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Current Perspectives on Systemic Hypertension in Heart Failure with Preserved Ejection Fraction

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is a prevalent but incompletely understood syndrome. Traditional models of HFpEF pathophysiology revolve around systemic HTN and other causes of increased left ventricular afterload leading to left ventricular hypertrophy (LVH) and diastolic dysfunction. However, emerging models attribute the development of HFpEF to systemic proinflammatory changes secondary to common comorbidities which include HTN. Alterations in passive ventricular stiffness, ventricular-arterial coupling, peripheral microvascular function, systolic reserve, and chronotropic response occur. As a result, HFpEF is heterogeneous in nature, making it difficult to prescribe uniform therapies to all patients. Nonetheless, treating systemic HTN remains a cornerstone of HFpEF management. Antihypertensive therapies have been linked to LVH regression and improvement in diastolic dysfunction. However, to date, no therapies have definitive mortality benefit in HFpEF. Non-pharmacologic management for HTN, including dietary modification, exercise, and treating sleep disordered breathing, may provide some morbidity benefit in the HFpEF population. Future research is needed to identify effective treatments, perhaps in more specific subgroups, and focus may need to shift from reducing mortality to improving exercise capacity and symptoms. Tailoring antihypertensive therapies to specific phenotypes of HFpEF may be an important component of this strategy.

Keywords

Heart failure with preserved ejection fraction; HTN; Heart failure phenotypes

Introduction

Heart failure with preserved ejection fraction (HFpEF) is defined as the clinical syndrome of heart failure (HF) in a patient with a left ventricular ejection fraction (LVEF) of greater than

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Compliance with ethical standards

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50% and abnormal diastolic function or alternatively structural and biochemical evidence of cardiac abnormalities if diastolic function is normal or indeterminate [1]. HFpEF represents approximately 50% of the estimated 5.7 million Americans with HF [2, 3]. The estimated number of Americans living with HF is projected to increase to greater than eight million by 2030 [3, 4]. The incidence of HFpEF is growing compared to that of heart failure with reduced ejection fraction (HFrEF) and comprises a different patient population [5]. When compared to patients with HFrEF, patients with HFpEF are older and less likely to have ischemic etiology and are more likely to be female, obese, and have a history of HTN (HTN) [6–9]. While the overall mortality of HFpEF is lower compared to HFrEF at baseline, mortality in HFrEF has been reduced as a result of a number of evidence-based medical treatments [2]. In contrast, mortality outcomes have not improved with HFpEF.

Traditional Model of HTN in HFpEF

HTN remains one of the major modifiable risk factors in HFpEF development and progression [1, 10]. Of nearly 400 cases of new HF in the Framingham study, 91% were preceded by the development of HTN [11]. Treatment of HTN has been shown to prevent the development of HF in several clinical trials, particularly among the elderly [12–15]. Reduced incidence of HF in post-menopausal women has also been associated with markers of healthy lifestyles including high-quality diet, increased physical activity, maintenance of normal body weight, and lack of tobacco use [16], which are similar to the non-pharmacological treatment recommendations for HTN [17].

The traditional model of HFpEF pathophysiology emphasizes the role of systemic HTN causing increased afterload on the left ventricle (LV), leading to left ventricular hypertrophy (LVH) and subsequent left ventricular diastolic dysfunction. In hypertrophied myocardium, there is reduced capillary density, limited coronary artery vasodilation, increased risk for ischemia, and altered electrical properties that can change the global function of the heart [18–21]. LV mass and hypertrophy are independent predictors of cardiovascular risk, and this risk can be mitigated with LVH regression [22–27].

Diastolic function is defined as the ability of the left ventricle to expand and relax [28], and abnormal function is determined by criteria from echocardiography or cardiac catheterization [1, 29]. This abnormal function can be related to impairment of active relaxation or passive stiffness of the left ventricle [30]. The identification of diastolic dysfunction increases with age and HTN, with approximately 25% of adults over the age of 45 having some echocardiographic evidence [31]. Even without overt signs and symptoms of clinical HF, diastolic dysfunction observed on echocardiography has been associated with increased mortality [31, 32].

While diastolic dysfunction and LVH present risk factors for developing HF, it is important to remember that HF is a clinical diagnosis based on symptoms and physical signs. A significant portion of HFpEF patients do not have evidence of LVH on echocardiogram [33] or have normal or indeterminate diastolic function [34]. Conversely, many older adults have LVH and/or ventricular diastolic dysfunction but do not have clinical evidence of HFpEF. This suggests that while HTN is an important driver in the development of HFpEF, the mechanisms are more complex than this traditional model implies.

Emerging Model of HTN in HFpEF

HFpEF is a heterogeneous disease entity with multiple contributors to its pathophysiology. A new paradigm for HFpEF development was recently proposed where comorbid conditions, including HTN, diabetes, obesity, iron deficiency, and chronic obstructive pulmonary disease, promote a systemic proinflammatory state that begins a downstream cascade leading to the development of HFpEF [35•]. It is postulated that systemic inflammation leads to coronary microvascular endothelial dysfunction, with subsequent reductions in nitric oxide (NO) bioavailability, cyclic guanosine monophosphate content, and protein kinase G activity. The reduction in protein kinase G activity favors cardiomyocyte hypertrophy, as well as decreased titin protein phosphorylation that increases passive stiffening. Endothelial dysfunction also allows for migration of inflammatory cells into the interstitial space causing collagen deposition and further ventricular stiffening.

Support for this hypothesis comes from a recent study examining myocardial biopsies from human HFpEF patients and rat models. This analysis confirmed that HFpEF is associated with increases in endothelial adhesion molecules and markers of oxidative stress as well as decreased NO-dependent signaling [36]. Correction of protein kinase G activity and increased NO bioavailability have been suggested as potential targets in this cascade for treatment of HFpEF [37]. This emerging theory of HFpEF development argues that HTN does more than simply increase afterload and cause LVH; it contributes to a proinflammatory state that is potentially associated with multiple pathophysiologic mechanisms.

Passive Ventricular Stiffness

In a study of isolated cardiomyocytes from biopsies of HFpEF patients, compared to controls, there were similar isometric forces generated in response to calcium ion solutions, but higher resting forces were seen in HFpEF samples [38, 39]. Administration of protein kinase A corrected this high passive tension, indicating that decreases in phosphorylation of sarcomeric proteins may be responsible. Titin is a giant protein typically responsible for the passive forces of cardiomyocytes, with differential isoform expression and hypophosphorylation implicated in increases of passive LV stiffness seen in HFpEF [40–44]. Alteration of the myocardial extracellular matrix via increased collagen deposition has also been implicated in the development of diastolic dysfunction. Studies of HFpEF patients have shown increases in collagen volume on myocardial biopsy [38, 45–47], serologic markers of active collagen turnover correlating to degree of diastolic dysfunction [48], and diffuse myocardial fibrosis on cardiac magnetic resonance imaging correlating to degree of diastolic dysfunction [49]. These changes at the level of the cardiomyocyte and interstitium work in tandem to contribute to overall ventricular stiffness.

Ventricular-Arterial Coupling

In addition to changes in ventricular compliance, arterial compliance is also compromised in HFpEF. HFpEF patients have ventricular and arterial stiffening beyond changes associated with aging or HTN alone [50], suggesting mechanisms beyond just hemodynamic considerations accounted for in the traditional model of HFpEF. These disturbances in LV and arterial stiffness can be quantified in terms of increased elastance. Left ventricular end-

systolic elastance (Ees) is a measure of LV contractility and arterial elastance (Ea) is a measure of the net arterial load; for optimal cardiac efficiency, Ea and Ees are closely matched to maintain cardiac output, systemic blood pressure, and LV pressure over a range of physiologic conditions [51]. When compared to patients with HTN without HF, HFpEF patients have a decreased exercise tolerance associated with blunted changes in Ea (impaired afterload modulation), Ees (impaired contractile reserve), and Ea/Ees (impaired ventricular-arterial coupling) [52, 53]. Antihypertensive therapies do have the potential to blunt the exaggerated systolic blood pressure response with exercise in HFpEF, with losartan and candesartan also improving exercise tolerance [54–56]. This effect may be a result of improvements in hemodynamics, as well as from alterations in underlying inflammatory states.

Peripheral Microvascular Dysfunction

In addition to the macrovascular changes seen in HFpEF, current evidence implicates dysfunction on the microvascular level as well. With HFpEF, in comparison to hypertensive patients without HF, there is a decrease in endothelial function as measured by cutaneous peak blood flow after arterial occlusion [57]. Microvascular blood flow was also assessed in a small study of HFpEF patients compared to healthy controls, which again found dysfunction in the periphery distinct from macrovascular disease [58]. The significance of this is unclear, though further providing systemic links to HFpEF pathophysiology.

Abnormal Systolic Reserve and Chronotropic Response

Abnormalities in cardiac function in HFpEF go beyond diastolic dysfunction. Augmentation of systolic function and heart rate is expected with exercise, but can be impaired in HFpEF patients. Despite having preserved LV ejection fractions, HFpEF patients also have been shown to have decreased systolic reserve with exercise, which may contribute to decline in exercise capacity [59–63]. Chronotropic incompetence is present [64–66], as well as abnormal heart rate recovery post-exercise [65, 67, 68]. This impairment in heart rate response has prognostic value and may also be a determinant of exercise tolerance [69–72]. These factors are important to consider when selecting medical therapies for HFpEF.

Effect of Antihypertensive Therapies on HFpEF Pathophysiology and Outcomes

Studies utilizing a variety of agents such as beta-blockers, diuretics, and calcium channel blockers demonstrated regression of LVH, though medications targeting the renin-angiotensin-aldosterone system (RAAS) led to higher rates of LVH reversal [73–77]. Few studies have specifically addressed the effects of antihypertensive therapies on diastolic dysfunction. The Valsartan in Diastolic Dysfunction (VALIDD) trial, a randomized study of the angiotensin receptor blocker (ARB) valsartan, evaluated changes in echocardiographic markers of diastolic function in patients with known HTN and diastolic dysfunction [78•]. The study design included treatment of all hypertensive patients to a goal of 135/80 mm Hg or less, with the use of additional agents as needed. Both groups demonstrated reductions in systemic blood pressure and improvements in diastolic function, with no between-group

differences. This study suggests that adequate antihypertensive management, irrespective of agent, leads to improvement in diastolic function.

RAAS Inhibition

Recent randomized studies have investigated the potential benefit of RAAS inhibition in patients with HFpEF. Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) was a trial of perindopril, an angiotensin-converting enzyme inhibitor (ACEi), in 850 elderly patients with LVEF >40% and diastolic dysfunction [79]. There was a trend toward reduced mortality or hospitalization, mainly owing to the reduction in hospitalization at 1 year (hazard ratio [HR] 0.63, 95% confidence interval [CI] 0.41–0.97, $p = 0.033$). Major criticisms of PEP-CHF included an under-powered study secondary to low enrollment, low overall event rates, and crossover to open-label ACEi use after 1 year [80]. The Candesartan in Heart Failure Reduction in Mortality (CHARM)-Preserved trial assessed the role of candesartan, an ARB, on over 3000 patients with symptomatic HFpEF with a history of a hospitalization for a cardiovascular problem [81]. There was no difference in the primary outcome of cardiovascular death or a hospitalization for congestive heart failure compared to placebo, though there was a significant reduction in hospitalizations for congestive heart failure (230 vs. 279 subjects, $p = 0.017$). Another ARB, irbesartan, was studied in the Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction (I-PRESERVE) trial of over 4000 patients with recent HF hospitalization and symptomatic HFpEF [82]. There was no significant difference in the primary endpoint of all-cause mortality or hospitalization for HF. In contrast to these clinic trials, support for ACEi and ARB use in HFpEF has been seen in registry data. The Swedish Heart Failure Registry examined 16,216 patients with HFpEF and found the use of ACEi or ARB medications were associated with decreased all-cause mortality in age and propensity matched cohorts [83].

Recently, combined angiotensin receptor neprilysin inhibitors (ARNi) have generated much interest. In addition to RAAS inhibition, these medications also mediate decreased breakdown of natriuretic peptides by way of neprilysin inhibition. To date, valsartan-sacubitril has been shown to decrease all-cause mortality in patients with HFrEF and New York Heart Association (NYHA) class II–IV symptomatology based on results of the Prospective Comparison of ARNi with ACEi to Determine Impact on Global Morbidity and Mortality in Heart Failure (PARADIGM-HF) trial [84]. Mean lowering of systolic blood pressure in the intervention arm was also noted. With regard to HFpEF, valsartan-sacubitril has been investigated against valsartan alone in a phase 2 trial [85]. Though the trial was not powered for clinical outcomes, N-terminal pro B-type natriuretic peptide (NT-proBNP) levels were significantly lower in the ARNi group at 12 weeks (though the difference was not sustained at 36 weeks). Secondary outcomes such as left atrial size and systolic blood pressure (SBP) were also significantly improved in the ARNi group [85]. The Prospective Comparison of ARNi with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction (PARAGON-HF) trial is underway to assess clinical outcomes and safety between valsartansacubitril compared to valsartan alone in HFpEF (NCT01920711).

Mineralocorticoid Antagonists

Further targeting of the RAAS system has been explored with mineralocorticoid receptor antagonists (MRA). In the international Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, 3445 patients with symptomatic HFpEF and a HF hospitalization and/or elevated B-type natriuretic peptide (BNP) were randomized to spironolactone or placebo [86•]. There was no difference in the primary endpoint of death from cardiovascular cause, aborted cardiac arrest, or hospitalization for HF. The frequency of hospitalization for HF was less in the spironolactone group (HR 0.83, 95% CI 0.69–0.99, $p = 0.04$), but not the endpoint of all-cause hospitalization. Subsequent subgroup analyses demonstrated substantial geographic differences, with higher event rates (27.3 vs. 9.3%) and significant improvement with spironolactone in patients recruited in the Americas (HR 0.82, 95% CI 0.69–0.98, $p = 0.026$) compared with those from Russia and Georgia (HR 1.10, 95% CI 0.9–1.51, $p = 0.576$).

Studies of MRA in HFpEF have also focused on improving exercise capacity. In the recent Spironolactone in Myocardial Dysfunction with Reduced Exercise Capacity Trial (STRUCTURE), 150 patients with symptomatic HFpEF were randomized to spironolactone or placebo [87]. At study completion, the spironolactone group met the primary endpoints of improvement in exercise capacity and reduction in exercise-induced markers of diastolic dysfunction. In contrast, the larger Aldosterone Receptor Blockade in Diastolic Heart Failure (Aldo-DHF) trial demonstrated modest improvement in NT-proBNP levels, but no improvement in symptoms or HF-related quality of life, and a small reduction in 6-min walk distance with spironolactone [88].

While clinical results of MRA use in HFpEF have been mixed, it still remains an important agent in the treatment algorithm of HTN. A recent meta-analysis reviewed several randomized trials involving the addition of spironolactone to an antihypertensive regimen consisting of three medications in patients with resistant HTN [89]. Analysis revealed a significant reduction in office and ambulatory blood pressure values. The randomized Prevention And Treatment of Hypertension with Algorithm based Therapy number 2 (PATHWAY-2) study assessed the efficacy of spironolactone head-to-head against an alpha-blocker and a beta-blocker in patients with resistant HTN [90•]. Spironolactone produced a greater reduction in mean SBP compared to placebo (−8.70 mmHg, 95% CI −9.72 to −7.69, $p < 0.0001$), doxazosin (−4.03 mmHg, 95% CI −5.04 to −3.02, $p < 0.0001$), and bisoprolol (−4.48 mmHg, 95% CI −5.5 to −3.46, $p < 0.0001$). In addition to addressing sodium retention, it has been postulated that mineralocorticoid receptor antagonism counteracts higher circulating aldosterone levels and increased mineralocorticoid receptor activity in patients with resistant HTN.

Beta-adrenergic Blockade

In addition to RAAS inhibition, beta-blockers have also been studied as a means of neurohormonal blockade in HFpEF. The Swedish Doppler-echocardiographic (SWEDIC) study was a randomized trial of 113 patients comparing carvedilol with placebo in patients with symptomatic HFpEF [91]. Carvedilol resulted in significant improvement in the ratio of mitral peak velocity of early-to-late diastolic filling, particularly in those with high resting

heart rates, but not other echocardiographic markers of diastolic function (deceleration time, isovolumic relaxation time, pulmonary vein flow velocity). The Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) trial compared nebivolol with placebo in 2128 elderly patients with HF [92]. There was a reduction in all-cause mortality or cardiovascular admission (HR 0.86, 95% CI 0.74–0.99, $p = 0.039$). LVEF did not affect outcomes (<35 vs. $>35\%$), but the study included very few patients with LVEF $>50\%$. In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry of elderly adult patients with HF hospitalizations, beta-blocker use in the HFpEF population was not associated with reduction in hospitalizations or mortality [93]. Data from the Swedish Heart Failure Registry also found unclear benefit of beta-blocker use in HFpEF patients, with use associated with decreased all-cause mortality but not combined all-cause mortality or HF hospitalization [94].

Nitrites and Nitrates

The use of organic and inorganic nitrates and nitrites in HFpEF as a means of increasing bioavailable NO is a growing area of research. Organic nitrates were explored in the Nitrate's Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction (NEAT-HFpEF) randomized study of 110 patients with HFpEF comparing isosorbide mononitrate to placebo [95]. Isosorbide mononitrate did not improve 6-min walk distance, quality-of-life scores, or NT-proBNP levels. Interestingly, activity levels on isosorbide mononitrate were significantly lower (-439 accelerometer units, 95% CI -792 to -86 , $p = 0.02$).

While there is no clear benefit with organic nitrate use, acute use of inorganic nitrates and nitrites has shown early promise. In a randomized, parallel-group study of 28 patients with HFpEF, patients receiving intravenous sodium nitrite had significantly lower measures of exercise pulmonary capillary wedge pressure (PCWP) when compared to placebo (19 ± 5 vs. 28 ± 6 mmHg, $p = 0.0003$) [96]. A follow-up study assessed the acute effects of inhaled sodium nitrite in 26 HFpEF patients and similarly found this intervention to lower exercise PCWP (25 ± 5 vs. 31 ± 6 mmHg, $p = 0.022$) [97]. Further evidence of possible benefit comes from a randomized, crossover study in 17 HFpEF patients assessing the effects of ingested dietary inorganic nitrates [98]. The primary outcome of exercise efficiency was not significantly different. However, secondary outcomes of peak oxygen consumption and total work performed were significantly improved with ingested nitrates.

As a result of data suggesting a possible benefit from inorganic nitrates and nitrites, the Inorganic Nitrite Delivery to Improve Exercise Capacity in HFpEF (INDIE-HFpEF) study is underway (NCT02742129). This phase 2, randomized, crossover, multicenter trial will assess the effect of inhaled sodium nitrite on aerobic capacity as measured by peak oxygen consumption after 4 weeks of treatment.

Diuretics

Several studies have pointed to a benefit from diuretic use in the prevention and treatment of HFpEF. A secondary analysis of the ALLHAT study demonstrated a reduction in new-onset

hospitalized HFpEF incidence with chlorthalidone compared with amlodipine (0.69, 95% CI 0.53–0.91, $p = 0.009$), doxazosin (HR 0.74, 95% CI 0.56–0.97, $p = 0.032$), and lisinopril (HR 0.53, 95% CI 0.38–0.73, $p = 0.001$) [99]. Once HFpEF is diagnosed, diuretics play an important role in volume management. The benefit of tightly regulated diuretic use was seen in the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial, which utilized an implanted ambulatory pulmonary artery pressure monitor to guide therapy in HF patients [100]. Compared to standard clinical assessment-guided therapy, pressure-guided management resulted in higher diuretic doses and reduced HF hospitalizations; benefits were similar in patients with HFrEF and HFpEF. However, while diuretics are key for HFpEF management, care must be taken with excessive use as these patients tend to be more preload sensitive given abnormalities in ventricular-arterial coupling and variability in pressure-volume relationships [101, 102].

Non-pharmacological Treatments for HTN in HFpEF

Dietary and lifestyle Modification

Blood pressure salt sensitivity may be an important contributor to HFpEF development and progression. Mechanisms of salt sensitivity have been recently reviewed [103•] and are multi-factorial. The Dahl S (salt-sensitive) rat, an inbred animal model, develops severe HTN, LVH, diastolic dysfunction, and eventually HFpEF during high-salt feeding [104], implying that dietary factors could alter disease course. A recent pilot study implemented a sodium-restricted Dietary Approaches to Stop Hypertension diet in 13 patients with HFpEF with a goal of reducing oxidative stress and cardiovascular damage [105]. The diet was associated with reductions in clinic (155 ± 29 to 138 ± 22 mmHg, $p = 0.02$) and 24-h ambulatory systolic (130 ± 4 to 123 ± 4 mmHg, $p = 0.02$) blood pressure, confirming the salt sensitivity of the cohort. In the same cohort, the dietary change was associated with improvement in carotid-femoral pulse wave velocity (marker of arterial stiffness), urinary F2-isoprostanes (marker of oxidative stress), ventricular diastolic function, and ventricular-arterial coupling [106].

Aerobic exercise is not only recommended for HTN management, but also has clear benefits in HFpEF. This was explored in a recent randomized trial of 100 obese patients with chronic, stable HFpEF [107]. Caloric restriction and aerobic exercise were implemented in a 2×2 design. These strategies individually and additively increased peak oxygen consumption, though there was no significant effect on HF-related quality of life. Additional benefits of exercise training in HFpEF have been explored in six small randomized trials, with a recent meta-analysis demonstrating improvement in the primary outcome of change in peak oxygen uptake [108•]. Improvement was also seen in quality of life, but not LV systolic or diastolic function.

Sleep-Disordered Breathing

Obstructive sleep apnea (OSA) is a risk factor for both HTN and HF. There is a high prevalence of sleep disordered breathing, which includes OSA and central sleep apnea in patients with HFpEF [109, 110]. Often, poorly controlled HF and congestion are the

underlying causes, and sleep-disordered breathing may improve with HF treatment. In a study of 15 patients with HFpEF and severe OSA, diuretic use reduced systolic blood pressures and OSA severity and was associated with increased oropharyngeal junction area, suggesting contributions from resolving upper airway edema [111]. In 109 consecutive patients on HF medical therapy with moderate to severe sleep-disordered breathing, non-invasive positive pressure ventilation (NIPPV) has been shown to provide an improvement in right heart function and pulmonary function as well as a reduction in all-cause mortality [112]. However, in a study of 101 patients newly diagnosed with HFpEF on hospital admission, 58 patients underwent screening for sleep apnea which confirmed a diagnosis in 39 patients [113]. These 39 patients all received non-invasive positive pressure ventilation. At 6-month follow-up, there were reductions in BNP levels from admission, but not to similar levels as the non-OSA HFpEF controls. This suggests OSA is associated with increased cardiovascular risk despite treatment. The use of adaptive servo-ventilation has also been explored in a small study of 36 patients with moderate-to-severe sleep-disordered breathing and HFpEF and may improve symptoms, diastolic dysfunction, and arterial stiffness [114]. However, the use in the HFrEF population has been shown to increase mortality [115], and it is unclear if this risk translates to HFpEF as well.

Future Perspectives

Ongoing clinical trials may provide more effective therapies for the HFpEF population, but currently, there is a lack of evidence-based interventions to reduce mortality. This in part is due to the heterogeneous nature of HFpEF, which makes it difficult to target and effectively treat all patients with a single intervention. Given this, the approach to conducting HFpEF research may need to be altered. The focus may need to turn to assessing therapies in specific subgroups that have previously been equivocal in the general HFpEF population. While clinical trials have not shown a mortality benefit, some have met secondary outcomes of symptom and exercise capacity improvement and reduction in HF hospitalizations, which are not trivial measures for a patient's quality of life. Recent studies have taken these issues into account, such as the NEAT-HFpEF study which used accelerometer-based physical activity as its primary endpoint [95].

Based on current evidence, a pragmatic approach to managing HFpEF would be to tailor specific antihypertensive therapies based on a patient's comorbidities and underlying disease mechanisms (Table 1). Phenotyping of HFpEF patients can be achieved through either a comorbidity-based or hemo-dynamic approach. A comorbidity-based treatment strategy was proposed by Shah et al. with identification of the predominant contributors to the development of HFpEF and using this as a platform for pharmacotherapy choice [116•]. With particular relevance to HTN, work by Maurer et al. identified different hemodynamic profiles for pressure-volume relationships in HFpEF that differ in their response to changes in loading conditions [102]. Knowledge of the specific hemody-namic profiles for each patient may allow for personalized medication regimens. Novel systems biology-based computer modeling of the circulatory system may be able to improve such phenotyping [117, 118].

Conclusions

Systemic HTN is frequently present in and likely contributes to the pathophysiology of HFpEF in most cases. The simple construct of “diastolic” heart failure has recently been updated, and HFpEF is now recognized as a multifactorial syndrome with several contributing mechanisms. Nonetheless, the management of HTN is a cornerstone of HFpEF management, and careful matching of antihypertensive treatments to patient phenotype holds great promise for improving outcomes in patients with HFpEF.

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Table 1

Tailored antihypertensive therapies for HFpEF

Agent	Mortality/hospitalization outcomes	Comorbidities to consider	Cautions for use/Contraindications	Additional comments
Angiotensin-converting enzyme inhibitor Angiotensin receptor blocker	Neutral mortality benefit in RCTs, favorable in registries Reduction in HF hospitalization in RCT	Left ventricular hypertrophy Diabetes with microalbuminuria	Renal artery stenosis CKD	-
Angiotensin receptor-neprilysin inhibitors	-	-	Hypertakemia CKD	Reduction in NT-proBNP in phase 2 studies Current RCT in progress
Aldosterone antagonist	Neutral mortality benefit in international RCT, though significant benefit seen in Americas Reduction in HF hospitalization in RCT	Resistant hypertension	CKD Hypertakemia	Improvement in exercise capacity in patients with increased PCWP on exercise
Beta-blockers	Benefits unclear in limited RCTs and registries	Coronary artery disease	Chronotropic incompetence Severe reactive airway disease	-
Organic nitrites/nitrates	-	-	Phosphodiesterase-5 inhibitors	Reduction in activity level in RCT
Loop diuretics	Reduced hospitalizations with pulmonary artery pressure-guided therapy	HFpEF patients with volume overload	Preload dependence, CKD, electrolyte derangements	-

HFpEF heart failure with preserved ejection fraction, RCT randomized clinic trial, CKD chronic kidney disease, NT-proBNP N-terminal pro B-type natriuretic peptide, PCWP pulmonary capillary wedge pressure