Heart failure with preserved ejection fraction: A review

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Abstract: Heart failure is the final stage of evolution of a large number of cardiovascular diseases and represents a health problem worldwide, due to increased prevalence of cardiovascular diseases. The patients with heart failure with preserved ejection fraction (HFP EF) represent about a half of the patients with heart failure and the prevalence of HFP EF is on the rise. HFP EF is mainly a disease of the elderly patients, who have numerous cardiovascular diseases – hypertension, myocardial ischaemia, atrial fibrillation, valvular disease, and also non-cardiovascular comorbidities, such as obesity, diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, and obstructive sleep apnoea. HFP EF is more prevalent in women than in men, but women have a better prognosis than men. The pathophysiological changes that appear in HFP EF are: ventricular stiffening, cardiomyocyte hypertrophy and hypercontractility, myocardial fibrosis and inflammation, which lead to abnormal diastolic function with delayed relaxation and inappropriate filling, in the presence of a normal systolic function of the left ventricle. The diagnosis of HFP EF is based on clinical, echocardiographic and biological criteria. In contrast to HFr EF, there is no effective treatment for HFP EF. The treatment of HFP EF includes diuretics for clinical improvement and treatment of comorbidities. The prognosis of patients with HFP EF is similar with those with HFr EF. Currently, the main objectives of the treatment in patients with HFP EF are to improve clinical status and decrease hospitalizations. Further studies are needed to establish an effective treatment to increase survival in these patients. Therefore, HFP EF continues to be a challenge for clinicians regarding the optimal therapy.

Keywords: heart failure with preserved ejection fraction, diastolic dysfunction, myocardial fibrosis, natriuretic peptides

INTRODUCTION

Heart failure is the final stage of evolution of a large number of cardiovascular diseases. Heart failure is a major health problem worldwide, due to increased prevalence of cardiovascular diseases and prolonged survival of some categories of patients with cardiovascular diseases, after successful treatment of their conditions.

The most frequent causes of heart failure are: myocardial ischaemia, valvular diseases, arrhythmias, atrio-ventricular conduction disorders, myocarditis, pericarditis. Often, heart failure has more than one cause. It is extremely important to determine the aetiology of heart failure in order to establish the specific therapeutic options (for exemple to reduce

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heart rate in tachyarrhythmias, to replace a valve in valvular disease, revascularization of the coronary arteries in patients with myocardial ischaemia, etc.) [1].

Currently, heart failure is classified into heart failure with reduced ejection fraction (less than 40%) - HFrEF, mid-range ejection fraction (between 40-49%) – HFmrEF, and preserved ejection fraction (≥ 50%) – HFpEF. HFmrEF is a new category of heart failure, first introduced in the classification of heart failure in 2016, in the European Society of Cardiology Guidelines [1]. HFmrEF is usually studied in trials along with HFpEF, so in this paper we will use the terminology of HFpEF, including both entities. Until now, the majority of clinical trials regarding the treatment of heart failure have focused on patients with HFrEF. While in the case of HFrEF, it had been proven that the treatment can reduce both morbidity and mortality, in the case of HFpEF there is no drug which can reduce mortality or morbidity. This is why HFpEF is more challenging for the clinician regarding the diagnosis and treatment.

Patients with HFpEF associate many comorbidities, such as hypertension, diabetes mellitus, vascular disease, atrial fibrillation, metabolic syndrome, chronic kidney disease, which complicate even more the evolution of HFpEF and increase the risk of mortality.

**PREVALENCE OF HFpEF**

In the last years, the prevalence of HFpEF increased, because of the demographic changes and the changes in the risk factors prevalence, such as the increasing prevalence of hypertension, atrial fibrillation and diabetes mellitus that are all risk factors for HFpEF [2]. HFpEF currently affects more than 7 million people in Europe and is the only cardiovascular condition that has increasing incidence and prevalence [3]. The increasing prevalence of HFpEF can also be a result of the changes in clinicians’ awareness over time and of the fact that the diagnostic methods have evolved during the last decades.

The patients with HFpEF represent about a half or even more of the patients with heart failure and the prevalence of HFpEF is on the rise [4-8]. HFpEF is mainly a disease of the elderly, who associate numerous cardiovascular and non-cardiovascular comorbidities [9]. HFpEF is more prevalent in women than in men, with a ratio women to men of 2:1, explained by the different sex cardiomyocyte remodeling pattern in women than men [10,11]. In men, the eccentric left ventricle remodeling is more frequent, while in women the concentric remodeling is more frequent, as a response to aortic stenosis or hypertension [10]. Due to the concentric remodeling, women have a smaller left ventricle cavity and an increased wall thickness, with less collagen deposition [10]. Consequently, women have a better contractility and ejection fraction of the left ventricle, with the predominance of HFpEF. Women with HFpEF are more likely to be obese, hypertensive or to have renal disease or diabetes mellitus, while men are more likely to have coronary artery disease, atrial fibrillation, chronic obstructive pulmonary disease, anemia [12]. Even if HFpEF is more common in women, they have a better prognosis, with a rate of hospitalization with 20% less than men and a lower risk of cardiovascular and non-cardiovascular events. [12]

**RISK FACTORS**

Traditional cardiovascular risk factors, such as smoking, obesity, diabetes mellitus, hypertension, precede the onset of both heart failure with reduced and preserved ejection fraction, but there are specific risk factors for each of them. While male sex, myocardial infarction, left bundle branch block or high potassium level represent major risk factors for HFrEF, the risk factors for HFpEF are female sex, higher systolic blood pressure, right bundle branch block and atrial fibrillation [13-15].

Hypertension is common in patients with HFpEF and increases the risk of developing heart failure. The optimal treatment of hypertension improves diastolic filling, leads to the regression of left ventricular hypertrophy and may reduce the progression of heart failure. Atrial fibrillation (AF) and HFpEF are related, and each of the diseases predisposes to the other. AF occur in
approximately two thirds of the patients with HFpEF and contribute to the progression of the illness, due to the uncontrolled ventricular rates and the loss of atrial contraction and its contribution to the left ventricle filling, leading to a shorter filling time and diastolic dysfunction of the left ventricle [16]. When present together, HFpEF and AF lead to a worse outcome than each condition separately [17]. Patients with HFpEF and AF have a higher risk of stroke and mortality. All patients with HFpEF and AF should receive an oral anticoagulant and should have a good control of the ventricular rate.

Myocardial ischemia may contribute to HFpEF, too, by altering the diastolic filling. Significant coronary artery disease is present in more than half of the patients with HFpEF. Patients with HFpEF and myocardial ischemia have a greater risk of ventricular dysfunction and mortality than those without myocardial ischemia. Coronary revascularization can improve the prognosis of patients with HFpEF and myocardial ischemia.

Regarding patients with diabetes mellitus, particularly patients with insulin-dependent diabetes mellitus have an increased risk to develop major adverse cardiovascular events, including cardiovascular mortality, hospitalization for heart failure, non-fatal myocardial infarction, non-fatal non-hemorrhagic stroke, aborted cardiac arrest. Therefore, patients with HFpEF and diabetes have a worse quality of life and poorer outcomes than those without diabetes mellitus.

Comorbidities such as obesity, diabetes mellitus, chronic kidney disease, anemia, chronic obstructive pulmonary disease, and obstructive sleep apnea are related to the worsening of heart function in HFpEF. The treatment of these comorbidities improves the prognosis of heart failure and reduces mortality [18-20].

PATHOPHYSIOLOGY OF HEART FAILURE WITH PRESERVED EJECTION FRACTION

HFpEF is characterized by a normal systolic function, but abnormal diastolic function, with inappropriate filling of the left ventricle in the presence of normal pressure, initially. In more advanced stages, it associates also elevated filling pressures, especially during physical exercise. High filling pressures are considered the primordial cause of dyspnea and exercise intolerance [21]. The abnormalities encountered in HFpEF include delayed relaxation, stiffening of the myocardium and inappropriate filling dynamics.

The changes that occur in the cardiomyocytes are the key to understand the dysfunction that appears in HFpEF and consequently to discover a specific treatment. An important element is cardiac hypertrophy. The extent of hypertrophy is a major predictor for HFpEF outcome. Other elements that contribute to HFpEF are fibrosis, left ventricle filling pressure, left ventricle end-diastolic volume, systemic inflammation, and metabolic disorders [22].

HFrEF is characterized by a diminished contractile response of the cardiomyocyte, reduced availability of calcium activator and inadequate storage of calcium in the sarcoplasmic reticulum [22]. Knowing these mechanisms, HFrEF may benefit of a specific treatment which acts at the level of renin-angiotensin-aldosterone system and beta-adrenergic receptors. The treatment for HFrEF is ineffective in HFpEF, because of the different pathophysiological mechanisms.

In the case of HFpEF, there are no animal models, which is a major problem to a complete understanding of the pathophysiological mechanisms, in order to establish a specific therapy.

A study published in June 2018 suggests a new theory regarding HFpEF: hypertrophic cardiomyocytes develop also hyperfunction and elevated availability of systolic calcium activator [23]. In vivo, it is present a diastolic dysfunction and in vitro, hypercontractility of the cardiomyocytes. The researchers also noticed discrete, focal areas of fibrosis and in vivo, propensity to arrhythmias, caused by the instability of the calcium from the sarcoplasmic reticulum, and sudden death [23]. Apparently, the hypercontractility due to the increase of the L-type calcium channel density is responsible for the normal systolic function [23]. On the other hand, the high level of calcium limits the relaxation and promotes the stiffness of the ventricle.
It was noticed also a deficit in cardiomyocytes, which leads to the compensatory hypertrophy of surviving myocytes [23]. Therefore, when failure occurs, diastolic dysfunction is predominant, but ejection fraction is preserved and end-diastolic volume is normal. There have been also observed the hypertrophy of the cardiomyocytes, the stiffness of the ventricle walls and focal interstitial fibrosis.

Arrhythmias can occur in HFrEF and they are related with the high levels of operational calcium, which confer instability, and with spontaneous release of calcium from the sarcoplasmic reticulum during diastole. Arrhythmias increase the risk of sudden cardiac death [23].

Myocardial fibrosis contributes to diastolic dysfunction. Patients with HFrEF have a profibrotic state. Fibrosis is organized in focal areas, observed especially near the interventricular septum. Fibrosis increases the stiffness of the walls. Collagen type I and III are elevated in HFrEF, collagenase and metalloproteinase-1 are reduced, but tissue inhibitor of matrix metalloproteinase-1 is increased, changes which contribute to fibrosis [23]. In tissue biopsy of patients with HFrEF, inflammatory cells have been also found. Hypertrophy is related to a diminished population of cardiomyocytes at an early-stage of growth. Hypercontractility predisposes to cardiomyocytes rupture and substitution with fibrotic tissue. Consequently, the integrity of the cardiac muscle is affected by focal fibrosis and the change of the ventricle geometry. In time, as the failure progresses, the diastolic function is totally compromised, but the systolic function, measured by the ejection fraction, is conserved [23].

Ventricular stiffening is associated with vascular stiffening in HFrEF. Vascular stiffening increases with age and is related to hypertension, chronic kidney disease, diabetes mellitus and obesity [24-26]. Vascular stiffening requires increased cardiac output to fill the rigid arteries that contributes to ventricular stiffening. Thus, ventricular-vascular stiffening is a common association in patients with HFrEF.

Inflammation has an important role in HFrEF. Comorbidities, such as renal disease, diabetes mellitus, may contribute to the proinflammatory state [27]. Several proinflammatory cytokines are increased in HFrEF, such as interleukin-6, tumor necrosis factor α, pentraxin 3 and soluble ST2 [27]. These patients have systemic inflammation and endothelial dysfunction, caused by the elevated expression of vascular cell adhesion molecules: VCAM-1, E-selectin, reactive oxygen species (ROS) [20]. The high level of ROS leads to the reduction of nitric oxide and consequently aggravates cardiomyocyte stiffness, hypertrophy and fibrosis [20,26].

**DIAGNOSIS OF HFrEF**

Heart failure can be initially suspected based on clinical criteria. For a definite diagnosis, it is mandatory to perform an echocardiography.

At echocardiography, the ejection fraction of the left ventricle, the thickness of the ventricular walls, the cavities’ geometry and dimensions, the associated pathologies, such as valvular stenosis or insufficiency, are evaluated.

The clinical and paraclinical elements necessary for the diagnosis of HFrEF/HFmrEF are:

- The presence of symptoms and signs of heart failure.
- A left ventricle ejection fraction ≥ 50% for HFrEF and 40-49% for HFmrEF.
- Increased levels of natriuretic peptides: BNP > 35 pg/mL; NT-proBNP > 125 pg/mL.
- Objective elements of structural and/or functional disorders of the heart as a possible cause for the clinical presentation.
- If the diagnosis is uncertain, a stress test or invasive measurement of increased left ventricle filling pressure may be necessary [1].

The specific symptoms of heart failure are breathlessness at variable degrees of effort or at rest and exercise intolerance. Dyspnea interferes with the daily activities and impairs the quality of life. On physical examination, patients with heart failure have pulmonary crackles, bilateral ankle edema, jugular venous dilatation, laterally displaced apical beat.

Echocardiography is the conclusive method for the
diagnosis of heart failure. The left ventricle ejection fraction (LVEF) is the most important parameter used to determine the systolic function of the left ventricle and a powerful predictor of death in patients with reduced ejection fraction [27]. LVEF is an important predictor for fatal and nonfatal cardiovascular events in patients with heart failure, including heart failure-related death, sudden cardiac death, hospitalization, myocardial infarction, especially in patients with reduced ejection fraction [28]. A 10% reduction of the ejection fraction is associated with a 39% higher risk of cardiovascular mortality [27].

In patients with HFrEF, echocardiography reveals a normal or near-normal ejection fraction and inadequate diastolic relaxation and left ventricle filling.

The structural elements of HFrEF are the left atrial volume index > 34 mL/m², a left ventricular mass index ≥ 115 g/m² for males and ≥ 95 g/m² for females [1].

The diastolic dysfunction has 3 stages that can be evaluated by echocardiography. The first stage is delayed relaxation, with an E/A ratio under 0.8, deceleration time of E wave > 200 ms, E/e' medium ratio less than 8. The second stage is pseudonormal function, with E/A ratio between 0.8 and 1.5, deceleration time of E wave between 160 ms and 200 ms, E/e' medium ratio between 9 and 12. The last stage is the restrictive pattern, with E/A ratio more than 2, deceleration time of E wave less than 160 ms, E/e' medium ratio more than 13 [28].

If echocardiography at rest is inconclusive, the diastolic stress test, using a semi-supine bicycle to measure the pulmonary artery pressures and cardiac output changes with exercise, may be necessary [1]. Another paraclinical test is invasive measurement of the filling pressures – the pulmonary capillary wedge pressure ≥ 15 mmHg, left ventricular end-diastolic pressure ≥ 16 mmHg [1].

In the presence of atrial fibrillation, the echocardiographic diagnosis of HFrEF is more difficult, because the left atrial volume index is higher, the functional parameters of diastolic disorder are not well established. Also, the values of natriuretic peptides are higher in patients with atrial fibrillation. On the other hand, atrial fibrillation can be a mark of HFrEF. Patients with HFrEF and atrial fibrillation may have more advanced heart failure than those with HFrEF and sinus rhythm [1].

Biomarkers measured with highly specific and sensitive assay play an important role in the diagnosis of heart failure and its risk stratification [27]. The Brain Natriuretic Peptide (BNP) is higher in patients with HFrEF than in patients without heart failure, but lower than in patients with HFrEF [28]. BNP is associated with diastolic left ventricle walls stress and pressure. Biomarkers of extracellular matrix and fibrosis (soluble ST2, galectin-3, type I procollagen C-terminal propeptide, type I and II collagen amino-terminal propeptide, collagen telopeptides, matrix metalloproteinases – MMP-1, MMP-2, MMP-8, MMP-9, tissue inhibitor of metalloproteinases – TIMP-1, TIMP-4, osteopontin) can be increased in patients with HFrEF [6]. Renal biomarkers, such as cystatin C and urinary albumin, and cardiac troponins are also elevated6. All these biomarkers may sustain the diagnosis of HFrEF, but have a poor prognostic role and, excepting natriuretic peptides, cannot be used to guide the treatment [6]. The natriuretic peptides values are related to the severity of the disease, therefore higher levels of natriuretic peptides are linked with more advanced HFrEF [6].

**TREATMENT OF HFrEF**

There is no specific or effective treatment for patients with HFrEF, in order to reduce the mortality rate [29]. In clinical practice, fewer patients with HFrEF appear to receive beta-blockers, diuretics, angiotensin-converting enzyme inhibitors, angiotension receptor blockers and aldosterone antagonists than patients with HFrEF and if they receive these drugs, it may be to treat comorbidities, such as hypertension, coronary artery disease, atrial fibrillation [29,30].

Renin-angiotensin-aldosterone system blockers have been studied in patients with HFrEF, due to their effects on hypertension, fluid retention and fibrosis. Also, beta-adrenergic blockers were studied due to their effects of prolonging diastole and increasing the filling time of the left ventricle. Despite their well-known benefits in patients with HFrEF, in those with
HFpEF beta blockers offer only a modest symptomatic improvement and do not reduce mortality [31,32]. Some studies revealed a decreased hospitalization rate with angiotensin converting enzyme inhibitors/angiotensin receptors blockers [6]. The study „The Effects of Candesartan in Patients with Heart Failure and Preserved Left-Ventricular Ejection Fraction” concluded that patients with HFrEF who received candesartan had fewer hospitalizations for decompensated heart failure compared with placebo, but without influence on the mortality rate [6]. Probably, renin-angiotensin-aldosterone-system does not have such an important role in HFpEF as in HFrEF, this is why its blockers have much less benefits [6].

The use of aldosterone antagonists was also tested in HFpEF. The results of the study ALDO-DHF, published in 2013, showed an improvement of the diastolic function, but no improvement was noticed in the maximal exercise capacity, clinical symptoms and quality of life [6]. The TOPCAT study, whose results have been published in 2014, also did not achieve its primary outcomes — cardiovascular mortality or aborted cardiac arrest, only a small decline in hospitalization rate has been observed [6,33].

Sildenafil, a phosphodiesterase-5 inhibitor, was tested in RELAX study and showed no advantage on mortality or symptomatic relief [6].

Statins can be prescribed in patients with HFpEF and have shown a significant impact on survival, due to their pleomorphic anti-inflammatory effects [6].

Considering the lack of results on mortality rate with beta-blockers use, ivabradine was also studied. Ivabradine slows the sinus node rate, but does not affect contractility and peripheral vasculature, in contrast to beta-adrenergic blockers [6]. Studies on mice revealed an improvement in the left ventricle function and lowering of aortic stiffness and fibrosis after four weeks of therapy with ivabradine [6]. A clinical trial, including 61 patients with HFpEF, has found an improvement in exercise capacity and decreased exercise-induced E/e’ ratio, which represents diastolic pressure index, with ivabradine versus placebo [6]. No side effects appeared. Ivabradine cannot be used in patients with bradycardia or chronotropic incompetence and neither in patients with restrictive type of diastolic disorder, because filling occurs early and rapidly in these patients and decreasing heart rate would worsen cardiac output even more [6].

Introduction of device therapy was a great progress for patients with HFrEF, with pacemakers, implantable cardioverter defibrillators, and resynchronization therapy. In patients with HFpEF, asynchrony is rarer than in HFrEF, thus device therapy has no applicability in HFpEF [6].

No treatment has yet been found to diminish morbidity and mortality in patients with HFpEF and HFmrEF. An important objective of the treatment in these patients is to improve symptoms and the quality of life. Diuretics are prescribed to reduce pulmonary and systemic congestion signs and symptoms. As mentioned before, aldosterone antagonists and beta-blockers do not improve symptoms in patients with HFpEF, only a relative improvement in NYHA class with candesartan was observed [1].

Regarding hospital admission, patients with HFpEF in sinus rhythm may benefit from the use of nebivolol, spironolactone and candesartan, which decrease hospital admission1. For patients who associate atrial fibrillation, beta-blockers are ineffective and digoxin has not yet been studied [1].

Arterial hypertension should be carefully treated in patients with HFpEF/HFmrEF, who have often systolic arterial hypertension. The antihypertensive drugs recommended are diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and aldosterone antagonists [1]. Beta-blockers appear to be less effective [1].

The specific therapy for comorbidities is also important, for example losing weight in obese patients, oral anticoagulants for atrial fibrillation or other arrhythmias, medical and/or interventional treatment for coronary artery disease, treatment of diabetes mellitus, preferably with metformin [1], renal disease treatment [34-37], treatment of anemia, chronic obstructive pulmonary disease and obstructive sleep apnea.
The most challenging situation is the treatment of HFpEF when different kinds of surgical procedures are required [38-40]. Either is abdominal surgery [41-44] or pelvic interventions [45-47], in males [48-51] or females procedures [52-55], the management of these comorbidities involves complex treatment strategies from surgeons, cardiologists or anesthesiologist.

Thus, the management of HFpEF includes diuretics, which reduce systemic congestion and improve the filling pressure of the left ventricle, and treatment of comorbidities, which improves considerably the clinical outcome [56].

**PROGNOSIS OF PATIENTS WITH HFpEF**

Overall, the prognosis of patients with HFpEF is similar with those with HFrEF [57]. Patients with HFpEF have more frequent a non-cardiovascular cause of death or hospitalization, in contrast to the patients with HFrEF, who have commonly a cardiovascular cause for hospitalization or death [1]. Renal involvement in patients with HF is a reducible complication, especially in patients with increased blood pressure [58-61].

The left ventricle hypertrophy and elevated left ventricle filling pressure correlate with hospitalizations for heart failure [62,63]. Recurrent hospitalizations are as frequent in HFpEF as in HFrEF and are associated with higher mortality rate [62].

There are sex-related differences between the risk factors for HFpEF. Hypertension, obesity and renal disease are more common in women, while ischemia, atrial fibrillation, chronic obstructive pulmonary disease and anemia are more frequent in males [12]. Women have a 20% lower risk of hospital admission than men, and also a lower risk of cardiovascular and non-cardiovascular events [12]. Women have an overall better prognosis than men [12]. The prognosis is modified by the presence of atrial fibrillation, stable angina pectoris, and renal disease in both sexes [12].

**CONCLUSIONS**

Patients with heart failure with preserved/mid-range ejection fraction represent approximately a half of the patients with heart failure. The diagnosis of HfpEF is based on clinical signs and symptoms, echocardiography, natriuretic peptides levels and stress tests or invasive measurement of filling pressures and left ventricular end-diastolic pressure, if necessary. Overall, the prognosis of patients with HFpEF is similar with those with HFrEF, with the difference that in these patients the death of non-cardiovascular cause is more common, in contrast to the patients with HFrEF, in whom the cardiovascular death is more frequent.

There has not yet been found a specific therapy for HFpEF that may reduce morbidity and mortality, in contrast to HFrEF. The main objective of the treatment in patients with HFpEF is to improve clinical status and decrease hospitalizations.

Further studies are needed to establish an effective treatment, to increase survival in these patients. In conclusion, HFpEF continues to be a challenge for clinicians regarding the optimal treatment.

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