HFpEF – Unraveling the Causes and Finding New Treatments

The 7th Annual International Hawaii Symposium
November 30 – December 2, 2017
Island of Hawaii

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Paradox of the Stiff Heart

Heart Failure with Preserved Ejection Fraction (HFpEF)

• Signs and symptoms of HF occurring in patients with normal or near-normal EF (>0.50 or 0.45).
• Doesn’t exclude some abnormalities in systolic function, but mildly reduced EF is not usually associated with HF in the absence of other factors.
• The constellation of clinical signs and symptoms which lead to the consideration of HFpEF can be caused by diverse cardiac (e.g. constriction) as well as non-cardiac etiologies (e.g. obesity, anemia, COPD).
Prevalence of HFpEF

13 Community Based Studies
1997-2006

Median = 52%  Mean = 55%

Reviewed by Hogg K et al, 2004 and Owan T et al, 2005, Owan T, NEJM, 2006; Bursi F, JAMA, 2006
Secular Trends in the Prevalence of HFpEF

Survival Trends in HF Patients With and Without Preserved EF

A. Patient with Reduced Ejection Fraction

B. Patient with Preserved Ejection Fraction

Owan et al. NEJM. 2006; 355:251-259.
60- to 90-Day Survival Post-Discharge

*\( p = 0.459 \)

<table>
<thead>
<tr>
<th>LVSD</th>
<th>2294</th>
<th>2188</th>
<th>1994</th>
<th>469</th>
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</thead>
<tbody>
<tr>
<td>No LVSD</td>
<td>2604</td>
<td>2471</td>
<td>2195</td>
<td>441</td>
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</tbody>
</table>

*\( P \) value (40% ≤ EF ≤ 50% vs EF >50%).


% Deaths Due to Non-CV Causes

Olmsted County MN 1979-2002

HPpEF
- CAD 29%
- Non-CAD CV 22%
- Non-CV 49%

HFrEF
- CAD 43%
- Non-CAD CV 21%
- Non-CV 36%

1,063 Pts: 5-Year Mortality 55%; HFpEF=HFrEF

Deaths due to Non-CV Causes More Common in HFpEF

Henkle DM: Circ-HF 2008
HFpEF vs HFrEF

**Differences**
- More women
- Older
- Less CAD and MI
- More hypertension (past and current)
- Smaller, thicker LV
- Less LBBB and IVCD

**Similarities**
- Race
- Diabetes
- Tobacco
- Atrial fibrillation
- Lipids
- Weight
Differentiating HFpEF From HFrEF

Baseline signs, symptoms and radiographic findings in the CHARM study

HFpEF hard to differentiate from HFrEF clinically
Diagnosing HFpEF

- Confirm that signs and symptoms are due to HF – need to exclude other cardiac or non-cardiac diseases (e.g. anemia, COPD, deconditioning, obesity).
- Natriuretic peptide levels are often (but not always elevated).
- Use echo to: 1. measure EF (assure test quality) and R/O other conditions (e.g. valvular disease, HCM), 2. detect ‘fellow travellers’ of HFpEF (e.g. LVH, LAE and pulmonary HTN).
- Echo measures of diastolic function helpful but not necessary.
- Right heart cath can help when there is uncertainty.
- Stress test or angiography in selected cases.
Pulmonary Artery Systolic Pressure

Prevalence of PH (PASP >35):
2% in CON; 8% in HTN; 83% in HFpEF

Adjusted P*<0.05 vs CON; †<0.05 vs HTN

Pulmonary HTN is very common in HFpEF patients

Lam C et al: JACC 2009
Diastology

DIASTOLIC HEART FAILURE

Normal

Impaired Relaxation

Pseudonormal

Restrictive

Mitral Doppler Velocity

Pulmonary Vein Velocity

Doppler Tissue Imaging
Tissue Doppler and PCWP

Ratio of $E$ to $E'$

- Normal $E$: 80 cm/s,
  Normal $E'$: 8-12 cm/s
- Normal $E/E'$: <15

$E$: 72, $E'$: 12, $E/E'$ = 6
Tissue Doppler and PCWP

**Ratio of E to E’**

- **E/E’ >15-20:**
  - High PCWP
- **E:140, E’:7**
  - E/E’ : 35
If the Diagnosis is in Doubt…Go to the Table of Truth!

Mechanisms of HFpEF

• Diastolic abnormalities
  - impaired cardiomyocyte relaxation
  - myocardial fibrosis
• Contractile abnormalities not detected by measurement of resting EF
• Increased vascular stiffness
• Chronotropic incompetence
Decreased Relaxation

\[ \downarrow \text{speed and extent (\uparrow \tau)} \]

- Age (\(\downarrow \beta\) adrenergic responsiveness)
- \(\uparrow\) afterload
- Ischemia (\(\downarrow\) ATP; \(\uparrow\) ADP)
- Asynchrony (RWMA, fibrosis)
- Hypertrophy
- Systolic dysfunction

Most important at rapid heart rate, so controlling rate is an important way to diminish symptoms
Stiffness in HFpEF

Zile M et al: NEJM, 2004
Diastolic Stiffness

- Age
- Female sex
- Hypertrophy
- ↑ extracellular matrix (fibrosis)
- Titin
- Myocyte abnormalities
  - Acute
  - Chronic

*Prevention and regression of hypertrophy can reduce LV stiffness and congestive symptoms*
Risk for All-Cause Hospitalization Versus Number of Noncardiac Comorbidities

Ather S et al. JACC. 2012: 59;998–1005
Comorbidities Drive Myocardial Dysfunction and Remodeling in HFPEF

Myocardial Remodeling in HFPEF
Importance of Comorbidities

- Overweight/Obesity
- Hypertension
- Diabetes Mellitus
- COPD
- Iron Deficiency

IL-6
TNF-α
sST2
Pentraxin 3

ROS
ONOO−
NO−
VCAM–E-selectin
Leukocytes
TGF-β
Fibroblasts
Myofibroblasts

Cardiomyocytes
sGC
cGMP
Hyper trophy
PKG

Paulus W and Tschope C. JACC, 2013:62;263–271
Treating HFpEF

THE THEORY  hundreds of papers!

THE EVIDENCE  virtually none!!
Clinical Trials in HFrEF and HFpEF

- CHARM-Alternative
- SOLVD
- DIG

Hazard Ratio for Death or HF Hospitalization

### ACC/AHA Guidelines – Class I Recommendations

<table>
<thead>
<tr>
<th>ACC/AHA Guidelines – Class I Recommendations</th>
<th>How to Accomplish Treatment Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Control BP ($&lt;130/80$ mmHg)</td>
<td>• Agent not specified</td>
</tr>
<tr>
<td>• Control of tachycardia in AF</td>
<td>• Dig, BB, CCB, amio/dronedarone</td>
</tr>
<tr>
<td>• Reduction of central blood volume</td>
<td>• Low salt diet, diuretics, nitrates</td>
</tr>
</tbody>
</table>
ACC/AHA Guidelines

Class IIa

• Coronary revascularization if ischemia is thought to be causing diastolic dysfunction
Implications of CAD in HFpEF Patients

Impact of Revascularization on Survival in Patients With HFPpEF

ACC/AHA Guidelines

*Class IIb*

- Restoration of sinus rhythm in AF
- If BP controlled, these might help ↓ Sx
  - ACE/ARB
  - Beta blockers
  - Calcium blockers
- Digitalis – use not well established
Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT)

- Randomized, double-blind, placebo-controlled, MCT of 3445 pts.
- Patients had evidence* of HF, LVEF ≥45%, SBP <140 mm Hg** and serum K <5.0 mmol/L.
- Patients were either hospitalized for HF ≤12 months or had elevated BNP ≥100 pg/mL or NTproBNP ≥360 pg/mL.
- Pts randomized to placebo or spironolactone 15-45 mg qd.
- Potassium monitored baseline, weeks 1 & 4, then q4 months.
- Primary end-point was a composite of CV death, aborted cardiac arrest, or HF hospitalization.

*≥1 sign and ≥1 symptom

**or <160 if on 3 meds

Spironolactone Failed to Demonstrate Clinical Benefit for the Primary Endpoint in TOPCAT

## Did Regional Outcomes Determine Outcome of TOPCAT?

<table>
<thead>
<tr>
<th></th>
<th>Americas (n=1767)</th>
<th>Russia/Georgia (n=1678)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>72 (64, 79)</td>
<td>66 (59, 71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age ≥75 y, n (%)</td>
<td>720 (41)</td>
<td>228 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>882 (50)</td>
<td>893 (53)</td>
<td>0.05</td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>1384 (78)</td>
<td>1678 (100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>58 (53, 64)</td>
<td>55 (50, 60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA class, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>99 (6)</td>
<td>10 (1)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1043 (59)</td>
<td>1151 (69)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>610 (35)</td>
<td>511 (30)</td>
<td>0.0061</td>
</tr>
<tr>
<td>4</td>
<td>10 (1)</td>
<td>5 (&lt;1)</td>
<td></td>
</tr>
<tr>
<td>Stratum, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>976 (55)</td>
<td>1488 (89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BNP</td>
<td>791 (45)</td>
<td>190 (11)</td>
<td></td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>117 (7)</td>
<td>243 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>129 (118, 138)</td>
<td>130 (120, 140)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>70 (62, 80)</td>
<td>80 (80, 85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>68 (61, 76)</td>
<td>68 (62, 75)</td>
<td>0.49</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>32.9 (28.0, 38.4)</td>
<td>29.4 (26.7, 33.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any cardiovascular disease history, n (%)</td>
<td>815 (46)</td>
<td>1208 (72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>743 (42)</td>
<td>471 (28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>788 (45)</td>
<td>330 (20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin-treated</td>
<td>379 (21)</td>
<td>48 (3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic kidney disease, n (%)</td>
<td>855 (48)</td>
<td>477 (28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction, n (%)</td>
<td>359 (20)</td>
<td>534 (32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percutaneous coronary intervention or coronary artery bypass graft surgery, n (%)</td>
<td>567 (32)</td>
<td>246 (15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angina, n (%)</td>
<td>486 (28)</td>
<td>1127 (67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>1250 (71)</td>
<td>823 (49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease, n (%)</td>
<td>291 (16)</td>
<td>112 (7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>158 (9)</td>
<td>107 (6)</td>
<td>0.005</td>
</tr>
<tr>
<td>Sodium</td>
<td>140 (138, 142)</td>
<td>143 (140, 146)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>4.2 (3.9, 4.5)</td>
<td>4.4 (4.1, 4.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.1 (0.9, 1.4)</td>
<td>1.0 (0.9, 1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate, mL/min per 1.73 m²</td>
<td>61 (49, 77)</td>
<td>69 (58, 81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BNP, pg/mL‡</td>
<td>234 (145, 391)</td>
<td>375 (175, 702)</td>
<td>0.016</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL‡</td>
<td>900 (557, 1920)</td>
<td>1045 (585, 1885)</td>
<td>0.24</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.8 (11.7, 14.0)</td>
<td>13.7 (12.6, 14.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Is HFpEF Preventable?

Preventing HFpEF Is the Best Treatment
Relation Between Age and E’

VALIDDD Randomised Patients

Change in Lateral E’ for Each Quartile of SPB Reduction

Normalized Peak VO2 Increases With Lifelong Exercise

Bhella PS et al JACC, Volume 64, Issue 12, 2014, 1257–1266
LV End Diastolic PV Relationships Are Related with Life Long Exercise Patterns

Bhella PS et al JACC, Volume 64, Issue 12, 2014, 1257–1266
Diet and Exercise Training Improve Exercise Capacity of HFpEF Patients

Effects of a 20-Week Caloric Restriction Diet on Exercise Capacity and Quality of Life in HFpEF

Summary: Update on Treating HFpEF

• >50% of HF patients have preserved EF.
• Causes of HFpEF are multifactorial.
• Diagnosis depends on presence of HF, preserved EF and absence of other causes.
• Effective management includes measures to relieve congestion, normalize blood pressure, control heart rate, and prevent myocardial ischemia.
• Use of MRA therapy remains controversial.
• Prevention and healthy life style choices remain the best therapies.