Hemodynamic Support of Acute and Chronic Rejection in Cardiac Transplantation

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U.S. Demographics of CHF

- 500,000 new cases/year
- 6 million patient prevalence
- Single largest U.S. Medicare admission diagnosis, • $34 billion/yr
- 1 year mortality of 40% (1/8 deaths)
- 75% of CHF patients > 65 yo
- Only 2,200 U.S. transplants/year
- 50% of transplant recipients are BTT
- LVAD has surpassed transplant volume
Projected Mortality for AHF Exceeds Other Terminal Diseases

Data on file, Thoratec Corporation.
U.S. Demographics

Projected Elderly Population Age 65+
(millions)

1990: 31.5 million (12.6% total US population)
2000: 65.6 million (21.8% total US population)
2010: 75 million
2020: 80 million
2030: 85 million
Age relation of HF

Age Distribution Of Cardiac Transplant Recipients 2006-12
90% of US transplants in 2009 were on Status 1A or 1B patients

Almost 1500 pts. Have died waiting for Tx between 2006-2009

ScandiaTransplant - Denmark, Finland, Norway, Sweden, Iceland

Eurotransplant - Austria, Belgium, Croatia, Germany, Luxembourg, The Netherlands, Slovenia
Adult Heart Transplants

% of Patients Bridged with Mechanical Circulatory Support*
(Transplants: January 2000 – December 2014)

% of Patients

Year of Transplant


* LVAD, RVAD, TAH, ECMO
Adult Heart Transplants
Kaplan-Meier Survival by Era
(Transplants: January 1982 – June 2014)

Median survival (years):

All pair-wise comparisons were significant at p < 0.05.
Adult Heart Transplants
Relative Incidence of Leading Causes of Death
(Deaths: January 1994 – June 2015)

Since only leading causes of death are shown, the sum of percentages for each time period is less than 100%.
Adult Heart Transplants
Cumulative Incidence of Leading Causes of Death
(Transplants: January 1994 – June 2014)

- CAV
- Malignancy (non-Lymph/PTLD)
- Infection (non-CMV)
- Graft Failure
- Renal Failure
- Acute Rejection
- Multiple Organ Failure

Incidence of Cause-Specific Deaths vs. Years

ISHLT - INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION
JHLT. 2016 Oct; 35(10): 1149-1205
Survival (%)

Adult Heart Transplants

Kaplan-Meier Survival by Era (Transplants: January 1982 – June 2014)

Diagnosis: Retransplant

Median survival (years):

All comparisons were significant at p < 0.05 except 2002-2008 vs. 2009-6/2014.
% of Recipients Experiencing *Treated* Rejection Between Transplant Discharge and 1-Year Follow-Up by Era

Analysis is limited to patients who were alive at the time of the follow-up.

Treated rejection = Recipient was reported to (1) have at least one acute rejection episode that was treated with an anti-rejection agent; or (2) have been hospitalized for rejection.
Adult Heart Transplants

% of Recipients Experiencing Any Rejection Between Transplant Discharge and 1-Year Follow-Up by Era

- Analysis is limited to patients who were alive at the time of the follow-up.

- Any rejection = Recipient was reported to (1) have at least one acute rejection episode; or (2) have been hospitalized for rejection.
Background Terminology

- Immediate donor organ failure
- Early donor organ failure
- Long-term donor organ failure
Causes of Immediate / Early Cardiac Failure

- Donor injury
- Preservation
- Immunological Match
- Recipient factors
Prevention of Donor Failure

- Selection of good donor
- Proper match of donor and recipient
- Shortened ischemic time
- Chemical RVAD
Chemical RVAD

- Inhaled Nitric Oxide
- β Agonists
  - Isuprel, Dobutamine
- Mixed agents
  - Dopamine, Epinephrine
- α agonists
  - Vasopressin, Levophed
- Other Factors
  - HR, ABG, Volume,
Which Side is Failing

- Right
- Biventricular
- Left
Medical Management

- Hemodynamic support
  - Chemical RVAD
  - IABP
- Plasmapheresis
- Polyclonal antibody (ATG)
Options for Mechanical Support

- ECMO
- Impella
- RVAD
- LVAD / BiVAD
- TAH
ECMO

I’d Like to Help, but... You Need ECMO, Not Elmo.
1985
A lot has changed...
Support has changed too
Open Chest ECMO
ECMO Femoral Cannulation
What does ECMO look like
What does ECMO look like
ECMO Precautions

- Left heart decompression
  - Lung preservation
- Bleeding
- Cavity thrombosis
Impella
Hemodynamic Stabilization with Impella®

Unloads Left Ventricle & Coronary Perfusion

End Organ Perfusion

Right Side Support

Escalation & Ambulation

Right Side Impella RP
Left Side Impella 2.5/CP/5.0

Seyfarth et al., JACC, 2008
Remmelink M et al., Cath Card Interv. 2007
Lam K. et al., Clin Res Cardiol, 2009
Casassus et al., JOIC, 2015
Anderson MB. et al., J Ht Lg Transplant. 2015
Lima B. et al., Am J Cardiol 2016
IMPELLA® HEART PUMP: HOW IT WORKS

Placement in Left Ventricle

Outflow

Impeller and blood outflow

Inflow
**Impella® Reduces Need for Inotropes/Pressors**

**Impella 2.5**
Reduction in Inotropes/Pressors in 24 Hours

ISAR-SHOCK RCT¹
N=25

- **IABP**
- **Impella 75%**

**Impella 5.0**
Reduction in Inotropes/Pressors Over days

RECOVER I FDA IDE Study²
(N=16)

1- Seyfarth et al. JACC 2008
PHP Catheter – Distal Features

- Dual Radiopaque Markers
- Flexible Inner Sheath
- Collapsible Elastomeric Impeller
- 13F Outer Sheath
- Collapsible Thoralon-coated Nitinol Cannula
HeartMate PHP™: clinical study activity & update

Completed CE Mark study leading to approval in 2015
  • 50 patients undergoing high-risk PCI (HRPCI)
  • Primary endpoints: avoidance of major adverse events at 30 days, device and procedural success

Pivotal US IDE underway: SHIELD II
  • Multicenter randomized trial studying PHP support in patients undergoing a HRPCI procedure
  • 425 patients undergoing high-risk PCI
  • Randomized 2:1 against Impella 2.5
  • Plan to complete SHIELD II enrollment in 2017

*CAUTION – HeartMate PHP™ is currently in development and not approved for sale.
HeartMate PHP (Percutaneous Heart Pump)

- Low-profile, rapid-insertion, catheter-based percutaneous heart pump
- Designed to provide high forward flow at low RPMs to unload the LV and perfuse end organs
  - Delivers over 4 lpm average flow
- Collapsible elastomeric impeller and nitinol cannula
- Designed for hemocompatibility with operating speeds of 16,000-20,500 RPM
- 14F profile expanding to 24F when unsheathed across aortic valve
Fully Magnetically Levitated Pump
• Acute, Short-term Device
• Centrifugal Pump
• RVAS, LVAS, or BiVAS

Typical speeds:
• 3000-4000 RPM
• Generating Flow: 4-5 LPM
• Afterload sensitive pump
• Preload Dependent

Cannulation Options:
• LVAS: LA or LV to Ascending Aorta
• RVAS: RA to Pulmonary Artery
• Cannulae available or surgeon preference

Target ACT: 160-180 seconds
PTT: 50-60 seconds

Flow Probe
• Accurate to 10 LPM
• Move every 8 hours

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Pump Specifications:
• Priming Volume: 31mL
• Max Pump Flow: 10 lpm
• Max Pressure: 600mmHg
• No bearings or seals

Other Points:
• Volume dependent
• LVAD flow ≥ RVAD flow
• Can be used as hybrid

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LVAD: Indicated for extracorporeal support for up to 6 hours of use.

RVAD: Indicated for use as a Temporary RVAD for patients in Cardiogenic Shock due to Acute Right Heart Failure for up to 30 days of support. HDE and 510(k) approved.
CENTRIMAG BLOOD PUMP SYSTEM:
SURGICAL IMPLANTATION: BIVENTRICULAR CANNULATION

LVAD Inflow: Left Atrium (LA)
LVAD Outflow: Aorta
LVAD: Blood moves from the LA or LV to the CentriMag Blood Pump then back into the Aorta then to the rest of the body

RVAD Inflow: Right Atrium (RA)
RVAD Outflow: Pulmonary Artery (PA)
RVAD: Blood moves from the RA to the CentriMag Blood Pump then back into the PA then to the lungs

LVAD Inflow can also be Left Ventricle (LV) (not pictured)
CENTRIMAG BLOOD PUMP SYSTEM:
SURGICAL IMPLANTATION: BIVENTRICULAR CANNULATION
Total Artificial Heart
Total Artificial Heart Benefits

- Immediate excellent biventricular support
- Removes the antigenicity
- Easy to insert
Total Artificial Heart Detriments

- Cumbersome drivers
- Needs larger chest
- Stroke
- Maybe stuck with a sensitized patient
Sharp Transplant Experience
Sharp Transplant Experience

Estimated Hazard Ratio at 3 Years (Adjusted for Patient Risk)

HAZARD RATIO

LOWER IS BETTER

CALIFORNIA TRANSPLANT CENTERS

EXPECTED
Dilemmas or Transplantation vs. LVAD

**Transplantation**
- Restrictive patient selection
- Not readily available
- Limited donor pool
- Consequences of immunosuppression

**LVAD**
- Driveline exit site
- Adverse events
- Batteries
- Durability of device
## Results LVAD Transplant Comparison

<table>
<thead>
<tr>
<th>Factor</th>
<th>Transplant (N=59)</th>
<th>HeartMate II (N=102)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (year)</strong></td>
<td>52</td>
<td>63</td>
<td>P&lt;.01</td>
</tr>
<tr>
<td><strong>Gender, (%)</strong></td>
<td>64% (38/59)</td>
<td>86% (88/102)</td>
<td>P&lt;.05</td>
</tr>
<tr>
<td><strong>LOS (days)</strong></td>
<td>18</td>
<td>22</td>
<td>N.S.</td>
</tr>
<tr>
<td><strong>Survival n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At time of Discharge (n=161)</td>
<td>97%</td>
<td>95%</td>
<td>N.S.</td>
</tr>
<tr>
<td>1 Year</td>
<td>95%</td>
<td>82%</td>
<td>P&lt;.01</td>
</tr>
<tr>
<td>3 Years</td>
<td>88%</td>
<td>69%</td>
<td></td>
</tr>
<tr>
<td><strong>Cost Changes</strong></td>
<td>+17%</td>
<td>-41%</td>
<td>P&lt;.05</td>
</tr>
</tbody>
</table>
HeartMate II vs. Transplant Survival

- Survival (%)
  - Tx: 95 ± 3%, 92 ± 4%, 88 ± 6%
  - HMII: 82 ± 4%, 73 ± 5%, 69 ± 6%

- P (log-rank) = 0.016
- Hazard Ratio (LVAD) = 2.9 (1.8 - 7.3)
- P (adjusted for age) = 0.059

- At Risk:
  - 0.0 years: 59, 102
  - 0.5 years: 53, 82
  - 1.0 years: 45, 56
  - 1.5 years: 39, 40
  - 2.0 years: 34, 26
  - 2.5 years: 27, 17
  - 3.0 years: 20, 11

- Time (Years)
Sharp Hospital Five Year Cost Comparison

2006 2007 2008 2009 2010

- $0
- $50,000
- $100,000
- $150,000
- $200,000
- $250,000
- $300,000
- $350,000

Transplant
HMII
Results

- All 102 HMII patients, 86% (88/102) male, mean age 63 years were compared to 59 Tx recipients 64% (38/59) male, mean age 51.6 years. (P<.05 for age and NS for gender)

- Length of stay for the HMII was a mean of 22 days vs. Tx 18 days, 95% (97/102) of HMII discharged alive vs. 97% (57/59) Tx and survival at 1 and 2 years was HMII 77% and 67% vs. Tx 94% and 89%. (P> .05)

- Over the last 5 years there was a significant reduction in average hospital cost for HMII patients of 41% whereas the Tx costs increased by 17%. HMII/Tx hospital cost ratio was 3.14 in 2006 and 1.6 in 2010. Device and donor organ expenses were the largest percentage of costs (52% HMII vs. 33% Tx) followed by operating room fees (5% HMII vs. 13% Tx), pharmacy (8.5% HMII vs. 12% Tx), SICU (6.5% HMII vs. 10% Tx) and intermediate care unit (4% HMII vs. 7.4% Tx).
Sharp Team
“We made it!”