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Case report

Contemporary approach to diagnosis and treatment of patients with heart failure with preserved ejection fraction

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Abstract Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous syndrome characterized by impaired left ventricular filling. It affects approximately 50% of patients with heart failure worldwide. Its complex pathophysiology involves the interaction between cardiomyocyte dysfunction and numerous comorbidities, including older age, female sex, type 2 diabetes, obesity, sleep apnea, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, coronary artery disease, and atrial fibrillation. Obesity, as a major risk factor, is chronic systemic inflammatory state that induces hemodynamic derangements and hormonal abnormalities that stress the cardiovascular system, with central obesity in women particularly contributing to HFpEF development. Diagnosis relies on clinical evaluation, measurement of natriuretic peptides, echocardiographic assessment, and exercise testing. Therapy includes SGLT-2 inhibitors, GLP-1 agonists, mineralocorticoid receptor antagonists, optimized diuretic therapy, management of comorbidities, lifestyle modifications, and structured exercise, improving prognosis and quality of life for patients.

Key words heart failure with preserved ejection fraction, echocardiography, SGLT-2 inhibitors

Introduction

Heart failure (HF) is a clinical syndrome resulting from complex pathophysiological processes that impair left ventricular structure and/or function, prohibiting the ventricle from either filling with or ejecting the blood[1]. It is estimated that around 64 million people worldwide suffer from HF[2]. The prevalence of HF is steadily rising, and in general population, it ranges from 1-3%[2,3]. HF is classified based on left ventricular ejection fraction (LVEF) into HF with preserved LVEF (LVEF ≥ 50%), HF with mildly reduced LVEF (LVEF 41%–49%), and HF with reduced LVEF (LVEF ≤ 40%), and HF with improved LVEF (previous LVEF ≤40% and a subsequent measurement of LVEF ≥ 40%). HF with preserved ejection fraction (HFpEF), previously known as diastolic heart failure, in addition to the LVEF ≥ 50%, is characterized by evidence of spontaneous or provokable increased left ventricular filling pressures. Approximately, 50% of patients with HF are classified as HFpEF[4].

Pathophysiology of HFpEF

The pathophysiology of HFpEF is still not entirely clear, but it is known to be a consequence of variety of simultaneous risk factor. Most important risk factors include: increasing age, female sex, type 2 diabetes, obesity, sleep apnea, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, iron deficiency, with or without anemia, coronary artery disease, atrial fibrillation[5]. The clinical manifestations of HFpEF are considered to be due to complex pathophysiological processes in cardiomyocyte structure and function[6]. Obesity, as a major risk factor, is chronic systemic inflammatory state that induces hemodynamic derangements and hormonal abnormalities that stress the cardiovascular system[7,8]. Additionally, central obesity is associated with age-related increases in ventricular end-systolic elastance in women but not in men, meaning that obesity and female sex combined are significant risk factors for the development of HFpEF[9]. The presence of abnormalities in skeletal muscles and vascular endothelium has been also observed[10]. In addition, patients with HFpEF demonstrate impaired peripheral oxygen extraction during exercise. The exact cause of these impairments are still unknown, but may represent dysfunction of skeletal muscle, vascular endothelium, or mitochondria[11, 12]. Patients with HFpEF demonstrate a reduction in total arterial compliance during submaximal and peak exercise[13]. While oxygen transport and utilization are defected in all patients with HFpEF, regardless of the degree of exercise intolerance, exact level of impairment vary among patients, and is determined by underlying comorbidities[11,14].

In any case if not adequately treated, symptoms in patients with HFpEF are progressive, and are a result of a complex dysfunctional changes on cellular, tissue on organ level[2,6,10-14]. Thus, it is important to distinguish HFpEF from conditions known as “HFpEF mimics”, such

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Table 1. Diagnostic systems in diagnosing HFpEF

Score	Full Name Meaning	Main Components	Scoring System
HFA-PEFF[22]	Heart Failure Association diagnostic algorithm: P: Pretest Assessment E: Echocardiography & Natriuretic peptide F: Functional testing F: Final etiology	1. Pre-test assessment 2. Echocardiography and natriuretic peptides 3. Functional testing 4. Final etiological work-up	Score 0–1: HFpEF unlikely Score 2–4: Intermediate, needs further testing Score 5–6: HFpEF likely
H2FPEF[23]	H: Heavy (BMI > 30) H: Hypertension (≥ 2 meds) F: Atrial Fibrillation P: Pulmonary Hypertension E: Elder (age > 60) F: Filling pressures (E/e' > 9)	• BMI > 30 (1 pt) • ≥ 2 antihypertensives (1 pt) • Atrial fibrillation (2 pts) • PASP > 35 mmHg (1 pt) • Age > 60 (1 pt) • E/e' > 9 (1 pt)	Score 0–1: Low probability Score 2–5: Intermediate Score 6–9: High probability

HFpEF – heart failure with preserved ejection fraction; BMI – body mass index, PASP – pulmonary artery systolic pressure; pt – points

as restrictive and hypertrophic cardiomyopathy, constrictive pericarditis, and valvular heart disease[5], especially as there is a distinctive cause-specific treatment in latter entities.

Hemodynamic changes in HFpEF

The most prominent hemodynamic change in patients with HFpEF is elevated left ventricular filling pressure (LVFP)[6]. In early stages, resting LVFP is within the normal range and its increase is often observed during exercise[15,10]. As the condition progresses, the LVFP becomes elevated during rest[10]. It is believed that elevated LVFP is a consequence of left ventricular diastolic dysfunction due to incomplete myocardial relaxation, increased ventricular stiffness with subsequent decrease in ventricular distensibility[16-18]. Elevated LVFP leads to the left atrial enlargement and remodeling[20]. Such environment is more likely to lead to atrial fibrillation, and further remodeling and dysfunction of the left atrium[19-20]. The subsequent development of pulmonary hypertension leads to right ventricular dysfunction which altogether significantly increases the risk of death in patients with HFpEF[21].

How to diagnose HFpEF

Establishing the diagnosis of HFpEF can be challenging. Exertional dyspnea is one of the most common clinical symptoms. Clinical symptoms and signs of HFpEF are common to all subtypes of HF[5]. Two important diagnostic algorithms have been developed in order to identify patients with HFpEF, presented in **Table 1**[22,23].

Increase in plasma natriuretic peptides, N-terminal pro–B-type natriuretic peptide (NT-proBNP) (> 600 pg/mL) and B-type natriuretic peptide (BNP) (> 100 pg/mL) is a compensatory mechanism, as the heart releases these peptides in response to increased pressure and stretch caused by the failing heart. Their increase is also associated with increased risk of adverse outcomes, including mortality and HF hospitalization[24,25]. Still, it has been shown that up to 20–25% of HFpEF patients have low BNP and/ or NT-proBNP levels[25,26]. Additionally, it has been noted that in obese patient's natriuretic peptide levels do not always reflect the severity of cardiac dysfunction most likely due to an increased degradation of natriuretic peptides in lipid tissue[27].

There are a number of echocardiographic measurements that can be applied for HFpEF diagnosis. The most studied and applied is the estimation of filling pressures, shown as the ratio of early diastolic trans-mitral inflow velocity to mitral annular tissue velocity (E/e')[28-31]. While an elevated E/e' ratio has excellent specificity for identifying high LVFP filling pressure (77–100%), it also displays poor sensitivity (range 0–73%), thus it is not an effective tool to exclude HFpEF[31-33]. Another criterion for diastolic dysfunction could include increased left atrium volume index (> 34 ml/m^2)[34-36].

In events of a normal resting echocardiography, diastolic stress echocardiography can be useful in detection of subclinical LV diastolic dysfunction[37]. During exercise, normally, both e' and mitral E velocity increase, and the overall E/e' ratio remains unchanged. Whereas, in patients with diastolic dysfunction and HFpEF mitral E velocity becomes progressively higher with exercise, but e' velocity remains reduced, resulting in a higher E/e' ratio[3]. In brief, the HFpEF diagnosis is considered positive if: 1) septal e' velocity < 7 cm/s or lateral e' velocity < 10 cm/s at rest; 2) average E/e' > 14 or septal E/e' ratio > 15 at rest or with exercise; 3) peak tricuspid regurgitation velocity > 2.8 m/s with exercise[38,39]. Cardiopulmonary exercise testing (CPET) is most useful test to differentiate HFpEF from non-cardiac dyspnoea. In addition to diagnostic evaluation of HFpEF, CPET testing is particularly effective in rehabilitation of patients and in documenting the effectiveness of therapeutic interventions[40].

Therapeutic approach to patients with HFpEF

Until recently, overall aim of HFpEF therapy was to reduce symptoms, improve quality of life, prevent disease progression, reduce hospitalizations, and effectively manage underlying comorbidities[2]. However, the HFpEF armamentarium has been recently expanded with drugs that prolong survival, namely SGLT-2 inhibitors, GLP-1 agonists and Finerenone, mineralocorticoid antagonists. SGLT-2

Table 2. Major trials in HFpEF treatment

Trial	Patient characteristics	Conclusion
EMPEROR – Preserved[41]	LVEF > 40%; ↑natriuretic peptides; NYHA II-IV. Empagliflozin vs. placebo	**Empagliflozin** – decreses risk of CV death & HF hospitalization
Preserved – HF[42]	LVEF > 40%; ↑natriuretic peptides; NYHA II-III Dapagliflozin vs. placebo	**Dapagliflozin** – improves symptomes and excercise function
PARAGON – HF[43]	LVEF > 45%; ↑natriuretic peptides; NYHA II-IV Sacubitril/valsartan vs. valsartan	**Sacubitril/valsartan** – no significant benefit in CV death & HF hospitalizaton, but improvement in quality of life and reduced heart failure symptoms. Superior than valsartan alone
DELIVER[44]	LVEF > 40%; ↑ natriuretic peptides; NYHA II-IV Dapagliflozin vs. placebo	**Dapagliflozin** – reduction in CV death & HF hospitalization
FINEARTS[45]	LVEF > 40%; ↑ natriuretic peptides; NYHA II-IV. Finerenon vs. placebo	**Finerenon** – reductuin in CV death & HF hospitalization
SUMMIT[46]	LVEF > 50%;↑ natriuretic peptides; NYHA II-IV; BMI > 30kg/m^2 Tirzepatid vs. placebo	**Tirzepatid** –reduction in CV death & HF hospitalization
Pooled analysis SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM[47]	**SELECT-** CVD and high BMI **FLOW**- CKD and and T2D **STEP-HFpEF** and **STEP-HfpEF DM** – obesity related HF Semaglutide vs. placebo	**Semaglutide** – reduction of the combined endpoint of CV death or HF, reduction of HF events alone, non significant effect on CV death alone

HFpEF – heart failure with perserved ejection fraction; LVEF – left ventriculair ejection fraction; NYHA – New York Heart Association; CV – cardiovascular; CVD – cardiovascular disease; HF – heart failure; BMI – body mass index; CKD – chronic kidney disease; T2D – type 2 diabetes

inhibitors and Finerenone, as well as GLP-1 agonists in specific patient population, have become the indispensable part of treatment in HFpEF patients. The combination of Sacubitril/Valsartan can also be considered after the results of PARAGON-HF trial which demonstrated improved quality of life and reduced heart failure symptoms and HF hospitalizations in comparison to valsartan alone[41]. The details of major studies, that define contemporary medical treatment approach to HFpEF patients are described in Table 2.

In patients with HFpEF there is a volume overload, thus diuretic therapy should be the cornerstone treatment[48,49]. Therapy is initiated with loop diuretics, and for patients not responding to the therapy, mineralocorticoid receptor antagonists (MRA) should be added. MRAs have been included in the 2022 American Heart association (AHA) HF guidelines for treatment of HFpEF[49], however it is reasonable to expect that there will be an upgrade in recommendation from current IIb after the results of Finearts trial have been published. In addition, the treatment of comorbidities that are common in HFpEF patients (hypertension, diabetes…) is necessary[5, 48]. Caloric restriction and sodium intake reduction are also proven to be beneficial in improving ventricular diastolic function and arterial elastance, especially in obese patients with hypertension.[51,52]

Finally, it has been documented that exercise training improves cardiorespiratory fitness, reduces hospitalization rate of heart failure and improves quality of life in patients with HFpEF[53,54]. Thus, aerobic exercise should be the integral part of treatment in stable, compensated HFpEF patients.

Conclusion

HFpEF is a heterogeneous clinical entity. It is a result of a complex interplay between diverse etiologies and overlapping comorbidities. The knowledge in this field is continuously evolving, as understanding of the pathophysiology and treatment options expand. Utilizing up-to-date diagnostic strategies and evidence-based treatments play a crucial role in the early recognition of HFpEF and in enhancing the patient outcomes and quality of life.

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Sažetak

Savremeni pristup dijagnozi i lečenju pacijenata sa srčanom insuficijencijom sa očuvanom ejekcionom frakcijom

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Srčana insuficijencija sa očuvanom ejekcionom frakcijom (HFpEF) je heterogeni sindrom koji karakteriše poremećaj punjenja leve komore. Javlja se kod oko 50% pacijenata sa srčanom insuficijencijom širom sveta. Odlikuje je kompleksna patofiziologija, koja uključuje interakciju između disfunkcije kardiomiocita i brojnih komorbiditeta, među kojima se ističu starija životna dob, ženski pol, tip 2 dijabetes, gojaznost, apneja u snu, hipertenzija, plućna hipertenzija, hronična opstruktivna bolest pluća, koronarna bolest i atrijalna fibrilacija. Gojaznost, kao glavni faktor rizika, predstavlja hronično inflamatorno stanje koje izaziva hemodinamske poremećaje i hormonske abnormalnosti, a posebno centralna gojaznost kod žena doprinosi razvoju HFpEF. Dijagnoza se zasniva na kliničkoj proceni, analzi natriuretskih peptida, ehokardiografskoj evaluaciji i testovima fizičkim opterećenjem. Terapija uključuje SGLT-2 inhibitore, GLP-1 agoniste, antagoniste mineralokortikoidnih receptora, optimizovanu diuretsku terapiju, kontrolu komorbiditeta, promene životnog stila i strukturirane vežbe, čime se poboljšava prognoza i kvalitet života pacijenata.

Ključne reči: *srčana insuficijencija sa očuvanom ejekcionom frakcijom, ehokardiografija, SGLT-2 inhibiotri*