Overview

1. What are clinical and diagnostic tools – pros/cons of each

2. How do we put together a practical clinical approach for HFpEF diagnosis?

3. Breakout Session: Can we develop a clinical roadmap for HFpEF diagnosis?
Guideline and Trial Definitions of HFpEF

<table>
<thead>
<tr>
<th>Reference</th>
<th>ACC/AHA</th>
<th>ESC</th>
<th>HFSA</th>
<th>TOPCAT</th>
<th>PARAGON</th>
<th>I-PRESERVE</th>
<th>RELAX</th>
<th>GLAHF</th>
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<td>Signs</td>
<td>E/e'&gt;15</td>
<td>LVH, LAE, valve dz.</td>
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<td>Echo</td>
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<td>HF admission</td>
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<td>Exclude</td>
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<td>HFpEF-MRI</td>
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Elevated E/e' >15, LVH, LAE, valve dz.

Ho JE ... Lewis GD, Circulation, 2019
Bozkurt B et al, J Card Fail, 2021

Heterogeneity across HFpEF Definitions

MGH CPET sample:
- 461 patients with NYHA class II-III symptoms and LVEF>50%
- ~53% met physiologic criteria for HFpEF

Ho JE ... Lewis GD, Circulation, 2019
Natriuretic Peptides for HFpEF Diagnosis

Current recommendations:

- **Class I**: Patients with dyspnea, NPs to support / exclude HF diagnosis
- **Cut-points**:
  - BNP, pg/mL
    - Ambulatory: ≥35
    - Hospitalized: ≥100
  - NT-proBNP, pg/mL
    - Ambulatory: ≥125
    - Hospitalized: ≥300

- ≥125 pg/mL cut-point: sensitivity 77%, specificity 53% for HFpEF
- In general, NPs are lower in HFpEF vs HFrEF (less wall stress)
- NPs are 3-3.5 fold higher in atrial fibrillation vs NSR → ESC algorithm uses different cutpoints

[References]
Heidenreich P et al, JACC, 2022
Bozkurt B et al, JCF, 2021
Iwanaga Y et al, JACC 2006
Pieske B et al, EHJ, 2019
Reddy YNV et al, Circ, 2018

False negatives:
- Mayo CPET sample: ~35-40% had NT-proBNP<125

Pitfalls in NPs for HFpEF:
- 20-35% with HFpEF have low NPs
- **NP deficiency**: obesity, NPPB gene polymorphisms, insulin resistance, androgens, others

Questions:
- Role of NP in HFpEF diagnosis (‘rule in’ vs ‘rule out’ tests)?
- Specific thresholds based on BMI, sex, AF, NP deficiency states?
Echocardiography for HFpEF Diagnosis

- HFpEF: LVEF ≥ 50%
- "Abnormality in cardiac structure and/or function"

<table>
<thead>
<tr>
<th>Cardiac structure</th>
<th>UDHF 2021</th>
<th>ACC/AHA 2022</th>
<th>ESC HFA-PEFF 2019</th>
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</thead>
<tbody>
<tr>
<td>Chamber enlargement</td>
<td>• LAVI&gt;29 (SR) / &gt;40 (AF)</td>
<td>• LVMi&gt;116 (M), &gt;96 (F)</td>
<td>• LVMi&gt;115 (M), &gt;95 (F)</td>
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<tr>
<td>Mod/sev LVH</td>
<td>• RWT&gt;0.42</td>
<td>• RWT&gt;0.42 or RVWT&gt;0.12</td>
<td>• RWT&gt;0.42 or LVWT&gt;12</td>
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</tbody>
</table>

Cardiac function

- E/e’>15
- E/e’ ≥ 15
- Septal e’<7
- Mitral e’ (age<75): sept <7, lat <10
- Mitral e’ (age≥75): sept ≤5, lat ≤7
- Mitral E/e’ (avg): ≥ 15; 9-14
- TR velocity >2.8, PASP >35
- GLS <16%

*grey font indicates minor criteria

Bozkurt B et al, JCF, 2021
Heidenreich P et al, JACC, 2022
Piecke B et al, EHJ, 2019

PARAGON-HF: 32% with HFpEF had no echocardiographic abnormalities
Test characteristics for each criterion are variable (26-70% sensitivity, 59-88% specificity)
E/e’ correlation with invasive LV filling pressures r~0.62 across 9 studies

Questions:
- Interpretation in context of aging and other comorbidities?
- Clinical applicability of advanced measures (GLS)?
provocative testing in diagnosis of HFpEF

Exercise

• Exercise intolerance is the hallmark symptom of HFpEF
• Exercise can “unmask” abnormal cardiovascular reserve even in the absence of apparent volume overload

Other provocative maneuvers

• Passive leg raise
• Volume challenge

kitzman d et al, jama, 2002
borlaug ba et al, circ heart fail, 2010
fujimoto n et al, circ, 2012
d’alto m et al, chest, 2021

exercise echocardiography

hfa-peff criteria for ‘abnormal’ diastolic stress test:
• Average E/e’ increases to ≥15 +/- TR velocity >3.4 m/s

limitations:
• E/e’ not measurable in 10% at submax, 20% at peak exercise
• TR detected in only half

ha, j-w, et al, jacc cv imaging, 2020
obokata m et al, circulation, 2017
Invasive Hemodynamic Testing

Resting RHC:
- ‘abnormal’ mPCWP ≥15mmHg

What is abnormal with exercise?
- supine PCWP ≥25mmHg
- PCWP/CO slope >2
- PCWP/workload >25.5
- Associated with adverse CV outcomes

Other provocative maneuvers:
- Passive leg raise: PCWP ≥19mmHg had specificity of 100% at HFpEF diagnosis

Questions
- Who should be considered for advanced testing?
- Non-invasive correlates or other approaches that may improve accessibility?

Borlaug BA et al., Circ Heart Fail, 2010
Eisman AS et al., Circ Heart Fail, 2018
Ho JE et al., Circulation, 2019
Dorfs B et al., Eur Heart J, 2014
van de Bovenkamp AA et al., Circ HF, 2022

Diagnostic Algorithms

Reddy YNV et al., Circulation, 2018
Pieske B et al., Eur Heart J, 2019
A Practical Approach to HFpEF Diagnosis

Assess rest congestion
- abnormal exam
- HF hospitalization
- splanchnic peptides

Assess exercised intolerance - first line diagnostic tools
- tachyarrhythmias
- Holter monitor
- functional capacity (CPET, 6MWT)
- integrated risk stratification (HFA/PEPCHF, HFpEF

Intermediate care

Advanced testing
- LV filling pressures at rest RV/C
- LV filling pressures during CPET
- abnormal diastolic stress test

Rule out "secondary HFpEF"
- Uncontrolled valvular disease
- Pericardial disease
- Isolated right-sided heart failure
- Primary diastolic dysfunction
- High-output states
- Alternates idiopathic states

Ho JF, Redfield MM, Lewis GD, Paulus, WJ, Lam CSP. Circulation, 2020

Thank you