Heart failure with preserved ejection fraction in the elderly: pathophysiology, diagnostic and therapeutic approach

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome characterized by symptoms and signs of heart failure with elevated left ventricular filling pressures at rest or during exercise. It is the most common type of heart failure in the elderly and its prevalence increases with age and is higher in females at any given age. HFpEF is frequently accompanied of comorbid conditions such as diabetes mellitus, obesity, atrial fibrillation and renal dysfunction. The diagnosis relies in the integration of clinical information, laboratory data and interpretation of cardiac imaging and hemodynamic findings at rest and during exercise. Conditions that have a specific treatment such as coronary artery disease, valvular disease, cardiac amyloidosis and constrictive pericarditis should be considered and evaluated as appropriate. Aggressive management of comorbidities, optimization of blood pressure control and volume status using diuretics as needed are among the current treatment recommendations. There are no specific therapies that have shown to decrease mortality in HFpEF. In symptomatic patients with history of hospital admission for decompensated heart failure, the implantation of a wireless pulmonary artery pressure monitor should be considered. Finally, given the high mortality of this condition, goals of care discussion should be initiated early and involvement of palliative care medicine should be considered.

Keywords: Echocardiography; Ejection fraction; Heart failure; Pharmacology; The elderly

1 Introduction

HFpEF is the most common type of heart failure in the elderly and affects more than 2 million Americans. Its prevalence increases with age and is higher in women at any given age. Comorbid conditions such as diabetes, atrial fibrillation, and obesity are frequent and has been reported that 50% of the affected individuals will have at least five comorbid conditions. The estimated 1 year and 5 year mortality after the diagnosis of HFpEF is 20% and 50% respectively.[2] Given its poor prognosis attention to detail is necessary to avoid missing conditions that may have a specific treatment (e.g., cardiac amyloidosis, constrictive pericarditis, valvular heart disease, coronary artery disease). In this manuscript, we will review the pathophysiology and current and emerging approaches to the diagnosis and treatment of HFpEF.

2 Pathophysiology

HFpEF is characterized by elevated left ventricular end diastolic pressure with an upward and leftward shift of end diastolic pressure-volume curve. Zile, et al.[3] showed using conductance catheters that patients with HFpEF have a prolonged time constant of LV isovolumic pressure fall (tau) and an increase in LV passive stiffness compared to healthy controls. Abnormal intracellular calcium handling, desensitization of beta-adrenergic receptors, abnormalities in the function and structure of titin, and development of interstitial fibrosis due to up regulation of transforming growth factor-β related pathways and derangements in the activity of matrix metalloproteinases are among the mechanisms described in the development of LV diastolic dysfunction.[4] Microvascular dysfunction manifested as abnormal coro-
Pulmonary hypertension is defined by mean pulmonary pressure and pulmonary hypertension. Post-capillary pulmonary hypertension is characterized by increased left atrial pressure, increased pulmonary venous strain, and systolic function as measured by global longitudinal strain is common in patients with HFpEF.\[7\]

Ventricular-arterial stiffening is an important element of HFpEF pathophysiology. A stiff ventricle has lower contractile and stroke volume reserve and is inefficient from the energy utilization standpoint. The stiff artery will increase total afterload and will decrease the impact of reflect waves in coronary perfusion during diastole. The interaction between both components is best visualized in the pressure-volume domain as a decreased in the relationship between effective arterial elastance (Ea)—a measure of vascular stiffness that integrates non pulsatile (systemic vascular resistance) and pulsatile load- and end systolic elastance (Ee)—measure of ventricular stiffness. This means that the increase in left ventricular stiffness is out of proportion to the increase of arterial stiffness. The elderly patient with HFpEF lives in a state of severe homeostenosis where small changes in after-load, preload or contractility can lead to exaggerated changes in blood pressure or volume status, rapidly fluctuating from pulmonary edema to hypotension and oliguria when standard doses of diuretics are used. In addition, the greater dependence of systolic blood pressure for coronary artery perfusion exposes these patients to a higher risk of ischemia/infarction in the context of arterial hypertension.\[8\]

Left atrium (LA) enlargement is a marker of chronically elevated LV filling pressures and is frequently present if patients with HFpEF. More recently, the importance of LA mechanical dysfunction has been recognized as another key player in the HFpEF pathophysiology. The left atrium serves as a conduit, reservoir and as a contractile chamber. Recent studies using invasive hemodynamics and strain cardiac magnetic resonance have shown that reservoir and conduit strain are lower in patients with HFpEF when compared with controls and are associated with decreased exercise tolerance.\[9\]

Chronotropic incompetence defined as an inadequate heart rate response to exercise has been detected in more than 30% of patients with HFpEF. In addition, abnormal heart rate recovery is also frequent affecting approximately 20% of patients with HFpEF. Careful analysis of exercise stress testing may help to detect these abnormalities.\[10\]

Increased left ventricular end diastolic pressure leads to increased left atrial pressure, increased pulmonary venous pressure and pulmonary hypertension. Post-capillary pulmonary hypertension is defined by mean pulmonary pressure \(\geq 25\) mmHg and pulmonary capillary wedge pressure \(\geq 15\) mmHg. Pulmonary vascular resistance is normal or only mildly elevated. Progressive remodeling or presence of comorbidities (e.g., chronic obstructive pulmonary disease) may lead to mixed pre and post-capillary pulmonary hypertension where pulmonary vascular resistance parameters are increased. Approximately 30% of the patients with HFpEF will have pulmonary hypertension.\[11\]

High pulmonary capillary wedge pressure decreases pulmonary vascular compliance for any degree of pulmonary vascular resistance and increases net right ventricular afterload due to elevation of pulsatile load and may lead to right ventricular dysfunction.\[12\] Right ventricular (RV) dysfunction in HFpEF has a frequency between 18% and 28% depending of the method used. RV function may be preserved at rest in patients with HFpEF and might display an impaired RV reserve during exercise explaining the independence between the PCWP and RV function. In general, RV dysfunction and PH are strong predictors of adverse outcomes in patients with HFpEF.\[13\]

Fat infiltration of the skeletal muscle, reduced slow-twitch type I fibers, type I-to-type-II fiber ratio and capillary-to-fiber ratio are present in patients with HFpEF and contribute to exercise intolerance.\[14\]

### 3 Approach to diagnosis

High index of suspicion is necessary when evaluating patients with symptoms compatible with HFpEF given that physical examination may be normal at rest. The presence of risk factors for this condition including advanced age, female sex, hypertension, obesity and/or prior history of coronary artery disease and comorbidities frequently present in HFpEF (e.g., diabetes mellitus) should trigger further evaluation (Figure 1).

The diagnosis of HFpEF requires the presence of signs and symptoms of heart failure, left ventricular ejection > 50% and evidence of increased left sided filling pressures at rest or with stress. The evaluation of biomarkers (elevated natriuretic peptides), cardiac structure (left atrial enlargement, increased LV mass) and function (elevated E/e’ ratio at rest or with exercise and/or increased pulmonary capillary wedge pressure at rest or with exercise) are essential to start the diagnostic work up.

The 2D echocardiogram and Doppler examination is the cornerstone of the initial diagnostic strategy. Determination of left ventricular ejection fraction is the first step. Accurate imaging is of paramount importance to make the correct diagnosis. Foreshortening for example may lead to overestimation of left ventricular ejection fraction whereas undercontrolled hypertension may lead to underestimation of LVEF. The presence of concentric LV hypertrophy defined as an
indexed LV mass >149 g/m² in males and 122 g/m² in females and a relative wall thickness > 0.42 is associated with diastolic dysfunction. Left atrial volume indexed to body surface area > 34 mL/m² is one of the major morphological criteria for HFrEF diagnosis. [15]

It is important to recognize that diastolic dysfunction is not the same as elevated filling pressures. The presence of normal tissue Doppler velocities at rest should raise the suspicion for alternative diagnosis (e.g., constrictive pericarditis, dynamic mitral regurgitation, chronotropic incompetence, angina equivalent) for the patient’s symptoms. In general, if average e’ is less than 9 cm/s and the ratio E/e’ is greater than 13 the diagnosis of HFrEF is favored in the context of above mentioned structural abnormalities. Other parameters that support the diagnosis are E/A > 2, deceleration time < 160 ms, isovolumic relaxation time < 60 s and estimated systolic pulmonary arterial pressure > 35 mmHg. Importantly, if suspicion for HFrEF is high and resting echocardiogram is normal, exercise echocardiogram Doppler should be considered. [16]

The use of myocardial strain imaging may help in the identification of the cause of hypertrophy. Patients with LV hypertrophy secondary to hypertension and/or aortic stenosis have higher global longitudinal strain values than patients with hypertrophic cardiomyopathy or infiltrative disease. Examination of the patterns of abnormal strain may provide clues to the diagnosis of specific cardiomyopathies. Apical sparing is classically seen in cardiac amyloidosis. On the contrary, significant apical abnormal strain is present in apical hypertrophic cardiomyopathy. [17]

The presence of elevated natriuretic peptides is useful for the diagnosis of HFrEF (NT pro-BNP > 220 pg/mL or BNP > 80 pg/mL). However, a low value does not rule out the diagnosis. Typical false negative results are observed in obese patients and patients with symptoms only present on exertion. Paroxysmal or persistent atrial fibrillation is present in 1/3 of the patients with HFrEF and approximately 1/4 of the patients with atrial fibrillation will have HFrEF. BNP are elevated in both conditions and different cut offs have been proposed for their interpretation in this context (NT pro-BNP > 660 pg/mL or BNP > 240 pg/mL). [18]

Scores that incorporate clinical, echocardiographic and laboratory variables have been reported. Recently a single center validated score has been reported with a good performance to assign a probability of HFrEF (AUC, 0.886) has been reported. The variables included in the H2FrEF score are: Heavy BMI > 30 kg/m²: 2 points and Hypertensive 2 or more medications for hypertension: 1 point, Atrial fibrillation: 3 points, Pulmonary systolic hypertension > 35 mmHg: 1 point), Elderly age > 60 years: 1 point), Filling pressures E/e’ > 9: 1point. Low (0–1 points) and high (6–9) represent low probability and high probability of HFrEF. [19]
When the diagnosis of HFpEF is uncertain, two diagnostic modalities are particularly useful. Cardiopulmonary exercise testing (CPET) has the potential to discriminate HFpEF from non-cardiac causes of dyspnea. Reddy, et al.\[20\] reported that very low peak VO$_2$ (< 14 mL/kg per min) had excellent specificity (91%) but poor sensitivity (50%) for the diagnosis of HFpEF and that preserved peak VO$_2$ (> 20 mL/kg per min) excluded HFpEF with high sensitivity (90%) but low specificity (49%). In patients with symptoms limiting quality of life and without clinical evidence of hypervolemia the performance of exercise right heart catheterization may help in the early diagnosis of HFpEF. Approximately half of those patients will show abnormal increase in left sided filling pressures (exercise pulmonary capillary wedge pressure (PCWP) ≥ 25 mmHg).\[21\] The importance of performance exercise during right heart catheterization cannot be overemphasized, even if osteoarticular problems limit the capacity of an elderly patient to use recumbent bike, the performance of handgrip maneuver is a possibility and should be pursued if necessary.\[22\]

In the elderly patient, dyspnea on exertion may represent an angina equivalent and ruling out coronary artery disease should be considered using non-invasive or invasive methodologies as appropriate.\[23\] Cardiac Magnetic resonance imaging is useful for the diagnosis of infiltrative cardiomyopathies, regurgitant valvular disease, hypertrophic cardiomyopathy and evaluation of pericardial disease and ventricular interdependence.\[10\]

## 4 Phenotypic classification

HFpEF is a complex syndrome with multiple risk factors and causes that occurs in patients with a high prevalence of multi-morbidity. Shah, et al.\[24\] proposed a multiaxial phenotypic classification of HFpEF. This classification serves a framework for the implementation of phenotype specific therapies.\[25\] The classification incorporates several elements depicted on Table 1.

## 5 Treatment

A domain management approach has been proposed to treat elderly patients with heart failure. In the medical domain the evaluation of the stage of HFpEF, pharmacotherapy optimization, comorbidity management and nutritional status evaluation are the main components. Other domains include: mind and emotion, physical function and social support.\[26\] (Figure 2).

### Table 1. Approaches to classification of HFpEF.

| Pathophysiologic presentation | Etiology | Risk | Phenomics |
|------------------------------|----------|------|----------|
| Diastolic dysfunction (impaired relaxation and/or reduced compliance). | Garden variety: associated with hypertension, diabetes, obesity, metabolic syndrome and chronic kidney disease. | Low: no symptoms at rest with exercise induced increases LV filling pressures with normal LV pressures at rest. | Involves the integration of information from different sources (clinical, imaging, genetics, proteomics) using sophisticated phenotyping techniques along with machine learning to characterize different subtypes of HFpEF. Initial validation studies have reported positive results in terms of risk stratification in a validation cohort.\[26\] |
| Longitudinal systolic dysfunction (e.g., decreased global longitudinal strain). | CAD associated: Multivessel disease or CAD as a cause of HFpEF. | Intermediate: Clinical evidence of volume overload, dyspnea, exercise intolerance and cardiac structure abnormalities. | |
| Endothelial dysfunction. | Atrial fibrillation predominant HFpEF. | High: High morbidity and mortality represented by patients with pulmonary hypertension and RV failure. |
| Abnormal ventricular arterial coupling. | Right Ventricle failure predominant | | |
| Impaired systemic vasodilator reserve. | Hypertrophic Cardiomyopathy induced or like HFpEF: typically, small cavities and thick walls. | | |
| Pulmonary hypertension and pulmonary vascular disease with right heart failure in the setting of left heart disease. | Multivalvular HFpEF. | | |
| Chronotropic incompetence. | Restrictive cardiomyopathies. | | |
| Extra cardiac causes of volume overload in the susceptible heart (examples include obesity, chronic kidney disease) | Anemia. | | |
| | Etiology | | |
| Pathophysiologic presentation | Etiology | Risk | Phenomics |
| Counterpulsation (e.g., decreased left ventricular relaxation and/or increased contractility). | Garden variety: associated with hypertension, diabetes, obesity, metabolic syndrome and chronic kidney disease. | Low: no symptoms at rest with exercise induced increases LV filling pressures with normal LV pressures at rest. | Involves the integration of information from different sources (clinical, imaging, genetics, proteomics) using sophisticated phenotyping techniques along with machine learning to characterize different subtypes of HFpEF. Initial validation studies have reported positive results in terms of risk stratification in a validation cohort.\[26\] |
| | CAD associated: Multivessel disease or CAD as a cause of HFpEF. | Intermediate: Clinical evidence of volume overload, dyspnea, exercise intolerance and cardiac structure abnormalities. | |
| | Atrial fibrillation predominant HFpEF. | High: High morbidity and mortality represented by patients with pulmonary hypertension and RV failure. | |
| | Right Ventricle failure predominant | | |
| | Multivalvular HFpEF. | | |
| | Restrictive cardiomyopathies. | | |

CAD: cardiovascular disease; HFpEF: heart failure with preserved ejection fraction; LV: left ventricle.
5.1 Pharmacological management

For patients with HFpEF current guidelines have only three class 1 recommendations: control blood pressure according current guidelines, use diuretics in symptomatic patients with volume overload and patients who had persistent hypertension after management of volume overload should be prescribed guideline directed medical therapy and titrated to attain systolic blood pressure < 130 mmHg.[27]

Several drugs have been tested in clinical trials including irbesartan, candesartan, perindopril, nebivolol, digoxin, ivabradine, sildenafil, isosorbide mononitrate, inhaled inorganic nitrates and spironolactone but none have shown an improvement in outcomes in this patient population.[10,28,29] A post hoc analysis of the TOPCAT trial showed that patients enrolled in the Americas (United States, Canada, Brazil, and Argentina) had a higher overall incidence of the primary endpoint and a statistically significant reduction in events when treated with spironolactone compared to patients randomized in Russia or Republic of Georgia which had overall lower incidence of the primary endpoint and showed no benefit with spironolactone.[30] This significant regional variation and potential benefit has increased the controversy regarding the use of spironolactone HFpEF.

In a phase II randomized multicenter clinical trial in which NT-pro BNP reduction from baseline at 12 weeks was the primary outcome Neprylisin inhibitor LCZ696 was superior to valsartan.[31] The PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction) trial is a randomized, double-blind, parallel group, active-controlled, event-driven trial comparing the long-term efficacy and safety of valsartan and sacubitril/valsartan in patients with chronic HFpEF with a composite primary endpoint of cardiovascular death and total HF hospitalization. This trial has finished enrollment (4822 participants) and is expected to be completed around May 2019.[32]

Vericiguat is oral soluble guanylate cyclase stimulator which increases the sensitivity of this enzyme to endogenous NO increasing the production cyclic guanosine monophosphate which has been associated with anti-fibrotic effects and systemic and pulmonary vasodilation.

In the SOCRATES-PRESERVED (SOluble guanylate Cyclase stimulatoR in heArT failurE patientS with PRE-SERVED EF) study vericiguat was not superior to placebo in decreasing NT pro BNP and left atrial volume but was associated with improvements in quality of life.[33] Patient-reported Outcomes in Vericiguat-treated Patients With HFpEF (VITALITY-HFpEF) is currently underway to evaluate the effect of vericiguat in the change in Kansas City Cardiomyopathy Questionnaire physical limitation score from baseline to week 24.[34] Estimated completion of the study is January 2020.
In patients with diabetes type 2 and established cardiovascular disease defined as ≥ 1 of the following: coronary artery disease, peripheral vascular disease or history of myocardial infarction or stroke, empagliflozin, an inhibitor of sodium–glucose cotransporter 2, reduced the rate of the primary composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. In addition, hospitalization for heart failure that was another prespecified outcome was also significantly reduced (HR = 0.65 (95% CI: 0.50–0.85); P = 0.0017) when compared with placebo. Because of this EMPEROR-Preserved (EMPagliflozin outcome of Patients With chrOrnic heaRt Failure With Preserved Ejection Fraction) was designed to include patients with established heart failure with LVEF > 40%. Of note the diagnosis of diabetes is not required to enter the study. The study is active and currently enrolling patients.

Borlaug, et al reasoning that intravenous beta-agonists decreased pulmonary vascular resistance tested the inhaled beta agonist albuterol in patients with HFpEF and showed an improvement of pulmonary vascular reserve without worsening left heart congestion. Further studies are needed to fully characterize the impact of this emerging therapy in HFpEF.

5.2 Hemodynamic monitoring and interventions

In patients with heart failure with preserved ejection fraction with NYHA III and a previous hospitalization for heart failure within 12 months, the use of wireless pulmonary artery pressure monitoring guided management reduced hospitalization for decompensated heart failure. Of note, this is the first intervention to decrease morbidity in this patient population.

REDUCE LP-HF (Reduce Elevated Left Atrial Pressure in Patients With Heart Failure) evaluated the safety and hemodynamic efficacy of a transcatheter interatrial shunt device (IASD) in patients with HF LVEF ≥ 40% with PCWP ≥ 15 mmHg at rest or ≥ 25 mmHg during exercise. No major adverse periprocedural events occurred. At one month patients who underwent IASD implantation showed greater reduction in PCWP compared with sham control. Mild increase in RV size was observed in patients with IASD. Future studies are needed to understand the effect of this therapy in symptoms and clinical outcomes.

5.3 Physical activity and exercise

A meta-analysis of randomized trials of exercise training in patients with HFpEF that included 276 patients showed improvement in cardiorespiratory fitness and quality of life compared to control group. In addition, caloric restriction in elderly obese patients is associated with an increase in peak VO2 and its effects appears to be additive to exercise training. Nevertheless the implementation of this valuable intervention is limited because most insurances in the United States do not cover cardiac rehabilitation for patients with HFpEF.

5.4 Palliative care

Non cardiovascular death represents an important competing risk in patients with HFpEF. In addition the presence of frailty and multimorbidity further complicates prognostic evaluation. As discussed previously the poor prognosis of patients with HFpEF merits careful consideration of palliative care evaluation to assess goals of care and ensure appropriate control of symptoms that are refractory to conventional medical therapy.

6 Conclusions

HFpEF is a complex systemic syndrome, frequently accompanied by multimorbidity that is characterized by functional limitation and poor prognosis. Evaluation of causes that can have specific therapies (e.g., amyloidosis, valvular disease, coronary artery disease, constrictive pericarditis) is of paramount importance. Appropriate management of hypertension and related comorbidities and treatment of volume overload with diuretics if appropriate remain the main therapeutic strategies. In patients with history of hospitalizations and NYHA III implantation of wireless pulmonary artery pressure monitor should be considered. New therapies are undergoing evaluation and results of large pragmatic clinical trials will be available in the next couple of years.

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