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Heart Failure with Preserved Ejection Fraction: An Enigma

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Abstract

Heart failure with preserved ejection fraction(HFpEF) is an entity showing an upward trend. The affected population is rising on account of rise in the geriatric population as well as expanding incidence of comorbidities,thus underlining the necessity of greater therapeutic avenues. The underlying disease mechanisms are complicated. Irrespective of EF, HFpEF negatively influences quality of life and hard clinical endpoints. Greater research into HFpEF phenotypes, criteria for definition and improvement in prognosis is the need of the hour.

Keywords: HfpEF, diastolic function, sacubitril-valsartan

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a problem of considerable magnitude worldwide. HFpEF is described as a condition in which the heart is incapable of pumping blood without increase in filling pressure. Initially called diastolic heart failure and then,heart failure with normal ejection fraction. The 2021 European Society of Cardiology (ESC) guidelines categorises heart failure (HF) into three types on the basis of ejection fraction: heart failure with preserved ejection fraction (HFpEF, LVEF ≥ 50%), heart failure with reduced ejection fraction (HFrEF, LVEF ≤ 40%), and heart failure with mildly reduced ejection fraction (HFmrEF, LVEF 41–49%).[1]

Notwithstanding all developments in identification and management of heart diseases, the patient population of this illness is projected to rise in future on account of improvement in lifespan and increase in diabetes and hypertension. Presently,out of all heart failure cases needing inhospital treatment, HFpEF contributes 50%. Considered to be milder than HFrEF in the beginning, the variable clinical profile and causation of HFpEF impedes the diagnosis. It is more commonly observed in females, advanced age and patients with other illnesses like diabetes, hypertension, nephropathy, lung disease and increased body weight. All these ailments are becoming increasingly common and hence,the burden of disease is expected to rise in future. Moreover, Covid has been seen to be associated with increasing occurrence and severity of HFpEF. In addition, certain conditions like hereditary cardiomyopathy, Fabry's disease, amyloidosis and constrictive pericarditis may manifest as HFpEF.[2] The financial implications of the illnesss are immense considering that more than half of all HF admissions are due to HFpEF. Yet,

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management is suboptimal due to lack of effective drugs and predominantly elderly patient population.

It is observed that the mechanistics of HFpEF are not limited to diastolic function impairment and the crux of the illness is a rise of left ventricle (LV) diastolic pressure for which multiple pathways are responsible. Reduced myocardial compliance is due to alteration of contents of interstitial tissue and changes in calcium signalling of sarcomeres. In addition, changes in titin lead to altered expression of isoforms. Inflammation and impaired endothelial function are contributory as evidenced by clustering of multiple illnesses in the same patient. The current understanding of the genesis of HFpEF is nebulous and hence, therapeutic agents are hard to evolve.

Transthoracic echocardiography is the mainstay of diagnosis of HFpEF as LVEF>50% is the sole defining criterion. The disadvantage however is that EF is derived from volume measurement from a planar view. According to American Society of Echocardiography and European Association of Cardiovascular Imaging(ASE/EACVI) guidelines, the mitral E/A ratio determines the grade of diastolic dysfunction. If E/A>2,LV filling pressure is raised whereas if it is between 0.8 and 1.9, raised LA volume index, TR velocity>2.8 m/s and E/e' >14 is indicative of raised LA pressure.[3]

Multiple therapeutic agents have been tried in HFpEF with the majority of the trials providing discouraging results. One possible reason is the overreliance on EF as the sole criterion for definition. The disease entity appears to be a poorly demarcated motley group of many different patient populations where a single drug may not be effective. Hence, it is still contentious if LVEF should be the only parameter to identify HFpEF. The combination of sacubitril-valsartan has been found superior to valsartan if inititated as soon as possible in an acute setting.[4] Moreover, in an HF cohort, drug efficacy has been shown to fall with rising EF. Multiple substudies of the PARAGON trial demonstrate beneficial effect in contrast to the negative results of the entire trial. Usage of the drug in the initial period of hospitalisation and female gender favored drug efficacy while higher EF attenuates it.[5] Hence, apart from EF, patient characteristics should be taken into account for therapeutic decision making.

The routine administration of beta blockers is another example of the same phenomenon. HFpEF patients have been studied in SENIORS and J-DHF for the role of beta blockers.[6] While favorable result was observed in EF>35% group,subsequent study with 50% as threshold did not show benfit. Admittedly, these trials were not exclusively conducted on a HFpEF population and hence, the results should not be considered binding. From these issues arose the need for labelling those with EF between 40-50% as heart failure with mid-range EF(HFmrEF) whose features leans more towards HFpEF.Constituting about 15% of HF patients, the features and hence,management lean towards HFpEF.

Sacubitril-valsartan has earned a class IIa recommendation in treatment of HFpEF. PARAGON showed considerable benefit (although not statistically significant), especially when EF<57%, thus furthering the argument for changing the threshold value for HFpEF. A substantial improvement in NYHA class and kidney parameters was noted. The drug was associated with greater frequency of hypotension and angioedema but lesser renal impairment and hyperkalaemia.In a study comparing ARNI versus ACEI/ARB over 12 weeks, NT-proBNP was significantly decreased with fall in HF hospitalisation and nephropathy but functional capacity as assessed by 6-minute walk test did not improve.[7] Quality of life assessment,based on KCCQ score also remained unchanged after 24 weeks. Multiple trials are underway to clarify the management of HFpEF. In the PRISTINE-HF trial, multiple clinical endpoints are being evaluated in a cohort of 60 patients. NT-proBNP assessment between two groups(sacubitril-valsartan vs valsartan) is being studied in PARAGLIDE-HF trial.[8] The cognitive state of HFpEF patients on sacubitril-valsartan vs valsartan is the subject of analysis in the PERSPECTIVE trial. The ARNIMEMS trial is currently studying the effect of sacubitril-valsartan in HFpEF and pulmonary hypertension on multiple parameters.[9]

The foundation was however laid by by the phase II PARAMOUNT trial that demonstrated fall in NT-proBNP, decrease in LA size and NYHA class betterment by sacubitril-valsartan vis-à-vis

valsartan. ENHANCEMENT-HIV is assessing the efficacy of the same drug in HIV-related HFpEF. In short, the objective is to observe the effect of the drug on parameters pertaining to inflammation in HIV through left atrial volume index and myocardial fibrosis.

ACE inhibitors

Available information implicates angiotensin II in causation of poor effort tolerance in HFpEF and hence, a possible therapeutic avenue. PEP-CHF,the first trial using ACE inhibitors used perindropril in old age patients with a EF range 40-50%. The result was negative for a combination of mortality and hospital admission on account of nominal number of events and a number of trial partticipants discontinuing prescribed therapy after 1 year. Fall in hospital admission for HF and in primary endpoint reached significance at the end of 1 year. In contrast, there was no significant effect on death and suffering. Enalapril was tried in diastolic dysfunction but over 1 year,revealed no amelioration in effort tolerance,compliance of aorta or LV parameters.

SGLT2 inhibitors

The Empagliflozin in HF with a Preserved Ejection Fraction (EMPEROR-Preserved) study from 2021 investigated the efficacy of an SGLT2 inhibitor in patients with HF and preserved ejection fraction. The EMPEROR-Preserved study investigated the combined occurrence of cardiovascular death or hospitalisation for HF (HHF) as a primary outcome, occurrence of all hospitalisations for HF as a first secondary outcome and the rate of decline in eGFR as a second secondary outcome.[10] Additionally, subgroup analysis of patients according to EF was performed. The EMPEROR-Preserved study found that treatment with empagliflozin reduced the occurrence of HHF and cardiovascular death as a combined primary outcome. Specifically, SGLT2 inhibition led to a 21% lower relative risk of the primary outcome in the cohort of patients treated with empagliflozin. The study found a reduced number of hospitalisations from 11.8% in the placebo group to 8.6% in patients being treated with empagliflozin [21]. However, it did not show any statistical difference in cardiovascular death (or death fother causes) between patients taking empagliflozin and the placebo[21]. Whereas several studies investigating sacubitril/valsartan, spironolactone and candesartan in HFpEF have been unable to provide undisputable proof for their effectiveness in patients with an EF of 50% or more[15–17, 22, 23], subgroup analysis of the EMPEROR-Preserved patient cohort showed that empagliflozin reduced the number of primary outcome events (cardiovascular death or HHF) in patients with an EF ranging between 50% and 60% and more than 60%, when compared with placebo. Furthermore, the EMPEROR-Preserved study also investigated the protective effect of empagliflozin on the kidneys. The study demonstrated that patients receiving empagliflozin had a slower decline in estimated glomerular filtration rate (eGFR) when compared with patients receiving placebo: a decline in eGFR of 1.25 mL per year in patients receiving empagliflozin compared with a decline in eGFR of 2.62 mL in patients receiving placebo[21]. The results from the EMPEROR-Preserved study suggest that empagliflozin is beneficial for patients with HFpEF. This study is the first randomised controlled trial (RCT) to demonstrate a mortality benefit and significant morbidity benefit in patients with HFpEF, who have previously been limited to treatments for symptom control and risk factor management.

Conclusion

Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous syndrome and a diagnosis based solely on LVEF may be insufficient. The diagnostic process should ideally use the recently introduced H2FPEF and HFA-PEFF algorithms. HFpEF therapy must include the adequate treatment of comorbidities and risk factors, as they influence prognosis. Avoiding fluid overload by diuretic treatment to increase quality of life is an essential part of HFpEF therapy. If available, telemonitoring should be incorporated into HFpEF management to detect fluid overload before signs and symptoms of congestion. LCZ696 has been granted an expanded indication for patients with LVEF < 50% by the FDA. Empagliflozin is the first drug to significantly reduce morbidity and mortality in HFpEF patients and should be the cornerstone of any HFpEF treatment.Further research is needed to enhance our understanding of the complex syndrome of HFpEF and help improve HFpEF management.

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References

1. McHugh K, DeVore AD, Wu J, et al. Heart failure with preserved ejection fraction and diabetes: JACC State-of-the-Art review. J Am Coll Cardiol 2019;73:602–11.
2. Youn JC, Ahn Y, Jung HO. Pathophysiology of heart failure with preserved ejection fraction. Heart Fail Clin 2021;17:327–35.
3. Hong GR, Vannan MA, Bossone E. Heart failure with preserved ejection fraction: current opinion and future perspectives. Heart Fail Clin 2021;17:xiii–v.
4. Xanthopoulos A, Triposkiadis F, Starling RC. Heart failure with preserved ejection fraction: classification based upon phenotype is essential for diagnosis and treatment. Trends Cardiovasc Med 2018;28:392–400.
5. Uijl A, Savarese G, Vaartjes I, et al. Identification of distinct phenotypic clusters in heart failure with preserved ejection fraction. Eur J Heart Fail 2021;23:973–82.
6. Kato M, Yamamoto K. Sleep disorder and heart failure with preserved ejection fraction. Heart Fail Clin 2021;17:369–76.
7. Lee CJ, Park S. Hypertension and heart failure with preserved ejection fraction. Heart Fail Clin 2021;17:337–43.
8. Rossi AP, Nguyen NTV, Tran DT, et. al. Clinical phenotypes and agerelated differences in presentation, treatment, and outcome of heart failure with preserved ejection fraction: a Vietnamese multicenter research. Cardiol Res Pract 2021;2021:4587678.
9. Toth PP, Gauthier D. Heart failure with preserved ejection fraction: strategies for disease management and emerging therapeutic approaches.Postgrad Med 2021;133:125–39.
10. Ananthram MG, Gottlieb SS. Renal dysfunction and heart failure with preserved ejection fraction. Heart Fail Clin 2021;17:357–67.