HFpEF Mimics and When to Look for Them: Plenary Session #3: Novel Concepts in the Diagnosis and Treatment of HFpEF

Heart Failure Update 2020

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Outline of Discussion

- The impact of co-morbid disease in HFpEF
- Pitfalls and pearls in the diagnosis of HFpEF
- Mimics?
  - Outside of the HFpEF diagnosis
  - Inside the HFpEF diagnosis
The Challenge of HFpEF

### Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

<table>
<thead>
<tr>
<th>Type of HF</th>
<th>HFpEF</th>
<th>HFmrEF</th>
<th>HFrEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Symptoms ± Signs*</td>
<td>Symptoms ± Signs*</td>
<td>Symptoms ± Signs*</td>
</tr>
<tr>
<td>2</td>
<td>LVEF &lt;40%</td>
<td>LVEF 40-49%</td>
<td>LVEF ≥50%</td>
</tr>
<tr>
<td>3</td>
<td>Elevated levels of natriuretic peptides; a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).</td>
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</tr>
</tbody>
</table>

*Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.

DNP = B-type natriuretic peptide; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFmrEF = heart failure with mid-range ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B type natriuretic peptide.

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Dunley S. Nat Rev Cardiol 2017; 591
Zakeri et al; Heart 2018; 104:377-384
The Co-morbid Collection in HFpEF

**Comorbidities**
- HTN
- Sleep apnea
- Diabetes
- Coronary disease
- Atrial fibrillation
- Chronic kidney disease

**Cardiac and pulmonary vascular function**
- LV dysfunction only
- LV and LA dysfunction and/or atrial fibrillation
- Pulmonary vascular dysfunction
- RV dysfunction

**Haemodynamics**
- ↑ LVFP with exercise only
- ↓ Pulmonary vasodilatation with exercise
- ↑ LVFP at rest with pulmonary hypertension
- ↑ RVFP and LVFP at rest

**Extra-cardiac structure and function**
- ↑ Arterial stiffness
- Endothelial and coronary microvascular dysfunction
- Sarcopenia and mitochondrial dysfunction
- Tissue fibrosis

**Biomarkers**
- Normal natriuretic peptide levels
- Pro-inflammatory markers
- Cardiac injury markers
- Fibrotic markers

**Increasing disease severity and risk of adverse outcomes**
Relationship of Comorbid Burden to Outcome in Heart Failure

Ergatoudes C; Clin Res in Cardiol 2019:108:1025-1033
Interplay Between Comorbid Disease and Underlying Molecular Mechanisms in HFpEF

- Comorbidities: HTN, Obesity, Diabetes, CKD, COPD, Anemia
- Systemic inflammation
  - Fibroblasts → myofibroblasts
  - Monocytes
  - Macrophages
  - DIO

- Microvascular inflammation
  - Coronary microvascular dysfunction

- Myocardial fibrosis
  - Passive stiffness

- IMPAIRED SYSTOLIC + DIASTOLIC CARDIAC MECHANICS

- Tauboe disruption
  - Care leak/overload

- ENDOTHELIUM
  - Loss of eNOS
  - eNOS → NO

- NPs act through a receptor guanylate cyclase (rGC) pathway that results in the creation of cGMP and stimulation of PKG, which has a variety of beneficial effects in the heart and multiple other organs. There is also an intracellular, soluble guanylate cyclase that is stimulated by nitric oxide (NO), which also leads to increased cGMP and activation of PKG. Phosphodiesterase (PDE) 5 results in the breakdown of the NO-based cGMP pool, whereas PDE9 results in the breakdown of the NP-based cGMP pool.

- Because of insufficient NPs and NO, PKG is reduced in HFpEF, which leads to decreased cardiac chamber passive stiffness. Because of insufficient NPs and NO, PKG is reduced in HFpEF, which leads to decreased cardiac chamber passive stiffness.

- Increased NPRA, there is increased cGMP and protein kinase G (PKG) production, leading to lipolysis and the brown-fat thermogenic program. With increased NPRC, there is increased cGMP and protein kinase G (PKG) production, leading to lipolysis and the brown-fat thermogenic program.

- With increased NPRC, there is increased cGMP and protein kinase G (PKG) production, leading to lipolysis and the brown-fat thermogenic program.

- Adipose tissue, where the relative ratio of the NP receptor A (NPRA) to NP receptor C (NPRC) are important in dictating whether beneficial NP effects are possible. With increased NPRA, there is increased cGMP and protein kinase G (PKG) production, leading to lipolysis and the brown-fat thermogenic program. With increased NPRC, there is increased cGMP and protein kinase G (PKG) production, leading to lipolysis and the brown-fat thermogenic program.

- Several factors promote a relative natriuretic peptide (NP) deficiency state in HFpEF, including obesity, sedentary lifestyle, African ancestry, insulin resistance, increased androgenicity in women, genetic variation in the NPPB genes, and a lower amount of wall stress for the severity of heart failure (compared with heart failure with reduced ejection fraction).

- In a recent study that used a novel 2-hit mouse model of HFpEF, derived NO is reduced in HFpEF, inducible NO synthase (iNOS), which is activated by systemic inflammation, is upregulated and could be a pathogenic factor leading to cardiac dysfunction (in multiple organs), and coronary microvascular dysfunction, leading to abnormal systolic and diastolic cardiac mechanics and poor cardiac reserve. Systemic inflammation also leads to the activation of monocytes and macrophages, which release profibrotic cytokines, including IL-10 and transforming growth factor-β (TGF-β).

- Figure 1. Proposed molecular mechanisms underlying heart failure with preserved ejection fraction (HFpEF).
Beyond Diastolic Dysfunction: HFpEF is a Systemic Disease

Cardiac and metabolic comorbidities
Ischemia, Atrial Fibrillation, Obesity, Hypertension, Diabetes, Anemia

LV Diastolic Dysfunction
LV Systolic Dysfunction
Pulmonary HT
RV Dysfunction & Remodeling
LA Dysfunction

Enhanced DVI
Vascular Stiffening
Microvascular Dysfunction
Peripheral Abnormalities
Chronotropic Incompetence

Heart Rate (bpm)

Exercise Duration (secs)

HFpEF CONTROL
HFpEF Diagnosis: Not for the Faint of Heart….

<table>
<thead>
<tr>
<th>First Author (Ref. #) Year</th>
<th>n</th>
<th>Guideline (Ref. #)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>AUC</th>
<th>Indeterminant (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reddy et al. (101) 2018</td>
<td>414 (HFpEF 267)</td>
<td>ESC (105)</td>
<td>57</td>
<td>78</td>
<td>0.67</td>
<td>0</td>
</tr>
<tr>
<td>Obokata et al. (102) 2017</td>
<td>74 (HFpEF 50)</td>
<td>ASE/EACVI (5)</td>
<td>34</td>
<td>83</td>
<td>0.65</td>
<td>24</td>
</tr>
<tr>
<td>Obokata et al. (102) 2017</td>
<td>74 (HFpEF 50)</td>
<td>ESC (105)</td>
<td>60</td>
<td>75</td>
<td>0.68</td>
<td>0</td>
</tr>
</tbody>
</table>

ASE/EACVI = recommendations for the evaluation of left ventricular diastolic function by echocardiography from the American Society of Echocardiography and the European Association of Cardiovascular Imaging; AUC = area under the curve; ESC = European Society of Cardiology; other abbreviations as in Table 1.

- Lack of a single objective marker to define the syndrome
- High frequency of comorbidities that can mimic or accompany the HF syndrome
- Natriuretic peptide levels often below typical clinical thresholds
- Notion that diastolic function required to diagnose HFpEF
- Underuse of provocative testing to elicit functional abnormalities
Real World Diagnostics of HF Patients

50% of Patients with an ICD code of HF had EF data available

50% of Patients with an ICD code of HF and no EF measurement also had no NTproBNP assessment
Use of Echocardiography After a HF Diagnosis in the Champlain LHIN

- Data obtained from ambulatory care setting 2009-2013
- In all sub regions, ~1/3 of those with HF had an echo within 6 month of prior diagnosis. This number doubled when looking at ECHO within a year of the diagnosis.
- Women were less likely than men to have an Echo within one-year of diagnosis than men.
TABLE 2. Physicians Who Reported Awareness of HFpEF Diagnostic Guidelines and Use of Left Ventricular Diastolic Dysfunction and BNP to Rule In or Rule Out a Diagnosis of HFpEFa

<table>
<thead>
<tr>
<th>Diagnostic consideration</th>
<th>Noncardiologists n (%)</th>
<th>Cardiologists n (%)</th>
<th>P value</th>
<th>Question No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aware of ESC or ACC/AHA diagnostic guidelines</td>
<td>49 (27.4%)</td>
<td>20 (62.5%)</td>
<td>.001</td>
<td>23</td>
</tr>
<tr>
<td>Exclude HFpEF diagnosis if DD not present on TTE</td>
<td>66 (38.4%)</td>
<td>2 (6.5%)</td>
<td>.001</td>
<td>27</td>
</tr>
<tr>
<td>Diagnose HFpEF in all patients with DD present on TTE</td>
<td>58 (33.9%)</td>
<td>1 (3.2%)</td>
<td>.001</td>
<td>28</td>
</tr>
<tr>
<td>Use low BNP level to exclude a diagnosis of HFpEF</td>
<td>58 (33.3%)</td>
<td>8 (25.8%)</td>
<td>.41</td>
<td>24</td>
</tr>
</tbody>
</table>

aACC = American College of Cardiology; AHA = American Heart Association; BNP = B-type natriuretic peptide; DD = diastolic dysfunction; ESC = European Society of Cardiology; HFpEF = heart failure with preserved ejection fraction; TTE = transthoracic echocardiography.

TABLE 3. Physicians Who Reported That Certain TTE Findings Individually Would Cause Them to Consider a Diagnosis of HFpEF in the Absence of Other TTE Abnormalitiesb

<table>
<thead>
<tr>
<th>TTE finding</th>
<th>Noncardiologists n (%)</th>
<th>Cardiologists n (%)</th>
<th>P value</th>
<th>Question No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV diastolic dysfunction</td>
<td>161 (89.9%)</td>
<td>26 (81.3%)</td>
<td>.15</td>
<td>29</td>
</tr>
<tr>
<td>Left atrial enlargement</td>
<td>71 (39.7%)</td>
<td>26 (81.3%)</td>
<td>&lt;.001</td>
<td>29</td>
</tr>
<tr>
<td>LV hypertrophy</td>
<td>94 (52.5%)</td>
<td>19 (59.4%)</td>
<td>.47</td>
<td>29</td>
</tr>
<tr>
<td>Elevated RVSP</td>
<td>75 (41.9%)</td>
<td>20 (62.5%)</td>
<td>.03</td>
<td>29</td>
</tr>
<tr>
<td>RV enlargement</td>
<td>47 (26.3%)</td>
<td>16 (50.0%)</td>
<td>.007</td>
<td>29</td>
</tr>
<tr>
<td>LV dilation</td>
<td>44 (24.6%)</td>
<td>8 (25.0%)</td>
<td>.96</td>
<td>29</td>
</tr>
</tbody>
</table>

bHFpEF = heart failure with preserved ejection fraction; LV = left ventricular; RV = right ventricular; RVSP = right ventricular systolic pressure; TTE = transthoracic echocardiography.

bCorresponding question number in the Supplemental Appendix.
HFpEF Diagnosis: Not for the Faint of Heart….

**Clinical History and Physical Exam**

Orthopnea, PND: highly specific
Dyspnea, fatigue: more sensitive
Obesity: OR 3.46
AF: OR 12.35

**Exercise testing**

Invasive/noninvasive
PWP>15 at rest and >25 during exercise
Reduced cardiac output reserve

**Integrated Diagnostic Approach**

Increased E/e’ and PASP
LAE, decreased e’, reduced global longitudinal strain

**Natriuretic peptides**

Lower wall stress due to small cavity size and thicker walls
Effect of obesity

**Echo**

PWP>15 at rest and >25 during exercise
Reduced cardiac output reserve

*Echo*
**H$_2$FPEF Score: A validated Diagnostic Algorithm for HFpEF**

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Values</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>H$_2$ Heavy</td>
<td>Body mass index &gt; 30 kg/m$^2$</td>
<td>2</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>2 or more antihypertensive medicines</td>
<td>1</td>
</tr>
<tr>
<td>F Atrial Fibrillation</td>
<td>Paroxysmal or Persistent</td>
<td>3</td>
</tr>
<tr>
<td>P Pulmonary Hypertension</td>
<td>Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure &gt; 35 mmHg</td>
<td>1</td>
</tr>
<tr>
<td>E Elder</td>
<td>Age &gt; 60 years</td>
<td>1</td>
</tr>
<tr>
<td>F Filling Pressure</td>
<td>Doppler Echocardiographic E/e' &gt; 9</td>
<td>1</td>
</tr>
</tbody>
</table>

**H$_2$FPEF score**

<table>
<thead>
<tr>
<th>Total Points</th>
<th>Score of HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.2</td>
</tr>
<tr>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>2</td>
<td>0.4</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
</tr>
<tr>
<td>4</td>
<td>0.6</td>
</tr>
<tr>
<td>5</td>
<td>0.7</td>
</tr>
<tr>
<td>6</td>
<td>0.8</td>
</tr>
<tr>
<td>7</td>
<td>0.9</td>
</tr>
<tr>
<td>8</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Probability of HFpEF:
- Score 0-1: Low
- Score 2-5: Intermediate
- Score 6-9 High

Reddy et al. Circ 2018; 138:861-870
HFA-PEEF Algorithm: Consensus Recommendation from HFA and ESC

The HFA-PEFF Algorithm for the Diagnosis of HFpEF

**P**

**Initial Workup**  
(Step 1 (P): Pretest Assessment)

- Symptoms and/or Signs of HF  
- Comorbidities / Risk factors  
- ECG  
- Standard Echocardiography  
- Natriuretic Peptides  
- Ergometry / 5 min walking test or Cardiopulmonary Exercise Testing

**E**

**Diagnostic Workup**  
(Step 2 (E): Echocardiographic and Natriuretic Peptide Score)

- Comprehensive Echocardiography  
- Natriuretic Peptides, if not measured in Step 1

**F1**

**Advanced Workup**  
(Step 3 (F1): Functional testing in Case of Uncertainty)

- Diastolic Stress Test: Exercise Stress Echocardiography  
- Invasive Haemodynamic Measurements

**F2**

**Aetiological Workup**  
(Step 4 (F2): Final Aetiology)

- Cardiovascular Magnetic Resonance  
- Cardiac or Non-Cardiac Biopsies  
- Scintigraphy / CT / PET  
- Genetic testing  
- Specific Laboratory Tests

---

**HFA-PEFF score**

<table>
<thead>
<tr>
<th>Domains</th>
<th>Major criteria (2 points)</th>
<th>Minor criteria (1 point)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional</td>
<td>Septal e’&lt;7 cm/s</td>
<td>Average E/e’ ratio 9–14</td>
</tr>
<tr>
<td></td>
<td>Lateral e’&lt;10 cm/s</td>
<td>Global longitudinal strain  &lt;16%</td>
</tr>
<tr>
<td>Morphological</td>
<td>LAVI &gt;34 ml/m²</td>
<td>LAVI 29–34 ml/m²</td>
</tr>
<tr>
<td></td>
<td>LVMI ≥149/122 g/m²</td>
<td>LVMI &gt;115/95 g/m² (m/w)</td>
</tr>
<tr>
<td></td>
<td>(m/w) and relative wall thickness &gt;0.42</td>
<td>Left ventricular wall thickness ≥12 mm</td>
</tr>
<tr>
<td>Biomarker (sinus rhythm)</td>
<td>NT-proBNP &gt;220 pg/ml</td>
<td>NT-proBNP 125–220 pg/ml</td>
</tr>
<tr>
<td></td>
<td>BNP &gt;80 pg/ml</td>
<td>BNP 35–80 pg/ml</td>
</tr>
<tr>
<td>Biomarker (atrial fibrillation)</td>
<td>NT-proBNP &gt;660 pg/ml</td>
<td>NT-proBNP 365–660 pg/ml</td>
</tr>
<tr>
<td></td>
<td>BNP &gt;240 pg/ml</td>
<td>BNP 105–240 pg/ml</td>
</tr>
</tbody>
</table>

**Probability of HFpEF:**

Score 0-1: Low  
Score 2-4: Intermediate  
Score 5-6: High

*Pieske et al; Eur J HF 2020; 22:391-212*
HFA-PEEF Algorithm: Consensus Recommendation from HFA and ESC
Mimics of HFpEF in a patient with Established or High Probability of HFpEF

Why is my Patient SOB?

-cardiac ischemia
-anemia
-chronotropic incompetence
-obesity deconditioning
-un-treated sleep apnea
-un-treated lung disease

PATHOPHYSIOLOGIC PHENOTYPES IN HFpEF

- Arterial stiffening
  - Aortic compliance
  - Vasorelaxation with exercise
  - Blood pressure lability

- Skeletal myopathy
  - Diffusive O₂ conductance
  - Capillary density
  - Muscle quality
  - Exercise capacity

- Obese hypertension
  - Myocyte injury
  - Exercise capacity
  - LV reserve
  - Mortality

- Inflammation
  - NO-cGMP
  - Endothelial dysfunction
  - LV stiffness
  - Epicardial adipose tissue

- Cardiometabolic comorbidities
  - Ventricular remodeling
  - Myocardial fibrosis
  - LV reserve
  - Exercise capacity

Pulmonary vascular & RV dysfunction
- PA pressure
- PV remodeling
- RV reserve
- Exercise capacity
- Mortality

The Role of Noninvasive Exercise Testing

Figure 4

Step 3(F): Functional tests in cases of diagnostic uncertainty. (A) Its how stress tests work up with exercise echocardiography. If key haemodynamic abnormalities are identified, a definite heart failure with preserved ejection fraction (HFpEF) diagnosis can be made. (B) Its how invasive haemodynamic measurements (left) or during exercise (right) can complement stress echocardiography and are recommended in cases with remaining diagnostic uncertainty. LVEDP, left ventricular end-diastolic pressure; PCWP, pulmonary capillary wedge pressure; TR, tricuspid regurgitation.

During supine exercise in healthy control subjects, cut-offs for peak PCWP and LVEDP are <20–23 mmHg and <25 mmHg, respectively. Patients with values <25 mmHg during peak exercise are classified as having non-cardiac dyspnoea. A steep increase in PCWP during exercise is a typical haemodynamic response in HFpEF, indicating that the dyspnoea on exertion is mainly of cardiac origin. Patients with peak exercise PCWP \( \geq 25 \) mmHg are classified as having HFpEF (online supplementary Appendix S).

An increase in LV filling pressure during exercise that is not accompanied by increases in end-diastolic volume, indicates limitation to LV filling or the development of pericardial constraint. A high increase in PCWP during exercise predicts poor outcomes from HFpEF. Patients with a normal mPCWP at rest (<12 mm Hg) but a steep increase during exercise (to \( \leq 25 \) mmHg) have a two-fold increase in mortality. Ten-year mortality was 6.6% if resting mPCWP was <12 mm Hg and peak exercise mPCWP was <25 mmHg; 28.2% in patients with low mPCWP at rest and high exercise mPCWP; and 35.2% in those with high resting mPCWP and high peak exercise mPCWP (\( \leq 25 \) mmHg).

Exercise mPCWP reclassifies patients with a normal resting mPCWP and stratifies risk. If other investigations have been inconclusive, invasive measurement of mPCWP or LVEDP is considered as the clinical reference investigation for diagnosing HFpEF (see online supplementary Appendix S about how to perform an invasive stress test). Other causes such as significant CAD, mitral stenosis, or pericardial constriction must be excluded.

Step 4(F2): Final aetiology

Most cases of HFpEF are related to common risk factors and comorbidities, but the possibility of a specific underlying aetiology should always be considered (Table 2, Figure 5; online ©2020 European Society of Cardiology Pieske et al; Eur J HF 2020; 22:391-212).
Invasive Exercise Testing in HFpEF

During supine exercise in healthy control subjects, cut-offs for peak PCWP and LVEDP are <20–23 mmHg and <25 mmHg, respectively. Patients with values <25 mmHg during peak exercise are classified as having non-cardiac dyspnoea. A steep increase in PCWP during exercise is a typical haemodynamic response in HFpEF, indicating that the dyspnoea on exertion is mainly of cardiac origin. Patients with peak exercise PCWP ≥25 mmHg are classified as having HFpEF (online supplementary Appendix S1). An increase in LV filling pressure during exercise that is not accompanied by increases in end-diastolic volume, indicates limitation to LV filling or the development of pericardial constraint.

Patients with a normal mPCWP at rest (<12 mm Hg) but a steep increase during exercise (to ≥25 mmHg) have a two-fold increase in mortality. Ten-year mortality was 6.6% if resting mPCWP was <12 mm Hg and peak exercise mPCWP was <25 mmHg; 28.2% in patients with low mPCWP at rest and high exercise mPCWP; and 35.2% in those with high resting mPCWP and high peak exercise mPCWP (<25 mmHg).

Exercise mPCWP reclassifies patients with a normal resting mPCWP and stratifies risk. If other investigations have been inconclusive, invasive measurement of mPCWP or LVEDP is considered as the clinical reference investigation for diagnosing HFpEF (see online supplementary Appendix S1 about how to perform an invasive stress test). Other causes such as significant CAD, mitral stenosis, or pericardial constriction must be excluded.

Step 4(F2): Final aetiology

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Maron; Circ 2013: 123

Pieske et al; Eur J HF 2020; 22:391-212
Pulmonary Hypertension in Left Heart Disease

Limitations of studies of pulmonary hypertension
The epidemiology of pulmonary hypertension is much more difficult to study than the epidemiology of systemic hypertension because a reliable diagnosis requires right heart catheterisation, which is an invasive procedure. Therefore, large-scale population-based studies have to rely on echocardiography because invasive tests for epidemiological studies would be neither ethical nor feasible. The interpretation of these data must take into account that echocardiography is not a reliable method to diagnose pulmonary hypertension.

Several catheter-based studies have been done in patients at risk for pulmonary arterial hypertension and in patients with left-sided heart disease and chronic lung disease. The results of these studies have been largely consistent, therefore confirming each other and also to a large extent, confirming studies on the basis of echocardiography.

Interpretation should be done with caution as most of the underlying evidence has been derived from populations at risk for pulmonary hypertension and echocardiography data rather than from population-based studies involving right heart catheterisation. Data from the developing world are particularly sparse. Additionally, variations exist within the world regions. In Latin America, for instance, schistosomiasis highly prevalent in Brazil, Venezuela, and the Caribbean, but not in other countries. Schistosomiasis is also prevalent in sub-Saharan Africa and Southeast Asia, but there is almost no data on the association between schistosomiasis and pulmonary arterial hypertension from these areas. HIV is not evenly distributed in Africa and is particularly frequent in some areas of sub-Saharan Africa.

PROPOSED NEW DEFINITIONS OF PH IN LEFT HEART DISEASE:

- Isolated post capillary PH (IpcPH)
  - PCWP > 15 mmHg AND mean PAP > 20 mmHg AND PVR ≤ 3 WU

- Combined Post and Precapillary PH (CpcPH)
  - PCWP > 15 mmHg and mean PAP > 20 mmHg AND PVR > 3 WU

6th World Symposium on PH (Nice 2018)
Combined Pre and Post Capillary PH in HFpEF

**Clinical Analysis**
- Cpc-PH Similar to PAH:
  - Younger Age
  - Severe Pulmonary Vascular Disease
- Cpc-PH Similar to Ipc-PH:
  - Medical Comorbidities
  - Severity and Chronicity of LV Disease

**Genetic Analysis**
- Ipc-PH SNPs
- Cpc-PH SNPs
- PAH SNPs

- 141 SNPs with lung expression
  - Actin Binding
  - Extracellular Matrix
  - Basement Membrane
  - MHC II Proteins

**Isolated post cap PH**

**Pre and post cap PH**

Right Heart Failure Phenotype in HFpEF

HFpEF Phenotypes

- EXERCISE INDUCED DIASTOLIC DYSFUNCTION
  - Phenotype A: Long-standing HTN, NYHA II, Exercise intolerance, Minimal fluid retention, No HF hospitalizations, LVEF 70%, 2+ LAE, Grade I-II DD, PASP 10-25 mmHg at rest, Exercise E/e’ > 14

- VOLUME OVERLOAD
  - Phenotype B: HTN, CAD s/p CABG, NYHA III, Severe DOE, 2+ LE edema, Recent HF hospitalization, LVEF 50%, 3+ LAE, Grade III DD, PASP 45 mmHg at rest, 2+ MR, 2+AR

- PULMONARY HYPERTENSION RV FAILURE
  - Phenotype C: HTN, DM2, CKD, obese, NYHA III, Severe SOB, DOE, 3+ edema, ascites, Frequent HF hospitalizations, LVEF 65%, 4+ LAE, Grade IV DD, PASP 60 mmHg at rest, RVH + RV dysfunction

Sample patients

- Clinical course
- BNP level
### Is This “Garden Variety” HFpEF or Something Else?

#### Abnormalities of the Myocardium

<table>
<thead>
<tr>
<th>Ischemic</th>
<th>CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxic</td>
<td>Substance use</td>
</tr>
<tr>
<td></td>
<td>EtoH, cocaine, steroids</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>Copper, iron, lead, cobalt</td>
</tr>
<tr>
<td>Immune and inflammatory</td>
<td>Infection</td>
</tr>
<tr>
<td></td>
<td>HIV, hepatitis, parasites</td>
</tr>
<tr>
<td>Non-infectious</td>
<td>Lymphocytic myocarditis, CTD, eosinophilic myocarditis</td>
</tr>
<tr>
<td>Infiltrative</td>
<td>Malignant</td>
</tr>
<tr>
<td></td>
<td>direct infiltration</td>
</tr>
<tr>
<td></td>
<td>metastases</td>
</tr>
<tr>
<td>Non-malignant</td>
<td>Amyloid, sarcoid, hemochromatosis, storage disease, Pompe, Gaucher’s</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Hormonal</td>
</tr>
<tr>
<td></td>
<td>Thyroid, parathyroid, Cushing, Addison, Conn’s</td>
</tr>
<tr>
<td>Nutritional</td>
<td>Thiamine, selenium, complex</td>
</tr>
<tr>
<td>Genetic</td>
<td>HCM</td>
</tr>
<tr>
<td></td>
<td>Early muscular dystrophy</td>
</tr>
<tr>
<td>Endomyocardial</td>
<td>EMF, carcinoid, Pagets, endocardial fibroelastosis</td>
</tr>
</tbody>
</table>
## Important “Mimics” of HFpEF

<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
<th>Clinical Clues</th>
<th>Echo Clues</th>
<th>Confirmatory /Ancillary Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertrophic CM</td>
<td>Presyncope/syncope, arrhythmia, younger age, family history</td>
<td>Asymmetric hypertrophy, ↑ wall thickness, LVOT obstruction, SAM</td>
<td>CMR Genetic testing</td>
</tr>
<tr>
<td>Constrictive pericarditis</td>
<td>Previous surgery, exposure, JVP findings</td>
<td>Pericardial thickening, septal bounce, increased respiratory variation in M/T flow, hepatic vein diastolic flow reversal during expiration, absence of IVC collapse</td>
<td>CT, CMR Right heart catheterization</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>Murmur</td>
<td>Morphological valve abnormality, Doppler</td>
<td>Detailed echo assessment, TEE</td>
</tr>
<tr>
<td>CAD</td>
<td>Risk factors, ischemic pain</td>
<td>Regional WMA, thinning</td>
<td>Perfusion imaging Coronary angiography</td>
</tr>
<tr>
<td>High output states</td>
<td>Anemia, sepsis, pregnancy, AV fistula, thyrotoxicosis</td>
<td>Increased Doppler derived CO, increased 4 chamber volumes</td>
<td>Right heart catheterization</td>
</tr>
</tbody>
</table>
Important “Mimics” of HFpEF: Cardiac Amyloid

- 5-13% of patients considered to have HFpEF have CA
- ATTRwt CA identified in 32% of PM cases of "HFpEF” >75 years age
- All forms of amyloid can present with typical HF symptoms
- Consider:
  - Decreased exercise tolerance
  - Low BP
  - Syncope
  - Arrhythmia and conduction blocks
  - Amyloid associated neuropathy (autonomic or sensorimotor)

- Diagnostic delay associated with:
  - Increased cardiac biomarkers
  - Worsening conduction abnormalities and arrhythmia
  - Worse prognosis

**Echo Clues:**
- Small LV cavity
- Increased LV wall thickness
- Sparkling myocardium
- Apical sparing
- Severely reduced tissue doppler
- Pericardial effusion
- Hepatic vein diastolic flow reversal during inspiration

**Subsequent Testing:**
CMR
Nuclear scintigraphy
Biopsy
Important “Mimics” of HFpEF: Pulmonary Arterial Hypertension

Clinical Cues
- Evidence of “Associated Conditions”
- Variable age distribution

Echo Clues
- No evidence of increased LV filling pressure
- Isolated right heart dilatation
- PA dilatation
- RV outflow tract doppler mid systolic notch

Subsequent Testing
Right Heart Catheterization
Important “Mimics” of HFpEF: Chronic Thromboembolic PH

Chronic Thromboembolic Disease

Clinical Cues
- History of DVT/PE
- Hypercoaguable state

Echo Clues
- No evidence of increased LV filling pressure
- Isolated right heart dilatation
- PA dilatation
- RV outflow tract doppler mid systolic notch

Subsequent Testing
- VQ scan
- CT pulmonary angiogram
- Right heart catheterization
Summary

• HFpEF is the dominant form of HF worldwide
  • Continues to present a diagnostic and therapeutic challenge

• HFpEF diagnosis requires an integrated approach
  • Clinical evaluation
  • Biomarkers
  • Echocardiography is essential in assessing pathophysiologic mechanisms and phenotyping
  • Exercise testing may help to solicit the cause of a patient's undiagnosed dyspnea

• HFpEF mimics exist inside and outside the diagnosis
  • Identification and treatment of co-morbidities
  • Functional testing
  • High index of suspicion for diagnoses with distinct natural history and management