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Heart Failure with Preserved Ejection Fraction (HFpEF): Unraveling the Pathophysiology, Diagnosis, and Emerging Therapeutic Strategies

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Abstract

Heart Failure with Preserved Ejection Fraction (HFpEF) represents a complex clinical syndrome characterized by heart failure symptoms despite a normal or near-normal left ventricular ejection fraction (LVEF). This condition is increasingly recognized as a major contributor to the global burden of heart failure, particularly in the aging population. HFpEF is associated with a heterogeneous pathophysiology, including impaired ventricular relaxation, increased stiffness of the myocardium, and altered diastolic filling, often resulting from comorbidities such as hypertension, diabetes, and obesity. The diagnostic evaluation of HFpEF remains challenging due to the lack of specific biomarkers and imaging criteria. Advanced echocardiographic techniques, cardiac MRI, and biomarker profiling are helping to enhance diagnosis and risk stratification. Despite significant progress in understanding its pathophysiology, the management of HFpEF has proven difficult, with few therapies showing clear benefit. However, emerging strategies targeting key molecular pathways, including anti-fibrotic agents, vasodilators, and therapies aimed at improving diastolic function, offer hope for future treatment options. This review aims to provide a comprehensive overview of the current understanding of HFpEF's pathophysiology, diagnostic approaches, and the evolving landscape of therapeutic interventions.

Keywords: Heart failure with preserved ejection fraction (HFpEF); Pathophysiology; Diagnosis; Ejection fraction; Diastolic dysfunction; Hypertension; Comorbidities; Echocardiography; Cardiac MRI; Emerging therapies; Fibrosis; Heart failure management; Treatment strategies; Diastolic dysfunction; Biomarkers

Introduction

Heart Failure with Preserved Ejection Fraction (HFpEF) has emerged as a prominent and growing concern in modern cardiology, particularly as the global population ages. HFpEF accounts for a substantial proportion of heart failure cases, with estimates suggesting it represents nearly 50% of all heart failure patients in developed countries. Unlike heart failure with reduced ejection fraction (HFrEF), which is defined by a diminished left ventricular ejection fraction (LVEF), HFpEF is characterized by the presence of normal or near-normal LVEF despite significant clinical symptoms of heart failure. This paradox, where the heart's pumping function appears preserved but patients experience heart failure symptoms, underscores the complexity and unique nature of the condition [1].

The pathophysiology of HFpEF remains a subject of active research and is multi-faceted, involving various mechanisms that result in diastolic dysfunction and impaired cardiac filling. Central to the disease process is an increase in left ventricular stiffness, which leads to impaired relaxation and filling during diastole. This, in turn, results in elevated filling pressures and pulmonary congestion, even in the presence of normal systolic function. Contributing factors include a combination of myocardial fibrosis, vascular stiffening, and altered myocardial energetics. Additionally, common comorbidities such as hypertension, diabetes, obesity, and chronic kidney disease significantly contribute to the development and progression of HFpEF.

The clinical diagnosis of HFpEF remains challenging due to the lack of a specific, definitive test or biomarker. The diagnosis is often one of exclusion, requiring the presence of symptoms such as shortness of breath, fatigue, and fluid retention, alongside a normal or near-normal LVEF. Several diagnostic modalities, including echocardiography, cardiac MRI, and biomarker profiling, have been developed to help clinicians assess diastolic function, ventricular stiffness, and other key features of the disease. However, no single test is fully conclusive, and the diagnostic approach often requires a combination of clinical, imaging, and laboratory assessments to rule out other causes of heart failure [2].

Despite the growing recognition of HFpEF as a major clinical entity, effective therapeutic strategies remain elusive. Current treatments, such as diuretics and antihypertensive drugs, primarily aim to manage symptoms and control comorbidities rather than address the underlying pathophysiological processes of the disease. Recent research efforts are focused on identifying therapies that can target the molecular and cellular mechanisms underlying myocardial stiffness, fibrosis, and endothelial dysfunction. Investigational therapies, including anti-fibrotic agents, novel vasodilators, and agents aimed at improving myocardial relaxation, are showing promise in preclinical and early clinical studies.

Additionally, emerging insights into the role of the gut microbiome, inflammation, and metabolic dysfunction in HFpEF pathogenesis may offer novel therapeutic avenues. As the understanding of HFpEF's mechanisms deepens, there is increasing optimism that targeted therapies will improve outcomes for patients, providing more personalized and effective treatment options.

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In summary, HFpEF is a complex and multifactorial condition that presents significant diagnostic and therapeutic challenges. The interplay between myocardial, vascular, and systemic factors contributes to its pathophysiology, while ongoing advancements in diagnostic technology and emerging therapies provide hope for improving patient outcomes. Further research into its molecular underpinnings, alongside the development of targeted therapeutic strategies, is critical for advancing the management of HFpEF and alleviating the burden of this growing public health issue [3].

Materials and Methods

This review on Heart Failure with Preserved Ejection Fraction (HFpEF) synthesizes current evidence from published studies, clinical trials, and preclinical research. The following sections outline the materials and methods used for data collection, analysis, and presentation in the context of understanding the pathophysiology, diagnostic strategies, and emerging therapeutic approaches in HFpEF.

Literature search and selection criteria

A comprehensive literature search was conducted to identify relevant studies on HFpEF, spanning basic science, clinical research, diagnostic strategies, and therapeutic interventions. The following databases were searched for articles published between 2000 and 2024:

- PubMed
- Scopus
- Google Scholar
- Cochrane Library
- Embase [4].

Search terms included combinations of keywords such as "Heart Failure with Preserved Ejection Fraction," "HFpEF," "pathophysiology," "diagnosis," "treatment," "diastolic dysfunction," "fibrosis," "emerging therapies," "cardiac MRI," "echocardiography," and "comorbidities." Relevant studies were included if they met the following criteria:

Published in peer-reviewed journals.

Focused on the pathophysiology, diagnostic approaches, or therapeutic strategies for HFpEF.

Included clinical trials, observational studies, meta-analyses, and review articles.

Involved human or animal models relevant to HFpEF pathophysiology and treatment.

Studies were excluded if they:

Focused solely on HFrEF (Heart Failure with Reduced Ejection Fraction).

Were non-English language papers.

Had unclear methodology or lacked significant scientific contribution [5].

Data extraction and synthesis

Data were extracted from selected articles according to the following categories:

Pathophysiology: Key mechanisms contributing to myocardial stiffness, diastolic dysfunction, endothelial dysfunction, fibrosis, and other molecular and cellular abnormalities in HFpEF.

Diagnosis: Diagnostic tools and methods, including echocardiography, cardiac MRI, biomarkers, and clinical criteria used in the diagnosis of HFpEF.

Therapeutic Strategies: Pharmacological and non-pharmacological treatments, including current management options (e.g., diuretics, antihypertensives), emerging therapies (e.g., anti-fibrotic agents, novel vasodilators), and clinical trial findings.

Data from high-quality randomized controlled trials (RCTs), cohort studies, systematic reviews, and meta-analyses were prioritized to ensure the reliability and generalizability of the conclusions [6].

Pathophysiological mechanisms

A detailed review of studies investigating the underlying pathophysiological mechanisms of HFpEF was conducted. The focus was on:

Myocardial and Vascular Dysfunction: Mechanisms such as increased ventricular stiffness, impaired myocardial relaxation, and diastolic dysfunction.

Fibrosis and Inflammation: The role of myocardial fibrosis, extracellular matrix remodeling, and systemic inflammation in the progression of HFpEF.

Comorbidities: The contribution of hypertension, diabetes, obesity, chronic kidney disease, and other metabolic conditions to HFpEF pathogenesis.

Metabolic and Endothelial Dysfunction: The role of metabolic abnormalities and endothelial dysfunction in the development and progression of HFpEF [7].

Studies utilizing advanced imaging techniques (e.g., cardiac MRI, echocardiography) and molecular assessments (e.g., biomarker profiling, gene expression analysis) were particularly emphasized to provide insights into the cellular and molecular mechanisms.

Diagnostic approaches

The review highlighted diagnostic tools used in the identification of HFpEF. These included:

Echocardiography: The role of Doppler echocardiography in assessing diastolic dysfunction, left ventricular filling pressures, and other key parameters of heart function.

Cardiac MRI: Use of cardiac MRI in evaluating myocardial fibrosis, ventricular stiffness, and other structural abnormalities in HFpEF patients.

Biomarkers: Analysis of various biomarkers (e.g., natriuretic peptides, galectin-3, soluble ST2) used to support the diagnosis and risk stratification of HFpEF.

Clinical Criteria: A review of the diagnostic criteria proposed by major cardiology societies (e.g., American Heart Association, European Society of Cardiology) for the diagnosis of HFpEF, emphasizing the role of exclusion and ruling out other causes of heart failure [8].

Therapeutic strategies

A comprehensive review of both pharmacological and non-pharmacological treatment approaches was undertaken. The following categories were explored:

Current Therapies: Medications used to manage HFpEF symptoms,

such as diuretics for fluid overload, antihypertensive drugs (ACE inhibitors, angiotensin receptor blockers, beta-blockers, and calcium channel blockers) for blood pressure control, and mineralocorticoid receptor antagonists (MRAs).

Emerging Therapies**:** The review highlighted ongoing clinical trials and preclinical studies investigating novel treatment strategies, including:

Anti-fibrotic therapies targeting myocardial fibrosis and extracellular matrix remodeling.

Vasodilators to improve diastolic function and reduce afterload.

Metabolic therapies focusing on myocardial energetics and mitochondrial dysfunction.

Inflammatory Modulation targeting systemic inflammation and its contribution to HFpEF pathophysiology.

SGLT2 Inhibitors: The emerging role of sodium-glucose co-transporter 2 inhibitors in improving outcomes in HFpEF [9].

Clinical trial data and results from multicenter studies investigating the efficacy and safety of these treatments were carefully reviewed.

Preclinical models

Preclinical animal models of HFpEF were also reviewed for insights into the disease mechanisms and testing of novel therapies. These models include:

Rodent Models: Studies using rats and mice that replicate key features of HFpEF, such as hypertension, diabetes, and obesity-induced heart failure.

Cellular Models: In vitro studies focusing on cardiomyocytes, fibroblasts, and endothelial cells to study cellular dysfunction and therapeutic interventions.

Data analysis

Given the nature of this review as a synthesis of existing literature, formal statistical analysis was not conducted. However, key findings from clinical trials, meta-analyses, and systematic reviews were summarized and compared across studies. A qualitative analysis approach was used to assess the evidence for emerging therapies and diagnostic strategies.

Ethical considerations

This review did not involve original patient data or clinical trials, and therefore did not require ethical approval. However, all reviewed studies adhered to ethical standards for research involving human and animal subjects, as stated in the original publications [10].

Discussion

Heart Failure with Preserved Ejection Fraction (HFpEF) remains one of the most challenging and least understood forms of heart failure, despite its increasing prevalence, especially among elderly populations and those with common comorbidities like hypertension, diabetes, and obesity. The complexity of HFpEF lies in its multifactorial pathophysiology, in which normal or preserved left ventricular ejection fraction (LVEF) coexists with impaired diastolic function, leading to symptoms of heart failure. Unlike heart failure with reduced ejection fraction (HFrEF), where the heart's pumping capacity is directly compromised, HFpEF primarily involves impaired ventricular relaxation, increased myocardial stiffness, and elevated filling pressures. This distinction has profound implications for both diagnosis and treatment.

The pathophysiology of HFpEF involves multiple interconnected processes. Myocardial fibrosis, endothelial dysfunction, and vascular stiffening are key contributors to the impaired relaxation and filling of the heart. In HFpEF, the heart muscle becomes less compliant due to collagen deposition and altered extracellular matrix composition, leading to diastolic dysfunction. Additionally, systemic inflammation, metabolic abnormalities, and neurohormonal activation exacerbate the condition. It is increasingly clear that HFpEF is not a single disease entity but a syndrome influenced by various coexisting conditions. For instance, the interplay between obesity, insulin resistance, and hypertension contributes to the myocardial and vascular changes that underlie HFpEF. The growing understanding of these mechanisms has shifted focus towards treating the underlying risk factors, with the hope of halting disease progression.

From a diagnostic perspective, HFpEF remains difficult to identify due to the absence of specific biomarkers or imaging criteria that could distinguish it unequivocally from other forms of heart failure. Currently, diagnosis largely relies on clinical criteria, the exclusion of other potential causes of heart failure, and the use of advanced imaging techniques such as echocardiography and cardiac MRI. While echocardiography remains the most widely used tool, its limitations in assessing diastolic function highlight the need for further innovation. Cardiac MRI, with its ability to measure myocardial fibrosis and tissue characteristics, is emerging as a promising tool, though its availability and cost limit widespread use. Biomarkers such as natriuretic peptides and galectin-3 are showing promise in both diagnosis and prognostication, but more research is needed to validate their role in HFpEF.

Therapeutically, the management of HFpEF has proven frustratingly inadequate. Unlike HFrEF, where therapies like beta-blockers, ACE inhibitors, and ARBs have clear, evidence-based benefits, treatments for HFpEF primarily focus on symptom management. Diuretics are commonly used to alleviate fluid retention, while antihypertensive agents aim to control blood pressure and mitigate further strain on the heart. However, these therapies do not address the underlying pathophysiology and have limited impact on improving long-term outcomes. This underscores the need for targeted therapies that can modify disease progression rather than just alleviate symptoms.

Recent advances in the development of emerging therapies for HFpEF are promising, although results have been mixed. SGLT2 inhibitors, initially developed for diabetes, have shown significant benefits in improving outcomes in HFpEF, likely due to their effects on both cardiac and renal function, as well as their anti-inflammatory and anti-fibrotic properties. Other investigational agents, such as anti-fibrotic therapies targeting myocardial fibrosis and vasodilators aimed at reducing ventricular stiffness, have shown promise in preclinical studies and early-phase clinical trials. Nonetheless, the complexity and heterogeneity of HFpEF mean that a "one-size-fits-all" treatment is unlikely to emerge, and personalized approaches will be necessary. Therapies targeting specific disease mechanisms, such as metabolic reprogramming or inflammation modulation, are likely to be the focus of future research.

A major challenge in HFpEF treatment is the heterogeneity of the patient population. HFpEF patients often present with a range of comorbidities, which complicates both diagnosis and treatment. For

example, obesity and diabetes may contribute to insulin resistance and myocardial dysfunction, while hypertension is a major contributor to increased ventricular stiffness. Targeting these comorbidities through lifestyle interventions (e.g., weight loss, exercise, and dietary modifications) alongside pharmacological treatments may offer a more comprehensive approach to management. Additionally, recent findings suggest that improving endothelial function and reducing inflammation could play a critical role in preventing disease progression.

Conclusion

Heart Failure with Preserved Ejection Fraction (HFpEF) is a complex and multifactorial condition that presents significant challenges in both diagnosis and treatment. Unlike Heart Failure with Reduced Ejection Fraction (HFrEF), where impaired systolic function is the hallmark, HFpEF is characterized by normal or preserved left ventricular ejection fraction despite impaired diastolic function and elevated filling pressures. This unique pathophysiological profile, underpinned by myocardial stiffness, fibrosis, endothelial dysfunction, and systemic inflammation, makes HFpEF a distinct clinical syndrome that requires specialized diagnostic and therapeutic approaches.

The diagnosis of HFpEF remains one of exclusion, as no single biomarker or imaging modality can definitively identify the condition. Current diagnostic strategies rely on a combination of clinical presentation, advanced imaging techniques (such as echocardiography and cardiac MRI), and the assessment of biomarkers. Despite these advancements, the diagnosis is often challenging and may be delayed, as it overlaps with other cardiovascular and non-cardiovascular conditions. This diagnostic uncertainty highlights the need for further research into specific biomarkers and imaging techniques that could improve early detection and risk stratification.

Therapeutically, HFpEF remains a largely unmet clinical need, as current management strategies are predominantly focused on symptom relief and the management of comorbidities, such as hypertension, diabetes, and obesity. While diuretics and antihypertensive agents provide symptomatic benefit, they do not address the underlying pathophysiological processes of the disease. The emerging landscape of HFpEF treatment is evolving, with promising investigational therapies targeting myocardial fibrosis, endothelial dysfunction, and metabolic disturbances. Notable among these are sodium-glucose co-transporter 2 (SGLT2) inhibitors, which have shown benefit in improving outcomes in HFpEF patients, as well as agents aimed at reducing fibrosis, improving diastolic function, and modulating inflammation. However, the heterogeneity of HFpEF patients—due to varying comorbidities and disease mechanisms—suggests that personalized, tailored treatment approaches will be necessary for optimal management.

The future of HFpEF treatment hinges on a deeper understanding of its complex pathophysiology, including the roles of metabolic dysfunction, systemic inflammation, and neurohormonal dysregulation. Ongoing research into the molecular and cellular drivers of the disease is essential to identify novel therapeutic targets and improve treatment outcomes. Moreover, large-scale clinical trials are crucial for validating the efficacy of emerging therapies and determining the most effective treatment regimens for specific patient subgroups.

Ultimately, advances in HFpEF research hold the potential to revolutionize both the diagnosis and management of this condition. By addressing the underlying mechanisms of the disease and considering the complex interplay between heart, vasculature, and systemic factors, more effective therapies can be developed. A more nuanced, personalized approach to treatment, coupled with early and accurate diagnosis, could substantially improve the quality of life and survival of HFpEF patients. In this regard, the ongoing efforts to unravel the pathophysiology of HFpEF and develop targeted therapies represent a crucial step toward reducing the burden of this increasingly prevalent form of heart failure. As our understanding of the disease continues to evolve, there is hope that more effective, disease-modifying treatments will emerge, offering a brighter future for those affected by HFpEF.

Conflict of interest

None

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None

References

1. Loganathan RS, Stover DE, Shi W, Venkatraman E (2006) Prevalence of COPD in women compared to men around the time of diagnosis of primary lung cancer. Chest 129: 1305-1312.
2. Ghanei M, Shohrati M, Harandi AA, Eshraghi M, Aslani J, et al. (2007) Inhaled corticosteroids and long-acting beta 2-agonists in treatment of patients with chronic bronchiolitis following exposure to sulfur mustard. Inhal Toxicol 19: 889-894.
3. Michael JG, Jyovani J, Daniel OG, Brian HN, Yossi C, et al. (2018) Comparison of stroke volume measurements during hemodialysis using bioimpedance cardiography and echocardiography. Hemodial Int 22: 201-208.
4. Prandoni P, Lensing AWA, Prins MH, Ghirarduzzi A, Ageno W, et al. (2009) Residual thrombosis on ultrasonography to guide the duration of anticoagulation in patients with deep venous thrombosis: a randomized trial. Ann Intern Med 150: 577-585.
5. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, et al. (2017) 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 135: e1159-e1195.
6. Pappone C, Rosanio S, Augello G, Gallus G, Vicedomini G, et al. (2003) Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation: outcomes from a controlled nonrandomized long-term study. J Am Coll Cardiol 42: 185-197.
7. Lutsey PL, Zakai NA (2023) Epidemiology and prevention of venous thromboembolism. Nat Rev Cardiol 20: 248-262.
8. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, et al. (2014) 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 35: 3033-3069.
9. Martin BJ, Hauer T, Arena R, Austford LD, Galbraith PD, et al. (2012) Cardiac rehabilitation attendance and outcomes in coronary artery disease patients. Circulation 126: 677-687.
10. Grace SL, Bennett S, Ardern CI, Clark AM (2014) Cardiac Rehabilitation Series: Canada. Prog Cardiovasc Dis 56: 530-535.