Review Article

Heart Failure with Preserved Ejection Fraction (HFpEF)

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It has been estimated that Heart Failure with Preserved Ejection Fraction (HFpEF) may account for over 60% of patients hospitalized for HF. Key haemodynamic alterations in HFpEF include subtle systolic dysfunction (depicted by despite reduced average LV global longitudinal strain despite a preserved LVEF), pulmonary hypertension, right ventricular dysfunction, chronotropic incompetence. Diagnosis of HFpEF is established by typical signs and symptoms of HF, LVEF>50%, elevated natriuretic peptides and characteristic echocardiographic features of cardiac structural and functional alteration (eg increased LV mass index, LA volume index, E/E' ratio). Treatment mainly comprises of relief of congestion with diuretics, control of blood pressure and tachycardia. Exercise training has a significant role to play in symptomatic improvement. Disease modifying therapies like RAAS blockers, Mineralocorticoid Receptor Antagonists etc. have proved to be futile in HFpEF. Several emerging therapeutic modalities including device therapy are now being studied.

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Key words **: E/E' ratio, Pulmonary hypertension, RV dysfunction, Congestion, Exercise-training.**

It has been projectedthat underlying HFpEFmay account forup to 65% of patients hospitalised for HF. Although diagnostic accuracy is limited in patients with more than one contributors fortheir dyspnoea, the overall prevalence of HFpEF has been estimated as being between 1.1 and 3% of the whole population, with much higher percentage of patients having subclinical diastolic dysfunction[2]. In-patients over the age of 65 years, the prevalence ranges from 3.1 to 5.5%[3]. The Trivandrum HF Registry (THER) reported a prevalence of 26% for HFpEF in a patient population whose mean age was 61.2 years[4]. In another study from AIIMS comprising of rural population in Northern India, overall prevalence of heart failure was 1.2/1000 and two-thirds had HFpEF and all of them had uncontrolled hypertension[5].

The increase in HFpEF prevalence reflects the changing demographic of the general population, including increasing longevity, obesity and diabetes and the persistent presence of poorly controlled hypertension Table 2)[6]. Each of these factors is known to affect myocardial and vascular stiffness, pulmonary systolic pressure and left ventricular diastolic dysfunction[1]. Communitystudies of healthy volunteers demonstrate that derangements in diastolic function are more common than in systolic function, and progress at a greater rate[7]. Non-cardiac comorbidities such as chronic kidney disease, anaemia, malignancy and thyroid dysfunction quite frequent common in HFpEF; chronic kidney disease in particular may play a dual role in that it contributes to extracardiac volume overload and the development of the cardiorenalsyndrome[8,9]. Obesity is a predictor for HFpEF but not for HFrEF, and the adverse cardiac remodelling and biochemical abnormalities linked with the metabolic syndrome predispose to the development of increased myocardial stiffness and diastolic dysfunction[10,11]. The total influence of comorbidities on myocardial dysfunction and functional capacity is higher in patients with HFpEF than in those with HFrEF[10]. Largescale studies are in progress to target this mechanism[12].

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Preamble to Understanding of Hemodynamic Abnormalities in Heart Failure :

Architectural arrangement of LV myocardial fibres comprises of endo and epicardialfibres and mid-myocardial circumferential fibres. Shortening of longitudinal fibres in systole causes displacement of the LV basal plane towards more stationery apex and contraction of circumferential fibres causes inward deformation of the LV cavity. LV ejection fraction (LVEF) refers to contribution by both longitudinal and circumferential fibres without distinguishing between relative contributions of the two. However, in many cardiac pathologies, longitudinal muscles fibre shortening is impaired prior to any impairment of circumferential muscle fibre shortening and infact, in this initial period, circumferential function can even to a certain extent compensate for the impaired longitudinal function. This accounts for situations where despite a normal or even increased LVEF, subclinical LV dysfunction caused by deranged longitudinal function sets the breakdrop of "Heart Failure with Preserved Ejection Fraction" (HEpEF). Assessment of myocardial deformation in

different planes can now be studied by several echocardiographic methods eg, tissue doppler imaging and more recent two and three dimensional speckle-tracking echocardiography which can provide data on myocardial deformation by measuring strain and strain rate. Strain and strain rate is less load-dependent than LVEF and provides earlier insight into myocardial dysfunction than LVEF. When there is an ultimate impairment of circumferential deformation with disease progression, an impairment of LVEF occurs, inducing the transition from HFpEF to HFrEF (Heart Failure with reduced Ejection Fraction).

Cardiac Factors in HFpEF Haemodynamics :

Significantly, it has been shown that HFpEF patients – despite the measured LVEF in the normal or near-normal range,– have subtlesystolic dysfunction at rest as demonstrated by reduced LV strain at echocardiographic imaging, andthis dysfunction has prognostic relevance[13,14]. Moreover, it has been suggested thatcontractile dysfunction may contribute to inadequate myocardial response to exertion, leadingto the appearance and exacerbation of HF symptoms[15,16]. Indeed, a recent study in HFpEF subjects examined cardiac systolic reserve during exercise and found that positive contractilityresponse was depressed[17]. Hence, the exercise test may unravel mild deficits in systolicfunction in HFpEF.

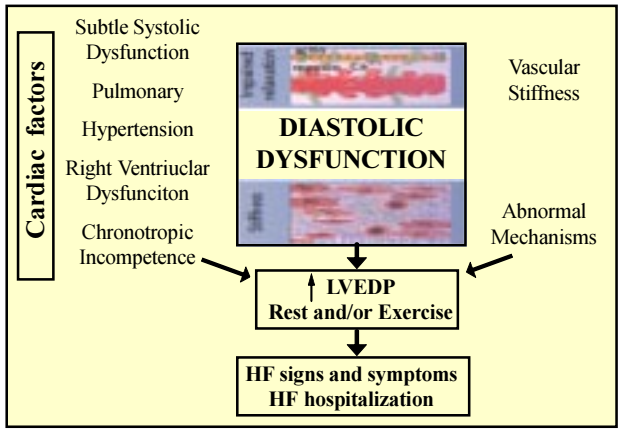
There is a high prevalence of pulmonary hypertension (PH) in HFpEF[18]. A study has shown that pulmonary artery systolic pressure (PASP) rises along with pulmonary artery capillary wedge pressure (PAWP) in patients with both hypertension and HFpEF[19]. However, PASP remains higher in HFpEF, even when adjusting for PAWP, suggesting a pre-capillary component to PH on top of pulmonary venous hypertension.

An invasive haemodynamic study has recently shown that RV dysfunction is common inHFpEF and is contributed by both RV contractile impairment and afterload mismatch from PH[20]. It has also been demonstrated that patients with HFpEF exhibit impaired RV reserve during exercise that is associated with high filling pressures and inadequate cardiac output responses[21]. These findings emphasizes the co-existence of biventricular dysfunction in HFpEF haemodynamics.

Chronotropic incompetence represents another important facet of HFpEF, which hasbeen described in approximately 30 % of patients[22,23,24]. Chronotropic incompetence may help to partially explain why most patients with HFpEF complain of symptoms predominantly during physical exertion. Since the rise in plasma catecholamine with exercise is similar in HFpEF and healthy controls, it has been proposed that chronotropic incompetence may be linked to deficits in beta-adrenergic stimulation[22]. In addition, autonomic dysfunction may be a contributing factor, as heart rate recovery is abnormal and baroreflex sensitivity is attenuated in HFpEF[23].

Cardiac function is determinedby the net balance between afterload and preload[25]. Central aortic stiffness, increasing systolic load andnegatively directedventricular–vascular coupling, may accelerate HF development in at-risk patients. Aortic stiffness increases with age,ventricular systolic stiffening also increases, and this coupled ventricular–vascular stiffeningis a hallmark of HFpEF[26,27]. This restricts LV systolic reserve, augments the cardiac energy demands required to enhance cardiac output, and plays a key role in arterial pressure liability accompanying small changes in LV preload[28].

Schematic Representation of HFpEF Haemodynamics :



HFpEF has remained a diagnostic challenge with variable definitions over the past decade, culminating in the development of a stricter definition in the recently published European Society of Cardiology guidelines (Table 1)[29]. The diagnosis of HFpEF can be somewhatdifficult to make, and often occurs after significant much delay and consideration of alternative diagnoses for dyspnoea. For most patients, recognition of the typical features of HFpEF on resting echocardiography with the clinical syndrome of HF aids the diagnosis, and where the diagnosis remains unclear stresstesting should be considered. An approach to diagnosing HFpEF is given in the Flowchart (Table 2).

Treatment :

The heterogeneity of thepatient population, the wide range of clinical phenotype and short-comings with a clear definition around HFpEF have led to largely negative clinical trials and a paucity of effective treatment options. Despite these limitations, acareful application of the trial outcomes together with a mechanistic understanding have led to basic principles for the treatment of the patient with HFpEF, as listed in Table 3[30].

Table 1 — *Diagnostic Criteria for HFPEF*[28]

- Presence of symptoms and signs typical of heart failure
  - ✓ note that signs are not always evident in patients with HFpEF, as filling pressures may only increase with exercise, the JVP may not be elevated at rest
  - ✓ typical signs and symptoms include breathlessness, reduced exercise tolerance, fatigue and ankle swelling; features such as a displaced apex beat and third heart sound are absent
- A preserved ejection fraction (LVEF ≥ 50%)
  - ✓ previous studies have included patients with LVEF ≥ 40%
  - ✓ new guidelines suggest a grey zone between LVEF 40 and 50%
- Elevated levels of natriuretic peptides#
  - ✓ BNP level ≥35 pg/mL
  - ✓ NT-proBNP level ≥125 pg/mL
- Objective evidence of other cardiac structural or functional alteration
  - ✓ either left ventricular hypertrophy (increased left ventricular mass index) or left atrial enlargement
  - ✓ diastolic dysfunction on echo (increased E/e' or decreased e') or cardiac catheterization (increased LVEFP or PCWP, particularly with exercise)

[Abbreviatrions: BNP=brain natriuretic peptide; HFpEF=heart failure with preserved ejection fraction; JVP=jugular venous pressure; LVEFP=left ventricular end diastolic pressure; LVEF=left ventricular ejection fraction; NT=N-terminal; PCWP= pulmonary capillary wedge pressure]

Adapted from the 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart failure[1].

Non-pharmacological Therapy Approaches in HFpEF :

Exercise : In the Ex-DHF pilot trial[31], 64 patients with HFpEF were treated either according to the current recommendations or were exposed to an additional dedicated training programme. After 3 months, patients in the intervention group exhibited an improved peak VO_2 and improved physical fitness. This was associated with an improvement of both diastolic and atrial function. These finding were corroborated by a recent meta-analysis by Pandey*et al*[32].

Diet : In a very small study, 3 weeks of treatment with a salt-restricted DASH diet improved diastolic function, arterial stiffness, and ventricular-arterial coupling in 13 subjects with HFpEF[33]. Further, a 20-week caloric restriction diet was feasible in obese HFpEF patients, and improved symptom burden, peak oxygen consumption, and quality of life. Quantitatively, the improvement in quality of life was greater with diet than exercise. The combination of diet with endurance exercise training appeared supplementary[34].

However, much larger studies are required before making firm clinical recommendations.

Management of Comorbid Conditions :

It has been suggested that the root cause of myocardial, vascular and peripheral dysfunctionin patients with HFpEF may be precipitated by the pro-inflammatory milieu created by the presence of multiple comorbid conditions[10,35,36]. Increasing numbers of comorbidities correlate with higher frequency of hospital admissions, and patients with HFpEF have higher rates of noncardiac comorbidities compared with those with HFrEF[37]. Patients with HFpEF who have diabetes have greater left ventricular wall thickness and reduced physical function compared with those withHFpEF without diabetes[38]. Patients with COPD have a worse prognosis in HFpEF than see with HFrEF[39].

Fluid Retention :

In HFrEF, fluid retention can be treated with diuretics. Mechanistically, patients with HFrEF and HFpEF differ regarding changes in total blood volume (TBV). TBV expansion in HFpEF is mainly characterized by a red cell mass deficit, indicating that true anaemia (ie, haemoglobin concentration <12 mg/d) and a compensatory plasma volume expansion reflects the qualitative changes of TBV in most of the decompensated HFpEF patients[40]. Loop diuretics, thiazide and thiazide-like drugs are necessary to overcome TBV expansion and congestion in both forms of HF[41]. Differences among loop diuretics for the treatment of HFpEF could be of great potential interest, since smaller studies have suggested that torasemide, in contrast to furosemide, may have additional positive effects on collagen metabolism by inhibition of procollagen type I (PIP)[42]. The Hong Kong Diastolic Heart Failure Study[43] showed that the quality of life can be improved by a monotherapy with diuretics, and this effects was amplified when ACEi was added . Thus, diuretics appear indispensable for the improvement of symptom relief. According to the report of a small study, adding the vasopressin antagonist tolvaptan can be effective in severe cases accompanied by hyponatraemia[44]. However, an excessive preload reduction by diuretics can lead to an under-filling of the left ventricle and therefore, to a reduction of stroke volume and cardiac output. This can be a specific a problem in HFpEF patients with pronounced left ventricular hypertrophy and small ventricles.

Atrial Contraction :

Patients withHFpEFtolerateatrial fibrillationpoorly, especially when ventricular heart rate is high. Cessation of the atrial contraction diminishes the left ventricular fill-

Table 2 — *An approach to diagnosis of heart failure with preserved ejection fraction*

Patient presents with exertional dyspnoea

- Take history and perform physical examination
- Measure natriuretic peptides
- Exclude other causes (pulmonary disease, Ischaemic heart diseases, anaemia, physical deconditioning)
- Assess risk factor profile (advanced age, hypertension, raised BMI)

Clinical diagnosis of heart failure made when following diagnostic criteria met:

- Presence of typical symptoms and signs of heart failure (including breathlessness, reduced exercise tolerance, fatigue and ankle swelling) features such as a displaced apex beat and third heart sound may be absent in heart failure
- Elevated natriuretic peptides (BNP > 35 pg/ml or NT-proBNP ≥125pg/mL).
- Other causes excluded (pulmonary disease, Ischaemic heart disease, anaemia. Physical deconditioning)

Perform transthoracic echocardiography (resting)

The following features on resting echocardiography are consistent with a diagnosis of HFpEF (not all need be present) :

- Raised pulmonary pressures (TR jet velocity> 2.8 m/s)
- Left atriai enlargement (left atriai volume index >34 mL/M^2)
- Reised E/e' ratio (≥13)*
- Increased wall thickness (LV mass index >115 g/m^2 for men: >95 g/m^2 for women)

Consider exercise study in consultation with cardiologist to confirm impaired diastolic performance and elevated filling pressures

- Exercise right heart catheterisation – the gold standard measurement of haemodynamics, but not available in all centres
- Stress echocardiography- noninvasive, but relles on good image quality and the presence of tricuspid regurgitation

*Abbreviations : BMI = body mass index: BNP = brain natriuretic peptide: HFpEF= heart failure with preserved ejection fraction: LV= left ventricle: NT=N-terminal : TR=tricuspid regurgitant: *E/e' measured on tissue Doppler echocardiography.*

ing and along with that, decreases cardiac output[45]. Hence, restoration of sinus rhythm including ablation strategies and pharmacologic interventions including class I, II or III antiarrhythmic drugs may improve clinical symptoms. If this is not possible, ventricular heart rate should be lowered using beta-blockers or heart rate lowering calcium antagonists[46]. Theoretically, late sodium current-inhibitors like ranolazine or eleclazine may exhibit ancillary antiarrythmic effects and may be considered in HFpEF patients with angina symptoms to maintain sinus rhythm.

ACE Inhibitors and Angiotensin Receptor Blockers :

ACE inhibition has become a pharmacological mainstay in the treatment of patients with low ejection fraction HF (ie, HFrEF), significantly reducing morbidity and mortality and also favorablyaltering ventricular remodelling[47,48]. Neurohormonal activation is evident across the spectrum of HF, irrespective of ejection fraction; however, one study of perindoprial in HFpEFhas shown benefits on HF hospitalisation with ACE inhibitor therapy within the first year, but did not achieve its primaryendpoint[49]. Two large trials have examined the role of angiotensin receptor blockade in patients with HFpEF. I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction Study), a large trial of more than 4000 patients with HFpEF, with clinical characteristics typical of HFpEF, showed no impact of irbesartan on death, hospitalisation or quality of life[50]. CHARM-Preserved (Candesartan in Heart Failure – Assessment of Mortality and Morbidity; in patients with LVEF higher than 40%) demonstrated a modest impact of candesartan on hospitalization in an HFpEF, although it is important to note the less stringent entry criteria in thistrial, including inclusion of patients with an ejection fraction down to 40%[51].

Aldosterone Blockade :

Aldosterone has a major role in myocardial collagen formation, suggesting arole for spironolactone in the treatment of patients with HFpEF. Early trials demonstrated a reduction in left ventricularfilling pressures, culminating in the international TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial), which enrolled 3445 patients[52]. Although the study was neutral regarding mortality and hospitalisation, post hoc analysisdemonstrated significant re-

Table 3 — *Principles of Management in Patients with HFPEF*

(A) Avoid tachycardia — Use digoxin or beta-blockers in patients with atrial fibrillation

(B) Control Blood Pressure — ACE inhibitors, angiotensin receptor blockers and mineralocoticoid receptor antagonists may be of greatest benefit due to the physiological benefits seen in HFREF; further studies are required

(C) Treat Comorbid conditions — Optimise cardiac and non-cardiac conditions (commonly atrial fibrillation, pulmonary disease, anaemia and obesity)

(D) Relieve congestion with diuretics — Juducious use of loop diuretic with careful monitoring of renal function

(E) Encourage Exercise Training — Improves exercise capacity and physical function

[Abbreviations: ACE=angiotensin converting enzyme; HFpEF= heart failure with preserved ejection fraction]

gional variation in outcomes between patients enrolled in Russia/Georgia and those from the Americas, with the latter group demonstrating a significant reduction in cardiovascular death and hospitalization for HF[53]. In support of these findings, asmaller randomised study of 131 patients with HFpEF demonstrated improvements in exercise capacity and echocardiographic parameters of diastolic function after taking spironolactone for sixmonths.

These findings support future trials with aldosterone antagonists. However, it is important to remember that impaired renal function and hyperkalaemia were more common in patients taking spironolactone, particularly in the patients who gained most benefit, and that renal function and biochemistry must be carefully monitored for patients on these agents.

Heart Rate Modification :

Diastole is shortened during tachycardia, and a reduction in heart rate would be presumed to improve symptoms in patients with HFpEF. Trials of beta blockers have been negative in this regard, probably due to the presence of chronotropic incompetence in certain patients with HFpEF[54,55]. Trials of heart rate modification with ivabradine, an If-channel blocker with effects on heart rate but not blood pressure, have shown early positive results, but not consistently across all studies[56,57].

Other Pharmacotherapy :

Pulmonary hypertension secondary to elevated left ventricular pressures is a key component in the pathophysiology of HFpEF, however trials of sildenafil, soluble guanylate cyclase inhibitors and isosorbidemononitrate have been neutral[58,59,60]. Neprilysin inhibition, recently demonstrated to reduce mortality with startling success in patients with HFrEF, is under investigation in patients with HFpEF. In the ongoing PARAGON trial[61,62].

Device Therapy :

The management of patients with HFrEF has become noteworthy for the beneficial combined effects of pharmacotherapy and device therapy, including implantable cardiac defibrillators and cardiac resynchronization therapy demonstrating remarkable impacts on morbidity and mortality[63]. In patients with HFpEF, the fundamental physiological target is the elevated left atrial pressure. To offset left atrial pressure, an interatrial shunt can be inserted percutaneously, with recent trial results suggesting significant improvements in quality of life and functional capacity[64]. Beyond this approach, large trials targeted to offset chronotropic incompetence and improve dyssynchrony with atrial pacing, with larger trials are yet to be completed[65].

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