Using VADs as a Platform to Promote Heart Failure Recovery Remission

Disclosures: None

My sincere thanks to Stavros Drakos
I am slightly less thankful for Nir Uriel

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For Dr. Frazier
Reverse Remodeling and Cardiac “Recovery”

The Failing Human Heart Can Improve

- Toxic Insults
- Alcohol
- Chemo-therapy
- Peripartum
- Inflammation
- ALM
- Beta Blockade
- CPAP
- Neurohormonal Activation
- RAAS Blockage
- LVAD
- Reverse LV Remodeling
- Abnormal Energetics
- Tachycardia
- Thyroid Disease
- Re-vascularization
- CRT
- CSD
- AVR
- MVR
- Hemodynamic Overload

Hellawell & Margulies, Cardiovascular Ther 2012; 20:172
Excess Load/Wall Stress Drives Cardiac Remodeling and HF Progression

Hypothesis:
Defining Recovery/Remission

“A reversal of the pathological state of the myocardium with significant improvement in cardiac structure and function sufficient to achieve a sustained remission from recurrent heart failure events.”
VAD Explantation Rates in INTERMACS

INTERMACS - Competing Outcomes for Continuous Flow LVADs (without RVAD implant at time of LVAD operation)
Primary Prospective Implants: June 23, 2006 to September 30, 2014

Proportion of Patients

Months after Device Implant

- Alive (device still in place)
- Death (before transplant)
- Transplant
- Explanted (recovery)

19.8% 17.6% 62.0%
INTERMACS – Rates of Myocardial Functional Improvement

Myocardial Recovery in Patients Receiving Contemporary Left Ventricular Assist Devices
Results From the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)

Veli K. Topkara, MD, MSc; A. Reshad Garan, MD; Barry Fine, MD, PhD; Amantine F. Gooneran-Fermont, PhD; Alexander Breskin, BS, MPH; Barbara Caglioni, RN, MSN; Melana Yuzefpolskaya, MD; Koji Takeda, MD, PhD; Hiroo Takayama, MD, PhD; Donna M. Mancini, MD; Yoshihumi Naka, MD, PhD; Paolo C. Colombo, MD

13,454 CF LVAD

Device Explantation for Myocardial Recovery
1.2% (n=163)

Device NOT explanted for myocardial recovery
98.8% (n=13,291)

8,805 pts with follow up LVEF Data

No LVEF improvement on LVAD support
91.4% (n=8,044)

LVEF improvement to >40% on LVAD support
8.6% (n=761)

Topkara, V. et al. Circ HF. 2016
Cardiac Recovery Rates **With** Vs. **Without**
Myocardial Function ‘Monitoring Screening Tools’

**Prospective Studies**

LVAD Recovery - Explantation

- ~15%

Adapted from Drakos S & Mehra M. JHLT 2016
Utah Cardiac Recovery Program (UCAR)

I-CARS Score: INTERMACS-Derived Recovery Prediction Score To Guide Pre-VAD Patient Selection

**TABLE 4**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Age &lt;50 yr</th>
<th>Nonischemic</th>
<th>Time from discharge &lt;2 yrs</th>
<th>Implanted</th>
<th>Creatinine &gt;1.5</th>
<th>LVEF &lt;60%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coefficient</td>
<td>0.65</td>
<td>1.54</td>
<td>0.78</td>
<td>1.30</td>
<td>0.68</td>
<td>0.59</td>
</tr>
<tr>
<td>Score</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**INTERMACS Cohort**

- High Probability (I-CARS ≥7)
  - BTR Strategy: 24.5%
  - Non-BTR Strategy: 8.1%

- Intermediate Probability (I-CARS 4-6)
  - BTR Strategy: 4.8%
  - Non-BTR Strategy: 1.3%

- Low Probability (I-CARS ≤3)
  - BTR Strategy: 0%
  - Non-BTR Strategy: 0.2%

**UCAR Cohort**

- 38.9%
- 6.3%
- 0%
Duration of Unloading Required for Response May Offer Clues For Potential Mechanisms

Prospective Evaluation - 80 LVAD All Comers

Wever-Pinzon, Drakos. J Am Coll Cardiol 2013
Understanding Mechanical Unloading and Recovery

Ongoing Research Targets

1. Structure-function correlation
2. Impact of HF etiology
3. Time from initial insult (‘HF history duration’)
4. Extent of pre-LVAD remodeling
5. Type of unloading: pulsatile vs. continuous vs. counterpulsation
6. Targeted adjuvant therapies
7. Progress evaluation protocols
8. Optimal duration of unloading
9. Determinants of myocardial recovery
Current Strategy to Promote Clinical LV Functional Recovery following VAD

RAMP study
- Maximally unload LV
- Maintain septum in midline
- AV opening controversial

Avoid over-pumping
First 24-48 Hours

VAD Therapy and Monitoring
- HF meds
- Serial echo
- Intermittent RAMP studies

Prior to discharge
Months

LV recovery detected:
- Differential loading conditions
- Exercise
- Hemodynamics
- Examine contractile reserve

Weeks

Explant
# How Should a VAD be Weaned?

<table>
<thead>
<tr>
<th>Maximal Medical Therapy</th>
<th>Labs</th>
<th>Echo</th>
<th>Exercise</th>
<th>Hemodynamics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berlin&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Anti-β&lt;sub&gt;1&lt;/sub&gt; receptor Ab</td>
<td>On and off support. Success=EF &gt; 45% and LVEDd ≤ 55 mm. No DSE</td>
<td>NA</td>
<td>RHC</td>
</tr>
<tr>
<td>LVAD Working Group&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Not mandated by protocol</td>
<td>NA</td>
<td>Full and reduced support. If EF &gt; 40→ DSE</td>
<td>CPX</td>
</tr>
<tr>
<td>Birks&lt;sup&gt;3&lt;/sup&gt;</td>
<td>NA</td>
<td>LVEDD &lt; 60 at reduced support start clenbuterol.</td>
<td>6MWD &gt; 450 m</td>
<td>RHC, LHC</td>
</tr>
<tr>
<td>Maybaum&lt;sup&gt;4&lt;/sup&gt;</td>
<td>NA</td>
<td>Full and reduced support</td>
<td>CPX with full support and exercise echo with VAD weaned</td>
<td>RHC with full support and VAD reduced then exercise RHC with VAD weaned</td>
</tr>
</tbody>
</table>

2. Circulation 2007;115:2497-2505
3. Circulation 2011; 123:381-90
Facilitated Myocardial Recovery: Medications

Continuous Flow VAD
Are Heart Failure Medications Beneficial to Promote Remodeling/Recovery?

LVAD alone (no HF Meds) significantly improves the structure & function of the unloaded heart.

LVAD + All HF Meds appears to exert incremental anti-remodeling effects.
Facilitated Myocardial Recovery: Mesenchymal Precursor Cells
Is Recovery Sustained?

Instead of Explant, Would It Have Been Better To Get Transplanted?

Long-term Survival Post-LVAD Weaning Vs. Post-Transplant

* p = ns

BTR post explant (n = 40)
BTT post transplant (n = 52)
Current Needs in Myocardial Recovery Research

- Development of large animal models of chronic heart failure that replicate human disease
  - Identification of pathways critical to recovery
- Evaluation of strategies to reload the heart
- Identification of markers that predict durable myocardial function following mechanical support
- Define the role of adjunctive therapies during mechanical support that promote recovery