Complications of Contemporary Continuous Flow LVAD Therapy

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Disclosures

• Thoratec Inc Medical Advisory Board
• Chair, AEC DuraHeart BTT Trial
• DSMB, Sunshine Heart Trial
• Site PI for HMII, Heartware, ROADMAP, REVIVE-IT Trials
VAD Classification

By Location:
- Intracorporeal
- Paracorporeal
- Extracorporeal
- L, R, Bi, TAH

By Mechanism:
- Pulsatile flow
- Continuous flow
  - axial
  - centrifugal

By Intention:
- Bridge to transplant
- Destination therapy
- Bridge to candidacy
- Bridge to decision

By Duration of Support:
- Short term (temporary)
- Mid term
- Long-term
VAD Classification

By Location: Intracorporeal

By Mechanism: Continuous flow, axial, centrifugal

By Intention: Bridge to transplant, Destination therapy, Bridge to candidacy

By Duration of Support: Long-term
Use of a Continuous-Flow Device in Patients Awaiting Heart Transplantation

Leslie W. Miller, M.D., Francis D. Pagani, M.D., Ph.D., Stuart D. Russell, M.D., Ranjit John, M.D., Andrew J. Boyle, M.D., Keith D. Aaronson, M.D., John V. Conte, M.D., Yoshifumi Naka, M.D., Donna Mancini, M.D., Reynolds M. Delgado, M.D., Thomas E. MacGillivray, M.D., David J. Farrar, Ph.D., for the HeartMate II Investigators

Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device

Mark S. Slaughter, M.D., Joseph G. Rogers, M.D., Carmelo A. Milano, M.D., Stuart D. Russell, M.D., John V. Conte, M.D., David Feldman, M.D., Ph.D., Benjamin Sun, M.D., Antone J. Tatooles, M.D., Reynolds M. Delgado, III, M.D., James W. Long, M.D., Ph.D., Thomas C. Wozniak, M.D., Waqas Ghumman, M.D., David J. Farrar, Ph.D., and O. Howard Frazier, M.D., for the HeartMate II Investigators*
Use of an Intrapericardial, Continuous-Flow, Centrifugal Pump in Patients Awaiting Heart Transplantation

What Have We Learned?

- Humans tolerate nonpulsatile flow
- CFLVAD superior to pulsatile technology:
  - Less infection
  - More reliable
  - Better QOL - noise, battery life
  - Easier surgery, less bleeding
- Here to stay but not final iteration
Traditional Complications

- Early
  - Bleeding
    - Most common complication
    - Decreasing incidence
  - Right Heart Failure
    - Most feared complication
    - Unpredictable
    - Defined as need for RVAD or inotropes for > 2 weeks
    - Incidence about 7%
Traditional Complications

- **Late**
  - **Infection**
    - Pump related or unrelated
    - Driveline exit site most common
    - Pump infection rare
  - **Thromboembolism**
    - Stroke
    - Peripheral embolism
  - **Device malfunction/failure**
    - Extremely rare
New Complications

- Not seen with any frequency in previous generation (pulsatile) devices
- Iatrogenic
- Unpredictable and unexplained
  - GI Bleeding
  - Pump Thrombus
  - Aortic Insufficiency
CFLVAD and GI Bleeding
Common and significant medical problem
- Mortality UGIB: 3.5-13%
- Mortality LGIB: 1 - 5%
- Morbidities and costs associated with:
  - Readmission
  - Transfusion
  - Diagnostic imaging/Rx
- Asa and coumadin independent risk factors for both UGIB and LGIB
“...I have seen at least 10 patients with calcific aortic stenosis who had massive gastrointestinal bleeding for which I could discover no cause, ....hoping that a letter to a prominent journal might elicit some response about the matter”

Dr. Edward Heyde, 1937
Letter to New England Journal of Medicine
Heyde’s Syndrome

Aortic Stenosis

Bowel AVM
HYPOTHESIS

Aortic stenosis and bleeding gastrointestinal angiodysplasia: is acquired von Willebrand's disease the link?

T.E. Warkentin, MD, D.G. Morgan, MD, J.C. Moore, ART
Mediates plt adhesion under high shear stress conditions

Impaired thrombus generation
AS, GIB, aVWD and reversal with AVR

Figure 2. Analysis of Highest-Molecular-Weight Von Willebrand Factor Multimers in One Patient, before and 3 Hours, 24 Hours, and Seven Days after Valvular Replacement.

Vincentelli et al. NEJM 2003;349:343-9
LVADs and GIB

Gastrointestinal Bleeding From Arteriovenous Malformations in Patients Supported by the Jarvik 2000 Axial-Flow Left Ventricular Assist Device

George V. Letsou, MD, a Nyma Shah, BS, b Igor D. Gregoric, MD, b Timothy J. Myers, BS, b Reynolds Delgado, MD, c and O. H. Frazier, MD b.d

- First description, 3 pts
- 2 patients resolved after OHT
- 1 patient died MSOF
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<th>Author</th>
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Heyde’s Syndrome $\approx$ CF LVAD Physiology

- Reduced Pulse Pressure
- Shear Stress

Aortic Stenosis

Small Bowel AVM
Can Axial Flow Pumps Cause Acquired avWD?
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Not the Whole Story...

- All CFVAD pts develop aVWS
- Most CFVAD recipients do not have GIB !
- Many CFVADs pts that bleed have conventional GIB sites…
- Clearly, other factors must explain the high incidence (eg., age)
- Does non-pulsatile flow cause AVMs?….or do AVMs pre-exist and in the presence of low pulsatility, shear stress and antithr Rx, GIB occurs?
GIB (and other mucosal bleeding) is a significant AE following CFLVAD support

Loss of HMW vWF is universal

AVM frequent etiology of GIB

Other factors must play a role in the genesis of GIB

Dx may require unconventional imaging (Pillcam, DBE)

Reinitiation of anticoag/antiplt is done cautiously

Most common cause of readmissions after successful LVAD implant
Role of speed reduction to induce aortic valve opening and pulsatility unclear

Adjunctive Rxs like estrogen, octreotide unclear - thrombotic potential (pump thrombus)

More data needed to elucidate other potential factors

aVWD likely a contributor to the process
  - GIB & avWD ceases after AVR despite persistence of AVMs!
CFLVAD and Aortic Insufficiency
Prevalence of de novo aortic insufficiency during long-term support with left ventricular assist devices

Sang-Woo Pak, MD, a Nir Uriel, MD, b Hiroo Takayama, MD, PhD, a Sarah Cappleman, BA, a Robert Song, BS, a Paolo C. Colombo, MD, b Sandy Charles, MD, b Donna Mancini, MD, b Linda Gillam, MD, b Yoshifumi Naka, MD, PhD, a and Ulrich P. Jorde, MD b

The Development of Aortic Insufficiency in Left Ventricular Assist Device-Supported Patients

Jennifer Cowger, MD, MS; Francis D. Pagani, MD, PhD; Jonathan W. Haft, MD; Matthew A. Romano, MD; Keith D. Aaronson, MD, MS; Theodore J. Koliaps, MD
LVAD and AI: Flow Paradox

LVAD pumps blood into the aorta (to the body)

Blood from the left ventricle enters the LVAD

= High VAD Flow
Low Systemic Perfusion
Questions That Need Answers

• How much preop AI is “too much”?  
• How do you manage “too much” AI?:  
• What to do if patient develops AI post-op?
“Too Much” AI

- Expert consensus is > mild (1+) AI should be addressed
- Important: AI needs to be reevaluated in OR while patient on CPB - elevated LVEDP may “diminish” true AI
Options for AI

Repair
- Park Stitch
- Floppy valve leaflet
- Aortic valve

Close
- Suture
- Patch

Replace
- Bioprosthesi
## Imperfect Options for AI

<table>
<thead>
<tr>
<th>Repair</th>
<th>Close</th>
<th>Replace</th>
</tr>
</thead>
<tbody>
<tr>
<td>• May fall apart</td>
<td>• No “out” if pump fails</td>
<td>• Valve typically fuses and closes</td>
</tr>
<tr>
<td>• Recurrent AI</td>
<td>• Limited exercise because native valve doesn’t open</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No recovery option</td>
<td></td>
</tr>
</tbody>
</table>
Post op AI

- Difficult situation, particularly in DT patient
- Medical management (BP)
- Intervention needed if Sx
- Options include:
  - Reoperation and AVR
  - Revisit transplant candidacy
  - Non conventional - TAVR, amplatzer plug
CFLVAD and Pump Thrombus
Why Talk About Pump Thrombus?

- Known and potentially fatal complication
- Death knell of MicroMed-DeBakey VAD
- Increasing “noise” among clinicians and VAD coordinators
- Described for both available CF LVADs
- No recommendations regarding Dx and management
LVADs and Thrombosis

- Hemocompatibility: max blood flow; reduce stasis/hemolysis/turbulence/retrograde flow
- LVADs activate coagulation and endothelial systems
- Blood contacting surfaces play role in thrombotic complications and mandate anti-plt and anti-coag Rxs
Thrombus in Literature

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Device</th>
<th># Pts</th>
<th>POD</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller L et al.</td>
<td>2007</td>
<td>MicroMed</td>
<td>8</td>
<td>53-430d</td>
<td>rTPA, 100mg IV</td>
<td>Full resolution, minor epistaxis, no bleeding complication</td>
</tr>
<tr>
<td>Delgado</td>
<td>2005</td>
<td>Jarvik 2000</td>
<td>2</td>
<td>9d, 116d</td>
<td>Intracavitary rTPA 1mg/min</td>
<td>1 died from complications on pump thrombosis</td>
</tr>
<tr>
<td>Studer</td>
<td>2006</td>
<td>DeBakey Child</td>
<td>1</td>
<td>1 month</td>
<td>Plavix 150 mg</td>
<td>Recurrent thrombus successfully treated with plavix 150mg</td>
</tr>
<tr>
<td>Tschirkov</td>
<td>2007</td>
<td>INCOR</td>
<td>1</td>
<td>155d</td>
<td>Intracavitary reteplase</td>
<td>Full resolution</td>
</tr>
<tr>
<td>Jahanyar</td>
<td>2007</td>
<td>MicroMed</td>
<td>1</td>
<td>110d</td>
<td>TPA IV</td>
<td>3 recurrent episodes, all resolved with TPA</td>
</tr>
<tr>
<td>Hayes</td>
<td>2007</td>
<td>Jarvik 2000</td>
<td>1</td>
<td>39d</td>
<td>IV tenecteplase</td>
<td>Full resolution</td>
</tr>
<tr>
<td>Blais</td>
<td>2008</td>
<td>HMII</td>
<td>1</td>
<td>196d</td>
<td>Integrelin, Heparin</td>
<td>Recurrence successfully treated with argatroban</td>
</tr>
<tr>
<td>Thomas</td>
<td>2008</td>
<td>HVAD</td>
<td>1</td>
<td>140d</td>
<td>Hep/Plavix/Tirofiban</td>
<td>Recurrence/transplantation</td>
</tr>
<tr>
<td>Meyer</td>
<td>2008</td>
<td>HMII</td>
<td>1</td>
<td>2 months</td>
<td>Hirudin</td>
<td>Full resolution</td>
</tr>
<tr>
<td>Bhamidipati</td>
<td>2010</td>
<td>HMII</td>
<td>1</td>
<td>18d</td>
<td>Pump exchange</td>
<td>Full resolution</td>
</tr>
<tr>
<td>Kiernan</td>
<td>2011</td>
<td>HVAD</td>
<td>1</td>
<td>5 months</td>
<td>Intracavitary alteplase</td>
<td>Full resolution</td>
</tr>
<tr>
<td>Paluszkiewicz</td>
<td>2011</td>
<td>HMII</td>
<td>1</td>
<td>1 month</td>
<td>Thrombolysis</td>
<td>Full resolution</td>
</tr>
<tr>
<td>Bashir</td>
<td>2011</td>
<td>HMII</td>
<td>1</td>
<td>3d</td>
<td>Pump exchange</td>
<td>Full resolution</td>
</tr>
<tr>
<td>Alsaawi</td>
<td>2012</td>
<td>Heartware</td>
<td>6</td>
<td>ND</td>
<td>Pump exchange (6)</td>
<td>Full resolution</td>
</tr>
<tr>
<td>Mishkin</td>
<td>2012</td>
<td>HMII</td>
<td>1</td>
<td>2 months</td>
<td>Disconnected pump</td>
<td>Awaiting transplant</td>
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<tr>
<td>Al-Quthami</td>
<td>2012</td>
<td>HMII</td>
<td>2</td>
<td>33, 42 days</td>
<td>Hep/Eptifibatide</td>
<td>Full resolution</td>
</tr>
</tbody>
</table>

- Miller L et al. NEJM 2007;357:885-97: n=2 (2%); 0.03 ERPPY
- Pagani F et al. JACC 2009;54:312-21: n=4 (1%); 0.02 ERPPY
- Boyle A et al. JHLT 2009;28:881-7: n=3 (0.9%); 0.014 ERPPY
- Slaughter M et al. NEJM 2009;361:2241-9: n=5 (4%); 0.02 ERPPY
- Aaronson K et al. Circ 2012;125:3191-200: n=3 (2.1%); 0.03 ERPPY
Predisposing Factors

Patient Related

- Atrial fibrillation
- Pre-existent LV thrombus/trabeculation
- Mechanical prostheses
- Infection
- Hypercoagulable state
- Non-compliance
Predisposing Factors

**Pump Related**

- Heat generated by spinning pump
- Blood-contacting surface interactions
- Sheer stress induced platelet activation
- Regions of flow stasis
- Inflow malposition
  - Change over time (weight changes)
- Outflow graft kink/compression
  - Bleed
  -Disconnected graft protector w impingement (HM2)
- Positional
Predisposing Factors

Management Related

- Subtherapeutic INR
- Suboptimal or absent antiplatelet Rx
- Inflow cannula malposition at implant
- Infection management
- Low flow due to low pump speeds:
  - Induce pulsatility: manage GIB, prevent AI
  - Recovery
  - Suboptimal HTN management
Signs/Symptoms

• Asymptomatic:
  – Transient or sustained power elevations
  – Isolated LDH elevations

• Symptomatic:
  – CHF (left- ± right-sided)
  – Hemolysis (pfhgb, bilis, LDH, dark urine)
Diagnostic Evaluation

- Imaging
  - CXR
  - CTA
  - Echo
    - Usual windows
    - Ramp studies
  - LHC: V-gram, Outflow-gram
- Hemodynamics: RHC
Imaging - X Ray

- Assess Inflow and Outflow (HMII)

- Suboptimal inflow angle
- Detached outflow protector
Imaging - CT(A)

Mishkin et al. Circ Heart Fail 2012;5:e27-9
Imaging - CT(A)

Inflow Thrombus

Malpositioned Inflow
Imaging - Echo

- LV thrombus
- Dilated LV
- Mitral regurgitation
- Aortic valve opening
- Failure to reduce LVEDD with increase RPMs - Ramp study
Imaging - Echo

Laterally displaced inflow
Stepwise increase in LVAD speed with Echo monitoring of LVEDD, PI, power, MR, AI and RVSP

Uriel N, et al. JACC In press 2012
RHC/LHC

- RHC: elevated PCWP and right sided pressures
- LHC: dye into LV cavity to assess outflow graft filling or direct dye into outflow via retrograde catheter
Imaging - Pathology
38 yo woman, non compliant w coumadin, red heart alarms

Inflow thrombus

Outflow graft thrombus

Outflow thrombus
Thrombosis Workgroup

- Clinicians interested in addressing pump thrombus/power spikes seen in last 24 mo among recipients of HMII

- Facilitated by Thoratec Inc.

- Goal: algorithm for pump thrombus evaluation and management
Definitions:
1. **Power Elevations**: 
   - Sustained (>24hrs) Power > 10W; or 
   - Sustained (> 24hrs) Power Increase > 2W from Baseline
2. **Isolated LDH Rise**: 
   - LDH > 3x Upper Limit of Normal (ULN)
3. **Hemolysis**: 
   - Clinical Diagnosis; or 
   - LDH > 3x ULN and pfHgb > 40
4. **Resolved**: Normal Powers, Normal LDHs, Sufficient LV Unloading, and No Clinical Evidence of Hemolysis

**Abbreviations**: LV, Left Ventricle; LDH, Lactate Dehydrogenase; pfHgb, Plasma-free Hemoglobin; RHC, Right Heart Cath; CXR, Chest X Ray

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**Figure 1**

- **Power Elevations**: Early or Late?
  - Early
    - Consider Echocardiogram (± Pump Speed Changes)
  - Late
    - LV Unloading?
      - Yes
        - Consider Echocardiogram (± Pump Speed Changes)
      - No
        - Close Follow Up

- **Isolated LDH Rise**: Early or Late?
  - Early
    - Optimize Anticoagulation
    - Check Serum Indices of Hemolysis
  - Late
    - LV Unloading?
      - Yes
        - Consider Echocardiogram (± Pump Speed Changes)
      - No
        - LV Unloading?
          - Yes
            - Increase INR
            - ASA 325 mg
            - Consider a Second Anti-platelet Agent
          - No
            - Close Follow Up

- **Evidence of Hemolysis**: Hemolysis?
  - Yes
    - Consider Echocardiogram (± Pump Speed Changes)
  - No
    - LV Unloading?
      - Yes
        - Chest CT Angiogram
      - No
        - Inflow Cannula Malposition or Outflow Graft Obstruction?
          - Yes
            - Consider Surgical Correction
          - No
            - LV Unloading?
              - Yes
                - Consider: Direct Thrombin Inhibitors
              - No
                - ICU – Add Inotropes, Diuresis as Needed

- **New CHF Symptoms**: LV Unloading?
  - Yes
  - Hemolysis?
    - Yes
      - Consider Echocardiogram (± Pump Speed Changes), Consider RHC
      - Monitor LDH, pfHgb, indirect bilirubin, Haptoglobin, Renal Function
    - No
      - Evaluate Other Causes of CHF and Hemolysis
  - No
    - Resolved?
      - Yes
        - Consider: Direct Thrombin Inhibitors
      - No
        - Pump Exchange or Urgent Transplantation or Explant for Recovery

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Close Follow Up
Summary

• Pump thrombus is a dreaded complication of CF LVAD technology.
• Assessment of modifiable risk factors is essential (afib, mech valve, etc).
• Imaging and functional studies (ramp) can confirm diagnosis.
• A consensus algorithm can serve as a launching point when confronted with suspected thrombus.
THANK YOU
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