Left and Right Heart Support as a Bridge to Cardiac Transplantation in Patients with Pulmonary Hypertension Due to Left Heart Disease

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Director Pediatric Artificial Heart Program
University of Alberta, Stollery Children's Hospital and Mazankowski Alberta Heart Institute

3RD INTERNATIONAL Neonatal & Childhood Pulmonary Vascular Disease Conference

Pulmonary Hypertension

• Patients with fixed PVH (PVR>2.5WU) have a significantly worse prognosis after HTX than patients with reversible pulmonary hypertension, mainly due to the increased risk of acute right ventricular dysfunction

Pulmonary Hypertension

• Fixed PVH is considered to be present when elevated PVR cannot be significantly decreased (<20%) by pharmacologic interventions. Different vasodilators have been tested to reduce pretransplant PVR, such as sodium nitroprusside, inhaled nitric oxide, phosphodiesterase inhibitors, prostaglandins (PGE-1 and PGI-1), and levosimendan.


• Reviewed invasive pulmonary hemodynamics from 58 consecutive patients receiving LVAD support as a bridge to HTx from 1996 to 2003.

• Improvement in TPG occurred throughout LVAD support and was sustained after HTx/recovery.

• Levels of TPG reductions in patients with a baseline TPG in the highest quartile (14.1-26.0 mm Hg) were 8.6 +/- 3.5 vs 6.5 +/- 3.1 mm Hg in the lowest quartile (2.0-7.7 mm Hg) during LVAD support (p = 0.102), with 90% vs 100% 30-day post-HTx survival (P = 0.113).


Pulsatile left ventricular assist device support as a bridge to decision in patients with end-stage heart failure complicated by pulmonary hypertension.

Nair PK, et al Cardiovascular Institute, University of Pittsburgh, Pittsburgh, Pennsylvania, USA.
CONCLUSION:

• Pulmonary hemodynamics and post-HTx survival were similar after pulsatile LVAD support in patients with and without pre-implant PH

• LVAD support may be a useful strategy to reverse PH in carefully selected patients, thus improving candidacy for HTx

Pulsatile left ventricular assist device support as a bridge to decision in patients with end-stage heart failure complicated by pulmonary hypertension.
Nair PK, et al Cardiovascular Institute, University of Pittsburgh, Pittsburgh, Pennsylvania, USA.

Reversal of secondary pulmonary hypertension by axial and pulsatile mechanical circulatory support.
Torre-Amione G, Southard RE, Lohe MM, Youker KA, Bruckner B, Estep JD, Tierney M, Noon GP.
The Department of Cardiology, The Methodist DeBakey Heart & Vascular Center, The Methodist Hospital, Houston, Texas, USA.
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• Retrospective analysis of 9 heart failure patients with secondary pulmonary hypertension (transpulmonary gradient [TPG] > 15 mm/Hg). Two were treated with a pulsatile left ventricular assist device (LVAD) and 7 with an axial-flow LVAD

• RESULTS: After LVAD support, mean pulmonary artery pressure decreased from 39 +/- 7 to 31 +/- 5 mm Hg, and the TPG decreased from 19 +/- 3 to 13 +/- 4 mm Hg (p < 0.01)
CONCLUSION:

- Pulmonary hypertension that is secondary to congestive heart failure, as defined by a TPG > 15 mm Hg can be reversed by the use of pulsatile and axial-flow LVADs; furthermore, post-transplant survival for patients with secondary pulmonary hypertension treated with an LVAD was no different than for those without pulmonary hypertension who received LVAD support.

Reversal of secondary pulmonary hypertension by axial and pulsatile mechanical circulatory support.
Torre-Amione G, Southard RE, Loebe MM, Youker KA, Bruckner B, Einav JD, Tierney M, Noon GP.
The Department of Cardiology, The Methodist DeBakey Heart & Vascular Center, The Methodist Hospital, Houston, Texas, USA.
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Berlin Heart pediatric Experience

- Total Impl.
- US/Canada

- INTER-agency
- Registry
- Mechanically
- Assisted
- Circulatory
- Support
### INTERMACS Demographics at Time of Implant - Overall

<table>
<thead>
<tr>
<th>GENDER</th>
<th>n</th>
<th>PctN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>381</td>
<td>22.1%</td>
</tr>
<tr>
<td>Male</td>
<td>1342</td>
<td>77.8%</td>
</tr>
<tr>
<td>Total Gender</td>
<td>1723</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AGE GROUPS</th>
<th>n</th>
<th>PctN</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: 0-18</td>
<td>52</td>
<td>3.0%</td>
</tr>
<tr>
<td>B: 19-39</td>
<td>305</td>
<td>17.7%</td>
</tr>
<tr>
<td>C: 40-69</td>
<td>823</td>
<td>47.7%</td>
</tr>
<tr>
<td>D: 60-79</td>
<td>542</td>
<td>31.4%</td>
</tr>
<tr>
<td>E: 80+</td>
<td>1</td>
<td>0.0%</td>
</tr>
<tr>
<td>Total Age Groups</td>
<td>1723</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

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### Pediatric Assist Devices

- **Berlin Heart EXCOR Pediatric**
- **HeartMate® II**
- **Levitronix**
**EXCOR® Components**

- **Driving Units**
  - Ikus

- **Blood Pumps**
  - Children Infants
    - 10 ml
    - 25 ml
    - 30 ml
  - Adults
    - 50 ml
    - 60 ml
    - 80 ml

- **Cannulas**
  - Arterial Cannulas
    - Diameter from 3 to 12 mm
  - Atrial Cannulas
    - Diameter from 5 to 12 mm
  - Apex Cannulas
    - Diameter from 6 to 12 mm
  - Arterial Cannulas
    - Diameter from 12 to 16 mm
  - Atrial Cannulas
    - Nominal size 12 mm
  - Apex Cannulas
    - Diameter from 12 to 16 mm

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**Considered for Implantation of a VAD**

- inotrope-dependency
  (worsening signs/symptoms of heart failure when inotropic support is weaned or withdrawn)

**AND...**
AND

- evidence of compromise to at least one other organ system:
  - respiratory failure (e.g., requiring mechanical ventilation)
  - worsening renal function (e.g., rise in serum creatinine by at least 0.3 mg/dL)
  - hepatic dysfunction (e.g., AST >50 U/mL, conjugated bilirubin >1.0 or INR >1.5)
  - inability to tolerate enteral feeds
  - impaired mobility due to heart failure symptoms resulting in confinement to bed

OR

- the patient is in cardiogenic shock or impending cardiogenic shock
- ECMO or Unable to separate from cardiopulmonary bypass
Severe RV Dysfunction

Severe RV dysfunction
Qualitative Assessment by TEE
AND
CVP >= 20 mmHg
AND
Liver failure (Bili, AST, ALT 3 x normal)
With/Without Refractory Ascites

BVAD

Moderate RV Dysfunction

LVAD Implantation
LA < 10 mmHg
Reduction of RV afterload

Optimization of medical therapy
Nitric Oxide, Phosphodiesterase-Inhibitors
Inotropes

CI > 2.5 L/min
CVP < 15 mmHg
Improving RV function (in TEE)

CI > 2 - 2.5 L/min
OR
CVP 15 - 19 mmHg

CI < 2.0 L/min
Severe RV dysf.
Severe TR
Lactate > 3 mmol/l

No RVAD

At discretion of surgeon based on overall clinical assessment

RVAD

At discretion of surgeon based on overall clinical assessment
INTERMACS: Data entered as of June 30, 2009
Implant Dates: March 1, 2006 - June 30, 2009

Exhibit 4
INTERMACS Month of Implant by Device Position - Overall

<table>
<thead>
<tr>
<th>Device</th>
<th>Both (in the same OR visit)</th>
<th>Total Artificial Heart</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jun/2009</td>
<td>LVAD 30</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>1403</td>
<td>235</td>
<td>59</td>
</tr>
</tbody>
</table>

Edmonton Outcome

- 22 VAD’s since 2005 in 20 Patients
- 18 Berlin Hearts Pediatric
  6x10ml, 7x 25ml or 30ml, 5x 50ml or 60ml or 80ml
- 4 Levitronix
Edmonton Outcome Berlin Heart

05: 1BVAD, 1HTX
06: 3 LVAD, 2 HTX, 1 Wean
07: 2 LVAD, 2 HTX
08: 1 LVAD, 1 HTX,
    3 BVAD, 2 HTX, 1 Dead
09: 6 LVAD, 5 HTX, 1 Ongoing,
    1 BVAD, Ongoing
10: 1 LVAD, Ongoing

Outcome Berlin Heart Pediatric: 94.5%

Edmonton Outcome Pediatric Program

09: 4x bridge to decision (Levitronix)
    1x RVAD    HTX
    2x BVAD    Wean, HTX
    1x LVAD    switch to Berlin Heart

Outcome pediatric VAD Program: 95%
Patient Mobilization

Patient Mobilization
<table>
<thead>
<tr>
<th>INTERMACS profile</th>
<th>Shorthand</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>“Crash &amp; Burn”</td>
<td>Critical Cardiogenic Shock</td>
</tr>
<tr>
<td>2</td>
<td>“Sliding on Inotropes”</td>
<td>Progressive Decline</td>
</tr>
<tr>
<td>3</td>
<td>“Dependent Stability”</td>
<td>Stable, Inotrope Dependent</td>
</tr>
<tr>
<td>4</td>
<td>“Frequent Flyer”</td>
<td>Recurrent Decompensation</td>
</tr>
<tr>
<td>5</td>
<td>“Housebound”</td>
<td>Exercise Intolerant, OK at Rest</td>
</tr>
<tr>
<td>6</td>
<td>“Walking Wounded”</td>
<td>ADL OK, Easy Fatigue</td>
</tr>
<tr>
<td>7</td>
<td>“Advanced NYHA III”</td>
<td>Clinically Stable</td>
</tr>
</tbody>
</table>

**INTERMACS 1 & 2**

- **“Bridge To Decision”**
  - Post-Cardiomyotomy Arrest
  - Cath Lab

**INTERMACS 3 - 7**

- **HeartMate II**
  - “Bridge To Transplant”
  - “Destination Therapy”
HeartMate II LVAS

- Relatively Simple Design
  - Valveless
  - Only one moving part, the rotor
  - Blood immersed bearings designed for minimization of blood damage
  - All motor drive and control electronics are outside of the implanted blood pump
- Speed range: 6,000 to 15,000 rpm
- Flow range: 3 – 10 L/min

Exhibit 6
INTERMACS Patient Profile at Time of Implant - Overall

<table>
<thead>
<tr>
<th>Patient Profile Status</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Critical Cardio Shock</td>
<td>596</td>
<td>34.1%</td>
</tr>
<tr>
<td>2 Progressive Decline</td>
<td>678</td>
<td>39.3%</td>
</tr>
<tr>
<td>3 Stable but inotrope dependent</td>
<td>226</td>
<td>13.1%</td>
</tr>
<tr>
<td>4 Recurrent Adv HF</td>
<td>136</td>
<td>8.0%</td>
</tr>
<tr>
<td>5 Exertion intolerant</td>
<td>33</td>
<td>1.9%</td>
</tr>
<tr>
<td>6 Exertion limited</td>
<td>27</td>
<td>1.5%</td>
</tr>
<tr>
<td>7 Advanced NYHA Class 3</td>
<td>32</td>
<td>1.8%</td>
</tr>
<tr>
<td>Total</td>
<td>1723</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
HeartMate II LVAS Pump

- Flexible inflow conduit
- Textured surfaces
  - Inlet cannula, inflow and outflow elbows
  - Thrombo-resistant
- Outflow graft with bend relief
- Anastomosed to LV apex and ascending aorta
- Pump output varies over cardiac cycle
  - Follows native pulse
  - Afterload sensitive

Anatomical Placement
Thoratec Registry

- Patients implanted: Over 4,000+ worldwide
- Longest duration of support: 5+ years
- Age range: 11 - 87 years
- BSA range: 1.14 - 3.16 m²
- Transplanted, recovered, or supported to 18 months: 79%

Thoratec Registry Destination Trail

- Survival 68 percent and 58 percent at one year and two years
- The level of adverse events, including infection, sepsis and right heart failure was lower in major categories versus patients in the control group
- 60% walked 200 meters more during a six-minute walk test at a three-month
- Of the patients who were supported longer than three months, 43% improved by three NYHA classes, and another 43% improved by one or two NYHA classes.
Bridge to ??????

- Bridge to transplant
- Bridge to bridge or decision
- Bridge to recovery
- Destination Therapy

INTERMACS: Data entered as of June 30, 2009
Implant Dates: March 1, 2006 - June 30, 2009

Exhibit 5
INTERMACS Device Strategy at Decision of Implant - Overall

<table>
<thead>
<tr>
<th>Pre-Implant Device Strategy</th>
<th>n=</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bridge to Recovery</td>
<td>51</td>
<td>2.9%</td>
</tr>
<tr>
<td>Bridge to Transplant (patient currently listed for transplant)</td>
<td>794</td>
<td>46.0%</td>
</tr>
<tr>
<td>Possible Bridge to Transplant - Likely to be eligible</td>
<td>467</td>
<td>27.1%</td>
</tr>
<tr>
<td>Possible Bridge to Transplant - Moderate likelihood of becoming eligible</td>
<td>153</td>
<td>8.6%</td>
</tr>
<tr>
<td>Possible Bridge to Transplant - Unlikely to become eligible</td>
<td>80</td>
<td>4.6%</td>
</tr>
<tr>
<td>Destination Therapy (patient definitely not eligible for transplant)</td>
<td>155</td>
<td>8.9%</td>
</tr>
<tr>
<td>Rescue Therapy</td>
<td>17</td>
<td>0.9%</td>
</tr>
<tr>
<td>Other, specify</td>
<td>6</td>
<td>0.3%</td>
</tr>
<tr>
<td>Total</td>
<td>1723</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
Why does patient selection matter?

Patient Selection for the Use of Ventricular Assist Devices as a Bridge to Transplantation

Leslie W. Miller, MD
Division of Cardiology, University of Minnesota, Minneapolis, Minnesota

Patient selection is a critical factor in the outcome associated with the use of mechanical assist devices for the treatment of refractory heart failure. Numerous risk factors impact on the outcome, many of which can be identified and treated before device surgery. This manuscript reviews all the risk factors that have been identified to date and the use of composite risk scores to predict outcome.

The number of patients with advanced heart failure is increasing. Current estimates suggest that more than 5 million people in the U.S. have been diagnosed with heart failure (Gibbs II II). Of this total, an estimated 20% are asymptomatic, 50% are stable on oral drug therapy, and approximately 10% to 15% have advanced HF, with half of the latter group having refractory failure. Recent reports have shown that as many as 30% to 40% of patients selected for mechanical support do not survive to undergo transplantation (15-18). Table 1 shows that 30% to 35% mortality rate has been independent of the device used, or the period of use, including an analysis fluoroscopy.
Because pt selection often dictates outcome

Overall BTT Survival (N=420)

BTT Survival by Profile (N=420)

Pagani, Stevenson et al. on behalf of INTERMACS

Patient Selection in Pediatric VADs

*Censored at transplant.
Why is patient selection more challenging in pediatrics?

- Clinical heterogeneity (age, size, cardiac diagnosis, support types)
- Smaller sample sizes
- Limited safety data (currently) for most pediatric devices (e.g. if the risk of stroke were 5% vs 20% vs 40%?)

Number of children who died on the HT waitlist between 1999 and 2006

*Circulation. 2009;119;717-727*
Children awaiting HT face the highest risk of waiting list mortality in solid organ transplant medicine

Overall Risk of Death on the Waitlist

Circulation. 2009;119:717-727
Multivariate Predictors of Waitlist Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>Adjusted HRs</th>
<th>Status: 1A Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECMMO</td>
<td>3.1 (2.4–3.9)</td>
<td>&lt;0.001</td>
<td>3.0 (2.3–3.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ventilator support</td>
<td>1.9 (1.6–2.4)</td>
<td>&lt;0.001</td>
<td>1.9 (1.5–2.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac diagnosis of CHD</td>
<td>2.2 (1.8–2.6)</td>
<td>&lt;0.001</td>
<td>2.1 (1.7–2.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dialysis</td>
<td>1.9 (1.2–3.0)</td>
<td>0.006</td>
<td>2.0 (1.3–3.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>UNOS listing status 1A</td>
<td>2.2 (1.7–2.7)</td>
<td>&lt;0.001</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Nonwhite race, %</td>
<td>1.7 (1.4–2.0)</td>
<td>&lt;0.001</td>
<td>1.7 (1.4–2.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Year of listing 1999–2002</td>
<td>1.2 (1.0–1.5)</td>
<td>0.040</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Cox proportional hazards model.
Restrictive Cardiomyopathy (RCM)

- Frequency: RCM is the least common cardiomyopathy and represents approximately 2-5% of pediatric cardiomyopathies.
- Internationally: Reports from US, Australia, Europe and Asia suggest similar international infrequency.
- Race: No known racial predilection exists.
- Sex: Some studies suggest that idiopathic RCM may be slightly more common in girls than in boys.
- Age: In children, idiopathic RCM has been described in all ages.

Mortality:

- Mortality rates in children with idiopathic RCM are high, particularly in absence of heart transplantation.
  - Highest mortality in infants and girls.
- Rates have been reported as high as 63% within 3 years of diagnosis and 75% within 6 years of diagnosis (♀ > ♂).
- Survival range is 44-50% at 1-2 years after presentation and decreases to 29-37% at 3-4 years after presentation.
Restrictive Cardiomyopathy (RCM)

All patients (n=21), median survival 2.2 y (6,21 ♂, 1.73 ♀)


Pulmonary Hypertension in RCM
RCM Excor Pediatric Berlin Heart Registry

• n=14 (♀9, ♂5)

• Diagnosis of RCM alone in 11

• Restrictive physiology in 3, related to:
  Ross-OP 1, Valvuloplasty 1, Dextrocardia + TGA→Switch 1

• Age 1,1 – 16y (mean 5.8)

• LVAD 5, BVAD 9

• Apical cannulation 6 (!!!), atrial 8

RCM Excor Pediatric

Outcome

• Days on system 6 – 401 (mean 105)
• HTX 8
• Weaned 1
• Death 3 ( 2 cerebral bleeding, 1 Stroke )
• On system 3

• No patient required a Heart Lung Transplantation
• Post HTX 30 day survival 100%
Table 2: Use of LVAD for lowering severe fixed PVR in patients with CHF

<table>
<thead>
<tr>
<th>References</th>
<th>Patients number</th>
<th>Device</th>
<th>PVR reversibility</th>
<th>Time to PVR reversibility (days)</th>
<th>Pre-VAD PVR (mmHg)</th>
<th>Post-VAD PVR (mmHg)</th>
<th>HTV²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallagher et al. [3]</td>
<td>16</td>
<td>Novacor</td>
<td>16 (1.00)</td>
<td>61</td>
<td>3.8</td>
<td>1.5</td>
<td>16 (1.00)</td>
</tr>
<tr>
<td>Strohlein et al. [4]</td>
<td>6</td>
<td>TCI HeartMate</td>
<td>NA</td>
<td>NA</td>
<td>5.0</td>
<td>3.7</td>
<td>49 (38)</td>
</tr>
<tr>
<td>Admeon et al. [5]</td>
<td>1</td>
<td>TCI HeartMate</td>
<td>1 (1.00)</td>
<td>70</td>
<td>6.6</td>
<td>2.8</td>
<td>1 (1.000)</td>
</tr>
<tr>
<td>Nguyen et al. [6]</td>
<td>3</td>
<td>TCI HeartMate</td>
<td>3 (1.00)</td>
<td>100</td>
<td>6.3</td>
<td>3.6</td>
<td>3 (1.000)</td>
</tr>
<tr>
<td>Petroselli et al. [7]</td>
<td>1</td>
<td>Thoratec BVAD</td>
<td>1 (1.00)</td>
<td>50</td>
<td>12.2</td>
<td>3.1</td>
<td>1 (1.000)</td>
</tr>
<tr>
<td>Al-Khadri et al. [8]</td>
<td>1</td>
<td>Novacor</td>
<td>1 (1.00)</td>
<td>330</td>
<td>7.1</td>
<td>1.2</td>
<td>1 (1.000)</td>
</tr>
<tr>
<td>Martin et al. [9]</td>
<td>6</td>
<td>TCI HeartMate</td>
<td>6 (1.00)</td>
<td>191 ± 58</td>
<td>5.7</td>
<td>2.0</td>
<td>6 (1.000)</td>
</tr>
<tr>
<td>Non-pulsatile LVAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goldberg et al. [30]</td>
<td>6</td>
<td>DeBakey</td>
<td>6 (1.00)</td>
<td>42</td>
<td>29²</td>
<td>167.0</td>
<td>4 (67)</td>
</tr>
<tr>
<td>Ets et al. [30]</td>
<td>10</td>
<td>Intra/DeBakey</td>
<td>7 (70)</td>
<td>102 ± 118</td>
<td>4.9</td>
<td>2.2</td>
<td>5 (69)</td>
</tr>
<tr>
<td>Zupler et al. [31]</td>
<td>3</td>
<td>Novacor/DeBakey/DestHeart</td>
<td>24 (69)</td>
<td>42</td>
<td>6.1</td>
<td>2.0</td>
<td>24 (69)</td>
</tr>
</tbody>
</table>

Review of the literature, CHF: chronic heart failure; HTV, Heart transplant; PVR, pulmonary vascular resistance; LVAD, left ventricular assist device; LVAD, left ventricular assist device; NA, not available; HTV, heart transplantation. Percentage values are shown in parentheses. * Values are shown in parentheses. 

Is fixed severe pulmonary hypertension still a contraindication to heart transplant in the modern era of mechanical circulatory support?
A review
Andrea Garattia, Giuseppe Bruschib, Tiziano Colombob, Maria Frigeriob and Ettore Vitalib
Conclusion

- Our experience confirms the growing body of literature in which LVAD seems a promising option to treat selected CHF patients initially not eligible for HTx due to fixed PVH

- If PVR reversibility is not achieved after few months of mechanical unloading, permanent LVAD support becomes the final therapy for these patients

- Further implants are required to refine the indications and improve outcomes in this subgroup of patients
Thank you for your Attention