Mechanical Circulatory Support:  
*Past, present and future*  

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Chief, Cardiac and Thoracic Surgery
At Risk for Heart Failure

Stage A
At high risk for HF but without structural heart disease or symptoms of HF.

- e.g.: Patients with:
  - Hypertension
  - Atherosclerotic disease
  - Diabetes
  - Metabolic syndrome

  or

  - Patients using cardiotoxins with HFX CM

Therapy Goals
- Treat hypertension
- Encourage smoking cessation
- Treat lipid disorders
- Encourage regular exercise
- Discourage alcohol intake, illicit drug use
- Control metabolic syndrome

Drugs
- ACEI or ARB in appropriate patients (see text) for vascular disease or diabetes

Stage B
Structural heart disease but without symptoms of HF.

- e.g.: Patients with:
  - Previous MI
  - LV remodeling including LVH and low EF
  - Asymptomatic valvular disease

Therapy Goals
- All measures under stage A

Drugs
- ACEI or ARB in appropriate patients (see text)
- Beta-blockers

Stage C
Structural heart disease with prior or current symptoms of HF.

- e.g.: Patients with:
  - Known structural heart disease
  - Shortness of breath and fatigue, reduced exercise tolerance

Therapy Goals
- All measures under stages A and B
- Dietary salt restriction
- Drugs for Routine Use
- Diuretic for fluid retention
- ACEI
- Beta-blockers

Drugs in Selected Patients
- Aldosterone antagonist
- ARBs
- Digitalis
- Hydralazine/nitrates

Stage D
Refractory HF requiring specialized interventions.

- e.g.: Patients who have marked symptoms at rest despite maximal medical therapy (e.g., those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)

Therapy Goals
- Appropriate measures under stages A, B, C
- Decision re: appropriate level of care

Options
- Compassionate end-of-life care/hospice
- Extraordinary measures
- Heart transplant
- Chronic inotropes
- Permanent mechanical support
- Experimental surgery or drugs

Heart Failure

Development of Symptoms of HF

Structural Heart Disease
Heart Transplant: preferred therapy for aCHF

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
J Heart Lung Transplant 2009; 28: 989-1049
The “Natural Heart”

• Reliable – 3.4 million beats per month
• Grows
• Fights infection
• Self powered
• Adjusts output as needed
• Non-thrombogenic
• Filled with love
• Can be broken

Can Mankind make a replacement??
Heart Assist / Replacement Challenges

**Engineering**
- Power source
- Material durability
- Energy actuator
- Reliability
- Control

**Biological**
- Surface compatibility
- Blood component preservation
- Adequate support

**Economics**
- Development
- Trials

**Regulatory**
1st Generation Nuclear System
Nuclear Powered Systems
Heart Assist / Replacement Challenges

- Engineering
  - Power source
  - Material durability
  - Energy actuator
  - Reliability
  - Control
- Biological
  - Surface compatibility
  - Blood component preservation
  - Adequate support
  - Human interface
- Economics
  - Development
  - Trials
- Regulatory
The Journey Begins

- 1963 - Liotta Left Heart Bypass
  - 1963
- 1966 – NHLBI grant (10% of total budget)

Original system requirements

- 10Lpm flow
- 150mmHg Pressure
- Max rate 120 bpm
- Non-damaging to blood
- Responsive to demand

Three schools of thought

- Total Heart
- VADs
- Counterpulsation
The Total Artificial Heart

- 4 mechanical valves
- Large pneumatic external driver
- CVA
- Infection
- Size
Total Artificial Heart - SynCardia

- Bridge to transplant
- Biventricular failure or technical issues
- Anti-coagulation
- Excellent results
VADs

• LVAD enough for support

• Natural heart as backup

• Early 1970 – Thermedics to ThermoCardio Systems

• Late 1980 – Thoratec

• Late 1990 – Kriton to Heartware
HeartMate IP – VE - XVE

Pulsatile LVAD

Trial 1: 1976 to 1982
42 patient Post-Cardiotomy Trial
- 25 patients died within 24 hours
- 13 patients died within 1-7 days
- 4 patients survived

Trial 2: 1985 to 1994
116 patients, HM IP as BTT

Trial 3: 1992 to 1998
86 patients, HM VE as BTT

Trial 5: 1998 to 2003
140 patients, REMATCH, HM XVE DT

220M USD, 25 years
HMI TEXTURED SURFACES
HUMAN PNI, 243 DAYS
Human PNI Morphology on Integrally Textured Polyurethane

5 Days

19 Days

41 Days

(100X)
Pulsatile to Continuous Flow LVADs

• HM XVE benefits
  • Excellent LV support
  • No anti-coagulation
  • Minimal medical therapy

• But…
  • Poor durability
  • Large size
  • High driveline infection rate
  • Wampler, Nimbus, Hemopump
  • Technology behind HMII and HVAD

• Continuous flow
  • Quieter
  • Smaller
  • But will it work
  • First 9 patients died
HeartMate II – approved for BTT and DT

• Continuous axial flow pump
• Smaller and more durable than XVE
• Fewer moving parts
• No valves
• Needs anti-coagulation
• Partial assist
LVAD Survival DT

Percent Survival

LVAD Survival DT

Months

0 6 12 18 24

85%
68%
55%
52%
25%
58%

CF LVAD
LVAD REMATCH: 23%
PF LVAD 24%

OMM REMATCH 8%

* N Engl J Med 2001; 345:1435-43
Third Generation LVAD - HeartWare HVAD (DT and BTT approved)

- Centrifugal pump
- Magnetic and hydro-mechanically levitated
- Extreme longevity anticipated
- Up to 10 liters
- Intra-pericardial placement
  - less surgical trauma
  - Less bleeding
  - Shorter LOS
HVAD Development History

1995 - 1997

1997 - 1998

2000

2001

1999

Many iterations were required for the impeller, impeller suspension system, and the housing

Final HVAD design is 160 grams with a displaced volume of 70 cc and capable of providing 10 L/min
HeartWare Implant
Primary End Point Analysis (ITT)

**Survival at 24 months free of disabling stroke or reoperation to replace or remove the pump**

![Graph showing event-free survival rate over days for control and study groups.](image)

- **Event-free Survival Rate (%):**
  - 100
  - 80
  - 60
  - 40
  - 20
  - 0

- **Days:**
  - 0
  - 365
  - 730
  - 1095

- **No. at Risk**:
  - **Study group**:
    - 297
    - 211
    - 159
    - 33
  - **Control group**:
    - 148
    - 106
    - 82
    - 19

- **P=0.67 by log-rank test**
- **P=0.01 for noninferiority by Weibull model**

Rogers J et al. NEJM 2017
<table>
<thead>
<tr>
<th>Reported Metric</th>
<th>HVAD</th>
<th>Control</th>
<th>Statistically Significant?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients for Primary Endpoint</td>
<td>297</td>
<td>148</td>
<td></td>
</tr>
<tr>
<td>Cohort Characteristics: Age</td>
<td>63.9</td>
<td>66.2</td>
<td>Yes</td>
</tr>
<tr>
<td>Cohort Characteristics: Severe Tricuspid Insufficiency</td>
<td>11.8%</td>
<td>5.4%</td>
<td>Yes</td>
</tr>
<tr>
<td>Primary Endpoint – 2 year event-free rate</td>
<td>55%</td>
<td>57.4%</td>
<td>No</td>
</tr>
<tr>
<td>Reason for Endpoint ‘Failure’: Death</td>
<td>34.7%</td>
<td>26.4%</td>
<td>No</td>
</tr>
<tr>
<td>Reason for Endpoint ‘Failure’: Device malfunction, failure requiring exchange, urgent transplant, explant</td>
<td>8.8%</td>
<td>16.2%</td>
<td>Yes</td>
</tr>
<tr>
<td>Survival at 2 years</td>
<td>60.2%</td>
<td>67.6%</td>
<td>No</td>
</tr>
<tr>
<td>Adverse Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI Bleed</td>
<td>.55 EPPY</td>
<td>.44 EPPY</td>
<td>No</td>
</tr>
<tr>
<td>Driveline Infection</td>
<td>.18 EPPY</td>
<td>.12 EPPY</td>
<td>No</td>
</tr>
<tr>
<td>Stroke</td>
<td>.27 EPPY</td>
<td>.09 EPPY</td>
<td>Yes</td>
</tr>
<tr>
<td>Right Heart Failure</td>
<td>.31 EPPY</td>
<td>.22 EPPY</td>
<td>Yes</td>
</tr>
<tr>
<td>Pump exchange</td>
<td>.06 EPPY</td>
<td>.10 EPPY</td>
<td>No</td>
</tr>
</tbody>
</table>
ENDURANCE 2 – HVAD arm with improved BP control

- Freedom from death, disabling stroke (MRS ≥ 4), and
- Device malfunction or
- Failure requiring exchange, explant, or urgent transplant

**Superiority P value** = 0.0354

<table>
<thead>
<tr>
<th>Event Free Rate</th>
<th>Days</th>
<th>HVAD</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>180</td>
<td>66.9%</td>
<td>76.4%</td>
</tr>
<tr>
<td></td>
<td>365</td>
<td>66.9%</td>
<td>76.4%</td>
</tr>
</tbody>
</table>

**Superiority P value by Chi-Square test**
Life on a LVAD!!
Continuous Flow Pumps – class effect

• Sheer stress from high RPMs
  • Von Willebrand factor and platelet destruction
• Thrombosis and low level hemolysis
• Non-pulsatile flow
  • AV incompetence
  • GI bleed
  • Incomplete CHF recovery
• Infection
• CVA
  • Embolic
  • Intra-cerebral bleed
Pre-clinical or IDE devices

• Thoratec
  • Implanted TET system
  • HM III
HeartMate III: Full MagLev

- Pump rotor is levitated and completely suspended by magnetic forces
- Rotor stays centered in pump housing regardless of its orientation
- Full levitation even at zero speed
HeartMate 3 LVAS (approved for short term use - BTT)

- **Wide** blood-flow passages to reduce shear stress
- **Frictionless** with absence of mechanical bearings
- **Intrinsic Pulse** designed to reduce stasis and avert thrombosis

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Primary End Point Analysis (ITT)

Survival at 6 months free of disabling stroke or reoperation to replace or remove the pump

- **Non-inferiority Analysis**
  - Absolute difference +9.4% (95% LCB -2.1%), P<0.0001

- **Superiority Analysis**
  - HR 0.55, (95% CI 0.32-0.95), P=0.037

Survival rates:
- HeartMate 3: 86%
- HeartMate II: 77%

No. at risk:
- HeartMate 3: 152, 146, 138, 135, 130, 128, 127
- HeartMate II: 142, 125, 119, 116, 110, 106, 103

References:

Hemocompatibility as defined as absence of GI bleeding, hemolysis / thrombosis, any neurologic event*.
- 6 months
- HM2: 57.1%
- HM3: 69.2%
Mandeep M. NEJM 2017
Next Generation Pre-clinical or IDE devices – smaller and hopefully increased bio-compatibility

• Jarvik 2000
  • BTT and DT IDE
  • Small, MIS
Pre-clinical or IDE devices

• Heartware - MVAD
  • Axial flow
  • Up to 6 L flow
MVAD® Pump Platform

Miniaturization of technology allows for multiple configurations.
Investigational Device: ReliantHeart aVAD

- Intraventricular, full support device
aVAD – Improving Pulsatility

- Deep vanes (since they contain magnets)
- Flat HQ
- Low resistance to pressure transfer from LV

![Diagram comparing aVAD and HeartMateII](image)

- aVAD 1.23 x cubic displacement vs HMII
aVAD – Improving Pulsatility

• Deep vanes (since they contain magnets)
• Flat HQ
• Low resistance to pressure transfer from LV

In conclusion, Texas Heart Institute demonstrated, in vitro, a near physiologic pressure response of a modified ReliantHeart HeartAssist5® Continuous Flow Pump. O. H. Frazier, 2009, Texas Heart Institute
aVAD – Sentinel System for Early Alert

- True ultrasonic flow sensor built into outflow elbow
- Cellular capability to alert medical personnel and store data continuously in cloud

![Diagram of aVAD system with annotations for Aortic Valve Opening and Mitral Valve Closing]
Diagnostic Opportunity with Remote Monitoring

Dashboard for: [name] within: 30 Days

Flow
Latest: 4.8

Power
Watts
Latest: 6.7

Speed
kRPM
Latest: 8.9

Waveform
Latest
2014-07-31 09:52:13
Normal rhythm with aortic valve opening every beat.

Waveform
Latest
2014-08-08 15:51:22
Atrial fibrillation and aortic valve opening occasionally

Legend:
- 15 minute average
- Alarm level
- Alarm waveform
- Available waveform

Heart & Vascular
Center
Reliant Heart aVAD

- CE Mark received Aug 2016
- First Human implant – Sept 1, 2016
- Dr. Jan Schmitto Hanover Germany
- 14 patients implanted to date
  - 6 thoracotomy
Pre-clinical or IDE devices

• Circulite
  • Smaller surgery
  • Partial assist
  • Pump exchangeable
Timeline to major complication

Clinicians reluctant to use cfLVADs unless patients are desperately ill

cfLVADs placed as BTT: only 32% ever get transplanted

Exchange / Explant traumatic

First occurrence of infection, bleeding, device malfunction, stroke or death

Adult Continuous Flow LVADs & BIVADs, DT and BTT, n=4917
June 2006 – March 2012

One year rate and under-reported!

p < .0001
Clinical Need

- Circulatory support for advanced CHF (aCHF) patients that…
  - Is forward compatible to facilitate bridging to
    - Extended medical therapy
    - Transplant
    - Recovery
    - Durable LVAD
  - Decreases complications of bleeding, thrombosis, CVA, infection
  - Is minimally invasive (avoid sternotomy/thoracotomy and any access to heart)
  - Gives patient some control
  - Increase patient access
    - Standardizable, reproducible, “non-surgical”
    - Implant by Interventional CHF Cardiologist in community hospital setting
  - Energizing the circulation
    - Continuous flow direct blood pumps (cfLVADs)
Think Different: *counterpulsation to energize circulation*
**Counterpulsation – Intra-Aortic Balloon Pumps**

- Inflates when heart relaxes and deflates when heart pumps
- Natural way to augment the heart
- Rests and recovers heart
- Most commonly used aCHF device
- Effective but temporary
  - Limited to ICU use only
  - Designed and approved for immobilized patient

**Can chronic counterpulsation treat aCHF?**

**Can durable ambulatory counterpulsation be delivered minimal invasively?**
Counterpulsation – IABP via subclavian access

Successful (n=98)...
- Duration of support mean=24 days
- 93.4% of BTT patients (n=70) were transplanted
- 100% of B to MSC (n=24) were successfully optimized
- Ambulation
- Rehabilitation – aerobic and strength training
Minimally Invasive Counterpulsation

Initial idea
NuPulseCV iVAS: intravascular Ventricular Assist System

Skin Interface Device (SID) transdermal electro-mechanical conduit; designed to minimize infection

Patient Connector
Proprietary easy connect/disconnect of driveline by patient

Arterial Interface Device (AID)
Maintains access to artery; Facilitates easy pump replacement

Internal Drive Line

Subcutaneous ECG leads Access to heart not needed

NuPulseCV Drive Unit (NDU)
Portable; ambulatory
Blood Pump

- 50cc displacement;
- 19mm diameter Pump with variable diameter driveline (5mm in subclavian segment)
- Driveline kink resistant
- One piece; no wrinkles when deflated
  - Silicone end-groups
  - Herparin bonding not used
- Multilayered
Skin Interface Device (SID): *a technological feat*

Seals to underlying tissue to provide stability – designed to eliminate infection
- Textured titanium and silicone boot designed to minimize stress at skin's surface
- Minimize movement from pneumatic pumping

Cap rotatable with pneumatic integrity and air gapped electrical and data transmission
- Provide conduit for air
- Transformer provides power to circuit and pressure sensor
- IR data transmission

Preconditions ECG signal from subcutaneous electrodes
- 3 subcutaneous electrodes and one integral to the SID base
- Can optimize pairing
- Digitizes signal

Stores patient data
NuPulseCV Drive Unit - Overview

Directly pumps 1:1 (up to 120 bpm), 1:2, 1:3 including arrhythmias

Robust leak detect for safety
  • Closed mode
  • Open mode automatically switched by onboard humidity sensor

Sealed battery with 4 hours runtime; external adds 8 hours

FIH design is 5.6lbs – can be designed down to 4lbs

Similar sound level as oxygen concentrator

163 x 145 x 82mm
6.4 x 5.7 x 3.2”
weight ~ 5.6lbs
Clinical Pathway

First-In-Human
- Bridge-to-Transplant
- UNOS 1A/1B
- Hospital Discharge
- Single Site-UCMC

Completed

Feasibility
- Eligible for transplant
- Multiple sites (subclavian IABP experience)

Enrolling

Pivotal
- RCT
- Class III-IV
- Major centers + community hospitals
First-In-Human (FIH) Trial Design - UCMC

- Patient population
  - Bridge To Transplant listed UNOS status 1b or 1a, in-hospital (to mitigate risk during FIH)
  - Subclavian >7mm
  - Resting HR <100 without significant tachy arrhythmias; AV node ablation
  - Respond to IABP or > INTERMACS 2.5
  - Less than mild AI

- Short stay in ICU; predominantly in stepdown/telemetry
- Free to move within hospital; pts after #10 allowed to be discharged
- Success: transplant or 30 day survival
- RHC every 2 weeks; 6 min walk; 2 min step test
Patients Enrolled

- Total: 14 (one pt aborted and regular sclABP placed due to small artery)
  - 11 males; 2 female
  - Age: 60 years (range 52-71)

- Etiology of CHF
  - Idiopathic dilated: 9  Idiopathic arrhythmogenic: 1
  - Ischemic: 3

- UNOS listing
  - Status 1b n=10 ; Status 1a n=3

- INTERMACS classification
  - IM 2 n=3 ; IM 3 n=10
Results (1)

- Study outcomes n=13
  - 13 transplanted
- Intra-operative (12 left sided; 1 right sided)
  - 100% procedural success on patients proceeding with implant after visualizing the subclavian
  - No intra-op transfusions of any blood products
  - Extubation in OR
- Implant period – mean 30.2 days (range 4-76)
  - Mean HgB 11.5 to 9.2 (one PRBC transfused POD3 for HgB 7)
  - No hemolysis, thrombocytopenia
  - Ambulated POD1; 11 on telemetry floor (2 required ICU readmission)
  - No arm ischemia or thromboembolic events
  - Pain (shoulder, arm, SID site) usually resolved in 4 days
  - Paresthesia arm (n=2 resolved 2 weeks and 2 months)
  - Pericarditis n=1. Reason unknown
Results (3)

- **CVP**: $-19.9 \pm 34.7\%$
  - Pre-IABP: 7 mg Hg
  - Post-IABP (2wk): 0.5 mg Hg
  - Statistically significant at $p<0.05$

- **Mean PAP**: $-17.6 \pm 29.3\%$
  - Pre-IABP: 40 mg Hg
  - Post-IABP (2wk): 20 mg Hg
  - Statistically significant at $p<0.05$

- **PCWP**: $-18.9 \pm 36.4\%$
  - Pre-IABP: 3 mg Hg
  - Post-IABP (2wk): 0.5 mg Hg
  - Statistically significant at $p<0.05$

- **Mean BP**: $+3.1 \pm 18.7\%$
  - Pre-IABP: 105 mg Hg
  - Post-IABP (2wk): 110 mg Hg
  - Not statistically significant

- **CI**: $+30.7 \pm 25.6\%$
  - Pre-IABP: 3 L/min/m²
  - Post-IABP (2wk): 4 L/min/m²
  - Statistically significant at $p<0.05$

- **Cardiac Power**: $+47.9 \pm 18.7\%$
  - Pre-IABP: 100 W
  - Post-IABP (2wk): 120 W
  - Statistically significant at $p<0.05$
## Results (5)

- Functional capacity

<table>
<thead>
<tr>
<th></th>
<th>6 min walk (feet)</th>
<th>2 min step test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre iVAS (n=11)</td>
<td>1273 (490-1875)</td>
<td>58 (0-93)</td>
</tr>
<tr>
<td>iVAS 1 weeks (n=8)</td>
<td>1188 (500-1671)</td>
<td>72 (45-102)</td>
</tr>
<tr>
<td>iVAS 4 weeks (n=5)</td>
<td>1540 (1434-1791)</td>
<td>75 (60-90)</td>
</tr>
</tbody>
</table>

+267 feet (89meter) +20.9%
Biologic – Device Interface

- Hemocompatibility
  - Thromboembolic events – none
  - Device thrombosis / hemolysis – none
  - Thrombocytopenia – none
  - GI bleeding – none
  - Increase on (or creation of new) PRA – none
  - Anticoagulation: INR 1.2-2.2
Feasibility

- Patient population
  - Bridge To Transplant listed UNOS status 1b or 1a … or…. No contraindication for transplant (bridge to decision)
  - Respond to IABP or ≥ INTERMACS 2.5
  - Less than mild AI
- Success: transplant or 30 day survival
- Anticipate discharge and longer implant durations
  - 2 weeks, months 1,3,6,9,12– RHC; 6 min walk; 2 min step test
- Implants at:
  - UCM
  - MidAmerica KC
  - Duke
  - University of Louisville
UCM iVAS experience n=30

- Patient population
  - N=24 - Listed for Transplant; transplanted n=20; awaiting n=3; de-listed n=1
  - N=6 – bridge to decision
    - N=2 probationary period for transplant
    - N=2 – non-revascularizable intractable angina
    - N=2 – JW no renal improvement and received HVAD
- Hemodynamics
  - Overall: decrease in filling pressures and >30% increase in CI
  - Equal or better on support n=31
  - Deterioration requiring escalation n=1
  - Angina resolved n=2
- Demonstrated non-obligatory nature of device
Role of our PA-C

- Lot of independence
  - Very “top” of license
  - IABP – femoral and subclavian
  - Cannulate, de-cannulate
  - Close

- Sternal Plates
  - Invented at UCMC
  - Technique developed by PA-C

- Jehovah Witness Bloodless surgery
  - LVAD
  - Transplants
  - PA-C close

- iVAS
  - Pre-clinical to FIH
  - Helped develop insertion techniques

- PA-C very stable and experienced at UCMC
- Positions open up
- If interested please contact me directly at Jeevan@uchicago.edu
  Cell: 773-339-9707
Summary

• Many years to establish basis of current technology

• Current designs accelerated by computer aided design (CAD), microprocessors and communication

• Major milestones
  • Materials
  • LVADs enough instead of total heart in 90% of patients
  • Continuous flow devices reverse CHF

• How much support is required? 10L vs 2L

• How much pulsatility is required?
  • GI bleeding
  • CVA
  • Aortic Insufficiency

• Ambulatory counterpulsation - ?paradigm shift in aCHF management?

• MCS exciting field which is established yet evolving towards goal of emulating the human heart.
Dedication, Innovation, Skill, Hard Work, Incredible Team effort…