Disclosures

**Speaker’s bureau:** Servier International, Bayer, Merck Serono, Novartis, Boehringer Ingelheim

**Research grant:** Servier International, Boehringer Ingelheim

**Advisory Board:** Servier International, Novartis, Amgen, Boehringer Ingelheim
New paradigms for HFpEF

By Roberto Ferrari
Paradox in heart failure

• Striking improvement in the prognosis of “individual” CV conditions (hypertension, ACS, valvular and congenital heart diseases) but growing prevalence of heart failure

• We normally consider HF a disease due to reduced LV function....but
EURO HEART FAILURE SURVEY

Overall population

Measurement of LV function

10 701

6 806

3 658

LV systolic dysfunction

54%

3 148

Preserved systolic function EF ≥ 40%
Normal / Mild dysfunction

46%

Lenzen, Eur H J 2004
Prevalence of HFPEF in CHF cohorts

(%)

- Philbin
- Cohen-Solal
- Tsutsui
- Varela-Roman
- Malki
- Thomas
- Dauterman
- Ahmed
- Masoudi
- Gustafsson
- Varadarajan
- Smith
Preserved systolic function in octogenarians HF patients (n = 2780)

- EF > 45%
- Mild LVSD

What is different in HFpEF?

- No clear definition of the syndrome
  - Academic
  - Trialist
  - Clinician

- No generally accepted diagnostic approach

- No uniform management principles
HF can occur without reduction of EF

\[ y = 0.84x + 0.08 \]
\[ r = 0.83 \]
HF can occur without reduction of EF
Diagnosis of HF with preserved EF

1) signs or symptoms of HF
2) normal LV systolic function

and...... the problem

3) evidence of abnormal LV relaxation, filling or diastolic stiffness
Diagnosis of HFpEF: problem!

1) Measuring diastolic function is difficult
2) There are no clear diagnostic criteria for HFpEF
3) EF measurements are not representative of the causal physiology
Diagnosis of HFpEF: problems!

4) Patients with HFpEF also have coexistent abnormalities in systolic function

5) Some patients diagnosed as having HFpEF do not have abnormal diastolic function

6) Predictors of HFpEF are neither specific nor sensitive
BNP Levels in HFpEF

- although BNP is useful as a prognostic marker in HFpEF, normal BNP does not exclude the outpatient diagnosis of HFpEF

- Normal BNP levels are present in 35% of HFpEF patients

Anjan VY Am J Cardiol 2012;110:870
What is different in HFpEF?

- Clinical / demographic characteristics
- Pathophysiology & etiology
- Comorbidities and risk factors
- Time to overt disease development
- Structural and functional cardio-vascular remodeling
- Neuroendocrine activation and biochemical parameters
- Response to therapy
Different heart failure pathophysiology

LVEF preserved

LVEF reduced

slight

moderate

severe

NYHA

I

II

III

IV

Diastolic Heart Failure

Systolic Heart Failure

2 different diseases ???

Modified after: G. De Keulenaer, 2006
Pathways to Heart Failure in the Cardiovascular Continuum

Myocardial infarction

Coronary thrombosis

Myocardial ischemia

Renal disease

CAD

Arteriosclerosis LVH

Risk-factors (smoking, diabetes, cholesterol, hypertension)

Heart failure

End-stage heart disease

Dilation of ventricles

Remodeling

Arrhythmias

Sudden death
Pathways to Heart Failure in the Cardiovascular Continuum

- Myocardial infarction
- Coronary thrombosis
- Myocardial ischemia
- Renal disease
- CAD
- Arteriosclerosis
- LVH
- Risk-factors (smoking, diabetes, cholesterol, hypertension)
- End-stage heart disease
- "Concentric"
- Remodeling
- Arrhythmias
- Sudden death
- Dilation of ventricles
- "Eccentric (dilated) Form"

"Pathways to Heart Failure in the Cardiovascular Continuum"
HFpEF: 3 different clinical profiles

1) Exercise-induced diastolic dysfunction
ambulatory patients with NYHA class II-III symptoms, impaired LV relaxation (grade I), ~ normal BNP levels

Shah SJ et al. JACC2013 doi 10.16/j.jacc2013.07.010
HFpEF: 3 different clinical profiles

2) Chronic volume overload
patients with NYHA class II-IV with history of hypertension and of HF hospitalisation, elevated BNP, and/or left atrial enlargement

Shah SJ et al. JACC2013 doi 10.16/j.jacc2013.07.010
HFpEF: 3 different clinical profiles

3) Right HF/ pulmonar hypertension

patients with NYHA class III-IV symptoms with evidence of pulmonary vascular disease and/or right ventricular dysfunction

Shah SJ et al. JACC2013 doi 10.16/j.jacc2013.07.010
Classical risk factors for HFpEF

- Age
- Female sex
- Hypertension
- Metabolic syndrome & diabetes
- Obesity
- Renal dysfunction
- Waist-hip ratio
- Physical inactivity

HF with reduced or preserved EF are two distinct entities

- HFpEF is a systemic syndrome, driven by accumulated risk factors/comorbidities in vulnerable subjects, with an important cardiovascular component (*loss of compliance and adaptability*).
HF with reduced or preserved EF are two distinct entities

- **HFrEF** is a clinical syndrome, originated in the heart, driven by myocardial cell loss and fibrosis, with an important systemic component (*neuro-hormonal*).
Myocardial alterations in HF

### Clinical characteristics: HFrEF vs. HFpEF

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Reduced Ejection Fraction (N=2429)</th>
<th>Preserved Ejection Fraction (N=2167)</th>
<th>P Value</th>
<th>Adjusted P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>71.7±12.1</td>
<td>74.4±14.4</td>
<td>&lt;0.001</td>
<td>NA</td>
</tr>
<tr>
<td>Male sex (% of patients)</td>
<td>65.4</td>
<td>44.3</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body-mass index;‡</td>
<td>28.6±7.0</td>
<td>29.7±7.8</td>
<td>0.002</td>
<td>0.17</td>
</tr>
<tr>
<td>Obesity (% of patients);‡§</td>
<td>35.5</td>
<td>41.4</td>
<td>0.007</td>
<td>0.002</td>
</tr>
<tr>
<td>Serum creatinine on admission (mg/dl)</td>
<td>1.6±1.0</td>
<td>1.6±1.1</td>
<td>0.31</td>
<td>0.30</td>
</tr>
<tr>
<td>Hemoglobin on admission (g/dl)</td>
<td>12.5±2.0</td>
<td>11.8±2.1</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (% of patients)</td>
<td>48.0</td>
<td>62.7</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease (% of patients)</td>
<td>63.7</td>
<td>52.9</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation (% of patients)</td>
<td>28.5</td>
<td>41.3</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes (% of patients)</td>
<td>34.3</td>
<td>33.1</td>
<td>0.42</td>
<td>0.61</td>
</tr>
<tr>
<td>Substantial valve disease (% of patients)</td>
<td>6.5</td>
<td>2.6</td>
<td>&lt;0.001</td>
<td>0.05</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>29±10</td>
<td>61±7</td>
<td>&lt;0.001</td>
<td>NA</td>
</tr>
</tbody>
</table>

---

Owan et al.; NEJM 2006; 355:251-9
## Characteristics of patients

Table 2. Presenting Symptoms and Signs of Heart Failure.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reduced Ejection Fraction (&lt;40%) (N=1570)</th>
<th>Preserved Ejection Fraction (&gt;50%) (N=880)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute pulmonary edema</td>
<td>332 (21.1)</td>
<td>152 (17.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Dyspnea or shortness of breath</td>
<td>1511 (96.2)</td>
<td>835 (94.9)</td>
<td>0.11</td>
</tr>
<tr>
<td>Chest pain</td>
<td>399 (25.4)</td>
<td>212 (24.1)</td>
<td>0.47</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>729 (46.4)</td>
<td>374 (42.5)</td>
<td>0.06</td>
</tr>
<tr>
<td>Syncope</td>
<td>27 (1.7)</td>
<td>10 (1.1)</td>
<td>0.26</td>
</tr>
<tr>
<td>Paroxysmal nocturnal dyspnea</td>
<td>473 (30.1)</td>
<td>220 (25.0)</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Signs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral ankle edema</td>
<td>888 (56.6)</td>
<td>581 (66.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Wheezing</td>
<td>302 (19.2)</td>
<td>173 (19.7)</td>
<td>0.80</td>
</tr>
<tr>
<td>Neck-vein distention</td>
<td>962 (61.3)</td>
<td>506 (57.5)</td>
<td>0.07</td>
</tr>
<tr>
<td>Crackles or rales on lung examination</td>
<td>1324 (84.3)</td>
<td>743 (84.4)</td>
<td>0.95</td>
</tr>
<tr>
<td>Hepatojugular reflux</td>
<td>119 (7.6)</td>
<td>69 (7.8)</td>
<td>0.82</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>81 (5.2)</td>
<td>38 (4.3)</td>
<td>0.35</td>
</tr>
<tr>
<td>Presence of S3</td>
<td>196 (12.5)</td>
<td>74 (8.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Presence of S4</td>
<td>80 (5.1)</td>
<td>33 (3.8)</td>
<td>0.13</td>
</tr>
<tr>
<td>Chest radiographic signs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>814 (51.8)</td>
<td>414 (47.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>716 (45.6)</td>
<td>360 (40.9)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Bhatia RS et al.; NEJM 2006; 355:260-9
Do these patients really have heart failure?

- “Hypertensive, overweight women with swollen ankles”
- Outcomes in HFpEF compared to other populations
What Have We Learned About Patients With Heart Failure and Preserved Ejection Fraction From DIG-PEF, CHARM-Preserved, and I-PRESERVE?

Ross T. Campbell, MB ChB, BSc,* Pardeep S. Jhund, MB ChB, PhD,* Davide Castagno, MD,† Nathaniel M. Hawkins, MB ChB, MD,‡ Mark C. Petrie, MB ChB, BSc,§ John J. V. McMurray, MD*

Glasgow, United Kingdom; Turin, Italy; and Liverpool, United Kingdom

HF Hospitalization

<table>
<thead>
<tr>
<th>Study</th>
<th>Per 1000 patient years</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTION</td>
<td>4.6</td>
</tr>
<tr>
<td>HYVET</td>
<td>5.3</td>
</tr>
<tr>
<td>ANBP-2</td>
<td>5.5</td>
</tr>
<tr>
<td>LIFE</td>
<td>7.1</td>
</tr>
<tr>
<td>ACCORD</td>
<td>7.5</td>
</tr>
<tr>
<td>VALUE</td>
<td>11</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>11.5</td>
</tr>
<tr>
<td>I-Preserve</td>
<td>43</td>
</tr>
<tr>
<td>CHARM-Preserved</td>
<td>69</td>
</tr>
<tr>
<td>DIG-PEF</td>
<td>73</td>
</tr>
</tbody>
</table>
Prognosis of HF with or without reduced EF

Burkoff D. Eur Heart J 2012;33: 1718
PREVEND community-based study

Brouwers FP Eur Heart J 2013; 34: 1424
How do patients with HFP EF die?

- Annual mortality ranging from 10% to 30%
- Cardiovascular deaths are 51–60% in epidemiological studies and 70% in clinical trials.
- Sudden death and HF death are the leading cardiac modes of death, though their proportions are lower than in HFrEF

Chan MMY, Lam SP  Eur J Heart Fail  2013; 15: 604
How do patients with HFpEF die?

- Non-cardiovascular deaths constitute a higher proportion of deaths in HFpEF than in HFrEF (fewer coronary heart deaths)

- Key mortality risk factors include age, gender, body mass index, burden of co-morbidities, and coronary artery disease

Chan MMY, Lam SP Eur J Heart Fail 2013; 15: 604
2012 ESC Guidelines on Pharmacological treatment of HFpEF

- “No treatment has yet been shown, convincingly, to reduce morbidity and mortality in these patients”

- Diuretics are used to control sodium and water retention and relieve breathlessness and oedema
2012 ESC Guidelines on Pharmacological treatment of HFpEF

- Adequate treatment of hypertension and myocardial ischaemia with BB is important, as is control of HR if AF
- Drugs that should be avoided in HFrEF should also be avoided in HFpEF, with the exception of CCBs
Control Hypertension (I B)
Diuretics if needed (I C)
Beta-blockers, ACE-I in hypertensive (reasonable, IIa C)
ARBs in HFpEF (may be considered, II b B)
Revascularization (reasonable, IIa C)
Management of A Fib (reasonable, IIa C)
Drugs tested in RCTs and in cohort studies in HFpEF

**Negative results**
- RAAS sytem modulators (ACE-Is, ARBs, MCAs)
- Beta blockers (carvedilol, nebivolol)
- Ranolazine (small, exploratory study)
- Sildenafil
- Nitroprusside

**Positive results**
- Exercise
**HFPEF Treatment effect on mortality**

<table>
<thead>
<tr>
<th>Trial Name / Author</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLHAT - A</td>
<td>1.19 (0.81, 1.75)</td>
</tr>
<tr>
<td>ALLHAT - B</td>
<td>0.76 (0.49, 1.18)</td>
</tr>
<tr>
<td>ALLHAT - C</td>
<td>0.90 (0.47, 1.72)</td>
</tr>
<tr>
<td>CHARM - P</td>
<td>1.03 (0.87, 1.21)</td>
</tr>
<tr>
<td>DIG</td>
<td>1.00 (0.80, 1.25)</td>
</tr>
<tr>
<td>Hong Kong DHF Trial - A</td>
<td>0.30 (0.03, 2.77)</td>
</tr>
<tr>
<td>Hong Kong DHF Trial - B</td>
<td>0.16 (0.01, 2.98)</td>
</tr>
<tr>
<td>I-PRESERVE</td>
<td>1.02 (0.91, 1.14)</td>
</tr>
<tr>
<td>PEP - CHF</td>
<td>1.06 (0.75, 1.51)</td>
</tr>
<tr>
<td>SENIORS</td>
<td>0.93 (0.65, 1.31)</td>
</tr>
<tr>
<td>V-HeFT I - A</td>
<td>1.31 (0.77, 2.24)</td>
</tr>
<tr>
<td>V-HeFT I - B</td>
<td>1.06 (0.59, 1.91)</td>
</tr>
<tr>
<td>V-HeFT II</td>
<td>0.65 (0.39, 1.09)</td>
</tr>
<tr>
<td>Aronow et al. (1997)</td>
<td>0.73 (0.58, 0.93)</td>
</tr>
<tr>
<td>Overall (95 % CI)</td>
<td>0.99 (0.92, 1.06)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $I^2 = 17.1\%$, $P=0.267$
Test for overall effect: $P=0.699$

_Holland et al., JACC, vol.57, 2011; 16:1676-86_
Effect of endurance training in HFpEF

In stable compensated HFpEF patients undergoing physical exercise training, both peak VO2 and peak A-V oxygen difference increase suggesting that peripheral mechanisms (improved microvascular and/or skeletal muscle function) are involved in symptom generation and may improve in HFpEF.

PARIStrial, J Am Coll Cardiol 2012;60:120
ENVIRONMENT, DIET  \rightarrow  COMORBIDITIES  \rightarrow  GENETIC SUSCEPTIBILITY

\text{VULNERABLE HEART, VULNERABLE PATIENT}

\text{HFpEF}

\text{EXERCISE-INDUCED DIASTOLIC DYSFUNCTION} \leftrightarrow \text{VOLUME OVERLOAD} \leftrightarrow \text{PULMONARY HYPERTENSION RV FAILURE}

\text{SAMPLE PATIENTS}

- 72-year-old woman: HTN, NYHA II, Exercise intolerance, Minimal fluid retention, No HF hospitalizations, LVEF 70\%, 2+ LAE, Grade I DD, PASP 30 mmHg at rest, Exercices EE' = 14
- 66-year-old woman: 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
- 59-year-old woman: HTN, DM2, CKD, obese, NYHA III, Severe SOB, DOE, 3+ edema, ascites, Frequent HF hospitalizations, LVEF 65\%, 4+ LAE, Grade II DD, PASP 60 mmHg at rest, RVH + RV dysfunction

\text{THEORETICAL "MATCHED" THERAPIES}

- I_{1} BLOCKADE
- MRA
- PDE5 INHIBITOR
- EXERCISE TRAINING
- ARNI
- HEMODYNAMIC SENSOR

Shah SJ, JACC 2013; 62:1339
Targeting novel therapies to the HFpEF phenotype

HF symptoms
Preserved LVEF

Plus Primary Comorbidity(ies)

HTN
Fluid retention
Elevated filling pressure

Diabetes, obesity, metabolic syndrome, conditions associated with oxidative stress

Pulmonary hypertension or right heart involvement

Cardiac fibrosis

Ischemia

Renal

- ARB/ACEI
- MRA
- ARNI
- Autonomic modulation

- Glycemic control
- Metformin (pleiotropic effects)
- Weight loss, bariatric surgery, diet
- PKG stimulation
- AGE crosslink breakers?

- PDE5 inhibitor
- Orally active soluble guanylate cyclase stimulator

MRA

- Na channel blockers
- Nitrates
- Beta-blockers

- Sodium restriction
- ACEI or ARB

Senni & Pieske, Eur Heart J 2014; in press
Emerging therapies 2014

- **Targeting heart rate**
  - *Ivabradine (EDIFY Phase II)*

- **Targeting Aldosterone and extracellular matrix**
  - *Spironolactone (Aldo-DHF, TOPCAT)*

- **Targeting deficient energy production**
  - *Bendavia (mitochondrial enhancer)*

- **Targeting low cGMP levels**
  - *PDE5 inhibition (Sildenafil: RELAX)*
  - *Neprilysin inhibition (LCZ696: PARAMOUNT)*
  - *sGC stimulation (Vericiguat: SOCRATES)*

- **Targeting physical deconditioning**: Exercise training
HF$_2$EF is different from HFpEF: a condition with several unmet needs

- Understanding (research)
- Prevention (control of risk factors and comorbidities)
- Therapy (no specific therapy available)