An Interatrial Shunt Device for Diastolic Heart Failure

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Disclosure

- Consultant to Medtronic
- I will be discussing investigational devices (Corvia IASD and V-Wave shunt).
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

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

Survival HFrEF Vs. HFpEF

Survival is ~ 35% at 5 years

Owan TE et al, NEJM. 2006
Increased Diastolic Stiffness

Zile M et al., NEJM 2004

HFpEF: LV Response to Volume Loading

Zile M et al., NEJM 2004
HFpEF Treatment

- CHARM – Preserved (2003). Candesartan
- SENIORS (2005). Nebivolol
- DIG-PEF (2006). Digoxin
- RELAX – (2013) Sildenafil
- TOPCAT – (2014) Spironolactone
- NEAT-HFpEF-(2015). Long acting nitrate (Imdur)
- Ivabradine (2014, 2015), Edify in the EU (ongoing)
- PARAMOUNT- (2012). ARNI (entresto)
- PARAGON-HF - ARNI (ongoing)
- B-Preserve - Toprol Xl (ongoing)

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
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, THR was not achieved. 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

Exercise Hemodynamics Unmask pre-Clinical HFpEF
Elevated left atrial pressure, especially during exercise, is a near-universal finding in patients with HFPEF.

Increased LV passive stiffness
Reduced active LV relaxation
Reduced LA compliance
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.

**SYMPTOMS**

- Six minute walk (meters)
- Workload corrected PCWP (mmHg/W/kg)

**SURVIVAL**

- Work corrected PCWP > 25.5 mmHg/W/kg
- p = 0.03

- Work corrected PCWP > 25.5 mmHg/W/kg
- p < 0.001

HFpEF: A New Approach

**ENVIRONMENT, DIET**

**COMORBIDITIES**

**GENETIC SUSCEPTIBILITY**

- LA pressure

- HFpEF

**EXERCISE-INDUCED DIASTOLIC DYSFUNCTION**

**VOLUME OVERLOAD**

**PULMONARY HTN, RV FAILURE**

Shah SJ. JACC 2013

The Ohio State University Wexner Medical Center
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


Masked Left Ventricular Restriction in Elderly Patients With Atrial Septal Defects: A Contraindication for Closure?

Peter Ewert, MD, Felix Berger, MD, Nicole Nagdyman, MD, Oliver Kretschmar, MD, Sven Dittrich, MD, Hashim Abdul-Khaliq, MD, and Peter E. Lange, MD

Catheterization and Cardiovascular Interventions 52:177–180 (2001)
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InterAtrial Shunt Device - Mode of Action

Elevated LV filling pressures (Elevated LAP)
IASD area of intervention
Pulmonary Venous hypertension
Pulmonary Congestion & Dyspnea (rest/exercise)

Transcatheter interatrial shunt device
Corvia IASD System Components

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>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<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>
</tr>
</tbody>
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## 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>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)

**NYHA**
- Mean \( \Delta \) at 1 year: 0.8
- 77% improved 1.0 classes

**6MWT**
- Mean \( \Delta \) at 1 year: 30m
- 37% improved > 20m

**MLWHF**
- Mean \( \Delta \) at 1 year: 15 points
- 72% 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<0.01 vs baseline

** p<0.001 vs baseline

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Mean \( \Delta \) at 1 year: 15 points
- 72% improved > 5 points

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- 37% improved > 20m

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- 77% improved 1.0 classes

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Exercise Hemodynamic Results-1

**Exercise time**

- Baseline: 10 minutes
- 6M: 11 minutes
- 12M: 12 minutes

* p<0.05, ** p<0.01 vs baseline

**Workload**

- Baseline: 70 watts
- 6M: 80 watts
- 12M: 90 watts

** p<0.05, ** p<0.01 vs baseline

**PCWP**

- Baseline: 20 mm Hg
- 6M: 25 mm Hg
- 12M: 30 mm Hg

**Cardiac Output**

- Baseline: 7 L/min
- 6M: 9 L/min
- 12M: 11 L/min

** p<0.05, ** p<0.01 vs baseline

Exercise Hemodynamic Results-2

**Work indexed PCWP**

- Baseline: 100 mm Hg/(W/kg)
- 6M: 120 mm Hg/(W/kg)
- 12M: 140 mm Hg/(W/kg)

IASD therapy provides increased work capacity for a given LA pressure

* p<0.05, ** p<0.01 vs baseline
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 NHYA class, exercise capacity and QOL
  - Clinically meaningful reduction in normalized PCWP
- Randomized trials are undergoing

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
OSU Experience

- Close collaboration between heart failure & structural heart disease
- First enrollment in the USA
- First randomization in the USA
- Dr. Scott Lilly implanted the first IASD in the USA (2/3/2016)
- Research coordinator: Brittany Monk
- Top enrolling center (12 patients)

V wave - IASD with unidirectional shunt

- Limited experience in humans
- Good safety profile in a small feasibility study tested device implant in symptomatic class III with HFrEF (Lancet, 2016).
- Still in development, will include HFrEF as well
REDUCE LAP-HF II trial

- 1) NYHA > II with a history of NYHA III within the last 12 months
- 2) HF related hospitalization within the last 12 months or BNP > 50 within the last 6 months or intensification of oral diuretic within the last 12 months
- 3) EF > 40%

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Questions?