HFpEF
What’s New? (In 2019)
Felix J. Rogers, DO, FACC, FACOI
March 20, 2019

Meet Bill, my H.S. classmate
- Nov 27, 2018
  - “I get short of breath when I climb a flight of stairs”
    Feels exhausted at the end of a day in his tire repair shop
  - BP 126/78  HR 72  No JVD.  No murmur.
- Echo
  - LV normal size and thickness
  - LV EF  63%
  - Mild mitral annular calcification
  - Grade I LV diastolic dysfunction

Is this heart failure with preserved ejection fraction?
Meet Bill, my H.S. Classmate

• Nov 27, 2018
• “I get short of breath when I climb a flight of stairs”
  Exhausted at the end of the day
More information...

How Bill starts the day

Meet Bill, my H.S. classmate
More information

• Nov 27, 2018
• “I get short of breath when I climb a flight of stairs”
  Exhausted at the end of the day
• Additional history. He’s a triathlete
  — Exercises regularly. Runs 5-8 miles at least once a week
  — Works out for an hour at the Lexus Velodrome
  — Ranked No. 63 in the USA in his age group in 2018

___ Is this heart failure with preserved ejection fraction?
___ Is this diastolic heart failure?
___ Is this normal aging?
Today’s agenda

• Pathophysiology
  – Normal aging vs HFpEF
  – Fat, epicardial and visceral
  – Obesity
  – Acute decompensated HFpEF

• Treatment
  – Mechanical: reduction in LA pressure
  – Bariatric surgery
  – Medical: statins, mineralocorticoid inhibitors, SGLT2-
  – Exercise and lifestyle
  – Traditional cardiac risk factors

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
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
- Only capillary density decreased with age

Pathophysiology of aortic-LV dynamics in the aging CV system


Effect of age on hemodynamic changes during progressive exercise

Emil Wolsk et al. JCHF 2017;5:337-346
Effect of age on hemodynamic changes during progressive exercise

PCWP

Cardiopulmonary exercise testing

Peak exercise capacity

• “the maximum ability of the cardiovascular system to deliver oxygen to exercising skeletal muscle and of the exercising muscle to extract oxygen from the blood”

CPE in dyspneic pt with Normal EF

YNV Reddy, BA Borlaug, et al. JACC HF 2018; 6:665-75

• 206 patients with dyspnea and normal LV EF
  – Noncardiac dyspnea (NCD) = 72
  – HFrEF = 134

• Diagnostic evaluation
  – Transthoracic echocardiogram (TTE)
  – Upright bicycle cardiopulmonary exercise
  – Supine bicycle cardiopulmonary exercise in the cardiac cath lab with hemodynamic monitoring

Results – CPE testing

• HFrEF
  – Lower peak VO2 both supine and upright
  – Very low peak VO2 < 14 ml/kg/min clearly discriminated HFrEF from NCD
    • Specificity 91% Sensitivity 50%
  – Preserved VO2 > 20 ml/kg/min reliably excluded HFrEF with excellent specificity.
Results – CPE testing

- HFpEF

- Intermediate outcomes: Peak VO₂ greater than 14, but < 20 ml/kg/min

Non-invasive testing not adequate to discriminate HFpEF from non cardiac dyspnea.

Relationship between hemodynamics and exercise capacity

Characteristics of HFpEF with severely depressed aerobic capacity
Second Study

- Compare exercise hemodynamics of patients with HFrEF to normal controls.
- HFrEF Patients were enrolled from two trials,
  - REDUCE-LAP HF (Reduce Elevated Left Atrial Pressure in Patients With Heart Failure)
  - HemReX (Effect of Age on the Hemodynamic Response During Rest and Exercise in Healthy Humans)

Contribution of independent variables associated with HFrEF during exercise
Red = PCWP, Blue = Stroke volume, Gray = BMI
• Workload-Corrected Hemodynamic Variables Associated With HFpEF During Peak Exercise

• When the model was adjusted for BMI and age, workload-corrected PCWP was still the largest contributor to the HFpEF phenotype: PCWP/workload (64%), BMI (21%), age (10%).

New treatment based on increased LA pressure during exercise

• Novel therapy for patients with heart failure (HF) with preserved ejection fraction (EF >50%) or midrange EF (40% to 50%) utilizing an implanted device to create an atrial shunt (inter-atrial shunt device [IASD]).
• The objective of the IASD is to dynamically (at rest and during exercise) decompress left atrial pressure overload associated with HF with preserved EF and HF with midrange EF.
• At 1 month after randomization, the IASD treatment group had a significantly greater reduction in pulmonary capillary wedge pressure during exercise compared with the control group.
• Circulation. 2018;137:364–375.
Transcatheter Interatrial Shunt Device for the Treatment of Heart Failure With Preserved Ejection Fraction (REDUCE LAP-HF I [Reduce Elevated Left Atrial Pressure in Patients With Heart Failure]). Volume: 137, Issue: 4, Pages: 364-375, DOI: 10.1161/CIRCULATIONAHA.117.032094


NYHA Functional Class in HfPEF

Let’s brush up on the evaluation of diastolic function
Normal LV filling velocity and pressure

Mitral inflow patterns in diastole

Normal Grade I Dysfunction

LV relaxation: tissue Doppler
Diastolic parameters

- Tissue Doppler records the actual movement of the LV in early diastole, and reflects LV relaxation.

- The mitral flow characteristics reflect not only the flow velocity, but the left ventricular filling pressure when that flow occurs.

Normal LV filling

![Image of normal LV filling](image_url)

**Figure 1**: Example of normal filling from a patient study. Left shows normal LV size on parasternal long axis view, with normal mitral inflow pattern and E/A ratio = 1 in middle panel. Lateral a' velocity is normal at 12 inches/sec.

Diastolic parameters

- Tissue Doppler records the actual movement of the LV in early diastole, and reflects LV relaxation.

- The mitral flow characteristics reflect not only the flow velocity, but the left ventricular filling pressure when that flow occurs.

- 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')
Diastolic parameters

• Tissue Doppler records the actual movement of the LV in early diastole, and reflects LV relaxation

• The mitral flow characteristics reflect not only the flow velocity, but the left ventricular filling pressure when that flow occurs.

• 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’)

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

Diagnosis of HFpEF

• In some studies, up to 80% of patients enrolled as symptomatic HFpEF had normal or grade I LV Diastolic dysfunction.

• The diagnosis of HFpEF must include parameters that account for the hemodynamic and clinical abnormalities described earlier, including
  – Increased LA pressure
  – Increased PA pressure
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

Evidence of abnormal LV relaxation, abnormal filling, diastolic stiffness
  - Cardiac cath – elevated LVEDP > 16 mm Hg, mean PCWP > 12 mm Hg
  - NT-pro BNP > 220
  - Tissue Doppler Index E/e' > 15

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.
Aging: microvascular circulation

- Coronary microvascular disease (CMD)
  - refers to disorders affecting the structure and function of the coronary microcirculation
  - Is prevalent in patients across a broad spectrum of CV risk factors
  - Is associated with increased risk of adverse events.
- Most patients with CMD have macrovessel atherosclerosis

Schematic of the Epicardial Coronary Arteries and the Full Coronary Circulation

Normal & Abnormal Structure and function of the coronary macro- and microcirculation
Myocardial Dysfunction and Remodeling in HFPEF and HFREF

In HFPEF, myocardial dysfunction and remodeling are driven by endothelial inflammation and oxidative stress. 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.

Figure Legend:

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.
Case Presentation: CVM

- 69 year old female seen for shortness of breath and coronary calcium seen on CT images performed as part of low-dose protocol for cancer screening.
- Quit cigarettes 6 years ago. No CAC 5 years ago
- PE: 5'4, 167 lbs BMI 28.7
  BP 120/82
10 year pooled cohort risk: 8%

CVM CT for Cancer Detection
LAD embedded in epicardial fat

Circumflex (L) and RCA (R) embedded in epicardial fat.
Epicardial fat

- Milton Packer, MD
- “Epicardial adipose tissue may mediate deleterious effects of obesity and inflammation on the myocardium”
- J Am Coll Cardiol 2018; 71: 2360-72

Comparison of typical CAD with allograft angiopathy (TCAD)
Let’s look more closely at obesity

Mechanisms of obesity-related HFpEF

- Especially important in patients with T2D and HLD, who have marked increase in plasma volume and limited ventricular distensibility, most likely due to:
  - Cardiac microvascular disease acting in concert with:
  - Myocardial and pericardial fibrosis
- May be related to overproduction of aldosterone and neprilysin

Regional adipose distribution and exercise intolerance

- Regional adipose deposition may have important adverse consequences beyond total body adiposity
- Intra-abdominal fat was strongest independent predictor of impairment in VO2 and 6 minute walk test
- Epicardial fat was lower in patients with HFpEF than healthy controls

Haykowsky et al, JACC HF 2018; 6: 640-9
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>Study 1, 2012</td>
<td>30 (15+C)</td>
<td>Moderate</td>
<td>24</td>
<td>Peak exercise capacity</td>
</tr>
<tr>
<td>Study 2, 2013</td>
<td>20 (10+C)</td>
<td>Moderate</td>
<td>24</td>
<td>Peak exercise capacity</td>
</tr>
<tr>
<td>Study 3, 2014</td>
<td>40 (20+C)</td>
<td>High</td>
<td>52</td>
<td>Peak exercise capacity</td>
</tr>
<tr>
<td>Study 4, 2015</td>
<td>30 (15+C)</td>
<td>High</td>
<td>52</td>
<td>Peak exercise capacity</td>
</tr>
<tr>
<td>Study 5, 2016</td>
<td>40 (20+C)</td>
<td>High</td>
<td>52</td>
<td>Peak exercise capacity</td>
</tr>
</tbody>
</table>
**HFpEF Conclusions**

• The signs and symptoms of HFpEF are dramatically more pronounced with exertion than they are with rest.

*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

**HFpEF conclusions**

• HFpEF differs from normal aging and from non-cardiac dyspnea by marked increases in LA pressure and volume, especially with exertion

• Therefore, key echocardiographic markers are
  – Left atrial enlargement (LAVi > 34 ml/m²)
  – Pulmonary hypertension (PAPsys > 34 mm Hg)

• Key clinical markers are
  – Atrial fibrillation, elevated BNP
**HFpEF has two forms of inflammation**

1. **Chronic inflammation**, due to
   - Obesity
   - Hypertension
   - Diabetes
   - Chronic kidney disease
   - Lung disease
   • This inflammation creates microvascular coronary artery disease, myocardial fibrosis and abnormalities of skeletal muscle function

2. **Acute inflammation**, due to
   - Acute respiratory infection
   - Exacerbation of COPD
   - Sepsis

**Treatment**

- Mechanical: reduction in LA pressure
  - Bariatric surgery
- Medical: statins
  - Mineralocorticoid inhibitors
  - SGLT2-I
- Exercise and lifestyle changes
- Control traditional cardiac risk factors