%)

TGA/IVS
N = 129
Age ~ 7 ± 4 days

TGA/VSD
N = 42
Age = 18 ± 19 days

Low Flow Bypass
N = 63

Circulatory Arrest
N = 66

Low Flow Bypass
N = 21

Circulatory Arrest
N = 21

Survivors
168

Patients
171

Died
N = 3

191 Eligible

180 Consented
A COMPARISON OF THE PERIOPERATIVE NEUROLOGIC EFFECTS OF HYPOTHERMIC CIRCULATORY ARREST VERSUS LOW-FLOW CARDIOPULMONARY BYPASS IN INFANT HEART SURGERY

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ALDO R. CASTANEDA, M.D., AND JAMES H. WARE, PH.D.
Perioperative Results

Table 3. Neurologic Outcomes after Surgery, According to Ventricular Septal Status and Treatment Group.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>INTACT VENTRICULAR SEPTUM</th>
<th>VENTRICULAR SEPTAL DEFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CIRCULATORY ARREST</td>
<td>LOW-FLOW BYPASS</td>
</tr>
<tr>
<td></td>
<td>no. with abnormality/total no. (%)</td>
<td>p value*</td>
</tr>
<tr>
<td>Within 7 days after surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite clinical seizures</td>
<td>5/66 (8)</td>
<td>0/63</td>
</tr>
<tr>
<td>48-Hr continuous EEG†</td>
<td>9/58 (16)</td>
<td>6/49 (12)</td>
</tr>
<tr>
<td>Ictal activity‡</td>
<td>288 (72, 227)</td>
<td>181 (32, 85)</td>
</tr>
<tr>
<td>Recovery time (min)</td>
<td>21 (15, 45)</td>
<td>13 (4, 18)</td>
</tr>
<tr>
<td>First activity</td>
<td>139</td>
<td>57</td>
</tr>
<tr>
<td>Close bursts</td>
<td>1140 (143, 366)</td>
<td>1079 (66, 309)</td>
</tr>
<tr>
<td>Relative continuous</td>
<td>(541, 1740)</td>
<td>(602, 1626)</td>
</tr>
<tr>
<td>Continuous</td>
<td>59</td>
<td>43</td>
</tr>
<tr>
<td>CK-BB release (IU/liter)†</td>
<td>32 (84)</td>
<td>15 (88)</td>
</tr>
</tbody>
</table>
Probability of Clinical Seizures

Note: non-linear relationship

$p = .004$
At 16 Years the Groups Were Essentially Similar in all Neurodevelopmental Domains
The "Neurodevelopmental Phenotype" Associated With Complex Congenital Heart Disease
Executive Function

- Impulse Control/Self Regulation
- Working Memory
- Attention
- Flexibility
- Planning

Adaptive Function

- Independence in ADLs
- Academic Function
- Motor

Autism Spectrum

- Theory of Mind
- Alexithymia

Cognition

- Mild Decrease

Speech & Language

- Expressive Language & Articulation
- Receptive Language Intact

Behavioral

- Oppositionality/Defiance
- Anxiety, Depression
- ADHD

Motor

- Fine Motor/Visual-Spatial Integration
- Oral Motor Coordination/Feeding
- Gross Motor/Clumsiness
Developmental and Neurological Status of Children at 4 Years of Age After Heart Surgery With Hypothermic Circulatory Arrest or Low-Flow Cardiopulmonary Bypass

David C. Bellinger, PhD, MSc; David Wyij, PhD; Karl C. Kaban, MD, MSc; Leonard A. Rapoport, MD; Paul R. Hickey, MD; Gil Wernovsky, MD; Richard A. Jonas, MD; Jane W. Newburger, MD, MPH

Neurodevelopmental status at eight years in children with dextro-transposition of the great arteries: The Boston Circulatory Arrest Trial

David C. Bellinger, PhD, MSc; David Wyij, PhD; MSc; Marc J. Pitman, MD; Leonard A. Rapoport, MD; Richard A. Jonas, MD; Gil Wernovsky, MD, MPH

Adolescents With d-Transposition of the Great Arteries Corrected With the Arterial Switch Procedure: Neuropsychological Assessment and Structural Brain Imaging

David C. Bellinger, PhD, MSc; David Wyij, PhD; Michael J. Rubik, MD; David B. DeMarco, MD; Richard L. Robertson, Jr, MD; Carlyle Dorlus-Manzanares, BSN, RN; Leonard A. Rapoport, MD; Gil Wernovsky, MD; Richard A. Jonas, MD; Jane W. Newburger, MD, MPH

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Total Cost (through 30 year Adult Study) in $2018 dollars

$19,447,000

Age 8 - N=155 (97% of eligible)
Age 4 - N=158 (97% of eligible)
Age 16 - N=139 (87% of eligible)
N ~ 100 (~67% of eligible)
Age 1 - N=155 (92% of eligible)

Periop 1, 4, 8 years ~ $13M
16 years ~ $3.5M
Ongoing Adult Study ~ $3M
By 1995:

**It’s Not the Surgery!!!**

- Now that we had many more survivors, research into the “Brain-Heart Axis” began
  - **Defining the phenotype**
  - Recognizing that CNS risk factors are multiple and cumulative
  - Cardiopulmonary Bypass played a role, but it was relatively minor
  - Collaborative Research
  - **Surgeons, anesthesiologists now embraced Pediatric Neurologists**
Today is actually my 29th birthday and two weeks ago my wife and I had our first child. Due to my heart defect our child had to have a fetal echo (everything was perfect) and I...