British Cardiovascular Society
Editorials

Heart Failure with Preserved Ejection Fraction: Pathologies, Aetiology and Directions for Treatment

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Introduction

Heart failure with preserved ejection fraction is estimated to constitute up to half of heart failure diagnoses worldwide[1], yet this entity is difficult to classify and the pathology not well understood, which has contributed to a failure to develop useful treatments. Originally thought to represent the clinical manifestations of diastolic dysfunction (with the terms often used interchangeably), it is increasingly clear that there are diverse pathological factors at work and even more diverse aetiologies behind this. This review sets out to untangle some of the confusing pathology at play, explore some models of phenotyping within the condition and look at potential future therapies.

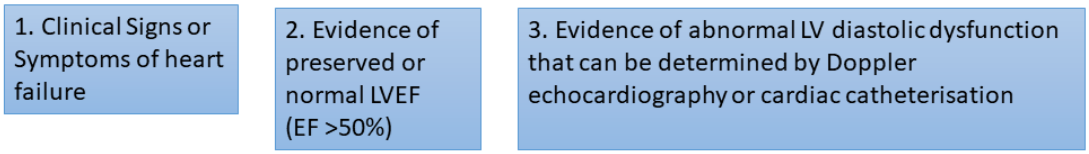
What do the current guidelines say about making a HFpEF diagnosis?

The American Heart Association[2] and European Society of cardiology[3] are broadly in agreement with their definitions of HFpEF as representing patients with signs and symptoms of heart failure, evidence of normal or preserved ejection fraction but objective evidence of other structural or functional alterations in cardiac structure. The ESC guidelines are a little more descriptive in terms of specifying particular markers of diastolic dysfunction and also taking into account stress testing, although both emphasize the importance of ruling out noncardiac causes of symptoms.

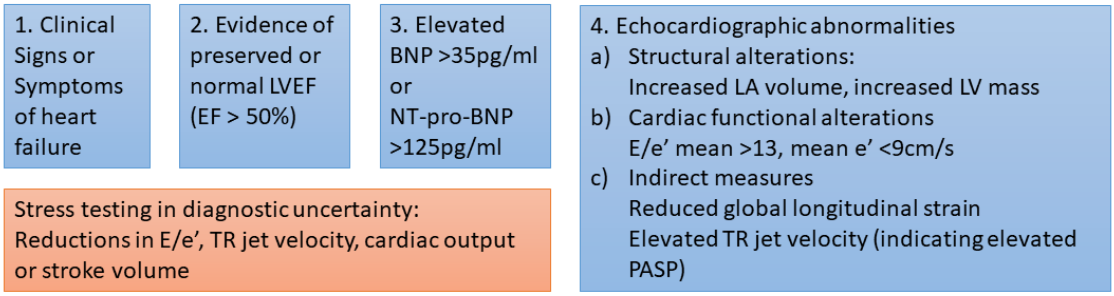
Take Home Points

- HFpEF is rising in prevalence but remains poorly understood.
- While diastolic dysfunction is at the centre of the condition, there are many aetiological factors at play.
- Different phenotypes have been identified: younger patients with low symptom burden and isolated diastolic dysfunction, obese patients with metabolic co-morbidities and older patients with arterial and myocardial stiffness.
- At present, treatment focusses around treating underlying factors but in future, modulating nitric oxide and energy metabolism may be potential targeted therapies.
- Separating out different sub-groups who will benefit could be the key to managing HFpEF effectively.

American Heart Association Guidelines on HFpEF diagnosis



European Society of Cardiology Guidelines on HFpEF diagnosis



These diagnostic algorithms have been criticised for the arbitrary use of 50% as a cut-off for left ventricular ejection fraction, not taking into account the impact of co-morbidities and over-reliance upon left ventricular diastolic measurements alone to make a diagnosis[4, 5]. Terms such as heart failure with mid range ejection fraction (HFmrEF) with ejection fraction 40-50% further muddy the waters. Another puzzling factor is how some patients with echocardiographic evidence of impairment of function can have normal BNP levels[6] and remain symptom free while others are grossly symptomatic.

What is the pathophysiology underlying HFpEF?

Many of the other pathological impairments noted in HFpEF are also seen in HFrEF and vice versa and we must ask whether HFpEF is a separate entity, a transition state into HFrEF or whether we are dealing with multiple different conditions where diastolic and systolic dysfunction are reflections of the underlying disease process.

A key area to consider in the pathogenesis is the response to exercise. A ventricle which may appear entirely normal at rest can respond abnormally when the patient is asked to exercise, with chronotropic impairment, diastolic changes or even frank systolic dysfunction occurring at higher heart rates.

The converse is also to consider changes in other body systems which place additional load upon the heart and cause contractile dysfunction owing to chronic changes in loading.

Many of the factors cannot be considered in isolation – as you will see, each impacts upon the other.

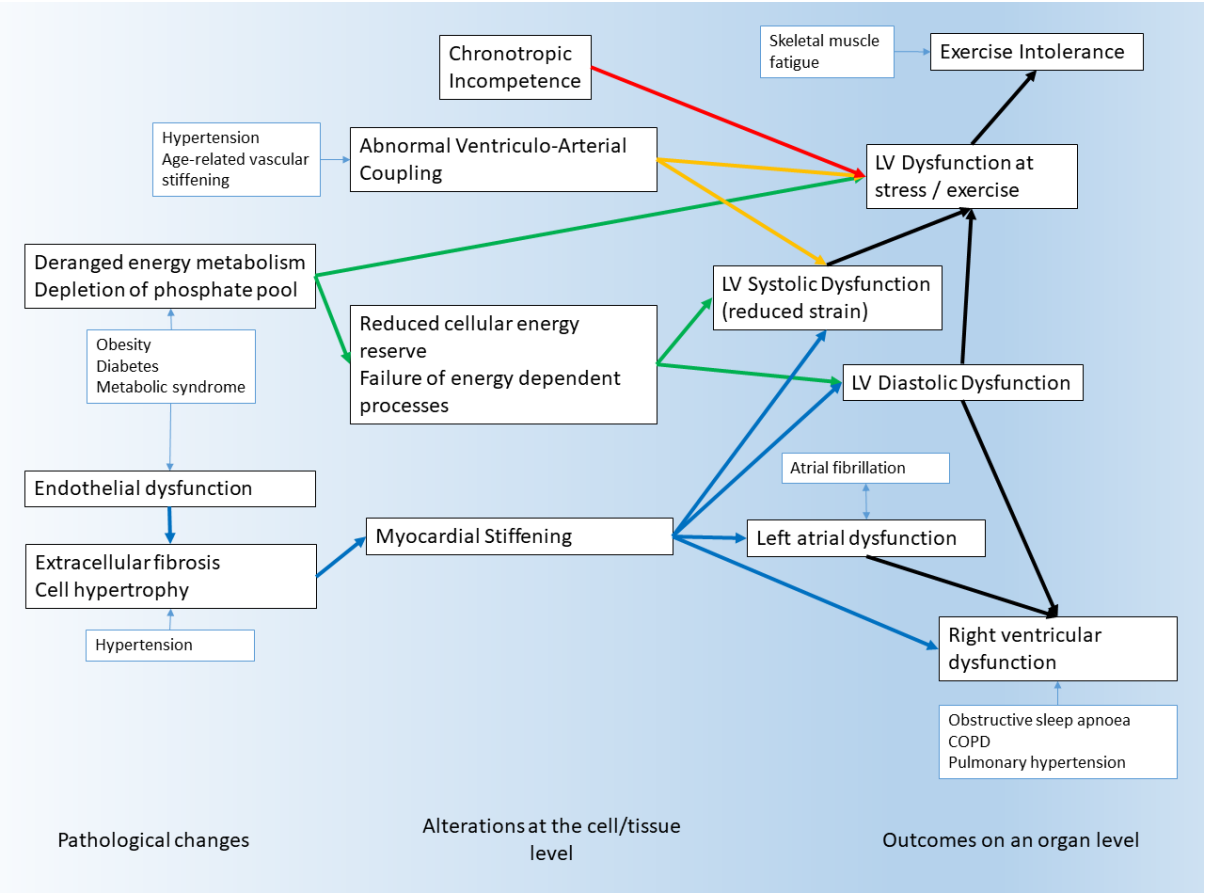


Fig 2: Diagram demonstrating the complex interplay between different pathologies in HFpEF and their effects on the heart.

Cardiac Physiological Factors

Diastolic Dysfunction

Defined as the inability to fill the ventricle to an adequate preload volume, diastolic dysfunction is at the core of heart failure with preserved ejection fraction (see Dr Patel's previous editorial on this subject). In some cases, such as in obesity changes in diastology are a primary dysfunction whereas in others such as prolonged hypertension they reflect other factors that change the loading conditions upon the heart. The effect of diastolic dysfunction becomes more pronounced upon exercise: the filling time remains prolonged, meaning the ventricle cannot completely fill in between beats, further reducing efficiency.

Chronotropic Incompetence

An inability to increase heart rate on exertion is frequently reported in HFpEF and seems to correlate with feelings of breathlessness. What is unclear is whether this is maladaptive or adaptive as it has been shown experimentally that stroke volume falls off at higher heart rates in HFpEF patients and cardiac output can fail to increase or even fall at high rates[7].

Systolic Dysfunction

Although overall ejection fraction is preserved, deficiencies in global longitudinal strain are identifiable, even in those with ejection fraction greater than 55%, indicating subtle systolic impairment[8].

In addition, limitations are frequently seen during stress in the HFpEF group. While a failure to augment contractile function with progressive exercise has been seen in some patient groups [7, 9], it is also important to consider the role of ventricular-arterial coupling: inappropriate increases in vascular tone reducing mechanical efficiency of the left ventricle, even when contractile function is preserved.

Atrial Dysfunction

Where the diastolic function of the left ventricle is impaired, the left atrium gains greater importance and HFpEF patients may be more reliant upon the LA's booster function. It seems loss of atrial contractile function occurs progressively (again, especially under stress) and it has also been observed that HFpEF patients tolerate atrial fibrillation very poorly[5]. When the left atria from patients with HFpEF and HFrEF are compared, there is a greater degree of stiffening in HFpEF, perhaps contributing to the rise in pulmonary pressures.

Right Ventricular Dysfunction / Pulmonary Vascular Disease

Even discounting the effects of elevated pulmonary artery pressures, there is both systolic and diastolic impairment of the right ventricle, much in the same way as the left[10]. Pulmonary vascular resistance itself is also commonly elevated (raising the PA pressures above the results of left atrial hypertension).

Underlying Cardiac Pathological Factors

Fibrosis

Concentric remodelling and increased collagen content are commonly reported in HFpEF and fibrosis is associated with worsening prognosis [11] There can be myriad factors contributing to fibrosis and causing different patterns: from a diffuse interstitial fibrosis accompanying hypertrophy to scarring induced by resolving myocarditis or even cardiac radiation exposure.

One key difference from HFrEF is where and how the fibrotic change occurs. In HFpEF, there seems to be an increase in extra-cellular fibrosis with maintained or increase cell mass whereas in HFrEF, individual myocytes die off and are replaced with fibrosis – borne out on extracellular volume measures detectable on MRI[12].

Nitric Oxide

Newer theories implicate nitric oxide (NO) in the pathogenesis of HFpEF. It has been demonstrated that systemic vascular inflammation (driven by various comorbidities but particularly obesity, chronic kidney disease, hypertension and diabetes mellitus) results in an excess of reactive oxygen species, which in turn reduces nitric oxide bioavailability within adjacent myocytes, inducing myocyte hypertrophy and pro-inflammatory processes[13].

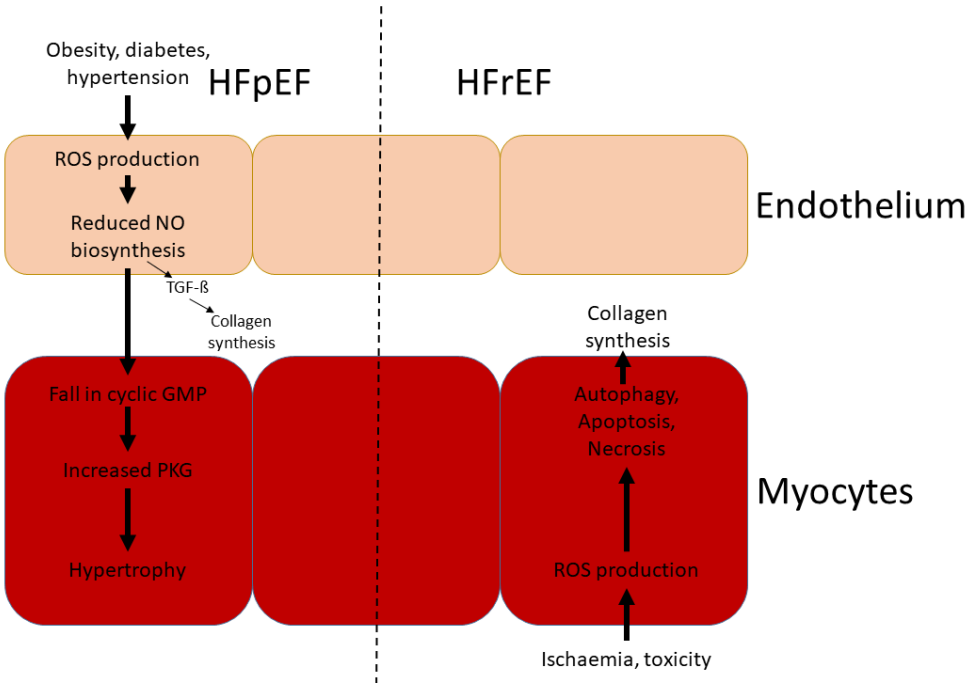


Fig 3: putative pathological mechanisms: differences between HFpEF and HFrEF

Energy Depletion

In obesity and diabetes, there is a reduction in glucose uptake by myocytes, with this loss of 'fuel' causing a deficit in myocardial ATP. The myocyte does not simply require ATP for contraction; diastole is also an ATP dependent process and SERCA (the Sarcoplasmic/Endoplasmic Reticulum ATPase required to actively pump Calcium out of the cell in relaxation) requires higher concentrations of ATP than any other process in the cell, making diastole the first process to be impaired as cellular ATP levels drop[14].

It has also been shown in animal studies that these myocytes fail to upregulate their glucose 'fuel' intake on exertion, leading to a progressive ATP deficit that correlates with the induction of diastolic and systolic dysfunction with progressive exertion[15].

Systemic Factors

Abnormal ventricular-arterial coupling

This refers to the interplay between the work done by the left ventricle and the load imposed upon it by the systemic vasculature. Increases in the vascular resistance and arterial compliance put greater load upon the left ventricle.

Abnormal rises in peripheral arterial vasoconstriction on exercise will cause abnormal rises in LV end systolic pressure on exertion, limiting ability to increase ejection fraction and this has been shown to occur in HFpEF and limit maximal cardiac output[16].

Stiffening with age causes a loss of compliance in the arterial system: the ability to distend to absorb cardiac ejection being lost, leading to a greater rise in arterial pressure in systole and therefore greater load upon the left ventricle. This has been shown to correlate with increases in left ventricular fibrosis over time [17].

Skeletal muscle fatigue

It has been observed that patients with heart failure across the board exhibit earlier muscle fatigability as measured by accumulation of lactate and depletion of phosphocreatine in skeletal muscle. Interestingly, this depletion occurs more rapidly in the HFpEF population than the HFrEF population and is correlated with intra-muscular accumulation of fat.

This suggests that underlying co-morbidities of obesity and diabetes lead to intra-muscular fat accumulation, reducing metabolic efficiency of skeletal muscle and contributing to the sensation of fatigue via separate pathways[18].

Exaggerated sensation of breathlessness

Increased ventricular filling pressures can of themselves induce a sensation of breathlessness, which has been put forward as an explanation for the observation that HFpEF patients often cease exercising during CPET prior to reaching their anaerobic threshold (suggesting breathlessness prior to reaching physiological limits)[7].

Comorbid Conditions

- Obesity
- Hypertension
- Pulmonary Disease
- Atrial fibrillation

Can we Phenotype HFpEF?

Retrospective analysis of large patient datasets from trials have allowed different phenotypes within HFpEF to emerge. Shah[19] used a machine learning algorithm on patient data from heart failure clinic attendances and identified three distinct clinical phenotypes with different aetiological and prognostic profiles.

1. Younger patients with moderate diastolic dysfunction and relatively normal BNP levels. This group was the lowest risk of the three in terms of mortality and heart failure hospitalisation.
2. Obese, diabetic patients with high levels of obstructive sleep apnoea and significant impairment of LV relaxation
3. Older patients with chronic kidney disease, electrical and structural myocardial remodelling, pulmonary hypertension and right ventricular dysfunction. These patients had the most abnormal ventricular-arterial coupling profile of the three cohorts. This group was at the highest risk.

Kao retrospectively analysed baseline and outcome data from the CHARM and i-PRESERVED trials and found a similar pattern. Older patients with high incidence of renal dysfunction and atrial fibrillation were at highest mortality risk, as were obese patients with high incidences of diabetes mellitus and dyslipidaemia[20].

Novel Investigative Techniques with MRI

Novel imaging techniques such as MRI T1 mapping and extracellular volume quantification also allow us to better understand myocardial changes in HFpEF such as fibrosis and pathological

hypertrophy[11], although this remains a research tool rather than something which can be integrated into clinical practice. Magnetic resonance phosphate spectroscopy allows us to quantify energy levels within the myocardium and has been in research use for over 20 years[21] but has yet to find clinical application.

What Treatments are Available?

Current guidelines advise treating co-morbid or contributory conditions and using diuretics to relieve symptoms.

Trials of treatment have been largely unsuccessful in HFpEF, for a variety of reasons. As suggested here, this may be a failure to identify different phenotypes which benefit from different interventions: perhaps identifying subtypes of HFpEF where fibrosis predominates will help discover patients likely to benefit from anti-fibrotic therapy.

Alterations in myocardial stiffness mean that the pressure-volume curve is shifted to the left (compared to that of HFrEF which is often right shifted), changing the end-systolic pressure volume ratio and substantially reducing the benefit from vasodilator therapy (see diagram below).

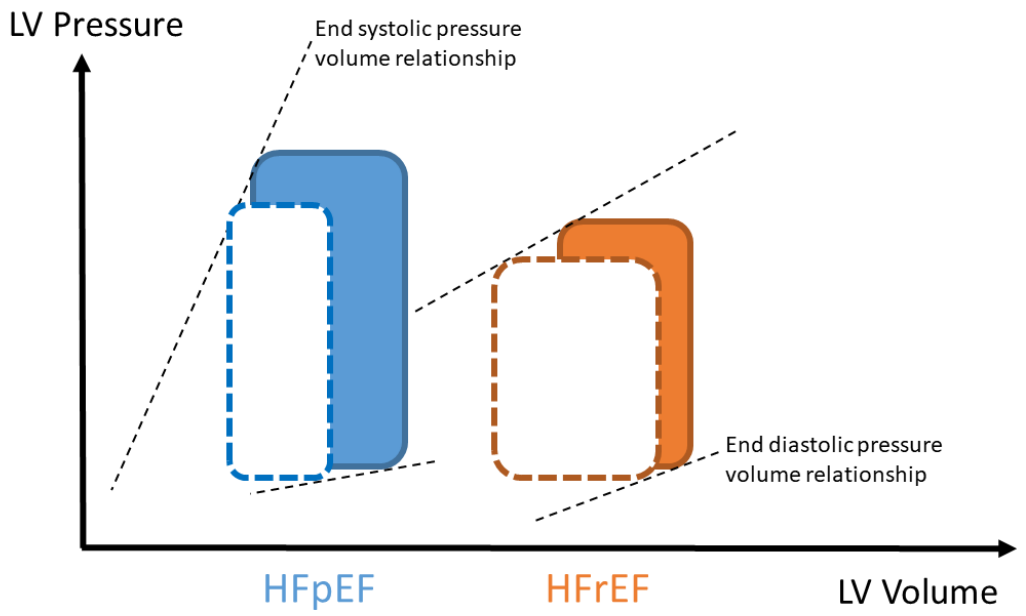


Figure 4: Effect of vasodilator therapy (dotted lines) on HFpEF and HFrEF. The steep end systolic pressure-volume relationship in HFpEF causes a fall in end systolic pressure from vasodilator therapy (y-axis) to cause a drop in ejection fraction (x-axis).

Further studies are currently ongoing: the effects of an angiotensin receptor antagonist with neprilysin inhibitor is being tested in the PARAGON-HF trial; phase 2 studies having shown improvements in NT-pro-BNP and LA volume compared to Valsartan. It is postulated that the

neprilysin inhibitor may have beneficial effects on nitric oxide metabolism, giving particular benefit in HFpEF[12].

Nitric Oxide Pathway Modulation

Clinical trials with direct cGMP donors (riociguat and vericiguat) have failed to yield benefit and treatment with isosorbide mononitrate actually had deleterious hypotensive effects, reducing exercise tolerance. Trials with direct nitrate donors are in progress[12].

Metabolic Modulation

Studies in obese mice have shown that when glucose uptake is increased using a GLP1 analogue, diastolic dysfunction can be reversed[22]. More work is needed in this area but in patients with demonstrable metabolic defects, this may provide a novel treatment. SGLT2 inhibitors are currently being trialled in HFpEF (the EMPEROR-Preserved study) following promising results in cardiovascular disease[23]. Ultimately, weight loss remains a tried and tested technique to normalise these deficits.

Summary

Heart failure with preserved ejection fraction is rising in prevalence and there are limited treatment options. A better clinical understanding from phenotyping studies and a greater understanding of underlying pathophysiology may be the way forward to allow us to synthesize treatments that target disparate underlying pathologies.

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