Heart Failure With Preserved Ejection Fraction

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It is now well established that among patients with the clinical syndrome of heart failure (HF), approximately half have preserved systolic function, known most commonly as heart failure with preserved ejection fraction (HFpEF). Although originally considered to be predominantly a syndrome that pathophysiologically involves abnormalities in diastolic function (relaxation and/or stiffness), ongoing investigation suggests that, although diastolic abnormalities may be present in many patients, other aspects of pathophysiology likely also contribute to symptoms.

Many recent articles have continued to explore aspects of this fascinating clinical syndrome. This review will summarize advances in understanding of the HFpEF syndrome, focusing on epidemiology, pathophysiology, and therapeutics.

Epidemiology

Lewis and colleagues1 examined data on >8000 patients enrolled in the Prevention of Events With Angiotensin Converting Enzyme Inhibition (PEACE) trial, a randomized trial of the angiotensin-converting enzyme inhibitor trandolapril for prevention of adverse events in patients with stable coronary artery disease and normal systolic function, to assess predictors of incident HF over a median of 4.8 years of follow-up after randomization. Several factors were associated with an increased risk of incident HF hospitalization or HF death, including older age, hypertension, and diabetes mellitus, whereas randomization to trandolapril reduced risk. A risk score was developed that showed good discrimination for incident HF with a C statistic of 0.80. Although this study did not report a reevaluation of left ventricular (LV) function at the time of the incident HF event, the data suggest that among patients with stable coronary artery disease and preserved ejection fraction (EF), clinical factors can risk-stratify patients in regard to the possibility of future HF for potential preventive strategies.

Of great interest are possible differences in risk factors and underlying disease states in patients with HFpEF compared with those with HF and reduced EF. The Framingham Study investigators examined clinical characteristics and risk factors at time of HF onset as well as long-term survival in patients according to preserved versus reduced EF.2 Predictors of HFpEF included increased systolic blood pressure, atrial fibrillation, and female sex, whereas HF with reduced EF was associated with prior myocardial infarction and left bundle-branch block QRS morphology. In this community-based population, long-term prognosis was equally poor in both HF types, as well as in men and women, with a median survival of 2.1 years. Such data support the concept that, although there may be some common factors of risk for these syndromes, there are also important differences in risk predictors, implying that distinct preventive strategies may be needed.

Although large randomized trials of therapeutic strategies in the HFpEF syndrome have been almost uniformly disappointing in their results, secondary analyses of the large trial databases have led to substantial insights into natural history. Using the database from the Irbesartan in Heart Failure With Preserved Ejection Fraction (I-PRESERVE) Trial, Zile and colleagues3 reported on the mode of death of patients with this syndrome during follow-up, a key aspect of outcome to understand if we are to better target therapies in the future. A clinical events committee had reviewed all deaths and classified them on the basis of available information. Annual death rate was 5.2% in the overall I-PRESERVE HFpEF cohort. The authors reported that the mode of death was cardiovascular in 60% of deaths (including 26% sudden death, 14% heart failure, 5% myocardial infarction, and 9% stroke death), noncardiovascular death in 30%, and unknown/not classified in 10%. As in other databases, a significant proportion of deaths were noncardiovascular. These data are very useful to inform the design of future trials.

The I-PRESERVE trial database also provided a large amount of data from which to examine predictors of adverse outcomes in patients with HFpEF. Komajda and coauthors4 reported that log N-terminal pro–B-type natriuretic peptide, age, diabetes mellitus, and previous hospitalization for HF were the most powerful factors associated with the I-PRESERVE primary outcome (all-cause mortality or cardiovascular hospitalizations) and with the HF composite end point (HF death or hospitalization). Log N-terminal pro–B-type natriuretic peptide, age, diabetes mellitus, and LV EF were the strongest independent predictors of all-cause mortality. Models were developed for all of the outcomes that allowed stratification of risk across a wide range of risk from low to very high. Similar to the data on mode of death, these results will be highly useful in planning future studies and understanding risk in such patients. Investigators from the I-PRESERVE trial also reported that obesity is common in HFpEF patients, and that there was a U-shaped relationship with adverse outcomes, with the greatest rate of adverse outcomes in the lowest and highest body mass index categories.5
An important performance measure for the care of HF patients is assessment of LV function because there are many obvious treatment implications. Curtis and colleagues examined data from the Centers for Medicare and Medicaid Services and found that as recently as 2007, nearly 40% of Medicare patients with new-onset HF do not undergo assessment of LV function. This would be an important target for quality improvement.

**Pathophysiology**

Controversy continues regarding the prevalence of true abnormalities of myocardial diastolic function in the syndrome of HFpEF. In a comprehensive invasive and noninvasive hemodynamic study in a group of highly selected patients with hemodynamically confirmed HFpEF, Prasad et al reported that compared with age-matched referent controls, increased static ventricular stiffness was not a universal finding in patients with HFpEF, although LV relaxation as assessed by tissue Doppler was consistently abnormal.

Substantial and growing attention has been given to the role of the cardiac interstitium in the pathophysiology of HFpEF. Zile and colleagues examined a panel of biomarkers for ability to discriminate symptomatic HFpEF from those with asymptomatic LV hypertrophy. This study showed that a panel of plasma biomarkers reflecting changes in extracellular matrix fibrillar collagen synthesis and degradation predicted the presence of HFpEF with an area under the curve of 0.79 and was more powerful than using N-terminal pro-B-type natriuretic peptide or clinical variables. Consistent with these findings, investigators from the Cardiovascular Health Study reported that biomarkers reflecting myocardial fibrosis, including carboxyl-terminal peptide of procollagen type I, carboxyl-terminal telopeptide of collagen type I, and amino-terminal peptide of procollagen type III, are significantly elevated in elderly patients with HFpEF and indeed are also elevated in those with systolic HF. Krum et al reported on a substudy from I-PRESERVE showing that increased baseline plasma levels of all collagen markers were associated with the I-PRESERVE primary outcome end point, although the relationship was not significant in a multivariable model. In a comprehensive human study, Westermann and colleagues interrogated the influence of cardiac inflammation on extracellular matrix remodeling in patients with HFpEF. Using endomyocardial biopsy samples to isolate primary human cardiac fibroblasts, the authors interrogated the gene expression of extracellular matrix proteins after stimulation with transforming growth factor-β. They reported an increase of cardiac collagen accompanied by a decrease in the collagenase system of the heart, as well as a correlation between cardiac collagen, inflammatory cells, and diastolic dysfunction. They concluded that inflammation contributes to diastolic abnormalities in HFpEF by stimulating extracellular matrix accumulation. All of these data suggest that the interstitium may be a promising therapeutic target if specific therapies can be deployed.

Although abnormalities in myocardial diastolic properties have been the focus of pathophysiological studies in patients with HFpEF in the past, many recent investigations have examined other structural and functional contributors. Kurt and colleagues reported that HFpEF patients have similar LV mass and left atrial volume in comparison with patients with LV hypertrophy who are not in HF, although a measure of left atrial strain was reduced, and left atrial stiffness was useful in discriminating patients with HFpEF from those with LV hypertrophy without HF symptoms.

Several studies examined pathophysiology in HFpEF patients during exercise stress, which is when most patients have symptoms. Phan and colleagues reported that chronotropic incompetence, as measured by the percentage of the heart rate reserve used during maximal exercise, was more commonly present in patients with HFpEF compared with referent controls, as was abnormal heart rate recovery. Usingdobutamine stress echocardiography with color tissue Doppler imaging, Chattopadhyay et al reported evidence of impaired diastolic reserve during stress, as well as stress-induced increase in the LV end-diastolic pressure, likely resulting in exercise intolerance because 6-minute walk distance was inversely correlated with the measures of diastolic function at rest and stress. Borlaug and colleagues examined hemodynamic responses to stress as a potential diagnostic approach in patients with exertional dyspnea, in whom making a specific diagnosis may be challenging. The investigators studied patients with exertional dyspnea, preserved EF, normal brain natriuretic peptide levels, and normal resting hemodynamics. Exercise-induced elevation in pulmonary capillary wedge pressure was used to define HFpEF and was associated with blunted increases in heart rate and cardiac output and blunted systemic vasodilation. An exercise pulmonary artery systolic pressure ≥ 45 mm Hg identified HFpEF with 96% sensitivity and 95% specificity. These data suggest that patients who present a challenge for specific diagnosis should undergo an exercise hemodynamic study.

Two studies examined clinical or echocardiographic variables that might be useful in estimating LV filling pressures in patients with HFpEF. Drazner et al reported that right atrial pressures often reflected left-sided filling pressures in HFpEF, suggesting that estimation of jugular venous pressure could be used to assess volume status. However, the echocardiographic indexes E/E′ and E/Vp did not appear to reliably track changes in left-sided filling pressures in patients with HFpEF.

Studies using translational models explored the underlying mechanism of the transition from compensated LV hypertrophy to a state of HF. In a transverse aortic constriction model adding mineralocorticoid (deoxyxycorticosterone acetate) excess, Mohammed et al reported that mice treated with deoxyxycorticosterone acetate showed progressive activation of markers of oxidative stress but no evidence of mineralocorticoid receptor–dependent gene transcription. They concluded that pressure-overload hypertrophy sensitizes the heart to mineralocorticoid excess and that the transition to HF with preserved EF is associated with mechanisms independent of mineralocorticoid receptor–dependent gene transcription. In a study of cardiac energy metabolism in which Dahl salt-sensitive rats fed a high-salt diet were used to drive a transition from compensated LV hypertrophy to HF, Kato and colleagues reported that glucose uptake increased with LV...
hypertrophy and further increased at the HF stage, with decreased fatty acid uptake and corresponding changes in gene expression related to the metabolic pathways as well as mitochondrial function with the onset of HF. Dichloroacetate, which enhances glucose oxidation, attenuated the transition to HF, associated with increased energy reserves and reduced oxidative stress. The data from these models suggest potential therapeutic directions for the future, although mineralocorticoid receptor antagonism is already under comprehensive study.

Therapeutics

As noted, large randomized trials in broad populations of patients with HFpEF in which agents such as angiotensin receptor blockers were used have generally shown neutral results. Smaller trials continue to explore potential therapeutic directions for this challenging-to-manage syndrome. Kitzman and colleagues randomized 71 elderly HFpEF patients with compensated symptoms and controlled blood pressure into a 12-month follow-up double-blind trial of enalapril 20 mg/d versus placebo. There was no effect of the angiotensin-converting enzyme inhibitor on the primary end point of peak exercise oxygen consumption and no effect on multiple secondary end points including 6-minute walk distance, aortic distensibility, LV mass, or neurohormones. The findings are consistent with the longer-term natural history outcomes of angiotensin receptor blocker trials.

Many of the same authors examined a nonpharmacological approach in a 16-week randomized trial of supervised exercise training in 53 elderly patients with HFpEF. The primary outcome was peak exercise oxygen uptake, which increased significantly in the exercise group compared with the control group (2.3±2.2 versus −0.3±2.1 mL/kg per meter; P=0.0002). Many secondary end points were also improved, including exercise time, 6-minute walk distance, and ventilatory anaerobic threshold. In contrast to some trials of exercise training, a key to the favorable results of this study may have been the good compliance with the exercise training regimen among the enrolled patients. These important data suggest an important therapeutic direction.

 Favorable results were also seen in a small study involving an important subgroup of HFpEF patients, those with pulmonary hypertension. Guazzi and coworkers randomized 44 such patients to sildenafil at a dose of 50 mg 3 times per day or to placebo for 6 months. At the end of the trial, sildenafil was associated with decreased mean pulmonary artery and reduced right atrial pressure and improved right ventricular function. They also reported reduced lung water content and improved alveolar-capillary gas conductance, as well as improved measure of left-sided systolic and diastolic cardiac function. Results were maintained at 12 months.

Hence, although large trials using neurohormonal antagonists that have been favorable in HF with reduced EF have not shown favorable results in HFpEF, these early studies suggest promising therapeutic directions to explore. Such studies also enhance our understanding of pathophysiology and point the way to larger and more definitive investigations.

Disclosures

None.

References


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