Pediatric Cardiac Surgery: Past, Present, and Future

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“Any surgeon who wishes to preserve the respect of his colleagues would never attempt to operate on the heart.”

(Theodore Billroth)
Evolution of Congenital Cardiac Surgery

**4 eras complete, 1 in process, more to come**

- Closed extra-cardiac operations (1937)
- Early closed or semi-closed intra-cardiac operations (1944)
- Complete intra-cardiac repair (1952)
- Refinement of technique (1971)
- Management of unforeseen co-morbidities (2000)
- Disease causality risk assessment and surgical planning (2015)

? ?
Evolution of Cardiac Surgery

4 historical eras

1. Closed extra-cardiac operations
   1937/8 - Ligation of patent ductus arteriosus (Strider and Gross)

2. Early closed or semi-closed intra-cardiac operations
   1944 - Coarctation repair (Craaford)
   1944 - Blalock-Taussig shunt
   1946 - Potts’ shunt
   1946 - Closed pulmonary valvotomy (Sellors)
   1948 - Blalock-Hanlon atrial septectomy
   1952 - Pulmonary artery band (Muller and Dammann)
Evolution of Cardiac Surgery

4 historical eras

3. Complete intra-cardiac repair
   - 1952 - Atrial well for ASD closure (Gross)
   - 1952 - ASD closure with inflow occlusion and hypothermia (Lewis)
   - 1954 - Controlled cross-circulation (Lillehei)
   - 1958 - Superior cavopulmonary anastomosis (Glenn)
   - 1962 - Waterston’s shunt
   - 1966 - Balloon atrial septostomy (Rashkind)
   - 1968 - Atriopulmonary connection (Fontan and Baudet)
Evolution of Cardiac Surgery

4 historical eras

4. Refinement of technique

1971 - Complex repair in neonates and infants with DHCA (Barratt-Boyes)
1975 - Arterial switch operation (Jatene)
1976 - Introduction of PGE$_1$ (Elliott)
1981 – Stage I palliation of hypoplastic left heart syndrome (Norwood)
1984 - Neonatal heart transplantation (Bailey)
PGE₁
PGE₁
$\text{PGE}_1$

Chemical structure of PGE$_1$

Surgeon → Image of a sleeping person
Ligation of patent ductus arteriosus

- 1937 John Stridor
- 1938 Robert Gross
Ligation of patent ductus arteriosus

- 1937 John Stridtor
- 1938 Robert Gross
Coarctation of the aorta repair

• 1944 Blalock-Park
• 1944 Craaford
Coarctation of the aorta repair

- 1944 Blalock-Park
- 1944 Craaford
Johns Hopkins Hospital, 1945

- Alfred Blalock
- Vivien Thomas
- William Longmire
- Denton Cooley
Palliation of cyanotic heart disease
B-H atrial septectomy
Rashkind
Atrial well technique of ASD closure-the wild west (Gross)
## Evolution of ASD closure

<table>
<thead>
<tr>
<th>Date</th>
<th>Surgeon</th>
<th>Technique</th>
<th>Institution</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1948</td>
<td>Murray</td>
<td>External suturing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1952</td>
<td>Gross</td>
<td>Atrial well-blind!</td>
<td>Boston Children’s</td>
<td>30.2%</td>
</tr>
<tr>
<td>1952</td>
<td>Lewis</td>
<td>Inflow occlusion</td>
<td>Mayo</td>
<td>12.1%</td>
</tr>
<tr>
<td>1953</td>
<td>Gibbon</td>
<td>Direct closure with CPB</td>
<td>Penn</td>
<td></td>
</tr>
<tr>
<td>today</td>
<td>all</td>
<td>CPB</td>
<td>everywhere</td>
<td>&lt;1%</td>
</tr>
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</table>
Cardiopulmonary Bypass Circuit
Cross circulation- Mayo experience
Cross circulation

- 1 y.o. 6.9 kg VSD, 11d survival
- support Owen Wangenstein
- 4 y.o. girl with a VSD
- 45 operations
- TOF, AVSD, VSD
- No operative deaths were directly attributable due to the cross circulation technique
- post-operative heart block was the real killer
Risk in Congenital Heart Surgery: Chronological improvement

- Mortality
- Year
- RACHS
  - 5
  - 4
  - 3
  - 2
  - 1
How do we crack the final percentage?
Today

- team oriented approach
- importance of co-morbidities
- operations for single ventricle physiology
- neurodevelopment
- fetal interventions
Tetralogy of Fallot
Patients with same disease have different responses

Post operative day 5, TOF
HLHS

- RV
- PA
- Aorta
- RPA
HLHS- Classic Norwood

Aorta

Inferior vena cava

Main pulmonary a.

Homograft
HLHS- Classic Norwood
Are surgeons to blame for everything?
<table>
<thead>
<tr>
<th>Abnormal Brain at Birth</th>
<th>Infancy</th>
<th>Pre-School</th>
<th>Middle School</th>
<th>Adolescence-Transition to ACHD</th>
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<tr>
<td>↓ head circumference</td>
<td>Seizures (cortex)</td>
<td>Delayed motor skills</td>
<td>Behavior problems</td>
<td>Depression and behavior problems</td>
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<tr>
<td>Structural abnormalities</td>
<td>↑ PVL (white matter)</td>
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<td>Inattention/Hyperactivity</td>
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<td>↓ Visual motor integration</td>
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<td>↓ Planning and executive function</td>
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Causes of adverse neurodevelopmental outcomes: Multifactorial, interactive, and ongoing

- **Fetus → Birth → Surgery → ICU → Stepdown → Home**

  - ↓ Substrate delivery
  - ↓ Oxygen delivery
  - ↑↓ Cerebral resistance
  - Placental abnormalities
  - Genetic syndromes
  - Delayed diagnosis

  - Anesthesia
  - Opiates
  - Benzodiazepines
  - CPB
  - Hypothermia
  - Circulatory Arrest

  - Early Modifiers
    - Genetic Polymorphisms
    - Alterations in CBF
    - Hypoxemia, hypocarbia, hypotension
    - Hyperthermia
    - Seizures Stroke

  - Late Modifiers
    - Hypoxemia
    - Reoperations
    - Socioeconomic Status
    - PTSD, maternal depression
    - Poor nutrition

**Preoperative Modifiers**
- Low Cerebral Blood Flow
- Low Cerebral O₂ Content
- ICU Morbidity (emboli, fever, etc.)
## Neurodevelopmental (Early and Latent) Outcomes

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### Causes of adverse neurodevelopmental outcomes: Multifactorial, interactive, and ongoing

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### Preoperative Modifiers
- Low Cerebral Blood Flow
- Low Cerebral O₂ Content
- ICU Morbidity (emboli, fever, etc.)

### Late Modifiers
- Hypoxemia
- Reoperations
- Socioeconomic status
- PTSD, maternal depression
- Poor nutrition
Collaborative Model of Care

Cardiology

Cardiac Nursing

Cardiothoracic Surgery

Cardiac Critical Care

Cardiac Anesthesia
What’s next

• precision therapies guided by genetics

• new and nano technology introduced drugs, devices, and materials

• robotic manipulations
What’s next

• precision therapies guided by genetics

• new and nano technology introduced drugs, devices, and materials

• robotic manipulations
What tools are in place

• patients and clinical data

• sequencing and bioinformatic tools

• biologic tools for variant verification

• ontologies that speak to each other
What tools are in place

• patients and clinical data

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• biologic tools for variant verification

• ontologies that speak to each other
How do we get many thousands of samples to analyze?

• I have thousands of DNA, hundreds of tissue, and tens of stem cells lines - not enough

• Collaboration to get the rest
  – single investigators
  – institutional BioBanks
  – larger initiatives
CHSS collaborative sites
CHSS enrolling institutions

- 2001: 11
- 2002: 12
- 2003: 16
- 2004: 15
- 2005: 19
- 2006: 20
- 2007: 19
- 2008: 17
- 2009: 13
- 2010: 19
- 2011: 22
- 2012: 28
- 2013: 30
CHSS study enrollment

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGA</td>
<td>895</td>
</tr>
<tr>
<td>IAA</td>
<td>494</td>
</tr>
<tr>
<td>Coarc</td>
<td>903</td>
</tr>
<tr>
<td>PAIVS</td>
<td>457</td>
</tr>
<tr>
<td>AVA</td>
<td>613</td>
</tr>
<tr>
<td>AVS</td>
<td>489</td>
</tr>
<tr>
<td>TA</td>
<td>349</td>
</tr>
<tr>
<td>PC</td>
<td>634</td>
</tr>
<tr>
<td>LVOTO</td>
<td>767</td>
</tr>
<tr>
<td>AAOCA</td>
<td>298</td>
</tr>
<tr>
<td>AVSD</td>
<td>105</td>
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Samples by diagnosis

n = 12,000
What tools are in place

• patients and clinical data

• sequencing and bioinformatic tools

• biologic tools for variant verification

• ontologies that speak to each other
Turn to development for answers

- Fish - transgenic zebrafish
- Mice - gene-targeted mice
- Human - genome sequencing and iPSC production
Chr 5 variation in the *ISL1* region
Chr 5 variation in the *ISL1* region
ISL1 risk by ethnicity
ISL1 risk by ethnicity
ISL1 risk by ethnicity

ACT haplotype
- White
  - Stage 1
  - Stage 2
  - Summary
- Black/AA
  - Stage 1
  - Stage 2
  - Summary

GCT haplotype
- White
  - Stage 1
  - Stage 2
  - Summary
- Black/AA
  - Stage 1
  - Stage 2
  - Summary
Total # SNPs by chromosome

Proband: Total=3,754,214

1/2 Sib 1: Total=3,169,270

1/2 Sib 2: Total=3,147,463
What’s next

• precision therapies guided by genetics

• new and nano technology introduced drugs, devices, and materials

• robotic manipulations
2 y.o. TOF/AVC

• 2 y.o. female with transitional AVC, dysplastic RAVV, and PV stenosis.

• primary repair in infancy

• secondary repair at 1 year with RAVV repair and RV-PA conduit.

• now with PA stenosis and severe RAVV regurgitation
Complete common AV canal
Native valve function- pre
Heimlich valve principal
ECM TV creation

- completed cylinder valve
- ends are tacked to ventricular wall
- other cylindrical end is sewed to annulus
ECM TV function- post
In vitro images
Risk in Congenital Heart Surgery: Chronological improvement

Mortality vs Year for different RACHS categories.
Generation of human iPS cells of patient specific tissue
Patient-specific cellular reprogramming in CHD

- 11 lines of AF: gest age 3@19, 3@20, 1@22, 1@25, 1@32, 1@33 weeks
- Average reprogramming time with clonal selection = 3 weeks
- Creation of >100 stable iPS cell lines
Reprogramming using amniocentesis-derived fibroblasts

<table>
<thead>
<tr>
<th>Experimental Time (Gest. Age)</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (14-20 weeks)</td>
<td>Amniocentesis</td>
</tr>
<tr>
<td>1 day (14-20 weeks)</td>
<td>Purification of amniotic fluid fibroblasts</td>
</tr>
<tr>
<td>1 week (15-21 weeks)</td>
<td>Expansion of fibroblasts</td>
</tr>
<tr>
<td>2 weeks (17-23 weeks)</td>
<td>Transduction of fibroblasts (4XF/miR)</td>
</tr>
<tr>
<td>1 week (18-24 weeks)</td>
<td>Selection of iPSC clones</td>
</tr>
<tr>
<td>1 week (19-25 weeks)</td>
<td>Screen iPSC clones</td>
</tr>
<tr>
<td>3 weeks (22-28 weeks)</td>
<td>Expansion iPSC clones</td>
</tr>
<tr>
<td>2-6 weeks (24-32 weeks)</td>
<td>Directed differentiation</td>
</tr>
<tr>
<td>4-8 weeks (28-40 weeks)</td>
<td>Assay of differentiated cell types</td>
</tr>
</tbody>
</table>
Cardiac differentiation of human iPS cells

Days post-directed differentiation

ISL1 expression

- iPS-1
- iPS-2
- iPS-3
- iPS-4
- iPS-5
Neuronal differentiation

Expanded iPS clones of two different patient with congenital heart disease and hES as a control (beta III tubulin)
Directed differentiation of patient-specific iPS cells may eventually help predict responses.

- cardiomyocyte
  - mechanical load
    - EP
    - drug responses
- neuron
  - hypoxia tolerance
    - drug responses
    - etc.
- etceterocyte
“This isn’t rocket science, it’s much harder” (A. Spiegel)