Heart failure with preserved ejection fraction (HFpEF) as a cause of dyspnoea

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Vice Chairman Department of Cardiology
Maastricht UMC+
The Netherlands
HFpEF as a cause of dyspnoea

• Diagnosis
• One disease? Different from HFrEF?
• Treatment failures
• What is different in HFpEF
• Pathophysiology – focus on co-morbidities
• Summary
Diagnosis of heart failure

New:

- Algorithm to diagnose heart failure
- Important role of natriuretic peptides (to exclude HF)
- New HF-symptom: Bendopnoea = dyspnoea if leaning forward
- Independent of LVEF

Ponikowski et al. HF guidelines 2016. doi:10.1093/eurheartj/ehw128
## Definition of heart failure

**HFrEF, HFpEF and new HFmrEF**

### Type of HF

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>HFrEF</th>
<th>HFmrEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Symptoms ± Signs&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Symptoms ± Signs&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>LVEF &lt;40%</td>
<td>LVEF 40–49%</td>
</tr>
<tr>
<td>3</td>
<td>_</td>
<td>1. Elevated levels of natriuretic peptides&lt;sup&gt;b&lt;/sup&gt;; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).</td>
</tr>
</tbody>
</table>

### HFpEF

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Symptoms ± Signs&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>LVEF ≥50%</td>
<td></td>
</tr>
</tbody>
</table>

1. Elevated levels of natriuretic peptides<sup>b</sup>; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).
How to Diagnose Heart Failure?

SHAPE study, Remme et al. Eur Heart J 2008; 29: 1739
Prevalence of HFrEF vs HFpEF

Hemodynamic basis of exercise limitation in HFpEF

Maeder et al. JACC 2010; 56: 855
HFpEF – one disease or many?

Kosmala et al. JACC 2016; 67: 659. E/e’ response to exercise was directly associated with symptoms. Moreover, systolic strain significantly reduced.

“..., it is safe to conclude ... that HFpEF patients are more similar than different, and it seems likely that global reserve limitations in the heart, arteries, and periphery are tied to common systemic processes. Now it is time to identify what these processes are to then determine how to treat them.”
Pathophysiology of HFpEF

Impaired LV filling

- Increased ECM stiffness
  - Increased Type I collagen synthesis and deposition
  - Decreased ECM degradation
- Increased cardiomyocyte stiffness
  - Myocyte hypertrophy
  - Cytoskeletal protein dysfunction
  - Titin hypo-phosphorylation
  - Cross-bridge detachment

Diastolic dysfunction

HFpEF

Ventricular-vascular uncoupling

- Increased vascular stiffness
- Decreased vascular distensibility
- Abnormal vaso-relaxation

Increased ventricular load

- Chronotropic incompetence
- Poor CV reserve
  - Abnormalities in beta receptor signaling
  - Myocardial ischemia
  - Abnormal myocardial energetics

Other contributory mechanisms

Meta-analysis of (NT-pro)BNP guided therapy: HFrEF vs HFrEF

Interaction p=0.016

HFrEF

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>BNP-guided Events</th>
<th>Control Events</th>
<th>Total</th>
<th>O-E</th>
<th>Variance</th>
<th>Weight</th>
<th>Hazard Ratio</th>
</tr>
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<tbody>
<tr>
<td>BATTLESCARRED</td>
<td>13</td>
<td>17</td>
<td>30</td>
<td>-1.44921</td>
<td>7.36531</td>
<td>9.8%</td>
<td>0.82 [0.40, 1.69]</td>
</tr>
<tr>
<td>Lancet</td>
<td>1</td>
<td>7</td>
<td>8</td>
<td>-1.66967</td>
<td>0.874323</td>
<td>1.2%</td>
<td>0.15 [0.02, 1.20]</td>
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<tr>
<td>PRIMA</td>
<td>28</td>
<td>39</td>
<td>67</td>
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<td>SignalHF</td>
<td>5</td>
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<td>TIME-CHF</td>
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<td>57</td>
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<td>31.6%</td>
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Total (95% CI) 787 793 100.0% 0.79 [0.63, 0.99]

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Total (95% CI) 144 149 100.0% 1.30 [0.81, 2.11]

Heterogeneity: Chi² = 5.08, df = 6 (P = 0.53); I² = 0%
Test for overall effect: Z = 2.05 (P = 0.04)

Interaction p=0.016

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Test for overall effect: Z = 1.08 (P = 0.28)

Nitrates helpful in HFpEF?

Redfield et al. NEJM 2015; 373: 2314
Evidence-based therapy in HFpEF

ACE inhibitors: no effect
ARBs: no effect
Spironolacton: no effect

Beta-blockers: undecided
Digoxin: undecided
Statin: undecided
Exercise: undecided
Sildenafil: undecided
Ivabradin: undecided
ARNI: undecided
TOPCAT: Spironolactone does not significantly improve prognosis in HFpEF

- Patients with LVEF≥45%
  - Median 56% [51%-62%]
  - HF hosp within last year 72%
  - Elevated (NT-pro)BNP levels 28%
- Mean age 69 years
- 52% women

Pitt et al. NEJM 2014; 370: 1383
TOPCAT: Differences between regions – What is HFpEF?
TOPCAT: Positive effects of spironolactone in HFmrEF?

Solomon et al. Eur Heart J 2016; 37: 455
What is different in HFpEF as compared to HFrEF?
Prevalence of HFpEF vs HFrEF

Owan et Redfield. Prog Cardiovasc Dis. 2005; 47: 320
Typical HFpEF patient

Ather et al. JACC 2012; 59: 998
Cause of death in TIME-CHF HFrEF versus HFpEF

Renal failure: 0.9 vs 11.1%  
P=0.006

*p<0.05

Rickenbacher et al. Eur J Heart Fail 2012; 14: 1218
Importance of co-morbidities in HFpEF

- Ventricular Dysfunction
  - Impaired relaxation
  - Impaired filling
  - Systolic dysfunction
- Atrial dysfunction
- Autonomic dysfunction
  - Chronotropic incompetence
- Vascular dysfunction
  - Vascular stiffening
  - Ventricle-arterial coupling
- Elevated Blood
  - Inadequate BP response to exercise
  - Pulmonary hypertension
- Valvular
  - Dynamic mitral regurgitation
- Lung Disease
  - COPD
- Iron Deficiency and Anemia
- Renal Dysfunction
  - Volume Overload
- Aging & Deconditioning
- Obesity & Sarcopenia
- Psychiatric Disorders
  - Depression
- Hypertension
  - Diabetes
  - ROS Production

Senni et al. Eur Heart J 2014; 35: 2797
Presence of COPD worsens symptoms and QoL

NYHA-class

<table>
<thead>
<tr>
<th>NYHA-class</th>
<th>No COPD</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td><img src="chart1.png" alt="Chart" /></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td><img src="chart2.png" alt="Chart" /></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td><img src="chart3.png" alt="Chart" /></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td><img src="chart4.png" alt="Chart" /></td>
<td></td>
</tr>
</tbody>
</table>

KCCQ score

- Social lim
- Symptom stability
- Symptoms
- Physical lim
- KCCQ score

Bektas et al. unpublished data
Impaired pulmonary diffusion capacity in HFpEF?

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Control (n = 26)</th>
<th>HFpEF (n = 20)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>65 ± 9</td>
<td>67 ± 11</td>
<td>0.4</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>69</td>
<td>75</td>
<td>0.7</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.1 ± 5.5</td>
<td>34.5 ± 6.8</td>
<td>0.004</td>
</tr>
<tr>
<td>NYHA functional class I/II/III</td>
<td>26/0/0</td>
<td>0/9/11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>62</td>
<td>85</td>
<td>0.11</td>
</tr>
<tr>
<td>Smoking history (%)</td>
<td>0</td>
<td>10</td>
<td>0.18</td>
</tr>
<tr>
<td>eGFR (ml/min)</td>
<td>80 ± 18</td>
<td>82 ± 39</td>
<td>0.8</td>
</tr>
<tr>
<td>Plasma BNP (pg/ml)</td>
<td>37 (16-61)</td>
<td>175 (58-200)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>14.0 ± 1.8</td>
<td>13.1 ± 1.3</td>
<td>0.08</td>
</tr>
<tr>
<td>Loop diuretic agent (%)</td>
<td>0</td>
<td>60</td>
<td>0.0005</td>
</tr>
</tbody>
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<thead>
<tr>
<th>Resting hemodynamics and echocardiography</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>70 ± 11</td>
<td>68 ± 13</td>
<td>0.7</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>133 ± 15</td>
<td>129 ± 20</td>
<td>0.4</td>
</tr>
<tr>
<td>LV mass index (mg/m²)</td>
<td>82 ± 24</td>
<td>87 ± 27</td>
<td>0.5</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>58 ± 5</td>
<td>60 ± 6</td>
<td>0.2</td>
</tr>
<tr>
<td>LA volume index (ml/m²)</td>
<td>31 ± 7</td>
<td>45 ± 14</td>
<td>0.0001</td>
</tr>
<tr>
<td>E/E' ratio</td>
<td>11 ± 4</td>
<td>20 ± 8</td>
<td>0.0004</td>
</tr>
<tr>
<td>Cardiac index (l/min*m²)</td>
<td>2.3 ± 0.6</td>
<td>2.3 ± 0.6</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Olson et al. JACC HF 2016; 4: 490
### Interaction between co-morbidities and both HFrEF and HFpEF

<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</td>
<td>More prevalent in preserved ejection fraction (HFpEF), compared to reduced (HFrEF); Higher mortality risk in HFpEF</td>
</tr>
<tr>
<td>Anemia</td>
<td>Adverse LV remodeling; adverse cardiorenal effects; increased neurohormonal and inflammatory cytokines</td>
<td>More prevalent in HFpEF; 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</td>
<td>More prevalent in HFpEF; 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</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</td>
<td>Similar prevalence in both groups; Unknown mortality differential associated with HFpEF vs. HFrEF</td>
</tr>
<tr>
<td>Obesity</td>
<td>Inflammation; reduced physical activity and deconditioning; hypertension; metabolic syndrome; diabetes mellitus</td>
<td>More prevalent in HFpEF; Obesity paradox; potential for a U-shaped association with mortality</td>
</tr>
</tbody>
</table>

Mentz et al. JACC 2014; 64: 2281
Common pathway in HFpEF? Inflammation: key or circumstantial?

- Diabetes Mellitus
- Hypertension
- Renal failure
- Atrial fibrillation
- Bradycardia
- Pulmonary hypertension
- Obesity
- Aging
- Gender
- COPD
- Coronary artery disease

= involvement of inflammation

Van Empel & Brunner-La Rocca. Int J Cardiol 2015; 189: 259
Biomarker levels HFpEF versus HFrEF

Myocyte stress/injury
Inflammation
Fibrosis / ECM
Vascular / endothelial
Metabolic / Oxid. stress
Renal function
Erythropoiesis

NT-proBNP
hsTnT
GDF-15
hsCRP
IL6
P1NP
ST2
sFlt
PLGF
PREA
Uric acid
Hb
Creatinin
BUN
CysC

Sanders-van Wijk et al. Eur J Heart Fail 2016; 17: 1006
Pathophysiology of HFpEF

- Diastolic dysfunction
- Abnormal vasodilation
- Endothelial dysfunction
- Systolic dysfunction
- Chronotropic incompetence
- Autonomic imbalance
- Right ventricular dysfunction
- Pulmonary hypertension
- Peripheral limitations
- Atrial fibrillation

(Additional text not translated)
HFpEF outpatient clinic – Focus on cause and co-morbidities

• Detailed analysis of cardiac as well as non-cardiac (co-) morbidities
  – Echocardiography
  – Exercise testing / 6-Min walking test
  – Holter-ECG
  – Broad lab testing
  – Lung function testing / Sleep testing
  – Screening CAD / Endothelial dysfunction
  – Ergospirometry / Re-catheter (with exercise)
  – Further analyses based on findings

• Specific treatment of all pathology
Effects of exercise training in HFpEF

Total n=276
No effects on diastolic function
HFpEF as cause of dyspnoea – Take home messages

• Still little understood, maybe not uniform disease
• Co-morbidities play an important role
  – Proper diagnosis important
• No specific treatment to improve outcome
  – Symptomatic treatment with diuretics
  – Exercise training
• Treatment of co-morbidities with probably positive effects on symptoms