TARGETING THE DIAGNOSIS OF HFpEF

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HFpEF:
Diagnosis Impossibilis?

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Somewhere in Toronto, possibly spring in 2018
Disclosures / COI / RWI / RWA

• Available online: thecvc.ca
• CCS.ca for HF guidelines (I was the chair)
HF – preserved ejection fraction

• Multiple phenotype(s) and trial design(s)
• Few ‘clear’ criteria
• Different patient demographics
• Comorbidities may co-exist with HFpEF
Definitions: What is it?
What’s in a name?

Ejection fraction

HF-REF
<40%

CHARM-pI-preserve PEP-CHF

HF-PEF
>50%

ESC
Zile: +Framingham
Vasan: +SSx + biomarkers + imaging +provocative

Zile Circulation 2003
Vasan Circulation 2000
ESC EHJ 2007
ESC EHJ 2016
What’s in a name?

- HF-REF: <40%
- HF-PEF: >50%
- HF-midrangeEF

Ejection fraction

DHF

HF-PSF
• HF with preserved EF (HFpEF): LVEF ≥ 50%
• HF with a mid-range EF (HFmEF): LVEF 41%-49%
• HF with reduced EF (HFrEF): LVEF ≤ 40%

• Recovered EF: patients who previously had HFrEF and now EF > 40%
HF-PEF: causation or association?

RULE-OUT and TREAT:
Anemia
COPD
Obesity
Afib
Deconditioning from other medical illness
<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Bidirectional Impact on Disease Progression</th>
<th>Heart Failure Specifics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>Inflammation; hypoxia; parenchymal changes; airflow limitation, leading to pulmonary congestion; abnormal left ventricular (LV) diastolic filling; inhaled beta-agonist cardiovascular effects. Elevated LV end-diastolic pressure and beta-blocker use may compromise lung function.</td>
<td>More prevalent in preserved ejection fraction (HfP EF), compared to reduced (HFr EF). Higher mortality risk in HfP EF.</td>
</tr>
<tr>
<td>Anemia</td>
<td>Adverse LV remodeling; adverse cardiorenal effects; increased neurohormonal and inflammatory cytokines. Inflammation; hemodilution; renal dysfunction; metabolic abnormalities exacerbate.</td>
<td>More prevalent in HfP EF. Similar increased risk for mortality in both groups.</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Diabetic cardiomyopathy; mitochondrial dysfunction; abnormal calcium homeostasis; oxidative stress; renin-angiotensin-aldosterone system (RAAS) activation; atherosclerosis; coronary artery disease. Incident and worsening diabetes mellitus via sympathetic and RAAS activation.</td>
<td>More prevalent in HfP EF. Similar increased risk for mortality in both groups.</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>Sodium and fluid retention; anemia; inflammation; RAAS and sympathetic activation. Cardiorenal syndrome through low cardiac output; accelerated atherosclerosis; inflammation; increased venous pressure.</td>
<td>Similar prevalence in both groups. Similar increased risk for mortality in both groups.</td>
</tr>
<tr>
<td>Sleep-disordered breathing</td>
<td>Hypoxia; systemic inflammation; sympathetic activation; arrhythmias; hypertension (pulmonary and systemic); RV dysfunction; worsening congestion. Rostral fluid movement may worsen pharyngeal obstruction; instability of ventilatory control system.</td>
<td>Similar prevalence in both groups. Unknown mortality differential associated with HfP EF vs. HFr EF.</td>
</tr>
<tr>
<td>Obesity</td>
<td>Inflammation; reduced physical activity and deconditioning; hypertension; metabolic syndrome; diabetes mellitus. Fatigue and dyspnea may limit activity; spectrum of metabolic disorders including nutritional deficiencies.</td>
<td>More prevalent in HfP EF. Obesity paradox; potential for a U-shaped association with mortality.</td>
</tr>
</tbody>
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Mentz, JACC 2014
<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>100% men</td>
<td>96% women</td>
<td>Men or women</td>
<td>100% women</td>
<td>100% men</td>
<td>mostly women (77.5%)</td>
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<tr>
<td>65 years</td>
<td>65 years</td>
<td>70 years</td>
<td>73 years</td>
<td>75 years</td>
<td>82 years</td>
</tr>
<tr>
<td>Low rates of Afib, renal disease, valvular disease</td>
<td>low rates of AF, renal dysfunction, and valvular disease</td>
<td>Obesity, DM, CAD, anemia</td>
<td>average rates of DM, hyperlipidemia, obesity, renal insufficiency</td>
<td>lower BMI, +AF +CAD.</td>
<td>lower BMI +AF, valvular disease, renal dysfunction, and anemia.</td>
</tr>
</tbody>
</table>

No difference in symptoms, SBP, BNP across groups

Kao, EJHF 2015
Suspected Heart Failure

Clinical History
- Symptoms
- Vital signs
- Weight
- Volume status
- Heart
- Lung
- Abdomen
- Peripheral Vascular

Physical Examination
- Drugs

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

Still Suspect Heart Failure?

YES
- Assess Natriuretic Peptides
- Assessment of Ventricular Function
- Echocardiogram

NO
- NT-proBNP > 125 pg/ml
- BNP > 50 pg/ml

Heart failure likely, treat accordingly

Additional Diagnostic Investigations
- Cardiac catheterization
- Cardiopulmonary exercise testing
- Others (MRI, MIBI, MUGA, CT scan)

PATIENT WITH SUSPECTED HF
(non-acute onset)

ASSESSMENT OF HF PROBABILITY
1. Clinical history:
   - History of CAD (MI, revascularization)
   - History of arterial hypertension
   - Exposition to cardiotoxic drug/radiation
   - Use of diuretics
   - Orthopnoea / paroxysmal nocturnal dyspnoea
2. Physical examination:
   - Signs
   - Bilateral ankle oedema
   - Heart murmur
   - Jugular venous dilatation
   - Laterally displaced/broadened apical beat
3. ECG:
   - Any abnormality

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

ECHO CARDIOGRAPHY

If HF confirmed (based on all available data):
- determine aetiology and start appropriate treatment

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

Not heart failure; work up other diagnoses

Ezekowitz, Can J Cardiol 2017.
• The presence of **symptoms** and/or **signs** of HF
• A ‘preserved’ **EF** (defined as LVEF ≥50% or 40–49% for HFmrEF)
• Elevated levels of **NPs**
  – BNP >50 pg/mL
  – NT-proBNP >125 pg/mL
• The presence of **symptoms** and/or **signs** of HF
• A ‘preserved’ **EF** (defined as LVEF ≥50% or 40–49% for HFmrEF)
• Elevated levels of **NPs** (BNP >35 pg/mL, NT-proBNP >125 pg/mL)
• **Objective** evidence of other cardiac functional and structural alterations underlying HF
  • LAVI, LVM, e/e’
• **In case of uncertainty**, a stress test or invasively measured elevated LV filling pressure may be needed to confirm the diagnosis
ESC 2016 criteria: do they hold up?

**Entire cohort**
- +LR 4.8
- -LR 0.42
- Sensitivity 51.8%
- Specificity 89.1%

**Minus HF-REF**
- +LR 4.7
- -LR 0.25
- Sensitivity 64.7%
- Specificity 86.1%

Ezekowitz, ESC-HF 2017
Does BNP help for Diagnosis?
Diastolic Stress Test

- Diastolic Stress Test: echo, exercise bike: e/e’, PAP, strain, SV
- Invasive: LVEDP w/or w/out exercise
Diastolic Stress Test

A

<table>
<thead>
<tr>
<th>Test</th>
<th>Rest</th>
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<td>Cath</td>
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<tr>
<td>Exercise Echo</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Ex E/e' alone</td>
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B

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Post-Test Diagnosis of HFpEF:

- Positive
- Negative
- Indeterminate

50 pts HFpEF, cath
24 pts control, cath

Diastolic Stress Test

HFpEF

Non-cardiac Dyspnea

Now ask why
Echocardiogram, ECG, plus recommended lab testing for all patients (CBC, creatinine, ferritin, TSH, troponin, NP)

- HFrEF (and HFmEF)
  - LVEF ≤ 40%, up to 49%
  - Tachyarrhythmia
  - Valve disease
  - Known or risk factors for CAD
  - LVH
    - CAD work-up
    - Hx of HTN?

- HFrEF
  - LVEF ≥ 50%
  - Congenital Heart Disease
  - Pericardial Disease
    - Further work-up and referral as appropriate

More common:
- Family history of dilated CMP
- Toxic agents
- Pregnancy history
- Inflammatory / Infectious / Immune
- Metabolic
- Nutritional
- Infiltrative diseases
- Genetic or hereditary

Less common:
- Genetics referral
- Hereditary / familial
- Obtain further history as needed

Appropriate blood or urine testing and/or CMR as directed by history and physical exam and other findings

Genetics referral.
### Web Table 4.4  Diagnostic tests for specific causes of heart failure with preserved ejection fraction

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<th>Test</th>
<th>Condition</th>
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<tr>
<td>Genetic testing (e.g. for ATTR amyloidosis and HCM; see also section 5.10.1)</td>
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<tr>
<td>Bence-Jones proteinuria (AL amyloidosis)</td>
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<tr>
<td>99mTc-DPD scintigraphy (wild-type transthyretin amyloidosis)</td>
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<tr>
<td>Eosinophilia, IL-2 receptor, ACE (sarcoidosis)</td>
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<tr>
<td>HS troponin, CK, CK-MB (myocarditis)</td>
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<tr>
<td><em>Borreliia burgdorferi</em> IgM (borreliosis)</td>
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<td>HIV serology (HIV cardiomyopathy)</td>
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<tr>
<td>Trypanosoma cruzi serology (Chagas disease)</td>
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<tr>
<td>Serum ferritin, genetic testing (haemochromatosis)</td>
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<tr>
<td>Alpha-galactosidase activity in leucocytes (Fabry disease)</td>
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<tr>
<td>Eosinophilia (Löffler endomyocarditis)</td>
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Top 5 for Diagnosis

1. A rest echo finding ≠ HF
2. ↑ RVSP, PASP, LAVi, LVH *lean towards* HFpEF
3. R/O CAD in all
4. Consider a provocative test
5. Ask ‘why’ do they have HFpEF
Summary

1. Definitions: apply what is clinically relevant
   EF>40% +/- Sx +/- signs + BNP
2. Complicated phenotype
3. Evaluate the comorbidity(s)
4. Don’t forget about provocative stress tests