Mechanical Cardiac Support in Infants

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Disclosure Statements

- National Principal Investigator for the Berlin Heart EXCOR Pediatric VAD Clinical Trial.
- Berlin Heart provides administrative support for the trial and offsets travel expenses.
- No personal compensation for role as the National Principal Investigator.
- Texas Children’s Hospital is contracted to be the Berlin Heart Reference and Training Center in the United States.
Demographics of Pediatric Heart Failure

Analysis of 15 million hospitalizations: HCUP Kids Inpatient Database

Data presented at the AHA 2009 Annual Meeting by Rossano et al.
AGE DISTRIBUTION OF PEDIATRIC HEART RECIPIENTS
By Year of Transplant

NOTE: This figure includes only the heart transplants that are reported to the ISHLT Transplant Registry. As such, this should not be construed as evidence that the number of hearts transplanted worldwide has increased and/or decreased in recent years.

J Heart Lung Transplant 2008;27:937-983
The outcome of pediatric DC is more likely to be determined by the etiology of the disease than the choice of medical therapy applied within the current framework of heart failure management options.
First VAD implant by Hall.

DeBakey did first successful VAD implant.

NHLBI made requests for proposals to develop LVAD and energy converters to control the device.

By 1994, Novacar LVAS®, HeartMate IP®, Abiomed BVS5000®, and the Thoratec VAD® were FDA approved and were used successfully in selected adult centers.

NHLBI made request for proposal to develop a pediatric VAD.

NHLBI awarded 22.5 million dollars grant to different research facilities for development of pediatric MCS.

FDA Approves first Ped VAD Trial.
Indications for MCS in Infants

- Cardiomyopathy
  - Myocarditis
  - Dilated Cardiomyopathy
- Post-cardiotomy
Criteria for MCS at TCH

- If patient has cardiac failure requiring an inotrope
  AND
- Failure of one other organ system:
  - Respiratory: intubation
  - GI: inability to tolerate enteral feeds, rising LFTs
  - Renal: rising creatinine
  - Inability to get out of bed, fatigue limiting any activity
  - Chronically requiring a second inotrope
  - Neuro: mental status changes
Heart Failure
(not responding to medical Rx)

Temporary
(i.e., Myocarditis, Graft rejection)

- < 40 kg → Rotaflow
- > 40 kg → Tandem Heart®

Long-term
(i.e., dilated, hypertrophic CM)

- < 1.3m² BSA → Berlin Heart®
- > 1.3m² BSA → HeartMate® II

Recovery

Long-term Device

Transplant

Texas Children’s Hospital Protocol
# TCH MCS Experience

## 1995 – Present

<table>
<thead>
<tr>
<th>Mode of MCS</th>
<th>Patients Supported</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECMO</td>
<td>71</td>
</tr>
<tr>
<td>Biomedicus or Rotoflow</td>
<td>24</td>
</tr>
<tr>
<td>Thoratec</td>
<td>12</td>
</tr>
<tr>
<td>Heartmate II</td>
<td>5</td>
</tr>
<tr>
<td>MicroMed DeBakey VAD</td>
<td>3</td>
</tr>
<tr>
<td>Berlin Heart</td>
<td>20</td>
</tr>
<tr>
<td>Tandem Heart</td>
<td>2</td>
</tr>
</tbody>
</table>
• 16 children with myocarditis (1995 – 2009)
  – Biomedicus (6)
  – DeBakey MicroMed (2)
  – Thoratec (1)
  – HM II (2)
  – Rotoflow (1)
  – Tandem Heart (1)
  – ECMO (8)
• BTT or BTR in 81% (13/16)
• In patients with recovery EF improved significantly (20% vs 62%)
Berlin Heart EXCOR® Pediatric Worldwide Experience

- > 600 applications worldwide
- Longest application > 480 d
- 4 Continents
- > 150 Pediatric centers
- 155 infants USA/310 World

Personal communication, Berlin Heart, Inc.
Adrian Coulson and his wife, Leigh Bills, with their son Miles, who is being kept alive by a heart pump brought from Germany.

Tubes, Pump and Fragile Hope
Keep a Baby’s Heart Beating

By DENISE GRADY
PALO ALTO, Calif. — In an Internet message to family and friends, Miles Coulson’s parents described the situation with the baby’s fragile heart, which has become accustomed to assistive devices: the tiny pump that keeps it operating and the tubes that provide medication.

“Tubes, Pump and Fragile Hope
Keep a Baby’s Heart Beating”

LAST RESORTS
Fourth article of a series.
Solicitations to the FDA for the Berlin Heart

E-mail communication from FDA
IDE Study Overview

- Prospective, Multicenter, Single arm

- Comparing safety and effectiveness of the Berlin Heart EXCOR® Pediatric Ventricular Assist Device “EXCOR® Pediatric” with a historical control population supported with ECMO as a bridge to cardiac transplantation in children.

- Endpoint: Survival to transplantation or recovery (defined as hospital discharge or 30 days after explant, whichever is longer) with acceptable neurological status.
Critical outcomes being evaluated in the trial:

- Success as a bridge to transplant
- Discharge survival
- Optimal anti-coagulation
- Neurological outcomes short- and long-term
IDE Enrollment by Cohort

- Cohort 1
- Cohort 2

IDE
- IDE: 24
- IDE CU: 27
- Non-IDE CU: 49
- Canada: 13

Canada: 9
Berlin Heart EXCOR® Pediatric VAD FDA Trial

FDA IDE Trial
IDE approval → May 9, 2007

Cohort 1 (n = 24)
< 0.7 m² BSA
Completed

Cohort 2
≥ 0.7 and < 1.5 m² BSA
Enrollment in progress

Approval of a Continued Access Protocol
Berlin Heart EXCOR® Pediatric VAD FDA Trial

- Compiling cohort 1 data for HDE application for approval of the system for use in patients with BSA < 0.7 m²
  - Pump sizes 10, 25 and 30 mL
1\textsuperscript{st} Berlin Heart EXCOR\textsuperscript{®} Pediatric VAD at TCH

- 4-month-old, 3.3 kg, 0.23 m\textsuperscript{2} BSA
- Critical AS
- Percutaneous balloon aortic valvotomy x 2
- Profound ventricular dysfunction
- Worsening CHF refractory to medical therapy
- 10 mL pump placed
Berlin Heart EXCOR®
Pediatric Implant
Ventricular assist device implantation in neonates: Adjustment of the BerlinHeart EXCOR arterial cannula with bovine pericardium

Tonny D. T. Tjan, MD, Andreas Hoffmeier, MD, Hans Heinrich Scheld, MD, and Stefan Klotz, MD, Münster, Germany

J Thorac Cardiovasc Surg 2010;139:783-4
Color through Device
Berlin Heart EXCOR®
Pediatric Explant
Single Center Experience in Treatment of Cardiogenic Shock of any Etiology in Children by Pediatric VADs

- 20 years experience with pediatric VADs
- 70% survival to discharge in the recent decade
- Infant survival 16/27 (14/15 in last decade)
- Neurologic outcomes acceptable (no routine imaging)

21 pediatric patients were supported with EXCOR (2005 – 2008)

- 86% Survival to transplant, recovery or continued support
- 100% Survival to transplant or recovery for children < 1 year
# Single Center Experiences with EXCOR

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Overall Survival to Transplant or Recovery</td>
<td>70%</td>
<td>86%</td>
<td>63%</td>
</tr>
<tr>
<td>Survival to Transplant or Recovery in Infants</td>
<td>44%</td>
<td>100% (5/5)</td>
<td>33% (1/3)</td>
</tr>
</tbody>
</table>


Bridging Children of All Sizes to Cardiac Transplantation: The Initial Multi-center North American Experience with The Berlin Heart EXCOR® Ventricular Assist Device

- 97 EXCOR® VADs were implanted at 29 different institutions
- 73 (75%) patients from 17 institutions had data available
- 42 LVADs and 31 BiVADs

Age (median [range])

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Number (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>22 (30%)</td>
</tr>
<tr>
<td>1 – 5 years</td>
<td>28 (38%)</td>
</tr>
<tr>
<td>6 – 10 years</td>
<td>11 (15%)</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>12 (17%)</td>
</tr>
</tbody>
</table>

Diagnosis

- DCM          42 (58%)
- Myocarditis  7 (10%)
- CHD          19 (26%)

Ventilator dependant

- ECMO         22 (31%)
- Ventilator (not ECMO) 53 (73%)
- Inotropes    70 (100%)

Submitted for consideration of publication in Circulation
**Bridging Children of All Sizes to Cardiac Transplantation: The Initial Multi-center North American Experience with The Berlin Heart EXCOR® Ventricular Assist Device**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>LVAD Transplanted</th>
<th>BiVAD Transplanted</th>
<th>LVAD Death (prior to transplant)</th>
<th>BiVAD Death (prior to transplant)</th>
<th>LVAD Recovery</th>
<th>BiVAD Recovery</th>
<th>Total (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 1 yr</td>
<td>10 (71%)</td>
<td>3 (38%)</td>
<td>3 (22%)</td>
<td>5 (62%)</td>
<td>1 (7%)</td>
<td>0 (0%)</td>
<td>14 (100%)</td>
</tr>
<tr>
<td>Age 1 - 5 yr</td>
<td>12 (80%)</td>
<td>8 (67%)</td>
<td>2 (13%)</td>
<td>4 (33%)</td>
<td>1 (7%)</td>
<td>0 (0%)</td>
<td>15 (100%)</td>
</tr>
<tr>
<td>Age &gt; 5 yr</td>
<td>9 (69%)</td>
<td>9 (82%)</td>
<td>1 (8%)</td>
<td>2 (18%)</td>
<td>3 (23%)</td>
<td>0 (0%)</td>
<td>13 (100%)</td>
</tr>
</tbody>
</table>

**Graph:**

- **Proportion of Patients**
  - Transplant: 1.0
  - Death (prior to transplant): 0.22
  - Explanted (recovery): 0.04
  - Alive (device in place): 0.67

- **Months after Device Implant:**
  - Transplant: 24 months
Bridging Children of All Sizes to Cardiac Transplantation: The Initial Multi-center North American Experience with The Berlin Heart EXCOR® Ventricular Assist Device

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11. Berlin Heart, Inc., The Woodlands, TX;
12. C.S. Mott Children’s Hospital, University of Michigan Health System, Ann Arbor, MI; and
13. St. Louis Children’s Hospital, Washington University in St. Louis School of Medicine, St. Louis, MO.
Excor IDE Trial

- Stroke/Neurologic Outcomes
- Bleeding/anticoagulation/thrombosis
- Effect on transplant outcomes/suitability
- Outcomes cannot be answered by single center series
- Secondary endpoints analysis
Pumps for Kids, Infants, and Neonates (PumpKIN) Program

- NHLBI contract totaling $23.6 million
- Goal: Preclinical testing of MCS devices for infants and young children
- Program length: 4 years
- Awardees:
  - Harvey S. Borovetz, Ph.D., University of Pittsburgh
  - Mark Gartner, Ph.D., Ension, Inc., Pittsburgh, PA
  - Bartley P. Griffith, M.D., University of Maryland, Baltimore, MD
  - Robert Jarvik, M.D., Jarvik Heart, Inc., New York, NY
• PI: Harvey Borovetz, Ph.D.
• Institution: University of Pittsburgh
• Mechanism: Continuous axial flow
• Target: Neonates – 2 y.o.
  (Intracorporeal)
• Current status: In-vitro and ovine studies

19.6 x 75 mm
50 gms

Pictures courtesy of Tim Baldwin, Ph.D.
Enson pCAS
Pediatric Cardiopulmonary Assist System

- **PI:** Mark Gartner, Ph.D.
- **Institution:** Ension, Inc.
- **Mechanism:** Continuous pump and oxygenator in 1 unit
- **Target:** 2 to 12kg Cardiac and pulmonary support
- **Current status:** In-vitro and animal studies

*Pictures courtesy of Tim Baldwin, Ph.D.*
• **PI:** Robert Jarvik, M.D.
• **Institution:** Jarvik Heart, Inc.
• **Mechanism:** Continuous axial flow
• **Target:** Infant and child priming volume 1 cc and 4 cc
• **Current status:** Animal studies

10.5 x 32 mm
10 gms

*Pictures courtesy of Tim Baldwin, Ph.D.*
PEDIATRIC APPLICATION OF THE THORATEC CENTRIMAG BIVAD AS A BRIDGE TO HEART TRANSPLANTATION

Yasutaka Hirata, MD, Kevin Charette, CCP, Ralph S. Mosca, MD, Jan M. Quaegebeur, MD, and Jonathan M. Chen, MD, New York, NY


Report of three successful applications of the CentriMag BiVAD as a bridge to pediatric heart transplantation.

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>32</td>
<td>39.8</td>
</tr>
<tr>
<td>LVAD flow (mL/min)</td>
<td>1.9–2.1</td>
<td>3.0–3.1</td>
</tr>
<tr>
<td>RVAD flow (mL/min)</td>
<td>1.9–2.1</td>
<td>3.0–3.1</td>
</tr>
<tr>
<td>Cannulas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVAD inflow</td>
<td>28F malleable lighthouse tip</td>
<td>28F malleable lighthouse tip</td>
</tr>
<tr>
<td>LVAD outflow</td>
<td>14F Biomedicus</td>
<td>14F Biomedicus</td>
</tr>
<tr>
<td>RVAD inflow</td>
<td>24F malleable lighthouse tip</td>
<td>28F malleable lighthouse tip</td>
</tr>
<tr>
<td>RVAD outflow</td>
<td>14F Biomedicus</td>
<td>14F Biomedicus</td>
</tr>
<tr>
<td>Transplantation</td>
<td>4 d</td>
<td>3 d</td>
</tr>
<tr>
<td>Outcome</td>
<td>Alive</td>
<td>Alive</td>
</tr>
</tbody>
</table>
ABIOMED® IMPELLA 2.5

- The Impella 2.5 is a minimally invasive, catheter-based cardiac assist device designed to:
  - Directly unload the LV
  - Reduce myocardial workload and oxygen consumption
  - Increase CO and coronary and end-organ perfusion
  - 9 Fr Catheter and 12 Fr Pump diameter
Future

- **Circulite® – Synergy Pocket Micro-Pump**
- **Smallest implantable device**
Circulite® – Synergy Pocket Micro-Pump

- Circulite received a Fast Track Phase I-II Small Business Innovation Research (SBIR) grant from the NIH
  - Phase I – up to $100,000 over 6 months
  - Phase II – up to $750,000 over 24 months
- First pilot trial in June 2007
- Designed for long-term use in NYHA class IIIb / early IV patients
- Provide up to 3 L/min of flow
- Easily implanted subcutaneously in a “pacemaker-like” pocket through a minimally invasive procedure
- 22 patients have been implanted with the Synergy device until March 2009
- In July 2009, Circulite received NIH Grant to develop Synergy micro-blood pump for children and infants
A total of 187 such devices were placed in 2006.

A sharp uptick from 2003.

In 2006, 40% of VADs were placed in children because of an underlying diagnosis or cardiomyopathy, 21% because of congenital heart disease, and 13% because of myocarditis.

70% of the 187 patients survived until hospital discharge.

Those patients treated by ECMO prior to receiving their VAD had significantly worse survival (40%) than to patients not needing ECMO (79%).

Survival was significantly better in patients who received VADs at large, high-volume teaching hospitals (89%) than among those treated at other hospitals (61%).
5-month-old girl with h/o familial DCM
  - Severely depressed systolic function
• Evaluated at OSH
• Family hx (brother and maternal grandmother)
• Echo: severe LV dilation, severe ↓ LV systolic func, EF 12%, RV compressed by dilated LV
• Medical Mx ACEIs and Lasix
Presentation
Progressively worsened, required multiple inotropes and intubation

End-organ dysfunction

Decision to proceed with VAD support

Centrifugal LVAD for 48 hrs with stable Hd

Transitioned to Berlin Heart and listed for OHT

Length of VAD support 87 days

Successful OHT and d/c
On Temporary Support
On Long-term Support
AH

- 4-month-old girl
- Referred from OSH to Heart Failure clinic
- Dilated cardiomyopathy
- Progressively worsened, became inotrope and ventilator dependant
- Listed for transplant
- Decision made to put her on Berlin Heart
Pre-implant
3 days Post Implant
Psychosocial, Rehabilitation and Developmental Considerations
Financial Considerations

- 10-month-old baby girl with DCM
- Medicaid patient
- Successfully bridged to OHT with BH
- Hospital LOS = 210 days
- Hospital Costs = $1.3 million
- Reimbursement rate 32¢ per $
VADs in Infants

- Challenging proposition, but with increasing promise
- Temporary Devices limited
- Durable Device = Berlin Heart
- Device development promising
- Effect on transplant waiting times, survival
- Destination therapy?