

Heart failure with preserved ejection fraction

Improving diagnosis and management

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Heart failure with preserved ejection fraction (HFpEF) is increasing in prevalence and often presents a diagnostic and therapeutic dilemma. The use of well-defined diagnostic criteria and exercise testing improves the accuracy of diagnosis, and new drugs and devices are being developed to treat these patients.

Case study

Ms DG, aged 72 years, presents with a four-week history of progressive exertional dyspnoea, particularly with inclines, as well as fatigue and mild peripheral oedema. She has a past history of hypertension. She is obese (body mass index, 32 kg/m²), her blood pressure is 160/90 mmHg and she has no significant cardiorespiratory abnormalities. Blood tests reveal a normal haemoglobin level and mildly impaired renal function. Lung function testing is unremarkable.

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KEY POINTS

- Heart failure with preserved ejection fraction (HFpEF, previously known as diastolic heart failure) is equally as common as heart failure with reduced ejection fraction (HFrEF, systolic heart failure) but is less well understood.
- HFpEF is an emerging epidemic, due to the increasing age of the population as well as the increasing incidence of common risk factors such as obesity and hypertension.
- Recognition of the typical signs and symptoms of heart failure in the setting of specific echocardiographic features is key to diagnosis. The diagnosis can be confirmed with exercise right heart catheterisation.
- Key principles of management in patients with HFpEF are blood pressure control, physical activity, optimisation of comorbidities and judicious volume management.
- Few therapies are effective at reducing morbidity or mortality in HFpEF at present. Active research is under way to develop appropriate diagnostic and management strategies.

1. CLASSIFICATION OF HEART FAILURE¹**Heart failure with reduced ejection fraction – HFrEF**

LVEF <40%

‘Grey zone’

Recently termed heart failure with mid range ejection fraction – HFmrEF
LVEF between 40 to 50%

Heart failure with preserved ejection fraction – HFpEF

LVEF >50%

Abbreviation: LVEF = left ventricular ejection fraction.

A transthoracic echocardiogram shows normal systolic function with an ejection fraction of 65%, with mild left ventricular hypertrophy and no valvular pathology. Comment is made on the presence of diastolic dysfunction, with an enlarged left atrium and elevated E/e' ratio.

You suspect that this patient may have heart failure with preserved ejection fraction. How would you confirm the diagnosis, and what treatment options do you offer?

Cardiovascular disease (CVD) is one of the most prevalent causes of death and disability, both in Australia and elsewhere. Although coronary artery disease accounts for a significant portion of this burden, improvements in access to care, primary prevention, medical therapy and percutaneous coronary intervention have significantly reduced death rates and hospitalisation over the past decade.

The clinical syndrome of heart failure (HF) is an increasingly prevalent form of CVD. HF results from the advanced manifestation of coronary artery disease and a range of other predisposing factors including, but not limited to, hypertension, ageing, diabetes, excessive alcohol consumption and genetic determinants together with a multitude of other factors. From a physiological standpoint, HF is

often classified on the basis of the left ventricular ejection fraction (LVEF) as a surrogate for systolic performance (Box 1). Previously, HF with preserved ejection fraction (HFpEF) was categorised as an ejection fraction of 40% or greater; recent classifications, however, have suggested the inclusion of a ‘grey zone’, covering the LVEF range 40 to 50%.¹ This suggestion is yet to be integrated into mainstream clinical practice and has been designed to stimulate research into patients with borderline systolic function.

HF with reduced ejection fraction (HFrEF) is an entity that is well recognised by physicians and health practitioners for its impact on mortality and morbidity.² In contrast, the syndrome of HFpEF, in which the principal physiological abnormality is impairment of diastolic function, is less well understood. Perhaps surprisingly, the symptomatic severities of HFpEF and HFrEF are often similar, their prevalences are similar and their mortality rates are also comparable.^{3,4} Therefore, the common misconception that a diagnosis of HF cannot be made in the presence of normal systolic function should be discounted.

Substantial incremental advances in the care of patients with HFrEF have been made over the past two decades or so. Medical therapy with ACE inhibitors and angiotensin II receptor blockers (ARBs), beta blockers and aldosterone antagonists have all demonstrated a mortality benefit, as have implantable devices such as implantable cardiac defibrillators and cardiac resynchronisation therapy with biventricular pacemakers. More recently, the addition of angiotensin receptor-neprilysin inhibitor therapy has shown promising results with reductions in mortality.⁵

Despite HFpEF having a similar prevalence as HFrEF and also a rising incidence, trials in therapy for this type of HF have been negative regarding effects on patient survival, and evidence for symptomatic benefit has also been limited. The reason for the apparent lack of

advancement in HFpEF therapy is complex, and includes heterogeneity of trial inclusion criteria, variable disease definitions, limited mechanistic understanding and the complexity and multisystem nature of the disorder. A recent statement from the American Heart Association highlighted the lack of studies in patients with HFpEF, particularly regarding the understanding of the mechanisms and the heterogeneity across the older population.⁶

Considering the marked rise in prevalence of HFpEF, in part due to its increased recognition, this is no longer a disease that can be ignored and there is an urgent need for improved clinician recognition, accurate diagnosis and effective treatment to fill this therapeutic gap.⁷ This article provides an evidence based overview of HFpEF as applied to clinical practice, and includes discussion of the epidemiology, mechanisms, diagnostic criteria and, importantly, management.

Epidemiology and risk profile

An estimated 1 million people in Australia now have HF, with half of those having HFpEF.⁸ Moreover, it has been estimated that underlying HFpEF may account for up to 65% of patients hospitalised for HF.⁷ Although diagnostic precision is limited in patients with multiple contributors for their dyspnoea, the overall prevalence of HFpEF has been estimated as being between 1.1 and 3% of the whole population, with many more patients having subclinical diastolic dysfunction.⁹ In patients over the age of 65 years, the prevalence ranges from 3.1 to 5.5%.¹⁰

The increase in HFpEF prevalence reflects the changing demographic of the general population, including increasing age, obesity and diabetes and the continued presence of poorly controlled hypertension (Box 2).⁸ Each of these factors is known to influence myocardial and vascular stiffness, pulmonary systolic pressure and left ventricular diastolic dysfunction.⁷ Community studies of healthy participants demonstrate that derangements in diastolic

2. RISK FACTORS FOR THE DEVELOPMENT OF HFpEF

- Age
- Obesity
- Sedentary lifestyle
- Hypertension
- Diabetes mellitus
- Chronic kidney disease
- Coronary artery disease

Abbreviation: HFpEF = heart failure with preserved ejection fraction.

function are more common than in systolic function, and progress at a greater rate.¹¹ Noncardiac comorbidities such as chronic kidney disease, anaemia, malignancy and thyroid dysfunction are also common in HFpEF; chronic kidney disease in particular may play a dual role in that it contributes to extracardiac volume overload and the development of the cardiorenal syndrome.¹²⁻¹⁴

Many patients with HFpEF are obese, a predictor not seen in patients with HFrEF, and the adverse cardiac remodelling and biochemical abnormalities associated with the metabolic syndrome contribute to the development of increased myocardial stiffness and diastolic dysfunction.^{15,16} The hypothesis of comorbidities driving the myocardial dysfunction seen in HFpEF has been proposed as the mechanism behind the myocardial dysfunction, and the total impact of comorbidities on functional capacity is higher in patients with HFpEF than in those with HFrEF.^{17,18} Large scale studies are in progress to target this mechanism.¹⁹

Definition and diagnosis

HF is a clinical syndrome of typical symptoms and signs that reflect the underlying reduction in cardiac output and/or elevated intracardiac filling pressures at rest or with stress.²⁰ HFpEF has remained a diagnostic challenge with variable definitions over the past decade, culminating in the development of a stricter definition in the

recently published European Society of Cardiology guidelines (Box 3).¹

The diagnosis of HFpEF can be difficult to make, and often occurs after much delay and consideration of alternative diagnoses for dyspnoea. For most patients, recognition of the typical features of HFpEF on resting echocardiography with the clinical syndrome of HF aids the diagnosis, and where the diagnosis remains unclear stress testing should be considered. An approach to diagnosing HFpEF is given in the Flowchart.

Symptoms and signs

Although many symptoms are associated with HF, they are often relatively nonspecific. In this context, the Framingham diagnostic criteria from 1971 have been well validated as a more specific set of symptoms and signs on which to base the diagnosis of HF.²¹ The major Framingham criteria are paroxysmal nocturnal dyspnoea or orthopnoea, neck vein distension, rales, cardiomegaly, acute pulmonary oedema, S3 gallop, increased venous pressure (greater than 16 cm water), circulation time 25 seconds or longer and hepatojugular reflux; the minor criteria are ankle oedema, night cough, dyspnoea on exertion, hepatomegaly, pleural effusion, vital capacity decreased one-third from maximum and tachycardia (120 beats/minute or higher). Weight loss of 4.5 kg or more in five days in response to treatment is a major or minor criterion.

It is important to recognise that the initial diagnosis of HF is clinical and that echocardiography can provide additional information regarding aetiology, stratification (using ejection fraction) and filling pressures. Resting endocardiography studies alone, however, do not exclude HF as a diagnosis.

BNP levels

Levels of natriuretic peptides such as brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) have been widely used in the diagnosis of HF.²² These proteins are released into the bloodstream in

3. DIAGNOSTIC CRITERIA FOR HFPEF^{1*}

- Presence of symptoms and signs typical of heart failure
 - note that signs are not always evident in patients with HFpEF; as filling pressures may only increase with exercise, the JVP may not be elevated at rest
 - typical signs and symptoms include breathlessness, reduced exercise tolerance, fatigue and ankle swelling; features such as a displaced apex beat and third heart sound are absent
- A preserved ejection fraction (LVEF $\geq 50\%$)
 - previous studies have included patients with LVEF $\geq 40\%$
 - new guidelines suggest a grey zone between LVEF 40 and 50%
- Elevated levels of natriuretic peptides[†]
 - BNP level ≥ 35 pg/mL
 - NT-proBNP level ≥ 125 pg/mL
- Objective evidence of other cardiac structural or functional alteration
 - either left ventricular hypertrophy (increased left ventricular mass index) or left atrial enlargement
 - diastolic dysfunction on echo (increased E/e' or decreased e') or cardiac catheterisation (increased LVEDP or PCWP, particularly with exercise)

Abbreviations: BNP = brain natriuretic peptide; HFpEF = heart failure with preserved ejection fraction; JVP = jugular venous pressure; LVEDP = left ventricular end diastolic pressure; LVEF = left ventricular ejection fraction; NT = N-terminal; PCWP = pulmonary capillary wedge pressure.

* Adapted from the 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure.¹

[†] These values are for non-acute presentations. For acute presentations, BNP ≥ 100 pg/mL and NT-proBNP ≥ 300 pg/mL should be used. Note that atrial fibrillation, age and renal failure may raise natriuretic peptide levels and the value may be disproportionately low in obese patients.

the setting of increased ventricular wall stress.²³ In patients with HFpEF this increased wall stress may only occur with increased exertion, with up to 30% of patients having a normal BNP at rest.²⁴

AN APPROACH TO DIAGNOSING HEART FAILURE WITH PRESERVED EJECTION FRACTION

Patient presents with exertional dyspnoea

- Take history and perform physical examination
- Measure natriuretic peptides
- Exclude other causes (pulmonary disease, ischaemic heart diseases, anaemia, physical deconditioning)
- Assess risk factor profile (advanced age, hypertension, raised BMI)

Clinical diagnosis of heart failure made when following diagnostic criteria met:

- Presence of typical symptoms and signs of heart failure (including breathlessness, reduced exercise tolerance, fatigue and ankle swelling) – features such as a displaced apex beat and third heart sound may be absent in heart failure
- Elevated natriuretic peptides (BNP ≥ 35 pg/mL or NT-proBNP ≥ 125 pg/mL)
- Other causes excluded (pulmonary disease, ischaemic heart diseases, anaemia, physical deconditioning)

Perform transthoracic echocardiography (resting)

The following features on resting echocardiography are consistent with a diagnosis of HFpEF (not all need be present)

- Raised pulmonary pressures (TR jet velocity >2.8 m/s)
- Left atrial enlargement (left atrial volume index >34 mL/m²)
- Raised E/e' ratio (≥ 13)*
- Increased wall thickness (LV mass index >115 g/m² for men; >95 g/m² for women)

Consider exercise study in consultation with cardiologist to confirm impaired diastolic performance and elevated filling pressures

- Exercise right heart catheterisation – the gold standard measurement of haemodynamics, but not available in all centres
- Stress echocardiography – noninvasive, but relies on good image quality and the presence of tricuspid regurgitation

Abbreviations: BMI = body mass index; BNP = brain natriuretic peptide; HFpEF = heart failure with preserved ejection fraction; LV = left ventricle; NT = N-terminal; TR = tricuspid regurgitant; * E/e' measured on tissue Doppler echocardiography.

Echocardiography

Echocardiography provides a widely available way of assessing systolic function, using either two- or three-dimensional measurements of ejection fraction together with newer measures such as longitudinal strain. The widespread use of ejection fraction as a measure of systolic function stems from its utility as a prognostic

measure.²⁵ For the purposes of categorisation an LVEF greater than 50% is defined as normal, however measurements can vary significantly, with a measurement error of up to 10%.

Echocardiography also provides several indices of diastolic function and diastolic filling pressure that are part of the basis of the diagnosis of HFpEF.²⁶ Of these, the

E/e' value, the ratio of the peak early mitral inflow velocity (E) to the early diastolic mitral annular velocity (e'), is often used to measure filling pressure because of its ease of acquisition and interpretation, with a value of 13 or greater considered abnormal.¹

Echocardiography can also accurately assess valvular heart disease and pericardial disease, other important causes of HF.

Diastolic stress testing

Across the spectrum of HF, most patients only experience symptoms during activity (i.e. excluding NYHA Class IV patients). For patients with HFpEF and exertional symptoms, the confirmation of impaired diastolic performance and elevated filling pressures may be difficult at rest. Accordingly, diastolic stress testing can be performed with either exercise echocardiography or with invasive haemodynamic measurements in the cardiac catheterisation laboratory.

Exercise echocardiography requires specialist experience and can be challenging in patients with larger body mass index and with concomitant chronic lung disease.

The definitive diagnosis can be made using exercise right heart catheterisation, confirming the presence of elevated filling pressures, with a significant rise in pulmonary capillary wedge pressure with exercise, although this technique is largely limited to specialist centres.²⁷ Although invasive, the test offers more detailed information than exercise echocardiography, and can often be performed via the brachial veins, with patients discharged an hour after the procedure.

Treatment

The heterogeneity of the patient population, the diverse clinical phenotype and difficulties with a clear definition around HFpEF have led to largely negative clinical trials and a paucity of effective treatment options. Despite these limitations, a careful application of the trial outcomes

together with a mechanistic understanding develops basic principles for the treatment of the patient with HFpEF, as listed in Box 4.²⁸

Lifestyle modification

Consistent with HFpEF being more common in patients with advanced age and obesity, lifestyle modification may play a significant role in reducing the symptom burden of these patients. Although the use of low sodium diets has been called into question recently in the broader population, there is evidence that a low sodium diet (e.g. the DASH [Dietary Approaches to Stop Hypertension] diet) not only reduces blood pressure but improves echocardiographic parameters of diastolic function.²⁹

Exercise intolerance is the hallmark symptom of patients with HFpEF.³⁰⁻³⁴ Lower lean body mass, reduced endothelial function and arterial stiffness have all been postulated as mechanisms through which exercise training may improve physical function.³⁴ Small trials of exercise training have demonstrated improvements in peak oxygen uptake and quality of life, although no significant changes in diastolic or endothelial function were seen.^{35,36}

Management of comorbid conditions

It has been proposed that the root cause of myocardial, vascular and peripheral dysfunction in patients with HFpEF may be instigated by the pro-inflammatory milieu generated by the presence of multiple comorbid conditions.^{17,37-39} Increasing numbers of comorbidities correlate with increasing hospital admissions, and patients with HFpEF have higher rates of noncardiac comorbidities compared with those with HFrEF.¹⁴ Patients with HFpEF who have diabetes have greater left ventricular wall thickness and reduced physical function compared with those with HFpEF without diabetes.⁴⁰ Patients with COPD have a worse prognosis in HFpEF than seen with HFrEF.¹⁴

Pharmacological therapy

Diuretics

Pulmonary congestion is one of the key limitations to exercise capacity and a cause of dyspnoea in patients with HFpEF, and a balance needs to be made between the often coexistent renal impairment and the risk of overdiuresis with worsening renal function. Patients with HFpEF also tend to have a relatively small left ventricular cavity, with a small stroke volume that can be adversely affected by excessive diuresis.⁴¹

ACE inhibitors and angiotensin receptor blockers

ACE inhibition has become a pharmacological mainstay in the treatment of patients with low ejection fraction HF (i.e. HFrEF), significantly reducing morbidity and mortality and also beneficially altering ventricular remodelling.^{42,43} Neurohormonal activation is evident across the spectrum of HF, irrespective of ejection fraction; however, one study has shown benefits on HF hospitalisation with ACE inhibitor therapy within the first year, but did not achieve its primary endpoint.⁴⁴

Two large trials have examined the role of angiotensin receptor blockade in patients with HFpEF. I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction Study), a large trial of more than 4000 patients with HFpEF, with clinical characteristics typical of HFpEF, showed no impact of irbesartan on death, hospitalisation or quality of life.⁴⁵ CHARM-Preserved (Candesartan in Heart Failure – Assessment of Mortality and Morbidity; in patients with LVEF higher than 40%) demonstrated a modest impact of candesartan on hospitalisation in an HFpEF, although it is important to note the less stringent entry criteria in this trial, including inclusion of patients with an ejection fraction down to 40%.⁴⁶

Aldosterone blockade

Aldosterone has a major role in myocardial collagen formation, suggesting a

4. PRINCIPLES OF MANAGEMENT IN PATIENTS WITH HFPEF²⁸

A: Avoid tachycardia

Use digoxin or beta blockers in patients with atrial fibrillation

B: control Blood pressure

ACE inhibitors, angiotensin receptor blockers and mineralocorticoid receptor antagonists may be of greatest benefit due to the physiological benefits seen in HFREF; further studies are required

C: treat Comorbid conditions

Optimise cardiac and noncardiac conditions (commonly atrial fibrillation, pulmonary disease, anaemia and obesity)

D: relieve congestion with Diuretics

Judicious use of loop diuretic with careful monitoring of renal function

E: encourage Exercise training

Improves exercise capacity and physical function

Abbreviations: ACE = angiotensin converting enzyme; HFpEF = heart failure with preserved ejection fraction.

role for spironolactone in the treatment of patients with HFpEF. Early trials demonstrated a reduction in left ventricular filling pressures, culminating in the international TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial), which enrolled 3445 patients.⁴⁷ Although the study was neutral regarding mortality and hospitalisation, post hoc analysis demonstrated significant regional variation in outcomes between patients enrolled in Russia/Georgia and those from the Americas, with the latter group demonstrating a significant reduction in cardiovascular death and hospitalisation for HF.⁴⁸ In support of these findings, a smaller randomised study of 131 patients with HFpEF demonstrated improvements in exercise capacity and echocardiographic parameters of diastolic function after taking spironolactone for six months.⁴⁹

These findings support future trials with aldosterone antagonists. However, it is important to keep in mind that impaired renal function and hyperkalaemia were more common in patients taking spironolactone, particularly in the patients who gained most benefit, and that renal function and biochemistry must be carefully monitored for patients on these agents.

Heart rate modification

Diastole is shortened during tachycardia, and a reduction in heart rate would be presumed to improve symptoms in patients with HFpEF. Trials of beta blockers have been negative in this regard, potentially due to the presence of chronotropic incompetence in certain patients with HFpEF.^{50,51} Trials of heart rate modification with ivabradine, an If-channel blocker with effects on heart rate but not blood pressure, have shown early positive results, but not consistently across all studies.⁵²⁻⁵⁴

Other pharmacotherapy

Pulmonary hypertension secondary to elevated left ventricular pressures is a key component in the pathophysiology of HFpEF, however trials of sildenafil, soluble guanylate cyclase inhibitors and isosorbide mononitrate have been neutral.⁵⁵⁻⁵⁷ Nephylisin inhibition, recently demonstrated to reduce mortality with startling success in patients with HFrEF, is under investigation in patients with HFpEF.^{5,58}

Device therapy

The management of patients with HFrEF has been notable for the beneficial combined effects of pharmacotherapy and device therapy, including implantable cardiac defibrillators and cardiac resynchronisation therapy demonstrating significant impacts on morbidity and mortality.^{1,59}

In patients with HFpEF, the fundamental physiological target is the elevated left atrial pressure. To offset left atrial pressure, an interatrial shunt can be inserted percutaneously, with recent trial results suggesting significant improvements in

quality of life and functional capacity.⁶⁰

Beyond this approach, early trials sought to offset chronotropic incompetence and improve dyssynchrony with atrial pacing, with larger trials yet to be completed.⁶¹

Finally, the wireless implantable haemodynamic monitoring system known as CardioMEMS, implanted percutaneously into the pulmonary artery, can provide clinicians with continuous data regarding pulmonary artery pressures. Large trials have demonstrated significant reductions in hospitalisation using therapy guided by data obtained via this system.^{62,63}

Managing the acute decompensation

Acute HF in patients with HFpEF is often precipitated by extrinsic factors, such as a myocardial ischaemia, fluid overload, excessive rise in blood pressure and tachyarrhythmia, particularly atrial fibrillation. Infection, surgery and exacerbation of respiratory disease can also lead to decompensation. Unlike in HFrEF, hypoperfusion is not a common feature in patients with HFpEF, in whom a rapid rise in intracardiac filling pressures and subsequent pulmonary congestion leads to acute dyspnoea.

In patients with HFpEF, seemingly slight changes to volume within a small, noncompliant ventricle can lead to significant changes in intracardiac pressure. Rapid diuresis with an intravenous loop diuretic such as furosemide (frusemide) can rapidly improve congestion; however, judicious ongoing dosing is essential to avoid overdiuresis and subsequent renal dysfunction. These patients are often hypertensive on presentation, and aggressive blood pressure control using vasodilator therapy in combination with loop diuretics is crucial in those presenting with acute pulmonary oedema. The adjunctive use of noninvasive ventilation can reduce respiratory distress, but is often only required for a brief period, usually only while the patient is in the emergency department. Finally, in patients with poorly controlled atrial fibrillation,

specifically a resting heart rate over 100 beats per minute, appropriate rate control is paramount.

Conclusion

The changing HF risk factor landscape has led to a situation in which HFpEF will become the most prevalent form of HF. In many cases, HFpEF remains a diagnostic and therapeutic dilemma for the treating clinician, and at present the evidence base of proven effective therapies is extremely limited.

Early recognition and the application of well-defined diagnostic criteria and the use of exercise testing will improve diagnosis of HFpEF, and further research is under way to develop new drugs and devices to treat these patients. **MT**

References

A list of references is included in the website version of this article (www.medicinetoday.com.au).

COMPETING INTERESTS: Dr Nanayakkara and Dr Mariani: None. Professor Kaye is a director of Cardiora, who are developing therapy for HFpEF.

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