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Heart failure with preserved ejection fraction: the challenge for modern cardiology

Niewydolność serca z zachowaną frakcją wyrzutową — wyzwanie dla współczesnej kardiologii

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous disease with multifactorial mechanisms of development. More than half cases of heart failure are diagnosed as HFpEF. Because of aging of society, the number of cases will increase. The following article presents the current knowledge about HFpEF.

Key words: heart failure with preserved ejection fraction, HFpEF

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Introduction

It is estimated that 1–2% of adult population in the developed countries suffers from heart failure. Over a half of those cases comprise heart failure with preserved ejection fraction (HFpEF). The number of patients suffering from this condition will continue to increase, as aging of the population and sedimentary lifestyle lead to increased prevalence of civilization diseases. It is estimated that HFpEF may affect as much as 5% of the population over the age of 60 [1]. Moreover, due to diagnostic difficulties and numerous comorbidities, which may modify the course and symptoms of heart failure, as well as variable access to specialist healthcare, the prevalence of HFpEF may be significantly underestimated, especially in the older groups of patients [2].

Diagnosis of HFpEF

HFpEF usually affects older people, more often women, with comorbidities, such as arterial hypertension, atrial fibrillation (AF), metabolic syndrome (obesity, type 2 diabetes), chronic kidney disease, anemia, sleep disorders (*e.g.*, sleep apnea) or chronic obstructive pulmonary disease (COPD). Identification of patients and establishing the diagnosis of HFpEF remains difficult. Currently, echocardiography is they key investigation to confirm HFpEF, although the number and the types of coexisting disorders could significantly influence the degree of progression and course of the disease, thus response to treatment. According to the European Society of Cardiology (ESC) guidelines [3], the following criteria are required for the diagnosis of HFpEF:

- presence of signs and/or symptoms of heart failure (HF);
- preserved systolic function of the left ventricle [left ventricular ejection fraction (LVEF) $\geq$ 50%];
- elevated levels of natriuretic peptides [B-type natriuretic peptide (BNP) > 35 pg/mL and/or N-terminal pro-B-type natriuretic peptide (NT-proBNP) > 125 pg/mL] and
- at least one additional criterion — presence of structural heart disease (left atrial enlargement or hypertrophy of the left ventricle) or diastolic dysfunction.

All of the above criteria must be met in order to establish the diagnosis.

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Additional diagnostic modalities, *i.a.* magnetic resonance imaging (MRI), are necessary in certain groups of patients in order to exclude specific disorders, such as storage diseases (Fabry's disease), hemochromatosis, or amyloidosis, which may require completely different management.

Therefore, the diagnostic process in HFpEF is much more complex in comparison to heart failure with reduced ejection fraction. In 2019, **HFA-PEFF** diagnostic algorithm [1] (Table 1) was developed, highlighting certain imperfections of the model proposed by the 2016 ESC guidelines, which underestimated the number of patients. A publication by Pieske et al. [1] presents the new HFA-PEFF algorithm and extensively discusses numerous diagnostic criteria that aid in proper identification of patients with HFpEF at the level of primary care physician, internist, cardiologist, or an HF specialist. Particular emphasis was put on the risk of missing the diagnosis of HFpEF when applying the 2016 classification to patients who do not fulfill all of the ESC criteria, *e.g.*, mildly symptomatic, patients with unspecific symptoms (*e.g.*, dyspnea with coexisting COPD) or with low natriuretic peptide levels (*e.g.*, obese individuals).

Patients with HFpEF constitute a heterogeneous group of patients representing diverse pathophysiology leading to the development of heart failure and, in consequence, with varying expression of individual components of the diagnostic process. It should not be forgotten that the diagnosis of HFpEF is based on the presence of symptoms — prolonged activation of compensatory mechanisms is possible in this disease with subsequent sudden severe manifestation of acute HF symptoms as a result of imbalance of bodily homeostasis. Moreover, heart failure is a dynamic entity that changes over time and failure to meet the ESC criteria at this point in time does not mean that they were not present at a different stage of the disease or will not be present in the future (*e.g.*, use of diuretics may diminish the symptoms of fluid overload, reducing the signs and symptoms of heart failure and leading to alteration of echocardiographic parameters).

Therefore, the **HFA–PEFF** diagnostic algorithm, which is based on the analysis of multiple factors and determination of the probability of diagnosis (with possible implementation of additional tests in selected groups of patients), seems to be superior to the scheme based on fulfilling the strict criteria specified in the 2016 ESC guidelines.

In 2018 Reddy et al. [4] suggested a simple screening tool for patients with dyspnea, which utilized the most common features coexisting with HFpEF — the **H_2FPEF** scale (Table 2). It is a scoring scale that takes into consideration the following variables: obesity, hypertension,

Table 1. HFA–PEFF diagnostic algorithm (based on [1])

P	Pre-test assessment	Primary care physician (GP, internist)	Symptoms ± signs Comorbidities/risk factors Standard laboratory tests + natriuretic peptides (if available) Resting ECG 6-minute walk test/spiroergometry Standard echocardiography
E	Echocardiography and natriuretic peptide levels	Cardiologist	Specialist echocardiographic assessment and natriuretic peptide levels taking into consideration cut–off values for coexisting atrial fibrillation — diagnosis is certain if 5–6 pts are obtained Natriuretic peptides (if not done in step P)
F	Functional echocardiography and hemodynamic	Cardiologist, HF specialist	In patients with insufficient basis to establish the diagnosis of HF in previous steps (2–4 pts in step E) Functional echocardiography (increased E/e', TR) Invasive assessment (PCWP, LVEDP) — at rest, on exertion
F2	'Find' Look for etiology	Cardiologist	PET MRI Endomyocardial biopsy SPECT Genetic testing Other laboratory investigations to diagnose the etiology of heart failure

GP — general practictiner; ECG — electrocardiography; HF — heart failure; E/e' — the ratio of the early diastolic transmitral flow velocity [E] and early diastolic mitral annual velocity [e']; TR — tricuspid regurgitation; PCWP — pulmonary capillary wedge pressure; LVEDP — left ventricular end-diastolic pressure; PET — positron emission tomography MRI — magnetic resonance imaging; SPECT — single-photon emission computed tomography

Figure 2. H_2FPEF diagnostic algorithm (based on [4])

	Clinical variable		Criteria	Points
H_2	Heavy	Obesity	BMI > 30 kg/m^2	2
	Hypertensive	Arterial hypertension	> 2 hypotensive medication	1
F	Atrial fibrillation	Atrial fibrillation	Paroxysmal or permanent	3
P	Pulmonary hypertension	Pulmonary hypertension	PASP > 35 mm Hg	1
E	Elderly	Elderly	Age > 60 years	1
F	Filling pressure	Filling pressure	E/e' > 9	1

BMI — body mass index; PASP — pulmonary artery systolic pressure; E/e' — the ratio of the early diastolic transmitral flow velocity [E] and early diastolic mitral annual velocity [e']

atrial fibrillation, pulmonary hypertension, age over 60, and filling pressure.

Scoring 0–1 pts on the above-described scale makes the diagnosis of HFpEF unlikely, while 6 points or more give 90–95% probability that the diagnosis of HFpEF is correct. Importantly, the scale was created based on a retrospective analysis of over 400 patients with dyspnea, who have undergone hemodynamic testing to determine whether the etiology of dyspnea was cardiogenic (HF) or non-cardiogenic.

In this scale the presence of an arrhythmia, such as atrial fibrillation, as a single factor is associated with 3 points, increasing the likelihood of diagnosis of HFpEF to 50–55%.

Pathophysiology of HFpEF

A lot has also changed with regard to our understanding of **pathophysiology leading to the development of HFpE**F, which may lead to the development of successful therapies. Currently, we distinguish the following hemodynamic and cellular processes in the pathophysiology of HFpEF [5]:

- diastolic dysfunction and left atrial enlargement;
- pulmonary hypertension and right-sided heart failure;
- fluid overload;
- systematic microvascular inflammation/systemic inflammatory reaction;
- abnormal cardiomyocyte metabolism;
- fibrosis of extravascular compartments.

These processes do not occur in isolation, but often coexist or one leads to another. Importantly, they affect the entire myocardium.

Diastolic dysfunction (manifesting as incomplete cardiac relaxation and increased passive stiffness of heart walls) and enlargement of the left atrium were the first processes to be described in literature as leading to the development of HFpEF. Arterial hypertension (a disease often coexisting in the HFpEF population) was thought to be the cause of those changes. Increased arterial wall stiffness leads to an increase in the left ventricular filling pressure in the presence of a relatively normal function of the mitral valve, which in turn increases pressure in the left atrium (in practice, it is equal to the end-diastolic left ventricular pressure), resulting in enlargement and remodeling of the left atrium. As the disease progresses, elevated left atrial pressure leads to the development of pulmonary hypertension and, in consequence, damage to the "right heart". Moreover, we observe pulmonary changes manifesting as a reduction in the gas exchange surface and impaired lung function as a result of remodeling of pulmonary vessels (*i.a.* intimal thickening).

In the initial phase, increased pressures in heart chambers occur mainly during exertion — at this stage the disease is usually mildly symptomatic. As it progresses over time, eventually it leads to persistently elevated pressures and presence of symptoms at rest or with relatively little exertion.

Fluid overload, which may be caused by coexisting diseases (*e.g.*, kidney disease, tendency to retain fluids as a result of excessive salt consumption), may lead to right ventricular overload (dilatation) or be a factor contributing to increase in filling pressures, resulting in disease progression (described above). At the moment, only this mechanism appears to be effectively managed in patients with HFpEF through administration of diuretics. It should be noted, however, that these agents only reduce symptoms, but do not affect survival.

Other than the hemodynamic processes leading to heart dysfunction described above, one should also mention the processes taking place at a cellular level.

Systemic inflammatory reaction theory, although needing further studies, seems very probable and explains the observed global myocardial dysfunction, as well as elevated levels of inflammatory markers in the HFpEF population. More importantly, most disorders coexisting in HFpEF population are associated with increased production of inflammatory factors (*e.g.*, diabetes, obesity, chronic kidney disease), resulting in inflammatory damage to the vessels and subsequent reduction in nitric oxide (NO) bioavailability, decreased cyclic guanosine monophosphate (cGMP) levels and alternative phosphorylation

of titin — a protein responsible for contraction of sarcomeres. Moreover, there are changes that take place within myocardial cells and switching to less favorable metabolic pathways manifesting through *i.a.*, changes in the structure of cardiac mitochondria, anaerobic glycolysis leading to increased production of lactic acid and elevated intracellular calcium levels, which affects the strength of myocardial cell contraction. In the context of augmented inflammatory response, we observe increased production of collagen and more pronounced connective tissue fibrosis, which leads to further impairment of diastolic function.

Prognosis and treatment of HFpEF

For many years, the contribution of HFpEF to morbidity and mortality has been underestimated. It seemed that in the view of theoretically less pronounced cardiac dysfunction *e.g.*, in echocardiographic assessment, it poses less of a danger than HFrEF. Now we know that this is not the case. An analysis of the OPTIMIZE-HF registry [6] showed an equally high risk of death or rehospitalization in patients with HFpEF and heart failure with reduced ejection fraction (HFrEF). In a study by Sartipy [7] nearly half of patients with HFpEF died during the follow-up period (2.9 years). Annual mortality ranges from 10 and 30%, of which 50–60% constitute deaths of cardiovascular causes [8]. However, it means that nearly half of all deaths is due to extracardiac causes, possibly associated with comorbidities, age, etc. Perhaps this diversity with regard to the mechanism of death is related to the lack of treatment of HFpEF, which could undoubtedly prolong survival, as with HFrEF.

According to the ESC guidelines [3] the only group of agents with proven efficacy in HFpEF-symptom reduction — are diuretics (class IB). Screening toward concomitant diseases and their treatment in accordance with the current therapeutic standards is recommended in all patients. Randomized clinical trials with angiotensin-converting enzyme inhibitor (ACE-I)/angiotensin receptor blocker (ARB) failed to demonstrate their impact on improved survival in patients with HFpEF. Although a trend towards reduction of the number of hospitalizations due to HF was observed in the CHARM study, studies with irbesartan (I-PRESERVE) did not yield similar results [9]. One of the trials [10] showed a reduction in the incidence of AF among patients with HFpEF who were taking statins, which is in line with the theory of systemic reaction and anti-inflammatory effects of those agents. Hopes are also associated with the use of sodium-glucose co-transporter-2 (SGLT2) inhibitors because their pleiotropic action might potentially involve blood pressure reduction (through osmotic diuresis) as well as modification of abnormal intracellular metabolism (switching to beta-oxidation of fatty acids). Following a post-hoc analysis of the results of TOPCAT trial [11] it has been established that in the American population the use of spironolactone in patients with HFpEF (LVEF > 45%) can be beneficial with respect to the reduction in the number of deaths of cardiovascular causes and hospitalizations due to heart failure. Results of this analysis changed the AHA recommendations for the use of spironolactone to reduce hospitalizations [12] and were included in the 2019 expert consensus of the Heart Failure Association of the ESC [13].

Although the results of PARAGON-HF trial [14] did not indicate significant reduction in hospitalizations or deaths for sacubitril/valsartan (vs. valsartan) in the general population of patients with HFpEF, it has been demonstrated that certain subpopulations might benefit from treatment with ARNI — patients with LVEF 45–57% as well as women. Treatment benefit was observed in patients with primarily impaired ejection fraction (*i.e.*, LVEF < 60%), while in the group with low EF reduction in the risk of cardiovascular death which was less pronounced; however, reduced risk of hospitalization due to HF exacerbation was noted in both groups. Moreover, greater benefit was seen in women (reduced number of hospitalizations due to HF) even with higher LVEF values [15]. At present it is not known whether this is due to different drug pharmacokinetics depending on sex or a "statistical anomaly" [16]. Lack of effective, survival-prolonging treatment and the results of randomized clinical studies showing that certain populations benefit from therapy more than other may in the future lead to personalization of pharmacotherapy. Presently, management of patients with HFpEF is focused on the treatment of comorbidities. It is not an easy task, as many patients with HFpEF suffer from at least several coexisting disorders — nearly half of them have five or more comorbidities [17]. Trials SHEP (Systolic Hypertension in the Elderly), HYVET (Hypertension in the Very Elderly Trial), and SPRINT (Systolic Blood Pressure Intervention Trial) demonstrated a reduced risk of HF in patients with well-controlled hypertension [18]. Taking into consideration the proinflammatory effect of diabetes and the risk of development of diabetic cardiomyopathy, proper management of this disease seems particularly important for therapy and prevention of HF. Particular hopes, especially after the results of the EMPAREG-OUTCOME trial, are associated with SGLT2 inhibitors.

Patients with heart failure and atrial fibrillation should receive anticoagulation after proper assessment of indications for such a therapy using standard scoring systems. In a population of HFpEF non-pharmacological methods aimed at body mass reduction, decreasing salt intake and improvement of overall fitness seem particularly important. Kitzman et al. [18] demonstrated that physical exercise and reduction of body weight through caloric restriction improve physical fitness and the effects are additive when both methods are used. Such interventions are of particular significance in view of the fact that as much as 85% of patients with HFpEF suffer from metabolic syndrome [8] and certain underestimation of the incidence of HFpEF is

Table 3. ABCDE treatment scheme (based on [19])

A	Avoid tachycardia	Avoid tachycardia
B	Blood pressure control	Control blood pressure
C	Comorbidities	Treat coexisting diseases
D	Diuretics	Use diuretics if necessary
E	Exercise training	Encourage physical activity

possible due to reduced levels of natriuretic peptides in obese individuals.

Management of patients with HFpEF can be summarized as ABCDE (Table 3) [19].

Conclusion

HFpEF poses a great challenge to contemporary cardiology. This is a multifactorial disease with great impact on mortality and quality of life. It encompasses a very heterogenous group and its diagnosis is based on a combination of symptoms and results of additional investigations.

Presently, there is no effective treatment for this disease, although numerous predefined clinical trials aimed at this population of patients are underway.

Conflict of interest

Participation in a study involving ARNI and empagliflozin.

Streszczenie

Niewydolność serca z zachowaną frakcją wyrzutową (HFpEF) to heterogenna jednostka chorobowa, u podłoża rozwoju której jest wiele różnorodnych mechanizmów. Szacuje się, że ponad połowę przypadków niewydolności serca stanowi HFpEF, a w związku ze starzeniem się społeczeństwa liczba chorych będzie się zwiększała. W poniższym artykule przedstawiono aktualny stan wiedzy dotyczącej HFpEF.

Słowa kluczowe: niewydolność serca z zachowaną frakcją wyrzutową, HFpEF

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