An Interatrial Shunt Device for Diastolic Heart Failure

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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

Vasan RS, Levy D. Circulation 2000

HFpEF: Increasing Prevalence

GWTG - HF: N=110,621 patients hospitalized with HF; P<0.0001 for trend of increased HFpEF prevalence (based on data from Steinberg et al. Circulation 2012)

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

Heart Failure Outcomes

Trends in Prevalence and Outcome of Heart Failure with Preserved Ejection Fraction

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

HFpEF, Few Established Therapies

Borlaug BA, Redfield MM. Circulation 2011;123:2006-2014
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

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic and diastolic blood pressure should be controlled according to</td>
<td>I</td>
<td>B (77,91)</td>
</tr>
<tr>
<td>published clinical practice guidelines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics should be used for relief of symptoms due to volume overload</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Coronary revascularization for patients with CAD in whom angina or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>demonstrable myocardial ischemia is present despite GDMT</td>
<td>Iia</td>
<td>C</td>
</tr>
<tr>
<td>Management of AF according to published clinical practice guidelines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>for HFpEF to improve symptomatic HF</td>
<td>Iia</td>
<td>C</td>
</tr>
<tr>
<td>Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HFpEF</td>
<td>Ila</td>
<td>C</td>
</tr>
<tr>
<td>ARBs might be considered to decrease hospitalizations in HFpEF</td>
<td>Iib</td>
<td>B (589)</td>
</tr>
<tr>
<td>Nutritional supplementation is not recommended in HFpEF</td>
<td>IIb</td>
<td>No Benefit C</td>
</tr>
</tbody>
</table>

Yancy, et al. JACC 2013
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: 8, PA: 34/13, PCWP: 15, CO/CI: 5/2.4

Next step:
A. Cardiac biopsy
B. RHC + Exercise
C. Tell her she does not have heart failure
D. Add Lasix 20 mg daily and follow up in 3 months

Heart Failure with Preserved Ejection Fraction

Patients with exertional dyspnea, EF > 50%, n = 55
- No significant coronary disease
- Normal brain natriuretic peptide, resting hemodynamics
  - mPAP < 25 mm Hg; PCW < 15 mm Hg
- Exercise PCW > 25 occurred in 32/55
  - 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 3:588-595.
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

Implications of Elevated LA Pressure in HFpEF

The magnitude of the exercise-mediated rise in PCWP in HFpEF is related to both symptoms and outcome.
Three types of HFpEF presentation

Shah SJ. JACC 2013

L → R Shunts may Reduce HF Symptoms

- Lutembacher syndrome described in 1916
- ASD in the context of mitral stenosis\(^1\)-\(^4\)
  - MS patients with congenital ASD did better compared to MS w/o ASD

\(^1\) Firket, 1880; \(^2\) Lutembacher, 1916; \(^3\) Rosenthal, 1956; \(^4\) Espino-Vela, 1959; \(^5\) Aldridge, 1965.
**Left to Right Shunts and Heart Failure**

*Masked Left Ventricular Restriction in Elderly Patients with Atrial Septal Defects.*

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.

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**InterAtrial Shunt Device - Mode of Action**

- Elevated LV filling pressures (Elevated LAP)
- Pulmonary Venous hypertension
- Pulmonary Congestion & Dyspnea (rest/exercise)

Transcatheter interatrial shunt device

CAUTION Investigational device. Limited by Federal (or United States) law to investigational use.
Corvia IASD System Components

Catheter

Implant
19mm OD
8 mm ASD

Handle

Exclusively for Clinical Investigation. CAUTION: Investigational device.
Limited by Federal (or United States) law to investigational use. 2 16F introducer compatible.

Left Atrial Decompression: IASD Rationale

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

Kaye et al JCardFail 2014
REDUCE LAP-HF Trial

Inclusion Criteria (n=64):
Open label
LVEF ≥ 40%,
NYHA class II-IV
Elevated PCWP
≥ 15 mmHg (rest) or
≥ 25 (supine bicycle exercise)

Objectives:
• Device Safety: major adverse cardiac, cerebrovascular and systemic embolic events – MACCE
• Device performance: L→R shunting (echocardiography)
• Clinical Benefits:
  ➢ clinical efficacy: NYHA class, quality of life (MLWHFQ), 6MW distance
  ➢ cardiac structure and function (echocardiography)
  ➢ rest and exercise hemodynamics

Baseline Characteristics (n=64)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Age (Y)</td>
<td>69±8</td>
</tr>
<tr>
<td>Gender (% Female/Male)</td>
<td>66 / 34</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>47 ± 7</td>
</tr>
<tr>
<td>NYHA Class (n, II/III/IV)</td>
<td>18/46/0</td>
</tr>
<tr>
<td>Minnesota Living with HF Score</td>
<td>49 ± 20</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>33 ± 6</td>
</tr>
<tr>
<td>Permanent AF (%)</td>
<td>36</td>
</tr>
<tr>
<td>NT-Pro BNP (median, IQR pg./ml)</td>
<td>377 (222-925)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>81</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>33</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>36</td>
</tr>
<tr>
<td>Diuretics at baseline (%)</td>
<td>91</td>
</tr>
<tr>
<td>Resting CVP (mm Hg)</td>
<td>9 ± 4</td>
</tr>
<tr>
<td>Resting PCWP (mm Hg)</td>
<td>17 ± 5</td>
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</table>
### Safety (MACCE) and Device Performance

#### MACCE event

<table>
<thead>
<tr>
<th>Event</th>
<th>Six months %</th>
<th>One year %</th>
</tr>
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<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>
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Device patency confirmed in 54 subjects (by echo or oximetry)

#### Effectiveness

<table>
<thead>
<tr>
<th>Effectiveness</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)

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>
Summary

- Implantation of an interatrial shunt device appears to be safe with an acceptable MACCE rate through one year of follow-up
- Interatrial shunt device patency was maintained through one year
- The clinical and hemodynamic benefit observed 6 months after implant was sustained through one year, with no evidence of adverse sequelae
  - Meaningful improvements in NYHA class, exercise capacity and QOL
  - Clinically meaningful reduction in normalized PCWP

REDUCE LAP-HF 1 (1st RANDOMIZED TRIAL)

- Multicenter, Prospective Randomized, Controlled, Patient Blinded Trial
- 1:1 randomization in the Cath. Lab
- Non-implant Intra Cardiac Echo (ICE) Control group
- Patients will be followed for 1 year, and annually every 12-months for 4 years after index procedure and implant
- 40 subjects at up to 20 investigational sites in the U.S.; and up to 5 investigational sites OUS.
- 1 month key outcome measure follow-up
  - Safety
  - PCWP change
**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**

```
CONTROL  IASD

PCWP (mmHg)

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Legs up</th>
<th>20W</th>
<th>Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTROL</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>IASD</td>
<td></td>
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</table>

*No adverse events at 30-d follow up in treated arm*
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Feldman et al., 2017 Circulation, AHA, in press

**II. Devices and Outcomes**

**Corvia Interatrial Shunt Device (IASD)**

*Early clinical experience suggests IASD Implantation associated with*

- No major device-related complications
- Procedural success
- No change in resting PCWP
- Decrease in exercise associated PCWP
- Stable shunt fraction ~ 1.3:1 up until 12-mos
- Improved 6-minute walk time, NYHA class, living-with-heart failure scores

Feldman, TCT 2017
II. Devices and Outcomes

**Corvia Interatrial Shunt Device (IASD) Studies**

- **Pilot study (n=11): non-randomized, single-arm**
  - Completed (Søndergaard L, et al. Eur J Heart Fail 2014); extended follow-up ongoing

- **CE Mark Study (n=64): non-randomized, single-arm**
  - Completed (Hasenfuß Lancet 2016; Kaye Circ. HF 2016); 2Y follow-up complete Q3 2017

- **REDUCE LAP-HF I (n=44): RCT mechanistic study**
  - FDA approved IDE; (enrollment complete); 1Y follow-up complete Dec 2017

- **REDUCE LAP-HF II (n=380): RCT pivotal study**
  - FDA approved IDE; recruiting

- **HFrEF Feasibility study**
  - FDA approved IDE; recruiting

- **REDUCE LAP-HF III (n=100): Post-market Registry Germany**
  - Recruiting

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**Our Experience…**

- **Recruitment**
  - EMR, cath lab database
  - Clinics

- **Research Coordinator**

- **Outreach**

- **Hemodynamics! Screen, screen, screen….”**
Strategies for LA Decompression

Although strongest hemodynamic rationale is perhaps HFpEF, trials to date have included HFrEF and pulmonary hypertension.

Affects degree and direction of shunt, different short-term goals, long-term ramifications.

Interatrial Shunt Device

II. Devices and Outcomes

The V-Wave Shunt Device

Porcine pericardial leaflets
- improves flow mechanics
- prevents R to L shunting and paradoxical embolization

Anticoagulation for 3 months

Right Atrium

Left Atrium
II. Devices and Outcomes

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

Feasibility

*\( p < 0.014 \) compared to baseline

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