MHIF Research Highlights: APRIL 2019

Congratulations on First Enrollments!

Dr. David Lin and Christine Majeski
Way to go on your FIRST IN THE WORLD enrollment for the Rhapsody study!

Dr. Yale Wang and Rose Peterson
Way to go on your FIRST IN THE WORLD enrollment for the RADIANCE II study!

FEATURED MHIF STUDIES
Open for Enrollment and Referrals!

COMPLEXA PH evaluating CXA-10 in patients with pulmonary arterial hypertension
CONTACT: Sarah Dennis, 612-863-6257

RADIANCE II assessing catheter directed renal denervation in managing essential and resistant hypertension
CONTACT: Rose Peterson, 612-863-6051

PROMINENT testing pemafibrate in patients with high triglycerides, low HDL, high CV risk
CONTACT: Ezi Ebere, 612-863-4393

MARK YOUR CALENDARS
For the Heart of Minnesota!
A Cardiovascular Nursing Conference
Friday, April 12
Grand View Lodge
Nisswa, MN

Cardiovascular Prevention Symposium!
Updates in Optimal Preventive Care in 2019
Thursday, May 2
Edina Country Club

SHARING GREAT RESEARCH...

Dr. Paul Sorajja in JACC: the largest experience published to date, the first 100 patients receiving Tendyne TMVR

Dr. Manos Brilakis shared practical learnings from hiking to apply to CTO PCI in the latest Cardiology Today
Ventricular Unloading
State of the Art and Future Directions
Howard B. Burchell Lecture 2019

Navin K. Kapur, MD, FACC, FSCAI, FAHA
Associate Professor, Department of Medicine
Interventional Cardiology & Advanced Heart Failure Programs
Executive Director, The Cardiovascular Center for Research & Innovation

Research Funding & Speaker/Consulting Honoraria:
Abiomed, Abbott, Boston Scientific, Maquet, Medtronic,
Liva Nova, MD Start, Cardiac Assist, Neurotronik
Equity and Consultant Honoraria: preCardia

RO1HL139785, RO1H133215
A Patient’s Saga of Acute MI, Heart Failure and Shock

**AMI-Shock**
- 10/2007
- Anterior MI
- LAD PCI and IABP
- LVEF 20%

**Acute HF Syndromes**
- 11/2007
- Readmitted Heat Failure
- LVEF 25%

**HR-PCI**
- 3/2008
- Impella Supported
- LAD and LCx PCI
- LVEF 25%

**Ambulatory Shock**
- 7/2012
- Readmitted Recurrent HF
- LVEF 20%

**Advanced HF-Shock**
- 3/2015
- Cardiogenic Shock
- Impella + VA-ECMO
- LVEF 10%

**Cardiogenic Shock**
- 12/2017
- Biventricular Centrimags
- LVEF 10%

**Orthotopic Heart Transplant**
- 4/2018
- LVEF 65%
Ventricular Wall Stress is a Major Determinant of Clinical Outcomes

Primary Target of Heart Failure Therapy: Reduce LV Wall Stress

Laplace’s Law: Wall stress = \( \frac{\text{Pressure} \times \text{Radius}}{2 \times \text{Wall Thickness}} \) = \( \frac{\text{ESP} \times \text{EDV}}{\text{LV Mass}} \)

What is Ventricular LOAD?

Load refers to any variable that increases myocardial oxygen consumption (demand)

Coronary Occlusion
Collateral Blood Flow
Multivessel Disease
Microvasc Dysfunction
Systemic Hypotension

Heart Rate
LV Wall Stress (P/2rh)
LV Systolic Pressure
LV Diastolic Pressure
LV Stroke Work

Myocardial Oxygen Supply

Myocardial Oxygen Demand
Pioneers in Our Understanding of Ventricular LOAD

Otto Frank 1865-1944
Ernest Starling 1866-1927
Carl Wiggers 1883-1963
Arthur Guyton 1919-2003
Hiro Suga
Kiichi Sagawa
Kenji Sunagawa
David Kass
Dan Burkhoff

40 Years of Fundamental Hemodynamic Science

Circa 1975

Circa 2015
Adverse Cardiac Remodeling is Load Dependent

LVEDP (>18mmHg) is associated with increased incidence of heart failure and infarct size

Acute Load and Poor Outcomes in STEMI

Kirtane and Gibson 2004 J Thromb Thromb

Ndrepepa and Kastrati CCI 2019
Acute Load and Poor Outcomes in STEMI
LVEDP (>24mmHg) is associated with increased mortality in STEMI

LOAD is BAD in Acute MI, but it is WORSE in SHOCK

Forrester-Diamond-Swan Classification (1977)
Cardiac Index and PCWP are associated with mortality

<table>
<thead>
<tr>
<th>Class</th>
<th>Cardiac Index</th>
<th>PAWP (mm Hg)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&gt;2L/min/m2</td>
<td>&lt;18</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>&gt;2L/min/m2</td>
<td>&gt;18</td>
<td>9</td>
</tr>
<tr>
<td>III</td>
<td>&lt;2L/min/m2</td>
<td>&lt;18</td>
<td>23</td>
</tr>
<tr>
<td>IV</td>
<td>&lt;2L/min/m2</td>
<td>&gt;18</td>
<td>51</td>
</tr>
</tbody>
</table>
Forty Years Later (2017)  
Back to Killip and Forrester

Contemporary Management of Cardiogenic Shock  
A Scientific Statement From the American Heart Association

<table>
<thead>
<tr>
<th>Volume Status</th>
<th>Wet</th>
<th>Dry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Classic Cardiogenic Shock</td>
<td>Euvolemic Cardiogenic Shock</td>
</tr>
<tr>
<td></td>
<td>(↓CI; ↑SVRI; ↑PCWP)</td>
<td>(↓CI; ↑SVRI; ↔PCWP)</td>
</tr>
<tr>
<td>Cold</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vasodilatory Cardiogenic Shock or Mixed Shock</td>
<td>Vasodilatory Shock (Not Cardiogenic Shock)</td>
</tr>
<tr>
<td></td>
<td>(↓CI; ↓/↔SVRI; ↑PCWP)</td>
<td>(↑CI; ↓SVRI; ↓PCWP)</td>
</tr>
<tr>
<td>Warm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Evolution of Ventricular Unloading Devices

<table>
<thead>
<tr>
<th>2007</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVADs</td>
<td>HVAD</td>
</tr>
<tr>
<td>Impella CP</td>
<td>Impella TH + 5.0</td>
</tr>
<tr>
<td>BiPellas</td>
<td>5.0 as a Bridge to Recovery</td>
</tr>
</tbody>
</table>
What is Ventricular Unloading?
Unloading refers to a reduction in myocardial oxygen consumption (demand) while maintaining systemic perfusion.

Coronary Occlusion
Collateral Blood Flow
Multivessel Disease
Microvasc Dysfunction
Systemic Hypotension

Heart Rate
LV Wall Stress (P/2rh)
LV Systolic Pressure
LV Diastolic Pressure
LV Stroke Work

Myocardial Oxygen Supply
Myocardial Oxygen Demand

The Spectrum of Acute MCS Devices in 2019

Left Ventricle
Pulsatile
Continuous Flow Pumps
Axial-Flow
Centrifugal Flow
IABP
Impella CP
PHP *
TandemHeart
VA-ECMO

Right Ventricle
Intracorporeal
Extracorporeal
Axial Flow
Centrifugal Flow
Impella RP
VA-ECMO
Tandem pRVAD
Protek Oxy-RVAD
Targeting Laplace’s Law: Impella CP and TandemHeart

A

**Impella CP: 3.1 LPM**

- End-Systolic Pressure
- Stroke Volume

B

**TandemHeart: 3.1 LPM**

C

**TandemHeart: 4.4 LPM**

Kapur et al. ASAIO 2014

Ventricular Unloading with a Trans-valvular Pump

Kapur NK et al. ASAIO 2013
Kapur NK et al. JACC HF 2015
The more dysfunctional the ventricle, the more functional a CF-AMCS device becomes.

Investigational Axial-Flow Catheter: HeartMate PHP

Abbott HeartMate PHP US IDE Trial
First enrollment: September 1, 2015
Trial suspension: January 30, 2017
Trial re-initiated: December 2018

Kapur, Jorde, Kandzari: SHIELD II Trial National PIs
Load Sensitivity is Most Clinically Important When Combining ECMO with an Impella

VA-ECMO Reduces Preload

VA-ECMO Increases Afterload
Minimal Pulsatility with VA-ECMO:
A Marker of Loading not Unloading

Predicting the Need for Venting with ECMO
Pre-ECMO EF + Post-ECMO Increase in MAP
Simultaneous Venoarterial Extracorporeal Membrane Oxygenation and Percutaneous Left Ventricular Decompression Therapy with Impella Is Associated with Improved Outcomes in Refractory Cardiogenic Shock

** Success in Cardiogenic Shock Requires Early Initiation of Acute MCS **

- Impella Pre-PCI
- Door to Support Time < 90 minutes
- Establish TIMI III Flow
- Right Heart Cath
- Wean off Vasopressors & Inotropes
- Maintain CPO > 0.6 Watts
- Improve survival to discharge to >80%

O'Neill W. JIC 2013
Impella before (Pre-PCI) reperfusion associated with Improved AMI-Cardiogenic Shock Outcomes

- Survival to Expant
  - Impella Quality Database
  - Pre-PCI: 59%
  - Post-PCI: 63%
  - P<0.001

- Survival to Discharge
  - USpella Registry
  - Pre-PCI: 65%
  - Post-PCI: 41%
  - P<0.003

- Survival to Discharge
  - Basir, et al, Am J Cardiol, 2017
  - cVAD Study
  - Pre-PCI: 48%
  - Post-PCI: 32%
  - P<0.04

- Survival to 30 Days
  - Meraj et al, J Int Cardiol 2017
  - cVAD Study
  - Pre-PCI: 48%
  - Post-PCI: 13%
  - P<0.001

- Survival to 1 Year
  - Schroeter et al, J Inv Cardiol 2016
  - University of Goettingen
  - Pre-PCI: 43%
  - Post-PCI: 13%
  - P<0.04

Best Practices for Shock

Optimal Components of a Shock Algorithm

- Hemodynamic Data
  - MAP, CO, PAPi, RA

- Metabolic Profile
  - GFR, Lactate Kinetics, ABG, LFTs, Coags

- Support Profile
  - Type/Level of Acute MCS Response to Acute MCS

- Revascularization Status
  - Complete/Incomplete

- Vascular Safety
  - Access sites, Sheath sizes, Limb perfusion
Can we change the trajectory of this patient's life?

<table>
<thead>
<tr>
<th>AMI-Shock</th>
<th>Acute HF Syndromes</th>
<th>HR-PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior MI</td>
<td>Readmitted Heart Failure</td>
<td>Readmitted HF</td>
</tr>
<tr>
<td>LAD PCI and IABP</td>
<td>LVEF 25%</td>
<td>ICD Implanted</td>
</tr>
<tr>
<td>Readmitted Recurrent HF</td>
<td>Impella Supported</td>
<td>Readmitted – HF/ACS</td>
</tr>
<tr>
<td>LVEF 20%</td>
<td>LAD and LCx PCI</td>
<td>LVEF 25%</td>
</tr>
</tbody>
</table>

Can we harness acute ventricular unloading as a therapeutic approach to improve myocardial recovery?

Mann D et al JACC 2012
To Change the Future, We have to Learn From the Past

Factors Influencing Infarct Size Following Experimental Coronary Artery Occlusions

By Peter R. Maroko, M.D., John K. Keehr, M.D., Burton E. Soker, M.D., Tan Watanabe, M.D., James W. Covell, M.D., John Ross, Jr., M.D., and Eugene Braunwald, M.D.

Of greatest interest, from the clinical point of view, is the finding that the severity and extent of myocardial ischemic injury resulting from coronary occlusion could be radically altered not only by pretreatment of the animal but also by an appropriate intervention as late as 3 hr after the coronary occlusion. This suggests that measures designed for reduction of myocardial oxygen demands and improvement of coronary perfusion, when effected promptly after a patient has been brought to a hospital, might potentially reduce the ultimate size of the infarction.

_Circulation, Volume XLIII, January 1971_

Timing is Everything
Balloon Angioplasty Arrived First in History

Andreas Gruentzig
1976 – AHA Preclinical Poster
1977 – First Coronary Angioplasty

O₂ Supply
Myocardial Perfusion

O₂ Supply ?
In STEMI, Timing is Everything

Time Delay to Treatment and Mortality in Primary Angioplasty for Acute Myocardial Infarction
Every Minute of Delay Counts

Every 30 minute delay in Ischemic Time is associated with a 7.5% increase in 1 year mortality and a 30% increase in infarct size.

A recent analysis of >2600 patients treated with Primary Reperfusion identified that for every 5% increase in myocardial infarct size 1-year all-cause mortality increases by 19% and HF hospitalization by 20%.

Stone, Selker, Udelson et al. JACC 2016

Current Practice is not good enough. We can do better.

Heart Attacks Lead to Heart Failure

Median Infarct Size Despite 1° PCI: 17.9% of Total LV Mass

A recent analysis of >2600 patients treated with Primary Reperfusion identified that for every 5% increase in myocardial infarct size 1-year all-cause mortality increases by 19% and HF hospitalization by 20%.

Stone, Selker, Udelson et al. JACC 2016
40 Years of LV Unloading Science (1978-2018)

<table>
<thead>
<tr>
<th>Animal Model</th>
<th>Year</th>
<th>Duration of Ischemia (min)</th>
<th>Duration of Reperfusion (min)</th>
<th>Mechanical Support Before vs After Reperfusion</th>
<th>Occluded Vessel</th>
<th>Method of Occlusion</th>
<th>Device</th>
<th>Reduction in Infarct Size?</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Canine</td>
<td>1978</td>
<td>480</td>
<td>X</td>
<td>Before vs After Reperfusion</td>
<td>LAD</td>
<td>Ligation</td>
<td>IABP Yes</td>
<td>No</td>
<td>Roberts &amp; Gay [6]</td>
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<tr>
<td>Baboons</td>
<td>1979</td>
<td>1440</td>
<td>X</td>
<td>Before vs After Reperfusion</td>
<td>LAD</td>
<td>Ligation</td>
<td>IABP No</td>
<td>No</td>
<td>Haston &amp; McNamara [7]</td>
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<tr>
<td>Porcine</td>
<td>1980</td>
<td>1440</td>
<td>X</td>
<td>Before vs After Reperfusion</td>
<td>LAD</td>
<td>Ligation</td>
<td>IABP No</td>
<td>No</td>
<td>Laas &amp; Repligle [8]</td>
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<tr>
<td>Porcine</td>
<td>2008</td>
<td>60</td>
<td>240</td>
<td>Before vs After Reperfusion</td>
<td>LAD</td>
<td>Ligation</td>
<td>IABP Yes</td>
<td>No</td>
<td>Ledoux &amp; Smalling [9]</td>
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<tr>
<td>Canine</td>
<td>1983</td>
<td>240</td>
<td>X</td>
<td>Before vs After Reperfusion</td>
<td>LAD</td>
<td>Ligation</td>
<td>IA-BP Yes</td>
<td>No</td>
<td>Catinella &amp; Spencer [12]</td>
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<tr>
<td>Porcine</td>
<td>1983</td>
<td>120</td>
<td>120</td>
<td>Before vs After Reperfusion</td>
<td>LAD</td>
<td>Balloon angioplasty</td>
<td>TandemHeart Yes</td>
<td>No</td>
<td>Kapur &amp; Karas [13]</td>
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<tr>
<td>Canine</td>
<td>1989</td>
<td>120</td>
<td>60</td>
<td>Before vs After Reperfusion</td>
<td>LAD</td>
<td>Snare ligation</td>
<td>Hemopump Yes</td>
<td>No</td>
<td>Mehrig &amp; Wampler [14]</td>
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<tr>
<td>Canine</td>
<td>1992</td>
<td>120</td>
<td>60</td>
<td>Before vs After Reperfusion</td>
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<td>Snare ligation</td>
<td>Hemopump Yes</td>
<td>No</td>
<td>Smalling &amp; Amirian [15]</td>
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<tr>
<td>Canine</td>
<td>2005</td>
<td>120</td>
<td>240</td>
<td>Before vs After Reperfusion</td>
<td>LAD</td>
<td>Snare ligation</td>
<td>Hemopump Yes</td>
<td>No</td>
<td>Ashour &amp; Smalling [16]</td>
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<tr>
<td>Sheep</td>
<td>2005</td>
<td>60</td>
<td>120</td>
<td>Before vs After Reperfusion</td>
<td>LAD</td>
<td>Ligation</td>
<td>Impella 5.0 Yes</td>
<td>No</td>
<td>Meyns &amp; Fleming [17]</td>
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<tr>
<td>Porcine</td>
<td>2013</td>
<td>90</td>
<td>120</td>
<td>Before vs After Reperfusion</td>
<td>LAD</td>
<td>Balloon angioplasty</td>
<td>Impella CP Yes</td>
<td>No</td>
<td>Kapur &amp; Karas [18]</td>
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<td>Porcine</td>
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<td>120</td>
<td>Before vs After Reperfusion</td>
<td>LAD</td>
<td>Ligation</td>
<td>Impella LD Yes</td>
<td>No</td>
<td>Sun &amp; Wang [20]</td>
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<tr>
<td>Porcine</td>
<td>2018</td>
<td>90</td>
<td>120</td>
<td>Before vs After Reperfusion</td>
<td>LAD</td>
<td>Balloon angioplasty</td>
<td>Impella CP Yes</td>
<td>No</td>
<td>Esposito &amp; Kapur [21]</td>
</tr>
</tbody>
</table>

Adequate LV unloading before not after reperfusion is required to reduce infarct size

Kapur, Meyns, Smalling et al JCTR In Press 2018

IABP Not Sufficient to Reduce Infarct Size

CRISP-AMI Trial

Pre-reperfusion IABP in Anterior MI (No Shock)

Primary End Point

Primary End Point

IABP | No IABP
--- | ---
Mean (95% CI) | 36.8 (27.4-42.1) | 42.1 (36.7-45.6) | 37.5 (34.3-40.8) | 0.05
Median (IQR) | 36.8 (26.0-62.2) | 42.8 (27.2-54.7) | 36.2 (25.9-49.4) | 0.05

Patel, M. R. et al. JAMA 2011
**Hypothesis:** Initially reducing LV work and *delaying coronary reperfusion* limits myocardial injury in AMI.

* Delayed reperfusion driven by necessity: technical implant of the TandemHeart device (trans-septal + 2 large cannulas) transition to PCI

---

**Percutaneous Left Atrial Decompression Reduces LV Wall Stress and Reduces Infarct Size**

*(30 minutes unloading before reperfusion)*

Introduced the idea that prioritizing therapy to LV Unloading, followed by Reperfusion may maximize myocardial salvage

Kapur NK et al Circulation 2013
First Attempt: Primary Unloading Trial

TandemHeart to Reduce Infarct Size (TRIS Trial) (TRIS)

This study has been withdrawn prior to enrollment.
(No participants enrolled)

Sponsor: CardiacAssist, Inc.

Information provided by (Responsible Party): CardiacAssist, Inc.

ClinicalTrials.gov Identifier: NCT02164058
First received: June 12, 2014
Last updated: December 3, 2015
Last verified: December 2015

Zero enrollment – engineering limitation

Percutaneous Trans-valvular Axial Flow Pump Reduces LV Wall Stress and Reduces Infarct Size (60 minutes unloading before reperfusion)

Kapur NK et al JACC HF 2015
Initiation of VA-ECMO Before Reperfusion Does Not Reduce Infarct Size

Unloading Mechanistic Impact 1
Reduced LV Wall Stress & Myocardial O2 Consumption

Swain L, Qiao X, Reyet L, and Kapur NK et al 2019

Courtesy of D. Burkhoff
Unloading Mechanistic Impact 2
Unloading Increases Perfusion without Reperfusion

Pressure-derived Collateral Flow Index (CFI)

Seiler and Meier et al. JACC 1998; Lee and Park et al. JACC 2000
Annamalai, Briceno and Kapur NK et al. 2019
Unloading Mechanistic Impact 2
Unloading Increases Perfusion without Reperfusion

LV unloading increases collateral blood flow (reduces ischemia)

Annamalali, Briceno and Kapur NK et al. 2019

Unloading Mechanistic Impact 2
Unloading Increases Perfusion without Reperfusion (Reduces the Area at Risk)

Immediate Reperfusion  Impella Pre-Reperfusion  VA-ECMO Pre-Reperfusion

CFI = \( \frac{P_w}{P_a} \) = \( \frac{\Delta}{\Delta} \)

Annamalali, Briceno and Kapur NK et al. 2019
What's the Mechanism Underlying the Cardioprotective Effect of LV Unloading and Delayed Reperfusion?

Re-visiting the Double-Edged Sword of Reperfusion

Reperfusion

Ischemia → Oxidative Phosphorylation → ATP Synthesis → ATP → Lactate → pH↓ → p53 Opening → Cellular Death / Necrosis

TIME IS MUSCLE

Myocardial Stunning
Reversible

Myocardial Hypercontracture
Irreversible

Stopping the Myocardial Injury Clock

Unloading Mechanistic Impact 3
Unloading Promotes Protective Myocardial Signaling

Esposito, Zhang, Qiao and Kapur NK et al. JACC 2018
Unloading Mechanistic Impact 4
Unloading Promotes Mitochondrial Integrity in Acute MI

Cardiomyocyte Survival Depends on a Proton Motive Flow Pump

Annamalali, Briceno and Kapur NK et al. 2019
Mitochondrial Complex 1 is an Essential Component of Energy Biogenesis

Unloading Mechanistic Impact 4
Unloading Promotes Mitochondrial Integrity in Acute MI

Primary Unloading Preserves Complex 1 Function

Swain L, Qiao X, Reyet L, and Kapur NK et al 2019
Unloading Mechanistic Impact 4
De-activation of Complex 1 Promotes Oxidative Stress

Unloading Preserves Complex 1 in the Active Form

Swain L, Qiao X, Reyet L, and Kapur NK et al 2019
Unloading Mechanistic Impact 4
Unloading Preserves Complex 1 in the Active Form, Preserves ATP Synthesis and Reduces Oxidative Stress

Unloading Preserves Complex 1 in the Active Form, Preserves ATP Synthesis and Reduces Oxidative Stress

Swain L, Qiao X, Reyet L, and Kapur NK et al 2019

Unloading Mechanistic Impact 5
Unloading Limits Scar Size and Promotes Recovery

Unloading Limits Scar Size and Promotes Recovery

Esposito, Zhang, Qiao and Kapur NK et al JACC 2018
How do we begin to translate the concept of First Unloading and then Delaying Reperfusion in Acute MI?

We need to perform a clinical trial.... BUT
Will patients and physicians participate?
Is this feasible?
Is this safe?

The Rationale for a Pilot Before a Pivotal Trial
Do we really need a 30 minute delay to reperfusion?
Electrocardiographic Confirmation
Informed Consent and Enrollment

Anterior STEMI Referred for Primary PCI

Patient preparation, draping, anti-coagulation, anti-platelet therapy, ultrasound guided femoral access, vascular angiogram, left ventriculography, 14 French sheath insertion, then Randomization to U-IR or U-DR

Impella CP Insertion + Activation

U-IR Group
Radial (or femoral access), coronary angiography, coronary wiring and angioplasty

U-DR Group
30 minutes of Unloading
Radial (or femoral access), coronary angiography, coronary wiring and angioplasty

Explant Impella CP after a minimum of 3 hours support

Independent Data Safety Monitor, Electrocardiographic, Angiographic, and Cardiac Magnetic Resonance Imaging Core Labs

Door To Unload: STEMI Pilot Trial: Study Design

50 patients enrolled randomized and Unloaded

U-IR (n=25)

No CMR Completed (n=5)
1 expired
1 metallic prosthesis
2 large body mass index
1 outside time window
(n=20) 3-5 Day CMR

No CMR Completed (n=4)
1 expired
2 claustrophobic
1 chronic kidney disease
(n=21)

U-DR (n=25)

No CMR Completed (n=1)
1 outside time window
(n=19) 30 Day CMR
(n=25) 30 Day MACCE

Kapur NK and O’Neill W et al Circulation 2018
Successful enrollment & protocol completion
Zero Bailout PCI in the U-DR Group

Kapur NK and O’Neill W et al. Circulation 2018

DTU-STEMI Results: Primary Safety Outcome
No Prohibitive Safety Signal

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>U-IR (n=25)</th>
<th>U-DR (n=25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV mortality, n (%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Reinfarction, n (%)</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke or TIA, n (%)</td>
<td>1 (4%)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Traditional 30-Day MACCE, n (%)</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Major Vascular Events, n (%)</td>
<td>0</td>
<td>2 (8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Total Composite 30-Day MACCE, n (%)</td>
<td>2 (8%)</td>
<td>3 (12%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

CV Mortality:
1 mortality on POD 24 due to chronic lung disease and 1 on day 1 due to shock on admission

Major Vascular Events:
2 iliofemoral dissections at the time of device removal

TIA = transient ischemic attack
MACCE = Major Adverse Cardiovascular and Cerebrovascular Events
Kapur NK and O’Neill W et al. Circulation 2018
Safety: Unloading and delaying reperfusion for 30 minutes did not increase infarct size

Unloading and Delayed Reperfusion may be Especially Beneficial in Large Anterior Infarcts (ST-Sum)
Despite 60 additional minutes of ischemic time, the delay arm of the STE>6 group had smaller infarct size.

- **Symptom Onset**
  - U-IR
  - U-DR

- **Treatment Timeline (minutes)**
  - Unload PCI
  - 64 mins of ischemia

- **Infarct / AAR**
  - Expected
  - Observed

- **Expected vs Observed**
  - N=14
  - N=16
  - *p = 0.04*

The STEMI-Door to Unload (DTU) Research Program

**Aim:** LV Unloading as an approach to limit infarct size and reduce heart failure after STEMI

**SAFETY & FEASIBILITY**

- Test primary hypothesis
- Study mechanism
- Determine optimal timing of unloading
- Examine late functional effect and remodeling

**Goal:** Establish safety & feasibility:
- Successful enrollment and protocol completion (Feasibility)
- No increase in infarct associated with 30 minute delay (Safety)
- No increase in major adverse cardiovascular or cerebral events (MACCE Safety)

**Multicenter, RCT in Anterior STEMI**

- DTU + 30 min Delay versus DTB: Standard of Care
- Anticipated Launch in 2019
Harnessing Fundamental Science to Improve Existing Paradigms and Promote Myocardial Recovery

**Acute MI**
- 10/2007: Anterior MI, LAD PCI and IABP, LVEF 20%

**Recurrent HF**
- 11/2007: Readmitted, Heart Failure, LVEF 25%
- 3/2008: Readmitted, HF, LVEF 25%

**HR-PCI**
- 4/2009: Readmitted, HF, Impella Supported, LAD and LCx PCI, LVEF 25%

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**Recurrent HF**
- 7/2012: Readmitted, Recurrent HF, LVEF 20%

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**Shock**
- 3/2015: Readmitted, Recurrent HF, LVEF 20%
- 12/2017: Cardiogenic Shock, Impella + VA-ECMO, LVEF 10%
- 4/2018: Orthotopic Heart Transplant, LVEF 65%

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The Importance of *Preload* in Heart Failure

**Fundamentals of HF Therapeutics**
- Preload
- Afterload
- Inotropy

**Stroke Volume**

**LVEDP or LVEDV**

1. Condition 1: 'Normal'
2. Condition 2: AMI
3. Condition 3: Acute Heart Failure
4. Condition 4: Cardiogenic Shock

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Otto Frank
1865-1944

Ernest Starling
1866-1927

MHIF CV Grand Rounds – April 8, 2019
Cardiac Unloading: An Important Target of Therapy in ADHF
Congestion is as Critical as Cardiac Output

Right atrial pressure is independently associated with in-hospital mortality.

Odds ratio 1.12 per 1mmHg increase in RA pressure (p<0.001)

Can we regulate Cardiac Preload using a Device Based Approach?

Therapeutic Superior Vena Caval Occlusion

A Disruptive Concept

No existing device therapy specifically reduces LV preload due to a concern that reducing preload will reduce LV systolic pressure (red dots), not just LV diastolic pressure (green dots) alone.
Extensive Preclinical Testing: SVC vs IVC Occlusion

SVC Occlusion Provides Effective & Reproducible LV Unloading

Kapur Lab
Clinical Proof of Concept Study
SVC Occlusion in Acute Heart Failure

Study Design: Prospective, single-arm, proof-of-concept study investigating superior venocaval (SVC) occlusion as a therapeutic approach to improve heart function in human subjects with advanced heart failure.

Primary Objective: confirm safety of transient SVC occlusion including neurologic assessment before, during, and for 24 hours post-procedure

Secondary Objective: measure acute hemodynamic changes associated with transient SVC occlusion

Study Population: 18-75 year old patients admitted with acutely decompensated heart failure with reduced ejection fraction referred for cardiac catheterization

IRB Approved Protocol
Clinical Proof of Concept Study
SVC Occlusion in Acute Heart Failure

A

B

Patients 1 - 5
Consent RHC SVC Occlusion RHC 24 Hours
* * * * * *

Patients 6 - 8
Consent RHC SVC Occlusion RHC SVC Occlusion RHC 72 Hours
* * * * * * * *

Clinical Proof of Concept Study
SVC Occlusion in Acute Heart Failure

Pre-Occlusion SVC Diameter | SVC Occlusion | Post-Occlusion Non-injured SVC
Clinical Proof of Concept Study
SVC Occlusion in Acute Heart Failure

Patient 4

Baseline SVC OCCLUSION RELEASE

Pressure (mmHg)

0 10 20 30 40 50 60
1 MIN 2 MIN 3 MIN 5 MIN Post 5 MIN

Baseline SVC OCCLUSION RELEASE

Clinical Proof of Concept Study
Clinical Proof of Concept Study
SVC Occlusion in Acute Heart Failure

![Graphs showing changes in various hemodynamic parameters](image)

From Proof of Concept to Device Development
preCARDIA Generation 1

Standard PA catheter with mounted SVC occlusion balloon
Pump Controller
- Programmable duty cycles: 5 minutes occluded, 10 sec unoccluded
- Monitors IJ & RA pressures to ensure occlusion, safe deflation of the balloon & overpressure in the venous system

Cart + Pump Controller

**preCARDIA** Generation 1

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**VENUS-HF**

**Early Feasibility Study (EFS)**

Prospective, multicenter EFS to confirm the safety and feasibility of the preCARDIA System.

- Enrolling 10-30 in-patients with acute congestive heart failure without shock
- Intermittent occlusions up to 12 hours (up to 24 hours after 3-5 patients)
- Patients followed for 30 days
- Primary Endpoint: Safety and Feasibility
- Early data supporting efficacy will be collected

For example: Hemodynamic response, renal function and urine output, length of stay, biomarker analysis
Acute Cardiac Unloading and Recovery (A-CURE)
A Global Team of Physicians and Scientists
August 2019: Paris, France

Clinical Excellence
Preclinical Testing
Fundamental Discoveries
Preclinical DTU Trial
Clinical DTU Pilot Trial Completed

Ventricular Unloading
State of the Art and Future Directions

Thank You
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