Foundations of HFpEF
July 10, 2018
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Presenters:
Adam DeVore, MD, MHS
Anita Deswal, MD, MPH, FACC, FAHA, FHFSFA
Nancy Albert, PhD, CCNS, CHFN, FAHA, FHFSFA
Our Presenters

Adam DeVore, MD, MHS
Assistant Professor of Medicine
Duke University Medical Center and the
Duke Clinical Research Institute

Anita Deswal, MD, MPH,
FACC, FAHA, FHFSA
Professor of Medicine
Winters Center for Heart Failure Research
Baylor College of Medicine
Chief, Section of Cardiology
Director Heart Failure Program
Michael E. DeBakey VA Medical Center

Nancy Albert, PhD, CCNS, CHFN
Associate Chief Nursing Officer, Office of Nursing
Research and Innovation
Cleveland Clinic Health System
Clinical Nurse Specialist
Kaufman Center for Heart Failure
Cleveland Clinic Main Campus
Foundations of HFpEF: Epidemiology and Pathophysiology

Adam DeVore, MD, MHS
Assistant Professor of Medicine
Duke University Medical Center
Durham, NC
Case Example

72 yo male with a recent diagnosis of acute heart failure here for follow-up

- Medical history: Hypertension, GERD, hernia repair
- Previously active but stopped exercising due to back pain
- Intermittent palpitations with tachycardia on his home BP machine since last Fall; recent diagnosis of atrial fibrillation treated with cardioversion and apixaban
- Hospitalized 3 weeks ago with orthopnea and edema and diagnosed with HF
Case Example

72 yo male with a recent diagnosis of acute heart failure here for follow-up

- NYHA Class II symptoms
- Amlodipine 5, apixaban 5mg twice daily, omega-3 fatty acids, metoprolol succinate 25mg daily
- Pulse 61 (sinus), BP 150/78, euvolemic, S4 on exam, warm extremities
- K 4.2, Cr 1.2
- Echocardiogram is shown
Case Example

72 yo male with a recent diagnosis of acute heart failure here for follow-up

- Does he have HFpEF or a condition that mimics HFpEF?
- Have we considered and treated predisposing conditions?
- Are therapies for his cormorbid conditions optimized?
- Are his filling pressures optimized?
- Can we reduce his risk of future HF events with medical or non-pharmacologic interventions?
The Changing Epidemiology of Heart Failure

PROPORTION OF HOSPITALIZED HEART FAILURE PATIENTS (%)

YEAR


~50% EF > 50%
~35% EF < 40%
~15% EF 40-50%
Mayo Data: Similar Survival for HFrEF and HFpEF

Survival

No. at risk
EF<50%
EF≥50%

Years
0 1 2 3 4 5

P=0.03

Owan T et al, NEJM, 2006
CHARM data: Health-related QOL in HFpEF vs HFrEF

HFpEF Potential Cardiac Mechanisms

- Left ventricular hypertrophy and fibrosis (reduced chamber compliance)
- Impaired diastolic relaxation and elevated left-sided filling pressures
- Systolic dysfunction (sometimes subclinical)
- Abnormal ventricular-vascular coupling
- Chronotropic incompetence and cardiovascular reserve
- Increased oxidative stress and depressed NO signaling (i.e., inflammation) leading to endothelial dysfunction
- Comorbidity-induced systemic inflammation
Extracardiac Mechanisms of HFpEF
HFpEF: Making the Diagnosis
The Search for “Other” Causes of HFpEF

- Hypertrophic cardiomyopathy
- Infiltrative or restrictive cardiomyopathy
- Pulmonary arterial hypertension
- Constrictive pericarditis
- High output heart failure
- Valvular disease
- Coronary artery disease
- Pulmonary embolism
- Right ventricular myopathies
## Phenotypic-specific Management

<table>
<thead>
<tr>
<th>HFpEF Clinical Presentation Phenotypes</th>
<th>Lung Congestion</th>
<th>+Chronotropic Incompetence</th>
<th>+Pulmonary Hypertension (CpcPH)</th>
<th>+Skeletal muscle weakness</th>
<th>+Atrial Fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight/obesity/metabolic syndrome/type 2 DM</td>
<td>• Diuretics (loop diuretic in DM) • Caloric restriction • Statins • Inorganic nitrite/nitrate • Sacubitril • Spironolactone</td>
<td>+Rate adaptive atrial pacing</td>
<td>+Pulmonary vasodilators (e.g. PDE5i)</td>
<td>+Exercise training program</td>
<td>+Cardioversion + Rate Control + Anticoagulation</td>
</tr>
<tr>
<td>HFpEF Predisposition Phenotypes</td>
<td>+Arterial hypertension</td>
<td>+ACEI/ARB + Rate adaptive atrial pacing</td>
<td>+ACEI/ARB + Pulmonary vasodilators (e.g. PDE5i)</td>
<td>+ACEI/ARB + Exercise training program</td>
<td>+ACEI/ARB + Cardioversion + Rate Control + Anticoagulation</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>+Ultrafiltration if needed</td>
<td>+Ultrafiltration if needed + Rate adaptive atrial pacing</td>
<td>+Ultrafiltration if needed + Pulmonary vasodilators (e.g. PDE5i)</td>
<td>+Ultrafiltration if needed + Exercise training program</td>
<td>+Ultrafiltration if needed + Cardioversion + Rate Control + Anticoagulation</td>
</tr>
<tr>
<td>CAD</td>
<td>+ACEI + Revascularization</td>
<td>+ACEI + Revascularization + Rate adaptive atrial pacing</td>
<td>+ACEI + Revascularization + Pulmonary vasodilators (e.g. PDE5i)</td>
<td>+ACEI + Revascularization + Exercise training program</td>
<td>+ACEI + Revascularization + Cardioversion + Rate Control + Anticoagulation</td>
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</table>

Important Comorbidities in Heart Failure

- Renal dysfunction
- COPD
- Diabetes
- Sleep apnea
- Fe Deficiency +/- anemia
- Depression
- Frailty
Medical Therapy for HFpEF: Trials and Guideline Recommendations

Anita Deswal, MD, MPH, FAHA, FACC, FHFSA
Professor of Medicine
Baylor College of Medicine
Chief of Cardiology
Michael E. DeBakey VA Medical Center
Houston, TX
Therapies demonstrated to Improve Survival in HFpEF

<table>
<thead>
<tr>
<th>HFrEF</th>
<th>HFpEF</th>
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<tbody>
<tr>
<td>• ACE Inhibitors</td>
<td></td>
</tr>
<tr>
<td>• Angiotensin Receptor Blockers (ARBs)</td>
<td></td>
</tr>
<tr>
<td>• Angiotensin Receptor Neprilysin Inhibitors (ARNI)</td>
<td></td>
</tr>
<tr>
<td>• Beta Blockers</td>
<td></td>
</tr>
<tr>
<td>• Aldosterone Receptor Blockers</td>
<td></td>
</tr>
<tr>
<td>• Hydralazine/Nitrates</td>
<td></td>
</tr>
<tr>
<td>• ICDs; CRT Cardiac Resynchronization Therapy</td>
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</table>
ABRs in HFpEF: CHARM-PRESERVED

ARBs & ACE-I in HFpEF

I-PRESERVE

Placebo
Irbesartan

HR (95% CI) = 0.95 (0.86-1.05)
p = 0.35

PEP-CHF

Proportion having an event (%)
(HR 0.92; 95% CI 0.70-1.21; P = 0.545)

Time to Death or HF Hospitalization

patients at risk
Perindopril: 424 374 184 70
Placebo: 426 356 186 69

No. at Risk
Irbesartan: 2097 1929 1812 1730 1640 1569 1513 1291 1088 816 497
Placebo: 2091 1921 1808 1715 1618 1539 1466 1246 1051 776 446

Aldosterone Receptor Blockers in HFpEF: TOPCAT

CV Death, HF Hosp, or Resuscitated Cardiac Arrest

HR = 0.89 (0.77–1.04)  
*p = 0.138

Placebo
18.6%
Spiromolactone
20.4%

HF Hospitalizations

HR = 0.83 (0.69–0.99)  
*p = 0.042

Placebo
12.0%
Spiromolactone
14.2%

Geographic Differences in Event Rates & Spironolactone Effect

US, Canada, Argentina, Brazil
HR=0.82 (0.69-0.98)
Placebo: 31.8%

Russia, Rep Georgia
HR=1.10 (0.79-1.51)
Placebo: 8.4%

Interaction p=0.122

**ARNI (Sacubitril/Valsartan) in HFpEF**

**PARAMOUNT Trial**

- **Primary composite endpoint of death or total HF hospitalizations (first and recurrent)**

**Secondary: LA volume significantly ↓, NYHA class improved**

**PARAGON-HF Trial:** ~ 5000 HFpEF patients: LVEF > 45%, LVH or LA dilation; ↑ NT-proBNP.

Other Endpoints and Trials in HFpEF

• Digoxin (post hoc in HFpEF group): Mortality↔, HF Hospitalizations↓, all Hospitalizations ↔

• SENIORS (BB – nebivolol): ↓ time to death/HF hospitalization, but few with LVEF>50%

• RELAX (sildenafil): no change in peak VO2

• NEAT (isosorbide mononitrate): decreased daily activity levels and did not improve submaximal exercise capacity, quality-of-life scores or NT-proBNP levels

• INDIE (inorganic nitrite): no change in peak VO2
2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

Developed in Collaboration With the American Academy of Family Physicians, American College of Chest Physicians, and International Society for Heart and Lung Transplantation

WRITING GROUP MEMBERS*

Clyde W. Yancy, MD, MSc, MACC, FAHA, FHFA, Chair
Mariell Jessup, MD, FACC, FAHA, Vice Chair
Biykem Bozkurt, MD, PhD, FACC, FAHA†
Javed Butler, MD, MBA, MPH, FACC, FAHA††
Donald E. C资源, Jr, MD, MPH, MBA, FACC†
Monica M. Colvin, MD, FAHA‡
Mark H. Drazner, MD, MSc, FACC, FAHA, FHFA†
Gerasimos S. Filippatos, MD†
Gregg C. Fonarow, MD, FACC, FAHA, FHFA**,FHFA†
Michael M. Givertz, MD, FACC, FHFA**†

Steven M. Hollenberg, MD, FACC#
JoAnn Lindenfeld, MD, FACC, FAHA, FHFA, FHFA††
Frederick A. Masoudi, MD, MSPH, FACC**
Patrick E. McBride, MD, MPH, FACC‡‡
Pamela N. Peterson, MD, FACC, FAHA‡‡
Lynne Warner Stevenson, MD, FACC‡‡
Cheryl Westlake, PhD, RN, ACNS-BC, FAHA, FHFA†

ACC/AHA TASK FORCE MEMBERS

Glen N. Levine, MD, FACC, FAHA, Chair
Patrick T. O’Gara, MD, FACC, FAHA, Chair-Elect
Jonathan L. Halpern, MD, FACC, FAHA, Immediate Past Chair††
Susan M. Al-Khatib, MD, MHS, FACC, FAHA
Kim K. Brichta, PharmD, MS, AACC
Biykem Bozkurt, MD, PhD, FACC, FAHA
Ralph G. Brundis, MD, MPH, MACC††
Joaquin E. Cigurroa, MD, FACC
Lesley H. Curtis, PhD, FAHA
Lee A. Fleisher, MD, FACC, FAHA

Federico Durante, MD, FACC
Samuel Gundling, MD, FAHA
Mark A. Hlatky, MD, FACC
John Ikonomidou, MD, PhD, FAHA
Jose Jorgar, MD, FACC, FAHA
Susan J. Pressler, PhD, RN, FAHA
Duminda N. Wijeyasurya, MD, PhD
### Guidelines: Medical Therapy for HFrpEF -I

**COR: Class of Recommendation: I-III**

- **I**: Strong; benefit >>> risk
- **IIa**: Moderate; benefit >> risk
- **IIb**: Weak; benefit > risk
- **III**: No benefit (moderate); benefit=risk
- **III**: Harm (strong); risk > benefit

**LOE: Level (quality) of Evidence: A-C**

- **A**: Best quality of evidence (often high quality RCTs)
- **B, C**

**The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFrpEF.**

**In appropriately selected patients with HFrpEF (with EF ≥45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate >30 mL/min, creatinine <2.5 mg/dL, potassium <5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations (83,166,167).**

**The use of ARBs might be considered to decrease hospitalizations for patients with HFrpEF (169).**
**Guideline: Medical Therapy for HFP EF -II**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
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<tbody>
<tr>
<td>III: No Benefit</td>
<td>B-R</td>
</tr>
<tr>
<td>See Online Data Supplement C.</td>
<td></td>
</tr>
</tbody>
</table>

Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QoL in patients with HFP EF is ineffective (171,172).

| III: No Benefit | C |

Routine use of nutritional supplements is not recommended for patients with HFP EF.

| I | C |

Diuretics should be used for relief of symptoms due to volume overload in patients with HFP EF.

### Guideline: Treatment of Hypertension in HFpEF

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B</td>
<td>Systolic and diastolic blood pressure should be controlled in patients with HFpEF in accordance with published clinical practice guidelines to prevent morbidity (164,165).</td>
</tr>
<tr>
<td>1</td>
<td>C-LD</td>
<td>Patients with HFpEF and persistent hypertension after management of volume overload should be prescribed GDMT titrated to attain systolic blood pressure less than 130 mm Hg (9,167,169,170,195-199).</td>
</tr>
</tbody>
</table>

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**Guideline: Treatment of Comorbidities in HFrEF**

- **Ila C**
  - Coronary revascularization is reasonable in patients with CAD in whom symptoms (angina) or demonstrable myocardial ischemia is judged to be having an adverse effect on symptomatic HFrEF despite GDMT.

- **Ila C**
  - Management of AF according to published clinical practice guidelines in patients with HFrEF is reasonable to improve symptomatic HF. (AF=Atrial fibrillation)

- **Ila C-LD**
  - In patients with NYHA class II-IV HF and suspicion of sleep-disordered breathing or excessive daytime sleepiness, a formal sleep assessment is reasonable.

- **Iib B-R**
  - In patients with cardiovascular disease and obstructive sleep apnea, CPAP may be reasonable to improve sleep quality and daytime sleepiness (204).

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</tr>
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<tbody>
<tr>
<td>I</td>
<td>B-R</td>
<td>In patients at increased risk, stage A HF, the optimal blood pressure in those with hypertension should be less than 130/80 mm Hg (189-193).</td>
</tr>
</tbody>
</table>

1. Treat symptoms of volume overload with diuretics

2. Treat hypertension: Goal in most patients < 130/80 mm Hg

3. In patients at high risk for HF hospitalization: may consider ARBs or aldosterone receptor antagonists (if no contraindications)

4. Treat comorbidities, e.g. atrial fibrillation, CAD
Non-Pharmacological Care, Transitions of Care and Future Possibilities in HFpEF

Nancy M. Albert PhD, CCNS, CHFN, FAHA, FHFSA
Associate Chief Nursing Officer
Nursing Research and Innovation, and
Clinical Nurse Specialist, Kaufman Center for Heart Failure, Cleveland Clinic
Cleveland OH
HFpEF Recap

- Increased prevalence
- High morbidity/ mortality
- No proven therapies
- Treat comorbidities
- Ensure disease management and transition care to reduce morbidity and mortality
Transitions of Care in HF

Before discharge & at EACH post discharge visit:

• Manage comorbid conditions:
  – Cardiac related (CAD, AF, HTN)
  – Mimics of HF symptoms: anemia, COPD, CRI…

• Address HF cause, barriers to care & limitations in support - Complex!

• Ensure HF education, self-care, emergency plans, and adherence; discuss “how”, not just “what”

• Discuss palliative or hospice care

H2H Strategies - Reduce HF Hospitalization

Quality Improvement (QI) resources and performance monitoring:

1. \( \geq 1 \) QI team for reducing readmission for HF
2. Monitor proportion of discharged patients with follow-up appointment within 7 days
3. Monitor 30-day readmission rates

HFpEF Recap

- ↑ prevalence
- High morbidity/ mortality
- No proven therapies
- Treat comorbidities

Common pathophysiologic thread:
- ↑ LA pressure at rest or with exertion
Exercise Hemodynamics in HFpEF

Conclusion:
• Euvolemic patients with exertional dyspnea, normal BNP, and normal cardiac filling pressures at rest may have markedly abnormal hemodynamic responses during exercise
• Chronic symptoms are related to HF
• Earlier /more accurate Dx using exercise hemodynamics may allow better targeting of interventions to treat / prevent HFpEF progression

N = 55; HFpEF, n = 32
NCD, noncardiac dyspnea, n=23

*, p<0.0001 for change PCWP
†, p< 0.001 vs baseline (within gp)
‡, p<0.01 vs baseline (within gp)

64 patients; mean age 70±8 yrs; mean 6MWT distance was 318±108 m

- At rest, only PCWP was associated with 6MWT
  - -5.4 (95% CI: -10.4, -0.5) p=0.033
- With light/moderate exercise, mean PAP was associated with 6MWT
  - -3.5 (95% CI: -6.8, 0.3) p=0.033
- During peak exercise, workload corrected PCWP was the only variable associated with 6MWT
  - -0.8 (95% CI: -1.3, -0.4) p<0.001

PCWP during Exercise - Long Term Mortality

- N = 355; 12 month follow-up

Unadjusted

Adjusted

PCWP at peak exercise to workload normalized to bodyweight [PCWL (mmHg/W/kg)]

Obese (BMI ≥ 30), clinical stable HFpEF patients aged 60+ years
• Mean age 67 [5] yrs; EF ~ 61%; NYHA FC II/III

**Intervention:** 20 weeks + telephone calls q 2 weeks from staff
• 1-hr supervised exercise (walking) 3x/week
• Hypocaloric diet; meals prepared in a metabolic kitchen (at Wake Forest Univ, Gen Clin Res Ctr)

**2x2 Factorial Groups:** 100 pts enrolled (92 analyzed)
• 25 (22) attention control
• 26 (24) exercise only
• 24 (24) diet only
• 25 (22) exercise + diet

**Baseline Medications:**
- ACEi/ARB: 37%/28%
- Ca antagonists: 35%
- Diuretics: 76%
- Nitrates: 9%
- B-Blockers: 40%

Combo of exercise + diet was additive: change in peak VO2 was 2.5 ml/kg/min
Change in peak VO2 was associated with change in lean body mass: $r=0.32$, $p=0.003$

Wireless PA Pressure Monitoring in HFpEF

Pulmonary artery pressure sensor is implanted via a RHC


> 6 month HF Hospitalization IRR:
  • 0.54; 95% CI, 0.38–0.70; $P<0.0001$

~ 17.6 month blinded FU HF Hospitalization IRR:
  • 0.50; 95% CI, 0.35–0.70; $P<0.0001$
Future Direction?

InterAtrial Shunt Device

Mode of action: dynamic decompression of overloaded LA chamber by shunting blood from LA $\rightarrow$ RA

Open-label, single-arm, phase 1 study of a transcatheter interatrial shunt device (IASD, Corvia Medical, Tewkesbury, MA, USA)

- Designed to assess performance and safety
- N=64

Conclusion:
- Is feasible
- Might be associated with improvements in exercise hemodynamics, functional capacity and quality of life
- Need to replicate findings in a randomized controlled blinded trial

Discussion - Questions and Answers
Contact Us to Learn More

Tanya Lane Truitt, RN MS
Senior Manager QSI Programs & Operations: Resuscitation & HF
Get With The Guidelines®
tanya.truitt@heart.org

Liz Olson, CVA
Program Manager, Get With The Guidelines – Heart Failure
lizolson@heart.org

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