Heart Failure with Preserved Ejection Fraction
An Ongoing Enigma

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KEYWORDS

• Heart failure • Preserved ejection fraction • Diastolic dysfunction • HFpEF • Review

KEY POINTS

- Heart failure with preserved ejection fraction (HFpEF) is an increasing epidemic with mortality and morbidity similar to heart failure with reduced ejection fraction, but is more multifactorial in cause and has limited evidence-based therapies.
- Its pathophysiology may be induced by a systemic proinflammatory state, resulting in combined ventricular and arterial stiffness and impaired chronotropic and cardiac output reserve.
- At present, recommended therapy for patients with HFpEF includes symptom relief and management of related comorbidities such as hypertension, atrial fibrillation, and coronary artery disease.
- Medications endorsed by the most recent American College of Cardiology Foundation/American Heart Association guidelines for HFpEF include only diuretics, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and omega-3 fatty acids.
- Ongoing investigations of potential HFpEF therapies include aldosterone antagonists, phosphodiesterase-5 inhibitors, advanced glycation end product crosslink breakers, physical exercise, and rate-adaptive pacing from implantable cardiac devices.

INTRODUCTION

With an estimated 50% (range 40%–71%) of all patients with clinical symptoms of heart failure (HF) having normal or near normal left ventricular (LV) ejection fractions (LVEF),[1–5] there has been an increasing need to understand and treat the complex syndrome of HF with preserved ejection fraction (HFpEF). The diagnosis of HFpEF requires a patient to have the typical symptoms of HF, such as dyspnea and fatigue, with normal LV volumes and contractility but increased LV filling pressure. HFpEF used to be called diastolic HF[6]; however, the terminology was controversial and has been updated over the past 8 years, initially to HF with normal ejection fraction (HFnEF),[7–11] then to HFpEF because the pathogenesis of HFpEF is not exclusively based on diastolic dysfunction. It is imperative to isolate the terminology diastolic dysfunction to describe an abnormality in LV relaxation or chamber compliance.[12] Diastolic dysfunction can be present regardless of the LVEF or symptoms. The threshold for defining preserved LVEF varies greatly, from LVEF greater than 40% to greater than or equal to 55%, with greater than or equal to 50% becoming more widely accepted.[1,11] Patients with LVEF of 40% to 49% represent an intermediate or borderline HFpEF group and may also be considered as HF with improved or recovered LVEF. In practice, the diagnosis of HFpEF is often established after echocardiography reveals preserved LV systolic function

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with signs of HF on examination and without valvular disease, pericardial disease, or other noncardiac causes accounting for dyspnea, edema, and fatigue.

EPIDEMIOLOGY

Over time, the proportion of patients with HFpEF has increased.[3,13] Although HF symptoms unify patients with HFpEF, there is marked heterogeneity in the clinical characteristics that potentially confer risk for this syndrome. Patients with HFpEF are typically older, more likely to be female, with higher body mass index and prevalence rates of hypertension and atrial fibrillation, and lower rates of coronary artery disease (CAD) and valve disease.[13,14] Hypertension (chronic pressure overload) remains the single most important predictor of HFpEF across multiple HF registries, epidemiologic trials, and large controlled trials.[15] Because patients with HFpEF have important comorbidities that strongly influence outcomes, the focus of HFpEF therapy is often on comorbid conditions (eg, hypertension, atrial fibrillation, diabetes, chronic kidney disease).

PATHOPHYSIOLOGY

Substantial attention has been devoted to better define the pathogenesis that leads to HFpEF in order to potentially target more effective treatment. Patients with HFpEF, even when well compensated, are characterized as having chronically increased left-sided filling pressures, reduced LV chamber distensibility (compliance), and increased diastolic wall stress. The classic paradigm is based on chronic LV afterload or pressure overload resulting in decreased LV compliance. Although impaired LV relaxation is usually present in patients with HFpEF, it is also considered part of the normal aging process, present in otherwise healthy seniors. What the HF community has not understood is why abnormal myocardial relaxation does not always indicate HFpEF.

Over the past decade, the pathogenesis of HFpEF has been shown to be related to ventricular stiffness combined with arterial or vascular stiffness.[16,17] Ventricular and arterial stiffness increases with advancing age[18] and is further amplified by comorbidities such as hypertension, diabetes, and chronic kidney disease.[19] However, increased end-diastolic static ventricular stiffness may not be a universal finding in patients with HFpEF compared with healthy, sedentary, age-matched controls.[20] In addition, left atrial stiffness has been reported as a predictor of discriminating patients with HFpEF from those with LV hypertrophy without HF symptoms.[19,21] It has been hypothesized that titan, the third myofilament of cardiac muscle, also plays an important role in diastolic function by defining cardiomyocyte passive stiffness.[22] Although there is ongoing debate regarding the degree and prevalence of primary myocardial stiffness in this syndrome, it seems that additional contributive mechanisms must be present in order for HF to manifest.

The cardiac interstitium has been of increasing interest in this conundrum. In particular, fibroblasts and changes in the extracellular matrix (ECM) can cause myocardial fibrosis and thus myocardial remodeling. In a cohort of symptomatic patients with HFpEF, compared with patients with asymptomatic LV hypertrophy, plasma biomarkers that indicate ongoing ECM collagen changes were present, suggesting that a disruption of collagen homeostasis may be related to the pressure overload–LV remodeling phenomenon.[23] The panel of biomarkers (matrix metalloproteinases [MMPs]) was a more powerful predictor of HFpEF than N-terminal-pro-B-type natriuretic peptide, and a few of these biomarkers (MMP-2, MMP-7, MMP-8) showed patterns that were specific to patients with HFpEF compared with patients with only LV hypertrophy. Endomyocardial biopsy samples of patients with HFpEF have shown increased cardiac inflammatory cells that expressed profibrotic transforming growth factor beta, resulting in substantially more cardiac collagen production (type I and III).[24] These findings suggest that inflammation may be a key trigger in the accumulation of ECM that leads to fibrosis and HFpEF.

Other cardiovascular abnormalities, namely impaired chronotropic and cardiac output reserve, have been observed and likely contribute to the pathogenesis and presentation of HFpEF.[16] Chronotropic incompetence, defined as an inadequate heart rate response to exercise, is exaggerated in patients with HFpEF compared with healthy or hypertensive controls.[25,26] Patients with HFpEF also had significantly delayed heart rate recovery, more impaired exercise tolerance and systemic vasodilation, and lower increase in cardiac output with exercise.[25,26] Although diastolic dysfunction promotes congestion and pulmonary hypertension with stress in HFpEF, reduction in exercise capacity is predominantly related to inadequate cardiac output relative to metabolic needs.[27]

As in HF with reduced ejection fraction (HFrEF), neurohormonal imbalances have also been implicated in HFpEF. The renin-angiotensin-aldosterone system (RAAS) is considered an important contributor to the development of HFpEF.[28] The neurohormones angiotensin II and aldosterone have effects on vascular tone, water