Diastolic Heart Failure (HFpEF)

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April 28, 2018
Case presentation

• MSO, an 81 year old woman was admitted to HFWH because of progressive dyspnea and difficult to control hypertension

• Active medical problems:
  • ASPVD Hypertension
  • Diabetes Acute on chronic CKD
  • Anemia Lung nodule
  • Recurrent pleural effusion
  • Possible renal artery stenosis

• Examination
  • 5’ tall, weight 87.5 lbs
  • BP last 24 hours: systolic 146 – 198/ diastolic 68 – 94
  • JVD to angle of jaw at 90 degrees
  • 2+ PTE
ECG, April 1, 2014
CXR, April 1, 2014
Case presentation

EKG: NSR at 76,
    Non-specific right precordial T inversion
CXR: Pulmonary edema
    Right pleural effusion
Lab: Lytes – Normal
    BUN 52, Creatinine 2.13
    Hb 10.6, Hct 31.8
    BNP 2742
    Troponin 0.04
Echocardiogram, April 2, 2014
Echo, April 2, 2014
Tissue Doppler Index, MSO

- Velocity of the lateral mitral annulus (Lateral e’) 3.12 cm/s
- Velocity of the medial mitral annulus (Medial e’) 3.02 cm/s
  \( (A \text{ measure of LV relaxation, normal } > 9 \text{ cm/s}) \)
- Peak E velocity 127 cm/s
  \( (A \text{ measure of LV filling pressure}) \)

- Tissue Doppler Index, E/e’ 40.7
  - Normal < 8
  - Gray zone 8 – 15
  - Abnormal > 15
Hospital course, cont’d

• Worsening renal function: Creatinine increased to 3.8 with proteinuria. Is this actually renal disease, some sort of glomerulopathy?

• Arrange 24 hour urine, schedule renal biopsy

• 24 hour urine: 1.4 grams of protein. Biopsy cancelled.
  • Pt elected to enter hospice.
So, what is this disease entity?

• **Active medical problems:**
  • ASPVD         Hypertension
  • Diabetes      Acute on chronic CKD
  • Anemia        Lung nodule
  • Recurrent pleural effusion
  • Possible renal artery stenosis

• **Add to that:**
  • Sarcopenia
  • Constipation
  • Mitral regurgitation
  • Hip, spine and back surgery
So, what is this disease entity?

• Is this diastolic heart failure?
• Are all the other problems just coincidental?
What’s in a name...

• Diastolic heart failure
• Heart failure with normal LV EF
• Heart failure with preserved LV EF
HFpEF

• Presently just as common as HFrEF, projected to be more common in the future
• Combined mortality and readmission rates similar to HFrEF
HFpEF

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• Combined mortality and readmission rates similar to HFrEF
• A key comparator:
  • HFpEF  30% of deaths are noncardiac
  • HFrEF  18% of deaths are noncardiac
HFpEF

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• Combined mortality and readmission rates similar to HFrEF
• A key comparator:
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• Heart Failure with preserved LV EF is a disorder characterized by comorbidities: diabetes  renal disease
  obesity  hypertension
  systemic and pulmonary vascular abn.
HFpEF Overview
Phenogroups of HFpEF

• 1. Younger patients with moderate diastolic dysfunction with relatively normal BNP

• 2. Obese, diabetic patients with high prevalence of obstructive sleep apnea who had the worst LV relaxation

• 3. Older patients with significant chronic kidney disease, electrical and myocardial remodeling, pulmonary hypertension and RV dysfunction
HFpEF: Diagnosis

• European Society of Cardiology

• 3 basic aspects
  - Signs or symptoms of heart failure
  - Normal or nearly normal LV EF (~50%)
  - Evidence of diastolic dysfunction
HFpEF: Diagnosis

• European Society of Cardiology

• 3 basic aspects

  1. Signs or symptoms of heart failure
  2. Normal or nearly normal LV EF (~50%)
  3. Evidence of diastolic dysfunction

    Evidence of abnormal LV relaxation, abnormal filling, diastolic stiffness

    • Cardiac cath – elevated LVEDP > 16 mm Hg, mean PCWP > 12 mm Hg
    • BNP > 200
    • Tissue Doppler Index E/e’ > 15
Tissue Doppler Index, E/e’

• Quick review of Doppler
• Mitral flow characteristics
  • Normal
  • Stiff LV
• Tissue Doppler

• http://www.echobasics.de/diastole-en.html
Impaired relaxation transmitral flow pattern, from Penicka M, *Heart* 2014
Impaired relaxation pattern (E < A) with corresponding tissue Doppler of the lateral corner of the mitral annulus, from Penicka M, *Heart* 2014
Impaired flow pattern and low e’ in male with dyspnea, from Penicka M, *Heart*, 2014

67 years old male with dyspnoea
- LV ejection fraction 65%
- No LV hypertrophy
- LA volume index 28 ml/m²
- sPAP 27 mmHg
- E/e’ 9
Diastolic stress echocardiography
Normal LV relaxation reserve

REST

EXERCISE
Diastolic stress echocardiography
Reduced LV relaxation reserve

REST
E 47 cm/s

EXERCISE
E 130 cm/s

e' 4 cm/s

E/e’ = 26
Stepwise approach to the diagnosis of heart failure with preserved EF in elderly ambulatory patients with equivocal symptoms. Penicka M, *Heart* 2014;100: 68-76
Pathophysiology of HFpEF

• Breathlessness is the predominant symptom due to elevated left ventricular diastolic pressure.

• Focus on abnormalities in active relaxation and passive stiffness
  • Extracellular matrix
    • Interstitial fibrosis
  • Cardiomyocyte itself
    • Incomplete relaxation of myocardial strips
    • Increased myocardial stiffness
Pathophysiology of HFpEF

• A new paradigm – Paulus & Tschope – comorbidities such as obesity, diabetes and COPD lead to a systemic pro-inflammatory state that induces coronary microvascular endothelial inflammation.

• This inflammation and resultant oxidative stress cause stiff myocytes and interstitial fibrosis.

• Although hypertension is commonly felt to cause HFpEF by afterload excess, this model changes the emphasis to inflammation
From: A Novel Paradigm for Heart Failure With Preserved Ejection Fraction: Comorbidities Drive Myocardial Dysfunction and Remodeling Through Coronary Microvascular Endothelial Inflammation


Myocardial Dysfunction and Remodeling in HFPEF and HFREF

In HFPEF, myocardial dysfunction and remodeling are driven by endothelial inflammation and oxidative stress. In HFREF, oxidative stress originates in the cardiomyocytes because of ischemia, infection, or toxic agents. ROS trigger cardiomyocyte autophagy, apoptosis, or necrosis. The latter attracts leukocytes. Dead cardiomyocytes are replaced by fibrous tissue. cGMP = cyclic guanosine monophosphate; HFREF = heart failure with reduced ejection fraction; other abbreviations as in Figure 1.
Pathophysiology of HFpEF

• **Vascular abnormalities**
  - Arterial stiffness increases with aging and is amplified by hypertension, diabetes and renal disease
• **With an increase in arterial stiffness, the ejected pressure wave is reflected back to the heart, altering systolic pressure load and diastolic function, increasing hydraulic work and myocardial oxygen consumption**
• This leads to impaired LV reserve function, labile systemic hypertension, diminished coronary flow reserve and increased diastolic filling pressures, leading to breathlessness.
Pathophysiology of HFpEF

• The end systolic stiffness of the LV and the arteries increases with aging, especially in women, who are disproportionately represented in HFpEF

• Women also develop more concentric LVH in the setting of pressure overload compared to men.

• With exercise, the patient with HFpEF has a limited vasodilator response to activity.

• These patients often have marked systemic hypertension with exercise stress.
Treatment of HFpEF

• Pharmacologic management of HFpEF
• Agents in investigational trials
  • Sildenafil (RELAX Trial)
  • Aldosterone antagonists (TOPCAT Trial)
  • Angiotensin-receptor neprilipsin inhibitor ARNI (PARAMOUNT Trial)

• In each case, the information for each trial shows no benefit of treatment.
More on TOPCAT

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Sites</th>
<th>Pt/site/mo</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>3,445 233</td>
<td></td>
<td>0.22</td>
<td>4.2-4.6</td>
</tr>
<tr>
<td>N &amp; S Am</td>
<td>1,767 188</td>
<td></td>
<td>0.14</td>
<td>6.5-7.7</td>
</tr>
<tr>
<td>East. Eur.</td>
<td>1,676 45</td>
<td>45</td>
<td>0.56</td>
<td>2.0-2.3</td>
</tr>
</tbody>
</table>
Diuretic Treatment in HF
Pharmacokinetic and Pharmacodynamic Properties of Loop Diuretics.

**Table 1. Causes of Diuretic Resistance.**

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate dose of diuretic</td>
</tr>
<tr>
<td>Nonsadherence</td>
</tr>
<tr>
<td>Not taking drug</td>
</tr>
<tr>
<td>High sodium intake</td>
</tr>
<tr>
<td>Pharmacokinetic factors</td>
</tr>
<tr>
<td>Slow absorption of diuretic because of gut edema</td>
</tr>
<tr>
<td>Impaired secretion of diuretic into the tubule lumen</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>Aging</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Nonsteroidal antiinflammatory drugs*</td>
</tr>
<tr>
<td>Probenecid</td>
</tr>
<tr>
<td>Hypoproteinemia</td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Antinatriuretic drugs</td>
</tr>
<tr>
<td>Nonsteroidal antiinflammatory drugs*</td>
</tr>
<tr>
<td>Antihypertensive agents</td>
</tr>
<tr>
<td>Low renal blood flow</td>
</tr>
<tr>
<td>Nephron remodeling</td>
</tr>
<tr>
<td>Neurohormonal activation</td>
</tr>
</tbody>
</table>

* These drugs inhibit the efficacy of loop diuretics through several mechanisms.
Table 2. Stepped-Care Pharmacologic Approach.*

<table>
<thead>
<tr>
<th>Level</th>
<th>Previous Oral Dose‡</th>
<th>Furosemide Bolus</th>
<th>Infusion Rate</th>
<th>Metolazone†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≤80 mg</td>
<td>40 mg</td>
<td>5 mg/hr</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>81–160 mg</td>
<td>80 mg</td>
<td>10 mg/hr</td>
<td>5 mg daily</td>
</tr>
<tr>
<td>3</td>
<td>161–240 mg</td>
<td>80 mg</td>
<td>20 mg/hr</td>
<td>5 mg twice daily</td>
</tr>
<tr>
<td>4</td>
<td>&gt;240 mg</td>
<td>80 mg</td>
<td>30 mg/hr</td>
<td>5 mg twice daily</td>
</tr>
</tbody>
</table>

* The goal of treatment is a daily urine volume of 3 to 5 liters until clinical euvoeemia is reached. The initial approach may involve the intravenous administration (in two doses) of 2.5 times the patient’s previous oral daily dose of furosemide or alternatively the infusion approach described above. The diuretic level can be increased daily to achieve urinary output between 3 and 5 liters per day by moving to the next step if the urinary output remains less than 3 liters. NA denotes not applicable.

† Hydrochlorothiazide (at a dose of 50 mg twice daily) or chlorothalidone (at a dose of 50 mg daily) may be substituted for metolazone. Adapted from Grodin et al. and Bart et al. The full algorithm includes additional considerations for vasodilator, inotropic, or mechanical therapy in patients who do not have a response within 48 hours.

‡ A dose of 40 mg of furosemide is considered to be equivalent to 1 mg of bumetanide or 20 mg of torsemide.
One more case: BS

• 74 year old female with symptoms of progressive dyspnea and exercise intolerance since February, 2014. No ankle edema.
  • She tries to exercise on her stationary bike for 10 minutes per day

• PMHx
  • Atrial fib, on warfarin, labetalol
  • Hypothyroid, on replacement
  • Hyperlipidemia
  • COPD and restrictive lung disease
  • Mitral regurgitation, moderate on 11/25/09

• Exam
  • 132/62, HR 58 and irreg.
  • Weight 181, Height 5’ 6,” BMI 29.2
  • No JVD
  • Trace ankle edema
One more case: BS
One more case: BS, Prior study.
One more case: BS
One more case: BS
One more case: BS
One more case: BS, mitral inflow
One more case: BS

Echocardiogram features

• Estimated RVSP (PA systolic pressure)  45 mm Hg
• Septal e’  7.6 cm/s
• E/e’  14.7
• Mitral valve deceleration time 201
One more case: BS

• Your diagnosis?

A) Atrial fibrillation with tachycardia cardiomyopathy
B) Diastolic heart failure (HFpEF)
C) Non cardiac dyspnea due to lung disease
D) Deconditioning
E) Labile hypertension
One more case: BS

• You would order

A) CXR
B) BNP
C) Add furosemide, increase until dyspnea resolved
D) Start sildenafil
E) Cardiac rehabilitation exercise, paid by medicare
Exercise and HFpEF
# Exercise in HFpEF

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of subjects (n)</th>
<th>Intensity</th>
<th>Length of training program (wks)</th>
<th>Major Conclusions</th>
</tr>
</thead>
</table>
| Smart\(^29\), 2012 | ET = 12  
Cnt = 13       | 60-70\% peak VO\(_2\)       | 16                               | ↑ Peak exercise capacity  
↔ QOL                                                     |
| Alves\(^24\), 2012  | ET = 20  
Cnt = 22       | 70-75\% HRmax for  
3-5 min (5-7 intervals) | 24                               | ↑ peak METS  
↑ rest LVEF  
↓ L. atrial pressure  
↓ LV stiffness                                             |
| Haykowski\(^27\), 2012 | ET = 22  
Cnt = 18       | 40-70\% HHR                  | 16                               | ↑ Peak exercise capacity  
↑ peak HR                                                  |
| Edelmann\(^28\), 2011 (EX-DHF) | ET = 44  
Cnt = 20       | 50-70\% HRmax,  
60-65\% PeakVO\(_2\),  
1Repetition max | 12                               | ↑ Peak exercise capacity  
↑ 6MWD  
↑ self-reported physical function                         |
| Kitzman\(^28\), 2010 | ET = 24  
Cnt = 22       | 40-70\% HRR                  | 16                               | ↑ Peak exercise capacity  
↑ 6MWD  
↑ physical QOL                                             |
| Gary\(^26\), 2006  | ET = 15  
Cnt = 13       | 40-60\% HRmax                | 12                               | ↑ 6MWD  
↑ physical QOL                                             |