Heart failure with preserved ejection fraction: A review of clinical status and meta-analysis of diagnosis by myocardial strain and effect of medication on mortality and hospitalization

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Abstract

Heart failure (HF)-related morbidity, mortality and health care burden remains unacceptably high, and with a rapidly increasing prevalence, the burden will increase substantially over the next few decades. Strongly associated with most of the increasing prevalence is an expanding population of HF patients with preserved ejection fraction (HFpEF), mostly precipitated or aggravated by a rapid increase in lifestyle and/or genetic conditions particularly hypertension, obesity and metabolic syndromes. Despite significant advances in therapies for HF with reduced ejection fraction (HFrEF), prognostic and clinical outcomes for HFpEF remain ominous. The paucity of research evidence supporting HFpEF therapies underscores the fundamental differences between HFpEF and HFrEF phenotypes of HF. The present review and meta-analysis summarizes the current understanding of the pathophysiology, diagnostic and therapeutic strategies to improve the current clinical management approaches.

Introduction

Heart failure affects about 26 million people worldwide and causes more than one million hospital admissions each year in the United States and Europe [1]. Therapeutic outcomes for ambulatory HFrEF have remarkably improved due to improvements of multiple evidence-based drug and device therapies. However, post-discharge mortality and re-admission rates for hospitalized HF remains unacceptably high and have not changed over the last two decades [2]. The proportion of patients classified as HFpEF continues to grow and may exceed HFrEF in a few years. The growth has serious clinical implications on effective clinical management of HF since HFpEF has poor characterization and lacks specific evidence-based therapies [3-5]. Attempts to deploy therapy with proven efficacy in HFrEF to HFpEF patients have been less successful [6-8]. Early research centered on diastolic dysfunction in pathophysiology of HFpEF but recent studies have revealed the contribution of multiple non-diastolic abnormalities [9]. In this review, etiopathogenic, diagnostic, and clinical trials are reviewed, along with meta-analysis of current diagnosis and clinical management.

History, definition, epidemiology and prognosis

History

Clinical interest in HFpEF emerged from the confluence of two research areas, one dealing with left ventricular diastolic dysfunction (LVDD) in hypertrophied hearts and the other with left ventricular (LV) remodeling post myocardial infarction (MI) [10]. In the late 1970s, studies began reporting association between LVDD and HF in patients with hypertrophic cardiomyopathy (HCM) [11,12], aortic stenosis [12,13] and hypertensive heart disease [14]. Consequently, HFpEF was recognized and investigated as a secondary outcome in

large HF trials on the use of angiotensin converting enzymes (ACE)-inhibitors in HFrEF in post-MI LV remodeling [15-17]. However, the HFpEF population recruited in these early large trials consisted of patients with limited MI at risk of eccentric LV remodeling. Several secondary analysis provided substantial natural history of HFpEF but also contributed to the present confusion surrounding the recognition of HFpEF as a distinct diagnosis [10]. Initially, HFpEF was termed diastolic HF because of the presence of LVDD evident from slow LV relaxation and increased LV stiffness, which distinguishes it from systolic HF traditionally associated with HFrEF. However, subsequent studies demonstrated that LVDD is not unique to HFpEF (also observed in HFrEF patients with a better correlation with symptoms) and the term abandoned and replaced by HFpEF or HF with normal EF (HFnEF) [18-20]. Despite acceptance, the term HFpEF is non-definitive since the ideation of a preserved LVEF already implies knowledge of a pre-existing EF but which is often always absent and the precise range of preserved LVEF is difficult to define [21,22]. It is also not well established whether HFpEF and HFrEF represent distinct forms of HF or are part of one HF spectrum [23] irrespective of the two exhibiting two distinct patterns of cardiac chamber and myocellular remodeling as well as disparate responses to medical therapies suggesting two discrete disease processes [10].

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Definition

Heart failure defines a complex clinical syndrome characterized by the inability of the heart to provide organ perfusion at a rate sufficient to meet the metabolic demands of the organs or doing so at the expense of elevated filling pressures [24]. The definition applies to both HFpEF and HFrEF phenotypes, and indeed, they exhibit comparable clinical signs, symptoms, functional limitations, morbidity and mortality [25]. Traditionally, HF has been measured based on pump dysfunction using LV ejection fraction by echocardiography. The traditional threshold for defining HFpEF has been echocardiography-defined EF (> 50%) in the presence of overt HF while HFrEF is EF < 40% [3,5,10,26-29]. Although the utility of EF alone in distinguishing HFpEF and HFrEF may be flawed [30,31], it is unlikely to be supplanted in the near future because of widespread availability of echocardiography and well-documented risk factors, pathophysiology and clinical outcomes in both phenotypes based on EF characterization [10,28]. Diastolic and systolic dichotomy have also been used to define and distinguish HFpEF from HFrEF but conceptual confusion exists [32]. Cardiovascular disease may cause diastolic dysfunction but isolated systolic dysfunction is very unlikely in clinical practice. A subset of patients with diastolic dysfunction may develop systolic dysfunction (Figure 1). Although diastolic dysfunction is one of the principal causes of HFpEF, it is not specific to HFpEF and systolic dysfunction may occur in some HFpEF patients but not consistently and depends on the index of systolic function used [33-35].

Epidemiology

The prevalence of HF varies based on the applied definition but estimated at 1 to 2% of the adult population in developed countries and increasing to ≥ 10% in people aged > 70 years old [36-39]. The prevalence of HFpEF relative to HFrEF is increasing rapidly at the rate of approximately 1% annually, which may turn HFpEF the most prevalent HF phenotype over the next decade [10]. Data on temporal trends indicates the incidence of hospitalized HF is decreasing with the HFrEF phenotype reporting a more pronounced decrease [40,41]. The proportion of HFpEF patients in HF ranges widely between 22 and 73% based on the definition used, the clinical setting, age and sex of the studies population, previous MU and publication year [38,42-

46]. The prevalence of HFpEF is higher in women while HFrEF is higher in males. Overall HFpEF increases with age particularly among patients > 64 years [47,48]. Patients with HFpEF are more likely to be female, have a higher body mass index (BMI > 30 kg/m^2) with a lower hemoglobin compared to HFrEF. The prevalence of hypertension and atrial fibrillation (AF) is higher but that of coronary artery disease and valve disease were lower compared to HFrEF [41].

Prognosis

Early observational studies (mostly retrospective) provide inconclusive and at most contradictory prognostication of HFpEF compared to HFrEF [49-51]. Data mostly drawn from ambulatory populations with insufficient information on hospitalized patients reveals HFpEF has a better prognosis based on survival relative to HFrEF [50,52,53] but some studies also reveal comparable survival rates irrespective of pump dysfunction (EF values) [51,54-56]. Recent prospective studies suggest comparable short-term survival rates for HFpEF and HFrEF. A five-year population-based prospective study [57] reports similar survival rates for HFpEF vs. HFrEF at 1, 3, and 5 years are 78% vs. 74%, 58% vs. 57% and 43% vs. 46%. The risk of cardiovascular and non-cardiovascular related deaths between HFpEF and HFpEF are also comparable (HR, 1.15; 95% CI, 0.87-1.53; p = 0.32) and (HR, 1.06; 95% CI, 0.69 - 1.61; p = 0.81). Significant independent predictors of poor prognosis in HFpEF are older age, AF on admission, history of MI, and co-morbidities (diabetes, stroke, peripheral artery disease) and cancer and anemia [57]. Another prospective population-based study [58] reports mortality rates for HFpEF are lower compared to HFrEF at 30 days (5.3% and 7.1%) and at one year (22.2% and 25.2%) but the difference was not significant. One-year hospital re-admission rates for HFpEF (13.5%) are also lower compared to HFrEF (16.1%) but the difference is not significant. Significant predictor of death for HFpEF patients are older age, presence of systolic dysfunction, peripheral vascular disease, hyponatremia (serum sodium < 135 mEq/l)), a history of cancer, renal dysfunction and anemia [58].

Etiopathophysiology

The exact pathophysiological perturbation resulting into HFpEF remains incompletely defined. The traditional model places a strong emphasis on LV remodeling due to hypertension (afterload or increased pressure overload) as the principal pathophysiologic mechanisms for inflammation and primary stimulus for LV hypertrophy and diastolic dysfunction [9,59] (Figure 2A). On the other hand, the emerging model suggests pro-inflammatory cardiovascular and non-cardiovascular comorbidities leading to systemic microvascular endothelial inflammation global cardiac and skeletal muscle inflammation and subsequent fibrosis (Figure 2B).

Traditional (hypertensive) model

In Figure 2, the traditional model implicates hypertension as the cardinal pathophysiological mechanisms for the development of HFpEF. The isolation of hypertension was based on many early studies reporting that most patients with HFpEF have a history of hypertension. Systemic vascular dysfunction due to hypertension causes pressure overload, which leads to concentric LV hypertrophy and fibrotic remodeling and diastolic dysfunction. Ultimately, LVDD leads to atrial hypertension and remodeling, pulmonary venous hypertension and RB and atrial remodeling and dysfunction. Chronic left atrial hypertension and consequent structural and electric remodeling explains the high prevalence of atrial fibrillation in HFpEF patients. However, emerging evidence suggest insufficiency of the traditional model to explain the pathophysiology of HFpEF based on hypertension.
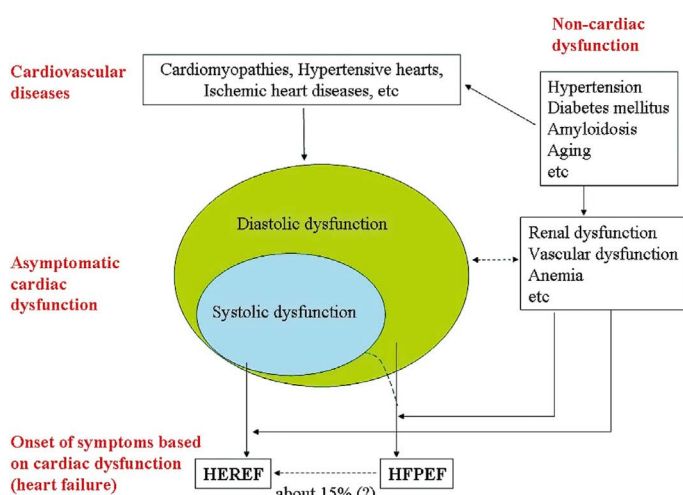

Figure 1. Transition from Cardiovascular Diseases to Heart Failure

Clinical distinction between HFpEF and HFrEF is lacking. Cardiovascular diseases cause diastolic dysfunction with or without systolic dysfunction. Systolic dysfunction without diastolic dysfunction is unlikely in clinical practice. Dysfunction of other organs may contribute to CVD and HF symptoms. About 15% of patients with HFpEF may develop HFrEF. Adapted from Yamamoto et al., 2009, pg. 405 [32]
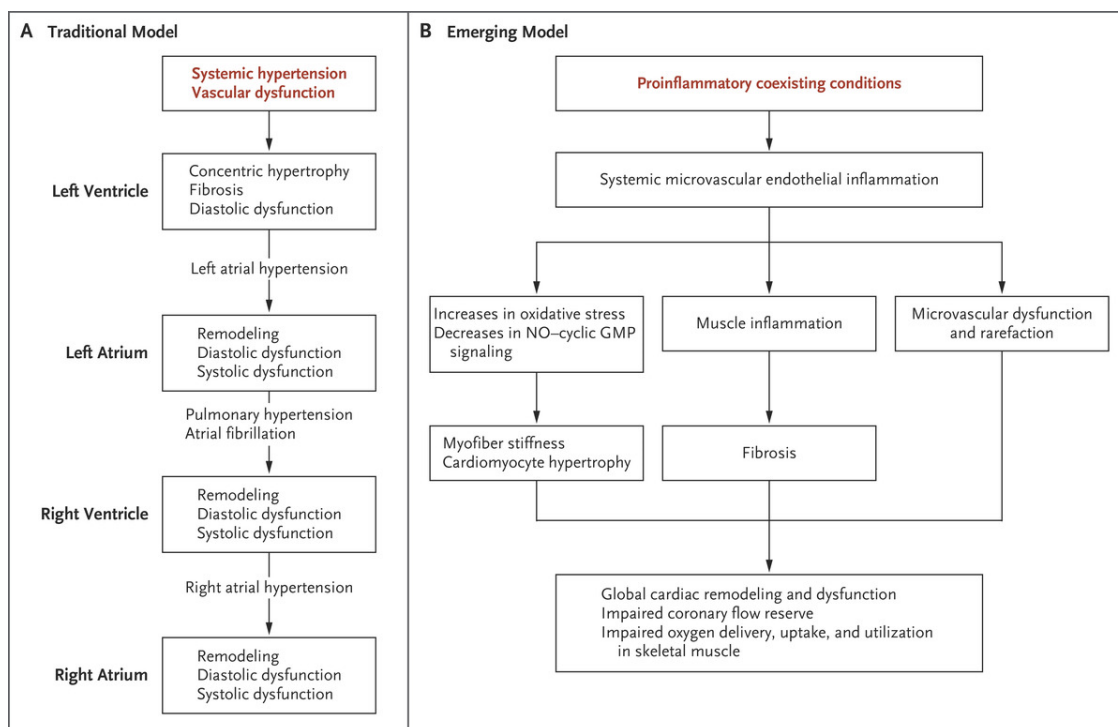
Figure 2. Traditional and Emerging Model of Pathophysiologic Mechanisms of HFpEF [59]

In the traditional model, pressure overload leads to concentric LV hypertrophic and fibrotic remodeling and diastolic dysfunction. LV diastolic dysfunction leads to left atrial (LA) hypertension and remodeling, pulmonary venous hypertension, and RV and atrial remodeling and dysfunction. Atrial fibrillation is common because of chronic LA hypertension. In the emerging model, pro-inflammatory cardiovascular and non-cardiovascular co-existing conditions lead to systemic microvascular endothelial inflammation, cardiac and skeletal muscle inflammation and fibrosis. These conditions lead to increased oxidative stress limiting nitric oxide production. Coronary microvascular inflammation results into microvascular dysfunction and rarefaction with reduced microvascular density and coronary flow reserve

On average, HFpEF patients have a higher LV mass (hypertrophy) compared to healthy controls or hypertensive patients without HF secondary to concentric remodeling [60,61] but 40% of these patients fail to meet the echocardiography criteria for LV hypertrophy [62] or the severity of hypertrophy fails to distinguish between hypertensive patients with or without HF [63]. Over time, LV systolic and diastolic stiffness increases in older patients despite increased used of anti-hypertensive therapy and decreased LV mass, casting doubts on the central role of progressive hypertrophic remodeling causing LV dysfunction in HFpEF [64]. Additionally, resting diastolic dysfunction may be common in hypertensive patients and may be unrelated to the presence or severity of LV hypertrophy [65]. In both invasive [63,64] and non-invasive LV assessment [28,66], HFpEF patients exhibit more impaired LV relaxation and diastolic stiffness compared to healthy or hypertensive controls without HF [67] but diastolic dysfunction and elevated filling pressures may be absent at rest in patients with impaired diastolic reserve [37].

Despite reports that diastolic dysfunction plays a cardinal role in the onset of HFpEF symptoms, non-invasive evidence of diastolic dysfunction is frequent in older patients without HFpEF. Thus, resting diastolic dysfunction plays a role but not sufficient in isolation to produce HFpEF [67]. The presence of increased LV diastolic stiffness implied by elevated resting LV filling pressures in HFpEF has also been demonstrated by invasive estimates of diastolic stiffness and by invasive pressure volume analysis [60]. However, the concept of heightened myocardial stiffness as a passive condition due to myocardial fibrosis has been abandoned based on the evidence that fibrosis and elevated collagen stiffness resulting from collagen cross-linking are present in HFpEF and linked to increased LV diastolic stiffness. Diastolic

myocardial stiffness is also elevated in patients without evidence of increased fibrosis and acute changes in myocardial diastolic stiffness could occur secondary to ischemia [68].

In addition to LV hypertrophy and dysfunction, the exact contribution of left atrium to the pathophysiology of HFpEF in the traditional model also remains unclear. Usually, HFpEF patients have enlarged left atrium (LA) and the extent of atrial remodeling provides an approximate index of the severity or chronicity of HFpEF [69]. A reduction in LA compliance due to atrial volume overload or upward shift of the LA pressure-volume relationship contributes to mean LA pressures. PASP and right heart load in left heart disease and presents as large V-waveforms during exercise and in the absence of mitral regurgitation. The waveforms are hemodynamic hallmark of HFpEF [67]. Chronic LA pressure overload and structural remodeling in HFpEF may result in electrical remodeling predisposing patients to AF, which is present in about 66% of HFpEF patients at some point during the natural course of the disease [70]. However, it is unclear whether AF is a prognostic marker for advanced LVDD and HF or contributes to the progression of HFpEF through perturbed atrioventricular synchrony or heart rate, or impaired LA compliance [9,67]. Several other factors may contribute to the pathophysiology of HFpEF include enhanced aortic stiffness, and impaired ventricular vascular coupling [71], chronotropic incompetence [72,73], and decreased vasodilator reserve [73] and pulmonary hypertension [63,74].

Emerging (comorbidities) model

The emerging model on the pathophysiology of HFpEF postulates endothelial dysfunction in the setting of pro-inflammatory cardiovascular and non-cardiovascular comorbidities plays a central

role in the development of HFpEF [9]. The support for the emerging model is the prevalence of various co-morbidities in HFpEF patients such as hypertension, diabetes, obesity, chronic kidney disease (CKD) and anemia frequently associated with poor prognosis and treatment outcomes [75]. The emerging model proposes a sequent of five key pathophysiologic mechanisms of HFpEF [76] (Table 1).

Comorbidities and pro-inflammatory state: Cardiovascular and non-cardiovascular comorbidities are very prevalent in HFpEF patients [75]. The main comorbidities include obesity, hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), anemia and CKD, which could induce a systemic inflammatory state [75,77]. In HFpEF, COPD causes chronic inflammation and is an independent predictor of mortality. Visceral obesity causes infiltration of macrophages into adipose tissue and produce pro-inflammatory cytokines leading to a systemic inflammatory state [78]. Obesity is also a significant prognostic marker for mortality based on a U shaped association between body mass index (BMI) and HFpEF mortality [79]. In hypertensive salt-sensitive patients, high salt intake may cause systemic oxidative stress due to renal secretion of pro-inflammatory cytokines [80,81]. In HF patients in the presence or absence of anemia, iron deficiency contributes to immune responses and oxidative stress [82]. Although arterial hypertension a key pathophysiologic mechanism of HFpEF, comorbidities cause a more pronounced deterioration of myocardial function and structure in HFpEF patients [76,83]. Comorbidities-induced systemic inflammatory states is a predictor of HFpEF incident but not HFrEF [84]. Systemic inflammatory state in HFpEF patients is evidence in high circulating concentration of interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) [76,85] and plasma levels of soluble ST2 and pentraxin 3 [86,87].

Endothelial inflammation and nitric oxide bioavailability: In myocardial biopsy samples, systemic inflammation state due HFpEF comorbidities causes over-expression of endothelial adhesion molecules – vascular cell adhesion molecule and E-selectin leading to the activation and sub-endothelial migration of circulating leukocytes [88]. Pro-inflammatory cytokines may also cause ECs to secrete ROS leading to high nitrosative/oxidative stress. High nitrotyrosine expression suggests limited NO bioavailability in HFpEF myocardium due to the scavenging of NO by superoxide anion to form peroxynitrite. Some comorbidities such as diabetes mellitus and physiological processes such as aging may increase secretion of ROS by the ECs. Aging and the exposure of the ECs to high glucose concentration causes fragmentation and dysfunction of mitochondria, secretion of ROS and the formation of nitrotyrosine [89,90]. Coronary ECs inflammation causes a reduction in vasodilator response of the microvascular bed, which correlates with LVDD [91].

Table 1. Five key pathophysiologic mechanisms in HFpEF

Steps	Description of the Pathophysiologic Processes
1	Cardiovascular and non-cardiovascular co-morbidities, especially obesity induce a pro-inflammatory state
2	Pro-inflammatory state causes coronary microvascular endothelial cells (ECs) to produce reactive oxygen species (ROS) limiting bioavailability of nitric oxide (NO).
3	Limited NO bioavailability causes a reduction in protein kinase G (PKG) in cardiac myocytes
4	Low PKG activity inhibits cardiac myocytes hypertrophy to induce concentric LV remodeling and stiffens cardiac myocytes die to hypophosphorylation of the giant cytoskeletal protein tintin
5	Stiffened cardiac myocytes and increased collagen deposition by myofibroblasts lead to LV dysfunction, the hallmark of functional deficit in HFpEF

Limited nitric oxide bioavailability and protein kinase g activity: Limited nitric oxide (NO) bioavailability and high peroxynitrite concentration inhibits the production of cyclic guanosine monophosphate (cGMP) by cardiac myocytes adjacent to dysfunctional ECs. Myocardial homogenates of HFpEF reveal low cGMP and decreased PKG activity [92,93]. Serum peptides such as B-type natriuretic peptide (BNP) particulate guanylate cyclase signaling is not able to preserve cGMP levels in HFpEF myocardium due to low diastolic wall stress in concentrically remodeled LV, which supports the low levels of BNP in HFpEF patients and the use of neprilysin inhibition to minimize the breakdown of BNP [92,94]. Low pkg activity and myocardial hypertrophy, relaxation and stiffness: PKG activity has been demonstrated in both clinical settings and experimental animal models to inhibit or even reverse myocardial hypertrophy [95,96]. In mice models, sildenafil (increases myocardial PKG activity) inhibited or reversed cardiac myocyte hypertrophy, while in diabetic patients caused a reduction in LV mass [96,97]. The relationship between myocardial PKG activity and cardiac myocyte hypertrophy is also evident in patients with aortic stenosis who exhibited less PKG activity but increased cardiac myocyte hypertrophy when diabetes mellitus was a comorbidity [95,98]. The endothelium to myocardium NO-cGMP-PKG signaling and high concentration of peroxynitrite also affect myocardial relaxation and explain the high resting tension at high pacing frequencies observed in isolated HFpEF myocardial strips [99]. The endothelium to myocardium NO-cGMP-PKG signaling also regulates myocardial stiffness. Infused NO decreased LV diastolic stiffness in human controls with aortic stenosis and dilated cardiomyopathy [100]. Sildenafil, which inhibits NO-mediated effects decreases diastolic stiffness in both animal models and humans [76]. Titin, a cytoskeletal protein, responsible for early cardiac myocytes diastolic recoil and late distension modulated through phosphorylation by PKG. cardiac myocytes from HFpEF patients have a high resting tension attributed to hypophosphorylation of titin [101].

Stiff cardiac myocytes, fibrosis and diastolic dysfunction: Stiffened cardiac myocytes described by increased collagen volume fraction, elevated expression of Collagen Type I and collagen cross-linking, contribute to LVDD [102]. The differentiation of fibroblast into myofibroblasts migrating from inflamed microvascular ECs could also lead to increased myocardial collagen deposition in HFpEF patients. ECs inflammation also augments proliferation of fibroblasts and myofibroblasts due to reduced nitric oxide bioavailability [76]. Arteria hypertension, very prevalent in HFpEF patients, has been linked with oxidative stress and microvascular inflammation lowering myocardial NO bioavailability to allow pre-hypertrophic stimuli induced by myocardial afterload (pressure overload) [76].

Clinical presentation and diagnosis

Signs and symptoms

Clinical signs and symptoms of HFpEF are non-specific and diagnosis requires a high index of suspicion with patients with significant risk factors or clinical signs and symptoms [59]. HFpEF should be suspected in patients presenting with typical signs of chronic heart failure: fatigue, weakness, dyspnea, orthopnea, peripheral edema and clinical signs such as third heart sound, jugular venous distension [103]. Specifically, HFpEF patients are more likely to be older, female, obese, lower hemoglobin compared to HFrEF and normal controls. Greater majority of HFpEF patients present with cardiovascular and non-cardiovascular comorbidities especially arterial hypertension. Other frequently encountered comorbidities are atrial fibrillation,

obesity, anemia diabetes and CKD [26]. A key clinical marker of HFpEF is exertional breathlessness and hemodynamic hallmark is an abnormal rise in pulmonary capillary wedge pressure and pulmonary artery pressure during exercise but at rest HFpEF have the same hemodynamic profiles with HFrEF and normal controls [104]. However, breathlessness is challenging to interpret in elderly and obese HFpEF patients, who form a large proportion of HFpEF patients [23].

Diagnosis criteria and work-up

The diagnosis of HFpEF is challenging because of the preserved LVEF and non-specific signs and symptoms that do not clearly discriminate HFpEF and other clinical conditions, and lack s validated gold standard diagnostic method. In particular, HFpEF diagnosis in the elderly with comorbidities and no signs of central fluid overload is difficult and cumbersome. To improve diagnostic specificity, several expert associations have published guidelines providing objective measures of cardiac dysfunction at rest and/or during exercise [23] (Table 2).

These early guidelines were published when HFpEF was assumed to be purely a diastolic dysfunction, affected about a third of HF patients, and its natural history was considered to be more benign compared to systolic heart failure [23]. Ove the past two decades, changes in epidemiology, additional knowledge on pathophysiology mechanisms and predisposing medical conditions, and the presence of LV diastolic dysfunction in other heart conditions, which made re-appraisal of diagnostic guidelines eminent [10]. However, these early guidelines provided the basis for the diagnosis of HFpEF, which included obligatory signs and/or symptoms of HF, evidence of normal systolic function, evidence of LVDD or surrogate markers of LVDD such as LV hypertrophy, LA enlargement, AF or elevated plasma natriuretic peptides [23].

The most recent guidelines are the 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure [108] and the 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines for the management of heart failure [29]. The two guidelines classify HF into two distinctive syndromes by measures of pump dysfunction: typically, echocardiography-defined LVEF (≤ 40%). However, the two criteria have important differences. The ESC provides specific classification and diagnosis of HFpEF while the ACCF/AHA is more general, based on classification of HF into four stages (A to D) defined by the absence or presence of HF symptoms and structural heart disease (Table 3).

The 2016 ESC guidelines is more specific for HFpEF and detailed, based on clinical signs and symptoms and the presence of normal or mildly dilated LV or the presence of structural and/or functional heart disease. The 2016 ESC diagnosis requires the fulfillment of four criteria:

i)   Clinical signs and symptoms;

ii) Preserved LVEF ≥ 45%;

iii) Elevated levels of NPs (BNP > 35 pg/mL and/or NT-proBNP > 125 pg/mL);

iv) Objective evidence of other cardiac functional and/or structural cardiac abnormalities underlying HF.

- LVEDV index < 97mL/m^2
- LVEDD index < 29 mm^2
- LVM index > 115 g/m^2 (M) 95 g/m2 (F)

Table 2. Earlier published diagnostic guidelines for HFpEF

Expert Group/Study	Year	Diagnostic Guidelines
The European Study Group on Diastolic Heart Failure [105]	1998	Evidence of LV diastolic dysfunction
The National Heart, Lung, and Blood Institute (NHLBI) Framingham Heart Study [106]	2000	Presence of signs ± symptoms of HF, normal LVEF (> 50%), and invasive evidence of LV diastolic dysfunction
Yturralde and Gaasch from the Lahey Clinic [107]	2005	A scoring system of major and minor criteria, LV hypertrophy and LA enlargement as surrogate markers of diastolic LV dysfunction
The Heart Failure and Echocardiography Associations of the European Society of Cardiology (ESC) [23]	2007	Presence of signs ± symptoms of congestive heart failure; presence of normal or mildly abnormal LV systolic function; and evidence of diastolic LV dysfunction

Table 3. Differences between the ESC and ACCF/AHA diagnostic criteria for HFpEF

	The 2016 ESC Criteria [108]	The 2013 ACCF/AHA Criteria [29]
Classification	HFrEF Symptoms Signs Reduced LVEF (< 45%) HFpEF Symptoms Signs Normal/mildly reduced LVEF, LV not dilated, relevant structural or functional heart disease	Stage A At risk for HF with not structural heart disease or symptoms Stage B Structural heart disease with no symptoms Stage C Structural heart disease with prior or current symptoms Stage D Refractory HF
Diagnosis	Should fulfil four conditions Presence of HF signs ± symptoms Preserved LVEF (≥ 45%) Elevated levels of NPs Evidence of structural heart disease (LVH/LAE) or diastolic dysfunction	Based on Stage C (Symptomatic) Known structural heart disease Typical signs and symptoms Preserved LVEF a. LVEF ≥ 50% - (HFpEF) b. LVEF 41-50% - (Borderline HFpEF)

F: Female; **HFpEF:** Heart failure with preserved ejection fraction; **LAV:** Left Atrial Volume; **LVEDD:** Left Ventricular End Diastolic Diameter; **LVEDV:** Left Ventricular End Diastolic Volume; **LVEF:** Left Ventricular Ejection Fraction; **LVM:** Left Ventricular Mass Indexed; **M:** Male.

- LAV index > 34mL/m^2
- E/e' ≥ 13
- E' average < 9cm/s

In case of uncertainty, a stress test of invasive measures of elevated filling pressures may be considered to confirm diagnosis.

Diagnosis of HFpEF begins with screening for signs and symptoms, which are similar for HFpEF and HFrEF. Presence of ECG abnormalities such as AF, LV hypertrophy and repolarization abnormalities makes diagnosis likely. A normal ECG and/or plasma concentrations natriuretic peptides (BNP < 35 pg/mL and/or NT-proBNP < 125 pg/mL) make diagnosis highly unlikely. The next step is advance work-up to detect structural alterations such as LA volume index or LA mass index, and key functional alterations such as E/e' and e average. Other echocardiography-defined surrogate markers for improving diagnosis include longitudinal strain or tricuspid regurgitation velocity (TRV). Echocardiography diastolic stress test may be considered using semi-supine bicycle ergometer exercise protocol (E/e') and pulmonary artery pressures (TRV), stroke volume and cardiac output changes with exercise and at rest [108]. However, diagnosis of HFpEF in patients with AF remains difficult since they have elevated levels of plasma NPs, which may require stratification by sinus rhythm (higher in AF patients).

Meta-analysis of hfpef diagnosis by myocardial strain

Current clinical guidelines for HFpEF diagnosis recommend the assessment of structural and/or functional myocardial abnormalities using LV diastolic volume, dimension, mass, left atrial volume (LAV) and E/e' ratio using conventional echocardiography along with tissue Doppler imaging (TDI) [108]. However, accumulating evidence strongly suggest global myocardial strain could be a valuable parameter to characterize alterations in systolic contractility in HFpEF patients. Observation studies report that a decrease in myocardial systolic strain causes a drop in ejection fraction but that is not often the case in hypertrophic LV diseases and HFpEF, where ejection fraction remains normal [109]. Global longitudinal strain (GLS) has also been shown to be a robust, well-validated and reproducible parameter for assessing LV longitudinal deformation. Global myocardial strain measured using 2D speckle tracking echocardiography (STE) could provide important prognostic and diagnostic information on HFpEF patients. Thus the aim of this meta-analysis is to combine patient data from individual clinical trials to determine whether global myocardial (longitudinal) strain is altered (deformed) in HFpEF patients compared to HFrEF and/or healthy controls.

Search strategy and inclusion criteria: Published studies investigating global longitudinal strain (GLS) in HFpEF patients using two-dimensional (2D)-STE were searched in PubMed, Medline, EMBASE and Cochrane online libraries. The key terms used for article search included heart failure with preserved ejection fraction or heart failure with normal ejection fraction echocardiography, and longitudinal strain. Additional studies were located through screening of citations in the selected studies as well as review articles. The inclusion criteria were, the studies (a) recruited HFpEF patients defined by LVEF ≥ 45%; (b) reported data on outcomes of 2D-STE defined GLS; and (c) reported data on healthy controls (normal or asymptomatic patients but with CVD risk factors) and/or HFrEF patients for comparison. There was no restriction on publication time and language. Studies recruiting the same population, the one with more readily extractable data or the most recent study was selected. To minimize bias, two reviewers independently screened all qualifying studies using title, abstract and full-text as well as abstracted data from the included studies. Any disagreement was resolved through consensus. Abstracted data included first author, publication year, patient characteristic (population, mean age and gender representation [percentage of male patients]), and global longitudinal strain values for HFpEF, HFrEF and/or healthy controls and their p-values (Table 4).

Study characteristics and outcomes: Online search and screening of citations retrieved 857 potential studies. Title and abstract screening excluded 721 studies. Finally, after strict application of the inclusion/exclusion criteria, twelve (12) studies were included in this meta-analysis [110-121]. All the studies compared GLS values between HFpEF patients and controls (asymptomatic or healthy patients). Six studies [112,113,115,118-120] compared GLS values between three groups of patients – HFpEF, HFrEF (or those systolic dysfunction) and controls. The twelve studies had a combined patient population of 2,405 constituting of 1,131 HFpEF patients, 533 systolic dysfunction patients, and 741 healthy controls. The mean age of the HFpEF patients was 68.25 years (SD = 6.07; range 57 – 78) with almost an equal gender representation (male HFpEF patients = 47%; range 23-70). Left ventricular systolic function differed between HFpEF patients and controls. HFpEF patients had significantly lower GLS (mean = -15.41%; range = -12% to -18.9%) than healthy controls (mean = -19.14%; range = -15.90% to -21.5%). In six studies [112,113,115,118-120] that compared GLS in HFpEF and HFrEF patients, HFpEF had significantly higher GLS (mean = -14.57%; range -12% to -17%) than HFrEF (mean = -7.38%; range -4.0% to -9.6%).

Discussion: Heart failure with preserved ejection fraction (HFpEF) has traditionally been considered a cardiac syndrome characterized by principally by LV diastolic abnormalities. The involvement of LV diastolic alterations in HFpEF have been confirmed by their inclusion in the current ESC and AFFC/AHA clinical guidelines for HFpEF diagnosis [29,108]. Measurements of LV end-diastole volume, LV end diastolic dimensions, LV mass, LA volume, LA enlargement and LV hypertrophy have been the common recommended parameters in the diagnosis work up of HFpEF using echocardiography [109]. Recent evidence based on 2D-STE imaging modality demonstrates impairment of the LV longitudinal systolic function in HFPEF patients. However, with mixed findings on whether GLS in HFpEF patients is lower relative to healthy or asymptomatic patients, the present meta-analysis analysis sought to assemble evidence that GLS is an accurate parameter for assessing and detecting alterations in longitudinal systolic function (contractility) in HFpEF patients. The findings confirm that in HFpEF patients, GLS assessed by 2D-STE is significantly lower in comparison to healthy or asymptomatic patients but significantly higher than in HFrEF patients.

The finding that longitudinal systolic function of the LV is altered (significantly lower GLS) in HFpEF patients is consistent with several previous studies. Although earlier observation studies suggested a

Table 4. Summary of included studies in HFpEF diagnosis

1st Author	Year	Patient Sample Size			HFpEF	HFpEF	Global Longitudinal Strain (%)			p-value
		HFpEF	Systolic	Controls	Mean Age (SD)	Male (%)	HFpEF	Systolic	Controls	
Wang et al. [110]	2008	50	30	17	58(16)	65	-12	-4	-19(2.0)	< 0.001
Liu et al. [111]	2009	26	23	40	68(13)	69	-14	-8	-20	< 0.001
Phan et al. [112]	2009	40	NA	26	67(10)	27	-17.8(3.3)	NA	-18.2(2.9)	< 0.763
Tan et al. [113]	2009	56	NA	67	72(7)	30	-18.9(3.5)	NA	-20.9(3.0)	0.018
Yip et al. [114]	2011	113	176	60	74(12)	36	-15.9(3.9)	-9.6(3.6)	-20.9(2.5)	<0.001
Kraigher-Krainer et al [115]	2014	219	NA	50	72(9)	39	-14.6(3.3)	NA	-20.0(2.1)	< 0.0001
Luo et al. [116]	2014	58	45	46	70(10)	60	-14.02(2.7)	-8.28(2.7)	-17.1(2.1)	<0.001
Menet et al. [117]	2014	40	40	40	70(13)	23	-17(3.0)	-7(3)	-19(3.0)	< 0.001
Pellicori et al. [118]	2014	138	NA	76	78(10)	63	-13.6(3.0)	NA	-15.9(2.4)	< 0.001
Toufan et al. [119]	2015	126	NA	60	57(10)	70	-17.3(3.5)	NA	-20.6(1.8)	< 0.001
Carluccio et al. [120]	2016	46	NA	40	65(15)	36	-15.4(3.5)	NA	-21.5(2.9)	< 0.0001
Bosch et al. [121]	2017	219	219	219	68(11)	48	-14.5(4.0)	-7.4(7.3)	-16.6(2.6)	< 0.05

NA: Not Applicable (did not include systolic/HFrEF patients)

link between ejection fraction and myocardial strain, it has been demonstrated that alterations in myocardial strain occur with a normal ejection fraction particularly in patients with hypertrophic LV disorders including HFpEF patients [109]. An Asian study reported impaired global longitudinal strain (GLS) defined by 2D-STE as < 15.8%) is a significant predictor of HF-related hospitalization, CVD-related mortality and aborted cardiac arrest in HFpEF patients [122]. In the present meta-analysis, mean GLS in HFpEF patients were < 15.8% suggesting significant alterations in LV longitudinal systolic function. Global longitudinal stress has also been shown to provide accurate assessment of LV systolic (contractility) function in patients with LV hypertrophy diseases and therefore a potential parameter for assessing LV longitudinal systolic dysfunction in HFpEF patients [109,119].

The present findings contribute new insights into HFpEF pathophysiology, and to improvement in diagnosis and treatment of HFpEF. Although current proposed pathophysiological mechanisms postulate that pro-inflammatory cardiac and extra cardiac co-morbidities, endothelial inflammation cause a cascade of pathogenic processes ultimately leading to cardiac myocyte hypertrophy and collagen deposition [75-77], present findings suggest alterations in LV longitudinal strain is present in HFpEF patients. The present findings also suggest GLS as a potential echocardiography marker for assessment of global myocardial strain and complement the current parameters assessing LV mass, dimension and volume [108]. Finally, the present findings could provide important insight into treatment of HFpEF. Many clinical trials have investigated medical and non-medical to restore LV diastolic function in HFpEF patients with the goal of improving prognosis. However, none of the current treatment regimens including HF medication has been shown to decrease mortality in HFpEF patients [123]. For this reason, other pathophysiological mechanisms such as altered LV longitudinal systolic function may be considered to design new clinical trials and treatment for HFpEF, which currently lacks a specific treatment approach. Altered LV longitudinal systolic function has also been associated with a greater CVD-related mortality and hospitalization suggesting its prognostic relevance warranting large clinical trials for validation.

Clinical management

Guidelines for clinical management

Both the ESC [108] and the ACCF/AHA [29] have published guidelines for clinical management of HFpEF but no treatment has demonstrated a reduction in morbidity or mortality (Table 5).

Treatment approaches

Treatment for HFpEF phenotype is challenging due to the lack of a precise definition. Whereas the HFrEF phenotype requires LVEF < 40%, that of HFpEF is less specific. Defined as LVEF ≥ 50%, patients with LVEF 40 to 49% (heart failure with mildly reduced LVEF [HFmEF]) are often included in treatment guidelines and protocols for HFpEF. With availability of additional new data and analysis, it may be possible to have different treatment recommendations for the HFpEF and HFmEF phenotypes, which is currently lacking. Although the use of medical therapy such as diuretics, beta-blockers, angiotensin-converting enzyme (ACE)-inhibitors/angiotensin II Type I receptor blockers (ARB), and mineralocorticoid receptor antagonist (MRA) are effective in HFrEF, fewer HFpEF patients receive these medications [94,123-125].

The limited use of traditional HF medication may suggest focus on the treatment of comorbidities such as hypertension, atrial

Table 5. Summary of the ESC and the ACCF/AHA HFpEF management guidelines

	The 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure	The 2013 ACCF/AHA Guidelines for the management of heart failure
Class I		Control of blood pressure (LoE B) Diuretics to relieve symptoms (LoE C)
Class IIa	No treatment has shown to reduce morbidity and mortality in HFpEF	Coronary revascularization in CAD (symptomatic or MI) (LoE C) AF management (LoE C) If hypertension use ACE-inhibitors and β-blockers (LoE C)
Class IIb		ARBs (LoE C)

LoE: Level of Evidence; **Class I, IIa, IIb:** Class of recommendations

fibrillation or coronary artery disease or a reduction in the new onset of the HFpEF phenotype in current clinical trials or the failure to distinguish between guidelines for HFpEF and HFrEF phenotypes [108,126]. Reduced use of HF medication support reports that the pathophysiology of HFpEF is heterogeneous and frequently associated with various cardiovascular comorbidities (arterial hypertension, AF, CAD and pulmonary hypertension) and non-cardiovascular comorbidities (CKD, COPD, anemia and obesity) [75,76].

Relative to HFrEF, a greater proportion of HFpEF deaths are associated with non-cardiovascular comorbidities [76,108]. Due to the high prevalence of comorbidities in HFpEF patients, The 2016 ESC guidelines recommend screening for cardiovascular and non-cardiovascular comorbidities, and if present, the primary therapeutic target should be their management using validated interventions to improve symptoms, well-being and clinical outcomes [108]. Currently, no treatment has shown convincing outcomes in reducing morbidity/ mortality in HFpEF patients. However, most of HFpEF patients are elderly and highly asymptomatic with poor quality of life [127]. Thus, important therapeutic target in HFpEF patients are to alleviate symptoms and to improve well-being [108] (Table 6).

Meta-analysis of hfpef medical therapy on mortality/ hospitalization

Patients with HFpEF constitute about 50% of patients with HF and their prevalence is increasing [10]. Unlike HFrEF, which has well-demonstrated treatment benefits, HFpEF patients lack specific treatment guidelines, and therapy usually focuses on treating comorbidities. Whether the conventional medical therapy for HF convey clinical benefits to HFpEF patients remains unclear. Large-scale clinical trials investigating conventional HF medical therapy have reported mixed outcomes on whether HFpEF patients have similar survival or HF-hospitalization rates compared to HFrEF patients. The aim of the present meta-analysis is to determine whether medical therapy improves survival rates and/or reduces CVD-related hospitalization for HFpEF patients compared to placebo group.

Search strategy and inclusion criteria: A systematic search for studies investigating clinical outcomes of medical therapy on HFpEF patients was done on online databases PubMed, Medline, EMBASE and Cochrane. The search used a combination of key words including heart failure, diastolic heart failure, heat failure preserved ejection fraction, or heart failure normal ejection fraction. Based on the results of the search, interventional and observational studies investigating medications on HFpEF patients were identified. To ensure as many as possible studies were identified, the citations of each potential study was

scrutinized for additional study not identified by the online search. The inclusion criteria included studies that (a) recruited patients diagnosed with HFpEF (documented LVEF ≥ 35%); (b) provided information comparing drug therapy with controls (placebo, no treatment, diuretic treatment or standard medical treatment); (c) provided information on primary and secondary endpoints (mortality and/or hospitalization); and (d) followed patients for at least 12 months. The exclusion criteria included trials (a) where EF could not be determined or substantiated; (b) pertinent data to analysis was not available; and (c) conference papers, which are subject to changes (are not final). However, studies were not excluded based on publication year and language. Two experienced reviewers screened the studies against the inclusion criteria and resolved any disagreement by consensus. Clinical, echocardiographic and outcome data were abstracted from all the included studies and entered into Microsoft Excel file. The collated data included author and publication year, patient population, cut-off LVEF, primary medication administered, hospitalization and mortality rates, and follow-up period (Table 7).

Study characteristics and outcomes: The electronic search and scrutiny of citations yielded 3161 articles. These articles were screened and evaluated for eligibility based on abstract and title only to remove duplicates and non-relevant studies. A further full-text evaluation was the conducted on all the remaining potential articles against the inclusion/exclusion criteria. Ultimately, eleven (11) studies were included in this meta-analysis [6,8,128-136]. The combined patient population in the eleven studies was 13,321 consisting of 6,650 HFpEF patients in study group (receiving medication) and 6,670 in the control group. The wide range of HF medications studied included candesartan, nebivolol, digoxin, perindopril, irbesartan, diuretic and beta-blockers (metoprolol, carvedilol and bisoprolol). The cut-off LVEF values for recruiting of HFpEF patients varied among studies (mean LVEF = 40%; range 35% to 45%). Within a mean follow-up period of 24.4±10.7 months, there was no significant differences in CVD-related-hospitalization rates for HFpEF patients on HF medication (15.7%) and control group (14%), and in mortality rates (18.3%) and (21.3%) respectively.

Discussion

Whereas HFrEF has evidence-based therapies, HFpEF lacks proven treatment. The current ESC and ACCF/AHA guidelines recommendation treatment of the precipitating co-morbidities [108]. However, the clinical benefits of these therapies on hard end-points (mortality and hospitalization) are often anticipated instead of proven in HFpEF patients. Although the traditional HF medication is usually administered to HFpEF patients, mixed outcomes from large-scale trials has made their clinical benefits unclear. This meta-analysis sought to aggregate evidence from individual large-scale studies to assess the effect of various HF medication on hospitalization and/or mortality in HF patients. This meta-analysis finds HF medication does not cause significant reduction in both mortality and hospitalization rates in HFpEF patients relative to controls.

The present findings are consistent with those of three related meta-analysis on the effect of medication on survival, quality of life and exercise tolerance [137-139]. Medical therapy in HFpEF patients demonstrates quantifiable improvement in exercise tolerance but does not cause any reduction in al-cause and CVD-related mortality [137]. HFpEF patients have a lower risk of death compared to HFrEF despite age, gender and HF etiology, but all-cause mortality is higher in HFpEF that HFrEF [139]. Comparing the effect of HF medication on survival in HFpEF patients, beta-blocker seems to have a superior protective effect on CVD-related mortality compared to other drug classes [138].

While medications might reduce mortality rates, the effect on HFpEF patients might be challenging to ascertain. HFpEF patients tend to be usually older, limited by disabling symptoms, poor quality

Table 6. Effect of medical therapy on HFpEF

Effect of on…	Primary Medication	Symptom Improvement
Symptoms	Diuretics	Improve congestion is present and consequently improved signs and symptoms of HF.
	Beta-blockers/MRAs	NO evidence on symptom relief
	ARBs/ACE-inhibitor	Inconsistent evidence. Only candesartan shows improvement in NYHA Class
Hospitalization	Nebivolol, digoxin, spironolactone and candesartan	May reduce HF hospitalization for patients with sinus rhythm.
	Beta-blockers	Not effective in reducing hospitalization in AF patients.
	ACE-inhibitors/ARBs	Inconclusive evidence
Mortality	Ace-inhibitors/ARBs, MRAs and beta-blockers	Failed to reduce mortality rates
	Nebivolol	In older patients reduced combines endpoint of death and cardiovascular hospitalization.

Table 7. Summary of included studies on efficacy of HFpEF medical treatment

1st Author [Ref #]	Year	Patient Population		LVEF (> %)	Medication	Hospitalization		Mortality		Mean Follow-up (months)
		Study	Placebo			Study	Placebo	Study	Placebo	
Yusuf et al. [8]	2003	1514	1509	40	Candesartan	170	170	241	276	36.6
Flather et al. [128]	2005	1067	1061	35	Nebivolol	123	145	256	276	21.0
Ahmed et al. [129]	2006	492	496	45	Digoxin	115	116	89	108	37.0
Cleland et al. [130]	2006	424	426	40	Perindopril	38	40	59	71	26.2
Dobre et al. [131]	2007	227	216	40	β-blockers	NR	NR	40	73	25.0
Masie et al. [6]	2008	2067	2061	45	Irbesartan	325	336	428	438	49.5
Yip et al. [132]	2008	73	75	45	Diuretic	6	6	3	1	12.0
Van Veldhuisen et al. [132]	2009	380	372	35	Nebivolol	85	94	33	39	21.0
Mulder et al. [134]	2012	133	138	35	Nebivolol	44	NR	49	52	21.0
Nevzorov et al. [135]	2012	154	191	40	β-blockers	120	NR	NR	77	24
Yamamoto et al. [136]	2013	120	125	40	Carvedilol	21	27	8	7	38.4

of life and with a high prevalence of comorbidities. HFpEF patients also have a higher non-cardiovascular-related mortality [56,57]. There are suggestions for a shift towards exercise tolerance, quality of life and improvement in symptoms as better indicators of treatment efficacy in HFpEF patients compared to the traditional mortality and hospitalization rates [138]. Further, the lack of a universally acceptable LVEF cut-off for consideration for HFpEF medication may undermine the accuracy of analysis of treatment efficacy. Trials stratified by LVEF thresholds do not find any significant differences in clinical outcomes because of ending up with smaller heterogamous subgroups with inconclusive evidence [138]. The present findings suggest the need to evaluate treatment effect on specific HFpEF phenotypes (based on precipitating comorbidity) to identify subgroups that may benefit from treatment. Newer insights into the pathophysiology of HFpEF may also help to guide research and development of newer therapies.

Conclusion

Heart failure (HF) with preserved ejection fraction (HFpEF) is a clinical syndrome characterized by left ventricular diastolic dysfunction (LVDD) and /or systolic dysfunction and distinguished by pump dysfunction (left ventricular [LV] ejection fraction (EF) (LVEF > 50%). It has the highest increasing prevalence in HF phenotypes, which is greater in women, the elderly, obese and diabetic patients. Significant markers for death or poor prognosis are older age, presence of systolic dysfunction, perivascular disease, hyponatremia, history of cancer, renal dysfunction, and anemia. Comorbidities are prevalence in HFpEF patients and implicated as the key causes of HFpEF pathophysiology. They induce systemic pro-inflammatory state leading to a sequence of events: microvascular endothelial inflammation, reduced nitric oxide (NO) and protein kinase G (PKG) activity, myocardial hypertrophy development, increased resting tension, and stiffened cardiac myocytes and interstitial fibrosis, elevated LV diastolic stiffness and ultimately the development of heart failure. The most frequent sign and symptom are exertional breathlessness and abnormal rise in pulmonary capillary wedge pressure and pulmonary artery pressure during exercise. Clinical diagnosis requires the presence of signs and symptoms of HF (fatigue, dyspnea, orthopnea, peripheral edema, third heart sound or jugular venous distension), preserved LVEF, elevated BNP and/or NT-proBNP, and evidence of structural heart disease or diastolic dysfunction. There are no specific therapies for HFpEF. There is limited use of the traditional HF medication to improve symptoms and reduce hospitalization but no significant effect on reducing mortality. However, the recommended treatment is the detecting and treatment of comorbidities.

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