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HEART FAILURE (AM CHANG, SECTION EDITOR)

# Heart Failure with Preserved Ejection Fraction

Michelle Mitchell[1]

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## Abstract

**Purpose of Review** The incidence of heart failure with preserved ejection fraction (HFpEF] is rapidly increasing, yet many physicians may feel less knowledgeable about HFpEF when compared with heart failure with reduced ejection fraction (HFrEF]. The purpose of this review is to discuss the incidence, pathophysiology, clinical diagnosis, treatment, and prognosis of patients with HFpEF.

**Recent Findings** Despite an increasing understanding of the pathophysiology and nature of HFpEF, there has been little advancement in therapies.

**Summary** Despite similar clinical presentations and treatments for HFpEF when compared to HFrEF, there are marked differences in the underlying pathophysiology. More research is needed in order to improve morbidity and mortality for patients with HFpEF.

**Keywords** HFpEF · Heart failure · Ejection fraction · Cardiology · Diastolic · HF

## Introduction

Heart failure is a generalized term that can be further classified. Broadly, heart failure is the inability of the heart to maintain adequate perfusion to the body. It can be further classified into heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).

According to the Heart Failure and Echocardiography Associations of the European Society of Cardiology, the following criteria need to be satisfied for the diagnosis of HFpEF: signs and symptoms of heart failure, normal or mildly abnormal systolic left ventricular (LV) function, and evidence of left-ventricular end-diastolic dysfunction [1]. Most authors define normal LVEF as greater than or equal to 50%. With the above definition, it is important to note that diastolic dysfunction is not synonymous with HFpEF; one must have evidence of heart failure in addition to diastolic dysfunction.

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✉ Michelle Mitchell
Michelle.s.mitchell@duke.edu

[1] Duke University Medical Center, Durham, NC, USA

## Prevalence and Demographics

Of all patients with HF, approximately half have ejection fractions of ≥ 50% [2]. Interesting, while the incidence of HF appears to be stable over the past two decades, the proportion of patients with HFpEF appears to be increasing. In fact, the incidence of HFpEF has increased by 45% during the same time period [3]. It has also been found that HFpEF is the most prominent type of heart failure among older adults ages 66 to 90, accounting for upwards of 77% of prevalence cases [4]. Therefore, in the near future, there will likely be more emphasis on treatment and improving morbidity and mortality of patient with HFpEF.

The risk factors associated with HFpEF are similar when compared with HFrEF, which include systemic hypertension, older age, coronary artery disease, diabetes mellitus, obesity, and kidney disease. When compared with HFrEF, which has a male predominance secondary to coronary artery disease, HFpEF is predominately associated with females. Additionally, increased age is also associated with HFpEF [Yancy]. As diastolic dysfunction typically occurs with aging, it is natural that the prevalence of HFpEF increases with age. Lastly, when compared to HFrEF, patients with HFpEF were less likely to have a prior myocardial infarction [5].

## Pathophysiology

A component of HFpEF includes left ventricular diastolic dysfunction. Diastolic dysfunction alone, as discussed above, does not equate with HFpEF, as diastolic dysfunction naturally comes with aging. However, its presence is a risk factor for later development of HFpEF. To appreciate the pathophysiology of HFpEFs, an understanding of diastolic dysfunction is required.

Diastolic dysfunction includes prolonged LV relaxation, slow LV filling, and increased diastolic LV stiffness. A patient typically increases his or her heart rate in response to an acute stressor that leads to tachycardia, such as physical exercise. As the heart rate increases, the duration of diastole shortens. This requires the rate of LV relaxation and filling to also increase to maintain cardiac output. Diastolic LV dysfunction consists of prolonged isovolumic LV relaxation and slow LV filling, therefore, making it difficult to achieve the balance between cardiac input and cardiac output.

Diastolic LV dysfunction also consists of increased diastolic LV stiffness, which affects preload. Preload refers to the degree of left ventricular stretch or length at end-diastole. This is illustrated by the Frank-Starling mechanism. As blood flows into the left ventricle, the left ventricle expands, which leads to stretching and lengthening of the sarcomeres. When the sarcomeres lengthen, the amount of force they generate increases, leading to an increase in cardiac output. There is an ideal length of the sarcomeres; anything above or below this will reduce the amount of cardiac output. Therefore, in diastolic dysfunction, the stretching of the sarcomeres is limited which results in potentially decreased filling of the left ventricle during diastole, resulting in decreased cardiac output. The increased LV stiffness seen in HFpEF results in increased LV pressure for any given volume of blood. During diastole, the chambers among the pulmonary veins, left atrium, and left ventricle are continuous. Therefore, as the pressure increases in the LV, it increases the pressure across the system. This is displayed as the classical dyspnea on exertion symptoms.

## Clinical Manifestations and Diagnosis

Manifestations of HFpEF are similar to those experienced by patients with HFrEF. Common symptoms include dyspnea, including orthopnea and dyspnea on exertion, along with fatigue [6]. Signs include evidence of volume overload including elevated jugular venous distention, lower extremity edema, and pulmonary rales. It is important to note that many signs of HFpEF may or may not be present on exam. Moreover, some patients may present with exertional chest pain as a first symptom of heart failure, which should prompt a HF work-up in addition to CAD.

When a patient presents with clinical signs and symptoms of heart failure, such as dyspnea, mimics of HFpEF should be excluded. This includes noncardiac etiologies, such as pulmonary disease, generalized deconditioning, anemia, and obesity. It also includes heart failure not caused by HFpEF, including various cardiomyopathies and valvular diseases. Many of these can be diagnosed on laboratory evaluation or imaging, such as a chest X-ray or echocardiogram.

If HFpEF is strongly suspected, the H2FpEF score can be used to determine if a patient has HFpEF or a noncardiac cause of dyspnea [7], as well as assist in decision-making as to appropriate work-up for exertional dyspnea. It is an acronym that includes the following:

- **H**eavy: a body mass index > 30 kg/m2 (two points)
- **H**ypertensive: two or more antihypertensive medications (one point)
- Atrial **F**ibrillation [AF]: either paroxysmal or persistent (three points)
- **P**ulmonary hypertension: pulmonary artery pressure > 35 mmHg (one point)
- **E**lder: age > 60 years (one point)
- **F**illing pressure: E/e' > 9 (one point)

The total score for H2FpEF ranges from 0 to 9. As the score increases, the probability of HFpEF increases. Lower score indicates that the symptoms are likely to be due to a noncardiac cause. An intermediate score, with a range from 2 to 5, carries a 40 to 80% probability of HFpEF. A brain natriuretic peptide (BNP) along with N-terminal pro-BNP level can be a helpful level to obtain in those patients who fall into the intermediate category. It is important to note that certain conditions, most notably obesity, will falsely lower the BNP level. If the BNP is elevated, and there is an absence of significant pulmonary disease, a diagnosis of HFpEF can be made. If there remains any uncertainty, a right heart catheterization is recommended. A high H2FpEF score (6 or greater) is associated with greater than a 90% probability of HFpEF.

## Treatment

Despite the rapidly increasing incidence of HFpEF, when compared with the treatment of HFrEF, very little advancement has been made regarding outcomes in HFpEF. The evidence surrounding the treatment of HFpEF have limited direct evidence, but are primarily focused on managing associated conditions, which most commonly include hypertension, coronary artery disease, obesity, diabetes mellitus, kidney disease, hyperlipidemia, and atrial fibrillation, along with symptom management. There are two strong recommendations based on the 2013 American College of Cardiology Foundation/American Heart Association [ACC/AHA] HF

guidelines [8••]. They include management of systolic and diastolic hypertension, along with diuretics for symptomatic treatment of volume overload.

Although the ACC/AHA recommends treating hypertension in patient with HFpEF, there is no evidence that treating hypertension improves the signs or symptoms of HFpEF. The available evidence primarily focuses on the management of hypertension to prevent the development of HFpEF. Nonetheless, there are several pharmacologic recommendations.

Selecting pharmacologic treatment for hypertension depends on the coexisting disease of the patient, particularly considering the presence of diabetes mellitus, chronic kidney disease, and chronic obstructive pulmonary disease. The standard HFrEF treatments for hypertension, including beta-blockers, angiotensin-converting enzymes (ACE) inhibitors, and angiotensin receptor blockers (ARB), do not have the same effect on HFpEF. These therapies have not been shown to reduce morbidity or mortality in HFpEF [9]. This likely highlights the difference in underlying pathophysiology between HFpEF and HFrEF [10]. However, there are a few recommendations for the treatment of hypertension in patient with HFpEF. The above-mentioned medications, including beta-blockers, ACE inhibiters, and ARBs are considered reasonable in treating hypertension in HFpEF [8••]. In the ALLHAT trial, when compared with amlodipine, lisinopril, and doxazosin, chlorthalidone reduced the incidence of new-onset HFpEF [11]. There is also evidence for the use of a mineralocorticoid receptor antagonist. In the Treatment of Preserved Cardiac Function Heart Failure with Aldosterone Antagonist [TOPCAT] trial, it was found that adding spironolactone therapy, while closely monitoring potassium levels, was found to have less frequent hospitalizations for heart failure [12].

Diuretics are often used to control symptoms related to volume overload, which have indirect evidence supporting the efficacy of diuretics to reduce morbidity in HFpEF. However, care should be taken when administering drugs such as diuretics and venodilators. The left ventricle is often stiff and small in patients with HFpEF, which can lead to increased sensitivity to changes in preload. This can subsequently leave to underfilling of the left ventricle resulting in decreased cardiac output.

Atrial fibrillation is another common condition seen in heart failure, with one study estimating its presence in two-thirds of patients with HFpEF. The presence of atrial fibrillation itself is associated with increased morbidity and mortality [13]. Controlling atrial fibrillation can be achieved by either rate or rhythm control. Some prefer rhythm control, particularly for younger patients. In patient with HFpEF, LV filling is more dependent on atrial contraction than in patients without HFpEF. Therefore, restoration of sinus rhythm is preferred, however, there have been no specific trials assessing rate versus rhythm control in patients with HFpEF. In terms of rate control, calcium channel blockers and beta-blockers are first-line pharmacologic management. Of course, anticoagulation should be considered based on patient's underlying characteristics.

Coronary artery disease is also a common condition associated with HFpEF. Patients are treated with standard therapies which do not significantly differ based on the classification of the patient's heart failure, which includes coronary revascularization. Unfortunately, there have been no studies to determine the impact of revascularization on symptoms or outcomes in HFpEF [8••]. In terms of hyperlipidemia, standard treatment is recommended again. Interestingly, however, the use of statins for treatment of hyperlipidemia has been shown to have a beneficial effect for patients with HFpEF but not for patients with HFrEF.

## Acute Decompensated Heart Failure

Acute decompensated heart failure (ADHF) is a common cause of hospitalization in older adults and is often a prognostic indicator of the future course of the disease, with high rates of rehospitalization and mortality [14]. There are several conditions that may trigger acute decompensated heart failure, with ACS being an important cause to consider. Additionally, as discussed above, patients with HFpEF poorly tolerate several certain conditions, including rapid changes in blood pressure and tachycardia.

With any patient presenting with ADHF, it is imperative to evaluate for ACS with serial EKGs and cardiac enzymes. Determining if a patient had an ACS that precipitated ADHF can be complex however. If there is a STEMI on EKG, then it is rather straight forward. However, it is not uncommon for patients with ADHF to have a type 2 myocardial infarction (MI), which is an MI due to ischemia secondary to increased oxygen demand or decreased supply. In ADHF, there is extra stress on the heart, which causes the heart to release troponin. Therefore, it can be difficult to determine if an ACS precipitated ADHF or if ADHF caused ACS.

Other common factors that could precipitate ADHF include nonadherence to medications or diet (e.g., sodium or fluid restrictions), concurrent infections that increase metabolic demand (e.g., pneumonia that causes hypoxia), pulmonary embolus, addition of drugs that has negative inotropic drugs (e.g., beta-blockers and calcium channel blockers), drugs that increase salt retention (e.g., NSAIDs and steroids), and endocrine abnormalities (e.g., thyroid disorders and diabetes.)

If you suspect a patient has ADHF, the initial approach is the same whether the patient has HFrEF or HFpEF. Airway assessment is paramount, with the goal to treat oxygen saturations of less than 90%. There have been suggestions that oxygen therapy is over-utilized and potentially detrimental

in patient with HF. One study has suggested that oxygen decreased heart rate and cardiac output, detrimental to patients with ADHF [15]. If oxygen is needed, a tiered approach is recommended with starting with a non-rebreather mask, followed by noninvasive ventilation, and then intubation if the prior treatments fail.

In terms of loop diuretics, patients should be treated promptly if there is evidence of ADHF and volume overload. A multicenter prospective trial demonstrated lower in-hospital mortality when patients received loop diuretics within 60 min of arrival [16]. Diuretics may be held if the patient is experiencing signs and symptoms of cardiogenic shock, including a systolic blood pressure of less than 90 mmHg. In addition to diuretics, vasodilators including nitroglycerin, nitroprusside, or nesiritide may be used as an adjunct for relief of dyspnea in patients without hypotension [8••]. However, vasodilators should be used cautiously in HFpEF as these patients are very volume sensitive.

## Prognosis

As with many other areas of care for the patient with HFpEF, the prognosis of patients with HFpEF is less defined than that of patients with HFrEF. While the survival rate for patients with HFrEF has improved over the past several years due to advancements in pharmacologic therapies [17], the same advancements have not be made for patients with HFpEF. The morbidity component, including hospitalizations, severity of symptoms, and quality of life, has been shown to be comparable between patients with HFrEF and patients with HFpEF. However, the survival rate for patients with HFpEF was slightly higher when compared to patients with HFrEF [18].

## Conclusion

The incidence of HFpEF is increasing, and will likely be the more dominant form of heart failure in the near future. Unfortunately, there has been little advancement in terms of treatments specifically directed at HFpEF. The majority of current day treatments have been adopted based on studies from HFrEF, with no therapies demonstrating improved survival in patients with HFpEF, which highlights the difference in pathophysiology between the two diagnoses.

### Compliance with Ethical Standards

**Conflict of Interest** The author declares that there are no conflict of interests.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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