Heart Failure with Preserved Ejection Fraction: the essential role of echocardiography in timely diagnosis

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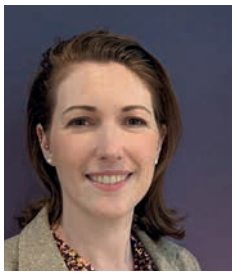

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Clinical case

You are a physiologist on an outpatient echocardiography list. You have received a direct-access GP request to perform an echocardiogram for a patient with breathlessness and a natriuretic peptide (NT-proBNP) level of 1200 ng/L. The GP suspects heart failure. Your patient is a 72 year old lady who has hypertension, type 2 diabetes mellitus, and is overweight with BMI of 30kg/m^2. As you perform the echocardiogram you note that she is in sinus rhythm but the left atrium is dilated, the left ventricular cavity is non dilated with mild global concentric hypertrophy, and the systolic function is preserved. There is no significant valvular disease. You suspect the patient has heart failure with preserved ejection fraction. What would be the next step in your assessment to confirm this diagnosis and why?

Introduction

The global incidence of heart failure is increasing, and in particular heart failure with preserved ejection fraction (HFpEF) which is estimated to constitute 50% of new heart failure diagnoses in the community.[1] In England alone, the prevalence of HFpEF is estimated to be in excess of 3 million.[2] HFpEF pathogenesis shares close links with a range of other chronic conditions such as obesity, type 2 diabetes mellitus, atrial fibrillation, hypertension, and chronic kidney disease (CKD).[3] The rise in obesity and diabetes, as well as the ageing population, is thought to be primarily responsible for the rising number of cases of HFpEF. Patients with HFpEF can present with non-specific symptoms like breathlessness and fatigue, which can overlap with other conditions and make diagnosis challenging.[4] Echocardiography is critical in identifying key features of HFpEF, such as diastolic dysfunction and elevated filling pressures, particularly in patients with unexplained breathlessness.[5]

Timely recognition of HFpEF opens the door to novel therapeutic strategies, such as sodium glucose co transporter 2 inhibitors (SGLT2i) Dapagliflozin or Empagliflozin. In addition, the glucagon-like peptide 1 agonist (GLP-1) Semaglutide can improve outcomes and quality of life in this patient cohort.[6-9]

This short review aims to outline the key mechanisms in HFpEF, as well as clinical presentation and diagnostic algorithms, whilst highlighting the important role of timely echocardiography for efficient diagnosis and improving patient outcomes. The recently published British Society of Echocardiography guidance on assessing diastolic function[10] is crucial for standardising and enhancing the accuracy of HFpEF diagnosis.

The pathophysiology of HFpEF

HFpEF is recognised as a heterogenous multisystemic disorder and often associated with other chronic conditions. Based on the close associations, HFpEF can be categorised into distinct groups ('phenotypic clusters') based on comorbidities and clinical characteristics.[11,12] Each phenotype exhibits unique pathophysiological mechanisms and clinical trajectories, emphasising the need for tailored therapeutic approaches in HFpEF management.[13]

These clusters include:

(1) **obesity/metabolic cluster** characterised by obesity, type 2 diabetes, and metabolic syndrome

(2) **hypertensive cluster** associated with longstanding hypertension, left ventricular hypertrophy, and atrial fibrillation

(3) **elderly/multimorbid cluster** often seen in older patients with multiple comorbidities such as chronic obstructive pulmonary disease (COPD), renal disease, and frailty.

The pathophysiology of HFpEF is multifactorial and complex. The most commonly accepted theory is that of 'systemic inflammation', whereby chronic comorbidities such as obesity and type 2 diabetes mellitus lead to chronic low-grade inflammation and oxidative stress.[14-16] This chronic inflammatory response over time leads to complex changes on a cellular level within the vessels and the heart itself, resulting in thickening and stiffness of the left ventricle, increased filling pressures, and over time progressive dilatation of the left atrium.[17, 14] Clinically, these changes can be detected as increased filling pressures, diastolic dysfunction, and increased LA volumes (all of which are hallmarks of HFpEF).[15] Left ventricular systolic function (as assessed by left ventricular ejection fraction) typically remains preserved.

Diagnosis of HFpEF

Diagnosing HFpEF involves integrating clinical symptoms (such as breathlessness, fatigue, leg swelling, and exercise intolerance) with echocardiographic findings of preserved ejection fraction (LVEF ≥ 50%) and evidence of diastolic dysfunction, elevated filling pressures, and cardiac remodelling such as increased left atrial volumes.[5] Usually, but not always, these patients will have increased body mass index.

Biomarkers like brain natriuretic peptide (NT-proBNP), which will usually be requested either by the patient's GP or cardiologist, can support the diagnosis, and elevated levels (>250 ng/L) indicate cardiac stress.[18] However, diagnosis in elderly, multimorbid patients is particularly challenging due

to overlapping symptoms from comorbidities like obesity, atrial fibrillation, and chronic kidney disease, which can not only mimic or mask HFpEF but also impact on circulating NT-proBNP levels. Additionally, age-related changes in the cardiovascular system, such as stiffening of the ventricles, can complicate differentiation between HFpEF and normal ageing, making timely and accurate diagnosis more difficult.

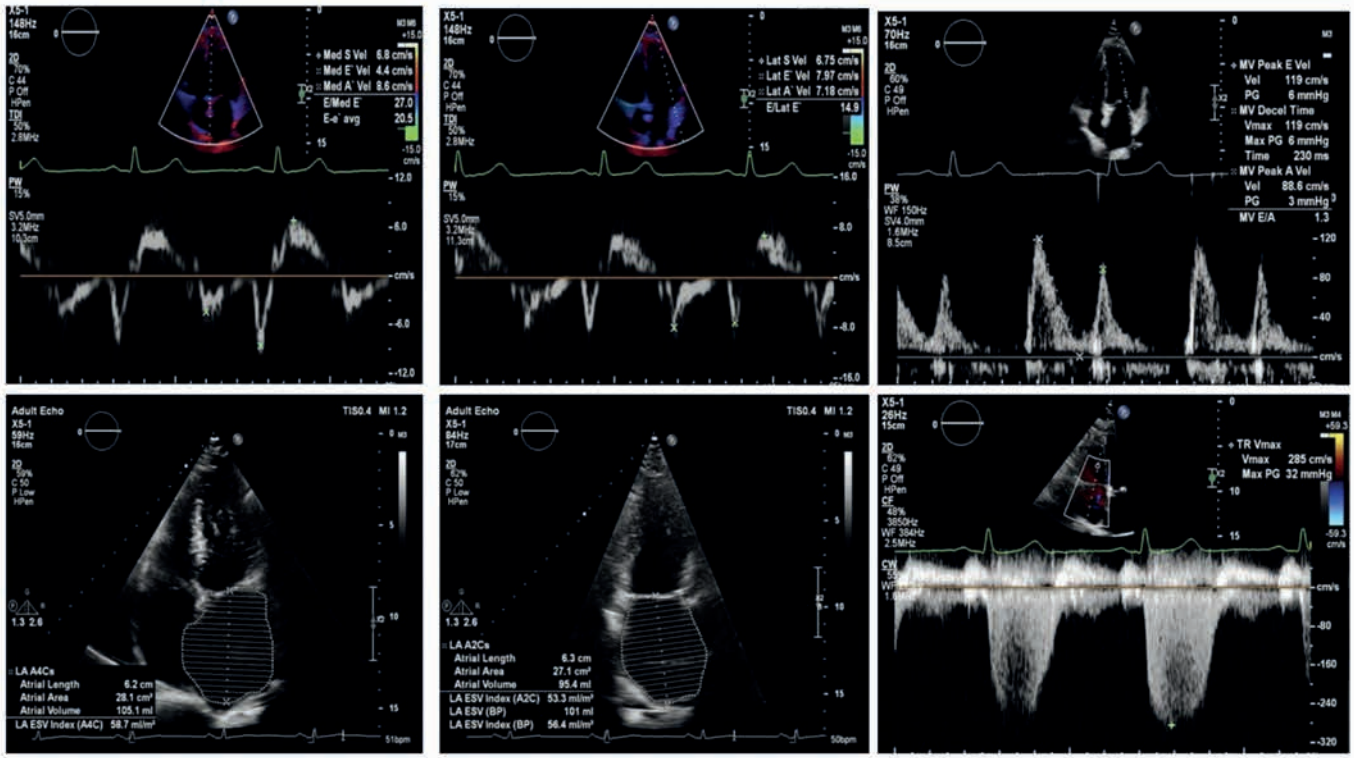


Fig 1. Typical echocardiographic features suggestive of HFpEF. From left to right: abnormal septal E', lateral E', MV deceleration time, dilated left atrium and elevated pulmonary pressures suggestive by TR Vmax.

Key echocardiographic features of HFpEF

Echocardiography is crucial to assessing patients with suspected HFpEF, with the common echocardiographic features summarised below, and as shown in an example in Figure 1.

However, it is important to first rule out common differentials such as significant left-sided valvular disease, hypertrophic cardiomyopathy, heart failure with reduced ejection fraction (HFrEF) and significant right heart disease. Patients with cardiac amyloidosis can have similar features to HFpEF, hence assessment of global longitudinal strain is useful in differential diagnosis. The new British Society for Echocardiography guidance on assessing diastolic function[10] is a very useful guide for standardising and enhancing accuracy of assessments.

In HFpEF, the left ventricular ejection fraction (LVEF) remains preserved (≥ 50%), but there are multiple indicators of diastolic dysfunction and structural changes as outlined below and shown in Figure 1, that can help clench the diagnosis.[19]

1. **Diastolic Dysfunction:** This is central to the pathophysiology of HFpEF and is often assessed through the E/e' ratio, which estimates left ventricular filling pressures. An E/e' ratio > 9 is suggestive of elevated left ventricular filling pressures and diastolic dysfunction. While this is a lower cut off threshold compared to recent BSE guidance (E/e' ratio > 14), an E/E' ratio > 9 is utilised in the HFpEF prediction clinical scoring systems. The e' (early diastolic mitral annular velocity) is typically reduced in HFpEF, reflecting impaired myocardial relaxation.[10]
2. **Left Atrial Enlargement:** Left atrial (LA) volume indexed to BSA > 34 mL/m^2 is a common finding, indicative of chronic pressure overload due to elevated filling pressures. However, this should be interpreted with caution in those with elevated body mass index as this will increase the BSA. Left atrial size reflects the chronicity and severity of diastolic dysfunction.[20] A 3D echocardiographic assessment of LA roof enlargement has been recently found to be the main feature on exercise stress testing of masked HFpEF cases.[21]
3. **Left Ventricular Hypertrophy (LVH):** Although ejection fraction is preserved, many patients with HFpEF display left ventricular hypertrophy, particularly in response to chronic hypertension. This is often seen as increased left ventricular wall thickness (LV mass index > 115 g/m^2 in men and > 95 g/m^2 in women).[22]
4. **Abnormal Mitral Inflow Pattern:** Doppler assessment of mitral inflow can show a reduced early diastolic filling velocity (E wave) and increased atrial filling velocity (A wave), with a decreased E/A ratio (< 1), reflecting impaired relaxation of the left ventricle.[5]
5. **Pulmonary Hypertension:** Elevated pulmonary artery systolic pressure (PASP) > 35 mmHg, assessed by tricuspid regurgitation velocity, can be present due to the backward transmission of elevated left-sided pressures.[10]
6. **Global Longitudinal Strain (GLS):** Though LVEF is normal, subtle systolic dysfunction can be detected using speckle-tracking echocardiography, which measures global longitudinal strain. In HFpEF, GLS may be mildly reduced (less negative than -16%), reflecting subclinical systolic impairment despite preserved ejection fraction.[23]
7. **Left Atrial Strain (LAS):** LAS is a useful index of the mechanical properties of the LA, and allows assessment of reservoir, conduit, and pump function. While LAS is not a direct marker of diastolic function, in patients with preserved LVEF a LASr (reservoir strain) <18% has a high specificity for increased filling pressures. It can therefore be incorporated into a multiparametric algorithm for the assessment of diastolic function and filling pressures.[24]

Diagnostic challenges and scoring systems

At present, there is no consensus on the optimal way to diagnose HFpEF. However there are scoring systems available which can aid the diagnosis. There are two scoring systems currently in use: HF2PEF[25] and HFA-PEFF scores.[26] These scoring systems are diagnostic tools used to assess the 'likelihood of HFpEF' based on clinical and echocardiographic criteria.

- **The HF2PEF score:** this is a simplified, six-point scoring system incorporating factors such as obesity, atrial fibrillation, hypertension, and echocardiographic parameters (the E/e' ratio > 9 and pulmonary artery systolic pressure PASP > 35 mmHg), with a score ≥ 6 indicating high probability of HFpEF.[25]
- **The HFA-PEFF score:** was developed by the Heart Failure Association. It is a more detailed scoring system than the HF2PEF score as it looks at three domains: functional, morphological, and biomarker criteria. Unlike the HF2PEF score it, includes natriuretic peptide (NT-proBNP) levels and requires more detailed echocardiographic findings. These include evidence of diastolic dysfunction (e.g. E/e' ratio > 9), left atrial size, presence of left ventricular hypertrophy, and global longitudinal strain (GLS) which is known to be impaired in HFpEF.[26] A score ≥ 5 on the HFA-PEFF scale indicates *confirmed HFpEF.*

The role of 2D and 3D echocardiography in diagnosis of HFpEF

In diagnosing HFpEF, both 2D and 3D echocardiography play significant roles, though their utility differs.[27] 2D echocardiography is the primary tool used for assessing diastolic function, left atrial enlargement, and parameters like the E/e' ratio, which are critical in HFpEF diagnosis. It is widely accessible and effective in detecting common features such as left ventricular hypertrophy and elevated filling pressures, making it the standard in clinical practice. However, 3D echocardiography can offer enhanced precision of measurements of left atrial and left ventricular volumes, and it provides more accurate quantification of global longitudinal strain (GLS), an important marker in HFpEF.-[27] While 3D is superior in terms of accuracy, especially for volume and strain measurements, it is less commonly used due to its complexity and specialised requirements. Thus, 2D echocardiography remains the cornerstone in HFpEF diagnosis, with 3D providing enhanced detail when available.

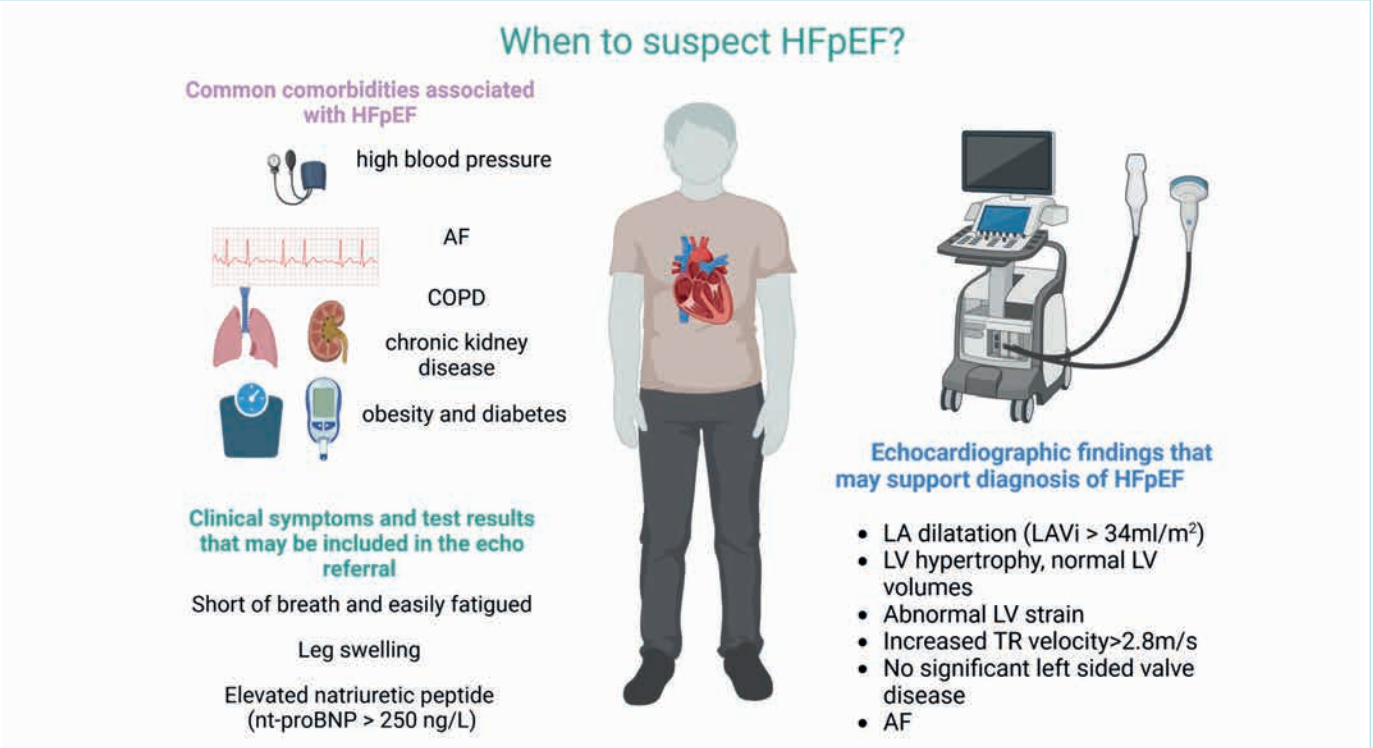
Cardiac magnetic resonance imaging can also be used if a diagnosis of hypertrophic cardiomyopathy or cardiac amyloidosis is suspected.

Current knowledge gaps

Despite significant advances in the understanding and management of HFpEF, there remain notable research limitations, particularly in refining its diagnostic criteria and tailoring treatment strategies. Current diagnostic tools, including echocardiography and biomarker analysis, often lack sensitivity in early disease stages and may not fully capture the heterogeneity of HFpEF phenotypes. Additionally, while therapies like SGLT2 inhibitors and Semaglutide show promise, their efficacy across diverse HFpEF populations, especially those with multiple comorbidities, remains under-researched. Further studies are necessary to develop more precise diagnostic algorithms, integrate novel imaging modalities, and explore personalised treatment approaches that account for the condition's phenotypic diversity and complex pathophysiology.

Conclusions

HFpEF presents a big challenge in modern healthcare due to its rising prevalence, particularly among the elderly and multimorbid groups. The diagnostic challenges of HFpEF often related to symptom overlap from comorbidities like obesity, diabetes, and atrial fibrillation. Echocardiography remains the key tool for identifying diagnostic features such as diastolic dysfunction and elevated filling pressures, particularly in patients with unexplained breathlessness. Accurate and early diagnosis of HFpEF is crucial for improving patient outcomes, as emerging medical therapies have the potential to significantly improve lives of these patients.



Key illustration summarising the essential clinical and echocardiographic features suggestive of HFpEF. AF: atrial fibrillation, COPD: chronic obstructive pulmonary disease, LA: left atrium, LV: left ventricle, nt-proBNP: brain natriuretic peptide; TR: tricuspid valve regurgitation

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