Diastolic Heart Failure (HFpEF)

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April 29, 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
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
Let’s brush up on the evaluation of diastolic function
Normal LV filling velocity and pressure
Mitral inflow patterns in diastole

**Normal**

- LV volume
- Atrial contribution
- Diastasis
- Rapid filling
- End-systole

**Grade I Dysfunction**

- Impaired Relaxation
- Reduced \(-dP/dt\)
- Reduced \(E\)
- Prolonged IVRT
LV relaxation: tissue Doppler
Diastolic parameters

- Tissue Doppler records the actual movement of the LV in early diastole, and reflects \textit{LV relaxation}

- The mitral flow characteristics reflect not only the flow velocity, but the \textit{left ventricular filling pressure} when that flow occurs.
Normal LV filling

Figure 7 Example of normal findings from a young subject. Left shows normal LV size in parasternal long-axis view, with a normal mitral inflow pattern and E/A ratio > 1 in middle panel. Lateral e’ velocity is normal at 12 cm/sec (left).

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• The best estimate of the diastolic function takes into account the mitral flow velocity (E wave) and the LV relaxation (tissue Doppler), the tissue Doppler index (E/e’).
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Grades of Diastolic Dysfunction

- Grade 1  Delayed early relaxation with normal filling pressure
- Grade 2  Delayed relaxation and increased LV end diastolic pressure
- Grade 3  Progressive reduction in LV compliance and elevation of LV filling pressures
Back to our patient.

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 measure of LV relaxation, normal > 9 cm/s)
- Peak E velocity 127 cm/s
  (A measure of LV filling pressure)

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

- BP difficult to treat
- Fluids hard to control
- 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

  - 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?
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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- A key comparator:
  - HFpEF 30% of deaths are noncardiac
  - HFrEF 18% of deaths are noncardiac
HFpEF

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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

[CENTERED ILLUSTRATION: Biological Phenotypes in HFpEF]

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

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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
Impaired relaxation transmitral flow pattern, from Penicka M, *Heart* 2014

72 y female with dyspnoea (impaired relaxation transmitral flow)

- Normal diastolic function for the age
- Preclinical diastolic dysfunction (normal LAP, no HFPEF)
- HFPEF (increased LAP)
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

E 45 cm/s

e’ 5.2 cm/s

EXERCISE

E 91 cm/s

e’ 13.5 cm/s

E/e’ = 7
Diastolic stress echocardiography
Reduced LV relaxation reserve

REST

E 47 cm/s

e’ 4 cm/s

EXERCISE

E 130 cm/s

e’ 5 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

In patients with normal LV EF

1. Average E/e’ > 14
2. Septal e’ velocity < 7 cm/s or Lateral e’ velocity < 10 cm/s
3. TR velocity > 2.8 m/s
4. LA volume index > 34 ml/m²

- <50% positive
  - Normal Diastolic function

- 50% positive
  - Indeterminate

- >50% positive
  - Diastolic Dysfunction
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
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

• 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)
  - ARB/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>Patients</th>
<th>Sites</th>
<th>Pt/site/mo</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>3,445</td>
<td>233</td>
<td>0.22</td>
</tr>
<tr>
<td>N &amp; S Am</td>
<td>1,767</td>
<td>188</td>
<td>0.14</td>
</tr>
<tr>
<td>East. Eur.</td>
<td>1,676</td>
<td>45</td>
<td>0.56</td>
</tr>
</tbody>
</table>
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

- You would order
  
  A) Add furosemide, increase until dyspnea resolved
  B) Start sildenafil
  C) Start spironolactone
  D) Cardiac rehabilitation exercise, paid by medicare
  E) Cardiac rehab, not covered by insurance
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Exercise and HFP EF (From Borlaug, JACC)
## Exercise in HFpEF

*(From Rogers, Serajian. *JAOA*, 2015)*

<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>
<tbody>
<tr>
<td>Smart&lt;sup&gt;29&lt;/sup&gt;, 2012</td>
<td>ET = 12 Cnt = 13</td>
<td>60-70% peak VO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>16</td>
<td>↑ Peak exercise capacity ↔ QOL</td>
</tr>
<tr>
<td>Alves&lt;sup&gt;24&lt;/sup&gt;, 2012</td>
<td>ET = 20 Cnt = 22</td>
<td>70-75% HRmax for 3-5 min (5-7 intervals)</td>
<td>24</td>
<td>↑ peak METS ↓ LVEF ↓ L atrial pressure ↓ LV stiffness</td>
</tr>
<tr>
<td>Haykowski&lt;sup&gt;27&lt;/sup&gt;, 2012</td>
<td>ET = 22 Cnt = 18</td>
<td>40-70% HHR</td>
<td>16</td>
<td>↑ Peak exercise capacity ↑ peak HR</td>
</tr>
<tr>
<td>Edelmann&lt;sup&gt;25&lt;/sup&gt;, 2011 (EX-DHF)</td>
<td>ET = 44 Cnt = 20</td>
<td>50-70% HRmax, 60-65% PeakVO&lt;sub&gt;2&lt;/sub&gt;, 1Repetition max</td>
<td>12</td>
<td>↑ Peak exercise capacity ↑ 6MWD ↑ self-reported physical function</td>
</tr>
<tr>
<td>Kitzman&lt;sup&gt;28&lt;/sup&gt;, 2010</td>
<td>ET = 24 Cnt = 22</td>
<td>40-70% HRR</td>
<td>16</td>
<td>↑ Peak exercise capacity ↑ 6MWD ↑ physical QOL</td>
</tr>
<tr>
<td>Gary&lt;sup&gt;26&lt;/sup&gt;, 2006</td>
<td>ET = 15 Cnt = 13</td>
<td>40-60% HRmax</td>
<td>12</td>
<td>↑ 6MWD ↑ physical QOL</td>
</tr>
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Exercise and aging
Exercise and aging *(Aging Cell 10.1111/2018)*

- 100 cyclists aged 55-79
- All cycle more than 100 miles/week
- Quadriceps muscle biopsy
  - Muscle fiber type
  - Muscle fiber size
  - ATP activity
  - Capillary density
  - Mitochondrial proteins
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- Only capillary density decreased with age
HFpEF Conclusions

*HFpEF is a clinical syndrome of dyspnea and fatigue where there is normal LV EF, a stiff ventricle and stiff arteries and veins.
*The stiff LV and vasculature is worsened by inflammation, and the clinical syndrome of acute decompensated heart failure may be triggered by inflammation, especially lung disease, obesity, hypertension
*The signs and symptoms of HFpEF are dramatically more pronounced with exertion than they are at rest.
*Concerning treatment

  With blood pressure and fluid excess, “go low and go slow”
  There may be benefit to spironolactone
  Exercise is demonstrated to improved functional status
Bottom Line (Personal opinion)

Failure with preserved ejection fraction is a disorder of increased stiffness of the heart, arteries and veins. It is primarily a consequence of the natural aging process, which is worsened by deconditioning and accelerated by inflammation.