Controversies and dilemmas in the diagnosis of heart failure with preserved ejection fraction

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Heart failure with preserved ejection fraction (HFpEF) comprises up to 50% of heart failure cases, has an increasing prevalence in ageing populations, and is associated with significant morbidity and mortality.[1-3] Recent landmark trials have provided evidence for the use of sodium–glucose cotransporter type 2 (SGLT2) inhibitors in the treatment of HFpEF, such that our focus must now pivot to streamlining the diagnosis of HFpEF in clinical practice.[4,5] However, the diagnosis remains challenging, with non-specific symptoms and signs that commonly overlap with other conditions and a high prevalence of associated multimorbidity that may contribute to the same symptoms as HFpEF. Furthermore, variable diagnostic criteria have been applied in clinical guidelines, diagnostic algorithms, and clinical trials, with limited concordance in head-to-head comparisons.[1-8] There remains no readily available "gold standard" diagnostic test, with the diagnosis of HFpEF largely one of exclusion. The aim of this perspective article is to summarise, compare and contrast the diagnostic approaches to HFpEF in order to highlight current controversies and dilemmas, and to ultimately inform the quest for a uniform approach that can be applied not only in clinical practice but also in the design of future trials.

HFpEF definitions in contemporary guidelines

Contemporary European, American and Australian heart failure guidelines suggest that HFpEF can be diagnosed when there are signs and symptoms of heart failure, preserved left ventricular ejection fraction (LVEF) ≥ 50%, and objective evidence of structural heart disease (left ventricular hypertrophy or left atrial enlargement) and/or diastolic dysfunction with elevated left ventricular filling pressures (echocardiographic, biochemical or at cardiac catheterisation).[1-3,6] Assessment of risk factors including age, obesity, diabetes, hypertension and coronary artery disease inform the pre-test probability. The key diagnostic tests are transthoracic echocardiography, serum natriuretic peptide testing (either B-type natriuretic peptide [BNP] or N-terminal pro-BNP [NT-proBNP]), and functional testing in cases where the diagnosis remains uncertain (diastolic stress echocardiography or exercise right heart catheterisation). The importance of excluding other causes of dyspnoea in older people, such as anaemia, lung disease, coronary ischaemia, valvular disease, and constrictive pericarditis, is highlighted.

Echocardiography in HFpEF

The echocardiographic hallmarks of HFpEF include left ventricular hypertrophy, as evidenced by increased wall thickness, and diastolic dysfunction. The assessment of diastolic function with echocardiography is complex and beyond the scope of this article. In brief, diastolic function is conventionally assessed by examining blood flow during diastole using Doppler echocardiography (mitral and pulmonary venous inflow), measurement of left atrial size, and assessment of myocardial motion (using tissue Doppler imaging) and right ventricular systolic pressure (as an upstream indicator of pulmonary venous congestion). Importantly, echocardiography also allows the measurement of the LVEF and exclusion of valvular heart disease as a cause of the patient's symptoms.

Clinical diagnostic HFpEF algorithms

The Heart Failure Association of the European Society of Cardiology proposed the HFA-PEFF stepwise algorithm for diagnosing HFpEF based on a standard clinical evaluation, including history, physical examination, 12-lead electrocardiography, standard echocardiography, and natriuretic peptide levels.[8] This may allow the diagnosis of HFpEF in patients with congestion, but if the diagnosis remains unclear, further workup including natriuretic peptide measurement (if not already performed) and comprehensive echocardiography (including left atrial size, left ventricular mass and geometry, diastolic function and strain) is recommended, with points accrued for specific echocardiographic measurements and natriuretic peptide levels. Patients with a score of ≥ 5 points are diagnosed with HFpEF, whereas patients with 2–4 points are indeterminate, and further advanced workup with either diastolic exercise stress echocardiography and/or invasive haemodynamic assessment is recommended. Further testing to determine the underlying aetiology including cardiac magnetic resonance imaging, tissue biopsy, bone scintigraphy (for transthyretin cardiac amyloidosis), and genetic testing is then considered in selected cases.

Using an invasive haemodynamic reference standard, the simplified H_2FPEF score[7] was developed and validated based on demographic (age), clinical (body mass index, taking two or more antihypertensives, atrial fibrillation) and echocardiographic (E/e' ratio, pulmonary artery systolic pressure) measures that could be applied at the clinical interface to estimate the probability of HFpEF. Of note, natriuretic peptide levels were not independently predictive of HFpEF, and were not included in the score. A score of < 2, 2–5, and ≥ 6 indicated a low, intermediate or high probability of HFpEF respectively. Patients with intermediate scores could be considered for further evaluation with diastolic stress echocardiography or invasive measurements. Although initial validation studies were favourable,[7,9] concordance between HFA-PEFF[8] and H_2FPEF[7] scores and conventional clinical guidelines has been suboptimal,[10,11] suggesting that further refinement is needed before they can be adopted into routine clinical practice.

Landmark HFpEF clinical trials

Until recently, none of the major HFpEF clinical trials[12-16] achieved their primary endpoint. Favourable results with SGLT2 inhibitors in other populations led to their evaluation in patients with HFpEF, with the EMPEROR-Preserved[4] and DELIVER[5] trials reporting reductions in composite endpoints of cardiovascular death or heart failure hospitalisation with empagliflozin and dapagliflozin respectively. These studies included patients with elevated NT-proBNP levels > 300 pg/mL for patients in sinus rhythm and > 600–900 pg/mL for those in atrial fibrillation. Despite evidence of left atrial dilatation and left ventricular hypertrophy, the thresholds were set very low such that the specificity of the structural echocardiographic criteria could be questioned. It is, therefore, clear that the final diagnosis of heart failure was heavily weighted towards the natriuretic peptide levels. Indeed, the primary aim of echocardiography was somewhat limited to quantifying LVEF. This approach contrasts with current guidelines and diagnostic algorithms, which emphasise the value of comprehensive assessment of resting diastolic function, as well as advocate for the use of stress testing in indeterminate cases.

Biomarker-guided approach: issues and challenges

The release of natriuretic peptide in heart failure is understood to be proportional to wall stretch;[1] so, a non-dilated left ventricle with thickened walls would release less natriuretic peptide compared with a dilated left ventricle with reduced contractility. This combined with the observation that natriuretic peptide levels are lower in patients with obesity[1] likely explains why natriuretic peptide levels are lower in patients with HFpEF compared with heart failure with reduced ejection fraction (HFrEF). Conversely, comorbid conditions such as chronic kidney disease and atrial fibrillation are associated with higher natriuretic peptide levels,[1] limiting the specificity of this biomarker in patients with suspected HFpEF. At a practical level, natriuretic peptide testing is not funded by the Medicare Benefits Schedule for the diagnosis of heart failure in the community setting. In addition, the natriuretic peptide thresholds used in current international guidelines and the universal definition of heart failure differ from the thresholds recommended in the HFA-PEFF score,[8] which in turn are lower than the thresholds used in clinical trials.[1-5,7] Although the aim of guidelines and the universal definition have been to favour sensitivity and avoid underdiagnosis, clinical trials requiring higher natriuretic peptide levels favour the recruitment of higher risk patients, who are more likely to benefit from therapeutic interventions.

Left ventricular ejection fraction thresholds in trials and guidelines

Population-based studies suggest that the general lower limit of the normal LVEF is 53%,[17] though this is dependent on age and sex.[18] Clinical guidelines and the universal definition of heart failure have taken a pragmatic approach by defining an LVEF ≥ 50% as preserved, even though this is likely to include patients with reduced left ventricular contractility, given they are more commonly female and older with increased left ventricular wall thickness and smaller left ventricular volumes.[1-3,6] Indeed, all the major HFpEF clinical trials to date have included patients with heart failure with at least mildly reduced LVEF (HFmrEF; Box), and post hoc analyses suggest that these patients respond similarly to angiotensin receptor blockers, angiotensin receptor neprilysin inhibitors, β-blockers, and mineralocorticoid receptor antagonists as patients with HFrEF.[1] Although there was also a suggestion of attenuation of SGLT2 inhibitor efficacy in patients with higher LVEF in the EMPEROR-Preserved trial,[4] this interaction was not significant and was not noted in the DELIVER trial[5] or in a subsequent meta-analysis,[19] with a treatment effect across "the range of LVEF".

Diagnosing HFpEF without congestion

There is increasing recognition of HFpEF as a cause of exercise intolerance without clinical congestion at rest. These patients may have normal natriuretic peptide levels and diastolic function on resting echocardiography, requiring exercise provocation to elicit evidence of diastolic dysfunction and elevated left ventricular filling pressures.[20] Although exercise right heart catheterisation remains the gold standard for diagnosis, this is not readily available, with expertise restricted to largely academic research institutes. Diastolic stress echocardiography is a useful non-invasive alternative but has limited availability.[21] Patients well characterised by these methods were unlikely to be enrolled in the treatment efficacy studies, questioning whether the benefits observed in those studies may be seen in the broader HFpEF population.

HFpEF as a heterogenous syndrome

Although clinical guidelines and trials have implied that HFpEF is a defined clinical syndrome, evolving evidence suggests that heterogeneous underlying aetiological and pathophysiological processes are encapsulated by diagnostic criteria that have generally defined HFpEF by what it is not. Indeed, recent phenomapping analyses have identified that patients with a clinical diagnosis of HFpEF could be divided into three distinct groups that differed in their clinical characteristics, cardiac structure or function, and clinical outcomes.[22,23] This could allow for personalised, phenotype-specific treatments and may also explain why prior intervention studies evaluating neurohormonal modulation have failed to achieve their primary endpoint.[23]

Future directions

Recent studies have highlighted the value of alternative echocardiographic measures such as left atrial strain and minimal left atrial volume, with both measures shown to have better correlation with left ventricular filling pressure and/or outcomes compared with the current approach of using maximal left atrial volume.[24-26] Beyond natriuretic peptides, novel biomarkers such as galectin-3 have

Summary of diagnostic approaches to heart failure with preserved ejection fraction (HFpEF) in guidelines, selected clinical trials, and clinical algorithms in symptomatic patients

Diagnostic framework	LVEF	NT-proBNP or BNP	Supplementary resting echocardiographic criteria
Clinical trials			
DELIVER[5]	> 40%	• NT-proBNP ≥ 300 ng/L SR or ≥ 600 ng/L AF	• LA enlargement: either LA width/ diameter ≥ 3.8 cm or LA length ≥ 5.0 cm or LA area ≥ 20 cm or LA volume ≥ 55 mL or LAVI ≥ 29 mL/m^2 • LVH: septal or PW thickness ≥ 1.1 cm
EMPEROR-Preserved[4]	> 40%	• NT-proBNP > 300 ng/L SR or > 900 ng/L AF	• LA dilatation and or increased left ventricular mass
PARAGON-HF[12]	≥ 45%	• NT-proBNP > 200 ng/L SR if hospitalised for heart failure within previous nine months, otherwise > 300 ng/L (thresholds tripled if AF; ie, > 600 ng/L or 900 ng/L)	• LA enlargement: one or more of the following: LA width ≥ 3.8 cm, LA length ≥ 5.0 cm, LA area ≥ 20 cm^2, LA volume ≥ 55 mL, or LAVI ≥ 29 mL/m^2 • LVH: septal or PW thickness ≥ 1.1 cm
TOPCAT[13]	≥ 45%	• NT-proBNP > 360 ng/L or BNP > 100 ng/L	• None
I-PRESERVE[14]	≥ 45%	• No role	• LVH (PW + IVS thickness)/2 ≥ 1.3 cm or PW thickness ≥ 1.2 cm. Enlarged left atrium (LA) in the absence of atrial fibrillation: women ≥ 42 mm; men ≥ 46 mm
CHARM-Preserved[15]	> 40%	• No role	• None
PEP-CHF[16]	> 40%	• No role	• LA diameter > 25 mm/m^2 or > 40 mm; IVS or PW thickness ≥ 12 mm • E/A ratio < 0.5 or deceleration time > 280 ms from the mitral inflow pattern, or • An isovolumic relaxation time > 105 ms
Societal guidelines			
NHF/CSANZ[1]	≥ 50%	• NT-proBNP > 300 ng/L or BNP > 100 ng/L	• LV hypertrophy with increased wall thickness or LVMI > 115 g/m^2 for men or 95 g/m^2 for women, left atrial enlargement and/or diastolic dysfunction, with high filling pressure on Doppler echocardiography (at least three of reduced mitral annular velocity [septal e' < 7 cm/s or lateral e' < 10 cm/s], average E/e' > 14, LAVI > 34 mL/m^2, TRV > 2.8 m/s)
ESC[2]	≥ 50%	• NT-proBNP > 125 ng/L or BNP > 35 ng/L SR, or • NT-proBNP > 365 ng/L or BNP > 105 ng/L AF	• LVMI: ≥ 95 g/m^2 (women) or ≥ 115 g/ m^2 (men), RWT 0.42, LAVI > 34 mL/m^2, E/e' ratio at rest > 9, PASP > 35 mmHg, TRV > 2.8 m/s
AHA/ACC/HFSA[3]	≥ 50%	• NT-proBNP ≥ 125 ng/L or BNP ≥ 35 ng/L	• Non-invasive evidence of spontaneous or provokable increased LV filling pressures (parameters and thresholds not specified)
Universal definition[6]	≥ 50%	• NT-proBNP ≥ 125 ng/L or BNP ≥ 35 ng/L in ambulatory patients; NT-proBNP ≥ 300 ng/L or BNP ≥ 100 ng/L in hospitalised and/or decompensated patients	• None
Clinical algorithms/ composite scores			
H_2FPEF[7]	≥ 50%	• No role	• E/e' ratio > 9, pulmonary artery systolic pressure > 35 mmHg
HFA-PEFF[8]	≥ 50%	• NT-proBNP > 220 ng/L SR or > 660 ng/L AF • BNP > 80 ng/L SR or > 240 ng/L AF	• Left atrial volume index, left ventricular mass index, relative wall thickness, LV wall thickness, diastolic stress echo (exercise E/e', post-exercise peak TRV)

AF = atrial fibrillation; AHA/ACC/HFSA = American Heart Association/ American College of Cardiology/Heart Failure Society of America; BNP = B-type natriuretic peptide; ESC = European Society of Cardiology; IVS = interventricular septum; LA = left atrial; LAVI = left atrial volume index; LV = left ventricle; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index; PASP = pulmonary artery systolic pressure; NHF/CSANZ = National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand; NT-proBNP = N-terminal pro-BNP; PW = posterior wall; RWT = relative wall thickness; SR = sinus rhythm; TR = tricuspid regurgitation; TRV = tricuspid regurgitation velocity. ◆

also shown promise in refining HFpEF diagnosis and risk stratification.[27] There is also emerging awareness of different HFpEF phenotypes, which could partly explain the failure of previous treatment efficacy studies that have taken a "one-size-fits-all" approach to management. Indeed, recent studies have highlighted the possibility of using artificial intelligence and machine learning to phenogroup patients on the basis

of a broad range of clinical measures and may inform the design of future clinical trials, allowing tailored management, as highlighted above.[23]

Conclusions

A number of challenges and dilemmas continue to complicate the diagnosis of HFpEF in clinical practice. Considerable heterogeneity is noted in the approach to diagnosis between international guidelines, diagnostic algorithms, and clinical trials (Box). The availability of evidence-based therapies should be seen as a call to action to urgently streamline and unify the diagnosis of HFpEF at the clinical interface, so that the benefit of breakthrough therapies can be maximised by specifically identifying affected patients who stand to benefit.

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