INVASIVE MEASUREMENT:
THE NEW GOLD STANDARD FOR DIAGNOSIS OF HFpEF?

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Discuss the current diagnostic algorithms for the diagnosis of HFpEF

Understand the rationale and methodology for invasive exercise stress testing for the diagnosis of HFpEF

Discuss the role of invasive exercise testing in the context of other stimuli or non-invasive testing
Current Diagnostic Algorithms for HFpEF
Current Definitions for the Diagnosis of HFpEF

- **Evidence of HF syndrome**
- **“Preserved” Ejection Fraction**
- **HFpEF**

**SIGNS + SYMPTOMS**
- BNP

**ECHOCARDIOGRAPHY**

<table>
<thead>
<tr>
<th>Organization</th>
<th>Definition</th>
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</table>
| CCS (2017)   | HFP EF ≥ 50%
               | HFmEF 41-49%
               | “recovered EF” > 40% |
| ESC (2016)   | HFP EF > 50%
               | HFmrEF 41-49% |
| AHA/ACC (2013)| HFP EF ≥ 50%
               | HFP EF borderline 41-49%
               | Improved > 40% |

Canadian Journal of Cardiology, Volume 33, Issue 11, November 2017 Pager 1342-13
Circulation, Volume 128, Issue 16, October 2013
Symptoms and Signs of Heart Failure

Suspected Heart Failure

Clinical History
- Symptoms
- Functional limitation
- Prior cardiac disease
- Risk factors
- Exacerbating factors
- Comorbidities
- Drugs

Physical Examination
- Vital signs
- Weight
- Volume status
- Heart
- Lung
- Abdomen
- Peripheral Vascular

Initial Investigations
- Chest radiograph
- Electrocardiogram
- Lab work (CBC, electrolytes, renal function, urinalysis, glucose, thyroid function)

Stress testing, cath

Evaluation of Ischemia

Evaluation for infiltration
- MRI, iron studies/light chains, biopsy

Additional Diagnostics Relevant to HFpEF

Natriuretic Peptides
- NT-proBNP > 125 pg/ml
- BNP > 50 pg/ml (if available)

Not heart failure; workup other diagnoses

Echocardiography
- Echocardiogram
- Heart failure likely, treat accordingly

Additional Diagnostic Investigations
- Cardiac catheterization
- Cardiopulmonary exercise testing
- Others: E, X-RA, MRI, MUGA, CT MAI

?CPET
Figure 4.1 Diagnostic algorithm for a diagnosis of heart failure of non-acute onset

- **PATIENT WITH SUSPECTED HF⁺** (non-acute onset)
- **ASSESSMENT OF HF PROBABILITY**
  1. Clinical history:
     - History of CAD (PL revascularisation)
     - History of arterial hypertension
     - Exposure to cardioactive drug/thallination
     - Use of diuretics
     - Orthopnoea / paroxysmal nocturnal dyspnoea
  2. Physical examination:
     - Palpation
     - Bilateral ankle oedema
     - Heart murmur
     - Jugular venous dilation
     - Laterally displaced/broadened apical beat
  3. ECG:
     - Any abnormality

- **NATRIURETIC PEPTIDES**
  - NT-proBNP ≥125 pg/mL
  - BNP ≥35 pg/mL

- **ECHOCARDIOGRAPHY**

- **Symptoms and Signs of Heart Failure**

- **Natriuretic Peptides**

- **Echocardiography**

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Rationale for additional criteria to demonstrate HF pathophysiology in HFpEF

<table>
<thead>
<tr>
<th>Type of HF</th>
<th>HFrEF</th>
<th>HFmrEF</th>
<th>HFpEF</th>
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<tbody>
<tr>
<td><strong>CRITERIA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Symptoms and Signs*</td>
<td>Symptoms and Signs*</td>
<td>Symptoms and Signs*</td>
</tr>
<tr>
<td>2</td>
<td>LVEF &lt; 40%</td>
<td>LVEF 40-49%</td>
<td>LVEF &gt; 50%</td>
</tr>
<tr>
<td>3</td>
<td>1. Elevated levels of natriuretic peptides</td>
<td>1. Elevated levels of natriuretic peptides</td>
<td>1. Elevated levels of natriuretic peptides</td>
</tr>
<tr>
<td></td>
<td>2. At least 1 additional criterion</td>
<td>2. At least 1 additional criterion</td>
<td>2. At least 1 additional criterion</td>
</tr>
<tr>
<td></td>
<td>a. Relevant structural heart disease (LVH and/or LAE)</td>
<td>a. Relevant structural heart disease (LVH and/or LAE)</td>
<td>a. Relevant structural heart disease (LVH and/or LAE)</td>
</tr>
<tr>
<td></td>
<td>b. Diastolic dysfunction</td>
<td>b. Diastolic dysfunction</td>
<td>b. Diastolic dysfunction</td>
</tr>
</tbody>
</table>

* Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics
In the absence of a validated gold standard for HFpEF, there is a continuum of confidence for the diagnosis:

**UNCERTAIN**
- 73y F HTN, “mild asthma”
- Hx of dyspnea on exertion (NYHA 2-3), bending over
- BNP 50
- Echo: LVEF 60%, RVSP 40 mmHg, normal LV mass, E:e’ 8
- ?Deconditioning
- ?COPD
- ?Early HFpEF

**LESS CERTAIN**
- 78y F HTN, angina
- Hx of dyspnea on exertion (NYHA 2-3), treatment includes lasix
- BNP 130
- Echo: LVEF 55%, mild LAE, RVSP 47 mmHg, E:e’ 13
- ?HFpEF
- ?PAH

**CERTAIN**
- 84y F HTN, DM, AFib
- Hospital admission, pulmonary edema, eGFR 40, requiring diuretics
- BNP 500
- Echo: LVEF 72%, LVH, LAE, mod MR
- Rx CHFpEF

AHA stage C  AHA stage D
Supporting evidence of relevant structural heart disease or diastolic dysfunction: Echocardiography

- Left atrial volume index $\geq 34 \text{ml/m}^2$
- Left ventricular mass index $\geq 115 \text{g/m}^2$, $\geq 95 \text{g/m}^2$
- $E/e' \geq 13$, mean $e'$ septal and lateral $\leq 9 \text{cm/s}$
- TR jet velocity
  - Upwards of 80% HFpEF exhibit PH
  - Overlap: PAH versus PH-LHD
Supporting evidence of abnormal cardiac chamber physiology: Role of Cardiac Catheterization

• “In cases of uncertainty, a stress test or invasively measured elevated LV filling pressure may be needed to confirm the diagnosis”
  • *ESC HF Guidelines*

• “Right heart catheterization (RHC) is required to make the diagnosis of PAH” (and differentiate from PH-LHD)
  • *ESC PH Guidelines*
# Updated Hemodynamic Definitions for PH-LHD

<table>
<thead>
<tr>
<th>Hemodynamic classification</th>
<th>Definition</th>
<th>Updates</th>
<th>Clinical Group(s)</th>
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<tbody>
<tr>
<td>PH</td>
<td>mPAP &gt; 25 mmHg</td>
<td>mPAP &gt; 20 mmHg</td>
<td>All</td>
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<tr>
<td>Pre-capillary PH</td>
<td>mPAP &gt; 25 mmHg</td>
<td>mPAP &gt; 20 mmHg</td>
<td>Group 1,3-5</td>
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<tr>
<td></td>
<td>PAWP &lt; 15 mmHg</td>
<td>PAWP &lt; 15</td>
<td></td>
</tr>
<tr>
<td>Post capillary PH</td>
<td>mPAP &gt; 25 mmHg</td>
<td>mPAP &gt; 20 mmHg</td>
<td>Group 2 PH-LHD</td>
</tr>
<tr>
<td></td>
<td>PAWP &gt; 15 mmHg</td>
<td>PAWP &gt; 15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LVEDP &gt; 15 mmHg</td>
<td>LVEDP &gt; 15mmHg</td>
<td></td>
</tr>
<tr>
<td>Isolated post-capillary PH</td>
<td>DPG &lt; 7 mmHg</td>
<td>PVR &lt; 3WU</td>
<td></td>
</tr>
<tr>
<td></td>
<td>and/or PVR ≤ 3WU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined post-capillary and pre-capillary PH</td>
<td>DPG &gt; 7 mmHg</td>
<td>PVR &gt; 3 WU</td>
<td></td>
</tr>
<tr>
<td></td>
<td>and/or PVR &gt; 3 WU</td>
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Methodology and Interpretation of Invasive Hemodynamic Assessment
“Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction”

- Dyspnea of unknown origin
- Normal BNP and echo
- Subgroup with “exaggerated” PAWP response to even slight exercise
- Hypothesized to reflect diastolic impairment as a cause of dyspnea
Exercise hemodynamics likely to be useful, however exercise criteria cannot be reintroduced at the present time.

Prognostic and therapeutic implications of exercise-induced hemodynamic responses unclear.

Refinement of exercise stress protocol (position, type, intensity) required.

Age adjusted “normal” values or reference ranges in health are unknown.
Improving Standardization of Exercise Hemodynamic Testing

Wright et al, Heart 2016; 102:438-443

Maron BA et al, Circulation. 2013;127:1157-1164
Design of the Exercise Challenge: Necessary Elements

- Cycle Ergometry Preferred
  - Upright positioning
  - Supported body weight
  - Measurable workloads
  - Maximal or submaximal protocols
- Disadvantages – submaximal efficiency
- +/- metabolic testing
- Ensure 2-3 minute warmup to avoid sampling early after initiation or escalation of workrate

Wright et al, Heart 2016; 102:438-443
Hemodynamic Interpretation in Exercising Older Adults

PAWP > 25 mmHg considered as ULN in adults > 40 years

Wright et al, Heart 2016

Wolsk et al, JACC HF 2017
Additional Criteria: Increase in PAWP adjusted for the Increase in CO < 2mmHg/L/min

Reflects early ↑ in PAWP vs moderate ↑ in CO within initial exercise stage

As exercise duration and intensity ↑, PAWP ↔ or ↓ with further ↑ in CO

FIGURE 1. From Esfandiari et al, 2017 Med Sci Sport Ex. We studied healthy untrained older men and women using our submaximal exercise hemodynamic protocol. The PAWP responses at Light and Moderate exercise are depicted here: the PAWP (upper left panel), the PAWP adjusted for Workrate and body size, and the change in PAWP relative to the change in cardiac output (bottom left and right). All 3 metrics demonstrate “time variance”. By sustained moderate exercise, the mean values and range of the PAWP adjusted for either workrate or cardiac output are lowest and as such may be more reliable as a reference range. If exercise duration is short, there may be significant overlap in the PAWP responses between healthy normal subjects and patients with disease.
Towards Increasing Acceptance

“In patients presenting exercise intolerance, in which noninvasive and resting invasive measurements are inconclusive, provocative testing in the cardiac catheterization laboratory should be considered to determine the presence of a cardiac etiology. Cycle ergometry exercise is the most physiologically relevant and sensitive stressor and is preferred over other maneuvers such as saline loading or arm exercise”

The Society of Cardiovascular Angiography and Interventions
Heart Failure Society of America

Clinical Utility in HFpEF and Alternatives
Exercise versus Saline Challenge

- Exercise is a classic physiologic stressor that reproduces symptoms and the patient experience.
- More potent hemodynamic stress compared with saline.

![Graph showing the comparison between Saline and Exercise in HFrEF and Control groups.](image)

Andersen et al, Circ Heart Fail 2015;8:41-48
Non-Invasive Diagnostic Modalities In Situations of Uncertain HFpEF

• Diastolic Stress Echocardiography
  • Limitations of measuring E:e’ during exercise
  • Limitations of assessment of TR jet velocity
  • Studies directly comparing invasive and non-invasive diastolic stress testing limited

• Cardiopulmonary Exercise Testing (CPET)
  • Useful screen for exercise intolerance related to cardiac and pulmonary vascular limitation
  • + RHC, invasive CPET
Invasive Hemodynamic Exercise Testing: A New Therapeutic Target for HFpEF

**Inclusion Criteria**
- Exercise PAWP > 25mmHg
- PAWP:RA difference > 5mmHg

**Primary endpoint**
- Exercise PAWP

*Figure 3.* Pulmonary capillary wedge pressure during exercise hemodynamic testing: baseline versus 1-month postrandomization, stratified by treatment group. 
A, Control group. B, IASD treatment group. IASD indicates interatrial shunt device; and PCWP, pulmonary capillary wedge pressure. *P* values were calculated using paired t tests (within-group comparisons of baseline versus 1-month values). Between-group comparison of peak exercise PCWP was not statistically significant (*P*=0.144), as shown in Table 3. *P*<0.05; **P*<0.01.
Clinical Trials for HFpEF Rx using Exercise Hemodynamic Entry Criteria are Currently Enrolling Patients

<table>
<thead>
<tr>
<th>Agent</th>
<th>Study Design</th>
<th>Sponsor</th>
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<tbody>
<tr>
<td>AZD4831</td>
<td>Phase 2 RCT</td>
<td>Astra Zeneca</td>
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<tr>
<td>Metformin</td>
<td>Phase 2 Crossover</td>
<td>NIH</td>
</tr>
<tr>
<td>Myeloperoxidase inhibitor</td>
<td>Phase 1 RCT</td>
<td>Mayo Clinic</td>
</tr>
<tr>
<td>Saccubitril-Valasartan</td>
<td>Open label follow up</td>
<td>Mayo Clinic, NIH</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>RCT</td>
<td>St. Luke’s Health System</td>
</tr>
<tr>
<td>Oral Nitrate</td>
<td>Parallel design</td>
<td>NIH</td>
</tr>
<tr>
<td>Potassium Nitrate</td>
<td>RCT</td>
<td>University of Pennsylvania/Northwestern</td>
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</tbody>
</table>

Clinicaltrials.gov search terms HFpEF, intervention, actively recruiting, accessed March 14, 2019

<table>
<thead>
<tr>
<th>Clinical Variables</th>
<th>Values</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂ Heavy</td>
<td>Body mass index &gt; 30 kg/m²</td>
<td>2</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>2 or more antihypertensive medications</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>
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**H₂FPEF score**

Sum (0-9)