There is an emerging interest in heart failure with preserved ejection fraction (HFPEF) because of its high prevalence in the community and several specific characteristics compared with “classic” heart failure with reduced ejection fraction. HFPEF patients are older and more often female, and lack left ventricular dilatation. A likely principal cause of HFPEF is diastolic dysfunction, particularly ventricular stiffening; however, the clinical phenotype of HFPEF is also modulated by dysfunction of other organs such as kidney, vasculature, etc. Despite its social burden, the diagnostic criteria and therapeutic strategies remain to be established. In particular, the lack of established diagnostic criteria has resulted in conceptual confusions about HFPEF in clinical practice. In this review, what is known and unknown about HFPEF is discussed, and several challenging proposals about its diagnosis and therapy are raised.  

**Key Words:** Diastole; Heart failure; Ventricular function

**Pathophysiology of HFPEF**

**Cardiac Dysfunction**

The abnormality of LV relaxation and stiffness is present in HFPEF patients. Kawaguchi et al showed that the abnormality of the index for LV stiffness is present in HFPEF patients. Our experimental study in an HFPEF rat model of hypertension showed that the LV relaxation abnormality occurs at the compensatory hypertrophic stage, but that myocardial stiffening leads to overt HF without further progression of the relaxation abnormality. That result indicated that LV relaxation abnormality is an early sign of diastolic dysfunction, and that LV stiffening plays a crucial role in the transition from asymptomatic diastolic dysfunction to HFPEF.

One of the causes of LV stiffening is interstitial fibrosis. Exaggerated accumulation of collagen is associated with enhanced cross-linking and an increased ratio of collagen type I to III, and both the quantitative and qualitative alterations contribute to progressive stiffening. These alterations in extracellular matrix are induced through modulation of autocrine, paracrine, and endocrine factors. Another cause is myocyte hypertrophy with myocyte stiffening, but it should be noted that myocyte hypertrophy is not a simple phenomenon. Compensatory hypertrophy occurs to prevent an increase in wall stress caused by pressure overload, but subsequent excessive hypertrophy begins the transition to HFPEF. Compensatory hypertrophy is mediated by calcineurin, whereas the renin–angiotensin and endothelin systems contribute to the excessive hypertrophy. Myocyte stiffening associated with excessive hypertrophy is explained by a titin isoform expression shift from the compliant N2B to the stiff N2B isoform and/or lower baseline phosphorylation of titin.

**HFPEF vs HFREF**

LV dilatation increases wall stress and exaggerates mitral regurgitation, with dilatation of the mitral annulus and mitral tethering, and is associated with poor prognosis in
HFREF patients. However, LV dilatation may result from a compensatory mechanism to keep stroke volume through the Frank-Starling mechanism, rather than being a primary cause of the progression of HFREF. This is partly supported by the observation that surgical and pharmacological prevention or attenuation of LV dilatation fails to provide clinical benefit for HFREF patients.19–21 In contrast to HFREF, HFPEF is not characterized by LV dilatation, which is partly explained by the greater myocyte stiffness in HFPEF than in HFREF17 and also explains the more rapid increase in pulmonary artery diastolic pressure in the transition from chronic compensated to acute decompensated HF stage in HFPEF.22 The incapability of dilating the LV chamber limits the increase in stroke volume and induces excessive elevation of LV filling pressures during exercise, resulting in exercise intolerance.23 The lack of LV dilatation is a pathogenetic characteristic of HFPEF, and should not be interpreted as the absence of a risk factor of poor prognosis.

HFREF is considered an energy-deprived state.24 Our clinical study showed that cardiac energy efficiency did not differ between normal volunteers and HFPEF patients,25 indicating that attenuation of energy efficiency is not a principal cause of HFPEF. However, among the HFPEF patients, energy efficiency inversely correlated with the index for LV filling pressure. Inefficient energy utilization may contribute to progressive diastolic dysfunction in the diseased heart with preserved EF, but not in the normal heart.

Dysfunction of Other Organs
Our recent cross-sectional observation demonstrated that independent competing risks for DHF were female gender, obesity, progressive diastolic dysfunction and renal insufficiency in hypertensive patients with preserved EF.26 Once HFPEF occurs, its clinical outcome is aggravated by age,27 renal insufficiency,27,28 anemia,29,30 and diabetes mellitus.31 HFPEF should be understood as a systemic disease based on cardiac dysfunction. Anemia is associated with renal insufficiency, which is closely related to vascular stiffness.26,30 The prevalence of HFPEF increases among the older and female population, and Redfield et al showed that aging and female gender are associated with increased vascular and ventricular diastolic stiffness.32 Vascular stiffening is related to impaired exercise tolerance.33 Thus, HFPEF may be characterized as the combination of diastolic dysfunction and vascular stiffening. Although increased body mass index is an independent competing risk for HFPEF, the prognosis is poor in patients with low body mass index,27 for reasons that are unclear.

How to Diagnose HFPEF
The principal reason for the difficulty in understanding HFPEF in clinical practice is the lack of established diagnostic tools for LV diastolic dysfunction in contrast to the easy diagnosis of HFREF with measurement of EF.

B-Type Natriuretic Peptide
Diagnosis of HF based on clinical symptoms is unreliable,24 so objective markers are required. It is well known that plasma levels of B-type natriuretic peptide (BNP) are elevated in HF.35 Although the BNP level is also increased with progression of LV hypertrophy without HF,26,37 our
clinical study showed that BNP is increased in HFPEF patients, independent of the presence of LV hypertrophy,\(^{38}\) which is partly compatible with results of other clinical studies.\(^{39}\) A recent statement published by the European Society of Cardiology indicated BNP/N-terminal-proBNP as a first-line biomarker for the diagnosis of HFPEF among subjects with preserved EF.\(^{40}\) However, the concentration of BNP/N-terminal-proBNP rises in normal older and/or female individuals\(^{41}\) and in those with renal dysfunction\(^{42}\) or atrial fibrillation\(^{43}\) and decreases in obese subjects.\(^{44}\) Therefore, we should be cautious in using BNP alone to diagnose HFPEF.

**Doppler Echocardiography**

As a method of assessing diastolic function, the invasive measurement of LV pressure is the gold standard, but is not practical. Pulsed Doppler transmural flow velocity curves have been used for noninvasive detection of diastolic dysfunction, but are not reliable in subjects with preserved EF.\(^{45,46}\) Increased LV filling pressures secondary to diastolic dysfunction are associated with an increased ratio of peak mitral E to A wave velocities and a shortened deceleration time of mitral E wave in patients with reduced EF. However, these indices do not correlate with the LV filling pressures in patients with preserved EF.

The ratio of pulsed Doppler mitral E wave velocity to tissue-Doppler-derived peak early diastolic velocity of the mitral annulus movement (E/E’) correlates with LV filling pressures, independently of the patient’s EF.\(^{47,48}\) The European Society of Cardiology raised this index as a first-line Doppler echocardiographic index in the diagnosis of HFPEF\(^{49}\) but its relation with LV filling pressures is modest.\(^{47,49}\)

Several complementary parameters for use in detecting LV diastolic dysfunction and/or the elevation of LV filling pressures have been recommended: increased left atrial diameter/volume\(^{50}\), increased LV mass index (LV hypertrophy)\(^{51}\), increase in pulmonary A wave duration minus mitral A wave duration\(^{46}\) and the presence of atrial fibrillation. The pulsed Doppler transmural flow velocity curves are still helpful\(^{52}\) but no longer the first-line measurement.

**New Techniques of Noninvasive Assessment of Diastolic Function**

There are several challenges to noninvasive assessment of diastolic function. Advances in speckle tracking echocardiography enable noninvasive assessment of ventricular untwisting, which correlates with LV relaxation.\(^{53}\) We have shown that the early diastolic endocardial movement assessed with color-encoded echocardiographic imaging also correlates well with LV relaxation.\(^{54}\)

LV stiffening plays a crucial role in the transition to HFPEF, and its noninvasive assessment is awaited. We have recently reported that movement of the epicardial site of the LV free wall during diastole reflects LV wall stiffening, according to linear elastic theory, and we have demonstrated that its evaluation is helpful in the noninvasive assessment.\(^{55}\)

**How to Treat HFPEF**

**Pharmacological Therapy**

The prognosis of HFREF has improved through the proof of effective medications and adherence to guidelines based on the clinical evidence.\(^{3}\) In contrast, the prognosis of HFPEF is unchanged over the past 20 years. Patients with diastolic dysfunction have a poor prognosis, irrespective of a history of HF.\(^{56}\) Thus, therapeutic strategies for HFPEF and/or diastolic dysfunction need to be established.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) improve the clinical outcomes of HFREF. Ours and other experimental studies have shown that ACEIs, ARBs or their combination provide beneficial effects in an animal model of HFPEF.\(^{57-61}\) Kasama et al showed that ARBs improved cardiac sympathetic nerve activity in HFPEF patients\(^{52}\) and Komukai et al demonstrated that administration of ACEs and/or ARBs prevented rehospitalization for HF in HFPEF patients.\(^{53}\) However, large prospective clinical trials have failed to clearly show effectiveness. The CHARM-Preserved Trial showed that treatment with candesartan did not significantly reduce the primary outcome, but fewer patients in the candesartan group than in the placebo group were admitted to hospital for HF.\(^{64}\) The most recent clinical trial, I-PRESERVE, failed to show beneficial effects of irbesartan on either the primary outcome or HF-related events.\(^{55}\) The PEP-CHF study demonstrated that treatment with perindopril did not reduce the primary outcome;\(^{66}\) however, many patients withdrew from the assigned regimens 1 year after randomization. By the first year, hospitalization for HF had significantly reduced and the 6-min walk distance improved in the perindopril group compared with the placebo group. In the Hong Kong DHF study, neither irbesartan nor ramipril had an additional effect on symptoms compared with treatment with diuretics alone.\(^{67}\) However, diuretics in combination with irbesartan or ramipril marginally improved LV systolic and diastolic function, as assessed by tissue Doppler echocardiography, and lowered the level of N-terminal-proBNP. Thus, treatment with ACEIs and ARBs may have some benefits in HFPEF patients, but their clinical impact on HFPEF is likely to be less than that on HFREF.

Mineralocorticoid receptor blockers improve the prognosis of HFREF patients, and our study showed beneficial effects in an animal model of HFPEF.\(^{58}\) Mottram et al suggested benefits of spironolactone on diastolic function in HFPEF patients by demonstrating that treatment tended to decrease the left atrial area.\(^{69}\) Currently, a large, randomized trial (TOPCAT: Trial of Aldosterone Antagonist Therapy in Adults with Preserved Ejection Fraction Congestive Heart) is ongoing. Although the effects of mineralocorticoid receptor blockers will be clarified with the clinical trial, it remains unclear whether the principal effects of the drugs are provided through antagonizing of aldosterone. In classic aldosterone target tissues, such as kidney, colon and salivary glands, 11,\(\beta\)-hydroxysteroid dehydrogenase type 2, which converts active corticosterone into inactive 11-dehydrocorticosterone, is expressed at high levels, resulting in the mineralocorticoid receptor being stimulated selectively by aldosterone.\(^{70}\) However, the expression of 11,\(\beta\)-hydroxysteroid dehydrogenase type 2 is slight in the heart.\(^{67,71}\) The tissue level of aldosterone is much less than previously reported,\(^{68,72}\) the glucocorticoid level in the myocardium is 1,000-fold higher than the aldosterone level\(^{68}\) and both glucocorticoids and mineralocorticoids have affinity for the mineralocorticoid receptor.\(^{73}\) Ours and other experimental studies showed that glucocorticoids exaggerate myocyte hypertrophy\(^{74,75}\) and a recent clinical report indicated that the plasma level of glucocorticoid, as well as of aldosterone, is an independent predictor of increased mortality risk in HFPEF.
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HF and HFPEF patients. Thus, further studies are needed to clarify how mineralocorticoid receptor blockade exerts its effects in the heart.

The $\beta$-blocker therapy has the most powerful impact on the clinical outcomes of HFREF. Previous studies have shown that $\beta$-blocker therapy improves LV diastolic function in association with increases EF in HFREF patients but it is still unclear whether there are beneficial effects for HFPEF patients. Although HFREF is associated with the downregulation of the $\beta_1$-adrenergic receptor and translocation of G protein-coupled receptor kinase 2 to the plasma membrane in the heart, these phenomena were not observed in the HFPEF model rats. Thus, the effects of $\beta$-blocker therapy in HFREF cannot be extrapolated to HFPEF, and evidence from HFPEF is required. Ours and other experimental studies have shown that $\beta$-blocker therapy improves survival rate in an animal model of HFPEF through inhibition of oxidative stress, inflammatory changes, LV hypertrophy and fibrosis. Subanalysis of the SENIORS study and several retrospective clinical studies suggested the beneficial effects of $\beta$-blocker therapy in HFPEF patients but in contrast, the SWEDIC study failed to show that $\beta$-blocker therapy improves LV diastolic function or symptoms in these patients. Currently, a randomized trial, J-MELODIC, is addressing this issue in both HFPEF and HFREF patients.

Non-Pharmacological Therapy

Ischemic heart disease is one of the principal underlying cardiovascular diseases of HFPEF, and a history of myocardial infarction is associated with poor prognosis. Revascularization is a recommended therapeutic strategy to improve symptoms based on ischemia, although its efficiency is not established. It should be noted that coronary revascularization may not ameliorate prognosis, and future clinical trials are awaited.

To improve clinical outcomes, patient care after discharge may be important in both HFPEF and HFREF patients. Several studies have shown that HF programs involving a multidisciplinary team result in improved clinical outcomes of patients. Such programs improve treatment adherence rates, ensure self-care management and facilitate access to supportive services. The prevalence of HFPEF increases with aging, and these programmes may provide benefits particularly in the elderly population.

Summary

Many of the issues in HFPEF remain to be clarified: the differences and resemblances with HFREF, its principal pathophysiology, diagnostic criteria, treatment strategy, etc. HF is currently classified into HFREF and HFPEF, but the progress in understanding HFPEF may lead to a new classification that is independent of EF and then we may be able to depart from the “one-size-fits-all” concept of HF.
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