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Heart Failure With Preserved Ejection Fraction

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HEART FAILURE WITH PRESERVED EJECTION FRACTION: WHAT’S IN A NAME?

In Volume 16, Number 2, 2011 of Dialogues in Cardiovascular Medicine, the Editors stated that heart failure was a pathological condition under continuous development. How very true. In earlier, simpler days, as in 1933, heart failure was described with a mere 12 words by Sir Thomas Lewis (1881-1945) as “a condition in which the heart fails to discharge its contents adequately.”

From 1933 onwards, things get more complicated, with names well known to us (often of friends) contributing increasingly precise definitions (Paul Wood, Eugene Braunwald, Philip Poole-Wilson, Peter Harris—the list is not exhaustive), until names disappear and groups and task forces step in. Thus, in 2001, the definition of the European Society of Cardiology Task Force read: “(1) Symptoms of heart failure (at rest or during exercise) and (2) objective evidence, (preferably by echocardiography) of cardiac dysfunction (systolic and/or diastolic) at rest (both criteria 1 and 2 must be fulfilled) and (3) in cases where the diagnosis is in doubt, response to treatment directed towards heart failure.”

The issue of Dialogues referred to above was dedicated to the optimal pharmacological management of heart failure and described how therapeutic approaches evolved over the past several decades, starting from the early 50s when heart failure was treated with digitalis (already used by the Romans), diuretics, and bed rest. In the 1980s, in the wake of the first Vasodilator Heart Failure Trial (V-HeFT), vasodilators became the most popular treatment. The 1990s saw a CONSENSUS (COoperative North Scandinavian ENalapril Survival Study) being reached about the neurohormonal hypothesis. Subsequent clinical trials confirmed the hypothesis, demonstrating the benefits of angiotensin-converting enzyme inhibitors and β-blockers, and the usefulness of training programs for heart failure patients. Then came the devices and cellular and gene therapy. To stay on the pharmacological front, more recently, the importance of reducing heart rate was recognized by the cardiology community, and the positive results of the SHIFT study (Systolic Heart failure treatment with I1 inhibitor Ivabradine Trial) confirmed that in heart failure, heart rate was a risk factor that required being pharmacologically addressed.
Interestingly, and this is the point we are driving at, in the same 2011 issue of Dialogues, Martin Cowie addressed the issue of the treatment of heart failure by distinguishing between two types: systolic heart failure and diastolic heart failure. He pointed out that up to 50% of patients with heart failure had normal ejection fractions and, therefore, belonged to the category of diastolic heart failure. The proportion was highest in the elderly population, and as the world population was aging rapidly, the size of this problem was likely to increase steeply. The recent European Society of Cardiology Guidelines in Heart Failure have reviewed the terminology of this condition and suggest that it now be called “heart failure with preserved ejection fraction,” distinguishing it from “heart failure with reduced ejection fraction.”

The names for “heart failure” have thus become more complex, so much so that in the literature these two forms tend to be cited once in full, before switching—more conveniently, but undoubtedly less transparently—to “HFPEF” and “HFREF” (we follow here AMA terminological style, but many find the two abbreviations hard to distinguish at first glance and bend abbreviation rules by introducing a lower-case letter. HFPeEF and “HFReEF.” Typographical considerations aside, in this issue of Dialogues we turn our attention to “heart failure with preserved ejection fraction” and attempt to clarify its pathophysiology, epidemiology, diagnosis, and treatment.

This is no easy task as many cardiologists are critical of this distinction and argue that there is no difference between systolic and diastolic heart failure. They consider that, even in systolic heart failure, the first abnormalities involve diastole. Furthermore, clinical research so far has been aimed at finding therapeutic tools for heart failure with reduced ejection fraction, but not heart failure with preserved ejection fraction.

As of now, data seem to more empirical than “hard.” This is why in this issue we have decided to involve four experts in the hope that they can shed light on this difficult topic. Luigi Tavazzi gives us the state of the art of the understanding of heart failure with preserved ejection fraction. Burkert Pieske looks into how a more in-depth understanding of pathophysiology might help us better categorize patients clinically. Gerasimos Filippatos discusses patient populations and outcomes, comparing heart failure with preserved ejection fraction and heart failure with reduced ejection fraction. Lastly, Michel Komajda addresses the management of heart failure with preserved ejection fraction, in terms of what is now available and of what the future may hold.
During the last 15 years or so, it has been increasingly recognized that many patients with heart failure (HF) have normal or nearly normal left ventricular (LV) ejection fraction, a condition referred to as diastolic HF or HF with preserved ejection fraction (HFPEF). Schematically, two pathophysiological hypotheses of HFPEF development have been formulated. The first proposes a model of progressive alteration in LV diastolic function, with a progressive decline in LV ejection fraction liable to occur at any point along this continuum. The second lies in the principle that HF with reduced ejection fraction (HFrEF) and HFPEF are distinct conditions developing through different processes. Both hypotheses assume that a primary role would be played by a concurrence of multiple common risk factors and comorbidities in subjects vulnerable to biological insults. So far, the clinical research aimed at finding effective therapeutic tools was successful in HFrEF, but not in HFPEF. In this review, the diagnostic approaches, epidemiology, pathophysiology, and prognostic modeling of HFPEF are examined.

Keywords: epidemiology; heart failure; heart failure with preserved ejection fraction

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During the last 15 years or so, it has been increasingly recognized that many patients with heart failure (HF) have normal or nearly normal left ventricular (LV) ejection fraction, a condition referred to as diastolic HF or HF with preserved ejection fraction (HFPEF). This is noteworthy because, until then, HF was seen as a disorder of the “heart pump,” which could be quantified according to the reduction in ejection fraction. Current studies have reported a prevalence of HFPEF ranging from 30% to 70% (averaging about 50%) among patients with HF.1-3 Since the 1970s, hemodynamic studies investigating HFPEF4-7 mostly focused on diastolic LV dysfunction in hypertrophied hearts and with LV remodeling after myocardial infarction.8 The next seminal step was the observation that patients hospitalized with acute congestive HF could have normal systolic function, as evidenced by a normal LV ejection fraction (>50%).9,10 To explain such a “paradox,” it was supposed that such patients may have had transient LV systolic dysfunction during the initial acute phase of decompensation, which was no longer present after treatment.12 However, in a small group of patients hospitalized for an acute episode of hypertensive pulmonary edema, Gandhi et al found that, contrary to their expectations, the LV ejection fraction as well as the extent of regional wall motion measured during the acute event were similar to those found after the resolution of the congestion (>50%), when the blood pressure was controlled (Figure 1, page 206).12 The investigators published this landmark study in 2001. They concluded that in patients with hypertensive pulmonary edema, the cause of deterioration in heart function was an exacerbation of diastolic dysfunction by hypertension, and not a transient systolic dysfunction or mitral regurgitation. Subsequently, HFPEF has been extensively investigated. It was shown that the prevalence of HFPEF is high, and in most studies morbidity and mortality
rates were not different from those reported for patients with HREF. However, research on the effects of therapy was frustrating and no effective treatment has yet been identified. This review examines the diagnostic approaches, epidemiology, pathophysiology, and prognostic modeling of HFPEF.

**DIAGNOSIS**

As some HFPEF patients have neither an entirely normal EF, nor a major reduction in systolic function, the term HFPEF has been preferred, by most, to that of HF with normal ejection fraction. Another denomination of this “new” HF syndrome was “diastolic HF,” but when deeper investigations showed that ventricular dysfunction leading to a clinical HF syndrome was rarely exclusively diastolic, the term HFPEF was definitively confirmed. Moreover, it has been recognized that a subset of patients diagnosed previously with HREF had HF with a normal or nearly normal ejection fraction. These patients may be clinically distinct from those with persistently preserved or reduced ejection fraction, but further research is needed to confirm this finding. The cut-off to distinguish preserved vs reduced ejection fraction has been variably classified as >40%, >45%, >50%, and ≥55%. Different HFPEF diagnostic criteria were adopted by various clinical sources. For instance, the CHARM-Preserved trial (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity), the PEP-CHF trial (Perindopril in Elderly People with Chronic Heart Failure), and other contemporary trials on HFPEF enrolled patients who had a “normal” ejection fraction (≥40%) in combination with signs and symptoms of HF. In the PEP-CHF trial, additional echocardiographic criteria were required for enrollment, and the I-PRESERVE trial (Irbesartan in heart failure with PRESERVED systolic function) required an entry ejection fraction of ≥45%. As of today, five sets of guidelines for the diagnosis of HFPEF have been published. They all required the obligatory presence of signs and/or symptoms of HF, evidence of normal or near normal LV systolic function, and evidence of diastolic LV dysfunction or surrogate markers of LV dysfunction such as LV hypertrophy, left atrial enlargement,

**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>BNP</td>
<td>brain natriuretic peptide</td>
</tr>
<tr>
<td>CHARM</td>
<td>Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity</td>
</tr>
<tr>
<td>COMPASS-HF</td>
<td>Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure</td>
</tr>
<tr>
<td>DIG</td>
<td>Digitalis Intervention Group</td>
</tr>
<tr>
<td>E/E’</td>
<td>ratio of transmittal Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity</td>
</tr>
<tr>
<td>ePAD</td>
<td>estimate of pulmonary artery diastolic pressure</td>
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<tr>
<td>HF</td>
<td>heart failure</td>
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<td>HFFinCH</td>
<td>Heart Failure in Care Homes</td>
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<tr>
<td>HFPEF</td>
<td>heart failure with preserved ejection fraction</td>
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<td>HREF</td>
<td>heart failure with reduced ejection fraction</td>
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<tr>
<td>I-PRESERVE</td>
<td>Irbesartan in heart failure with PRESERVED systolic function</td>
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<tr>
<td>LV</td>
<td>left ventricular</td>
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<tr>
<td>MAGGIC</td>
<td>Meta-Analysis Global Group In Chronic heart failure</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>N-terminal pro-brain natriuretic peptide</td>
</tr>
<tr>
<td>PEP-CHF</td>
<td>Perindopril in Elderly People with Chronic Heart Failure</td>
</tr>
<tr>
<td>PREVEND</td>
<td>Prevention of REnal and Vascular ENd-stage Disease</td>
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<tr>
<td>TOPCAT</td>
<td>Treatment Of Preserved Cardiac function with an Aldosterone anTagonist</td>
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atrial fibrillation, or elevated plasma natriuretic peptide levels. The diagnostic criteria required according to the European Society of Cardiology (ESC) Heart Failure and Echocardiography Associations are as follows: (i) signs or symptoms of HF; (ii) normal or mildly abnormal systolic LV function (ejection fraction ≥50%); and (iii) evidence of diastolic LV dysfunction. Normal or mildly abnormal systolic LV function implies both an ejection fraction ≥50% and an LV end-diastolic volume index ≤97 mL/m². In turn, diastolic dysfunction can be obtained invasively (LV end-diastolic pressure >16 mm Hg or mean pulmonary capillary wedge pressure >12 mm Hg) or noninvasively by tissue Doppler ratio of transmural Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity [E/E’] >15]. If tissue Doppler yields an E/E’ ratio suggestive of diastolic LV dysfunction (15> E/E’ >8), additional noninvasive investigations are suggested, such as blood flow Doppler of mitral valve or pulmonary veins, echo measures of LV mass index or left atrial volume index, electrocardiographic evidence of atrial fibrillation, or plasma levels of natriuretic peptide. Figure 2 and Figure 3 (page 208) report the algorithms proposed by the ESC to confirm and exclude a diagnosis of HFPEF respectively, and Table I (page 209) reports the Doppler characteristics used to grade the diastolic dysfunction.

While early research mostly focused on the importance of diastolic dysfunction in the pathophysiology of HFPEF, recent studies have revealed that multiple non-diastolic abnormalities also contribute to cardiovascu-
lar dysfunction. In fact, diagnosis of HFPEF is frequently challenging, as it is mostly derived from the exclusion of other potential noncardiac causes of symptoms suggestive of HF. As emphasized by Shah and Solomon, the limitations of the present diagnostic approach to HFPEF are highlighted by the fact that traditional non-invasive parameters of diastolic function may perform poorly in discriminating HFPEF patients from comorbidity-matched asymptomatic subjects, are absent in approximately one-third of HFPEF patients, and fail to predict adverse events reliably among HFPEF patients. Recently, a 10-year analysis from the Copenhagen Hospital Heart Failure Study aimed at assessing the prevalence of HF by using the N-terminal pro-brain natriuretic peptide (NT-proBNP) for the diagnosis of HFPEF. Out of 1844 patients admitted, a clinical diagnosis of HF was made in 433; amongst these, 61% had HFPEF. An elevated NT-proBNP applied to the HF diagnosis drastically reduced the number of HF patients to 191, and amongst these, only 29% had a preserved ejection fraction. This experience further emphasizes the difficulty in obtaining a final correct diagnosis of

**How to exclude HFPEF**

**Breathless, without signs of fluid overload**

- NT-proBNP >120 pg/mL or BNP >100 pg/mL
- Evidence of pulmonary disease
- Consider pulmonary disease
- Consider valvular or pericardial disease
- Consider HFPEF
- Consider high output state

**Echocardiogram**

- Evidence of valvular or pericardial disease
- LV ejection fraction >50%
- LVEDVI <76 mL/m²
- LAVI <29 mL/m² and no atrial fibrillation
- LVMI <96 g/m² and <116 g/m²

**Tissue Doppler**

- S >6.5 cm/s and E/E’ <8
- no HFPEF

**Figure 3. Diagnostic flow chart on “how to exclude HFPEF” in a patient presenting with breathlessness and no signs of fluid overload.**

**Abbreviations:** BNP, brain natriuretic peptide; E, early mitral valve flow velocity; E’, early TD lengthening velocity; E/A, ratio of early (E) to late (A) mitral valve flow velocity; HFPEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; LAVI, left atrial volume index; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; LVEDVI, left ventricular end-diastolic volume index; LVMI, left ventricular mass index; mPAP, mean pulmonary capillary wedge pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; S, tissue doppler shortening velocity.

HFPEF. Though careful clinical evaluation and echo-Doppler cardiography remains of paramount importance for diagnosis, brain natriuretic peptide (BNP) evaluation, exercise testing, and sometimes invasive hemodynamic assessment may be needed to investigate the causes and characteristics of cardiac dysfunction to reach a solid diagnosis of HFPEF. Excellent and updated analyses on the challenging issue of HFPEF diagnosis have recently been published.8,25,31-33

**Epidemiology**

Prevalence of HF is increasing across the world, both in developed and developing countries. In low- to middle-income countries, the first cause of death and invalidity is cardiovascular disease, of which HF is prominent.34 In the US, HF has a prevalence of 5.8 million and is associated with high morbidity, mortality, and healthcare expenditures. Close to 1 million hospitalizations for HF occur annually, accounting for over 6.5 million hospital days and representing a substantial portion of the estimated $372 billion that is spent each year on HF.35 Recently, the US estimate of HF prevalence projected for 2020 to 2050 has been revised and the rate of incidence of HF diagnoses has more than doubled with respect to a previous estimate.1 About half of these patients have a normal (>50%) to mildly altered (40% to 50%) LV ejection fraction.

The overall epidemiological scenario is similar in Europe. However, long-term registries performed in northern European countries show a relative stability in the incidence of HF, and an increase of about 2 years in the mean age of death for HF, suggesting a later occurrence of the syndrome, a longer survival of affected patients, or both.36 Recent surveys of hospitalized HF patients showed that approximately one-third had a LV ejection fraction >50%, one-third had an intermediate value between 40% and 50%, and one-third had a LV ejection fraction <40%.37

Recently, in the context of the “Get With the Guidelines–Heart Failure” program, data from 275 hospitals that enrolled 110,621 patients from January 2005 to October 2010 have been reported. Patients were stratified by ejection fraction: 50% had HFREF (ejection fraction <40%), 14% had a borderline ejection fraction (40% to 50%), and 36% had HFPEF (ejection fraction >50%).38 From 2005 to 2010, the proportion of hospitalizations for HFPEF increased from 33% to 39% (P<0.0001). HFPEF is expected to overtake HFREF as the predominant form of acute HF over the next decade. The authors acknowledge that such an increase may represent heightened physician recognition of HFPEF as a disease process,38 but other studies have demonstrated similar rates of HFPEF among patients hospitalized for HF.14,39 Actually, the prevalence of HFPEF relative to HFREF is rising at a rate of ≈1% per year, which is alarming because no effective treatment for HFPEF is available, in contrast to HFREF, and no outcome improvements have been achieved in the past two decades.2

From both epidemiological and preventive points of view, it is of great interest to find out whether or not distinct risk markers and risk factors exist for the development of new-onset HFPEF compared with HFREF. In the PREVEND (Prevention of REnal and Vascular ENd-stage Disease) community-based cohort study, 8,922 middle-aged subjects were evaluated to assess the predictive value of risk factors and established cardiovascular biomarkers for new-onset HFREF (ejection

<table>
<thead>
<tr>
<th>Normal subjects</th>
<th>Normal/athletes/</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
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<tr>
<td>Septal e’ ≥8</td>
<td>Lateral e’ ≥10</td>
<td>Septal e’ &lt;8</td>
<td>Septal e’ &lt;8</td>
<td>Septal e’ &lt;8</td>
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<tr>
<td>Lateral e’ ≥10</td>
<td>LA ≥34 mL/m²</td>
<td>Lateral e’ &lt;10</td>
<td>LA ≥34 mL/m²</td>
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<td>LA ≥34 mL/m²</td>
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<tr>
<td>E/A &lt;0.8</td>
<td>DT &gt;200 ms</td>
<td>E/A 0.8 to 1.5</td>
<td>DT 160 to 200 ms</td>
<td>E/A ≥1.5</td>
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<tr>
<td>Average E/e’ &lt;8</td>
<td>Ar-A &lt;0 ms</td>
<td>Average E/e’ 9 to 12</td>
<td>Ar-A ≥30 ms</td>
<td>Ar-A ≥30 ms</td>
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<tr>
<td>Valsalva ΔE/A &lt;0.5</td>
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<td>Valsalva ΔE/A ≥0.5</td>
<td></td>
<td>Valsalva ΔE/A ≥0.5</td>
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Table 1. Grades of diastolic dysfunction.

Abbreviations: DT, deceleration time; E, peak early filling velocity; e’, annular motion; E/A, ratio of early (E) to late (A) mitral valve flow velocity; LA, left atrium; Ar-A, time difference between Ar velocity duration and mitral A-wave duration.

fraction ≤40%) vs HFPEF (ejection fraction ≥50%).

During a median follow-up of 11.5 years, 374 (4.4%) subjects were diagnosed with HF; 34% with HFPEF and 66% with HREF. The average time for diagnosis of new-onset HREF was 6 ± 3.6 years vs 8 ± 3.3 years for HFPEF (P = 0.001). Male sex was associated with new-onset HREF, whereas female sex was associated with new-onset HFPEF. Obesity, greater age, and raised NT-proBNP increased the risk for both HFPEF and HREF. Current smokers, increased troponin T, and previous myocardial infarction conferred a significantly increased risk of HREF, but not of HFPEF. Conversely, a history of atrial fibrillation, increased urinary albumin excretion, and cystatin C were significantly associated with the risk of HFPEF, but not of HREF. The investigators concluded that distinct risk profiles for HFPEF and HREF exist, which would support differential pathophysiological mechanisms for both HF subtypes.

In the Framingham Heart Study Database, new-onset HF cases between 1981 and 2008 were recorded and classified into HFPEF and HREF (cut off ejection fraction of 45%). Cox multivariable regression analysis predictors of 8-year risk of HF occurrence were identified. Among 6340 participants (60±12 years), 512 developed incident HF. Of 457 participants with a measured ejection fraction, 196 (43%) were classified as HFPEF and 261 (56%) as HREF. Older age, diabetes mellitus, and a history of valvular disease predicted both types of HF. Higher body mass index, smoking, and atrial fibrillation predicted HFPEF only, whereas male sex, higher total cholesterol, higher heart rate, hypertension, cardiovascular disease, left ventricular hypertrophy, and left bundle-branch block predicted risk of HREF. Again, the investigators concluded that these findings suggested that distinct clusters of risk factors determine the risk for new-onset HFPEF vs HREF.

**COMORBIDITIES**

In a large, representative, primary care database with universal registration of people accessing health-care services in Scotland, nearly a quarter (23%) of patients were multimorbid and in subjects over 65 years, multimorbidity was the norm. It is expected that the incidence and prevalence of HF, as well as of comorbidities, will increase exponentially in the following decades due to an aging population. In a recent observational study that enrolled HF patients of all ages from 12 European countries, 43% of patients had more than two comorbidities, while 5% had more than 4 comorbidities. In a cross-sectional study of 122 630 Medicare beneficiaries with HF (>65 years), the prevalence of comorbidities was 96% and it was calculated that patients with more than 5 comorbidities were responsible for 81% of all hospital days experienced by HF patients. High prevalence of comorbidities in patients with HF suggests common risk factors or a causal relation. It has been reported that patients with HF due to ischemic etiology are more likely to have comorbidities, and patients with more comorbidities are more likely to have clinical signs of congestion. Systemically raised venous pressure with ancillary neurohormonal responses may negatively impact noncardiac tissues and organs, thus facilitating the occurrence of so called comorbidities.

In an ambulatory cohort of veterans with HF, the comorbidity burden of 15 noncardiac comorbidities and the impacts of these comorbidities on hospitalization and mortality were compared between patients with HFPEF (2843) and those with HREF (6599) in a 2-year follow-up. Compared with HREF patients, those with HFPEF were older and had a higher prevalence of chronic obstructive pulmonary disease, diabetes, hypertension, psychiatric disorders, anemia, obesity, peptic ulcer disease, and cancer, but a lower prevalence of chronic kidney disease. Patients with HFPEF had similar overall hospitalization rates compared with HREF patients, but HF hospitalization rate was lower and non-HF hospitalization was higher in HFPEF patients. As expected, an increasing number of noncardiac comorbidities were associated with a higher risk of all-cause admissions. Overall, comorbidities had similar impacts on mortality in patients with HFPEF compared with those with HREF. Table II reports the rates of comorbidities observed in HFPEF patients enrolled in randomized controlled trials.

The frequency of multiple morbidities and the special characteristics of both social life and housing of the very elderly population led to expectations of a high prevalence of HF and of challenging conditions for appropriate diagnosis and care. The most relevant studies found a prevalence of 10% to 42% for HF in long-term care and 46% in older people presenting at the hospital with HF symptoms. To investigate this issue further, 405 residents in 33 UK care homes (65 to 100 years) were prospectively enrolled in the HFinCH study (Heart Failure in Care Homes), which aimed to ascertain HF prevalence and clinical management in this population. The presence of HFPEF was diagnosed in accordance with ESC guidelines and was modified when necessary for immobility, using clinical, echocardiographic, and BNP measurements. Patients...
with clinical features of HF whose ejection fraction was >50% and E/E’ > 15, or those with an equivocal E/E’ (8 to 15), but BNP > 200 pg/mL or NT-proBNP >220 pg/mL were diagnosed as having HFPEF. HF was diagnosed in 23% of patients (95% confidence interval [CI], 19–27); of these, 63% had HFPEF and 37% had HFR EF. Interestingly, 76% of previous HF diagnoses were not confirmed, and up to 90% of study cases were new. No symptoms or signs were reliable predictors of HF. The criteria for clinical diagnosis may need to be adapted in special situations in which, admittedly, the diagnosis of HF, specifically HFPEF, is challenging.

**PATHOPHYSIOLOGY**

Prolongation of early diastolic active relaxation, increase in LV passive stiffness, and slowing of diastolic filling have been considered the primary pathophysiological abnormalities in HFPEF. These ventricular functional abnormalities are mainly related to the stiffness of the extracellular matrix that links the cardiomyocytes to each other and are largely determined by the amount and composition of collagen, which in turn depends on collagen turnover. In most cases of HFPEF, the metalloproteinase tissue inhibitors are upregulated leading to an exaggerated synthesis of interstitial collagen, and the matrix metalloproteinases are downregulated with a reduction in collagen degradation. However, among patients presenting with HFPEF who underwent LV endomycocardial biopsy, one-third showed a normal collagen volume fraction associated with LV end-diastolic pressure and LV stiffness pattern comparable with HFPEF patients presenting with a raised collagen volume fraction. This finding suggests that in addition to collagen deposition, intrinsic cardiomyocyte stiffness can also contribute to diastolic LV dysfunction in HFPEF and their contributions may vary in each individual. Indeed, intrinsic cardiomyocyte stiffness has been shown in patients with HFPEF. The increased cardiomyocyte stiffness has been related to the cytoskeletal protein titin. Titin proteins are large elastic proteins expressed in cardiomyocytes in two main isoforms: N2B (a stiffer isoform) and N2BA (a more compliant isoform).
can occur and may be related to the phosphorylation status of the molecule or other biochemical processes. Several findings support the evidence that systolic cardiac abnormalities are also involved in the pathophysiology of HFPEF. Besides a global reduction in the ability of the myocardium to generate energy, a few studies reported that regional measures of ventricular systolic function, assessed by tissue Doppler imaging, are impaired in HFPEF. Numerous subsequent studies have similarly shown depressed longitudinal and radial systolic function in HFPEF. Borlaug and Paulus speculated that the same processes that promote diastolic ventricular stiffening in HFPEF can also increase systolic stiffening and contribute to reduced myocardial contractility and limited systolic reserve. These functional limitations of the heart coupled with abnormal exercise-induced and flow-mediated vasodilation as well as chronotropic incompetence lead to reduced aerobic capacity and symptoms of exercise intolerance.

A pivotal pathophysiologic determinant of HFPEF is the vascular dysfunction of both systemic and pulmonary vessels, resulting in vessel stiffening and the inability to adapt to the body’s variable needs with appropriate changes of vascular tone. Afterload elevation of the left ventricle, in the setting of ventricular-arterial stiffening typical of HFPEF, causes an excessive increase in blood pressure, which may result in further impairment of diastolic relaxation and marked increases in filling pressures during stress, as shown in Figure 4 (taken from a seminal review on the subject by Borlaug and Paulus).

Pulmonary hypertension is also frequent in HFPEF and predicts increased mortality. Pulmonary hypertension appears to be due to both elevated left heart pressures and high pulmonary vascular resistance. In early-stage HFPEF, pulmonary vasodilation with exercise may be preserved, exertional pulmonary hypertension being secondary to high left heart pressures. However, compared with hypertensive patients of the same age, most HFPEF patients showed an elevated pulmonary artery systolic pressure at comparable levels as pulmonary artery wedge pressure, documenting pulmonary vessel wall alterations independent of the LV end-diastolic pressure (Figure 5). Although important for both pulmonary and systemic circulations, the contribution of endothelial dysfunction may differ between them. The predominantly flow-endothelium–dependent pulmonary circulation may be more susceptible to
shear stress and endothelial dysfunction compared with the predominantly pressure-load–dependent systemic circulation.\(^\text{72}\)

Important incapacitating symptoms in patients with HFPEF are fatigue and reduced exercise capacity. The underlying pathophysiological mechanisms have been thoroughly investigated. A relevant contribution came from both the Mayo Clinic and Johns Hopkins Medical Institutions after assessment of 109 patients with HFPEF and 73 controls who were exercised to volitional fatigue with simultaneous invasive (n=96) or noninvasive (n=86) hemodynamic and oxygen consumption (\(\text{VO}_2\)) assessment, during upright or supine exercise.\(^\text{73}\) At rest, HFPEF patients had higher LV filling pressures, but a similar ejection fraction and cardiac output compared with controls. During exercise, HFPEF patients displayed a marked increase in LV filling pressures, associated with lower cardiac output and peak \(\text{VO}_2\) compared with controls. Reduced peak \(\text{VO}_2\) was predominantly attributed to cardiac output limitation because a similar absolute increase in arterial-venous \(\text{O}_2\) at peak exercise in both HFPEF patients and controls was associated with a greater arterial-venous \(\text{O}_2\) difference relative to \(\text{VO}_2\) in the HFPEF group. This indicates that in both groups, exhaustion of the available circulating oxygen was actually reached.

Further interesting insights regarding the exercise limitations of patients with HFPEF and HFREF have been reported by Zile et al.\(^\text{74}\) Eight subjects with HFPEF and 5 subjects with HFREF, undergoing symptom-limited Naughton protocol treadmill exercise tests, were investigated with implantable hemodynamic monitoring and echocardiographic recordings obtained before exercise and at peak exercise. Implantable hemodynamic monitor data were obtained during activities of daily life during a 24-hour time period. The exercise-related increase in cardiac output was blunted in both groups, but in HFREF a documented fall of LV systolic properties was partly compensated by the recruitment of Frank-Starling mechanisms associated with ventricular dilation. By contrast, patients with HFPEF showed no recruitment of Frank-Starling mechanisms (no ventricular dilation), but a small increase in LV systolic properties, which allowed for an increase in stroke volume. The authors concluded that although exercise limitations were similar between HFREF and HFPEF, there were significant differences in exercise-induced changes in LV systolic and diastolic properties, likely reflecting the different pathophysiologies of these clinical syndromes of HF.

Two schematic pathophysiological hypotheses on the development of HFPEF have been formulated, mostly relying on hemodynamic studies. Shah and Solomon\(^\text{26}\) proposed a model of progressive abnormalities in LV diastolic and systolic function underlying progressive HFREF. Early myocardial dysfunction, related to concurrent damage by cardiovascular risk factors, may be associated with coupled impairments in both diastolic function and LV longitudinal deformation. Initially, a concomitant augmentation of circumferential deformation can determine a preservation of ejection fraction. Decline in circumferential deformation paralleled by a continued, but gradual, impairment in diastolic function and longitudinal deformation could ultimately result in a reduction of LV ejection fraction. The clinical syndrome of HF can occur at any point along this continuum, with events triggering an abrupt alteration in this equilibrium or an acceleration of its components.

An alternative hypothesis lies in the principle that HFREF and HFPEF are distinct conditions developing through different processes. Paulus and Tschope\(^\text{25}\) recently reformulated a paradigm for HFPEF development according to this concept. In essence, a systemic proinflammatory state would be induced by common cardiovascular risk factors and comorbidities, representing the biological background of the cardiovascular ab-

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**Figure 5. Association of PASP with pulmonary venous hypertension.**

PASP increased with PCWP in patients with HFPEF, as well as in subjects with HTN without heart failure, but remained higher in HFPEF than HTN after adjusting for PCWP (\(P<0.001\)). Raw data points and linear regression line for the association are shown for HFPEF (in red) and HTN (in green).

Abbreviations: HFPEF, heart failure with preserved ejection fraction; HTN, hypertension; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure.

normalities in HFPEF and particularly of myocardial structural and functional alterations. According to this paradigm, a high prevalence of comorbidities such as obesity, diabetes mellitus, chronic obstructive pulmonary disease, and salt sensitive hypertension would induce a systemic and permanent proinflammatory state (shown to be predictive of incident HFPEF, but not of incident HFREF), which would cause coronary microvascular endothelial inflammation. In turn, this would reduce nitric oxide bioavailability, cyclic guanosine monophosphate content, and protein kinase G activity in adjacent cardiomyocytes, favoring the development of hypertrophy and raising resting tension because of titin hypophosphorylation. Both stiff cardiomyocytes and interstitial fibrosis would contribute to high diastolic LV stiffness and HF development.

As mentioned above, a systemic involvement of vessels, which gradually lose their endothelium-driven compliance and adaptability, is of paramount importance for the development of cardiocirculatory insufficiency. The cardiovascular endothelial system integrates the peripheral vascular endothelium with the central cardiac endothelium. Inflammatory oxidative stress causes endothelial activation, endothelial dysfunction, and organ-level dysfunction that may be observed in patients with HFPEF. Such a complex systemic process probably requires an individual susceptibility, leading to cardiovascular vulnerability, cumulative mechanical load of hypertension, and biological insults of metabolic comorbidities and aging.

Overall, by attempting to generate a synthetic definition, we might consider HFREF as a “primarily cardiac syndrome” with complex, prevalently neurohormonal, systemic responses including: (i) dominant cardiac abnormalities in systolic function; (ii) LV dilation; and (iii) eccentric remodeling. HFPEF may be seen as a “primary multimorbid systemic syndrome” with a prominent cardiovascular component, dominant cardiac abnormalities in diastolic function, normal LV size, and concentric remodeling.

**CLINICAL PROFILES**

In epidemiological studies, patients with HFPEF are older, often female, have a lower prevalence of coronary artery disease and a higher prevalence of hypertension, obesity, and chronic lung disease compared with HFREF patients. Other comorbidities (eg, atrial fibrillation, diabetes, anemia, chronic renal disease) are also frequent, but not consistently more so than in HFREF. This phenotypic picture even led to the suggestion that these patients may be little more than elderly, overweight women with circulatory peripheral disturbances, and not HF patients.

The clinical profiles of HFPEF patients enrolled in large pharmacological, randomized controlled studies are reported in Table II. Enrollees differed among these studies, mainly due to varied enrolling criteria. For instance, DIG-PEF (Digitalis Intervention Group—Preserved Ejection Fraction) and I-PRESERVE had an inclusion ejection fraction of 45% (but among randomized patients the median was 51% in DIG-PEF and 59% in I-PRESERVE), while CHARM-Preserved and PEF-CHF had an inclusion ejection fraction of >40% (a median of 52% and a mean of 64%, respectively) with different proportions of more (New York Heart Association [NYHA] III-IV) or less (NYHA I and II) severely symptomatic patients. PEP-CHF and I-PRESERVE had about 80% of patients in advanced NYHA class, while such patients were only 34% in TOPCAT (Treatment Of Preserved Cardiac function with an Aldosterone antagonist). In this trial, relatively healthier patients were enrolled with respect to previous studies, nevertheless the patients reported low activity levels, a poor quality of life, and a high prevalence of depression, confirming the heavy impact of the syndrome on quality of life.

A glance at the clinical profiles of the patients investigated and assessed in trials performed so far emphasizes patient heterogeneity and still undefined targets in selecting the populations of interest.

**HOW DO HFPEF PATIENTS DESTABILIZE?**

The complex cardiovascular adaptive changes in HF (LV dilation, depressed systolic LV function, abnormal neurohormonal responses in HFREF, stiff left ventricle, concentric hypertrophy, and rigid, noncompliant vasculature in HFPEF) is intrinsically unstable and exposed to acute decompensation. The transition from chronic compensated to acutely decompensated HF has been investigated with various approaches. Central, long-term hemodynamic monitoring by an implanted device is particularly informative. This was performed in both patients with HFREF and HFPEF (LV ejection fraction ≥50%) in the COMPASS-HF study ( Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure). The right heart pressures were continuously recorded by an implantable device and estimates of pulmonary artery diastolic pressure (ePAD) were obtained. The ventricular dimensions were measured noninvasively. Central hemody-
The biological scenario taking place during acute HF decompensation has been investigated in several studies. Most of the important biomarkers were evaluated and compared in patients with HFREF (n=219) and HFPEF (n=81) in the Diuretic Optimization Strategies Evaluation study.\textsuperscript{81} NT-proBNP was lower and both systolic blood pressure and cystatin C were higher in HFPEF than in HFREF. Despite higher systolic blood pressure and less renin-angiotensin-aldosterone system antagonist use in HFPEF, plasma renin activity and aldosterone levels were similar in HFPEF and HFREF, as were uric acid and procollagen type III N-terminal peptide levels. Changes in biomarker levels from the time of enrollment to day 60 were similar between HFREF and HFPEF. Thus, lower natriuretic peptide levels occur in decompensated HFPEF rather than in HFREF in association with similar clinical severity. Moreover, similar oxidative stress markers and collagen synthesis were found in both HFPEF and HFREF. Interestingly, among 159 consecutive symptomatic HF outpatients with an ejection fraction >50% and elevated pulmonary capillary wedge pressure, prospectively studied in the Northwestern University HFPEF Program, 46 (29%) had a normal BNP (<100 pg/mL).\textsuperscript{82} Ejection fraction and pulmonary capillary wedge pressures were similar in the normal and elevated BNP groups. However, elevated BNP was associated with enlarged left atrial volume, worse diastolic function, abnormal right ventricular structure and function, and worse outcomes (adjusted hazard ratio for HF hospitalization, 4.0; 95% CI, 1.6-9.7; \textit{P}=0.003), showing that although BNP is useful as a prognostic marker in HFPEF, normal BNP does not exclude the diagnosis of HFPEF.

Though the biological patterns described in patients with HFPEF and HFREF denote some differences between the two syndromes, clearly distinct biological profiles have not yet emerged from the available data.

**OUTCOMES OF HFPEF VS HFREF**

Assessing event rates in HF subgroups, defined by ejection fraction cutoffs, is difficult as ejection fraction measurements are rarely consistently available in trials. This approach suffers from well-known limitations related to the selection of patients according to a trial's inclusion and exclusion criteria. On the other hand, ejection fraction measurement, per se, implies selection, because it is undertaken less frequently in certain patient categories, such as the elderly, and severely symptomatic patients who may miss ejection fraction measurements more frequently than those less symptomatic. Consequently, exclusion of patients due to

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**Figure 6.** IHM-determined ePAD at rest (night-time minimum value) vs echocardiographically determined LV end-diastolic dimension obtained at enrollment.

The ratios of ePAD to LV end-diastolic dimension, an index of instantaneous diastolic distensibility, are plotted as red squares in patients with HFPEF, as blue circles in patients with HFREF, and as green triangles in normal control subjects. The ratio of ePAD to LV end-diastolic dimension was increased in the HFPEF patients vs HFREF patients. Dashed lines represent theoretic schematic diastolic pressure-dimension relationships on which the single calculated values may lie. The nonlinear lines are sketched estimates for illustration only.

**Abbreviations:** ePAD, estimated pulmonary artery diastolic pressure; HFPEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; IHM, implantable hemodynamic monitor; LV, left ventricular.

missing ejection fraction measurements can introduce systematic bias. However, the DIG and CHARM trials provided the opportunity to compare outcomes in patients with HFREF and HFPEF enrolled in the same trials. The mortality appeared consistently lower in HFPEF than in HFREF in both trials and the mortality rate in I-PRESERVE was similar to that in CHARM-Preserved. A review on this matter has been recently published. Mortality and HF hospitalization rates observed in these trials are comparatively reported in Figure 7.

In contrast, two large retrospective community-based studies reported similar mortality for patients with HFPEF and HFREF. Several comparisons of survival between patients with either HFPEF or HFREF in other observational studies gave inconsistent results. Two large and methodologically sound reports have recently been published, although unfortunately with inconsistent results. One example is MAGGIC (Meta-Analysis Global Group In Chronic heart failure), an individual patient meta-analysis, looking at 31 studies with 41,972 patients (3 pharmacotherapy RCTs, 4 management intervention RCTs, and 24 observational studies). Ejection fraction measurements were missing in 18% of the cases. Preserved ejection fraction was defined as ≥50%; 10,347 patients were classified as HFPEF and 31,625 as HFREF. The primary outcome of death from any cause occurred in 2422 (23.4%) patients with HFPEF and in 8332 (26.3%) in those with HFREF. Patients with HFPEF, although 5 years older, had a 32% lower risk of death over 3 years compared with HFREF patients. The hazard ratio (adjusted for age, sex, etiology, history of hypertension, diabetes, and atrial fibrillation) was 0.68 (95% CI, 0.64-0.71). Interestingly, the risk of death did not increase notably until the ejection fraction fell below 40%. The results were similar regardless of whether patients were hospitalized or not at baseline and whether they were involved in RCTs or observational studies. The difference
in mortality between patients with HFPEF and HREF was less pronounced with age, which would be consistent with a greater influence of noncardiovascular deaths among older patients.

The second study included 30,094 ambulatory adults with HF (mean age was 74 years, 46% women) enrolled in 4 integrated healthcare systems in the Cardiovascular Research Network in the US, between 2005 and 2008. LV ejection fraction was categorized as preserved (≥50% or normal), borderline (41% to 49% or mildly reduced), or reduced (<40% or moderately to severely reduced). LV ejection fraction was preserved in 49.5%, borderline in 16.2%, and reduced in 34.3% of patients. During a median follow-up of 1.8 years, 8,060 (26.8%) patients died, 8,108 (26.9%) were hospitalized for HF, and 20,272 (67.4%) were hospitalized for other reasons. The analytic approach was specifically designed to provide information on comparative risk factor performance across a wide range of covariates by ejection fraction categories. The main result was that none of the risk factors consistently interacted with ejection fraction. In other words, risk assessment was strikingly similar regardless of LV ejection fraction.

In a recent analysis, dealing with the in-hospital outcome of 51,428 patients with an ejection fraction <40% and 37,699 patients with an ejection fraction ≥50% included in the “Get With The Guidelines—Heart Failure” database, the sex prevalence differed in the two cohorts: 36% women and 64% men with ejection fraction <40%, and 65% women and 35% men with ejection fraction ≥50%. There were no sex differences in the in-hospital mortality (2.69% women and 2.89% men with ejection fraction <40%, \( P=0.20 \); 2.61% women and 2.62% men with ejection fraction >50%, \( P=0.96 \)). Risk factors such as age, systolic blood pressure, heart rate, and history of renal failure/dialysis were highly predictive of death for each sex/ejection fraction subgroup.

Besides the inconsistency of mortality rates in the two chronic HF populations identified by resting ejection fraction values in the studies reported above, the main issue remains that mortality is high in both HF syndromes. However, although many HF therapies did not prove to be effective for HFPEF, and are uniquely applied to patients with reduced ejection fraction, individual prognostic factor performance does not seem to be significantly related to the level of LV systolic function. The canonical conclusion that more data are needed to clarify the issue also applies in this case.

### How do HFPEF patients die

This important issue has been the focus of a few reports from controlled trials in which morbid and fatal events were adjudicated by an ad hoc committee. Recent pharmacotherapy trials have reported that cardiovascular deaths account for approximately 60% of all deaths in patients with HFPEF; with sudden death and death due to progressive HF appearing to be less common among patients with HFPEF compared with

<table>
<thead>
<tr>
<th>HFPEF, n (%)</th>
<th>HFREF, mean % (range)</th>
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<tbody>
<tr>
<td></td>
<td>Drugs</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>I-PRESERVE</td>
</tr>
<tr>
<td>Sudden death</td>
<td>231 (26)</td>
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<tr>
<td>Heart failure</td>
<td>125 (14)</td>
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<tr>
<td>MI</td>
<td>44 (5)</td>
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<tr>
<td>Stroke</td>
<td>76 (9)</td>
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<tr>
<td>CV procedure</td>
<td>13 (1)</td>
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<tr>
<td>Other cardiac</td>
<td>10 (1)</td>
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<td>Other vascular</td>
<td>32 (4)</td>
</tr>
<tr>
<td>Noncardiovascular</td>
<td>268 (30)</td>
</tr>
<tr>
<td>Unknown</td>
<td>81 (9)</td>
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**Table III. Mode of death distribution in HFPEF trials and in 20 HREF trials.**

**Abbreviations:** CHARM, Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity; CV, cardiovascular; DIG-PFEF, Digitalis Intervention Group—Preserved Ejection Fraction; HFPEF, heart failure with preserved ejection fraction; HREF, heart failure with reduced ejection fraction; I-PRESERVE, Irbesartan in heart failure with PRESERVEd ejection fraction study; n, number; PEP-CHF, Perindopril in Elderly People with Chronic Heart Failure; NR, not reported.

HFREF patients. Relatively few cardiovascular trials give a detailed breakdown of adjudicated cause of death. Compared with trials in patients with hypertension, a considerably higher proportion of all deaths in patients with HFREF was attributed to cardiovascular causes (60% to 70% [HFREF] vs 40% to 60% [hypertension]), particularly HF and sudden death. A greater proportion of death in patients with hypertension was attributed to stroke compared with HFREF patients (Table III, page 217).

In the I-PRESERVE trial the annual mortality rate was 5.2%. The mode of death was cardiovascular in 60% (including 26% sudden, 14% HF, 9% myocardial infarction, and 9% stroke), noncardiovascular in 30%, and unknown in 10% of the patients. This distribution in patients with HFPEF appears to differ from that reported for HFREF patients, with HFPEF patients having more noncardiovascular (30% vs 15%), fewer sudden deaths (26% vs 40%), and fewer HF deaths (15% vs 35%) than HFREF patients. Among other variables examined, age, female sex, and NT-proBNP (>339 pg/mL) were the strongest outcome predictors in I-PRESERVE. Subdividing the patients in ejection fraction quartiles, the lowest quartile (<53%) had significantly higher rates of all-cause mortality, cardiovascular death, and sudden death compared with the other 3 quartiles, which were all comparable. Table III shows the distribution in HFPEF trials compared with 20 HFREF trials.

In fact, patients with advanced HF, regardless of whether they have HFREF or HFPEF, exhibit high LV diastolic pressures, and may have a low cardiac output in spite of normal or moderately abnormal ejection fraction values. Such HF can lead to circulatory failure and death. The underlying clinical, structural, and functional factors that predispose to the development of arrhythmias causing sudden death are present in patients with both HFREF and HFPEF, however, their frequency and severity may differ. Fibrosis and scars may be distributed differently according to the etiology, intramyocardial coronary flow alterations may differ in dilated and hypertrophic hearts, and so forth. Obviously, noncardiovascular death rate is primarily related to the patient’s age and the nature, severity, and number of comorbidities present. Most occur at similar frequencies in both HFPEF and HFREF patients, but the number and extent of these comorbidities are greater in the former, in part because patients with HFPEF are older.

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Heart Failure With Preserved Ejection Fraction

Expert Answers to Three Key Questions

1. Can understanding of the pathophysiological mechanisms of heart failure with preserved ejection fraction lead to better patient phenotyping?
   
   B. M. Pieske

2. What are the patient populations and outcomes in heart failure with preserved ejection fraction?
   
   D. Farmakis, G. S. Filippatos

3. Heart failure with preserved ejection fraction: how do we treat it and what are the perspectives?
   
   M. Komajda
Heart failure with preserved ejection fraction (HFPEF) is a syndromal disease with multiple etiologies and phenotypic expressions. Left ventricular diastolic dysfunction is a key pathophysiological element and relates to increased myocyte stiffness and extracellular matrix changes. Systolic abnormalities, left atrial dysfunction, chronotropic incompetence, vascular stiffening, pulmonary hypertension, etc, contribute to HFPEF. Exercise incompetence of affected patients can be related to striking hemodynamic abnormalities in HFPEF at rest, and even more pronounced, during exercise. Common comorbidities, such as renal dysfunction, diabetes, and chronic obstructive pulmonary disease may aggravate the clinical picture and play a role in precipitating the disease.

Keywords: chronotropic incompetence; diastolic dysfunction; exercise hemodynamics; extracellular matrix; heart failure with preserved ejection fraction; myocyte function; pathophysiology; phenotypes

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Can understanding of the pathophysiological mechanisms of heart failure with preserved ejection fraction lead to better patient phenotyping?

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Heart failure with preserved ejection fraction (HFPEF) is a syndromal disease with symptoms and an outcome comparable to heart failure with reduced ejection fraction (HFREF). Nowadays, more than half of all heart failure patients suffer from HFPEF, and the prevalence of HFPEF has continuously increased over the last decades. However, therapies with proven benefits in HFREF have failed to work in HFPEF patients, and recommendations for management of these patients in current international guidelines are scarce. The lack of effectiveness of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor antagonists, and β-blockers...
in HFPEF has fueled the idea that HFPEF is a distinct disease entity with fundamental pathophysiological differences when compared with HREF. It has also promoted the notion that HFPEF is a syndromal disease where a one-size-fits-all therapeutic approach may not be successful. These insights, in line with the recent developments of novel pharmacological agents that target specific pathophysiological abnormalities, underline the need for a better mechanistic understanding of the HFPEF syndrome.

**THE HFPEF SYNDROME AND THE DEFINITION OF HEART FAILURE**

HFPEF is a syndrome with multiple phenotypic expressions and a variety of precipitating factors and comorbidities (Figure 1). Underlying pathophysiological mechanisms include: (i) impaired left ventricular diastolic suction and filling; (ii) subtle systolic dysfunction; (iii) impaired atrial function; (iv) pulmonary hypertension; (v) right heart dysfunction; (vi) autonomic disturbances with chronotropic incompetence; (vii) microcirculatory insufficiency with ischemia and metabolic imbalance; (viii) altered coupling of LV ejection to a stiffened vascular bed; (ix) inadequate blood pressure responses to exercise; and (x) dynamic valvular regurgitation. In addition, common comorbidities of the elderly, such as renal dysfunction and the ensuing volume overload, diabetes with cross-linking of myocardial and vascular structures by advanced glycation end products, hypertension, obesity and deconditioning, sarcopenia and muscle wasting, chronic obstructive pulmonary disease (COPD), anemia, and mood disorders contribute to the clinical picture of the HFPEF syndrome. Paulus et al have recently formulated the hypothesis that comorbidities such as diabetes and obesity induce a low-grade inflammatory state within the microcirculation that negatively impacts extracellular matrix accumulation and myocyte function in the heart, thereby explaining the common clinical association of comorbidities and HFPEF (Figure 2). In contrast with HREF, where signs and symptoms of heart failure together with a reduced ejection fraction are considered sufficient evidence for the disease, diagnosing HFPEF is hampered by a typically elderly patient population with comorbidities, the presence of a preserved ejection fraction (typically defined as EF ≥50%), and the lack of unequivocal diagnostic criteria for the disease. The Heart Failure Association of the European Society of Cardiology requires signs and/or symptoms, a preserved EF, and a nondilated LV (LVEDVI <97 mL/m²), as well as objective evidence of impaired LV diastolic function or filling (such as a LVEDP >16 mm Hg or a mitral inflow velocity to tissue Doppler (E/e) ratio >15). Many elderly patients suffer from dyspnea after exertion, edema, or other clinical signs not specific for heart failure, but present no clear evidence of a cardiac origin of their symptoms.

For these patients, it is of major importance to distinguish those with a cardiac origin from those without objective evidence of heart failure. To this end, a stress test to provoke functional changes in a patient otherwise in the diagnostic “grey zone” becomes increasingly accepted. Of note, heart failure is pathophysiologically described by altered filling pressures or stroke volume, or a combination of both at rest and/or during exercise. In consequence, “true” HFPEF patients demonstrate
an inappropriate increase in filling pressure without adequate stroke volume increases during exercise (see Figure 5, page 231). Noninvasive assessment of functional and hemodynamic alterations during exercise are increasingly accepted for better differentiation of HFPEF patients from elderly overweight persons with unspecific symptoms, but no underlying cardiac abnormality.

**STRUCTURAL REMODELING IN HFPEF**

HFPEF is frequently, but not always, associated with concentric LV remodeling or hypertrophy, typically on the basis of risk factors such as hypertension and diabetes. LV volumes are normal or may even be reduced in HFPEF. In large contemporary cohorts including healthy controls, patients with hypertension, and patients with HFPEF, Lam et al described smaller end-diastolic volumes and cardiac output, higher end-diastolic pressure, increased impairment and higher LV stiffness in HFPEF vs patients with hypertension and controls. Others have described slightly increased LV volumes in HFPEF, and these differences may be related to selection criteria (eg, prevalence of myocardial infarction). In the echo substudy of the I-PRESERVE trial (Irbesartan in heart failure with preserved ejection fraction), the majority of patients demonstrated concentric LV remodeling or hypertrophy and left atrium (LA) dilatation. As a consequence of both concentric remodeling/hypertrophy and a small cavity in HFPEF, wall stress (both systolic and diastolic) tends to be normal in HFPEF (in contrast with HREF). This has implications for secretion of wall-stress dependent hormones. Brain natriuretic peptide (BNP) and its inactive cleavage product (NT-proBNP) is markedly lower in HFPEF as compared with HREF, and this can be directly attributed to differences in wall stress.

**IMPAIRED LV DIASTOLIC FUNCTION**

Impaired LV diastolic function is a hallmark of HFPEF, and consists of prolonged isovolumic LV relaxation, slow LV filling, and increased LV diastolic stiffness. Zile et al convincingly demonstrated slow relaxation and elevated LV diastolic stiffness, the latter evidenced by a leftward and upward shift of the diastolic pressure-volume relation, in patients with HFPEF (see Figure 4, page 230). Using conductance catheterization, several groups showed that impaired diastolic function limits cardiac performance during exercise or atrial pacing.

LV relaxation and filling flaws occur by several mechanisms including changes to both myocytes and the extracellular matrix, which contribute to this central defect in HFPEF. LV relaxation is an active, ATP-dependent process related to Ca²⁺ influx into the sarcoplasmic reticulum (SR), an intracellular Ca²⁺ store. This explains why during ischemia, delayed relaxation and an increase in LV EDP occurs within seconds. Myocyte ion regulation is essential for coordinated contraction and relaxation. The excitation contraction coupling process involves the release of Ca²⁺ into the cytosol from the SR.
cytosolic Ca\(^{2+}\) binds troponin C, which leads to contraction by inducing an interaction between actin and myosin. Relaxation occurs by ATP-dependent Ca\(^{2+}\) influx into the SR via the SR Ca\(^{2+}\) pump, SERCA2a. Control of Ca\(^{2+}\) homeostasis and diastolic myocyte tone is obtained by the electrogenic Na\(^{+}\)/Ca\(^{2+}\) exchanger in the sarcolemmal membrane for Ca\(^{2+}\) removal (against a Na\(^{+}\) influx). Intracellular Na\(^{+}\) levels are controlled by the ATP-dependent Na\(^{+}/K^{+}\) pump.

In HFPEF, characteristic changes occur in the expression and regulation of major ion handling proteins, such as reduced SERCA2a activity and an increased activity of the Na\(^{+}/Ca^{2+}\) exchanger, which results in reduced systolic force generation, delayed relaxation, and increased Ca\(^{2+}\) dependent myofilament activation during diastole. The latter is further enhanced by a leakiness of the SR Ca\(^{2+}\) release channels (ie, the ryanodine receptors), resulting in a continuous leak of Ca\(^{2+}\) from the SR during diastole. Whether similar changes occur in HFPEF is a matter of debate. Data on human cardiac HFPEF tissue are scarce. However, key features involved in diastolic dysfunction in animal models for HFPEF (eg, the diabetic mouse model or the aortic banding compensated hypertrophic dog or cat model) include delayed transient Ca\(^{2+}\) decay, delayed relaxation, and increased diastolic SR Ca\(^{2+}\) leakage.\(^{15-18}\) SAEC0400, a reverse-mode Na\(^{+}/Ca^{2+}\) exchange inhibitor, attenuated LV stiffening and fibrosis and improved survival in an HFPEF animal model.\(^{19}\) Additionally, initial data suggests a beneficial effect of ranolazine, a late intracellular Na\(^{+}\) blocker, on diastolic function in HFPEF patients.\(^{20}\)

Besides ion dysregulation, cardiomyocyte stiffness can be modulated by alterations in the expression and phosphorylation of structural proteins within myocytes. Titin is a giant cytoskeletal protein that spans the myocytes from the Z-disk to the M-line and functions as a bi-directional molecular spring responsible for early diastolic recoil and late diastolic distensibility of myocytes.\(^{21}\) In HFPEF animal models and HFPEF patients, posttranslational titin modifications cause an isoform shift toward the stiffer N2B isoform. Titin hypophosphorylation has also been described and underlies increased intrinsic myofilament stiffness. In fact, in a HFPEF diabetic and obese rat model, 80% of myocyte stiffness was attributable to titin hypophosphorylation at specific phosphorylation sites.\(^{22}\) and stiffer titin was sufficient to induce HFPEF in a genetic mouse model.\(^{23}\) Reduced nitric oxide (NO) bioavailability and downregulation of both myocardial cyclic guanosine monophosphate and protein kinase G (PKG) signaling increases nitrosative and oxidative stress and has also been implicated in posttranslational modifications of titin, increased cardiomyocyte stiffness, and LV diastolic stiffness in HFPEF. In fact, van Heerebeck et al demonstrated, in human LV biopsies, that increased passive myocyte stiffness was related to reduced titin phosphorylation, reduced cGMP levels, and reduced PKG activity.\(^{24}\) In vitro, protein kinase A or G stimulation restored passive diastolic function. Consequently, pharmacological modulation of the cGMP/PKG pathway may be attractive for HFPEF patients with this abnormality. The ongoing Socrates-Preserved trial (Soluble guanylate Cyclase stimulator R in heART failure patients) specifically targets this pathophysiological phenotype in HFPEF patients with a new and orally active guanylate cyclase stimulator.\(^{25}\)
**Impaired LV Systolic Function and Systolic Stiffening**

While LVEF is the most commonly used measure of global systolic function, it is highly load dependent and relatively insensitive to subtle LV functional abnormalities. In fact, despite a preserved EF, systolic contractile function is often impaired in HFPEF. Initial evidence came from tissue Doppler imaging studies and suggested impaired longitudinal LV function. Recent data from the contemporary PARAMOUNT trial (The Prospective comparison of ARNI with ARB on Management Of heart failureUre with preserved ejection fraction Trial) demonstrate impaired systolic contractility by echocardiographic strain imaging in HFPEF. In this analysis, abnormal longitudinal and circumferential strain was prevalent in HFPEF, and differentiated HFPEF from asymptomatic hypertensive heart disease, was related to NT-proBNP levels, and was independent of measures of diastolic function. In addition to systolic contractility, several other features of regular LV contraction are impaired in HFPEF. LV rotational deformations (twisting and untwisting) are important contributors to suction, filling, and ejection. Echocardiographic parameters of torsion are impaired in HFPEF and exercise aggravates these disturbances. Recently, mechanical systolic and diastolic dyssynchrony was observed and was associated with myocardial contractile inefficiency in HFPEF. These findings were corroborated in a large HFPEF patient cohort where strain-derived systolic mechanical dyssynchrony was associated with LV remodeling and more severe diastolic dysfunction. Importantly, systolic dysfunction directly impacts diastolic filling, and mild deficits in resting systolic function may become aggravated with exercise.

The timing of ventricular-arterial coupling may also be important in HFPEF patients. Lower amplitude of mid-systolic wave reflections predicted better clinical outcomes in a substudy of the ASCOT trial (Anglo-Scandinavian Cardiac Outcomes Trial). Women demonstrate less efficient ventricular-arterial coupling than men (ie, higher wall stress development for any given LV geometry, arterial properties, and flow output), which may be a factor in HFPEF development. Modulation of the timing and amplitude of wave reflections merits further pathophysiologic investigation.

**Impaired Energy Metabolism and Mitochondrial Function**

Data on mitochondrial dysfunction and disturbances in energy metabolism in HFPEF are scarce, but the few reports available suggest that they have an important role in the pathophysiology of HFPEF. Using 31P magnetic resonance spectroscopy, Phan et al demonstrated a reduced cardiac creatine phosphate/adenosine triphosphate ratio in 38 patients with HFPEF versus 20 control subjects. Reduced energetic reserve was related to dynamic slowing of LV active relaxation, no increase in stroke volume, and abnormal ventricular-vascular coupling during physical exercise. Reducing mitochondrial reactive oxygen species by the novel compound SS-31 (Bendavia) substantially attenuated mitochondrial oxidative damage, which was concomitant with amelioration of angiotensin-induced cardiac hypertrophy, diastolic dysfunction, and fibrosis as demonstrated using a mouse model of angiotensin-2 induced hypertensive heart disease that induces pronounced diastolic dysfunction and mitochondrial protein oxidative damage. Whether mitochondrial dysfunction and energy metabolism are therapeutic targets in human HFPEF still needs to be clarified.

**Extracellular Matrix Alterations**

HFPEF is also characterized by quantitative and qualitative changes in the extracellular matrix. Fibrosis affects both the heart and the vascular system and impacts both diastolic and systolic function. Fibrosis leads to myocardial stiffening and impedes suction and filling, whereby the loss of early diastolic suction has deleterious effects on exercise capacity in HFPEF. Fibrosis is mediated by alterations in the amount and composition of collagen within the extracellular matrix. Collagen synthesis is enhanced during increased load or activation of the renin angiotensin aldosterone system (RAAS). In an animal model of pressure overload, mineralocorticoid excess promotes fibrosis and the transition from compensated hypertrophy to HFPEF. Downregulation of matrix metalloproteinases (MMPs) that degrade collagen and upregulation of tissue inhibitors of matrix metalloproteinases (TIMPs) occur in HFPEF, resulting in depressed collagen degradation.

The LV collagen volume fraction was increased by a factor of 2.3 in human HFPEF biopsies (as compared with a factor of 2.4 in aortic stenosis and 2.6 in HFREF patients). Consequently, extracellular collagen accumulation contributes to impaired diastolic LV function, but in contrast to prominent myocyte stiffening, this accumulation is a common finding in cardiac hypertrophy and failure. Galectin-3 is an emerging biomarker with potential utility for identifying patient subgroups that may specifically respond to antifibrotic therapy. Targeting fi-
brosis (eg, by using mineralocorticoid receptor antagonists) may represent an attractive therapeutic target in HFPEF patients depicting a fibrotic cardiovascular phenotype. Changes to both myocytes and their extracellular matrix composition are responsible for increased LV stiffness and impaired diastolic function of the LV (Figure 4).  

**LEFT ATRIAL DYSFUNCTION**

Left atrial (LA) dysfunction is common in HFPEF, and the decline in atrial function in the setting of poor diastolic filling may be a significant contributor to symptoms observed during exercise. In fact, LA size and dysfunction may indicate the severity of HFPEF and play a relevant pathophysiological role in this syndrome. LA dilatation, reduced LA pump and reservoir function, and atrial dyssynchrony are elements of LA dysfunction in HFPEF. In a recent subanalysis from the RELAX trial (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction trial) showed that HFPEF patients with atrial fibrillation have a more advanced disease and significantly reduced exercise capacity as compared with similar patients in sinus rhythm.  

**PULMONARY HYPERTENSION**

Pulmonary hypertension is a hemodynamic consequence of HFPEF with a reported prevalence of 53% to 83% in epidemiologic cohorts. Pulmonary hypertension is associated with higher mortality in patients with HFPEF, leading to the hypothesis that it is an active pathophysiologic factor in HFPEF progression, rather than solely secondary to left heart dysfunction. In fact, both precapillary (related to pulmonary arteriolar remodeling, intimal fibrosis, or reactive increases in pulmonary arterial tone) and postcapillary (pulmonary venous hyper-

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**Figure 4.** Impaired LV diastolic filling results from increased LV stiffness, evidenced by an upward and leftward shift of the diastolic pressure-volume relationship in HFPEF.

*Panel A.* Values measured for minimal LV pressure.

*Panel B.* Values measured for the minimal LV pressure that have been corrected for slow relaxation. The stiffness constant is represented by the exponential value in the equation for $P$.

**Abbreviations:** HFPEF, heart failure with preserved ejection fraction; LV, left ventricular; $P$, pressure; $V$, volume.

not be reproduced in the larger RELAX HFPEF trial that did not specifically include patients with pulmonary hypertension. 42

**AUTONOMIC DYSFUNCTION AND CHRONOTROPIC INCOMPETENCE**

Chronotropic incompetence is a common finding in HFPEF and is associated with exercise intolerance. 43 The cause of chronotropic incompetence may be due to the presence of autonomic dysfunction: these patients display reduced heart rate recovery, abnormal baroreflex sensitivity, and enhanced cardiac sympathetic stimulation. Since HFPEF patients with a small, stiff ventricle depend on heart rate reserve during exercise to increase their cardiac output, chronotropic incompetence may significantly contribute to exercise intolerance in HFPEF patients. This also has clinical implications, since β-blocker therapy in a patient with chronotropic incompetence may aggravate the clinical picture.

**VENTRICULAR-ARTERIAL STIFFENING**

Ventricular-arterial coupling, defined by the coupling ratio of arterial to ventricular systolic stiffness (elastance), is similar in HFPEF and controls. However, both components of this ventricular and arterial stiffness ratio are markedly elevated in HFPEF, which results in increased blood pressure, cardiac work, and energy demand to deliver a given stroke volume. Increased systolic ventricular stiffness (steep end-systolic pressure-volume relation) also results in greater susceptibility to blood pressure changes with vasodilators and vasoconstrictors. 44

**CARDIOVASCULAR RESERVE FUNCTION IN HFPEF**

Most mechanistic data has been obtained in vitro or during resting conditions. However, many patients complain of symptoms predominantly during exercise. Several recent studies demonstrate substantial abnormalities in ventricular-vascular reserve, defined by the change in cardiovascular function during exercise. Diastolic reserve function is blunted in HFPEF, which is evidenced by a lower increase in end-diastolic volume (preload) despite marked increases in filling pressure. 45 In addition to diastolic reserve dysfunction, systolic abnormalities may be unmasked during exercise. Furthermore, the physiological reduction in vascular resistance with exercise is attenuated in HFPEF, which hampers cardiac output reserve and contributes to a hypertensive response to exercise that leads to abnormal dynamic ventricular-arterial coupling. Endothelial dysfunction may play a significant role in the blunted vasodilatory response to exercise in HFPEF. Using radionuclide ventriculography, Phan et al demonstrated delayed relaxation, no increase in stroke volume, a smaller increase in heart rate, and impaired ventricular-vascular coupling in HFPEF patients as compared with controls. 31

Taken together, HFPEF patients with a correct diagnosis of heart failure demonstrate significant alterations in cardiac mechanical function and hemodynamics at rest and/or during exercise (Figure 5). 46

**SUMMARY**

HFPEF is not a uniform disease, but is comprised of a number of pathophysiological expressions in various combinations and various dominant phenotypic patterns. The core mechanistic alteration is impaired LV filling, but systolic dysfunction, dysynchrony, LA dysfunction, autonomic imbalance, vascular...
dysfunction, pulmonary hypertension, and others may all contribute to the disorder. A better mechanistic phenotyping of the individual patient on the basis of established pathophysiological concepts may help target specific therapies for dominant alterations in the future.

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What are the patient populations and outcomes in heart failure with preserved ejection fraction?

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Attkon University Hospital - Athens - GREECE

Heart failure with preserved ejection fraction (HFPEF) is defined as the presence of heart failure concomitant with normal or slightly reduced left ventricular ejection fraction and relevant structural heart disease and/or diastolic left ventricular dysfunction. HFPEF accounts for about half of hospital admissions for heart failure and its prevalence is growing with the aging of the population. Compared with heart failure with reduced ejection fraction (HREF), patients with HFPEF are older, more often female, and less likely to have ischemic heart disease as the etiology of heart failure. The outcome of HFPEF is similarly adverse as that of HREF, although HFPEF patients die more frequently from noncardiovascular causes. Lack of evidence-based therapies does not permit a systematic approach to management and currently constitutes the main challenge in HFPEF.

The concept of heart failure with preserved (or normal) ejection fraction (HFPEF), formerly termed diastolic heart failure, has emerged over the past years following the increasing recognition of the high prevalence and the important clinical impact of this entity.

A generally accepted definition of HFPEF is lacking. The European Society of Cardiology (ESC) defines HFPEF as the presence of signs and symptoms of heart failure in combination with normal or slightly reduced left ventricular (LV) ejection fraction and evidence of relevant structural heart disease and/or diastolic LV dysfunction, without providing a specific threshold for ejection fraction. Currently, a cutoff of 50% tends to be accepted by most. However, several previous papers have used a lower threshold of 40%, and others have defined reduced and preserved ejection fraction as <40% and >50%, respectively, thus leaving an undefined marginal zone of 40% to 50%. Data from the OPTIMIZE-HF registry (Organized Program To Initiate lifesaving treatment In hospitalIzed pa-tients with Heart Failure) showed

SELECTED ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ADHERE</td>
<td>Acute Decompensated HEart failure national REgistry</td>
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<td>ALARM-HF</td>
<td>Acute Heart Failure Global Survey of Standard Treatment</td>
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<td>CVRN</td>
<td>Cardiovascular Research Network</td>
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<td>DOSE</td>
<td>Diuretic Optimization Strategies Evaluation</td>
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<td>EHFS</td>
<td>EuroHeart Failure Surveys</td>
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<td>EPICA</td>
<td>EPidemiologia da Insuficiência Cardiaca e Aprendizagem–Epidemiology of Heart Failure and Learning</td>
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<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
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<tr>
<td>HFPEF</td>
<td>heart failure with preserved ejection fraction</td>
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<td>HREF</td>
<td>heart failure with reduced ejection fraction</td>
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<td>LV</td>
<td>left ventricular</td>
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<td>MAGGIC</td>
<td>Meta-Analysis of Global Group In Chronic heart failure</td>
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<td>OPTIMIZE-HF</td>
<td>Organized Program To Initiate lifesaving treatMent In hospitalIzed patients with Heart Failure</td>
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<td>NYHA</td>
<td>New York Heart Association</td>
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<tr>
<td>TOPCAT</td>
<td>Treatment Of Preserved Cardiac function heart failure with an Aldosterone anTagonist</td>
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Keywords: heart failure; HFPEF; HREF
Address for correspondence: Prof Gerasimos S. Filippatos, University of Athens, Department of Cardiology, Heart Failure Unit, 28 Donkisss Plakentias, 11523 Athens, Greece (e-mail: geros@otenet.gr)
What are the patient population and outcomes in HFPEF? - Farmakis and Filipatos

that there were significant differences in several clinical and laboratory features between heart failure patients with ejection fraction >50%, and those with ejection fraction within the marginal zone of 40% to 50%. As a result, the reported data may not be fully comparable among different studies.

According to different heart failure registries, HFPEF patients represent between 25% and 51% of cases admitted to hospital for heart failure (Figure 1). The prevalence of HFPEF seems to have increased progressively over the past decades. Among patients hospitalized for decompensated heart failure at Mayo Clinic Hospitals between 1987 and 2001, the mean prevalence of HFPEF increased from 38% during the period 1987-1991, to 47% during 1992-1996, and further to 54% during 1997-2001. In contrast, the prevalence of heart failure with reduced ejection fraction (HREF) over the study period remained stable. The prevalence of HFPEF also increases with age. According to data derived from the community-based EPICa study (EPIdemiologia da Insuficiência Cardiaca e Aprendizagem | Epidemiology of Heart Failure and Learning) from Portugal, the prevalence of HFPEF increases with age: approximately 2% at 50 to 59 years, 4% at 60 to 69 years, 6% at 70 to 79 years, and 9% at ≥80 years. Moreover, the age-related increase in HFPEF prevalence was much steeper in HFPEF than HFREF, particularly in women. As a result, the impact of HFPEF is gradually becoming more important given the aging of the general population.

**FEATURES OF THE HFPEF POPULATION**

The HFPEF population forms a heterogeneous group of patients with particular demographic and clinical characteristics. There are significant differences in in-hospital management and discharge prescriptions in HFPEF patients among different geographic regions, as depicted by a comparison between the ADHERE (Acute Decompensated HEart failure national Registries)–United States (US) and the ADHERE-International (I) registry, which enrolled patients from Asia-Pacific and Latin America countries. A comparison of the main clinical features between HFPEF and HREF is outlined in Table I (page 236).
What are the patient population and outcomes in HFPEF? - Farmakis and Filippatos

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Table I. A comparison of main clinical features between HFPEF and HFREF.

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<td>Outcome</td>
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Abbreviations: HFPEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; RAAS, renin-angiotensin-aldosterone system.

Table I. A comparison of main clinical features between HFPEF and HFREF.

The prescribed therapies are also different from those in HFREF. Several clinical trials testing drug therapies of proven effectiveness in HFREF such as renin-angiotensin-aldosterone system inhibitors (perindopril, candesartan, irbesartan, spironolactone) failed to provide evidence that these drugs were effective in HFPEF, while other more advanced or invasive therapies have not been tested in these patients. As a result, the prescription of such therapies is expected to be lower and dependent upon the individual clinical profile, as suggested by ESC guidelines. Indeed, according to data from the ADHERE and OPTIMIZE-HF registries, HFPEF patients are significantly less frequently prescribed renin-angiotensin-aldosterone system inhibitors. More specifically, in the ADHERE registry, the percentage of patients with HFPEF vs HFREF receiving angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) was 47% vs 52% on admission and 59% vs 71% at discharge, respectively. Similarly, in the OPTIMIZE-HF registry, the prescription of ACE inhibitors or ARB...
in patients with HFPEF vs HREF was 49% vs 56% on admission, and 61% vs 73% at discharge, respectively. Spironolactone prescription was also significantly less frequent in patients with HFPEF compared with those with HREF both on admission (5% vs 11% in ADHERE, 5% vs 10% in OPTIMIZE-HF, respectively) and at discharge (11% vs 27% in ADHERE, 8% vs 18% in OPTIMIZE-HF, respectively). β-Blockers were also less frequently prescribed to patients with HFPEF vs HREF both on admission and at discharge in OPTIMIZE-HF (52% vs 56% on admission, 60% vs 73% at discharge, respectively), but only at discharge in ADHERE (52% vs 63%, respectively). Similarly, the Cardiovascular Research Network (CVRN) reported a lower use of multiple cardioactive drug regimens or multiple heart failure–related drug therapies in patients with HFPEF, while HFPEF patients in the EuroHeart Failure Surveys also received less cardiovascular medication with the exception of calcium antagonists. However, it should be stated that the ongoing TOPCAT trial (Treatment Of Preserved Cardiac function heart failure with an Aldosterone antAgonist) is expected to provide more definite evidence on the effect of spironolactone on morbidity, mortality, and quality of life in HFPEF. Compared with patients with HREF, patients with HFPEF are less likely to be treated by a cardiologist as their primary physician or have a consultation with a cardiologist during hospitalization with a discharge diagnosis of heart failure.

**OUTCOME OF HFPEF**

Despite the clinical particularities of patients with HFPEF, the prognosis seems to be rather equally adverse compared with HREF patients. According to the ADHERE registry, in-hospital mortality was slightly, but significantly, lower in HFPEF than in HREF (2.8% vs 3.9%). The OPTIMIZE-HF registry also showed a similarly lower inhospital mortality rate in HFPEF (2.9% vs 3.9% in HREF). In the Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF), in-hospital mortality was higher compared with the previous two registries, but still significantly lower in HFPEF (7% vs 11% in HREF). The same applied to long-term survival in the Mayo Clinic Hospitals cohort; 5-year survival rate was slightly, but significantly better in HFPEF (68% vs 65% in HREF at 5 years). In the same cohort, survival rates remained stable in HFPEF, however it increased over time in HREF, probably reflecting the adoption of life-saving therapies. The better survival rates in HFPEF were also confirmed by a meta-analysis of 31 studies (121 deaths per 1000 patient-years vs 141 deaths per 1000 patient-years in HREF, adjusted hazard ratio, 0.68). In contrast, data from the OPTIMIZE-HF registry showed that HFPEF patients had similar rates of short- or mid-term postdischarge mortality and rehospitalization compared with HREF patients: 60–90-day mortality was 9.5% in HFPEF vs 9.8% in HREF, and 60–90-day rehospitalization was 29.2% vs 29.9%. Similarly, post-discharge short- and mid-term survival did not differ between HFPEF and HREF in a smaller cohort from Canada (7% vs 5% at 30 days and 26% vs 22% at 1 year). The association between atrial fibrillation and adverse outcomes was similar in HREF and HFPEF according to data derived by the CVRN PRESERVE trial and the Loire Valley Atrial Fibrillation Project.

The causes of death differ significantly between the two populations. In a community-based cohort, HFPEF patients died more frequently from noncardiovascular causes compared with HREF patients (49% vs 36%, respectively) and less frequently from coronary artery disease (29% vs 43%, respectively), while the incidence of cardiovascular deaths due to causes other than coronary artery disease was similar (22% vs 21%, respectively). It seems that the incidence of noncardiovascular deaths tends to increase as the ejection fraction rises, with a parallel decrease of deaths from worsening heart failure or arrhythmias.

**CONCLUSION**

HFPEF represents about half of hospital admissions for heart failure and its prevalence is growing as a result of an aging population. Patients with HFPEF are older, more often female, and less likely to have ischemic heart disease as the etiology of heart failure. They are further characterized by comparable clinical severity upon presentation, but lower natriuretic peptide levels compared with HREF patients. While HFPEF patient outcome is as adverse as that of HREF patients, HFPEF patients die more frequently from noncardiovascular causes. Finally, the impressive lack of evidence-based therapies does not permit a systematic approach to patient management and currently constitutes the main challenge in HFPEF.

**REFERENCES**

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Heart failure with preserved ejection fraction: how do we treat it and what are the perspectives?

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Management of heart failure with preserved ejection fraction remains empiric and symptom-oriented due to the lack of evidence-based therapies. Treatment of underlying etiology, such as hypertension or ischemic heart disease, and heart rate control is also recommended. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have failed to demonstrate an improvement in morbidity-mortality in large outcome trials, and the effect of β-blockers or calcium channel blockers has not been properly evaluated. An outcome trial using spironolactone is close to completion. Novel approaches may include dual-acting angiotensin receptor–neprilysin inhibitors, the late sodium current inhibitor ranolazine, the I1 current inhibitor ivabradine, advanced glycation end-product cross link breakers, or procedures restoring a normal calcium cycling in cardio-myocytes.

The socioeconomic burden of heart failure (HF) is increasing due to three main factors: (i) the ageing population; (ii) the medical management of conditions such as acute coronary syndromes, which has markedly improved so that people who used to die from these conditions now survive, often with left ventricular (LV) dysfunction; and (iii) the worldwide epidemic of conditions associated with HF such as diabetes and obesity.

Approximately 30% to 50% of patients with HF have a normal ejection fraction (EF) and this defines HF with preserved EF (HFPEF). The diagnosis of HFPEF is often challenging and requires three different components according to the consensus document published by the European Society of Cardiology (ESC):

1. signs and symptoms of HF preserved EF >50% in a nondilated heart, and evidence of abnormalities in LV filling, distensibility, or relaxation. Unlike HF with reduced EF (HFrEF), where the medical management is nowadays well established, the treatment of HFPEF remains largely empiric due to the lack of evidence of benefit demonstrated by outcome clinical trials.

The purpose of this paper is to review existing therapies, their impact on outcomes, and to discuss potential new treatment modalities in HFPEF.

THE CURRENT SITUATION: A LACK OF EVIDENCE

International guidelines acknowledge the fact that the management of this condition is lacking evidence: the most recent version of the ESC guidelines outlines the fact that “no treatment has yet been shown, convincingly, to reduce morbidity and mortality,” as was already stated in a previous version of these guidelines. These guidelines say that diuretic agents are useful to control sodium and water retention and relieve breathlessness and edema in HFPEF. Similarly, the American College of Cardiology/American Heart Association guidelines recognize the lack of evidence and the fact that clinical trials are inconclusive.

International guidelines also insist on the need to control two factors: (i) the underlying condition, ie, hypertension and/or myocardial ischemia, and (ii) heart rate, since increased heart rate or tachyarrhythmia is often poorly tolerated in these patients who have a stiff left ventricle, and may result in pulmonary edema.

β-BLOCKERS AND CALCIUM CHANNEL BLOCKERS

Prolongation of diastole by slowing heart rate should result in an improvement of LV filling in this condition characterized by abnormal
LV stiffness and prolonged relaxation. However, clinical evidence on the benefits of this intervention is lacking. Nebivolol, a third generation β-blocker, was tested in a large outcome trial including 2128 elderly patients (>70 years) with a history of HF (hospital admission for HF in the previous year) or known EF <35% (SENIORS [Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with heart failure]). The primary outcome was a composite of all-cause mortality or cardiovascular admission. There was a 14% risk reduction in favor of nebivolol, with no evidence of influence on EF, which was >35% in approximately one-third of patients. However, no conclusion can be drawn for HFP EF since the EF threshold used in this trial was >35%, which is already markedly reduced. In an echocardiographic substudy, there was no influence of this agent on parameters of systolic or diastolic function. In another trial, ELANDD (Effects of Long-term Administration of Nebivolol on the clinical symptoms, exercise capacity, and LV function of patients with Diastolic Dysfunction), nebivolol did not improve symptoms or exercise capacity of patients with HFP EF. Small sized studies have suggested that the bradycardic calcium channel blocker verapamil might improve symptoms and exercise capacity in these patients, but we are lacking documented evidence of this potential benefit.

### SELECTED ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>advanced glycation end-product</td>
</tr>
<tr>
<td>Aldo-DHF</td>
<td>Aldosterone receptor blockade in Diastolic Heart Failure</td>
</tr>
<tr>
<td>BENEFICIAL</td>
<td>evaluating the efficacy and safety of alagebrium (ALT-711) in patients with chronic heart failure</td>
</tr>
<tr>
<td>BNP</td>
<td>brain natriuretic peptide</td>
</tr>
<tr>
<td>CHARM</td>
<td>Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity</td>
</tr>
<tr>
<td>CUPID</td>
<td>Calcium Upregulation by Percutaneous administration of gene therapy in cardiac Disease</td>
</tr>
<tr>
<td>DIG</td>
<td>Digitalis Intervention Group</td>
</tr>
<tr>
<td>E/E'</td>
<td>ratio of transmitial Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity</td>
</tr>
<tr>
<td>ELANDD</td>
<td>Effects of Long-term Administration of Nebivolol on the clinical symptoms, exercise capacity, and left ventricular function of patients with Diastolic Dysfunction</td>
</tr>
<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>HFPEF</td>
<td>heart failure with preserved ejection fraction</td>
</tr>
<tr>
<td>HFREF</td>
<td>heart failure with reduced ejection fraction</td>
</tr>
<tr>
<td>I-PRESERVE</td>
<td>Irbesartan in heart failure with PRESERVEd systolic function</td>
</tr>
<tr>
<td>MAGGIC</td>
<td>Meta-Analysis Global Group In Chronic heart failure</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>N-terminal pro-brain natriuretic peptide</td>
</tr>
<tr>
<td>PARAMOUNT</td>
<td>Prospective comparison of ARNI with ARB on Management Of heart failUr with preserved ejectioN fraction Trial</td>
</tr>
<tr>
<td>PEP-CHF</td>
<td>Perindopril for Elderly People with Chronic Heart Failure</td>
</tr>
<tr>
<td>RAAS</td>
<td>renin angiotensin aldosterone system</td>
</tr>
<tr>
<td>RALI-DHF</td>
<td>RAnoLazIne for the treatment of Diastolic Heart Failure</td>
</tr>
<tr>
<td>RELAX</td>
<td>Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction trial</td>
</tr>
<tr>
<td>SENIORS</td>
<td>Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with heart failure</td>
</tr>
<tr>
<td>TOPCAT</td>
<td>Treatment Of Preserved Cardiac function heart failure with an Aldosterone anTagonist</td>
</tr>
</tbody>
</table>

### RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS) ANTAGONISTS

Three outcome trials have been conducted in HFPEF (Table I). The rationale for these trials is that angiotensin-II stimulation of type I angiotensin receptors promotes cardiac hypertrophy and fibrosis. It was therefore anticipated that the blockade of the synthesis of angiotensin-II by an angiotensin-converting enzyme (ACE) inhibitor or the direct blockade of the angiotensin receptor would result in favorable clinical effects. The PEP-CHF trial (Perindopril for Elderly People with Chronic Heart Failure) enrolled 850 patients with an EF >40% and echocardiographic evidence of diastolic dysfunction. There was no reduction in the primary composite outcome of all-cause mortality or HF hospitalization. This trial was obviously underpowered and suffered a long recruitment period with resulting cross-over, which may have diluted the potential benefit of perindopril.

Indeed, a post-hoc analysis made after one year of follow-up suggested a favorable trend, which was no longer present later on.
Heart failure with preserved ejection fraction: current management and perspectives - Komajda

3023 patients with an EF >40% were included in the CHARM-Preserved trial (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity). The intervention arm consisted of candesartan uptitrated to 32 mg/day. After 36.6 months of follow-up, there was no significant improvement in the primary composite outcome of cardiovascular mortality or HF hospitalization. The only favorable trend was a reduction in the total number of HF hospitalizations.

The I-PRESERVE trial (Irbesartan in heart failure with PRESERVED systolic function) enrolled 4128 elderly HF patients with an EF >45%. After nearly 50 months of follow-up, there was no difference between the irbesartan and placebo arms on the composite outcome of all-cause mortality or cardiovascular hospitalization, or on any secondary outcome. Here again, the recruitment was slow and the number of patients who received an open label RAAS inhibitor during the course of the study, or dropped out, was high.

Despite the lack of demonstration of benefit for RAAS antagonists in HFPEF in outcome trials, a large prospective study of a cohort of unselected 16 216 HFPEF patients from Sweden suggests that the use of RAAS antagonists is associated with a lower all-cause mortality.15

### Table 1. Outcome trials in HFPEF.

<table>
<thead>
<tr>
<th></th>
<th>PEP-CHF</th>
<th>CHARM-PRESERVED</th>
<th>I-PRESERVE</th>
<th>TOPCAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>850</td>
<td>3023</td>
<td>4128</td>
<td>3445</td>
</tr>
<tr>
<td>Drug</td>
<td>perindopril</td>
<td>candesartan</td>
<td>irbesartan</td>
<td>spironolactone</td>
</tr>
<tr>
<td>Target dosage (mg/day)</td>
<td>4</td>
<td>32</td>
<td>300</td>
<td>30/45</td>
</tr>
<tr>
<td>Mean follow-up (months)</td>
<td>26.2</td>
<td>36.6</td>
<td>49.5</td>
<td>42 (estimate)</td>
</tr>
<tr>
<td>Age at inclusion (years)</td>
<td>76</td>
<td>67</td>
<td>72</td>
<td>68.6</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>76/75</td>
<td>67/60</td>
<td>72/68</td>
<td>68.6</td>
</tr>
<tr>
<td>Age at inclusion (%)</td>
<td>45/55</td>
<td>60/40</td>
<td>40/60</td>
<td>48/52</td>
</tr>
<tr>
<td>Ejection fraction at inclusion (%)</td>
<td>LVWMI 1.4-1.6</td>
<td>&gt;40</td>
<td>≥45</td>
<td>≥45</td>
</tr>
<tr>
<td>BNP/NT-proBNP at inclusion (pg/mL)</td>
<td>-</td>
<td>-</td>
<td>&gt;360 (NT-proBNP)</td>
<td>&gt;100 (BNP)</td>
</tr>
<tr>
<td>Geometric mean or median (* value at baseline (pg/mL)</td>
<td>453* (placebo)/335* (active)</td>
<td>-</td>
<td>354/341*</td>
<td>950* (NT-proBNP)/234* (BNP)</td>
</tr>
<tr>
<td>Primary composite end point</td>
<td>All-cause mortality/HF hospitalisation</td>
<td>CV death/HF hospitalisation</td>
<td>All-cause death/CV hospitalisation</td>
<td>CV death/HF hospitalisation/aborted cardiac arrest</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.92</td>
<td>0.89</td>
<td>0.95</td>
<td>N/A</td>
</tr>
<tr>
<td>P value</td>
<td>0.54</td>
<td>0.12</td>
<td>0.35</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 1.** Outcome trials in HFPEF.

**Abbreviations:** BNP, brain natriuretic peptide; CHARM, Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity; CV, cardiovascular; HF, heart failure; I-PRESERVE, Irbesartan in heart failure with PRESERVED systolic function; LVWMI, left ventricular wall motion index; N/A, not applicable; NT-proBNP, N-terminal pro-brain natriuretic peptide; PEP-CHF, Perindopril for Elderly People with Chronic Heart Failure; TOPCAT, Treatment Of Preserved Cardiac function heart failure with an Aldosterone antagonist.

Based on data from references 9-12.

**DIGOXIN**

In the DIG trial (Digitalis Intervention Group), a subgroup of 988 North American HF patients with an EF >45% was randomized to placebo or to Digoxin. After 37 months of follow-up, there was no difference in the primary composite outcome of HF death or hospitalization, all-cause mortality, or cause-specific mortality. The only favorable trend was a reduction in HF hospitalizations after two years, but this effect was no longer observed at the end of the trial.

**REASONS FOR TRIAL FAILURE**

**Selection of patients**

The diagnosis of HFPEF is difficult and requires three different components. The most challenging one is the identification of abnormalities in LV relaxation, filling, stiffness, or distensibility. The gold standard recommended by the ESC conser-
sus document is echo-Doppler and, more specifically, the ratio of transmitial Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity (E/E’), or the use of surrogate parameters such as evidence of left atrial or ventricular hypertrophy, or natriuretic peptides. However, the only outcome trial that used echocardiographic parameters of diastolic dysfunction was PEP-CHF and this has raised the issue of potential inclusion of patients who did not have HF, but may have had a noncardiac reason for dyspnea, such as obesity, or simply LV hypertrophy without HF.

However, an analysis of the rate of cardiovascular events suggests that the rate of cardiovascular outcomes, in particular HF hospitalizations or cardiovascular death, was much higher in CHARM-Preserved and I-PRESERVE than in hypertensive trials with or without LV hypertrophy.17

Another confounding factor is the threshold used for EF in the different outcome trials: a value of 40% as used in PEP-CHF and in CHARM-Preserved suggests an already markedly compromised systolic function, and this may have resulted in the inclusion of patients with a HFREF profile.

**Pathophysiology**

The diagnosis of HFPEF is clinically challenging, inclusion of such patients in clinical trials has proven to be difficult, leading to extended inclusion periods of time. In addition, several of these trials have suffered a high level of drop-in/drop out, leading to a potential dilution of the effect of the tested drug: in PEP-CHF, 40% of patients included in the perindopril arm and 36% in the placebo arm stopped the study treatment, whereas more than one-third were treated by another ACE inhibitor during the course of the trial. Similarly, in the I-PRESERVE trial, nearly 19% of the patients included in the irbesartan arm received an ACE inhibitor during the follow-up period and approximately one-third dropped out of the active arm.

**Trial design and conduct**

Since the diagnosis of HFPEF is clinically challenging, inclusion of such patients in clinical trials has proven to be difficult, leading to extended inclusion periods of time. In addition, several of these trials have suffered a high level of drop-in/drop out, leading to a potential dilution of the effect of the tested drug: in PEP-CHF, 40% of patients included in the perindopril arm and 36% in the placebo arm stopped the study treatment, whereas more than one-third were treated by another ACE inhibitor during the course of the trial. Similarly, in the I-PRESERVE trial, nearly 19% of the patients included in the irbesartan arm received an ACE inhibitor during the follow-up period and approximately one-third dropped out of the active arm.

**Outcomes**

Although cardiovascular death is the most prevalent cause of death in HFPEF and accounts for approximately 60% of fatal cases, the proportion of HFPEF patients dying from noncardiovascular causes is greater in HFPEF than in HFREF.18,19 Since it is unlikely that medications targeting the cardiovascular system impact noncardiovascular death, this may have diluted the potential benefit of these drugs in HFPEF.

**CURRENT TREATMENT IN PRACTICE**

In the absence of evidenced-based clinical practice guidelines, the background treatment of HFPEF differs from that used in HFREF. It is empirical and mostly oriented toward symptom relief. In a large meta-analysis pooling 41,972 patients with HF, including 10,347 with HFPEF (MAAGIC [Meta-Analysis Global Group In Chronic heart failure]), the rate of prescription of ACE inhibitors/angiotensin receptor blockers, β-blockers, spironolactone, diuretic agents, and digoxin was significantly lower than in patients with HFREF.24 On the contrary, the rate of prescription of calcium channel blockers was increased and this might reflect the impact of an underlying etiology (hypertension).25,26

**FUTURE PERSPECTIVES**

Various therapeutic approaches are currently being tested in HFPEF (Table II).27-29

**Spironolactone**

Mineralocorticoid receptor activation by aldosterone induces sodium retention, fibrosis, endothelial...
dysfunction and hypertrophy, and thus contributes to the development of HF. Small preliminary studies suggest that mineralocorticoid receptor activators may be effective in diastolic HF.

The Aldo-DHF trial (Aldosterone receptor blockade in Diastolic Heart Failure) enrolled 422 ambulatory patients with HFPEF who were randomized to spironolactone 25 mg/day or placebo and followed up for 12 months. Diastolic function assessed by the E/E’ ratio on Doppler echocardiography was significantly, but modestly, decreased by spironolactone, as well as LV mass, whereas there was no change in maximal exercise capacity (peak oxygen consumption [VO2]), patient symptoms, or quality of life. It was argued that patients enrolled in Aldo-DHF had only moderate cardiac dysfunction or symptom limitation and therefore mildly reduced exercise capacity. These favorable trends need to be compared with those of TOPCAT (Treatment Of Preserved Cardiac function heart failure with an Aldosterone antagonist), a large outcome trial which is close to completion (Table I). The primary objective of TOPCAT is to determine whether spironolactone up-titrated to a maximum of 45 mg/day improves a composite outcome of cardiovascular mortality, aborted cardiac arrest, or HF hospitalization in an elderly population of 3445 patients with HFPEF.

### Neprilysin inhibitors

LCZ696 is a “first in its class” angiotensin receptor–neprilysin (neutral endopeptidase 24-11) inhibitor which combines a neprilysin inhibitor prodrug effect with the angiotensin receptor blocker valsartan, in one single molecule. Neprilysin degrades biologically active natriuretic peptides and its inhibition results in an increase in intramyocardial cyclic 3’5’ guanosine monophosphate (c-GMP), which improves relaxation and hypertrophy. The expected effect of this new complex molecule is to prevent degradation of natriuretic peptides and block the action of angiotensin on its receptor.

In the PARAMOUNT trial (Prospective comparison of ARNI with ARB on Management Of heart failure with preserved ejection fraction Trial), 301 HFPEF patients were randomly assigned to LCZ696 titrated to 200 mg twice daily or to valsartan titrated to 160 mg twice daily and treated for 36 weeks. The primary end point was the change in NT-proBNP, a marker of LV stress from baseline to 12 weeks. NT-proBNP was significantly reduced compared with valsartan, but this difference was no longer significant at 36 weeks. Results were consistent across all prespecified subgroups except diabetic patients who had a greater reduction in NT-proBNP compared with nondiabetic patients. Left atrial volume and dimensions

<table>
<thead>
<tr>
<th>Aldo-DHF</th>
<th>PARAMOUNT</th>
<th>RELAX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>422</td>
<td>266</td>
</tr>
<tr>
<td>Drug</td>
<td>spironolactone</td>
<td>LCZ696 (angiotensin receptor–neprilysin inhibitor) vs valsartan</td>
</tr>
<tr>
<td>Target dosage (mg/day)</td>
<td>25</td>
<td>400 (LCZ696)/320 (valsartan)</td>
</tr>
<tr>
<td>Ejection fraction at inclusion (%)</td>
<td>≥50</td>
<td>≥45</td>
</tr>
<tr>
<td>NT-proBNP at inclusion (pg/mL)</td>
<td>-</td>
<td>≥400</td>
</tr>
<tr>
<td>NT-proBNP baseline geometric mean or median (*) (pg/mL)</td>
<td>158*</td>
<td>794 (LCZ696)/870 (valsartan)</td>
</tr>
<tr>
<td>Primary end point</td>
<td>E/E’ peak VO2</td>
<td>Change in NT-proBNP</td>
</tr>
<tr>
<td>Duration</td>
<td>12 months</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

**Table II. Proof-of-concept studies.**

**Abbreviations:** Aldo-DHF, Aldosterone receptor blockade in Diastolic Heart Failure; E/E’, ratio of transmural Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity; LV, left ventricular; NT-proBNP, N-terminal pro-brain natriuretic peptide; PARAMOUNT, Prospective comparison of ARNI with ARB on Management Of heart failure with preserved ejection fraction Trial; RELAX, phosphodiesterase-5 inhibition to improve clinical status and exercise capacity in diastolic heart failure; VO2, oxygen consumption.

*Based on data from references 27-29.*
were also significantly reduced at 36 weeks whereas no other echocardiographic measures including LV volumes, EF, or measures of diastolic function differed. The tolerability of the new compound was similar to that of valsartan. These results suggest that LCZ696 reduces LV pressure and wall stress in HFPEF, and warrant outcome studies in this condition.

**Phosphodiesterase-5 (PDE-5) inhibitors**

Endothelial dysfunction has been associated with HFPEF and predicts cardiovascular events in this condition. Impaired endothelium-mediated nitric oxide bioavailability may lead to abnormal activation of the c-GMP pathway, which is the secondary messenger of many signaling pathways and acts through the activation of c-GMP-dependent protein kinase-G (PKG). c-GMP is inactivated by PDE-5. Blockade of c-GMP catabolism by PDE-5 inhibition could exert an antihypertrophic effect in cardiomyocytes and improve relaxation. Experimental data suggest that PDE-5 overexpression induces cardiomyocyte hypertrophy and that it is reversed by a selective PDE-5 inhibitor, sildenafil.

A small study demonstrated a reduction in pulmonary pressure and an improvement in LV diastolic function and hypertrophy after 12 months of exposure to sildenafil. The RELAX trial (phosphodiesterase-RasE-5 inhibition to improve cLini-cal stAtus and eXercise capacity in diastolic heart failure) was designed to test the hypothesis that sildenafil would improve exercise capacity as assessed by the change in peak VO2 after 24 weeks of therapy, compared with placebo, in a study including 216 HFPEF patients. Sildenafil was started at a daily dose of 20 mg three times a day after 12 weeks. Long-term inhibition of PDE-5 by sildenafil had no effect on maximal exercise capacity, 6-minute walk distance, clinical status, quality of life, LV remodeling, diastolic function, or pulmonary artery pressure. In addition, there was a significant increase in NT-proBNP and endothelin-1, and a modest, but significant, worsening of renal function in the sildenafil group.

Several explanations have been put forward in order to explain these disappointing results: insufficient duration of the trial, absence of pulmonary hypertension unlike what was observed in the previous trial, and a high prevalence of chronotropic incompetence that may have contributed to exercise limitation. It is also noteworthy that these patients had a significantly increased plasma level of NT-proBNP at baseline, suggesting that they were in an advanced stage of the disease and therefore may have been too sick to benefit from the pharmacological intervention. In any case, the RELAX results do not support the potential benefit of a strategy blocking the PDE-5 pathway in HFPEF.

**Ranolazine**

A small sodium (Na+) influx occurring during the late phase of the action potential is called the late sodium current (I-Na+). This current becomes more pronounced in cardiac failure, leading to an increase in intracellular Na+ and activates the sarcolemmal Na+/calcium (Ca2+) exchanger in the reverse mode, leading to Ca2+ overload, impaired relaxation, and proarrhythmic afterdepolarizations. Ranolazine is a selective late I-Na+ inhibitor which has been shown to improve diastolic function in an experimental model, as well as in a small group of patients with stable coronary artery disease. The RALI-DHF trial (RAnoLazIne for the treatment of Diastolic Heart Failure) was a randomized double blind trial including 20 patients. The purpose of the trial was to study the effect of an intravenous infusion of ranolazine for 24 hours, followed by oral treatment for 13 days, on diastolic function assessed by both invasive hemodynamics and echocardiography. There was a modest reduction of 2 mm Hg LV end-diastolic pressure and pulmonary capillary wedge pressure after 30 minutes of infusion without changes in LV end-systolic pressure and systemic or pulmonary resistance. There was also a modest reduction in mean pulmonary arterial pressure under pacing conditions. Relaxation parameters were unchanged, as well as the E/E’ ratio after 22 hours. After 14 days of treatment, the investigators did not observe any significant change in echocardiographic or cardiopulmonary exercise test parameters, or in NT-proBNP. This proof-of-concept study suggests that acutely administered ranolazine modestly improves hemodynamic parameters, but not relaxation kinetics. However, it is difficult to draw any conclusion from this small study, and in particular, the short duration of the trial (14 days) does not allow assessment of whether ranolazine improves relaxation in HFPEF in the long term.

The ERIPE study (EUDRA CT number 2011-000 805 27) will evaluate the effects of ranolazine, uptitrated to 1000 mg twice daily (bid), on six-minute walking distance and on a series of echocardiographic/Doppler parameters in a group of 120 patients treated for 26 weeks.

**Ivabradine**

The sinoatrial node I_f current inhibitor ivabradine has been tested successfully in HFREF, in sinus rhythm,
and with elevated heart rate. The only known mechanism of action of this new compound is to reduce heart rate when elevated. Selective heart rate reduction improves diastolic filling by prolonging diastolic period without inducing negative lusitropy compared with β-blockers. In a mouse model of diabetes with diastolic dysfunction, ivabradine improved vascular stiffness, LV contractility, and diastolic function.

An unpublished study randomized 111 patients with HFPEF to ivabradine uptitrated to 7.5 mg bid (n=53) or placebo (n=56). After 2 months of exposure, resting heart rate was significantly decreased and exercise capacity was improved. On echocardiography, there was no change in left atrial dimension, whereas E-wave deceleration time and isovolumetric relaxation time were significantly improved. The short duration of the study (2 months) may not have been sufficient to observe any structural change.

Another proof-of-concept study is currently ongoing (EUDRA-CT, number 2012 002742-20). This study will enroll 400 HFPEF patients and will assess the potential benefit of ivabradine uptitrated to 10 mg bid on diastolic function echocardiographic parameters (E/E'), exercise capacity (six-minute walk test), and change in NT-proBNP plasma levels, after an exposure for eight months.

**ADVANCED GLYCATION END-PRODUCT (AGE) CROSS LINK BREAKERS**

AGEs are end-products formed by oxidative or nonoxidative reactions between proteins and carbon hydrates and form cross links in the extracellular matrix that may induce myocardial diastolic dysfunction. Accumulation of AGEs induces functional and structural changes in the myocardium and vessels. AGE cross-link breakers have been developed and tested in experimental models and in a small series of patients. In 23 elderly patients with diastolic HF, alagebrium administered twice daily in an open label for 16 weeks reduced LV mass and improved diastolic function. The BENEFICIAL trial (evaluating the efficacy and safety of alagebrium (ALT-711) in patients with chronic heart failure) tested this molecule vs placebo in 102 patients with HFREF (EF <45%), with an alagebrium dosage of 200 mg twice daily for 36 weeks. At the end of the study, 97 patients were suitable for analysis; alagebrium did not improve the primary end point or exercise capacity (peak VO₂), nor did it change diastolic function assessed by E' and the E/E' ratio, NYHA functional class, patient or physician global assessment, AGE accumulation as assessed by skin auto fluorescence, or NT-proBNP. These findings do not support the hypothesis of a beneficial effect of AGE cross link breakers in systolic HF. It is, however, noteworthy that this compound has not been tested in HFPEF patients or in diabetic patients.

**OTHER POTENTIAL TREATMENTS**

Intracellular Ca²⁺ cycling is impaired in HF. In particular, ryanodine receptors, which trigger Ca²⁺ release from the sarcoplasmic reticulum during systole, are improperly opened during diastole, thus leading to Ca²⁺ leakage, impaired relaxation, and a proarrhythmic state through delayed afterdepolarizations. Down regulation of the sarcoplasmic reticulum Ca²⁺ ATPase isofom 2a (SERCA 2a), which is responsible for the rapid reuptake of Ca²⁺ within the intracellular stores (sarcoplasmic reticulum) leads to impaired Ca²⁺ sequestration and prolonged myocardial relaxation.

Restoration of ryanodine receptor function has been tested with a new compound, K201, on in vitro models with favorable effects on cardiac function. Whether this approach will go beyond preclinical studies remains an open question. A different, nonpharmacological approach has been used to restore SERCA 2a function by gene transfer using an adenovirus vector in HFREF. The preliminary results of the CUPID trial (Calcium Upregulation by Percutaneous administration of gene therapy In cardiac Disease) appear promising and the translation of this approach to HFPEF deserves consideration.

**CONCLUSION**

The current management of HFPEF remains empirical due to the lack of clear evidence based therapies. Treatment is mainly oriented towards symptom relief and disappointing results have been published regarding potentially promising novel approaches. Due to the growing contribution of HFPEF to the global burden of HF, studies utilizing drugs targeting new pathophysiological pathways are eagerly awaited. The heterogeneity of the profile of patients enrolled so far in published trials outlines the need for a careful selection of inclusion criteria for forthcoming studies.
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Heart Failure With Preserved Ejection Fraction

Summaries of Ten Seminal Papers

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1. The pathogenesis of acute pulmonary edema associated with hypertension

2. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction...
   W. J. Paulus and others. Eur Heart J. 2007

3. Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights...

4. Pulmonary hypertension in heart failure with preserved ejection fraction: a community based study
   C. S. Lam and others. J Am Coll Cardiol. 2009

5. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment
   B. A. Borlaug and W. J. Paulus. Eur Heart J. 2011

6. Phenotypic and pathophysiological heterogeneity in heart failure with preserved ejection fraction...

7. The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction...
   Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). Eur Heart J. 2012

8. Echo-Doppler assessment of diastole: flow, function and haemodynamics
   T. C. Gillebert and others. Heart. 2003

9. Predictors of new-onset heart failure: differences in preserved versus reduced ejection fraction
   J. E. Ho and others. Circ Heart Fail. 2013

10. Risk factors for adverse outcomes by left ventricular ejection fraction in a contemporary heart failure population
    L. A. Allen and others. Circ Heart Fail. 2013

Selection of seminal papers by Luigi Tavazzi, MD, FESC, FACC
Maria Cecilia Hospital - GVM Care and Research
Ettore Sansavini Health Science Foundation - Cotignola - ITALY

Highlights of the years by Sherri Smith, PhD
Publications Office
The pathogenesis of acute pulmonary edema associated with hypertension


**AIM**
To test the hypothesis that many patients hospitalized with acute pulmonary edema in association with hypertension have transient left ventricular (LV) systolic dysfunction, which is no longer present when the LV ejection fraction (LVEF) is evaluated after treatment.

**POPULATION**
14 men and 24 women, mean age 67±13 y, all with pulmonary rales on presentation.

**SCHEMATIC DESIGN**
Two-dimensional color Doppler transthoracic echocardiography and blood pressure were taken at the initial therapy and repeated after clinical stabilization 1 to 3 days later.

**RESULTS** (NS except blood pressure)

<table>
<thead>
<tr>
<th></th>
<th>Acute admission</th>
<th>Stabilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF</td>
<td>0.50±0.15</td>
<td>0.50±0.13</td>
</tr>
<tr>
<td>Regional wall motion index</td>
<td>1.6±0.6</td>
<td>1.6±0.6</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>200±26</td>
<td>139±17</td>
</tr>
</tbody>
</table>

**CLINICOPATHOLOGICAL IMPLICATIONS**
Contrary to the hypothesis, acute-episode EF and regional wall motion were similar to those after stabilization. Half the patients presenting with acute pulmonary edema and hypertension had a normal EF, suggesting HF due to isolated diastolic (not systolic) dysfunction. Even in the patients with systolic dysfunction (stabilization EF < 0.50), acute-episode EF was similar to that after stabilization. This similarity suggests that diastolic dysfunction may also be an important contributor to acute hypertensive pulmonary edema in patients with baseline systolic dysfunction. Normal stabilization EF indicates isolated, transient diastolic dysfunction as the cause of pulmonary congestion since transient systolic dysfunction and severe acute mitral regurgitation are infrequent during acute episodes in these patients.

William Hanna, cocreator of the most successful television animation studio, Hanna Barbara, dies at the age of 90; Simeon Saxe-Coburg-Gotha, the last Tsar of Bulgaria, is sworn in as Prime Minister of Bulgaria, becoming the first monarch in history to regain political power through a democratic election; and an anonymous donor gives 100 million USD to Johns Hopkins Bloomberg School of Public Health to fund a state-of-the-art research facility for the prevention and cure of malaria.
How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology


Eur Heart J. 2007;28:2539-2550

AIM
Diastolic heart failure (DHF) currently accounts for >50% of all cases of heart failure (HF). DHF is also referred to as heart failure with normal left ventricular ejection fraction (HFNEF) because there is a diastolic LV dysfunction, which is made evident by slow LV relaxation and increased LV stiffness. In light of improved cardiac imaging and widespread availability of plasma natriuretic peptide assays, the diagnostic criterion for HFNEF needs to be updated, which is the purpose of the current study.

PROPOSED DIAGNOSTIC CRITERIA

Conclusive diagnosis of HFNEF:
• Signs or symptoms of HF: reduced peak exercise oxygen consumption (VO₂max) reduced VO₂max <25 mL/kg/min; low VO₂max <14 mL/kg/min).
• Normal or mildly abnormal systolic LV function: LVEF >50% + LV end-diastolic volume index <97 mL/m².
• Evidence of diastolic LV dysfunction: LV end-diastolic pressure >16 mm Hg, mean pulmonary capillary wedge pressure >12 mm Hg, or tissue Doppler (TD).

Presumptive diagnosis of HFPEF (TD 15∗ E/E´ >8 or elevated natriuretic peptides):
Confirmatory investigations:
• Blood flow Doppler of mitral valve or pulmonary veins.
• Echo measures of LV mass index or left atrial volume index.
• Electrocardiographic evidence of atrial fibrillation.

Patients with breathlessness and no signs of congestion follow the same strategy to focus on a high negative predictive value of successive investigations to exclude HFNEF.

CLINICAL IMPLICATIONS
Updated strategies for the diagnosis and exclusion of HFNEF are useful, not only for individual patient management, but also for patient recruitment in future clinical trials exploring therapies for HFNEF.

Cristina Fernandez de Kirchner is elected as the first female president of Argentina; archaeologists in western Japan discover a 2100-year-old melon; and the International Olympic Committee announces that Sochi, Russia, a Black Sea resort, will host the winter games in 2014: a first for Russia or the former Soviet Union.
**AIM**
To use echocardiographic and implantable hemodynamic monitor data to examine the pathophysiology of chronic compensated and acute decompensated heart failure (HF) in patients with systolic HF (SHF) vs diastolic HF (DHF).

**POPULATION**
A total of 274 patients with NYHA class III or IV HF were recruited into the COMPASS-HF study (Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure). Patients underwent echocardiography and Doppler studies and transmitted weekly implantable hemodynamic monitor data: right ventricular (RV) systolic pressure, RV diastolic pressure, an estimate of pulmonary artery diastolic pressure (ePAD), maximum positive and negative changes in pressure over time (dP/dt, dP/dt), heart rate, and activity.

**SCHEMATIC DESIGN**

![Schematic Design](image)

**RESULTS** *(see right)*
Percentage of women, age, systolic blood pressure, and history of hypertension were all significantly higher in the DHF group. (*P*<0.05 for all variables except ePAD).

**CLINICAL IMPLICATIONS**
Significant structural and functional differences were found between patients with SHF and those with DHF; however, elevated diastolic pressures play a pivotal role in the underlying pathophysiology of both chronic compensated and acute decompensated HF as much in SHF as in DHF.

<table>
<thead>
<tr>
<th></th>
<th>DHF</th>
<th>SHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF, %</td>
<td>58±8</td>
<td>24±10</td>
</tr>
<tr>
<td>End-diastolic dimension, mm</td>
<td>50±10</td>
<td>68±11</td>
</tr>
<tr>
<td>ePAD, mm Hg*</td>
<td>16±9</td>
<td>18±7</td>
</tr>
<tr>
<td>Diastolic distensibility index (ratio of ePAD to end-diastolic volume), mm Hg/mL</td>
<td>0.11±0.06</td>
<td>0.06±0.04</td>
</tr>
</tbody>
</table>

*Acute decompensated HF was associated with significant increases in ePAD, from 17±7 to 22±7 mm Hg in DHF and from 21±9 to 24±8 mm Hg in SHF.

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**2008**
Yves Saint Laurent, the first living fashion designer to be honored by the Metropolitan Museum of Art, dies at age 71 from brain cancer; Thomas Beatie, the world’s first pregnant man, gives birth to a daughter; and Cape Verde joins the World Trade Organization, becoming its 153rd member.
Pulmonary hypertension in heart failure with preserved ejection fraction: a community based study

C. S. Lam, V. L. Roger, R. J. Rodeheffer, B. A. Borlaug, F. T. Enders, M. M. Redfield

*J Am Coll Cardiol.* 2009;53:1119-1126

**AIM**
To measure pulmonary artery systolic pressure (PASP), define the prevalence and severity of pulmonary hypertension (PH: PASP >35 mm Hg), and assess the association between PASP and pulmonary venous hypertension in patients diagnosed with heart failure with preserved ejection fraction (HFPEF) compared with control patients with preclinical hypertensive heart disease without HF (HTN).

**POPULATION**
244 HFPEF patients (76±13 y; 45% male) and 719 HTN controls (66±10 y; 44% male). Patients and controls followed by Doppler echocardiography over 3 years with PASP derived from tricuspid regurgitation velocity, and pulmonary capillary wedge pressure (PCWP) estimated from E/e.’

**SCHEMATIC DESIGN**

<table>
<thead>
<tr>
<th>HFPEF (EF ≥50%) n=244</th>
<th>HTN (EF &lt;50%) n=719</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population-based observational study</td>
<td></td>
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</table>

**RESULTS** *(P<0.001)*
*(see right)*

**CLINICAL IMPLICATIONS**
PH is highly prevalent and often severe in HFPEF. While pulmonary venous hypertension contributes to PH, it does not fully account for the severity of PH in HFPEF, suggesting that a component of pulmonary arterial hypertension also contributes. The potent effect of PASP on mortality lends support for therapies aimed at pulmonary arterial hypertension in HFPEF.

Bolivia becomes the first South American country to declare indigenous people the right to govern themselves; paleontologists announce the discovery of an *Ardipithecus ramidus* fossil skeleton—the oldest remains of a human ancestor; and the H1N1 influenza outbreak becomes the first since the Hong Kong flu to be deemed a global pandemic.
Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment

B. A. Borlaug, W. J. Paulus

Eur Heart J. 2011;32:670-679

FACT
Half of all patients with heart failure (HF) have a preserved left ventricular ejection fraction (HFPEF).

CONUNDRUM
Yet morbidity and mortality in HFPEF are no better than in HF patients with reduced EF (HFREF). In particular, outcome has not improved in the past two decades, unlike in HFREF. Why?

PATHOPHYSIOLOGY
The answer—and dismal prognosis—likely reflects the complex multisystem involvement characteristic of all HF, regardless of EF: this includes skeletal muscle and vascular dysfunction, pulmonary hypertension, renal failure, anemia, and atrial fibrillation. In addition to the primary role of diastolic LV dysfunction, important determinants include resting and exercise-exacerbated systolic dysfunction, impaired ventricular-vascular coupling, abnormal exercise-induced and flow-mediated vasodilation, and chronotropic incompetence.

TREATMENT
Large-scale trials show no improvement in outcome vs placebo with either an angiotensin-converting enzyme inhibitor (perindopril) or angiotensin receptor blocker (candesartan, irbesartan), in contrast to the positive effects of both classes in HFREF.

CLINICOPATHOLOGICAL IMPLICATIONS
HFPEF is a major and growing public health problem in Europe and the USA. Despite improved understanding, there are still no treatments with proven benefit, despite advances in diagnostic algorithms, imaging, and invasive assessment that provide earlier and more accurate diagnosis in all forms of HF. While important advances have been made in our understanding of the hemodynamic and cellular pathophysiology of the diastolic and nondiastolic mechanisms of the disease, further research is urgently required to determine how to target these abnormalities better to reduce the substantial burden of morbidity and mortality in this form of HF, which is reaching epidemic proportions.

2011

NASA launches its Curiosity rover, the largest Mars rover to be built; the genetic code of Yersinia pestis, the causative agent of the 14th-century Black Death, is reconstructed by scientists using DNA fragments from bacteria isolated from the teeth of medieval corpses found in London; and Norway is the victim of twin terror attacks: the first, a bomb, which targeted government buildings in central Oslo; the second, a massacre at a youth camp on the island of Utøya
Phenotypic and pathophysiological heterogeneity in heart failure with preserved ejection fraction [editorial]

A. M. Shah, S. D. Solomon

Eur Heart J. 2012;33:1716-1717

This EDITORIAL introduces two papers on the clinical features and pathophysiology of heart failure with preserved ejection fraction (HFPEF):


THE CLINICAL CHALLENGE

HFPEF is increasingly common, and causes substantial morbidity, mortality, and resource utilization, particularly among the elderly. Pathophysiological characteristics resemble those in HF with reduced EF (HFREF); patients experience similar rates of HF rehospitalization, functional decline, and face a significantly higher risk of death than age-matched controls. Despite multiple randomized controlled trials, no disease-specific therapy exists to improve prognosis in this heterogeneous syndrome.

THE CHALLENGE PERSISTS

Ho et al reported demographic and clinical findings at HF presentation that provided only modest discrimination of HFPEF compared with HFREF.

Ohtani et al presents a novel echocardiographic discriminator of LV function: the diastolic wall strain (DWS) index. However, the heterogeneity of DWS values in the HFPEF group was such that there was significant overlap with normal controls.

CONCLUSION

Shared risk factors leading to coupled abnormalities of cardiac systolic and diastolic performance underlie HF across the spectrum of LVEF. Both papers reinforce the striking heterogeneity of HFPEF and the substantial pathophysiological overlap between HFPEF, HFREF, and normal ejection fraction. They also support the growing belief that diastolic function abnormalities may not be the only pathophysiological factors at play in HFPEF and that systolic abnormalities may be just as central. Limited understanding of the clinical and pathophysiological heterogeneity underlying the HFPEF syndrome critically impairs the development of effective therapeutic strategies to address this growing public health concern.

2012

Ma Ying-Jeou, a Taiwanese politician, wins re-election as President of the Republic of China with 51% of the vote; French Polynesia establishes the world’s largest shark sanctuary, protecting all shark species from fishing in a 4.7 million square kilometers area; and The Lion King overtakes The Phantom of the Opera to become the highest grossing Broadway show.
The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis

Meta-analysis Global Group in Chronic Heart Failure (MAGGIC)

*Eur Heart J.* 2012;33:1750-1757

**AIM**
To resolve the inconsistent results of previous comparisons of survival between patients with heart failure with preserved ejection fraction (HFPEF) and heart failure with reduced ejection fraction (HFREF) by undertaking a meta-analysis using individual patient data.

**POPULATION**
41 972 HF patients with EF data from 31 studies.

**SCHEMATIC DESIGN**

| 41 972 HF patients | EF ≥50%, n=10 347
|-------------------|------------------
| Meta-analysis     | EF <50%, n=31 625 |

**RESULTS** *(see right)*

**CLINICAL IMPLICATIONS**
Mortality in patients with HFPEF is lower than in those with HFREF (adjusted for age, gender, etiology, history of hypertension, diabetes, and atrial fibrillation). The risk of death does not increase notably until EF falls below 40%. However, absolute mortality is still high in patients with HFPEF highlighting the need for a treatment to improve prognosis.

<table>
<thead>
<tr>
<th></th>
<th>HFPEF</th>
<th>HFREF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>71±12</td>
<td>66±12</td>
</tr>
<tr>
<td>Women, %</td>
<td>50</td>
<td>28</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>51</td>
<td>41</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>27</td>
<td>18</td>
</tr>
<tr>
<td>Ischemic etiology, %</td>
<td>43</td>
<td>59</td>
</tr>
<tr>
<td>ACE inhibition, %</td>
<td>75</td>
<td>44</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>60</td>
<td>31</td>
</tr>
<tr>
<td>Deaths per 1000 patient-years</td>
<td>60</td>
<td>31</td>
</tr>
</tbody>
</table>

*(all results \(P<0.001\))

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*Paedophryne amauensis*, a frog that measures just 7 mm in length and is the world’s smallest known vertebrate, is formally described by researchers in the United States; Queen Elizabeth II marks her 60th anniversary as Britain’s Monarch, the second longest reigning Monarch after Queen Victoria; and the British Library purchases *The St Cuthbert Gospel*, Europe’s oldest intact book, for 9 million pounds.
AIM
To highlight the most clinically relevant aspects of the latest European Association of Echocardiography/American Society of Echocardiography recommendations for the evaluation of left ventricular (LV) diastolic function by echocardiography.

DIASTOLE PHYSIOLOGY
- Diastolic function is related to myocardial relaxation and passive LV properties.
- Myocardial relaxation is determined by load, inactivation, and dyssynchrony.
- LV stiffness is determined by cardiomyocyte properties, extracellular matrix, and LV geometry.

GENERAL MEASURES OF DIASTOLIC FUNCTION
- LV mass, optimally acquired with 3D echocardiography, and scaling LV mass for body surface area (m²) or height (g/m¹.7) depending on the clinical question.
- Left atrium (LA) volume, scaled accordingly.
- Pulmonary artery systolic pressure and venous pressures.

SPECIFIC MEASURES OF DIASTOLIC FUNCTION
- Annular motion during rapid filling (e´) at the septal and lateral annulus.
  - Septal and lateral e´ values are averaged.
  - In selected cases septal or lateral e´ is not a reliable marker of diastolic function.
  - e´ is reduced in all degrees of diastolic dysfunction.
- Mitral inflow signal varies with filling pressure and is the best parameter of filling pressure for assessing serial echocardiograms in the same patient. Patterns include normal, impaired relaxation, pseudo-normal, and restrictive.

GRADING OF DIASTOLIC DYSFUNCTION
- Presence or absence of diastolic dysfunction relies on annular velocity e´ and LA size.
- Dysfunction is graded as 1 (impaired relaxation), 2 (pseudo-normal filling), or 3 (restrictive filling) based on mitral inflow and E/e´ ratio, supplemented in doubtful cases by the pulmonary vein signal or mitral inflow signal during the Valsalva maneuver.

DOPPLER ECHOCARDIOGRAPHY EVALUATION OF FILLING PRESSURES
- Feasible in most cases, even severe systolic HF.
- Based mainly on the E/e´ ratio and mitral inflow signal.
- Requires additional measures when E/e´ values are in the intermediate range or when mitral inflow is (pseudo)-normal.
- E/e´ is unreliable as a predictor of filling pressures in selected disease states.

Echo-Doppler assessment of diastole: flow, function and haemodynamics

T. C. Gillebert, M. De Pauw, F. Timmermans
Heart. 2013;99:55-64

Nelson Mandela, South Africa’s first black chief executive and the 1993 Nobel Peace Prize recipient, dies at the age of 95; DNA testing confirms that a medieval skeleton unearthed in Leicester, UK is that of the defeated King Richard III; and the most destructive meteor to strike Earth since 1908 impacts Chelyabinsk, Russia
Predictors of new-onset heart failure: differences in preserved versus reduced ejection fraction

J. E. Ho, A. Lyass, D. S. Lee, R. Vasan, W. B. Kannel, M. G. Larson, D. Levy

Circ Heart Fail. 2013;6:279-286

AIM
To identify clinical predictors of new-onset heart failure (HF) and explore the differences in risk factors predisposing patients to the two subtypes of HF: HF with preserved ejection fraction (HFPEF), which now accounts for half the total HF population, and HF with reduced ejection fraction (HFREF).

POPULATION
457 cases of new-onset HF with LVEF evaluation at diagnosis between 1981 and 2008 in 6340 Framingham Heart Study participants (60±12 y), classified into HFPEF (n=196 [43%]) and HFREF (n=261 [56%]) on the basis of EF >45% vs ≤45%.

SCHEMATIC DESIGN
Cox multivariable regression was used to examine predictors of 8-year risk of incident HF and competing-risks analysis to identify predictors that differ between HFPEF and HFREF.

RESULTS
Strongest predictors of overall HF (P≤0.0025):
- Older age.
- Diabetes mellitus.
- History of valvular disease.

Predictors of HFPEF only:
- Higher body mass index.
- Smoking.
- Atrial fibrillation.

Predictors of HFREF only:
- Male sex.
- Higher total cholesterol.
- Higher heart rate.
- Hypertension.
- Cardiovascular disease.
- Left ventricular hypertrophy.
- Left bundle-branch block.

CLINICAL IMPLICATIONS
Distinct clusters of risk factors determine the risk for HFPEF and HFREF, thus highlighting differences in pathogenesis; this knowledge can be used to design clinical trials for HF prevention strategies targeting either HFPEF or HFREF. The findings are particularly relevant to individuals without known structural heart disease, but who are at risk for HF; eg, angiotensin-converting enzyme inhibitors can reduce mortality in asymptomatic LV dysfunction. The identification of specific risk factors for HF subtypes could help tailor screening strategies (eg, biomarkers or imaging) to identify at-risk individuals who may benefit from specific therapies.

Abraham Nemeth, a blind American mathematician and creator of the Nemeth Braille Code for Mathematics and Science Notation, dies at the age of 95;
Pope Benedict XVI announces his resignation, the first pope to resign since 1415; and China lands the Jade Rabbit robot rover on the moon, making it the first soft landing on the moon in 37 years.
Risk factors for adverse outcomes by left ventricular ejection fraction in a contemporary heart failure population


_Circ Heart Fail._ 2013;6:635-646

AIM
To establish the relative importance of common predictor variables for important clinical outcomes across strata of left ventricular ejection fraction (EF) values in patients with heart failure (HF).

POPULATION
30 094 ambulatory adults with HF belonging to 4 integrated health care systems in the Cardiovascular Research Network. EF was stratified as preserved (HFPEF: ≥50%), borderline (HFB EF: 41% to 49%), and reduced (HFREF: ≤40%).

SCHEMATIC DESIGN

<table>
<thead>
<tr>
<th>30 094 patients with LV systolic function data (quantitative and qualitative EF)</th>
<th>HFPEF: n=14 907 (49.5%)</th>
<th>HFB EF: n=4862 (16.2%)</th>
<th>HFREF: n=10 325 (34.3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort study</td>
<td>HFPEF</td>
<td>HFB EF</td>
<td>HFREF</td>
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RESULTS
Significant risk factors (P<0.01) per outcome in the HFPEF and HFB EF strata vs HFREF were assessed with a median follow-up of 1.8 y.

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<tr>
<th>All-cause death</th>
<th>Dyslipidemia &amp; hypertension</th>
<th>Low-density lipoprotein</th>
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<tr>
<td>HF-related hospitalization</td>
<td>Systolic blood pressure</td>
<td>Age</td>
</tr>
<tr>
<td>All-cause hospitalization</td>
<td>Systolic blood pressure</td>
<td>Age &amp; hemoglobin</td>
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CLINICAL IMPLICATIONS
Multivariable models for each of the 3 outcomes were highly consistent across the 3 strata. Very few risk factors significantly interacted with EF for any outcome. Although EF dictates responsiveness to certain HF therapies, common risk factors perform similarly across all EF strata, with the number of significant differences differing little from that predictable by chance alone. HF risk models using traditional risk markers can thus be applied to broad HF populations.

François Jacob, a French biologist who shared the 1965 Nobel Prize in Medicine with Jacques Monod and André Lwoff, dies at age 92; Estonia becomes the first country to establish a national system of fast chargers for electric cars; and Scotland defeats Sweden to win the 2013 World Women’s Curling Championship
Heart Failure With Preserved Ejection Fraction

Bibliography of One Hundred Key Papers

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