Interatrial Shunt for the Treatment of Heart Failure with Preserved Ejection Fraction

Rami Kahwash, MD
Professor in Internal Medicine
Division of Cardiovascular Medicine
Section of Heart Failure/Transplant
The Ohio State University
Wexner Medical Center

Objectives

- Review the incidence and demographics of Heart Failure with preserved Ejection Fraction (HFpEF)
- Understand the pathophysiology for HFpEF
- Review management of HFpEF
- Discuss the role of Left Atrial Pressure (LAP) in symptoms & prognosis of HFpEF
- Highlight future directions for management of HFpEF including InterAtrial Shunt Device (IASD)
**Definition**

- HFpEF variably classified as EF >40%, >45%, >50%
- Syndrome of HFpEF:
  - clinical signs or symptoms of HF
  - evidence of preserved or normal LVEF
  - evidence of abnormal LV diastolic dysfunction by Doppler echocardiography or cardiac catheterization
- More challenging to diagnose than HFrEF – largely diagnosis of exclusion

---

**DD vs. DHF vs. HFpEF**

[Diagram showing the differentiation between DD, DHF, and HFpEF]

Courtesy of Sanjiv J. Shah, MD

Vasan RS, Levy D. Circulation 2000
H2-FPEF Score for Diagnosis

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Values</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_2$</td>
<td>Heavy</td>
<td>2</td>
</tr>
<tr>
<td>$F$</td>
<td>Hypertensive</td>
<td>1</td>
</tr>
<tr>
<td>$F$</td>
<td>Atrial Fibrillation</td>
<td>3</td>
</tr>
<tr>
<td>$P$</td>
<td>Pulmonary Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>$E$</td>
<td>Elder</td>
<td>1</td>
</tr>
<tr>
<td>$F$</td>
<td>Filling Pressure</td>
<td>1</td>
</tr>
</tbody>
</table>

H$_2$FPEF score = Sum (0-9)

By 2020, 65% of hospitalized HF pts will have EF > 40%
Heart Failure Outcomes

5-yr mortality: HFP EF 65%, HFr EF 68%, (HR 0.96, p < 0.03)
HFrEF: Survival increased over time (HR 0.98/yr, p = 0.005)
HFP EF: Survival did not change over time

HFpEF, Few Established Therapies
Management – General Principles

- Impaired response to stress
  - Atrial fibrillation: loss of atrial contraction reduces LV filling and stroke volume
  - Tachycardia: shortens duration of diastole
  - Elevated BP: increases ventricular wall stress worsening myocardial relaxation
  - Acute ischemia worsens diastolic function
- All may result in ↑ LVEDP, pulmonary congestion, or edema

HFpEF, Few Established Therapies

2017 Update: Class IIa recommendation for use of aldosterone antagonists in appropriately selected patients with HFpEF (with EF ≥45%, elevated BNP or HF admission within 1 year, estimated glomerular filtration rate >30 and creatinine <2.5 mg/dl, potassium <5.0 mEq/L), to decrease hospitalizations.
Pacing for HFpEF?

LV chamber size and compliance can be beneficially modulated by elevating heart rate for short periods of time.

Case Presentation

78 Year-old woman referred for evaluation of progressive DOE
- PMH: HTN, DM II
- MEDs: Norvasc, HCTZ, metformin
- ECG: NSR, LVH by voltage criteria, LAE
- CXR and PFT: unremarkable
- Lab: BNP~80
- Stress Echo: exercised 3 minutes and stopped due to SOB & fatigue. No stress induced WMA at HR achieved.
- Echo: mild LVH, normal LVEF, LAE, RVSP: 35 mm Hg
- LHC: mild plaque disease, LVEDP: 14 mm Hg
- RHC: RA: 5, PA: 34/13, PCWP: 14, CO/CI: 5/2

Next Step?
Amyloid Prevalence in HFpEF (13.3 %)

Heart Failure with Preserved Ejection Fraction

Patients with exertional dyspnea, EF > 50%, n = 55
- No significant coronary disease
- Normal brain natriuretic peptide, resting
- Exercise PCW > 25 mm Hg
- Greater increase in PCW
- Tempered increases in HR, cardiac output
- PASP > 45 mm Hg ~95% Sn and Sp

Borlaug et al. 2010; Circ Heart Fail
Exercise PCW Pressure in HFpEF

Retrospective study, n = 355 with suspected HFpEF

Exercise Hemodynamics can identify HFpEF, correlate to exercise capacity, and are more predictive of mortality
HFpEF: A New Approach

- Environment, Diet, Comorbidities, Genetic Susceptibility
- LA pressure
- HFpEF
- Exercise-induced Diastolic Dysfunction
- Volume Overload
- Pulmonary HTN, RV Failure

L → R Shunts may Reduce HF Symptoms

- Lutembacher syndrome described in 1916
- ASD in the context of mitral stenosis
  - MS patients with congenital ASD did better compared to MS w/o ASD

Left to Right Shunts and Heart Failure

Masked Left Ventricular Restriction in Elderly Patients with Atrial Septal Defect

18 patients had LA pressures measured during balloon occlusion.

In 7, LA pressure increased considerably.

Two of them proceeded with ASD closure and developed CHF.

InterAtrial Shunt Device - Mode of Action

Elevated LV filling pressures (Elevated LAP)

Pulmonary Venous hypertension

Pulmonary Congestion & Dyspnea (rest/exercise)

Transcatheter interatrial shunt device
Computer simulation demonstrated that an 8mm interatrial shunt device (IASD®) would provide acute LA decompression during exercise.

Kaye et al J Card Fail 2014

“One person with passion is better than forty people merely interested”.

~ E.M Forster
Corvia Interatrial Shunt Device (IASD)

Corvia Medical IASD® Clinical Studies

- Pilot study (N=11): non-randomized, single-arm
  - Completed (Søndergaard L, et al. Eur J Heart Fail 2014)
- REDUCE LAP-HF (CE Mark) Study (N=64): non-randomized, single-arm
  - Completed (Hasenfuß Lancet 2016; Kaye Circ. HF 2016)
- REDUCE LAP-HF I (N=44): RCT mechanistic study
  - FDA IDE 30 Day Complete (Feldman T… Shah SJ. Circulation. 2018;137:364–375)
  - 1Y follow-up complete
- REDUCE LAP-HF II (N=608): RCT pivotal study
  - FDA approved IDE; recruiting
- HF/EF Feasibility study
  - FDA approved IDE; recruiting
- REDUCE LAP-HF III (N=100): Post-market Registry Germany
  - Recruiting

Feldman T et al., Circ Heart Fail 2016
PCW increased from 17 → 35 mm Hg with exercise

Inclusion
- N = 64, LVEF ≥ 40%
- NYHA class II-IV
- PCWP ≥ 15 mmHg (rest), ≥ 25 (exercise)

1-year survival 95%; No device related adverse events

Key
Circ Heart Fail. 2016;9(1)
### Safety (MACCE) and Device Performance

#### MACCE event

<table>
<thead>
<tr>
<th>Event</th>
<th>Six months %</th>
<th>One year %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
<td>4.7 (3/64)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>1.5 (1/64)* (pt died)</td>
</tr>
<tr>
<td>MI</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Systemic embolic event</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Implant removal</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Device patency confirmed in 54 subjects (by echo or oximetry)

---

### Effectiveness

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Six months %</th>
<th>One year %</th>
</tr>
</thead>
<tbody>
<tr>
<td>L→ R Shunt flow (Echo)</td>
<td>100 (49/49)</td>
<td>100 (48/48)</td>
</tr>
<tr>
<td>R→ L Shunt flow (Echo)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Qp:Qs</td>
<td>1.27 ± 0.24</td>
<td>1.28 ± 0.25</td>
</tr>
</tbody>
</table>

Device patency confirmed in 54 subjects (by echo or oximetry)
Efficacy at 6 & 12 months
(Patients with data at all 3 time points)

**NYHA Class**
- Mean Δ at 1 year: -0.8
  - 71% improved to class I

**6MWT**
- Mean Δ at 1 year: 33m
  - 47% improved > 20m

**MLWHF**
- Mean Δ at 1 year: 15 points
  - 82% improved > 5 points

Invasive Hemodynamic Results (rest)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Six months</th>
<th>One year</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA pressure</td>
<td>8 ± 3</td>
<td>11 ± 6</td>
<td>10 ± 4</td>
</tr>
<tr>
<td>PA mean pressure</td>
<td>25 ± 8</td>
<td>23 ± 7</td>
<td>26 ± 8</td>
</tr>
<tr>
<td>Wedge pressure</td>
<td>19 ± 6</td>
<td>16 ± 8</td>
<td>17 ± 6</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>5.2 ± 1.3</td>
<td>6.3 ± 1.4**</td>
<td>6.7 ± 1.8**</td>
</tr>
</tbody>
</table>

*p < 0.0001

* Higher than at 6M: **p < 0.01 vs baseline
Corvia Medical IASD® Clinical Studies

- **Pilot study (N=11):** non-randomized, single-arm
  - Completed (Søndergaard L, et al. Eur J Heart Fail 2014)
- **REDUCE LAP-HF (CE Mark) Study (N=64):** non-randomized, single-arm
  - Completed (Hasenfuß Lancet 2016; Kaye Circ. HF 2016)
- **REDUCE LAP-HF I (N=44):** RCT mechanistic study
  - FDA IDE 30 Day Complete (Feldman T, Shah SJ. Circulation. 2018;137:364–375)
  - 1Y follow-up complete, submitted ESC
- **REDUCE LAP-HF II (N=608):** RCT pivotal study
  - FDA approved IDE; recruiting
- **HF/EF Feasibility study**
  - FDA approved IDE; recruiting
- **REDUCE LAP-HF III (N=100):** Post-market Registry Germany
  - Recruiting

**REDUCE LAP-HF I (n=44)**
Randomized, controlled trial (1:1)
NYHA III-IV, LVEF > 40%, HF Hosp or ↑BNP PCW ≥ 25 mm Hg (Exercise); PCW - RA ≥ 5 mm Hg

30-d Hemodynamic Outcomes

*No adverse events at 30-d follow up in treated arm*

Feldman et al., 2018 Circulation
At 12 months, there was a trend toward greater improvement in NYHA class compared to Control:

- More patients improved 2 classes
- More patients improved 1 class
- Fewer patients with an increase in NYHA class
- Greater reduction in median and mean NYHA class from baseline to 12 months

*powered for primary and not for secondary outcome measures*
Change in NYHA Functional Class: InterAtrial Shunt Device vs. Sham Control

Cumulative Incidence of MACCRE and Heart Failure Events Requiring Intravenous Diuretic Treatment Through 12 Months

MACCRE: Death, stroke, device/procedure related adverse events, renal dys
Baseline, 6-, and 12-Month Echocardiographic Parameters of Cardiac Structure and Function

- No significant change in left heart structure/function
  - Trend towards greater reduction in LA volume index in IASD vs. control at 12 months (6.3±10.7 vs. 1.5±14.2 ml/m²; p=0.078).
  - Increase in RVEDV (p=0.01) without any change in RVEF in the IASD arm.

Conclusions

- REDUCE LAP-HF I confirms the 1 year patency of the IASD
- Through 1 year of follow-up IASD treatment compared to sham-control:
  - Appears safe
  - Is associated with favorable trends in
    - MACCRE
    - HF hospitalization
    - NYHA class
One-Year Safety and Clinical Outcomes of a Transcatheter Interatrial Shunt Device for the Treatment of Heart Failure With Preserved Ejection Fraction in the REDUCE Elevated Left Atrial Pressure in Patients With Heart Failure (REDUCE LAP-HF I) Trial: A Randomized Clinical Trial

Published online August 27, 2018

Available at jama.com and on The JAMA Network Reader at

Available at jama.com and on The JAMA Network Reader at

REDUCE LAP-HF II Study
Multicenter, Prospective, 1:1 Randomized, SHAM Controlled, DOUBLE Blinded Trial

REDUCE LAP-HF II Study
N = 608

Primary endpoint composite of:
- Cardiovascular mortality or non-fatal, ischemic stroke through 12 months; and
- Rate of total (first plus recurrent) HF admissions, healthcare facility visits for IV diuresis for HF through 12 months; and
- Change in KCCQ score between baseline and 12 months.

Major secondary efficacy endpoints
- Change in NYHA class between baseline and 12 months
- Change in KCCQ score between baseline and 12 months

The Primary endpoint will be analysed using the Finkelstein-Schoenfeld methodology

ClinicalTrials.gov Identifier: NCT03088033
Porcine pericardial leaflets – improve flow mechanics – prevent R to L shunting and paradoxical embolization

- Anticoagulation for 3 months

14F delivery system

Nitinol frame

10/4/2019
II. Devices and Outcomes

Feasibility

Unidirectional left-to-right interatrial shunting for treatment of patients with heart failure with reduced ejection fraction: a safety and proof-of-principle cohort study

10 patients with HFrEF, NYHA 3, Mean LVEF 25%
100% successfully implanted
9/10 survived to 3 months

RA Pressure

Mean PA Pressure

PCWP (Rest)

6-min Walk

No Change Resting RA, mPA Pressure

Amat-Santos et al., 2015 EuroIntervention 10(9): 1127-1131

GW Stone, TCT 2017

V-Wave Open-Label
N = 38, 30 HFrEF, 8 HFrEF, 12-mo Follow up

Feasibility

- Reduced L → R shunt flow
  - Absent in 5/26 (15%)
  - Reduced in 13/36 (36%)
- Neointimal proliferation
  - Thickening, commissural fusion, fixation and stenosis
- Not associated with thromboembolic events

V-Wave
V-Wave Open-Label
N = 38, 30 HFpEF, 8 HFpEF, 12-mo
Follow up

P = 0.009 vs. baseline
P = 0.003 vs. baseline
P = 0.10 vs. baseline

GW Stone, TCT 2017

V-Wave Open-Label
N = 38, 30 HFpEF, 8 HFpEF, 12-mo
Follow up

Right Atrium
Left Atrium

"Exit Hood" to block potential paradoxical emboli

Inter-atrial septum
Nitinol frame

14F delivery system

Hourglass shape
- secure and atraumatic septal retention
- minimal ID 5.1 mm orifice

Full ePTFE encapsulation
- blocks tissue ingrowth

DAPT for 6 months

Generation 2: V-Wave Interatrial Shunt

 WT Abraham, TCT 2017
Reducing Lung Congestion Symptoms Using the V-wave Shunt in Advanced Heart Failure (RELIEVE-HF)

- Estimated enrollment 500 patients
- Inclusion: NYHA > III, HFrEF and HFpEF on GDMT, a HF hospitalization in 12 months, or BNP > 300.
- Exclusion: PASP > 70, RV dysfunction, moderate or greater valve disease
- Randomized 1:1
- Primary Outcomes
  1. (Safety) Device related adverse events, cardiovascular and neurological
  2. (Effectiveness) Composite death, transplant or LVAD, heart failure hospitalizations, and change in 6 minute walk test.

Enrolling now, estimated completion October 2021

Conclusions

- Devices that permit interatrial flow are emerging for a range of conditions
- Early experience suggests improved hemodynamics and functional status
- Ongoing trials and surveillance
  - Durability of functional improvement, shunt
  - Potential side effects
- Represent first device based therapies for HFpEF
THANK YOU