Mechanical Circulatory Support and Advanced Therapy for End Stage Heart Failure

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Medical Director, LVAD Program
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Disclosures

- Medtronic-Consulting, Honoraria, Research
- St Jude-Research, Fellowship Support
- Thoratec- Honoraria
- Actelion, Otsuka- Honoraria
Case Study

• 67 yo referred for HF Care
• Hx of nonischemic cardiomyopathy since 2007
• Intermittent Afib, Defibrillator placed 2009 for syncope
• Cath shows nonobstructive coronary disease
Case Study

• Symptoms: extremely tired, weight gain 20 pounds over past month
• Wife states he has been confused, Na+ 124
• Creatinine had been 1.0 last year, now 1.6
• PE: 84/64, HR 70, JVP 15 cm, lungs bilateral crackles, 1/6 MR, 2+ edema
Case Study-Treatment

- Admitted to hospital, diuresed but could not maintain renal function
- Creatinine fluctuated from 2.5 to 3.5
- Required Dobutamine and Dopamine to stabilize renal fx at 1.7
- Significant neuro/psych issues at first but these improved with inotropes and improving the serum Na+ with Tolvaptan
- LVAD implanted Oct 23, 2012
- Discharged 2 weeks after implant
Heart Failure Hospitalizations

The number of heart failure hospitalizations is increasing in both men and women.

CDC/NCHS: Hospital discharges include patients both living and dead.
AHA Heart and Stroke Statistical Update 2001
Hospitalization for HF is a Sentinel Event

Median hospital LOS: 6 days

National and Regional Trends in Heart Failure Hospitalization and Mortality Rates for Medicare Beneficiaries, 1998-2008

Jersey Chen, MD, MPH
Sharon-Lise T. Normand, PhD
Yun Wang, PhD
Harlan M. Krumholz, MD, SM

Context  It is not known whether recent declines in ischemic heart disease and its risk factors have been accompanied by declines in heart failure (HF) hospitalization and mortality.

Objective  To examine changes in HF hospitalization rate and 1-year mortality rate in the United States, nationally and by state or territory.
<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Admissions</th>
</tr>
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<tbody>
<tr>
<td>1999</td>
<td>1,010,700</td>
</tr>
<tr>
<td>2001</td>
<td>1,026,000</td>
</tr>
<tr>
<td>2003</td>
<td>1,048,100</td>
</tr>
<tr>
<td>2005</td>
<td>953,700</td>
</tr>
<tr>
<td>2007</td>
<td>820,000</td>
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</table>

**US Heart Failure Admissions**
Therapy for Heart Failure

• Medications- useful but sometimes not enough- 1980s-1990s

• Special pacemakers/Defibrillators-not appropriate for all patients 1990s-2000

• Heart Failure Programs-Not widely available, < 20% see a HF specialist

• Left Ventricular Assist Devices 2000-present
Stage A
High risk with no symptoms

Stage B
Structural heart disease, no symptoms

Stage C
Structural disease, previous or current symptoms

Stage D
Refractory symptoms requiring special intervention

Hospice
VAD, transplantation

Inotropes
Aldosterone antagonist, nevirapine
Consider multidisciplinary team
Revascularization, mitral-valve surgery
Cardiac resynchronization if bundle-branch block present
Dietary sodium restriction, diuretics, and digoxin
ACE inhibitors and beta-blockers in all patients
ACE inhibitors or ARBs in all patients; beta-blockers in selected patients
Treat hypertension, diabetes, dyslipidemia; ACE inhibitors or ARBs in some patients
Risk-factor reduction, patient and family education
Stage D
Refractory symptoms requiring special intervention

- Inotropes
- VAD, transplantation
- Hospice
Historical Perspective

- First Human Cardiac Transplant - Christian Barnard, Cape Town, South Africa, 1967
- Only a few centers in the US - Stanford preeminent because of difficulties with immunosuppression
- 1980 - Introduction of cyclosporin, made transplantation immunosuppression an order of magnitude simpler, transplant centers multiply
- Currently >20,000 transplant performed, about 2200 in US per year
Transplant evaluation process

- Referral—how ill is the patient? Are the medications correct
- Psychosocial evaluation
- Medical compliance
- Listing
- Reevaluation
Psychosocial Issues

- How will the patient cope with the surgery and post transplant follow up, steroids?
- Handle frequent clinic visits, biopsies, illnesses, rejection, yearly cath
- Family support, friends necessary
- Needs financial resources
Medical Evaluation

• Any contraindications present
• Is the patient sick enough?
  – Class IIIB, IV, low blood pressure
  – Metabolic exercise test,
  – Max oxygen uptake typically < 14 ml/O2/kg/min

Is the patient too sick?

Fixed pulmonary HTN-now less of a problem
Multiple medical problems, age
Contraindications

- Severe lung disease, FEV <1.3
- Fixed Pulmonary HTN Wood's Units >5.0, tranpulmonary gradient >15
- Hepatitis B, HIV+
- Diabetes with end organ damage
- Peripheral or cerebral vascular disease (relative)
- Parenchymal renal disease, creatinine >2.0
- Amyloidosis (absolute), sarcoidosis (relative)
- Substance abuse, smoking, alcoholism, drug abuse in recent past
NUMBER OF HEART TRANSPLANTS REPORTED BY YEAR

NOTE: This figure includes only the heart transplants that are reported to the ISHLT Transplant Registry. As such, the presented data may not mirror the changes in the number of heart transplants performed worldwide.

ISHLT

AGE DISTRIBUTION OF HEART TRANSPLANT RECIPIENTS BY ERA


**1992-2001 (N = 43,912)**

**2002-6/2010 (N = 31,398)**

% of transplants

`p < 0.0001`

ISHLT

Heart Mate One Device-2000

Diagram showing the placement and function of the Heartmate \textregistered Blood Pump, with connections to the aorta, diaphragm, and external air power supply.
REMATCH Survival

![Survival Rate Graph](image)

**Survival Rate (%) vs Months**

- **LV assist device**
- **Medical therapy**

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>68</th>
<th>38</th>
<th>22</th>
<th>11</th>
<th>5</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV assist device</td>
<td>38</td>
<td>22</td>
<td>11</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Medical therapy</td>
<td>61</td>
<td>27</td>
<td>11</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>
Heart Mate 2
Rapidly Improving Outcomes with LVADs

- Initial HeartMate II Destination Therapy (DT) trial demonstrated significant improvements in outcomes compared to randomized patients with pulsatile LVADs:
  - 68% survival at 1 year
  - 58% survival at 2 years

- Over 500 additional DT patients have been enrolled under continued access protocol (CAP).

References:

Source: Park SJ, AHA 2010
INTERMACS Annual Report Jan 2010 – 88% Survival (n=548)

Implant Dates: June 23, 2006 – March 31, 2009

Primary LVADs: n=1092
- Continuous flow pump, n=548, deaths=51
- Pulsatile pump, n=406, deaths=95

Primary LVAD, left ventricular assist device; BTT, bridge to transplant; BTC, bridge to candidacy

Event: Death (censored at transplant or recovery)

Kirklin JK et al: JHLT 2010
VADs are covered for patients with New York Heart Association (NYHA) Class IV end-stage ventricular heart failure who are not candidates for heart transplantation, and meet all of the following conditions:

a. Have failed to respond to optimal medical management (including beta-blockers, and ACE inhibitors if tolerated) for at least 45 of the last 60 days, or have been balloon pump dependent for 7 days, or IV inotrope dependent for 14 days; and,

b. Have a left ventricular ejection fraction (LVEF) < 25%; and,

c. Have demonstrated functional limitation with a peak oxygen consumption of ≤14 ml/kg/min unless physically unable to perform the test or the test is contra-indicated
Patient Selection for Ventricular Assist Devices

A Moving Target

Leslie W. Miller, MD, Maya Guglin, MD, PhD

*Tampa, Florida*
In San Diego Count
150-250 patients/year
(Current Indications)
Advanced HF
EF<25%
Optimal medical management
CRT if QRS>120 msec
- NYHA III-IV
- Six minute walk <300 m
- Peak VO2<14 mL/kg/min
- Frequent hospital admissions

Heart transplant/LVAD Evaluation

 Eligible for transplant, donor available
Heart Transplant

 Eligible for transplant, donor not available
LVAD as a bridge to transplant

Not eligible for transplant
- Too old
- High BMI
- High PVR
- Recent malignancy
- HIV
- Renal insufficiency
- Hepatic insufficiency

Consider LVAD

Figure 6 Algorithm for Selection of LVAD Candidates
% NYHA Class I or II

6 Minute Walk Distance

LVAD Duration

Percent of patients

n= 126;  55

n= 50;  19

Baseline 3 mo 12 mo 24 mo

Baseline 3 mo 12 mo 24 mo

p<0.001 over time

Both treatments

p<0.001 over time

Both treatments

CF LVAD

PF LVAD

NEJM 2009;361(23):2241-51
Well not really....

DICK CHENEY has no heartbeat. That might sound like the punch line to a political joke
### Table 3  INTERMACS Patient Profiles and Timeframe for Initiating Mechanical Circulatory Support

<table>
<thead>
<tr>
<th>Profile #</th>
<th>Description</th>
<th>Time to MCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>“Crashing and burning”—critical cardiogenic shock.</td>
<td>Within hours</td>
</tr>
<tr>
<td>2</td>
<td>“Progressive decline”—inotrope dependence with continuing deterioration.</td>
<td>Within a few days</td>
</tr>
<tr>
<td>3</td>
<td>“Stable but inotrope dependent”—describes clinical stability on mild-to-moderate doses of intravenous inotropes (patients stable on temporary circulatory support without inotropes are within this profile).</td>
<td>Within a few weeks</td>
</tr>
<tr>
<td>4</td>
<td>“Recurrent advanced heart failure”—“recurrent” rather than “refractory” decompensation.</td>
<td>Within weeks to months</td>
</tr>
<tr>
<td>5</td>
<td>“Exertion intolerant”—describes patients who are comfortable at rest but are exercise intolerant.</td>
<td>Variable</td>
</tr>
<tr>
<td>6</td>
<td>“Exertion limited”—describes a patient who is able to do some mild activity but fatigue results within a few minutes of any meaningful physical exertion.</td>
<td>Variable</td>
</tr>
<tr>
<td>7</td>
<td>“Advanced NYHA III”—describes patients who are clinically stable with a reasonable level of comfortable activity, despite history of previous decompensation that is not recent.</td>
<td>Not a candidate for MCS</td>
</tr>
</tbody>
</table>

INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; MCS, mechanical circulatory support; NYHA, New York Heart Association.
Less acutely ill, ambulatory patients in INTERMACS profiles 4-7 had better survival and reduced length of stay compared to patients who were more acutely ill in profiles 1-3.

*Boyle AJ et al. Clinical outcomes for continuous-flow LVAD patients stratified by pre-operative INTERMACS classification, JHLT, April 2011.*
Survival by Era

Percent Survival

<table>
<thead>
<tr>
<th>Implant dates</th>
<th>n</th>
<th>30 d</th>
<th>6 Mo</th>
<th>12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>a Apr '08 - Oct '10</td>
<td>1496</td>
<td>95%</td>
<td>89%</td>
<td>85%</td>
</tr>
<tr>
<td>b Apr '08 - Aug '08</td>
<td>169</td>
<td>96%</td>
<td>90%</td>
<td>85%</td>
</tr>
<tr>
<td>c Mar '07 - Apr '08</td>
<td>205</td>
<td>95%</td>
<td>86%</td>
<td>80%</td>
</tr>
<tr>
<td>d Mar '05 - Mar '07</td>
<td>281</td>
<td>92%</td>
<td>82%</td>
<td>73%</td>
</tr>
<tr>
<td>e Mar '05 - May '06</td>
<td>133</td>
<td>89%</td>
<td>75%</td>
<td>68%</td>
</tr>
</tbody>
</table>

a John et al STS 2011
b Starling et al JACC (in press)
d Pagani et al JACC 2009
e Miller et al NEJM 2007

John, Naka, Smedira et al: Presented at STS 2011
Current Indications for LVAD

- **Bridge to Transplant** - For patient accepted for cardiac transplant who requires an LVAD to survive or present organ deterioration.

- **Destination Therapy** - For patients who are NYHA Class IV with EF < 25%, who have been on appropriate medical therapy for the last 45 of 60 days. The patient is not currently a transplant candidate.
When to Refer for LVAD

- “Better 5 months to early then 5 minutes too late” Walt Dembitsky
- Worsening renal function, especially when it corrects with dobutamine or milrinone
- Nonresponders to CRT
- Patients who can not tolerate ACEI or BB or need their doses reduced
- 2nd admission for Heart Failure
- NYHA Class III B or IV patients
When to Refer for LVAD

- 5000 HF Deaths a year in San Diego
- Transplant 20-30, LVADs for 300-500?
- Concept of dying FROM Heart Failure vs dying With Heart Failure
- Whose duration and quality of life will be improved markedly by doing a major surgery?
On ACEI vs. CRLimit combined: p < 0.0001
Inotropes vs. no Inotropes: p = 0.0002
Number of patients remaining at 3-month intervals noted on plot.
Sick Patient…CRT or LVAD?

Favors CRT
- LBBB
- Female
- Nonischemic
- Class III
- “Walk in”

Class IV
- Lateral Scar
- Borderline QRS
- RBBB
- “Wheeled in..”
Hospitalization for HF is a Sentinel Event

Median hospital LOS: 6 days

<table>
<thead>
<tr>
<th></th>
<th>CRT</th>
<th>vs</th>
<th>LVAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class III/IV</td>
<td>Class IV some III</td>
<td>EF &lt; 35%</td>
<td>Class IV some III</td>
</tr>
<tr>
<td>EF &lt; 35%</td>
<td>EF &lt; 25%</td>
<td></td>
<td>EF &lt; 25%</td>
</tr>
<tr>
<td>Wide QRS, LBBB best</td>
<td>QRS Irrelevant</td>
<td>65% “response rate”</td>
<td>90+% response rate</td>
</tr>
<tr>
<td>65% “response rate”</td>
<td></td>
<td>Cost 50-60 K</td>
<td>200K</td>
</tr>
<tr>
<td>Cost 50-60 K</td>
<td>Cost 50-60 K</td>
<td>50 meter increase 6MW</td>
<td>200 m increase 6MW</td>
</tr>
<tr>
<td>50 meter increase 6MW</td>
<td>50 meter increase 6MW</td>
<td>Some Class IV too sick to benefit</td>
<td>Class IV benefit</td>
</tr>
<tr>
<td>Some Class IV too sick to benefit</td>
<td></td>
<td>Simple implant</td>
<td>Major surgery</td>
</tr>
</tbody>
</table>

Much easier to “pull the trigger” for CRT but that is sometimes a very bad decision if a patient has CRT for a month before the LVAD goes in…”
The Future

- LVADs that weight 3 ounces
- Totally implanted LVADs 2015?
- LVADs for NYHA Class III patients
- Percutaneously implanted LVADs
- LVADs coupled with stem cell/gene therapy to promote cardiac recovery
- Implanted hemodynamic monitors
HeartWare Device

- Currently approved for Bridge to Transplant
- Several Thousand HeartWare Pumps Implanted LVADs for NYHA
- Per
- LVADs coupled with stem cell/gene therapy to promote cardiac recovery
- Implanted hemodynamic monitors
HeartWare ventricular assist system for bridge to transplant: Combined results of the bridge to transplant and continued access protocol trial

Mark S. Slaughter, MD, a Francis D. Pagani, MD, PhD, b Edwin C. McGee, MD, c Emma J. Birks, MD, a William G. Cotts, MD, c Igor Gregoric, MD, d O. Howard Frazier, MD, d Timothy Icenogle, MD, e Samer S. Najjar, MD, f Steven W. Boyce, MD, f Michael A. Acker, MD, g Ranjit John, MD, h David R. Hathaway, MD, i Kevin B. Najarian, MS, i Keith D. Aaronson, MD, MS b

Heart Lung Transplant 2013;32:675–683
Clinical Results from HeartWare Registry

- 88.5% Transplant or Myocardial Recovery or Alive (original device in place)
- 67.1% Alive (original device in place)
- 21.4% Transplant or Myocardial Recovery (original device in place)
- 6.9% Death (original device in place)
- 4.5% Device Exchange
<table>
<thead>
<tr>
<th>Events</th>
<th>Overall (PY = 305.9) (N = 332)</th>
<th>Patients affected</th>
<th>Events</th>
<th>Event rate (PPY)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>% (n)</td>
<td>(n)</td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Requiring re-operation</td>
<td>14.8 (49)</td>
<td>57</td>
<td>0.19</td>
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<tr>
<td>Gastrointestinal</td>
<td>12.7 (42)</td>
<td>82</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Driveline exit site</td>
<td>16.9 (56)</td>
<td>75</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>17.2 (57)</td>
<td>70</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular</td>
<td>20.8 (69)</td>
<td>93</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Supraventricular</td>
<td>21.4 (71)</td>
<td>90</td>
<td>0.29</td>
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<tr>
<td>Renal dysfunction</td>
<td>9.6 (32)</td>
<td>39</td>
<td>0.13</td>
<td></td>
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<tr>
<td>Hepatic dysfunction</td>
<td>4.8 (16)</td>
<td>16</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Respiratory dysfunction</td>
<td>22.0 (73)</td>
<td>96</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>Hemolysis(^a)</td>
<td>1.2 (4)</td>
<td>5</td>
<td>0.02</td>
<td></td>
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<tr>
<td>Device exchanges</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Procedure-related</td>
<td>2.1 (7)</td>
<td>7</td>
<td>0.02</td>
<td></td>
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<tr>
<td>Suspected thrombus</td>
<td>4.2 (14)</td>
<td>15</td>
<td>0.05</td>
<td></td>
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<tr>
<td>Other</td>
<td>2.4 (8)</td>
<td>8</td>
<td>0.03</td>
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<td>Neurologic events</td>
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<td>CVA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>7.5 (25)</td>
<td>28</td>
<td>0.09</td>
<td></td>
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<tr>
<td>Hemorrhagic</td>
<td>7.8 (26)</td>
<td>28</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>4.8 (16)</td>
<td>17</td>
<td>0.06</td>
<td></td>
</tr>
</tbody>
</table>
Drive line infection

• Less of a problem with better dressing now
• Trauma from dropped controller can set this up
• Mild inflammation, no fever, without discharge, can be treated with oral antibiotics
• With drainage and/or fever - need to be admitted, cultured
Drive line infection

- 11 PM Management....
- Dressing needs to be removed, patient family can help
- Culture drainage site, supplies on 6W
- Is there evidence of deep infection. Tenderness, marked swelling? CT scan
- Blood cultures
- ID consult, start empiric antibiotics (listed in LVAD box 6W)
- Nurse on 6W can redress site
GI Bleeding

• Most patients go home on warfarin and low dose ASA

• Goal INR 2-2.5

• Transfuse as necessary

• Bleeding is very similar to patients with AS
  – Ulcers, Gastritis, AVM

• Ok to stop ASA/Warfarin if they are bleeding and to give FFP if you need to

• Call GI, usually scope in AM with capsule endoscopy

• Some patients on no anticoagulation
Pump Thrombosis

• Might call in with “high power, > 10 watts, heart failure
• “brown urine” -hemolysis
• Admit, look at power records with patients bring, in
download from device, Flows will be “+++” but this is an
artifact
• Check INR, LDH ( bad number about1500),
• Haptoglin always low, not helpful
• Plasma free Hemoglobin > 40
• Restore anticoagulation, call surgeon, stat Echo ( LV may
be be dilated)
Original Article

Unexpected Abrupt Increase in Left Ventricular Assist Device Thrombosis

Randall C. Starling, M.D., M.P.H., Nader Moazami, M.D., Scott C. Silvestry, M.D., Gregory Ewald, M.D., Joseph G. Rogers, M.D., Carmelo A. Milano, M.D., J. Eduardo Rame, M.D., Michael A. Acker, M.D., Eugene H. Blackstone, M.D., John Ehrlinger, Ph.D., Lucy Thuita, M.S., Maria M. Mountis, D.O., Edward G. Soltesz, M.D., M.P.H., Bruce W. Lytle, M.D., and Nicholas G. Smedira, M.D.

N Engl J Med
Volume 370(1):33-40
January 2, 2014
Study Overview

• The HeartMate II left ventricular assist device is widely used to support failing myocardium.

• In early 2011, one large center noticed an increasing frequency of thrombosis with this LVAD.

• It was confirmed at three other centers, but the cause has not been identified.
Overall Occurrence of Confirmed Pump Thrombosis at 3 Months after HeartMate II Implantation.

Occurrence and Incidence of Confirmed Pump Thrombosis Stratified According to Implantation Date.

Elevated Lactate Dehydrogenase (LDH) Levels within 3 Months after HeartMate II Implantation.

LDH Values before Confirmed Pump Thrombosis.


The Future

- Smaller, fully implanted devices
- Less anticoagulation, more pulsatile, less bleeding?
- Percutaneous implantation?