Small Platform Catheter-Based Left Ventricular Assist Device Support Suppresses Cardioprotective Beta Arrestin-Mediated Signal Transduction

Keshava Rajagopal, MD PhD, Progyaparamita Saha, PhD, Isa Mohammed, BS, Pablo G. Sanchez, MD PhD, Tieluo Li, MD, Zhongjun J. Wu, PhD, Bartley P. Griffith, MD

University of Maryland School of Medicine and Medical Center

AATS 95th Annual Meeting
Disclosures

• None
Post-Myocardial Infarction Left Ventricular Systolic Dysfunction

• A subset of acute myocardial infarction (MI) involves a large territory
• This MI subset commonly develops LV systolic dysfunction, within which heart failure (HF) or overt cardiogenic shock may manifest in the acute setting
  - Likelihood of HF α territory of MI, but also α time
• **Coronary arterial reperfusion** is the therapeutic cornerstone
• ~40% of **all** patients with MI **eventually** develop LV systolic dysfunction: acute -> persistent
  - Delayed reperfusion
  - Failure to achieve reperfusion
  - Reperfusion not attempted
  - “Reperfusion injury”: myocardial stunning ± MI extension
  - Pathologic LV remodeling <-> progressive LV dysfunction -> clinical HF
Short-term LV mechanical circulatory support in the treatment of large territory MI

• LV mechanical circulatory support (MCS) is well-established in the treatment of both acute and chronic HF

• Provides support or replacement of LV function
  - Improved cardiac output with…
  - Reduced LV diastolic volume and pressure

• However, while provision of improved $Q_s$ clearly occurs with MCS, it is less clear whether…

• LV MCS can truly reverse LV systolic dysfunction (independent of HF medical therapy), and whether…

• LV MCS at the time of an acute insult can prevent the development or progression of LV systolic dysfunction
7-transmembrane (7-TMR)/G protein-coupled (GPCR) receptors in the regulation of cardiac biology and function

From Rajagopal, K et al. J Clin Invest 2005 115(11): 2971-4
Experimental Model System

- Ovine MI without reperfusion: permanent ligation of mid-left anterior descending (LAD) coronary artery
- Placement of Impella 5.0 LVAD via descending thoracic aortic side-graft, advanced retrograde
- Extent of support: set at P2-P4, ~50% cardiac output support
- Duration of support: 2 weeks
- LVAD removed; animals followed for 10 additional weeks
- Animals did not receive adjunctive HF medical therapy
β-arrestin levels reduce with MI; Re-normalization with LVAD support
Levels of ubiquitinated β-arrestin1/2 reduce with LVAD support
β-arrestin1/2 interactions with the EGFR increase with MI; Attenuation with LVAD support
Akt activation is reduced with LVAD support
ERK1/2 activation is reduced with LVAD support
Homogeneous mRNA preparation for RNA sequencing analysis
Relative activation of specific target genes in the MI-adjacent zone; re-normalization (loss of regional heterogeneity) with LVAD support

<table>
<thead>
<tr>
<th>Gene</th>
<th>MI_A vs Control</th>
<th>MI_A vs MI_R</th>
<th>MI_A vs LVAD_A</th>
<th>LVAD_A vs LVAD_R</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPPA</td>
<td>1.779</td>
<td>4.674</td>
<td>4.408</td>
<td>-</td>
</tr>
<tr>
<td>F2RL1</td>
<td>3.248</td>
<td>2.185</td>
<td>2.713</td>
<td>-</td>
</tr>
<tr>
<td>SPP1</td>
<td>-</td>
<td>1.542</td>
<td>2.071</td>
<td>-</td>
</tr>
<tr>
<td>MYL4</td>
<td>-</td>
<td>3.007</td>
<td>1.247</td>
<td>-</td>
</tr>
<tr>
<td>MLY9</td>
<td>-</td>
<td>1.045</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MYL1</td>
<td>-</td>
<td>3.098</td>
<td>3.421</td>
<td>-</td>
</tr>
<tr>
<td>MYL7</td>
<td>1.413</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

INGENIUY PATHWAY ANALYSIS

These findings are most consistent with alterations in signal transduction through the angiotensin II type 1 (AT₁R) and α₁-adrenergic (α₁-AR) receptors.
Conclusions

• In this ovine experimental model system of MI, small platform catheter-based LVAD support was previously shown to attenuate pathologic remodeling and progressive LV systolic dysfunction

• We now demonstrate both beneficial and deleterious effects of LVAD support/LV unloading on cardiomyocyte signal transduction
  - Beneficial: normalization of MI-adjacent zone 7-TMR/GPCR signaling networks and downstream genetic targets
  - Deleterious: inhibition of β-arrestin-mediated signaling and downstream effector activation

• Implications
  - Extent and duration of MCS
  - Targeted “biased ligand” HF medical therapies

• Limitations/caveats
  - MI without reperfusion
  - Lack of adjunctive medical therapy