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Management of Heart Failure With Preserved Ejection Fraction: A Review

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ABSTRACT

Purpose: The purpose of this article was to review the clinical management of patients with heart failure with preserved ejection fraction (HFPEF).

Methods: For this critical review, electronic databases (MEDLINE, EMBASE, PubMed) were searched for relevant basic research studies and randomized clinical trials recently published or presented at major meetings. Details of in-progress or planned studies were obtained from the ClinicalTrials.gov website. The range of publication dates was the year 2000 to 2015. Search terms included HFPEF, heart failure with preserved ejection fraction, HFPSF, heart failure with preserved systolic function, diastolic heart failure, diastolic dysfunction, HFNEF, heart failure with normal ejection fraction, treatment, management, therapy.

Findings: Patients with HFPEF account for up to half of all patients with a clinical diagnosis of HF. Key contributing factors include hypertension, obesity, and atrial fibrillation, and other chronic diseases, including diabetes, chronic obstructive pulmonary disease, and anemia, frequently coexist. To date, large-scale clinical trials, particularly those focused on antagonism of the renin-angiotensin-aldosterone system, have provided limited evidence of clinical benefit.

Implications: The aggressive management of contributing factors, including hypertension, atrial fibrillation, and myocardial ischemia, is key in the management of HFPEF. New insights into the mechanisms and thus the identification of potential therapeutic strategies are urgently required. (*Clin Ther.* 2015;▮:▮▮▮–▮▮▮)

Key words: heart failure, management, preserved ejection fraction, treatment, HFPEF.

INTRODUCTION

Heart failure (HF) is one of the commonest and most disabling forms of cardiovascular disease. HF is particularly prevalent in older individuals, affecting up to 10% of the population aged over 75 years.[1] From clinical and epidemiologic points of view, the diagnosis of HF is based initially on the presence of well-recognized symptoms and signs, such as the Framingham criteria.[2] Subsequent to the clinical diagnosis, the application of diagnostic investigations, such as echocardiography, can be used for identifying the pathophysiology of the clinical phenotype, together with the provision of prognostic and therapeutic information. Among the echocardiographic parameters applied to the assessment of ventricular function, the ejection fraction (EF) remains in common use despite numerous limitations, including its sensitivity to loading conditions and technical issues with endocardial border definition and geometric assumptions.[3,4] This stated, we now appreciate that ~50% of patients with HF, both in community studies and in registries of patents admitted with acutely decompensated HF, have a normal or near-normal EF, termed *HF with preserved EF* (HFPEF).[5,6]

The clinical profile of patients with HFPEF differs substantially from those with HF with reduced EF (HFREF). Patients with HFPEF are older, more likely to be female, more obese, and have different contributing risk factors. Coronary artery disease (CAD) is less common, whereas rates of hypertension, diabetes, and atrial fibrillation are greater.[7] The black population may develop HFPEF at a younger age.[8] Consistent with the increased age of the population, the rate of noncardiac comorbidities is also higher,[9] including chronic lung disease, anemia, chronic kidney disease, and malignancy. These comorbidities are

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involved in a significant proportion of the morbidity and mortality associated with HFPEF, although the majority of limited exercise tolerance is cardiac related.[10] *Renal dysfunction,* defined as an abnormal glomerular filtration rate or as microalbuminuria, has been reported to independently predict changes in left ventricular (LV) geometry and has been suggested to be involved in the pathogenesis of HFPEF.[11] Diabetic patients with HFPEF have a significantly higher rate of hospitalization and a reduced exercise capacity.[12] Atrial fibrillation is common in this group (25%) and is associated with a risk for stroke similar to that in those with a reduced EF.[13]

The prevalence of HFPEF has risen significantly over the past 2 decades, and HFPEF is projected to become the most prevalent form of HF over the coming decade.[14] This change in the distribution of HF possibly represents the effect of improved diagnostic techniques, together with awareness of the condition, although more likely it reflects the rise in predisposing conditions, including aging, hypertension, diabetes, and atrial fibrillation.[5] Although the total mortality rate in patients with HFPEF has been suggested to be similar to, or slightly less than, that in those with HFREF in various studies, the absolute number is still high, with an adjusted mortality of 25% at 3 years.[15] The overall proportion of cardiovascular-related deaths is less in the HFPEF group, and as age increases there is an increasing contribution of noncardiovascular causes.[15]

In the context of the relative preservation of systolic function in HFPEF, attention has been focused on the contribution of diastolic dysfunction to the symptom complex associated with HFPEF. The pathogenesis of diastolic dysfunction has largely been ascribed to the accumulation of extracellular matrix (ie, myocardial fibrosis), consequent to the activation of the renin-angiotensin-aldosterone system. Autopsy studies have reported increased levels of cardiac fibrosis and microvascular rarefaction in patients with HFPEF compared with those in controls, with fibrosis levels similar to those in patients with HFREF.[16] Recently, additional mechanisms for fibrosis have been proposed, including the activation of the immune system, particularly with regard to the role of chronic inflammation and oxidative stress.[17,18] Histologic examination has revealed an increase in macrophages in the myocardium of patients with HFPEF, and inflammatory markers have been identified in the blood,[19] suggesting a systemic pro-inflammatory state, likely mediated by both mineralocorticoid receptor activation and the influence of other pro-inflammatory conditions, including obesity and diabetes.[20,21]

Beyond cardiac fibrosis, several other mechanisms contributing to abnormal cardiac performance have been proposed. In addition to the fixed fibrosis-mediated disturbance of diastolic performance, dynamic abnormalities have been reported, including the hypophosphorylation of titin.[22] Chronotropic incompetence,[23] right ventricular dysfunction,[24] abnormalities in systolic function not evident on standard echocardiography,[25,26] autonomic dysfunction,[27] and endothelial dysfunction[28] also have been postulated.

Comorbidities such as chronic lung disease, anemia, and obesity frequently exist in patients with HFPEF.[29,30] These all may cause exertional dyspnea and fatigue independent of abnormal diastolic function. In part, the challenges associated with the definitive diagnosis of HFPEF may have contributed to the relative failure of several large-scale clinical trials to date, including the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial.[31]

To enhance the diagnosis of HFPEF, the European Society of Cardiology has developed a diagnostic algorithm.[32] Based on the initial recognition of appropriate signs and symptoms of HF in the setting of a preserved LVEF and in the absence of LV dilatation, LV filling pressures and diastolic performance are then assessed either invasively, or noninvasively using echocardiographic measures (eg, E/e′ ratio measured on tissue Doppler echocardiography) and biochemical measures (B-type natriuretic peptide [BNP] or the N-terminal of the prohormone BNP). Recognizing that each of these measures has limited sensitivity and specificity, and that the symptomatic nature of HFPEF is often very dynamic, we recently recommended that exertion-based assessments also be included in cases in which clinical uncertainty remains (**Figure**).[33]

More recently, various statistical models have been developed to identify specific groups ("phenomapping") that have different clinical profiles within the larger pool of patients with HFPEF.[34] For example, older patients with significant chronic kidney disease, electric and myocardial remodeling, pulmonary hypertension, and right ventricular dysfunction appear to have the poorest outcome. Ultimately, this approach may lead to targeted therapies.