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Review Article

Myths and Facts About Heart Failure with Preserved Ejection Fraction: Risk Factors, Longevity, Potential Pharmacological and Exercise Interventions☆

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SUMMARY

Significant progress in our understanding of risk factors and interventions in heart failure, a leading cause of death and disability, has occurred in recent years. Several advances in therapy for heart failure with reduced left ventricular systolic function (i.e., systolic heart failure) have led to significantly improved outcomes. Treatment options for diastolic heart failure, also known as heart failure with preserved ejection fraction (HFpEF), by contrast, remain comparatively limited. In part, this is due to gaps in our understanding of the underlying pathophysiology and the lack of standardized criteria for its diagnosis and classification. Aging and hypertension remain the leading causes of HFpEF; increased ventricular and vascular stiffness is a feature of both. Comorbidities such as diabetes, renal insufficiency, and metabolic abnormalities further aggravate disease process, and data regarding effective treatment are lacking. This article discusses the risks, mechanisms, and outcomes of HFpEF from previous studies, and summarizes potential interventions that may provide new insights into our understanding of the disease and its treatment.

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1. Introduction

Heart failure (HF), a clinical syndrome associated with poor clinical outcomes, has traditionally been considered to be systolic HF with dilated ventricular volume and reduced systolic contractility and characterized as a reduction in ventricular ejection fraction[1–3]. This syndrome, which becomes more prevalent with age, affects almost 2% of western populations[4]. More recently, however, it has become clear that HF commonly exists in the midst of preserved ventricular systolic function[5–7]. This HF with preserved ejection fraction (HFpEF) affects 50% of all HF patients based on population-based studies[8]. Although the data on HFpEF are sometimes inconsistent and conflicting, patients classified as HFpEF share common clinical features and similarly grave prognosis as those with reduced systolic function[8,9]. In earlier studies, HFpEF prevalence varied from 13% to 74%[10], with recent reports of a prevalence of 40–71%, or an average of 54% of the HF population[11] (Fig. 1). The lack of diagnostic standardization, misdiagnosis, and existence of comorbidities or deconditioning were among factors contributing to the underlying inherent selection bias[12]. Additionally, differing sample inclusion criteria from recent large community-based samples in the USA (including the Olmsted Heart Study[13], Cardiovascular Health Study[14], and Strong Heart Study[15]) and some other European countries (including the UK[16], The Netherlands[17], Sweden[18], Portugal[19], and Finland[20]) were contributory. Although there is a potential for misdiagnosis and a lack of consensus for HfpEF, common clinical features do exist in this heterogeneous patient population. The prevalence of HFpEF increases with advancing age, female gender, and this is a consistent trend across the whole HF population[19]. The true prevalence of HFpEF in the community, however, may range from 1.1% to 5.5% of the general population[8].

☆ All contributing authors declare no conflicts of interest.

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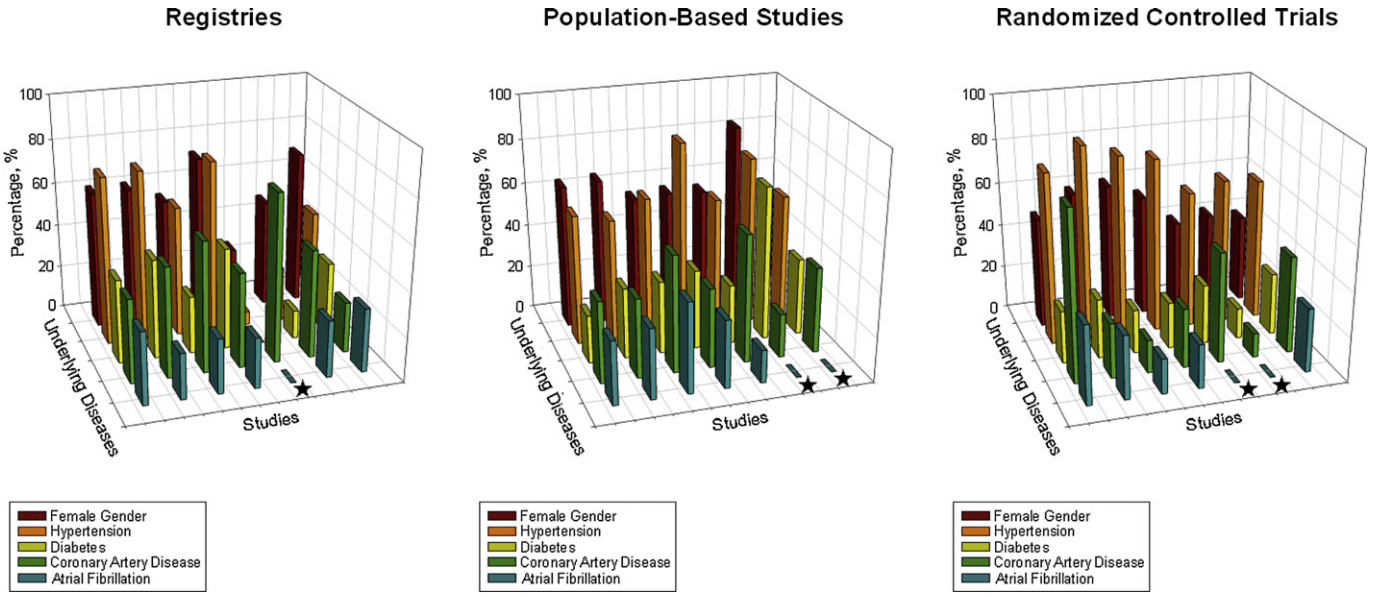

Fig. 1. The detailed percentage list of possible risks (including history of hypertension, diabetes, coronary artery disease, and atrial fibrillation) for the development of heart failure with preserved ejection fraction from various studies including registries, population-based studies, and controlled clinical trials. The black star denotes those data lacking in the original studies.

HF can be defined as a syndrome in which there is impairment of the heart's ability to eject or fill sufficiently to match the metabolic needs of whole body tissue perfusion, resulting in the classic constellation of clinical symptoms and signs[21]. Our major focus in this article is HFpEF, defined as either impaired left ventricular (LV) relaxation, diastolic suction, postsystolic recoil, or filling deficit that results in altered ventricular properties and persistent elevation in LV end-diastolic pressure at rest or exacerbated during exercise[22]. A comprehensive guideline for clinical diagnosis has been recently developed by the Echocardiography and Heart Failure Associations of the European Society of Cardiology[23]. The diagnostic criteria adopted comprise three major features: (1) clinical signs and symptoms of HF; (2) objective evidence of normal LV systolic function; and (3) evidence of diastolic dysfunction. A diagnostic flowchart based on a composite of conventional two-dimensional echocardiography, hemodynamic and tissue Doppler echocardiography, biomarkers such as brain natriuretic peptide and N-terminal pro-B-type natriuretic peptide (NT-ProBNP) have been developed as a guide to a more precise and standardized definition of HFpEF.

As previously noted, the clinical outcomes related to HFpEF are unfavorable, with an estimated annual mortality rate ranging from 3.5% to 6% in some of the large randomized clinical trials[4–12,15]. There is some discrepancy about the real causes of death between observational community-based studies[20,24,25] and controlled clinical trials[26–29]. The higher proportion of noncardiovascular deaths in community-based studies may reflect the high comorbidity burden in real world patients when compared to those enrolled in controlled clinical trials.

2. Risk factors and mechanisms of HFpEF

Various mechanisms including structural and functional anomalies may play a role in the transition from asymptomatic patients with established risk to HF development[7,30–34]. Diastolic dysfunction (DD) plays a central role in the development of overt HFpEF, although autonomic dysfunction[35], neuro-hormonal activation[36,37], and latent pulmonary hypertension[38,39] need to be excluded. Patients should also be evaluated for possible skeletal muscle dysfunction or intrinsic muscle receptor abnormality as potential causes of exertional dyspnea or fatigue[40].

Several risk factors are associated with HFpEF. In contrast to SHF or HF with reduced ejection fraction, HFpEF patients tend to be elderly females with a history[5] of hypertension[8] compared to the ischemic etiology that predominates in SHF. Fig. 1 summarizes the data on risk factors from previous registries[41–47] in population-based cohorts[8,9,15,48–51] and randomized studies[26–28,52–55]. In addition, cardiovascular risk factors are also highly linked to HFpEF in large-scaled studies; this includes obesity, diabetes, and hyperlipidemia[44]. Endothelial dysfunction may also contribute to this process via alternate pathways[56]. In addition, a higher prevalence of atrial fibrillation was observed in patients with HFpEF, possibly reflecting the loss of atrial function[14,32,47].

While aging and hypertension remain the major risk factors for HF development in epidemiological studies, phenotypic ventricular structural changes such as maladaptive concentric remodeling, most commonly accompanied by diastolic dysfunction[57], are believed to be the main substrate in HFpEF development[58,59]. Functional assessment by evaluation of ventricular diastolic function may provide key insights into the transition from LV diastolic dysfunction to overt clinical HF[57–61].

Because cardiac function shares a strong physiologic interaction with the rest of the vascular system—the ventricular-vascular coupling—simultaneous parallel functional decay may occur during the pathologic processes resulting in HFpEF[62,63]. Concurrent stiffening of both the systemic vasculature and the myocardium has been observed, resulting from increased extracellular matrix turnover, enhanced fibroblastic activity, and progressive fibrosis of normal myocardium—all crucial components in the observed functional decay[64,65]. This altered ventriculo-arterial coupling and stiffening typical of HFpEF is reflected in the steeper end-systolic pressure–volume relationship. Compensatory myocardial hypertrophy and reduction in chamber-level shortening occur in response to the persistent elevations in arterial pressures needed to overcome elevated LV wall stress and arterial stiffness[33,66].

3. Comorbidities involved and clinical scenarios mimicking HFpEF

Diabetes may induce HFpEF through elevated resting tension secondary to increased deposition of advanced glycation end products and a fibrotic myocardium[67]. Diabetic cardiomyopathy, a clinical spectrum ranging from impaired cardiac function with hypertrophied heart to overt dilated heart failure without obvious coronary artery disease, can increase susceptibility and complicate other clinical risks[68]. Renal dysfunction in terms of decreased glomerular filtration rate, a common clinical condition concomitant with worsening cardiac function in HF patients with or without preserved EF, can further increase mortality[69]. Coexisting metabolic abnormalities further complicate the clinical course of HF, resulting in a higher mortality rate.

Reduced exercise capacity and dyspnea raise the clinical suspicion for HFpEF, although no definite cardiac structural or functional abnormalities or minimal functional abnormalities can be ascribed[70]. Skeletal muscle pathology, anemia[71], pulmonary diseases[72], and deconditioned cardiopulmonary reserve, all need to be explored[12]. Obesity itself can lead to exercise intolerance through various mechanisms[73,74]. A clinical diagnostic challenge would be evaluating a patient presenting with exercise limitation for HFpEF who also has coexisting anemia, lung diseases, or obesity. All these factors can contribute to the pathogenesis of, or at least seem to share, clinical features in common with HFpEF through various pathways.

4. Clinical diagnostic tools in HFpEF – from DD to subclinical systolic dysfunction

DD, characterized by impaired ventricular filling including decreased diastolic distensibility and impaired relaxation during early diastolic phase, is thought to represent an important pathological intermediate between hypertension and heart failure[75,76]. DD is now associated with adverse clinical outcomes[77]. DD has been observed in patients with minor alterations in ventricular geometry, but which nevertheless can contribute to worse clinical outcomes[78]. At the cellular level, DD may be related to sarcomeric dysfunction and increased extracellular matrix deposition[30,79]. Regression of such fibrosis of the myocardium can occur with pharmacological intervention[80]. During the pathologic process, derangements in sarcoplasmic reticulum-mediated calcium cycling or sarcomeric thin filaments interaction may further impair diastolic relaxation and systolic contraction[81].

Characteristics of DD secondary to aging and hypertension may be derived from noninvasive studies. However, invasive measures, including pressure–volume curves used to assess ventricular filling pressure, remain the gold standard for diagnosing HF[82]. End-systolic elastance measured invasively may represent the degree of ventricular filling and contractile abnormality in response to arterial load at a specific end-systolic volume[62]. Isovolumic relaxation tau (τ) is another invasive measure obtained by fitting the exponential curve to the pressure fall of left ventricle during diastole and calculating the relaxation half-life[23,83].

Hemodynamic indices assessed by transthoracic echocardiography play a foundation role in the diagnosis of HFpEF[23]. However, tissue Doppler imaging (TDI) has emerged as a more robust, less load-dependent measure[84]. The utility of mitral inflow Doppler combined with TDI measures of diastolic function have been validated by invasive studies[85]. Yu et al reported that longitudinal systolic myocardial contraction may begin to deteriorate in HF patients even before chamber remodeling or dilatation[86]. Noninvasive measures, in conjunction with serum biomarkers such as BNP and NT-ProBNP, are included in the diagnostic criteria for HFpEF in the European Society of Echocardiography guidelines[23].

New myocardial deformation imaging techniques based on tissue Doppler or speckle-tracking permit more accurate quantification of global and regional myocardial function, and provides useful information and new insights into cardiac mechanics (Fig. 2)[87,88]. TDI-based techniques are angle-dependent and require optimal parallel alignment to the interrogation beam; speckle-tracking imaging (SIT) techniques are angle-independent. SIT-based techniques facilitate the analysis of cardiac motion and deformation independent of ultrasound beam direction, further advancing our understanding of the mechanisms involved in HFpEF[88]. Patients with HFpEF have impaired longitudinal and radial function with preserved circumferential function and ventricular twist as assessed by DTI and SIT techniques, thus giving credence to the concept of subclinical systolic dysfunction. In addition, studies using tissue velocity or deformation imaging by magnetic resonance imaging or advanced echocardiography techniques have demonstrated the coexistence of subclinical systolic dysfunction and diastolic impairment in which myocardial energy utilization deficits existed[86–88]. Interestingly, those categorized as HFpEF not only presented with less systolic and diastolic dysfunction at rest, but these abnormalities became more evident during exercise, implying a simultaneous decrease in functional reserve[89].

5. Pharmacological interventions in HFpEF and related studies

Several studies based on possible pharmacological interventions for HFpEF have recently been conducted. The rationale may actually involve the cessation of renin–angiotensin–aldosterone system (RAAS), which may theoretically halt the progress of target organ damage or myocardial fibrosis leading to subsequent cardiac chamber stiffness regression in terms of diastolic functional improvement[80]. Vascular stiffening is linked to impaired ventricular performance and has been shown to be the central factor of aging and hypertension in the pathogenesis of HFpEF, hence, calcium channel blockade aiming at relieving such disordered coupling has been reported to improve exercise capacity in elderly individuals[90]. Long-term treatment for hypertension is known to result in hypertrophy regression, and RAAS inhibition may theoretically benefit patients with heart failure and myocardial infarction beyond blood pressure lowering[91].

The Valsartan in Diastolic Dysfunction (VALIDD) study, the only randomized control enrollment research aiming at myocardial functional improvement in hypertension patients, was conducted to test the hypothesis that angiotensinogen-receptor blockade (ARB) may be superior to alternative antihypertensive therapy[76]. Both control and treatment arms had similar blood pressure reduction regardless of the medication used, in addition to reaching a similar increase in TDI defined myocardial relaxation. The study concluded that in the early stages of hypertension, the myocardial functional improvement came from blood pressure control rather than the medication used.

Some landmark pharmacological interventions related to HFpEF with the associated results have been reported in several large trials (Table 1)[28,29,53]. In the PEP-CHF study[53], angiotensin-converting enzyme inhibitor was introduced to elderly patients with HF symptoms with preserved EF. After 2 years' follow-up, the use of Perindopril was associated with an increase in exercise capacity and improvement of clinical symptoms. A trend toward decreased heart failure hospitalizations and all-cause mortality was also noted during the earlier stage (about 1 year), although the final result in the 3rd year did not show significant differences.

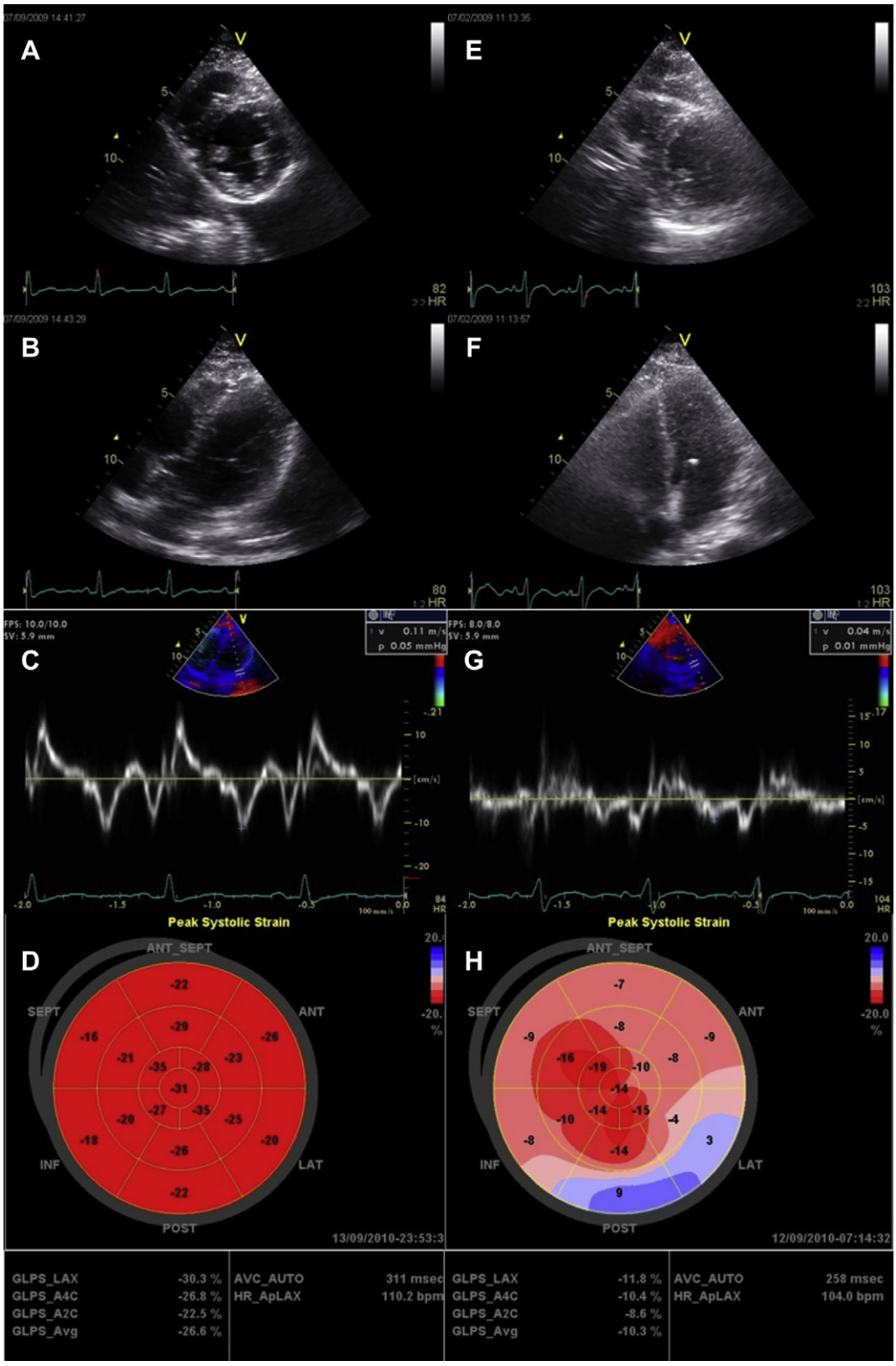

Fig. 2. (A–D) A normal adult without heart failure (HF) and free from systemic diseases; (E–H) a case with hypertension, old stroke, renal insufficiency and HF symptoms. (A,E) Both patients had normal left ventricular (LV) ejection fraction and preserved short-axis function without visible regional wall motion abnormality. Apical four-chamber view (B,F) showing preserved LV function and tissue Doppler imaging (TDI) revealed preserved (C:11 cm/s) and severely impaired diastolic function (G: 4 cm/s), respectively. Bull's-eye display imaging by automatic functional imaging from all three apical axis (D) showed preserved global longitudinal strain (mean: −26.6%) and (H) decreased longitudinal global strain (−10.3%) indicating impaired global longitudinal systolic function in HF patient. (Figure produced and processed by Lo, Chi-In MD, Mackay Memorial Hospital Taipei, Taiwan.) BMI = body mass index.

Table 1
Large clinical trials with pharmacological interventions related to heart failure with preserved ejection fraction.

Study name	Year[Ref.]	Regimen	Enrolled groups	NYHA (Fc III-IV)	LVEF (%)	Duration	Primary end-point	Results
CHARM (Preserved)	2003[28]	Candesartan (ARB) 32 mg/day	T. groups ($n = 1514$) P. groups ($n = 1509$)	583 604	54 54.1	36.6 mo (median)	CV death or unplanned Worsened HF hospitalization	Primary endpoint not met Reduced HF hospitalization
			Countries	International				
PEP-CHF	2006[53]	Perindopril	T. groups ($n = 424$)	97 (23%)	65	2.1 y	All cause death or HF hospitalization	Improved symptoms and 6-min corridor walk distance
		(ACEI) 4 mg/day	P. groups ($n = 426$)	109 (26%)	64	(median)		Reduced HF hospitalization at 1 y
			Countries	Europe				
I-PRESERVE	2008[29]	Irbesartan	T. groups ($n = 2067$)	1641 (80%)	59	49.5 mo	All cause death or CV hospitalization	Primary Endpoint not met
		(ARB) 300 mg/day	P. groups ($n = 2061$) Countries	1615 (79%) International	60	(mean)		

Note. From Epidemiology and clinical course of heart failure with preserved ejection fraction, by C.S. Lam, E. Donal, E. Kraigher-Krainer, and R.S. Vasan 2010, *Eur J Heart Fail. 13*, pp. 18–28. Copyright 2010, *Oxford University Press/ on behalf of the Taiwan Society of Geriatric Emergency and Critical Care Medicine*. Reprinted with permission.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensinogen-receptor blockade; CV = cardiovascular; Fc = functional class; HFpEF = heart failure with preserved ejection fraction; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; T. = Treatment; G. = Placebo.

The Digitalis Investigation Group *Congestive Heart Failure* (DIG-CHF) trial[27] by Ahmed et al, an ancillary study with 988 patients, found that HF death and hospitalization tended to decrease in the first 2 years. At the end of this study (37 months later), this beneficial effect was not observed. One possible reason is that a larger proportion in this study was composed of HF with ischemic origin. Subsequently, a higher incidence of unstable angina with hospitalization, which finally offset the borderline decrease of HF related clinical events, was observed in the digoxin group.

The Candesartan in Heart failure: Assessment of. Reduction in Mortality and morbidity (CHARM) study, a multicenter, international randomized trial comparing the usage of ARB candesartan added for optimal medical treatment in HF patients with and without systolic dysfunction, revealed promising results[28]. This large-scale study was the first randomized trial associated with HFpEF treatment, which underwent a median follow-up of 36 months. The clinical use of ARB in those with relatively preserved LV systolic function (Preserved Arm) showed a trend of reduced composite cardiovascular hospitalization and mortality, although the statistically nonsignificant primary endpoint was met.

Another study, the Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) trial assessed the clinical use of ARB irbesartan in patients with HF with preserved ejection fraction. After an average of 4 years follow-up, again there were no significant differences in death from any cause and cardiovascular hospitalizations[29]. The Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) study is a double-blinded, randomized, controlled trial with 150 US centers involved, evaluating the effects of spironolactone (titrated up to 45 mg daily) in patients with HFpEF (LV ejection fraction $\geq$ 45%) with primary outcomes in cardiovascular death, cardiac arrest, and hospitalizations for heart failure[92]. Even though it is currently ongoing, the results from this large trial may help to clarify whether potassium-sparing diuretics would add additional beneficial effects beyond other proven pharmacological interventions in this patient population.

So far, revascularization of heart failure patients using coronary intervention does not seem to be a promising treatment modality. The HEART study[93], currently the largest randomized study of revascularization for heart failure patients, failed to recruit the original planned number of patients. At a median follow up of 5 years with a mean age of 67, the study failed to reveal an all-cause mortality benefit in these patients, but the lack of a conclusive result may be underpowered by the obvious lack of a sufficient number of patients enrolled.

6. Role of exercise intervention in HFpEF

Exercise training can improve vascular endothelial cell function and efficiency of oxygen utilization of the peripheral muscle cell, as well as decrease NT-ProBNP, vasopressin, aldosterone, and arterial natriuretic peptide[94,95]. Potentially, exercise training can improve exercise intolerance and increase exercise capacity in patients with HFpEF. Even though it is well known that exercise training improves diastolic function in healthy patients, the effect of exercise intervention in HFpEF is still unclear based on current evidence. Few studies have examined the effects of exercise training in patients with HFpEF. Yu et al found that patients with coronary artery disease who had regular aerobic exercise training for 8 weeks, and only the subgroup with an abnormal left ventricular relaxation pattern revealed significant improvement in DD[96]. Smart et al investigated patients with DD, who had underwent a 16-week aerobic exercise regimen with cycle ergometry 3 times/week, and found a significant 19% increase in exercise capacity and 30% increase in peak oxygen uptake but without changes in diastolic function[97]. However, in a more recent study [Exercise Training in Tiastolic Heart Failure (Ex-DHF)], improvement of left ventricular diastolic indices and atrial reverse remodeling were observed to parallel the improvement of exercise capacity and peak O_2 uptake during a 3-month training interval in patients who presented with HFpEF[98]. As a result, it is likely that the improvement of peripheral mechanism may take place at the same time with diastolic improvement, such as improvement of muscular aerobic metabolism, increase muscular mass or increase vasculature density, rather than the increase of cardiac output that results in the gain in exercise capacity of patients with HFpEF leading to a better diastology in such clinical scenarios[40].

7. Summary

HFpEF as a clinical disease entity has gained much interest and research attention in the coming era of aging population, HFpEF as a clinical disease entity has gained much interest and research attention in the coming era of aging population. While several suggested imaging criteria or hints have been made in order to improve the diagnostic accuracy and recognition of patients at risk of clinical events in such population, there is limited consensus and agreements based on current body of knowledge for daily practice regarding this disease. Moreover, the lack of efficient care delivery in such population also urges more clinical works, either pharmacologic or physical approaches, on the conceptual development of

the exact pathological mechanisms underlying thus to help provide effective treatment directions in the future.

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