MHIF Research Highlights: APRIL 2019

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

**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!

**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*
2019 Howard B. Burchell Memorial Lecture
Ventricular Unloading: State of the Art and Future Directions

Speaker: Navin K. Kapur, MD, FAHA, FACC, FSCAI
Executive Director, The CardioVascular Center for Research and Innovation (CVCRI)
Director, Acute Circulatory Support Program
Director, Interventional Research Laboratories
Investigator, Molecular Cardiology Research Institute
Associate Professor, Dept of Medicine/Division of Cardiology
Tufts Medical Center, Boston, MA

Learning Objectives
At the completion of this activity, the participants should be able to:
• Define the physiologic parameters associated with ventricular loading and unloading.
• Discuss various approaches to unload the left or right ventricle.
• Discuss emerging clinical applications for ventricular unloading in AMI, Shock, and Heart Failure.

Minneapolis Heart Institute Foundation Cardiovascular Grand Rounds
Date: April 8, 2019 | Time: 7:00 – 8:00 AM | Location: Abbott Northwestern Hospital Education Building, Auditorium A/B

Webinar: If you cannot attend grand rounds in person, attend via webcast (you can join the webinar up to 15 minutes before the presentation starts at 7:00am).
Link to attend webinar: mhif.adobeconnect.com/gr/ Please enter as a guest (first and last name), not a registered user.
Dial in number: 1-800-351-4881, Passcode: 6659327. To receive credit, provide your credential when providing your name to the operator.

About: Dr. Howard B. Burchell
Howard B. Burchell, MD, was born in Athens, Ontario, Canada. He received his medical degree from the University of Toronto in 1932. He continued his training at Toronto General Hospital, the University of Pittsburgh, the Mayo Graduate School, and the London Hospital Medical School and Heart Hospital in England. After World War II, during which Dr. Burchell served in the U.S. Army Medical Corps, he returned to the Mayo Clinic as a consultant, ultimately becoming Professor of Medicine. In 1968, Dr. Burchell was appointed Chief in Cardiology at the University of Minnesota Medical School, a position he held until his official retirement in 1975.

After retirement, Dr. Burchell was Professor Emeritus of Medicine and an active participant in the medical academic life of the Minneapolis/St. Paul community. He received several professional honors both during his career and after retirement. Today he is widely recognized as one of the foremost authorities in cardiology during the 1950s and 1960s. He is considered to have set the stage, with his colleagues, for the ablation of accessory AV connections, which ultimately led to the current era of interventional cardiac electrophysiology. The annual Burchell lecture is a tradition that was created over fifteen years ago as a way to honor Dr. Burchell and his contributions to the world of medicine.
Accreditation

Physician
Allina Health is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. Allina Health designates this live activity for a maximum of 1.0 AMA PRA Category 1 Credit(s)TM. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Nurse
This activity has been designed to meet the Minnesota Board of Nursing continuing education requirements for 1.0 hours of credit. However, the nurse is responsible for determining whether this activity meets the requirements for acceptable continuing education.

Disclosure Policy and Statements
Allina Health, Learning & Development intends to provide balance, independence, objectivity and scientific rigor in all of its sponsored educational activities. All speakers and planning committee members participating in sponsored activities and their spouse/partner are required to disclose to the activity audience any real or apparent conflict(s) of interest related to the content of this conference.

The ACCME defines a commercial interest as “any entity” producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients. The ACCME does not consider providers of clinical service directly to patients to be commercial interests - unless the provider of clinical service is owned, or controlled by, an ACCME-defined commercial interest.

Moderator(s)/Speaker(s)
Dr. Navin Kapur has disclosed the following relationships. He receives Grant/Research Support and Honoraria from and is a consultant to Abiomed, Abbott, Boston Scientific, Medtronic and MD Strong/Maquet.

Planning Committee
Dr. Alex Campbell, Jake Cohen, Jane Fox, Dr. Mario Gössl, Dr. Kevin Harris, Dr. Kasia Hryniewicz, Rebecca Lindberg, Amy McMeans, Dr. Michael Miedema, Dr. JoEllyn Moore, Pamela Morley, Dr. Scott Sharkey, and Jolene Bell Makowesky have disclosed that they DO NOT have any real or apparent conflicts with any commercial interest as it relates to the planning of this activity/course. Dr. David Hurrell has disclosed the following relationship Boston Scientific: Chair, Clinical Events Committee.

Non-Endorsement of Commercial Products and/or Services
We would like to thank the following companies for exhibiting at our activity: Actelion Pharmaceutical Companies of Johnson & Johnson Janssen Pharmaceutical Companies of Johnson & Johnson
Accreditation of this educational activity by Allina Health does not imply endorsement by Allina Learning & Development of any commercial products displayed in conjunction with an activity. A reminder for Allina employees and staff, the Allina Policy on Ethical Relationship with Industry prohibits taking back to your place of work, any items received at this activity with branded and or product information from our exhibitors.

PLEASE SAVE YOUR SERIES Flier
When you request a transcript this serves as your personal tracking of activities attended. Most professional healthcare licensing/certification boards will not accept a Learning Management System (LMS) transcript as proof of credit; there are too many LMS’s across the country and their validity/reliability are always in question. If audited by a licensing board or submitting for license renewal or certification renewal, boards will ask you not the entity providing the education for specific information on each activity you are using for credit. You will need to demonstrate that you attended the activity with a copy of your certificate/evidence of attendance, a brochure/flier and/or the conference handout. Each attendee at an activity is responsible for determining whether an activity meets their requirements for acceptable continuing education and should only claim those credits that he/she actually spent in the activity. Maintaining these details are the responsibility of the individual.

PLEASE SAVE A COPY OF THIS Flier AS YOUR CERTIFICATE OF ATTENDANCE:

Signature: ____________________________________________

My signature verifies that I have attended the above stated number of hours of the CME activity.

Together, we can create a world without heart and vascular disease.
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 Heart Failure
LVEF 25%

11/2007
Readmitted - HF
ICD Implanted
LVEF 25%

3/2008
Readmitted Recurrent HF
LVEF 25%

HR-PCI

4/2009
Readmitted – HF/ACS
Impella Supported
LAD and Lx PCI
LVEF 25%

Ambulatory Shock

7/2012
Readmitted Recurrent HF
LVEF 20%

Advanced HF-Shock

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

12/2017
Cardiogenic Shock
Biventricular Centrimags
LVEF 10%

12/2017
Orthotopic Heart Transplant
LVEF 65%

4/2018
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

A

B

Pressure

Slope : Emax

PVA

Vo

Volume

Vo2

Oxygen cost of PVA

crossbridge cycling

EC coupling

Basal metabolism

PVA

A

LV Pressure (mmHg)

LV Volume (ml)

PVA=SW+PE

PE

SW

B

Oxygen for:

Mechanical Work

Calcium Cycling

Basal Metabolism

MV/O2 (mL/O2/min)

PVA (mmHg.ml)
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
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>
### 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><strong>Cold</strong></td>
<td>Classic Cardiogenic Shock (↓CI; ↑SVRI; ↑PCWP)</td>
<td>Euvolemic Cardiogenic Shock (↓CI; ↑SVRI; ↔PCWP)</td>
</tr>
<tr>
<td><strong>Warm</strong></td>
<td>Vasodilatory Cardiogenic Shock or Mixed Shock (↓CI; ↓/↔SVRI; ↑PCWP)</td>
<td>Vasodilatory Shock (Not Cardiogenic Shock) (↑CI; ↓SVRI; ↓PCWP)</td>
</tr>
</tbody>
</table>

*Circulation. 2017;136:e232–e268*

### Evolution of Ventricular Unloading Devices

- **2007**
  - IVADs
  - TH-RVAD
  - TH + 5.0
- **2017**
  - HVAD
  - Impella CP
  - BiPellas
  - 5.0 as a Bridge to Recovery

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MHIF CV Grand Rounds – April 8, 2019
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**
- Continuous Flow Pumps
  - Axial-Flow
    - Impella CP
    - PHP *
  - Centrifugal Flow
    - TandemHeart
    - VA-ECMO
- Pulsatile
  - IABP

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

A. Impella CP: 3.1 LPM

B. TandemHeart: 3.1 LPM

C. TandemHeart: 4.4 LPM

End-Systolic Pressure

Stroke Volume

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
Continuous Flow Physiology: Afterload Sensitivity

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

A

B

Patel and Bezerra et al ASAIO 2018

Success in Cardiogenic Shock Requires Early Initiation of Acute MCS

** QUALITY MEASURES **
- 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

O’Neill, et al, Am Heart J. 2018
Survival to Explant
Pre-PCI: 59% Post-PCI: 62% P<0.001

Survival to Discharge
Pre-PCI: 65% Post-PCI: 41% P=0.003

Basir, et al, Am J Cardiol, 2017
Survival to Discharge
Pre-PCI: 46% Post-PCI: 18% P<0.04

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

Schroeter et al., J Inv Cardiol 2016
Survival to 1 Year
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>Date</th>
<th>Event Description</th>
<th>LVEF</th>
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</thead>
<tbody>
<tr>
<td>10/2007</td>
<td>Anterior MI LAD PCI and IABP</td>
<td>20%</td>
</tr>
<tr>
<td>11/2007</td>
<td>Readmitted Heart Failure</td>
<td>25%</td>
</tr>
<tr>
<td>3/2008</td>
<td>Readmitted - HF ICD Implanted</td>
<td>25%</td>
</tr>
<tr>
<td>4/2009</td>
<td>Readmitted - HF/ACS Impella</td>
<td>25%</td>
</tr>
<tr>
<td>7/2012</td>
<td>Readmitted Recurrent HF</td>
<td>20%</td>
</tr>
<tr>
<td>3/2015</td>
<td>Readmitted Recurrent HF</td>
<td>20%</td>
</tr>
<tr>
<td>12/2017</td>
<td>Cardiogenic Shock Impella + VA-ECMO</td>
<td>10%</td>
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<td>12/2017</td>
<td>Cardiogenic Shock Biventricular Centrimags</td>
<td>10%</td>
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<tr>
<td>4/2018</td>
<td>Orthotopic Heart Transplant</td>
<td>65%</td>
</tr>
</tbody>
</table>

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

**A**

- Deformation of ductile material
- Plastic region
- Elastic region
- Stress
- Strain

**B**

- Myocardial Remission
- Irreversible Damage
- LV pressure
- LV volume

**C**

- Myocardial Recovery
- Reversible Damage
- LV pressure
- LV volume

Mann D et al JACC 2012

- Dilated CM
- Acute MI
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. Kjekshus, M.D., Burton E. Sobel, 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

US National Heart Attack Alert Program (NHAAF)
In STEMI, Timing is Everything

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.

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

Heart Attacks Lead to Heart Failure

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>
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<td>Before vs After</td>
<td>LAD</td>
<td>Ligation</td>
<td>IABP</td>
<td>Yes</td>
<td>Roberts &amp; Gay [6]</td>
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<td>Before</td>
<td>LAD</td>
<td>Ligation</td>
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<td>Haston &amp; McNamara [7]</td>
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<tr>
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<td>Before</td>
<td>LAD</td>
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<td>IABP</td>
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<td>Laas &amp; Replogle [8]</td>
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<td>Before vs After</td>
<td>LAD</td>
<td>Ligation</td>
<td>IABP</td>
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<td>Ledoux &amp; Smalling [9]</td>
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<td>Hemopump/IABP</td>
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<td>Yes / No</td>
<td>Ashour &amp; Smalling [16]</td>
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<td>Sheep</td>
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<td>120</td>
<td>Before</td>
<td>LCx</td>
<td>Ligation</td>
<td>Impella LD</td>
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<td>LAD</td>
<td>Balloon Angioplasty</td>
<td>Impella CP</td>
<td>Yes</td>
<td></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

<table>
<thead>
<tr>
<th>Infarct size, % of left ventricular mass</th>
<th>Per-protocol analysis, No. (%)</th>
<th>Primary End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IABP</td>
<td>No IABP</td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>36.8 (27.4-42.1)</td>
<td>42.1 (38.7-45.6)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>36.8 (29.0-52.2)</td>
<td>42.8 (27.2-54.7)</td>
</tr>
</tbody>
</table>

Patel, M. R. et al. JAMA 2011
Introducing the Concept of Primary Unloading

**Hypothesis:** Initially reducing LV work and *delaying coronary reperfusion* limits myocardial injury in AMI.

![Diagram of MI and MI + LV Unloading](image)

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

Kapur NK et al Circulation 2013

Percutaneous Left Atrial Decompression Reduces LV Wall Stress and Reduces Infarct Size (30 minutes unloading before reperfusion)

![Diagram of left atrial decompression](image)

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
History of Changes

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
Unloading Mechanistic Impact 2
Unloading Increases Perfusion without Reperfusion

Unloading Increases Perfusion without Reperfusion

Seiler and Meier et al. JACC 1998; Lee and Park et al. JACC 2000
Annamalali, Briceno and Kapur NK et al. 2019
LV unloading increases collateral blood flow (reduces ischemia)

Increased collateral blood flow reduces infarct size

Unloading Mechanistic Impact 2
Unloading Increases Perfusion without Reperfusion

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

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

Immediate Reperfusion

Impella Pre-Reperfusion

VA-ECMO Pre-Reperfusion

Annamalai, Briceno and Kapur NK et al. 2019

Annamalai, 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

Ischemia → Oxidative Phosphorylation → ATP Synthesis

Reperfusion

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

Primary Reperfusion

Primary Unloading

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
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 Mechanistic Impact 4
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

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

Unloading Mechanistic Impact 5
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?

Addressing The Ultimate Question: ‘So What?’

The Rationale for a Pilot Before a Pivotal Trial
Do we really need a 30 minute delay to reperfusion?
Door To Unload: STEMI Pilot Trial: Study Design

Anterior STEMI Referred for Primary PCI

- Electrocardiographic Confirmation
- Informed Consent and Enrollment

- 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

Kapur NK and O’Neill W et al Circulation 2018

Door To Unload: STEMI Pilot Trial: Patient Disposition

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
  - 3-5 Day CMR (n=20)

- U-DR (n=25)
  - No CMR Completed (n=4)
    - 1 expired
    - 2 claustrophobic
    - 1 chronic kidney disease
  - 30 Day CMR (n=21)
  - 30 Day MACCE (n=25)

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
DTU-STEMI Results: 3-5 Day CMR Parameters

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)

Increasing severity of MI

- All Patients: U-IR 51.6% vs U-DR 44.2%, p = 0.28
- ST Sum >4: U-IR 56.4% vs U-DR 45.0%, p = 0.10
- ST Sum >5: U-IR 57.7% vs U-DR 45.3%, p = 0.09
- ST Sum >6: U-IR 59.9% vs U-DR 44.1%, p = 0.04
Despite 60 additional minutes of ischemic time, the delay arm of the STE>6 group had smaller infarct size.

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 HUMAN STUDY**

- 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%

**Recurrence HF**
- 11/2007: Readmitted, Heart Failure, LVEF 25%
- 3/2008: Readmitted, HF, ICD Implanted, LVEF 25%
- 4/2009: Readmitted – HF/ACS, Impella Supported, LAD and LCx PCI, LVEF 25%

**Recurrence HF**
- 7/2012: Readmitted, Recurrent HF, LVEF 20%
- 3/2015: Readmitted, Recurrent HF, LVEF 20%

**Shock**
- 3/2017: Cardiogenic Shock, Biventricular CMAG, LVEF 10%
- 4/2018: Orthotopic Heart Transplant, LVEF 65%

The Importance of Preload in Heart Failure

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

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

**Stroke Volume**
- LVEDP or LVEDV

**Otto Frank**
- 1865-1944

**Ernest Starling**
- 1866-1927
Cardiac Unloading: An Important Target of Therapy in ADHF

Congestion is as Critical as Cardiac Output

**Conclusion:** Final PCWP and final right atrial pressure were stronger predictors of postdischarge outcomes than CI in patients with advanced heart failure. The ability to lower filling pressures appears to be more pronostically important than improving CI in the management of patients with advanced heart failure.

Right Atrial Pressure is Associated with Increased Mortality in Heart Failure

**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.

**Preload:**
The load imposed on the ventricle at the end of diastole. The most common measures of preload include end-diastolic volume (EDV), end-diastolic pressure (EDP).

The different loops are obtained with different levels of preload, but constant contractility.
Extensive Preclinical Testing: SVC vs IVC Occlusion

Kapur Lab

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  RHC  24 Hours

*  *  *  *  *

SVC Diameter

Pre-Occlusion SVC Diameter

SVC Occlusion

Post-Occlusion Non-injured SVC

Patients 6 - 8

Consent  RHC  SVC  RHC  SVC

*  *  *  *  *

5 mins  10 mins

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

Patient 4

Baseline | SVC OCCLUSION | RELEASE

Clinical Proof of Concept Study

Baseline | 1 MIN | 2 MIN | 3 MIN | 5 MIN | Post 5 MIN

Right Atrial Pressure
Mean Pulmonary Artery Pressure
Pulmonary Capillary Wedge Pressure
Right Internal Jugular Vein Pressure

HR
JVP
mPA
MAP
RA
PCWP

Mean Heart Rate (bpm)
Jugular Venous Pressure (mmHg)
Mean Pulmonary Artery Pressure (mmHg)
Right Atrial Pressure (mmHg)
Pulmonary Capillary Wedge Pressure (mmHg)
Pulmonary Venous Pressure (mmHg)

* indicates significant change from baseline.
Clinical Proof of Concept Study
SVC Occlusion in Acute Heart Failure

Right Atrial Pressure (mmHg)

P<0.01

Jugular Venous Pressure (mmHg)
P<0.01

Mean Arterial Pressure (mmHg)
P=NS

Cardiac Output (L/min)
P=NS

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

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

Ventricular Unloading
State of the Art and Future Directions

Thank You
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