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HEART FAILURE WITH PRESERVED EJECTION FRACTION: THE CENTRAL ROLE OF LIFESTYLE MODIFICATION AND NONPHARMACOLOGICAL THERAPIES

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ABSTRACT

Introduction: Heart failure with preserved ejection fraction (HFpEF) is a condition characterized by significant morbidity and mortality, as well as a considerable burden on healthcare systems. Until recently, sodium-glucose co-transporter 2 (SGLT2) inhibitors were the only drug class to demonstrate a consistent benefit in clinical outcomes among these patients. HFpEF is a complex, multifactorial disorder frequently associated with advanced age, obesity, hypertension, diabetes, and sedentary lifestyle. Many of these risk factors are potentially modifiable.
Aim of the Study: The aim of this article is to provide a comprehensive overview of the role of nonpharmacological interventions and lifestyle modifications in the management of HFpEF, emphasizing current evidence for their effectiveness and highlighting the importance of patient-centered, multidisciplinary approaches in improving clinical outcomes.
Materials and Methods: A thorough review of the literature was conducted using the PubMed database, Google Scholar with search terms including "heart failure with preserved ejection fraction", "HFpEF treatment", "lifestyle modification", "obesity", "diet", "exercise", vagus nerve stimulation" and related keywords.
Results and Conclusions: Nonpharmacological interventions, including exercise training, dietary modification, weight management, and patient education, have demonstrated significant benefits in improving functional capacity, quality of life, and cardiovascular risk profiles in patients with HFpEF. Although pharmacological treatment options remain limited, lifestyle-based strategies are essential components of comprehensive care for this population. Future research should continue to refine and personalize nonpharmacological approaches to further improve outcomes for individuals living with HFpEF.

KEYWORDS

Heart Failure, Lifestyle Modification, Exercise Training, Obesity, Vagus Nerve Stimulation

CITATION

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Epidemiology

Heart failure (HF) is a grave global health problem that affects millions of individuals around the world. In 2019, the number of patients diagnosed with HF was approximately 56.2 million, and in 2021, it increased to 64 million, representing approximately 1–3% of the general population [1-4]. The clinical manifestation of HF can be categorized into two primary phenotypes: heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) [1], [5]. HFpEF is a complex clinical syndrome characterized by symptoms of heart failure despite a normal or near-normal left ventricular ejection fraction (LVEF ≥50%). Its prevalence is increasing at a faster rate of 1% compared to that of HFrEF, primarily due to population aging and the advancements in survival outcomes for patients with other cardiovascular diseases [3]. This condition is prevalent among the elderly population, men remain at higher risk for HFrEF, while both sexes share comparable risk for HFpEF [6]. HFpEF has been shown to be less responsive to heart failure therapies such us Renin-Angiotensin-Aldosterone System (RAAS) Inhibitors, beta-blockers, Mineralocorticoid receptor antagonists (MRA), and Neprilysin Inhibitors (ARNI), with these therapies failing to show robust benefit in major clinical trials [7-11]. SGLT2 inhibitors are the first class to demonstrate clear efficacy in reducing hospitalizations in HFpEF patients [12], [13].

The rates of morbidity, mortality, and rehospitalization are high, resulting in a precipitous increase in direct healthcare expenses and the loss of quality-adjusted life years [14], [15]. Multimorbidity is prevalent in both types of heart failure, though it is slightly more severe in HFpEF, with approximately 50% of patients having five or more major comorbidities, including hypertension, diabetes, obesity, chronic kidney disease, and atrial fibrillation [16-18]. This increase in cases has placed substantial strain on outpatient clinics, inpatient beds, and healthcare budgets, thereby necessitating a shift in public health priorities toward the promotion of prevention and the acceleration of diagnoses. According to recent estimates, the annual global economic burden of heart failure is estimated to be approximately US$346 billion [3].

Diagnostics

Diagnosing HFpEF remains challenging, as there is no single definitive test. This is in contrast to HFrEF, where a reduced ejection fraction (≤40%) provides a clear diagnostic criterion. In HFpEF, a left ventricular ejection fraction (LVEF) of ≥50% does not distinguish between healthy and affected individuals. Therefore, diagnosis relies on a combination of indirect criteria, including clinical symptoms, biomarker levels, and imaging findings. However, symptoms such as exertional dyspnea, fatigue, or edema are non-specific and overlap with other cardiovascular, respiratory, or metabolic diseases (e.g., COPD, obesity, anemia) [5], [16], [19]. In elderly patients, symptoms may be subtle or atypical, and comorbidities may further obscure their presentation and limit the accuracy of ancillary tests. For instance, NT-proBNP concentrations may be normal in obese individuals, complicating the diagnostic process [16]. Echocardiography in HFpEF does not typically reveal the characteristic structural abnormalities seen in HFrEF. Advanced echocardiographic assessment of diastolic function and ventricular stiffness (e.g., E/e′ ratio, left atrial volume, A wave velocity) is often required, but such techniques may not be widely available and require specialized expertise [20]. Comprehensive diagnosis frequently necessitates exercise testing, via echocardiography or cardiac catheterization, since resting evaluations may be non-diagnostic; however, these approaches are costly and not universally accessible. The ultimate diagnosis is determined by the application of scoring scales such as the HFA-PEFF score (ESC) or H2FPEF score (Mayo Clinic). It is important to note that both scales have inherent limitations [5], [19]. A comparative analysis of the two is presented in the following table (Table 1).

Table 1. A comparative analysis of ESC 2021 and AHA/ACC/HFSA 2022

Diagnostic Element	ESC 2021 (European Society of Cardiology)	AHA/ACC/HFSA 2022 (American Heart Association/College of Cardiology)
Symptoms and/or signs	Required (e.g., dyspnea, fatigue, peripheral edema)	Required
Left Ventricular Ejection Fraction (LVEF)	≥50%	≥50%
Natriuretic peptides	Elevated BNP (>35 pg/ml) or NT-proBNP (>125 pg/ml)	Elevated BNP (>35 pg/ml) or NT-proBNP (>125 pg/ml)
Structural/functional changes (ECHO/MRI)	At least one: - Left atrial volume index (LAVI) >34 ml/m² - LV hypertrophy - E/e' >15	Suggestive findings: - LA enlargement - LV hypertrophy - Elevated E/e' ratio
Diagnostic scoring system	HFA-PEFF Score (0–6 points): ≥5 = HFpEF confirmed 2–4 = needs further testing ≤1 = HFpEF unlikely	No scoring system used
Additional testing	Stress echocardiography or right heart catheterization recommended if diagnosis unclear	May be considered if needed, but not routinely required
Etiology exclusion	Not required	Must exclude non-cardiac causes of symptoms

Note. Table created by the authors

Pathophysiology of HFpEF

Heart failure with preserved ejection fraction (HFpEF) has shown multiple overlapping pathophysiological mechanisms. In contrast to HFrEF, which is frequently precipitated by myocardial damage (e.g., ischemia), HFpEF is predominantly driven by a constellation of comorbidities, which often result in systemic inflammation, endothelial dysfunction, and myocardial stiffness. The unified model proposed by Paulus and Tschöpe in 2013 emphasizes the role of comorbidities in triggering a series of events that lead to myocardial dysfunction [21]. Below, we summarize the pathophysiological mechanisms affecting cardiomyocytes, ventricular and atrial remodeling, and consequently, patients' quality of life.

1. Comorbidities and low-grade inflammation

Conditions such as hypertension, obesity, type 2 diabetes, chronic kidney disease, and chronic obstructive pulmonary disease create a chronic, low-grade inflammatory state. This state is characterized by elevated levels of pro-inflammatory cytokines, reactive oxygen species (ROS), and adipokines [17], [21], [22]. Circulating cytokines reduce nitric oxide (NO) bioavailability and increase oxidative stress within the coronary microcirculation, priming the myocardium for stiffness and fibrosis [23].

2. Microvascular dysfunction and the NO–cGMP–PKG pathway

HFpEF hearts demonstrate a 30–50% reduction in microvascular density and impaired endothelium-dependent vasodilation [24]. Endothelial injury results in reduced NO (nitric oxide) bioavailability, leading to lower levels of cGMP (cyclic guanosine monophosphate) and diminished PKG (protein kinase G) activity [21], [25]. Reduced NO–cGMP–PKG signaling plays a central role in HFpEF by diminishing titin phosphorylation, promoting cardiomyocyte stiffness, stimulating TGF-β–driven fibroblast activation, and enhancing sodium-hydrogen exchanger activity. This worsens intracellular sodium and calcium loading [26].

3. Myocardial Remodeling and Atrial Dysfunction

Chronic inflammation and oxidative stress promote interstitial fibrosis and myocardial hypertrophy, increasing left ventricular stiffness and impairing diastolic function. Additionally, atrial enlargement and dysfunction impede ventricular filling and raise left atrial pressure, exacerbating heart failure symptoms [21], [26].

Elevated left atrial (LA) pressures cause LA remodeling, atrial fibrillation, and postcapillary pulmonary hypertension. Chronic afterload on the right ventricle produces right ventricular pulmonary artery (RV-PA) uncoupling and exercise dyspnea [27], [28].

4. Autonomic Imbalance: Sympathetic and Parasympathetic Systems

An additional, increasingly recognized pathophysiological component in HFpEF is autonomic nervous system dysregulation. Patients with HFpEF typically exhibit increased sympathetic activity and reduced parasympathetic (vagal) tone [29]. Heightened sympathetic drive promotes vasoconstriction, tachycardia, sodium retention, and adverse cardiac remodeling, all of which exacerbate diastolic dysfunction and volume overload [30]. Conversely, diminished vagal activity weakens the anti-inflammatory “cholinergic anti-inflammatory pathway,” allowing unchecked systemic and myocardial inflammation. This autonomic imbalance—sympathetic predominance and parasympathetic withdrawal—not only worsens myocardial stiffness and fibrosis but is also associated with impaired heart rate variability, baroreflex sensitivity, and increased arrhythmic risk [29], [31. Moreover, the interplay between autonomic dysfunction and chronic inflammation creates a vicious cycle that perpetuates disease progression and worsens patient outcomes.

Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) is a neuromodulation technique in which mild electrical impulses are delivered to the vagus nerve to influence brain and body function [32]. VNS technique, either invasive or transcutaneous, improves autonomic balance in HFpEF by enhancing parasympathetic activity and suppressing sympathetic overactivity. This modulation triggers anti-inflammatory effects via the cholinergic anti-inflammatory pathway, reducing cytokines activation of the vagus nerve triggers the cholinergic anti-inflammatory pathway, resulting in suppression of proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-8, IL-11, IL-18, and IL-23A, and attenuates myocardial fibrosis, which is intimately linked to diastolic dysfunction in HFpEF [33], [34]. Additionally, VNS directly influences cardiac electrophysiological stability by reducing arrhythmogenic indices (e.g., T-wave alternans and heterogeneity) and improves baroreflex sensitivity, further mitigating the risk of adverse cardiac events [34], [35]. These mechanisms collectively contribute to improved cardiac structure, function, and clinical outcomes in HFpEF. In animal models of HFpEF, chronic low-level transcutaneous VNS (LLTS) has been shown to reduce blood pressure, LV hypertrophy, and diastolic dysfunction. LLTS also decreases myocardial inflammation and fibrosis by downregulating pro-inflammatory and pro-fibrotic genes, effects that correlate with improved cardiac strain and function, without altering heart rate or ejection fraction [33]. Recent clinical trials have

demonstrated that both invasive and non-invasive VNS are safe and feasible in HFpEF [32]. The ANTHEM-HFpEF study found that chronic cervical VNS improved NYHA class, exercise tolerance, quality of life, and autonomic markers, while reducing arrhythmia risk, despite no significant group-level changes in echocardiographic mechanical function parameters such as E/e′ ratio or left ventricular mass index [34]. Complementary to this findings, a randomized, sham-controlled trial of LLTS showed significant improvements in global longitudinal strain and inflammatory biomarkers, with a strong correlation between cytokine reduction and cardiac function improvement [35]. Case report support the rapid hemodynamic effects of tVNS in HFpEF. For example, tVNS improved renal venous flow and right heart function in a patient with diuretic-resistant congestion, demonstrating acute benefits on both autonomic tone and organ congestion [36].

Lifestyle Changes

The 2021 ESC guidelines on HF and the 2022 AHA/ACC/HFSA guidelines emphasize the importance of lifestyle and treatment of comorbidities in HFpEF as class I recommendations for optimizing treatment outcomes [5], [19]. Effective nonpharmacological treatment targets both the underlying pathophysiology and symptoms of HFpEF.

Exercise Training

Studies have shown that aerobic training significantly improves exercise capacity, vitality, and quality of life (QOL) in patients with HFpEF. When discussing the impact of exercise on HFpEF, it is important to mention maximal oxygen consumption (VO_2max), as this parameter shows the greatest improvement. VO_2max is an indicator of aerobic fitness, providing information about physical condition and the body's ability to perform prolonged exercise, which is why its increase contributes to an improvement in patients' quality of life [37-39]. No significant changes in cardiac diastolic function or natriuretic peptide concentrations were observed [39]. Pooling echocardiographic indices (E/A ratio, E/e′ ratio, deceleration time) showed no significant improvement after training, suggesting that the functional benefits arise mainly from peripheral adaptations rather than reverse cardiac remodeling [37]. The optimal intensity and duration of physical training for patients with HFpEF are uncertain - there are no large clinical studies exploring this issue. To date, the effects of HIIT (High-Intensity Interval Training) have been studied and compared with MCT (Moderate-Intensity Continuous Training). HIIT involves short bursts of intense exercise followed by brief recovery periods, while MCT is a steady state workout at a moderate intensity for a longer duration. At this point, HIIT has shown a slight advantage over MCT in improving exercise capacity. In randomized control trials directly comparing intensity, HIIT increased VO_2 peak by an additional +1.25 ml kg^{-1} min^{-1} compared to MCT [39]. However, the fact that benefits were observed with both training methods, as well as with mixed programs, makes maintaining any consistent routine more important than recommending one best method [38]. An additional challenge in this area is exercise intolerance among older people with HFpEF. This is associated with reduced quality of life and poor clinical outcomes. VO_2peak is reduced by approximately 35% in patients with HFpEF, often falling below the thresholds necessary for independent functioning in daily life [40]. Older patients with HFpEF, especially those recently hospitalized, are often in poor physical condition and have physical impairments in many areas, including balance, mobility, and strength, as well as endurance [40], [41]. They may benefit more from innovative, early, individualized, multifaceted physical function intervention than patients with HFrEF, as demonstrated in the recent REHAB-HF study. The mortality rate after exercise was also lower in patients with HFpEF, suggesting that such programs may be a particularly valuable strategy for high-risk populations that are not adequately treated [42]. Physical training is an effective and inexpensive method; however, given the lack of significant structural changes, exercise should be viewed as a symptomatic and functional therapy that complements but does not replace pharmacological disease-modifying treatment [37].

Dietary Changes

Studies have shown that short-term lifestyle changes, including dietary modifications and physical exercise, lead to significant weight loss in patients with HFpEF. In randomized controlled trials, these interventions were associated with an average weight reduction of approximately 5.3 kg (11.7 lbs) over three to six months. Participants also reported reductions in systolic and diastolic blood pressure and improvements in functional capacity, as measured by distance walked in a six-minute walk test, New York Heart Association (NYHA) functional class, and health-related quality of life (as assessed by the Minnesota Living with Heart Failure Questionnaire) [43], [44]. For obese individuals, intentional weight loss, whether through diet or medication, is currently the most consistent and beneficial nutritional intervention. It is associated with an improvement in the hemodynamic profile, a reduction in pulmonary pressure, and better diastolic function [43-45]. However, in clinical practice, it is important to distinguish between beneficial weight loss and harmful wasting, which is a metabolic complication of HFpEF. As many as one-third of ambulatory patients with

HFpEF are at moderate or high risk of malnutrition [46]. In older people without obesity, early weight loss likely reflects real deterioration in the catabolic/stagnant state (higher BNP levels, functional limitations, and anorexia) and increases mortality fivefold. Therefore, a loss of ≥5% within six months should prompt a reassessment of cachexia and optimization of heart failure (HF) treatment, nutritional support, and exercise rehabilitation. In obese patients, however, weight loss is often associated with an aggressive diuretic strategy and does not translate into a worse prognosis. This suggests that the change in body weight is mainly due to weight reduction rather than cachexia [47].

In small groups of patients with HFpEF, studies on the low-sodium DASH diet were also conducted. The results showed that this diet had an impact on accompanying cardiac diseases: lowering blood pressure, reducing arterial stiffness, and improving diastolic heart function [46]. However, more targeted studies involving a larger number of patients are needed to explore this aspect in more detail. In addition, it is recommended to quit smoking and limit alcohol consumption to a minimum in order to reduce cardiovascular risk, prevent arrhythmias, and reduce oxidative stress [5], [19].

Importance of Patient Education and Self-Monitoring in HFpEF

The primary objectives of patient education are to enhance patients' understanding of their disease, enable the recognition of early warning signs, and foster greater engagement in self-management. Through targeted educational interventions, patients are empowered to actively participate in decision-making regarding their treatment and daily care, which has been shown to significantly improve clinical outcomes [19], [48]. The involvement of general practitioners, physiotherapists, and dietitians is crucial, as they play a major role in encouraging patients to work on changing their lifestyle. Structured education programs have demonstrated efficacy in reducing all-cause mortality and hospital readmission rates among heart failure patients. Patients who receive comprehensive education are more likely to adhere to prescribed therapies and recommended lifestyle changes, which can lead to improved quality of life and reduced health care utilization [19], [49].

Self-monitoring is a core aspect of self-care for HFpEF patients. Regularly tracking weight, blood pressure, and heart rate helps patients identify early signs of decompensation, such as sudden weight gain or worsening shortness of breath, and seek timely intervention. Advancements in digital health technology, including smartphone applications and telemonitoring systems, have facilitated self-monitoring and improved patient-provider communication. Studies suggest that the integration of these tools into routine care is associated with better self-care adherence and reduced rates of hospitalization [50], [51].

The Human Side of Heart Failure Care

Social support, particularly emotional support, has been consistently linked to improved self-care in patients with HFpEF, including better medication adherence. Patients who are married or living with others often experience greater involvement in their medical care. Spouses or intimate partners most frequently provide reminders about medication, participate in medical decision-making, and accompany patients to medical appointments. However, instrumental support, such as practical help with daily tasks, has shown a weaker association with self-care behaviors than emotional encouragement [52]. Older patients often perceive higher levels of social support, potentially due to increased needs related to age and disease progression. These findings underscore the importance of social support as a protective psychosocial factor for patients with HFpEF. There is evidence that social support may help reduce anxiety, regardless of cardiac biomarker levels. Therefore, interventions aimed at improving social support may be beneficial for reducing anxiety in HFpEF patients [53]. Ultimately, fostering an environment that includes encouragement, empathy, and understanding from family, friends, and healthcare providers can meaningfully improve the lives of individuals with HFpEF.

Conclusions

Current evidence shows that lifestyle changes, such as structured exercise programs, dietary interventions, intentional weight management, and multidisciplinary rehabilitation, offer significant benefits to patients with HFpEF. These approaches improve functional capacity, exercise tolerance, and quality of life. They also address the underlying pathophysiological mechanisms and comorbidities that drive disease progression. Patient education, self-monitoring, and strong social support further improve self-care and clinical outcomes.

Novel therapeutic strategies, such as vagus nerve stimulation, show promise in targeting autonomic imbalance and systemic inflammation, but require further clinical investigation. Ultimately, effective HFpEF management requires a patient-centered, multidisciplinary approach that emphasizes modifiable risk factors and empowers individuals to actively participate in their care.

Given the limited efficacy of currently available drug therapies, nonpharmacological interventions should be prioritized and integrated into routine clinical practice. Ongoing research is needed to further refine these strategies and develop personalized approaches to optimize outcomes for individuals living with HFpEF.

Disclosure

Authors contribution

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