Heart Failure with Preserved Ejection Fraction: An Emerging Epidemic

Rebecca Cogswell, MD
Assistant Professor of Medicine
Advanced Heart Failure and Cardiac Transplantation

Case
70 F
- Decreasing exercise tolerance
- 5 blocks, stops with 2nd flight stairs
- Otherwise cardiac ROS negative
- PMHx: HTN, DM, obesity, asthma
- Never been admitted with CHF, no prior MI

Meds: lisinopril, amlodipine, lasix 40 BID, ASA 81, statin, albuterol
- BP 150/80, HR 85, BMI 32
- Exam: JVP 10 cm, PMI focal, + s4, lungs clear, 1+ LE edema

ECHOCARDIOGRAM
- IVSD: 1.4 cm
- LA volume indexed: 40 ml/m2
- EF 60%
- PASP: 45 mmHg
- IVC slightly dilated
- Other: PFTs normal, labs: nt-bnp 1200, lexiscan negative

Question:
Which of the following is the most likely diagnosis based on the available information?

A) Pulmonary arterial hypertension
B) HOCM
C) Heart failure with preserved ejection fraction (HFpEF)
D) Obesity/deconditioning
E) Chronic PEs

Answer:
C) Heart failure with preserved ejection fraction (HFpEF)

Overview
- HFpEF – current definition(s)
- Epidemiology
- Pathophysiology
- Trials
- UMN HFpEF clinic
- Work up/management
- The future
**Definition HFpEF**

- Normal LVEF - 50%
- Signs or symptoms of heart failure

**Diagnosis challenging**

- Exclude other potential causes of symptoms
- Exclude infiltrative, valve, constrictive pericarditis, high output

**Epidemiology HFpEF**

- 5.1 million in US with HF
- HFpEF - ⅔ of hospitalizations, increasing
- $24 billion in 2015, $47 billion by 2030
- Demographics compared to HFrEF
  - older, female, HTN, obese, atrial fibrillation
  - DM: HFpEF = HFrEF
  - “Less CAD”

*Go AS et al. Circulation 2013
* Owan et al, NEJM, 2005 Hogg K et al, 2004

**Pathophysiology**

- Impaired relaxation (active)
- Increased diastolic stiffness (passive)

While the EF is normal, contractility is NOT***

**Proposed Paradigm for Development of HFpEF:**

1. High prevalence of comorbidities such as obesity, DM, COPD, salt-sensitive HTN, CKD; these induce systemic pro-inflammatory state
2. Systemic proinflammatory state causes coronary microvascular endothelial inflammation
3. Coronary microvascular endothelial inflammation reduces nitric oxide bioavailability, cGMP content, and protein kinase G (PKG) activity in adjacent cardiomyocytes
4. Low PKG activity favors hypertrophy development and increases resting tension because of hypophosphorylation of titin
5. Stiff cardiomyocytes and interstitial fibrosis contribute to high diastolic LV stiffness and heart failure development

Echo

Echo clues for you...

- LA enlargement
- Left ventricular hypertrophy
- Pulmonary hypertension
- “Restrictive filling”
- “Elevated left sided filling pressures”

HFpEF Survival

35% survival at 5 years after HF hospitalization, regardless of LVEF

Next question..

Now that we have diagnosed our patient with HFpEF

What evidence based pharmacologic regimen should be prescribed to reduce mortality and HF hospitalizations in this patient?

A: Ace-i/ARB only
B: Ace-i/ARB, beta blocker
C: Ace-i/ARB, beta blocker, aldosterone antagonist
D: sildenafil, ASA
E: None of the above

Answer

E: None of the above
There are no therapies for HFpEF that reduce mortality or HF hospitalizations
Heart Failure Trials…

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

Why is nothing helping?

One hypothesis:
Heterogeneous population- several pathophysiologic mechanisms

• Impaired pulmonary vasodilation
• Right heart failure
• Pulmonary hypertension
• Chronotropic incompetence
• Extra-cardiac causes of fluid overload
• Ischemia mediated

****RESEARCH NEEDED IN THIS AREA

Relax Trial  –  Sildenafil

• HFpEF  –  Sildenafil 24 weeks (up to 60 mg TID)
• Primary endpoints: change in peak VO2
• Secondary endpoints: change in cardiac structure or function
• No difference between groups

Redfield et al, JAMA 2013

TOP CAT

• Spironolactone
• 3400 patients
• EF ≥ 45 %
• Hospitalization within last year, OR
• NT-BNP
• Primary endpoint (CV mortality, aborted cardiac arrest, hospitalization for CHF)
  • HR: 0.89 (0.77-1.04, p = 0.138)
  • Heart failure hospitalization: 0.83 (0.69-0.99), p =0.042

Pfeffer, Nov 2013

Exploratory (post-hoc): Placebo vs. Spiro by region

Placebo: 282/1011 (31.1%)

Placebo: 71/104 (6.8%)

US, Canada, Argentina, Brazil

HR=0.82 (0.69-0.98)

Interaction p=0.122

Russia, Rep Georgia

NEAT-HFpEF

• Long-acting nitrates are commonly prescribed to increase exercise tolerance in pts w/ HFpEF
• Might minimize pulmonary congestion w/ exercise and improve exercise capacity
**NEAT-HFpEF**

<table>
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<th>Week</th>
<th>Study Drug 1st Period (51 pts)</th>
<th>Placebo 2nd Period (59 pts)</th>
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<tr>
<td>2</td>
<td>No study drug</td>
<td>No study drug</td>
</tr>
<tr>
<td>3</td>
<td>50mg daily Imdur</td>
<td>5 tablets placebo</td>
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<td>4</td>
<td>100mg daily Imdur</td>
<td>2 tablets placebo</td>
</tr>
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<td>5</td>
<td>150mg daily Imdur</td>
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</tr>
<tr>
<td>6</td>
<td>200mg daily Imdur</td>
<td>4 tablets placebo</td>
</tr>
</tbody>
</table>

Impact of CAD...

Borlaug, 2014 JACC

**Other therapies (RCTs)**

- Exercise training
- DASH diet
- Sildenafil for PH-HFpEF

**Question**

60 M with HFpEF, new referral
- 3 hospitalizations in 5 months
- Medically compliant
- SOB with minimal activity, volume overloaded on exam
- Bilateral carpel tunnel
- Echo - normal EF, “restrictive filling”, severe LVH, moderate RVH, moderate pulmonary hypertension

**HFpEF Guidelines**

**Class I**
- Control blood pressure (A)
- Control HR in A fib (C)
- Diuretics (C)

**Class IIA**

1. Coronary revascularization if ischemia believed to be the cause of diastolic dysfunction (C)

**Guidelines**

**Class IIB**

1. Restore to sinus rhythm from AF (C)
2. Symptoms despite BP control - adding beta blocker, ace-I or calcium channel blocker may help
**ECG**

**What might be the diagnosis?**
- Cardiac amyloid with restrictive physiology
  - Next:
    - Confirmatory testing
    - Typing of amyloid protein

**University of Minnesota HFpEF Program**
- Modeled after Northwestern HFpEF clinic
- Northwestern top enroller in TOPCAT, >1000 patients thus far
- Goals of clinic
  - Access to CLINICAL TRIALS
  - Forming HFpEF consortium with Mayo, Northwestern
  - Improved classification

**HFpEF screening protocol**
- EPIC REPORT
  - Diagnosis CHF, elevated NT-BNP
  - EF >50 % → invitation to HFpEF clinic

**In the HFpEF clinic...**
- Work up:
  - ECHO, ECG, nt-BNP
  - Pseudo normal, restrictive filling
  - Infiltrative disease
  - Septal bounce, high E': image pericardium
  - Ischemia evaluation
  - Sleep evaluation
  - Cardiac monitor
  - Cardiopulmonary stress test
  - Right heart catheterization — select patients

**Management**
- Get them out of heart failure
- Treat BP
- Treat sleep apnea, DM, CAD
- Add aldactone if low risk
- If they are dilated at all, borderline EF → treat as HFrEF
- CLINICAL TRIALS ENROLL
PARAGON
- LCZ696 vs Valsartan
- Age ≥ 55 %
- EF ≥ 45 %
- Symptoms
- On diuretics >30 days
- CHF hospitalization in last 9 months OR
- nt-bnp >300

Where is HFpEF going?

Summary teaching points
- HFpEF incidence increasing
- control BP, heart rate, volume
- Look at the echo and go from there
- Think about mimicking diagnoses (amyloid, infiltrative, restrictive, constriction)
- Think about revascularization
- Consider referral for clinical trials!