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A LITERATURE ANALYSIS OF THE PATHOPHYSIOLOGY OF EMERGING THERAPIES FOR HEART FAILURE WITH PRESERVED EJECTION FRACTION AND PRECISION MEDICINE

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ABSTRACT

Heart Failure with Preserved Ejection Fraction (HFpEF) is a multifaceted and heterogeneous syndrome that accounts for more than half of all heart failure cases worldwide. It is primarily characterized by impaired diastolic relaxation and increased ventricular stiffness, leading to elevated filling pressures despite a normal ejection fraction. HFpEF predominantly affects older adults, women, and individuals with comorbidities such as hypertension, obesity, diabetes, atrial fibrillation, and chronic kidney disease. Despite its growing prevalence and significant contribution to morbidity, mortality, and healthcare costs, effective therapies for HFpEF have historically remained elusive. In recent years, however, substantial progress has been made in understanding the pathophysiology and management of this condition. The emergence of sodium–glucose cotransporter 2 (SGLT2) inhibitors, including empagliflozin and dapagliflozin, represents a major breakthrough, demonstrating consistent reductions in heart failure hospitalizations and improvements in symptoms irrespective of diabetic status. Angiotensin receptor–neprilysin inhibitors (ARNIs), particularly sacubitril/valsartan, have shown beneficial effects in select patient subgroups, while mineralocorticoid receptor antagonists (MRAs) continue to play an important role in carefully monitored patients. Furthermore, soluble guanylate cyclase (sGC) stimulators and disease-specific therapies such as tafamidis for transthyretin amyloid cardiomyopathy (ATTR-CM) highlight the shift toward targeted and precision-based treatment approaches. Despite these promising developments, no single therapy has yet demonstrated a universal mortality benefit in the diverse HFpEF population. Future strategies should emphasize precision phenotyping, integrating clinical data with multi-omics, artificial intelligence (AI), and machine learning to identify distinct HFpEF subtypes and optimize individualized therapy. Moreover, digital health technologies—including remote patient monitoring, predictive analytics, and wearable sensors—offer significant potential for early detection of decompensation and proactive management. The evolving therapeutic landscape of HFpEF signifies a paradigm shift from symptom management toward disease modification, personalization, and technology-driven care. Continued interdisciplinary collaboration and integration of advanced analytics into clinical practice will be essential to translate these emerging therapies into meaningful improvements in outcomes and quality of life for patients with HFpEF.

KEYWORDS: Heart Failure with Preserved Ejection Fraction (HFpEF), SGLT2 inhibitors, ARNI, mineralocorticoid receptor antagonists.

INTRODUCTION

Heart failure is a chronic, progressive condition in which the heart is unable to pump enough blood to meet the body's needs. It does not mean the heart has stopped working, but rather that it has become less efficient—either because it cannot contract forcefully enough (systolic dysfunction) or because it cannot relax properly to fill with blood (diastolic dysfunction).

The condition affects millions of people worldwide and is a leading cause of hospitalization among older adults. Symptoms such as shortness of breath, fatigue, and swelling in the legs develop gradually, often limiting quality of life and daily activity.

Heart failure can be classified based on the heart's pumping ability, measured by the left ventricular ejection fraction (LVEF). When the LVEF is reduced, the condition is known as Heart Failure with Reduced Ejection Fraction (HFrEF), whereas Heart Failure with Preserved Ejection Fraction (HFpEF) occurs when the pumping function appears normal, but the heart's relaxation is impaired. Heart failure with preserved ejection fraction (HFpEF), which makes up almost 50% of all HF patients globally, has become one of the main subtypes of HF.[1,2] An estimated 64 million people worldwide suffer from heart failure, and HFpEF is expected to rise as the population ages and the prevalence of obesity, diabetes, and hypertension rises.[3,4] The majority of HFpEF patients are older people, especially women, who are disproportionately affected by the illness.[5]

Heart failure is traditionally classified according to left ventricular ejection fraction (LVEF):

- HFrEF (Reduced EF) — LVEF ≤ 40%
- HFmrEF (Mildly Reduced EF) — LVEF 41–49%
- HFpEF (Preserved EF) — LVEF ≥ 50%

While HFrEF is typically due to impaired contractility (systolic dysfunction), HFpEF primarily reflects abnormal ventricular relaxation and increased stiffness (diastolic dysfunction). Importantly, HFpEF now accounts for over half of all HF cases, especially among older adults, women, and those with comorbidities such as obesity, diabetes, and hypertension.

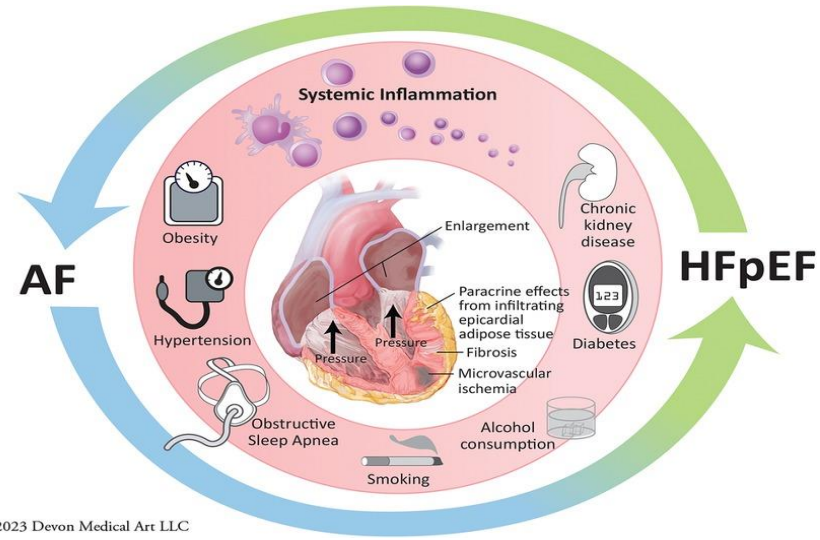

Fig. 1: Pathogenesis and progression of atrial fibrillation and heart failure with preserved ejection fraction.

HFpEF is currently the most common kind of HF in developed countries, and it is also rapidly spreading to low- and middle-income areas, according to recent epidemiologic research.[6] With a 30-day readmission rate close to 21% and a 1-year mortality rate between 20% and 29%, the mortality rate for HFpEF is still high. [7] HFpEF may have a somewhat lower mortality risk than heart failure with reduced ejection fraction (HFrEF), but the burden of morbidity and hospitalization is similar.[8]The combination of aging, cardiometabolic risk factors, and systemic inflammation akes HFpEF a growing public health problem that accounts for significant healthcare expenditures and reduced quality of life.[9]

Pathophysiology

A complicated, multivariate etiology rather than a single heart defect is what defines HFpEF. A multisystem illness affecting the heart, vasculature, kidneys, skeletal muscle, and systemic metabolic pathways, HFpEF was once thought to be a condition of left ventricular (LV) diastolic failure.[10,11]

Due to myocardial fibrosis, hypertrophy, and increased extracellular matrix deposition, the main cardiac anomaly in HFpEF is increased LV stiffness and poor relaxation.[12] Despite having a maintained ejection fraction, these anomalies raise LV filling pressures, especially during exertion.

Endothelial and microvascular dysfunction are important factors in addition to diastolic dysfunction. Comorbid conditions such obesity, diabetes, and hypertension cause chronic systemic inflammation, which in turn causes oxidative stress, decreased nitric oxide bioavailability, and coronary microvascular rarefaction.[13] These mechanisms exacerbate stiffness, encourage ventricular-arterial uncoupling, and reduce myocardial perfusion.

Vascular stiffness and compromised ventricular-arterial communication lead to increased afterload, which lowers diastolic filling and LV compliance.[14] Exercise-induced cardiac output enhancement is limited by systolic reserve impairment and chronotropic incompetence. [15] Further contributing to symptoms and the advancement of the disease are pulmonary hypertension, right ventricular (RV) impairment, and left atrial (LA) dysfunction. [16]

Additional complications associated with HFpEF include systemic inflammation, skeletal muscular weakness, and renal failure. As a result, obese-metabolic, hypertensive-aging, and atrial fibrillation-related subtypes of HFpEF are increasingly seen as a heterogeneous syndrome with several overlapping features. [17] Modern HFpEF research is based on the identification and targeting of these traits.

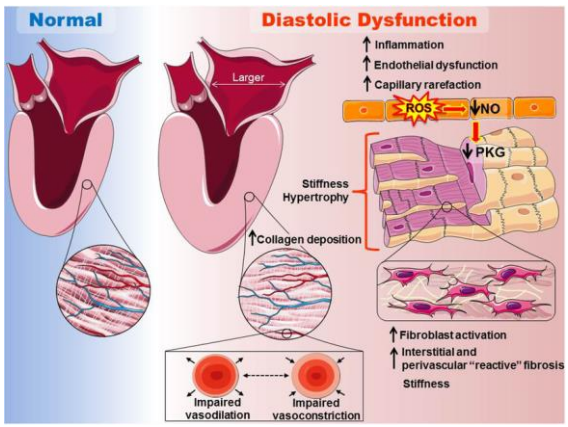

Fig. 2: Heart failure with preserved ejection fraction (HFpEF).

Left panel: At the organ level, HFpEF is marked by cardiac hypertrophy, a higher left ventricular mass-to-volume ratio (concentric remodeling), increased ventricular stiffness, and often enlargement of the left atrium. Right panel: Coronary microvascular inflammation is believed to play a central role in HFpEF progression. This involves endothelial dysfunction and impairment of the nitric oxide (NO)-cyclic guanosine monophosphate (cGMP)-protein kinase G (PKG) pathway. Increased stiffness of both cardiomyocyte myofilaments and the extracellular matrix contributes to diastolic dysfunction. Myofilament stiffness may result from reduced PKG-mediated titin phosphorylation, which normally regulates passive elasticity of heart muscle cells. Matrix stiffness is linked to fibrosis caused by excessive collagen deposition and cross-linking, driven by decreased cGMP/PKG anti-fibrotic signaling and inflammatory activation of cardiac fibroblasts. Diastolic dysfunction likely occurs early in HFpEF and interacts with cellular remodeling processes to promote disease progression.

THERAPEUTIC CHALLENGES

HFpEF continues to be one of the most difficult cardiovascular conditions to manage, even with its increasing prevalence. In the past, the majority of pharmacologic treatments that were very successful in treating HFrEF (such as beta-blockers, ACE inhibitors, and ARBs) did not show the same advantages in treating HfpEF.[18]

Disease heterogeneity is a significant obstacle; HFpEF comprises several endotypes with unique pathophysiologic processes, making a standard therapeutic approach frequently ineffective.[19] Additionally, there is still a problem with diagnostic uncertainty; many patients have symptoms that are similar to those of obesity, renal dysfunction, or pulmonary illness, which makes it more difficult to determine who should be included in clinical studies.[20]

Until recently, clinical trials yielded neutral or modest results. For example, the PARAGON-HF trial of sacubitril/valsartan showed only borderline benefit in selected subgroups such as women and those with ejection fraction ≤57%.[21] The lack of robust mortality benefit from traditional neurohormonal blockade reflects the complex interplay between cardiac and systemic factors. Comorbid conditions that frequently dominate the clinical picture and restrict responsiveness to therapy, such as diabetes, chronic renal disease, and atrial fibrillation, present another therapeutic challenge.[22] An integrated management approach that targets metabolic, vascular, and systemic inflammatory pathways in addition to heart dysfunction is necessary due to the complex nature of HFpEF.

But the field of therapy is changing quickly. A paradigm shift has been brought about by the introduction of SGLT2 inhibitors, such as empagliflozin and dapagliflozin, which have shown notable decreases in HF hospitalizations in the EMPEROR-Preserved and DELIVER trials.[23, 24] There is new hope for individualized treatment thanks to ongoing research into device-based therapies (such interatrial shunts), GLP-1 receptor agonists (like semaglutide), and mineralocorticoid receptor antagonists (like finerenone). Thus, while HFpEF remains a therapeutic challenge, recent advances in understanding its pathophysiology and phenotype-guided strategies herald a new era of targeted treatment approaches.

Established and Emerging Pharmacologic Therapies in HFpEF

Heart failure with preserved ejection fraction (HFpEF) is a complex, multifactorial syndrome that has traditionally lacked effective therapies. Recent advances in understanding its pathophysiology—including myocardial stiffness, endothelial dysfunction, systemic inflammation, and metabolic derangements—have led to the development of several pharmacologic strategies targeting different mechanisms.

Sodium–glucose cotransporter-2 (SGLT2) inhibitors, such as empagliflozin and dapagliflozin, have emerged as cornerstone therapies. Initially developed for diabetes, SGLT2 inhibitors improve osmotic diuresis and natriuresis, thereby reducing both preload and afterload, while also enhancing cardiac energy metabolism and exerting anti-inflammatory effects. Clinically, these drugs reduce hospitalizations for heart failure, improve quality of life, and are recommended as first-line therapy in HFpEF irrespective of diabetic status.[17,18]

Nonsteroidal mineralocorticoid receptor antagonists (MRAs):finerenone, represent another important class of therapy. Excess aldosterone activity contributes to myocardial fibrosis, vascular inflammation, and sodium retention, all of which exacerbate diastolic dysfunction. Unlike steroidal MRAs, finerenone has a lower risk of hyperkalemia and renal impairment while retaining potent anti-fibrotic and anti-inflammatory effects. This makes it especially beneficial in HFpEF patients with comorbid kidney disease or diabetes.[18,19]

Angiotensin receptor–neprilysin inhibitors (ARNIs), such as sacubitril/valsartan, act by dual mechanisms: neprilysin inhibition augments beneficial natriuretic peptides, improving vasodilation and promoting sodium excretion, while angiotensin receptor blockade reduces vasoconstriction and myocardial remodeling. Although overall trial outcomes in HFpEF were modest, subgroups including women and patients with mildly reduced ejection fraction showed greater benefits. ARNIs can improve diastolic function, lower filling pressures, and reduce hospital admissions in selected patients.[20,21]

Metabolic modulator glucagon-like peptide-1 (GLP-1) receptor agonists such as semaglutide, offer a novel approach targeting obesity-related HFpEF. By promoting weight loss, enhancing insulin sensitivity, and reducing systemic inflammation, GLP-1 receptor agonists improve exercise capacity, symptom burden, and overall quality of life. Their use is especially relevant in obese or metabolically compromised HFpEF patients, and combination therapy with SGLT2 inhibitors is being explored to address both metabolic and hemodynamic contributors to the disease.[22,23]

DEVICE-BASED AND NONPHARMACOLOGIC INTERVENTIONS IN HFPEF

While pharmacologic therapy remains central to managing HFpEF, device-based and lifestyle interventions provide complementary strategies, particularly for patients with persistent symptoms or exercise intolerance. **Interatrial shunt devices (IASDs)** have emerged as a novel therapeutic strategy for patients with heart failure with preserved ejection fraction (HFpEF), particularly those with elevated left atrial pressures and symptomatic exercise intolerance. These devices create a controlled, permanent left-to-right atrial shunt, allowing blood to flow from the high-pressure left atrium to the lower-pressure right atrium. By decompressing the left atrium, IASDs reduce pulmonary venous congestion, decrease pulmonary pressures during exertion, and improve cardiac filling dynamics without significantly compromising systemic cardiac output.[32,33] The primary goal of IASD therapy is symptomatic relief, especially during physical activity, rather than altering disease progression.

Clinical evaluation of IASDs has been conducted in trials such as REDUCE LAP-HF I and II. The REDUCE LAP-HF I trial demonstrated the safety and feasibility of device implantation, with favorable hemodynamic effects, including reduced left atrial pressure during exercise. In REDUCE LAP-HF II, however, outcomes were mixed; while some patients experienced improvements in exercise capacity and quality of life, the trial did not show a significant reduction in the primary composite endpoint of heart failure events and cardiovascular death. These findings underscore the

importance of careful patient selection, with ongoing research focusing on identifying subgroups most likely to benefit, such as patients with elevated left atrial pressure during exertion or preserved right ventricular function.[34,35]

Mechanistically, IASDs offer a unique nonpharmacologic approach to HFpEF management by directly targeting the pathophysiologic hallmark of elevated left atrial pressure and pulmonary congestion, which are not fully addressed by current pharmacologic therapies. Their integration into clinical practice may complement lifestyle interventions and medical therapy, particularly in patients with persistent symptoms despite optimal medical management.[34] Long-term studies are underway to clarify their durability, optimal sizing, and impact on clinical outcomes. Clinical trials, such as REDUCE LAP-HF II, have shown mixed outcomes, highlighting the importance of careful patient selection and individualized device optimization. Despite some variability in results, IASDs remain a promising strategy for symptomatic HFpEF with elevated left atrial pressures.[24,25]

Baroreceptor activation therapy (BAT) and other neuromodulation techniques target the autonomic imbalance that often characterizes HFpEF. That is innovative device-based intervention aimed at modulating autonomic imbalance in patients with heart failure, including those with preserved ejection fraction (HFpEF). HFpEF is characterized by heightened sympathetic activity and impaired parasympathetic tone, which contribute to increased vascular stiffness, elevated blood pressure, myocardial fibrosis, and diastolic dysfunction. BAT involves the implantation of a device that electrically stimulates carotid sinus baroreceptors, triggering reflex inhibition of sympathetic outflow and enhancing parasympathetic activity. This neurohormonal modulation leads to reductions in systemic vascular resistance, left ventricular filling pressures, and afterload, potentially improving exercise tolerance and symptom burden.

Early clinical studies and pilot trials have shown promising results. In HFpEF populations, BAT has been associated with improvements in exercise capacity, quality of life, and functional class, along with favorable hemodynamic changes such as reduced systolic blood pressure and pulmonary capillary wedge pressure. While these findings are encouraging, larger randomized trials are still needed to establish long-term safety, efficacy, and optimal patient selection. BAT represents a mechanistically targeted, nonpharmacologic approach that complements medical therapy by addressing autonomic dysfunction, one of the key pathophysiologic drivers of HfpEF.[25,26]

MONITORING CHECKLIST HEART FAILURE WITH PRESERVED EJECTION FRACTION

Table 1: monitoring checklist heart failure with preserved ejection fraction.

Drug/class	Baseline tests before start	Ongoing monitoring	When to hold or stop
SGLT2 inhibitors (empagliflozin, dapagliflozin)	Creatinine (eGFR), electrolytes, volume status, BP, diabetes history	Periodic renal function, review diuretic dose, assess for genital infections	Acute volume depletion, symptomatic hypotension, AKI — hold if severe; signs of DKA in diabetics
ARNI (sacubitril/valsartan)	BP, K+, creatinine; ensure ACEi stopped ≥36 hrs	K+, creatinine periodically; symptomatic hypotension	Angioedema signs → stop & urgent evaluation; persistent symptomatic hypotension or severe renal impairment
MRA (spironolactone)	K+, creatinine, eGFR	K+ every 1–3 months initially, then periodically; monitor for gynecomastia	K+ >5.5 mmol/L, rising creatinine — reduce/stop
sGC stimulators (vericiguat)	BP, review nitrates/PDE-5 inhibitor use	BP monitoring, fall risk assessment	Syncope, recurrent symptomatic hypotension, concomitant nitrates/PDE-5 use

Tafamidis (ATTR-CM)	Confirm diagnosis of ATTR (specialist), baseline clinical status	Routine clinical follow-up; monitor	Severe intolerable GI side effects or intercurrent severe infection — manage clinically

NONPHARMACOLOGIC LIFESTYLE INTERVENTIONS IN HFPEF

Nonpharmacologic lifestyle interventions form a foundational component of HFpEF management, particularly given the high prevalence of comorbidities such as obesity, hypertension, diabetes mellitus, and sedentary lifestyle. Structured exercise training is among the most evidence-supported interventions. Both aerobic and resistance training have been shown to improve peak oxygen consumption (peak VO_2), enhance skeletal muscle oxidative capacity, and improve endothelial function, which collectively reduce exercise intolerance and fatigue in HFpEF patients. Exercise also positively influences myocardial compliance and diastolic function by promoting favorable cardiac remodeling and reducing myocardial stiffness.[26] Importantly, exercise benefits extend across HFpEF phenotypes, including older adults and patients with obesity or metabolic syndrome, though individualized programs are necessary to optimize safety and adherence.

Weight management and dietary modification are critical, especially in the obese HFpEF phenotype. Excess adiposity promotes systemic inflammation, increases left ventricular filling pressures, and contributes to impaired exercise tolerance. Hypocaloric diets, dietary counseling, and structured weight-loss programs have been shown to reduce body mass index, improve insulin sensitivity, lower blood pressure, and enhance exercise capacity. In combination with exercise, weight loss can lead to meaningful reductions in left ventricular filling pressures and improvements in patient-reported quality of life.[27]

Additional lifestyle strategies, such as sodium restriction, moderation of alcohol intake, and smoking cessation, may further improve hemodynamic status and reduce HFpEF symptom burden. Sleep optimization is also increasingly recognized as important, given the high prevalence of sleep-disordered breathing in HFpEF, which exacerbates hypertension, sympathetic activation, and diastolic dysfunction. Overall, these interventions not only target the systemic and metabolic contributors to HFpEF but also complement pharmacologic and device-based therapies, highlighting the importance of a multidisciplinary, individualized approach that addresses both cardiac and extracardiac determinants of disease severity.[25-31]

CONCLUSION

Heart Failure with Preserved Ejection Fraction (HFpEF) represents one of the most complex and heterogeneous syndromes in contemporary cardiovascular medicine. Unlike Heart Failure with Reduced Ejection Fraction (HFrEF), therapeutic breakthroughs in HFpEF have been limited for decades, largely due to its multifactorial pathophysiology and the diverse clinical phenotypes it encompasses.

The emergence of SGLT2 inhibitors (such as empagliflozin and dapagliflozin) marks a major milestone, demonstrating consistent benefits in reducing heart failure hospitalizations and improving quality of life regardless of diabetes status. ARNIs (sacubitril/valsartan) have also shown potential to enhance outcomes in selected patient subgroups, while MRAs (spironolactone, eplerenone) continue to offer benefit in carefully monitored patients. Meanwhile, soluble guanylate cyclase (sGC) stimulators and disease-specific agents like tafamidis for transthyretin amyloid cardiomyopathy (ATTR-CM) represent targeted advances in precision-based therapy.

Despite these developments, no single treatment has yet demonstrated a universal mortality benefit in the HFpEF population. The condition's heterogeneity demands a personalized approach, focusing on comorbidity management, and pathophysiological targeting. Future strategies should integrate artificial intelligence, machine learning, and multi-omics analyses to identify distinct HFpEF subgroups and guide individualized therapy selection.In parallel, digital health technologies—including remote monitoring, predictive analytics, and patient-reported outcome tracking—offer new avenues to optimize care delivery and detect early signs of decompensation. The integration of these tools into routine clinical practice could enable proactive, continuous, and patient-centered heart failure management.

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REFERENCES

1. Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. *Nat Rev Cardiol*, 2020; 17(9): 559–573.
2. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*., 2021; 385(3): 254–262.
3. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*., 2021; 385(16): 1451–1461.
4. McDonagh TA, Metra M, Adamo M, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*., 2021; 42(36): 3599–3726.
5. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol*, 2019; 16(12): 713–722.
6. Shah SJ, Borlaug BA, Kitzman DW, et al. Phenotype-specific treatment of HFpEF: a call for precision medicine. *Circulation*, 2022; 146(4): 230–249.
7. Tromp J, Shen L, Jhund PS, et al. Age and sex differences in HFpEF: insights from global registries. *Eur J Heart Fail*, 2022; 24(2): 211–222.
8. Tsao CW, Lyass A, Enserro D, et al. Temporal trends in the incidence of heart failure with preserved ejection fraction. *JACC Heart Fail*, 2023; 11(1): 1–12.
9. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Heart Failure Guidelines. *J Am Coll Cardiol*, 2022; 79(17): e263–e421.
10. Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol*, 2023; 20(1): 23–36.
11. Lam CSP, Voors AA, de Boer RA, Solomon SD, van Veldhuisen DJ. Heart failure with preserved ejection fraction: mechanisms and management. *Lancet*, 2023; 402(10400): 1211–1225.
12. Shah SJ. Inflammation, microvascular dysfunction, and HFpEF. *Eur Heart J*., 2024; 45(3): 340–352.
13. Paulus WJ, Tschöpe C. A novel paradigm for HFpEF: comorbidities drive myocardial dysfunction through systemic inflammation. *JACC*, 2019; 73(5): 535–549.

14. Reddy YNV, Carter RE, Obokata M, et al. Aortic stiffness and ventricular-arterial coupling in HFpEF. *Hypertension*, 2020; 75(2): 539–546.
15. Kitzman DW, Brubaker PH, Morgan TM, et al. Chronotropic incompetence and exercise intolerance in HFpEF. *Circulation*, 2021; 143(20): 2024–2036.
16. Obokata M, Reddy YNV, Borlaug BA. The role of pulmonary hypertension and right heart failure in HFpEF. *Eur Heart J*., 2022; 43(3): 301–312.
17. Segar MW, Patel KV, Ayers CR, et al. Machine learning–based phenotyping in HFpEF. *Circulation*, 2021; 143(17): 1759–1773.
18. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med., 2021; 385(16): 1451–61.
19. Solomon SD, McMurray JJV, Claggett D, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med., 2022; 387(12): 1089–98.
20. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin M, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure. J Am Coll Cardiol, 2022; 79(17): e263–421.
21. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. J Am Coll Cardiol, 2021; 78(12): 1177–87.
22. Pitt B, Filippatos G, Agarwal R, Anker SD, Bakris GL, Rossing P, et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. N Engl J Med., 2021; 385(24): 2252–63.
23. Pieske B, Anker SD, Butler J, Filippatos G, Lam CSP, Lam C, et al. Finerenone in heart failure with preserved ejection fraction (FINEARTS-HF). Eur Heart J., 2024; 45(18): 1657–68.
24. Hasenfuß G, Borlaug BA, Lam CSP, Redfield MM, Suthahar N, Butler J, et al. Interatrial shunt devices for heart failure with preserved ejection fraction: current evidence and future directions. Eur Heart J., 2022; 43(5): 412–26.
25. Feldman T, Mauri L, Kahwash R, Redfield MM, Borlaug BA, Kaye DM, et al. Randomized trial of an interatrial shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF II). J Am Coll Cardiol, 2021; 77(18): 2215–27.
26. Gronda E, Seravalle G, Calciati A, Bombardini T, Quarti-Trevano F, Mancia G. Baroreflex activation therapy in heart failure with preserved ejection fraction: mechanisms and clinical results. Eur Heart J Suppl., 2020; 22(Suppl A): A17–25.
27. Abraham WT, Zile MR, Yu CM, et al. Autonomic modulation in HFpEF: review of baroreflex activation therapy and neuromodulation approaches. J Card Fail, 2023; 29(3): 405–16.
28. Pandey A, Kitzman DW, Whellan DJ, et al. Exercise training in heart failure with preserved ejection fraction: meta-analysis of randomized controlled trials. Circulation, 2021; 143(4): 355–65.
29. Kitzman DW, Brubaker PH, Morgan TM, et al. Effect of caloric restriction or exercise on peak oxygen consumption in obese older patients with HFpEF: a randomized clinical trial. JAMA, 2020; 324(5): 490–500.
30. Rossi A, Rognoni A, Palermi S, et al. Nonpharmacologic strategies in HFpEF: exercise, weight loss, and lifestyle modification. Heart Fail Rev., 2022; 27(3): 923–39.
31. Pandey A, Garg S, Khawaja MZ, et al. Role of weight management in heart failure with preserved ejection fraction: mechanistic insights and clinical impact. Eur Heart J, 2023; 44(15): 1280–92.

32. Feldman T, Mauri L, Kahwash R, Redfield MM, Borlaug BA, Kaye DM, et al. Randomized trial of an interatrial shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF II). J Am Coll Cardiol, 2021; 77(18): 2215–27.
33. Hasenfuß G, Borlaug BA, Lam CSP, Redfield MM, Suthahar N, Butler J, et al. Interatrial shunt devices for heart failure with preserved ejection fraction: current evidence and future directions. Eur Heart J., 2022; 43(5): 412–26.
34. Kaye DM, Redfield MM, Marwick TH, et al. Hemodynamic effects of interatrial shunt devices in heart failure with preserved ejection fraction. Circulation, 2020; 141(22): 1745–56.
35. Borlaug BA, Redfield MM, Kaye DM, et al. Left atrial decompression via interatrial shunt: rationale, mechanism, and clinical application. Heart Fail Rev., 2019; 24(5): 659–69.