Curr Treat Options Cardio Med (2018) 20: 90
DOI 10.1007/s11936-018-0689-9

Imaging (Q Truong, Section Editor)

Imaging and Management of Heart Failure and Preserved Ejection Fraction

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Published online: 27 September 2018

This article is part of the Topical Collection on *Imaging*

Keywords Heart failure · HFpEF · Cardiovascular imaging · Review

Abbreviations *HFpEF* Heart failure with preserved ejection fraction · *AHA* American Heart Association · *ACC* American College of Cardiology · *HFSA* Heart Failure Society of America · *ESC* European Society of Cardiology · *LAVI* Left atrial volume index · *LVMI* Left ventricular mass index · *e'* Early diastolic mitral annular velocity · *E/e'* Ratio of early diastolic trans-mitral to mitral annular velocities · *BNP* Brain natriuretic peptide · *NT* ProBNP N-terminal pro-B-type natriuretic peptide · *PCWP* Pulmonary capillary wedge pressures · *GLS* Global longitudinal strain · *ECV* Myocardial extracellular volume

Abstract

Purpose of review The prevalence of heart failure with preserved ejection fraction (HFpEF) is rising and in some places, it is already the most prevalent form of heart failure. The usual treatments of HF do not improve mortality or outcomes in HFpEF, suggesting a distinct pathophysiology that remains poorly characterized. The neutrality of clinical trial results is also attributable to the heterogeneity of patient profiles, and by poor characterization offered by classical echocardiography parameters. Emerging imaging modalities may overcome this problem. We therefore aimed to summarize recent advances offered by cardiovascular imaging in disease characterization, and the implication of findings to new phenotype-specific treatment options.
Recent findings Novel cardiovascular imaging techniques such as LV global longitudinal strain, left atrial strain, tissue characterization by magnetic resonance T1 time, as well as incorporation of systolic and diastolic stress testing offer greatly improved characterization, diagnosis, and stratification of disease pathogenesis. These techniques offer insight into identification of HFpEF sub-phenotypes that are resistant to, or responsive to therapies.
Summary There is a growing body of evidence that novel cardiovascular imaging modalities are able to characterize HFpEF patients with much greater accuracy than current guideline-

driven parameters. Whether this information can be synthesized to adequately stratify patients into sub-phenotypes with clearer disease pathogenesis amenable to targeted intervention will be of particular future interest.

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a complex and heterogeneous condition with a rapidly rising prevalence that already affects up to 1 in 10 elderly individuals, and is becoming the most common form of heart failure (HF) [1]. To date, there remains no identified therapy that can reduce mortality, and this contributes to it being a major public health challenge. The syndrome of HFpEF is inherently heterogeneous, and we lack a single international consensus that can accurately characterize patients with HFpEF among the community of patients with chronic exertional dyspnea.

Imaging and diagnosis of HFpEF Two main commonly accepted HFpEF phenotypic definition have been derived from American (ACC/AHA/HFSA [2]) and European (ESC) guidelines [3]. Both definitions require clinical diagnosis based on classical patient symptomatology as initially defined by the Framingham criteria [4]; LV ejection fraction (EF) ≥ 50%; combined with exclusion of valvular and non-cardiac causes. In addition, the 2016 ESC criteria offers specific cutoff values for noninvasive diagnosis defined as echocardiographic evidence of cardiac structural and/or functional alterations (LAVI > 34 mL/m^2, or LVMI ≥ 115/95 g/m^2 for males/females, or mean E/e′ ≥ 13 and mean e′ < 9 cm/s), and elevated natriuretic peptide levels (BNP > 35 pg/mL and/or NT-proBNP > 125 pg/ml). This is an interesting choice, both because obesity is strongly linked to HFpEF and also linked to disproportionally low BNP levels for the ambient hemodynamic status, as well as the fact that many patients with HFpEF are symptomatic and have increased wall stress only with exercise [5]. If such individuals exercise little, then it is likely that BNP will not be elevated. Both of these conditions likely lead guideline-based diagnosis to be specific but insensitive.

In contrast, the ACC/AHA/HFSA guidelines cite disease stages stratified by symptom status, and no absolute requirement for serum biomarker elevation. There are many dyspneic patients in whom a cardiac etiology is suspected despite preserved EF. Although recommendations are made for invasive determination of elevated filling pressures, which remain the gold standard for true HFpEF diagnosis—including when performed during exercise [6]—it is not feasible to perform widespread invasive investigation at the population level. Therefore, guideline-driven diagnosis of HFpEF, for which the presence of diastolic dysfunction and/or structural remodeling is a prerequisite, by and large continues to rely on classical echocardiographic parameters such as estimated LV filling pressures E/e′. As a result, current noninvasive recommendations can be effective in identifying HFpEF in an acute, decompensated setting. However, both ESC and ACC/AHA/HFSA guidelines offer poor noninvasive combined sensitivity and specificity to accurately classify chronically dyspneic HFpEF patients. There is therefore a need to identify novel cardiovascular imaging parameters that can accurately characterize this growing population of individuals with debility and cardiovascular mortality and morbidity.

The search for phenotypic homogeneity Over recent decades, therapies have been shown to improve outcomes and quality of life in HF with reduced ejection fraction (HFrEF) patients. Neutral results in several large randomized controlled trials have confirmed that the same principles cannot be applied to HFpEF. Based on the lack of significant reduction of cardiovascular death in HFpEF provided by angiotensin receptor blockade with the use of candesartan in the CHARM-Preserved Trial [7], and the absence of significant improvement in patient symptoms, exercise capacity or quality of life with long-term aldosterone receptor blockade using spironolactone in the Aldo-DHF Randomized Controlled Trial [8], it has been concluded that pharmacological inhibition of the renin angiotensin aldosterone system (RAAS) is ineffective. Similarly, spironolactone

also failed to significantly reduce the incidence of cardiovascular mortality or hospitalization in HFpEF in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial [9]. More recently, a meta-analysis of 18,000 patients in 25 randomized controlled trials confirmed neutrality in all-cause mortality reduction in HFpEF with the use of RAAS blockade [10••]. Although this analysis showed that beta blockade may confer a mortality benefit (RR 0.78, 95% CI 0.65–0.94, $p = 0.008$), this improvement was strongly influenced by ischemic heart disease [10••]. Moreover, a recent multicenter double-blind study targeting the nitric oxide pathway with isosorbide mononitrate failed to demonstrate significant improvements in HFpEF [11•]. These results highlight that no individual class of medication is known to improve outcomes in HFpEF. Howver, combined treatment may offer some benefit in HFpEF, with improvement in exercise tolerance (exercise capacity graded by treadmill time) demonstrated in a meta-analysis of 183 patients in 6 randomized controlled trials (weighted MD 51.5, 95% CI 27.3–75.7, $p < 0.001$) [12].

The limitations of current diagnostic tools for HFpEF are a major challenge in modern cardiology. In our aging population, with increasing numbers of comorbidities, the numbers of individuals with HFpEF are increasing, with outcomes comparable to HFrEF [1, 13, 14], but no available therapy. There is an urgent need for the discovery of parameters that can categorize homogeneous subphenotypes in these individuals. This step may be an important key to successfully tailoring individual therapies.

Imaging clues to etiology and pathogenesis in HFpEF

Etiology The etiology of HFpEF itself is broad, and remains poorly characterized. HFpEF is multifactorial, risk factors include older age and female sex, as well as an increasing number of comorbidities such as hypertension, obesity and diabetes mellitus [15, 16]. Hypertension is particularly prevalent in HFpEF, affecting up to 60% of individuals [17]. Older age (OR: 1.057, 95% CI 1.015–1.100, $p = 0.007$) and obesity (OR: 1.096, 95% CI 1.035–1.161, $p = 0.002$) are key contributors to dyspnea, and demonstrate an independent association with NYHA class [18]. Moreover, right ventricular dysfunction [19], atrial fibrillation [20], and renal dysfunction are also common [21]; and associated with worse outcomes than HFpEF patients without these sequelae [18, 20, 22]. HFpEF is characterized by hypertensive LV remodeling in 60% of patients, whereby the LV wall is thickened but the LV cavity is not dilated, and is accompanied by diastolic dysfunction in nearly 70% of patients, engendering left atrial enlargement in over 65% of individuals as a reflection of increased filling pressures [23].

Pathophysiology In contrast to HFrEF, the pathophysiology of HFpEF remains incompletely understood. The contributors are such that no single resting parameter can reliably characterize these individuals. Indeed, clinical trials have often relied on poorly defined means to stratify patients, including exclusion of patients with normal natriuretic peptide levels—even though these are present in up to 29% of hemodynamically verified individuals with HFpEF [24]. Therefore, the lack of definitive positive trial outcomes may in fact be engendered by the large heterogeneity of individuals with HFpEF, compounded by the limited specificity and sensitivity of guideline-driven noninvasive measures of diastolic dysfunction [25].

Despite its heterogeneity, common pathophysiologic features of HFpEF are increased myocardial stiffness (contributed to by excess interstitial collagen deposition, cross-linking, and aberrant myocardial cytoskeletal protein modifications such as titin). This is evidenced by upward and leftward shift in end-diastolic pressure-volume relationship, particularly during physiological stress. In addition, prolongation of active myocardial relaxation is a consequence of impaired active muscular inactivation and contraction dyssynchrony manifest by prolongation of the time constant of isovolumetric relaxation (tau) [26, 27]. Novel measures such as untwisting rate, precursor to isovolumic pressure decay, can also noninvasively reflect active myocardial relaxation properties [28•]. Myocardial stiffness and delayed relaxation restrict LV diastolic inflow, which in turn leads to elevated filling pressures. Such elevated pressures are exacerbated by even modest physical exertion in HFpEF, which is a key determinant of the debilitating symptoms of dyspnea and fatigue experienced by these patients [29]. In fact, the extent of the exercise-mediated elevation in filling pressures, invasively determined by pulmonary capillary wedge pressures (PCWP), carries great prognostic importance and is the strongest hemodynamic predictor of outcomes in HFpEF [30].

Nevertheless, multiple other factors synergistically worsen HFpEF symptomatology and add to the complexity of its pathophysiology. In conjunction to

decreased ventricular compliance, impaired ventriculo-arterial coupling, arterial stiffness and endothelial dysfunction are often present [31, 32]. These features contribute to heightened sensitivity of the HFpEF phenotype to loading conditions, and greater predisposition to pulmonary edema under small increments of loading. Skeletal muscle dysfunction has also been demonstrated, for example, by increased muscular fat content that is strongly associated with peak VO_2 in HFpEF [33]. There is also evidence of impaired oxygen extraction and oxidative metabolism in HFpEF [34]. Coronary microvascular dysfunction is another contributor to disease pathogenesis. Impaired coronary flow reserve in the absence of overt coronary artery disease is independently associated with worse echocardiographic evidence of diastolic dysfunction (e′ and E/e′, $p < 0.0001$); and associated with worse cardiovascular outcomes (adjusted HR: 2.38, 95% CI 1.21–4.67, $p = 0.01$) and hospitalizations (HR: 2.47, 95% CI 1.09–5.62, $p = 0.03$) in HFpEF [35••]. HFpEF patients also display baroreflex and peripheral autonomic dysfunction, with blunted exertional responses showing a 40% lower increase in heart rate [36]. The resulting inadequate chronotropic responses are associated with exercise limitation in HFpEF [37••]. Moreover, atrial mechanics [38], as well as systolic performance are also of increasingly recognized importance in HFpEF, and have direct implications to the non-invasive assessment of disease progression and diagnosis.

Diastolic dysfunction and diagnosis of HFpEF

Implications for imaging—is this necessarily a diastolic disease? The paradigm of HFpEF as an isolated disease of diastolic function originated as a result of erroneous interpretation of the information that is conveyed by EF measurement. Normal systolic function in HFpEF cannot be established on the basis of preserved EF alone, as EF is highly load dependent (both preload and afterload), and also highly influenced by structural changes with variations in end-diastolic volume greatly altering EF irrespective of contractility [39]. Several pathophysiological features of HFpEF, such as myocardial fibrosis and microvascular dysfunction, can affect both diastolic and systolic function. In fact, there is now clear evidence of significant systolic impairment in HFpEF, such as decreased contractility, which is associated with greater mortality [40]. Importantly, systolic function reserve is particularly affected with HFpEF patients showing significantly lower cardiac output reserve [31, 37••], that is also present in the right heart [41].

"Classical" diagnosis of diastolic dysfunction The echocardiographic evidence of diastolic dysfunction falls short of providing a unifying characterization in HFpEF. The previous recommendations for diastolic assessment were complex and ambiguous [42]. The current recommendations have been simplified but now recognize a greater proportion of studies as non-diagnostic [3]. Part of the problem is that the markers of diastolic dysfunction (E/A ratio, E/e′, LA volume) are the same as have been used for the last few decades, but the sequence of their use has been revised. Perhaps the diagnostic content of the echocardiogram would be increased by adding newer parameters.

Although diastolic impairment is common, up to 30% of patients show normal resting diastolic function by standard echocardiography [23]. Surrogate markers such as E/e′ are load dependent, and have poor predictive ability to detect true elevation of filling pressures, especially as measures are usually only performed at rest. The American Society of Echocardiography cutoff for mean E/e′ has poor sensitivity in detecting elevated filling pressures, estimated to be as low as 37% [43]. Moreover, diastolic dysfunction is not exclusive to HFpEF, and is often present in patients without HF [44].

Problems with late-stage disease Multiple pathogenic contributors further complicate the development of late stages of HFpEF. Diastolic dysfunction alone is unlikely to explain the transition to clinically overt symptomatology. There are also significant contributions by impaired systolic and chronotropic responses, particularly during physiological stress, to worsening hemodynamic phenotype [37••]. A number of comorbidities, including coronary artery disease [45], atrial fibrillation [22] and right ventricular dysfunction [18] contribute to impaired contractile reserve and higher mortality in the late stages of HFpEF.

Alternative resting parameters and diagnosis of HFpEF

LV global longitudinal strain Speckle-tracking analysis is an evolving modality with additive value to standard echocardiography. Acoustic reverberations of the myocardium, or "speckles", can be computationally identified and tracked over time to measure segmental and global myocardial mechanical properties across the cardiac cycle that extend beyond standard volumetric

and velocity measures. LV global longitudinal strain (GLS) is relatively independent of traditional diastolic parameters such as E/e′ and e′ [46]. In contrast to ejection fraction, GLS reflects the performance of longitudinally arranged subendocardial fibers that are affected early in disease pathogenesis, allowing detection of even subtle impairment [47]. Such systolic deficits have been reported in HFpEF [31, 37••], with confirmation of profound impairment in GLS (− 14.6% vs − 20%, $p < 0.001$) demonstrated in a large analysis where > 2/3 of the 219 HFpEF patients included showed systolic deficit on the basis of GLS [46].

GLS is associated with circulating levels of collagen synthetic biomarkers [48•], and independently associated with natriuretic peptide levels [46]. It shows discriminative diagnostic capacity for HFpEF based on the noninvasive ESC criteria [49••]. Importantly, we have recently demonstrated the diagnostic capacity of GLS, based on hemodynamically verified HFpEF diagnosis at rest and peak exertion using PCWP [50]. GLS impairment is associated with greater risk of cardiovascular death or hospitalization, even following adjustment for clinical and conventional echocardiographic parameters (adjusted HR 2.14, 95% CI 1.26–3.66, $p = 0.005$) [51••]; thus, GLS assessment of systolic longitudinal function will be of growing importance in HFpEF characterization and phenotype-driven interventions (Table 1).

Left atrial strain In a similar fashion, speckle-tracking echocardiography applied to the left atrium (LA) has recently yielded promising results. There is a clear and profound impairment in LA mechanics in HFpEF, depicted by reductions in both reservoir and booster functions [63, 64], related to elevated natriuretic peptide levels [58] and to reduced exercise capacity [59]. Given the strong relationship between elevated LA pressures and mortality in HFpEF [30], it is not surprising that impaired LA strain is associated with worse outcome [60•], being independently associated with cardiovascular hospitalization, HF or death even following adjustment for clinical parameters, RV and LV systolic function ($B = 1.43$, 95% CI 1.05–1.95, $p = 0.02$) [61•].

Moreover, impaired LA reservoir strain appears to be strongly related to worse hemodynamic profiles of pulmonary artery pressures, pulmonary elastance, cardiac index, and stroke volume index in HFpEF [62]. Importantly, worse LA reservoir strain is also independently associated with higher exercise PCWP following adjustment for indexed LV mass, indexed LA volume, mean E/e′ and exercise systolic blood pressure ($B = -0.66$, 95% CI −0.87 to −0.46, $p < 0.001$). LA reservoir strain at a cutoff of ≤ 33% also has significant diagnostic ability with a net reclassification improvement of 16% in comparison to current noninvasive guidelines (Fig. 1) [62].

T1 mapping In contrast to echocardiography, cardiac magnetic resonance imaging (cMR) has the advantage of providing excellent contrast resolution that allows detailed tissue characterization. Late gadolinium enhancement requires a frame of normal reference that is unavailable in the diffusely diseased heart. However, novel techniques such as T1 mapping, using a variety of methodologies for calculation of T1 times, such as the modified Look-Locker inversion recovery (MOLLI) sequence, have shown promising results in HFpEF phenotyping. The quantification of myocardial fibrosis from myocardial extracellular volume (ECV) underpins one of the pathophysiologic mechanisms of increased stiffening in HFpEF [65]. HFpEF patients demonstrate significantly higher levels of ECV that are independently associated with invasively attained LV stiffness [52•], and associated with cardiac events [53, 54•]. T1 mapping-derived ECV is also able to discriminate between hypertensive heart disease and the diagnosis of HFpEF by the ESC noninvasive criteria [49••]. In the analysis of 117 invasively verified HFpEF patients, ECV correlates with natriuretic peptide levels, aerobic capacity as well as symptomatic status in HFpEF [54•].

Use of the exercise response in HFpEF

Exercise testing is an important and under-used step in the evaluation of patients with dyspnea. First, it provides an objective assessment of exercise capacity—sometimes obesity and lack of physical fitness are the primary drivers of exercise intolerance, rather than myocardial disease. Second, it provides a means of excluding a functional contribution from myocardial ischemia. Testing for myocardial ischemia should be performed in at risk patients as this group of individuals benefit from established phenotype-specific therapy such as revascularization and beta blockade [45]. Finally, it provides a means to unmask impairments that can be subtle and undetected at rest, especially in early disease, but are exacerbated during exercise in HFpEF patients.

Invasive testing using thermodilution at right heart catheterization are able to detect deficits in cardiac index at rest in HFpEF patients [66]. Although such subtle systolic impairments at rest are often not detected with noninvasive imaging, exercise in HFpEF patients have markedly

Table 1. Pathophysiology of HFpEF and implications for novel diagnostic testing

Pathophysiology	Traditional testing	Novel imaging testing	Implication of novel testing in HFpEF
Increased myocardial stiffness	Pressure-volume relationship; Time constant of isovolumetric relaxation (tau)	Untwisting rate; T1 mapping of myocardial extracellular volume (ECV)	Noninvasive and applicable to large populations; Untwisting rate reflects active myocardial relaxation properties [28•]; ECV is independently associated with invasively attained LV stiffness [52•], and is associated with cardiac events [53, 54•]. It shows diagnostic capacity [49], and correlates with natriuretic peptide levels, aerobic capacity as well as symptom status [54•].
Elevated filling pressures	Invasive pulmonary capillary wedge pressure (PCWP); resting E/e'	Exercise E/e'	Usefulness in exclusion of intermediate risk HFpEF with increased diagnostic sensitivity to 90% at a cost of decreased specificity [55••]; Associated with systolic function reserve, fibrosis biomarker, exercise capacity and incidence of HF hospitalization [37••, 56•].Associated with cardiovascular outcomes independently of natriuretic peptide levels and clinical characteristics [57].
Impaired atrial function	Left atrial volume indexed (LAVI)	Left atrial strain	Related to elevated natriuretic peptide levels [58] and to reduced exercise capacity [59]. Associated with worse outcome [60•], independently of clinical parameters, RV and LV systolic function [61•]. Related to worse hemodynamic profiles, independently associated with exercise PCWP and shows significant diagnostic improvement to current noninvasive guidelines [62].
Impaired systolic function	Ejection fraction (EF)	LV global longitudinal strain (GLS)	Associated with circulating levels of collagen synthesis biomarkers [48•] and natriuretic peptide levels [46]. Provides diagnostic information for HFpEF [49]. Associated with cardiovascular death or hospitalization following adjustment for clinical and conventional echocardiographic parameters [51].

impaired augmentation of stroke volume and cardiac output easily identified by noninvasive measurement [31]. Moreover, a large proportion of HFpEF patients show normal resting filling pressures even during invasive testing, despite significant hemodynamic impairment during exercise [55••]. Thus, the focus of current HFpEF diagnostic guidelines on resting parameters contributes to poor diagnostic sensitivity, as estimated normal filling pressures by E/e' cannot exclude HFpEF diagnosis even in combination with normal natriuretic peptide levels [66].

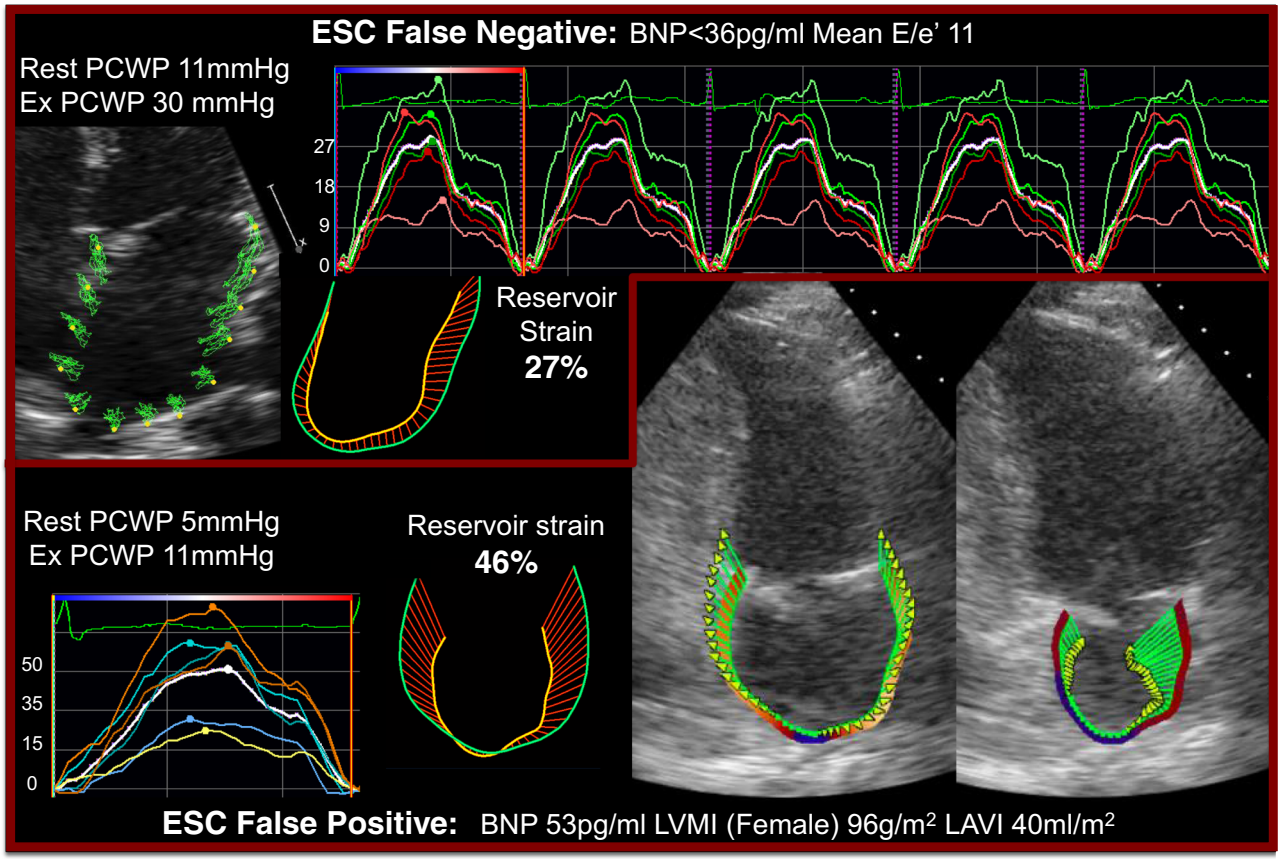

Figure 1. Example of HFpEF reclassification improvement offered by left atrial strain: Global left atrial strain at cutoff ≤ 33% is able to provide significant reclassification improvement in comparison to the 2016 ESC criteria for the noninvasive diagnosis of HFpEF. This example shows false negative (top) and false (positive) patients according to the ESC criteria that were correctly reclassified by reservoir strain.

Exercise E/e' Diastolic impairment in HFpEF is exacerbated by physiological stress. This leads to increases in both pulmonary venous and pulmonary artery pressure that is well characterized by invasive testing [55••]. In the presence of tricuspid regurgitation, the latter can also be assessed from the velocity of the regurgitant jet, although high velocity (e.g., > 3.5 m/s) is more meaningful at low rather than high levels of exercise [67].

Assessment of diastolic function via E/e' measurement during exercise has the ability to increase current noninvasive diagnostic sensitivity due to unmasking of impairments in intermediate risk patients. Using the cutoff value of exercise E/e' > 14, the sensitivity of hemodynamically verified diagnosis can be increased to 90% [55••]. However, this comes at a cost of decreased specificity, suggesting usefulness of diastolic stress testing in exclusion of intermediate risk HFpEF in patients that do not warrant costly invasive assessment [55••]. Moreover, exercise diastolic impairment also carries prognostic importance in HFpEF. Symptomatic patients with elevated exercise E/e' show worse longitudinal systolic function reserve, higher levels of the fibrosis biomarker galectin-3, lower exercise capacity and greater incidence of HF hospitalization [37••, 56•]. Elevated exercise E/e' is also associated with composite endpoint of cardiovascular hospitalization or death independently of natriuretic peptide levels and clinical characteristics (HR 2.69, 95% CI 1.44–5.04, $p = 0.002$) [57]. However, despite the advantages of noninvasive diastolic stress testing, this test can be limited by image quality. While the feasibility of obtaining diagnostic-quality measurements decreases with increasing levels of exercise, this is not commonly a problem in symptomatic patients (Table 2).

Systolic stress testing: exercise GLS physiological stress testing in HFpEF has the ability of unmasking impairments in cardiac reserve that are well described in HFpEF

Table 2. Advantages and disadvantages of novel parameters in HFpEF assessment

Parameter	Advantages	Disadvantages
	Resting imaging	
LV global longitudinal strain (GLS)	Relatively independent of traditional diastolic parameters such as E/e' and e' [46]. Reflects the performance of longitudinally arranged subendocardial fibers that are affected early in disease pathogenesis, allowing detection of even subtle impairment [47]. Low cost and easily accessible testing.	Requires adequate apical views that can be limited in the obese phenotype of HFpEF. Frame rate dependent. Requires adequate operator training. Analysis algorithms have previously differed between different types of software, so absolute values have varied. This problem has largely been resolved.
Left atrial strain	Measurements at rest are independently associated with hemodynamic profiles with exercise [62]. Low cost and easily accessible testing.	
T1 Mapping	Excellent contrast resolution that allows detailed tissue characterization. Does not require a normal site for a frame of reference.	Relatively high cost. Requires advanced operator skill. Limited temporal resolution.
	Exercise imaging	
LV global longitudinal strain (GLS)	Advantages of resting GLS plus allows quantification of deficits in systolic function reserve.	Does not take speed of contraction into account (no temporal component). Temporal resolution is lower than that of tissue Doppler.
Exercise E/e'	Unmasking of impairments in intermediate risk patients. Excellent temporal resolution, superior to speckle tracking. Low cost and easily accessible testing.	Diagnostic specificity is suboptimal with current cutoffs. Feasibility of obtaining diagnostic-quality measurements decreases with increasing levels of exercise.

[31, 37••]. Parameters such as exercise GLS show marked deficits in HFpEF that are exacerbated by exertion [50]. In receiver operator curve analysis, exercise has excellent predictive ability to differentiate symptom status in HFpEF patients (AUC: 0.78) [37••]. Exercise GLS also has diagnostic capacity in cohort where HFpEF is identified on hemodynamically grounds (AUC: 0.67) [50].

There are two disadvantages to the use of GLS for assessing systolic reserve. First, GLS lacks a temporal component, and therefore ignores speed of contraction, which is impaired in myocardial disease. Second, the temporal resolution of speckle-tracking echocardiography is lower than that of tissue Doppler, which may be the preferable modality for assessing responses during tachycardia.

Targeting of management to pathophysiology and phenotype

Recent advances in HFpEF therapy have in part originated from strategies aimed at hemodynamic consequences of disease pathogenesis. A novel interatrial shunt device targeting the pathological rise in exercise PCWP in HFpEF [68•] shows an effective response in reducing filling pressure [69•]. Similarly, the use of type III phosphodiesterase inhibition via intravenous milrinone have also led to reductions in exercise PCWP [70•].

An alternative strategy has been phenotype-specific stratification of HFpEF, which thus far has been largely focused on comorbidities such as obesity, hypertension, coronary artery disease, atrial fibrillation, kidney disease, and skeletal muscle dysfunction [25, 71]; or clinical parameters combined with traditional echocardiography markers [72]. A number of promising imaging modalities have shown significant improvement in the noninvasive characterization of HFpEF. Metabolic indexes of ventricular stiffness have been shown to offer good HFpEF stratification, resulting in identification of a HFpEF biochemical phenotype of high collagen cross-linking that identifies patients resistant to spironolactone therapy with no effect

of improving diastolic dysfunction [73••]. Similarly, by selecting HFpEF phenotypes with more severe diastolic impairment evidenced by the presence of exercise-induced E/e′ > 13, the STRUCTURE (SpironolacTone in myocaRdial dysfUnCTion with redUced exeRcisE capacity) trial identified a sub-group of patients responsive to spironolactone [74••], which conferred significant improvement in peak VO_2 in comparison to placebo (2.9 ml/min/kg, 95% CI 1.9–3.9 vs. 0.3 ml/min/kg, 95% CI 0.5–1.1; $p < 0.001$) [74••]. Whether advances in cardiovascular imaging can be similarly applied to further stratify HFpEF patients into homogenous groups with clearer pathophysiological basis of disease, amenable to targeted intervention, will be of particular public health interest.

Conclusion

HFpEF remains a major challenge in modern cardiology, with an incompletely understood pathophysiology, rising prevalence, high morbidity and mortality but without available effective therapy. The lack of response to therapies is contributed by the heterogeneity of patient profiles, and poor characterization by classical parameters. The response to this challenge may be to better define the sub-phenotypes, and imaging may be the best way to accomplish this. Novel cardiovascular imaging modalities offer greatly improved characterization in these patients. Whether this information can be synthesized to adequately stratify patients into sub-phenotypes with clearer disease pathogenesis amenable to targeted intervention will be of particular future interest.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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