

Heart Failure with Preserved Ejection Fraction (HFPEF)



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Heart Failure (HF) is a growing epidemic in the United States (U.S.). New data from the American Heart Association (AHA) estimates that in 2010 6.6 million adults \geq 18 years of age had HF in the U. S. They estimate that by 2030, an additional 3 million more Americans will develop HF, a 25% increase from 2010. (1) HF continues to be the number one cause of hospital admissions in individuals over the age of 65. (1) Seventy-five percent of HF cases have antecedent hypertension and it continues to have a high mortality rate of 50% in five years.(1) The type of HF that is most familiar is HF with reduced ejection fraction (HFREF) which occurs when the left ventricle is dilated and enlarged with poor systolic function. In this type of HF, the ejection fraction (EF) is defined as less than 40%. HFREF occurs in about 50% of patients with HF, which leaves the other 50% with a normal ejection fraction or preserved ejection fraction. This is usually defined as an EF equal to or greater than 50%, although some studies have used a limit as low as 40%. .

In both the ADHERE and the OPTIMIZE-HF Registries, 50% of the patients admitted to the hospital with decompensated HF had normal ejection fractions. (2,3). It is now well established that about half of individuals with HF have a normal or preserved EF. The clinical manifestation of HFREF and HFPEF are very similar but there are distinct differences in risk factors, patient characteristics, and pathophysiology between the two types of HF. Several large randomized clinical trials guide the treatment of HFREF. However, those trials are less prevalent in HFPEF and medications proven very beneficial in HFREF have not shown the same benefit in HFPEF. This has led to much discussion and ongoing research to help determine the exact pathophysiology of HFPEF so treatments that are more effective can be developed. In the meantime, we have approximately 3.2 million individuals with HFPEF who need the expertise and care of HF nurses. The purpose of this article is to examine what is currently known about the risk factors, patient characteristics, pathophysiology, diagnosis, and treatment of HFPEF.

Historically HF with a normal ejection fraction was referred to as diastolic HF because it was believed that most patients with the symptoms of HF and a normal EF had some type of diastolic dysfunction. However, as investigators gained a greater depth of knowledge regarding the pathophysiology of HFPEF, it became apparent that individuals with HFPEF may not have diastolic dysfunction. Therefore, the name diastolic HF was changed to HF with a normal EF and is now referred to as HF with preserved EF. HFPEF is usually diagnosed when the clinical symptoms of HF are present in the setting of preserved systolic function and some evidence of diastolic dysfunction on Echocardiography (ECHO), cardiac catheterization, or cardiac biomarkers and the absence of valvular disease. (4,5,6)

One study that reported the high prevalence of HFPEF was a retrospective analysis conducted over a 15-year period. The analysis was done using patients discharged with a diagnosis of decompensated HF from the Mayo Clinic in Olmsted County.(7) The results of the research showed that the prevalence of HFPEF was 49% in those patients over 65 and 40% in those who were younger than 65. The result of the analysis indicated that the majority of patients with HFPEF were older, more likely to be

a female, had a higher mean body-mass index, more likely to be obese, and had lower than normal hemoglobin levels. (7) The patients in this study also had a higher incidence of hypertension and atrial fibrillation but less Coronary Artery Disease (CAD) and valvular disease. The study also found that the prevalence of HFPEF increased over time. In the first 5 years, 38% of the patient admissions had HFPEF, the second five years the percentage increased to 47%, and the last five years the percentage increased to 54%. (7) The survival rate for those individuals with HFPEF was slightly higher than those with reduced EF. (7) In addition, the survival rates increased over the 15 years for those patients with HFREF but did not improve for those with HFPEF. A second study was conducted using Olmsted County residents who had incident or prevalent HF to determine EF measurement, diastolic function and Brain Natriuretic Peptide (BNP) in community residents with HF. Patients were enrolled over a two-year period in this prospective study. There were 556 total patients with 55% of them having HFPEF. (8)

The ADHERE registry included 105,000 admissions for acute decompensated HF from 274 centers. LVEF was determined in 52,000 of those admissions and 50% had HFPEF. (2) In the OPTIMIZE-HF registry, 51% of the 41,000 patients had an EF greater than 40%. (3) In both sets of data, the patients with HFPEF were older, with an average age of 73.9 and 75.1 respectively. There was also a higher percentage of women with HFPEF in both registries, and a lower percentage of African Americans. In both registries, the incidence of CAD or previous history of Myocardial Infarction (MI) was less in those patients with HFPEF. Hypertension or a history of hypertension was significantly higher in both groups who had HFPEF. (2,3)

Of even greater importance is that the data from the ADHERE registry showed that with the exception of Angiotensin Receptor Blockers (ARBs) all standard oral HF medications were used significantly less often during patient episodes with HFPEF. (2) Intravenous agents including vasodilators, nesiritide, and inotropes were also used less frequently. (2) At discharge, the use of other standard HF medications was less except for the use of diuretics. Presentation characteristics and length of stay (LOS) were the same for both groups of HFREF and HFPEF. In-hospital mortality and Intensive Care Unit (ICU) management was significantly less in those patients with HFPEF. (2) Similar data was observed in the OPTIMIZE-HF registry with those patients who had HFPEF receiving less standard HF medications, such as ACE inhibitors (ACEIs), aldosterone inhibitors, and beta blockers, on admission and at discharge. (3) Mortality rates were significantly higher in those hospitalized with HFREF. (3) However, LOS, rehospitalization rates, and unadjusted all-cause mortality at 60 and 90 days were the same between those patients with HFREF and HFPEF. (3)

By looking at this data, a profile of those patients with HFPEF is distinguished. These individuals will be older, more likely to be women, and have many comorbidities such as hypertension, atrial fibrillation, diabetes, and obesity. Although CAD is common in both types of HF, it is less common in those individuals with HFPEF. The data on mortality rates for those individuals with HFPEF is variable. In the Olmsted County study mentioned above (7), the mortality rate for HFPEF was slightly less than those individuals with HFREF. This was also found to be true in the Candesartan in Heart

Failure (CHARM) study; the mortality rate in this study for those with HFPEF was 22%. (9) Data from the OPTIMIZE-HF registry data showed lower in-hospital mortality for the HFPEF patients but similar mortality rates between HFREF and HFPEF at 60 and 90 days. (3) Morbidity is also similar between the two types of HF with a 50% chance of re-hospitalization in 60 days. (6) Kitzman, et al. (10) compared three groups of subjects to see if there were differences between those with HFREF, HFPEF, and age-matched healthy controls. The study measured LV structure and function, exercise performance, neuroendocrine function, and quality of life. The results of the study demonstrated that exercise performance was markedly reduced in both groups of patients with HF compared to the control group, with more severe impairments in those with HFREF. Levels of norepinephrine, BNP, and Atrial Natriuretic Peptide (ANP) were significantly elevated compared to the control group. However, ANP and BNP were significantly higher in the HFREF group compared to those with HFPEF. Finally, quality of life scores were lower than controls in both groups. This study provides the opportunity to recognize that patients with HFPEF have similar symptoms and issues as those patients with HFREF.

The pathophysiology of HFPEF is currently evolving as scientists and cardiologists attempt to answer the question of what exactly is the etiology of HFPEF. Currently the diagnosis of HFPEF is mainly one of exclusion and a better understanding of the exact pathophysiology may lead to more specific diagnostic criteria. A substudy done from the Irbesartan in HFPEF trial (I-PRESERVE) looked at Echocardiographic changes in 745 of the 4128 patients enrolled in the study. This substudy showed that there was a high prevalence of structural remodeling characterized by significant concentric left ventricle (LV) remodeling and left ventricular hypertrophy (LVH) and a high prevalence of diastolic dysfunction as evidenced by increased left atrium (LA) area (11). The presence of these changes in structure and function was independently associated with an increased risk of morbidity and mortality. (11) This data is similar to other studies that have shown the incidence of diastolic dysfunction in patients with HFPEF is close to 70%. (8,10,12,13,14) Developing a better understanding of diastolic dysfunction will enhance knowledge of best practice regarding pathophysiology and symptoms associated with HFPEF. Diastolic dysfunction is not the only mechanism involved in HFPEF and as we gain more insight into these other mechanisms, new treatments may evolve.

The two main mechanisms involved in diastolic dysfunction are abnormal relaxation and passive stiffness or decreased compliance of the left ventricle (15). Diastolic HF occurs when the ventricular chamber is unable to accept an adequate blood volume during diastole, at normal diastolic pressures, and at volumes sufficient to maintain an appropriate stroke volume. (14) The American College of Cardiology (ACC)/AHA guidelines defines diastole as the phase in the cardiac cycle when the myocardium shortens and returns to an unstressed length and force. Diastolic dysfunction occurs when this process is prolonged, slowed, or incomplete. (5)

Active relaxation requires energy and occurs in a series of energy consuming steps. (15) It begins at the end of systole with closure of the aortic valve and occurs

during a process referred to as isovolumetric relaxation and early ventricular filling. (15) One of the mechanisms necessary for relaxation to occur is the sarcoplasmic reticulum calcium ATP-ase (SERCA) pump, which removes calcium from the cytosol. (15,16) Decreased levels or activity of SERCA can decrease the removal of calcium from the cytosol, which impairs relaxation of the ventricles. Several factors can affect the SERCA pump. Some of these factors include ischemia, LVH, aortic stenosis, advanced age, and hypothyroidism. (16) Ischemia decreases the energy for SERCA to remove calcium. Pathological LVH secondary to hypertension and aortic stenosis also results in decreased SERCA activity. There is a naturally occurring SERCA inhibitory protein called phospholamban and increased levels of this protein impair relaxation. Pathological LVH and hypothyroidism increase the levels of phospholamban. (15,16) The other mechanism present in diastolic dysfunction is passive stiffness. This mechanism returns the myocardium to its resting force and length. It is a passive process and dependent on both intracellular and extracellular structures. (14) This passive stiffness tends to increase with age due to diffuse fibrosis of the myocardium. (16) It also increases in patients with focal scar or aneurysms following a MI. (16) End-diastolic pressures are higher and the end-diastolic volume is lower when passive stiffness is present. (15) As a result of this increase in passive stiffness, the normal diastolic pressure-volume relationship is affected. The diastolic pressure-volume relationship shifts upward and to the left, indicating a disproportionate and a greater increase in diastolic pressure for any increase in diastolic volume. (17) If there is also a decrease in end-diastolic volume, then a decrease in stroke volume occurs. (17) This process often contributes to elevated filling pressures leading to dyspnea both at rest and with exercise. In contrast, in those patients with HFREF the diastolic pressure-volume line shifts downward and rightward indicating decreased contractile function. (17) This downward shift in the pressure-volume curve allows greater changes in volume before intraventricular pressures rise. With diastolic dysfunction, the only abnormality in the pressure-volume relationship occurs during diastole. In those individuals with HFREF, there are abnormalities in the pressure-volume relationships during systole that include decreased EF, stroke volume and stroke work. (14) In addition, there are changes in the diastolic portion of the pressure-volume relationship. These changes result in increased diastolic pressure in symptomatic patients, which indicates the presence of combined systolic and diastolic HF. (14) Patients with HFREF and increased diastolic pressures have a combined systolic and diastolic HF. (14)

Hypertension is believed to be the initial point for many of the cardiovascular changes that lead to HF with or without preserved EF. Hypertension was present in 55-86% of patients in epidemiologic trials and 60-88% of patients in HFPEF clinical trials. (18) Prolonged hypertension causes LVH, a decrease in renal function, and vascular changes. (18) All of these factors combined impair microvascular function and cause silent ischemia, even with normal coronary arteries. This increased pressure acts mainly on capillaries and small resistance coronary vessels, disrupting autoregulation and vasodilation. (16, 18, 19) This eventually leads to organ remodeling, myocardial fibrosis, myocyte hypertrophy, apoptosis, necrosis, and LV mass increase leading to either HFPEF or HFREF. (18, 19) Hypertension is the strongest population-attributable risk factor for new-onset HF. After adjusting for age and other HF risk factors, the risk of developing

HF was approximately two-fold higher in hypertensive men and threefold higher in hypertensive women than in normotensive subjects. (19)

The stimulation of the Renin-Angiotensin-Aldosterone System (RAAS) is also present in individuals with hypertension. Angiotensin II and aldosterone both contribute to myocardial fibrosis leading to LVH. RAAS inhibition reduces extracellular matrix deposition, myocyte hypertrophy, cardiac inflammation and endothelial damage. (18) However, clinical trials studying the effects of RAAS inhibition in HFPEF have not proven very effective. It is possible that inhibition of the RAAS is not an appropriate target for individuals with HFPEF and diastolic dysfunction.

There are several other mechanisms likely responsible in the development of diastolic dysfunction. These other mechanisms include extracellular matrix alterations (fibrosis), cardiomyocyte abnormalities, endothelial dysfunction and inflammation. (18) Most of these mechanisms appear to be exacerbated by hypertension and are under further investigation as causes of HFPEF. There is hope that looking for biomarkers that indicate fibrosis or inflammation may be helpful in the diagnosis and treatment of HFPEF in the future. (20) There is also new evidence that individuals with HFPEF have chronotropic incompetence, which contributes to shortness of breath (SOB) during exercise. Rate adaptive atrial pacing is being evaluated to try to improve exercise capacity in patients with HFPEF. (18,20) Pulmonary hypertension occurs in about 80% of patients with HFPEF and studies are underway to evaluate the effectiveness of medications like sildenafil. (18) However, it is still unclear why some patients predominantly develop diastolic dysfunction in response to long-standing arterial hypertension while others respond with increased LV volumes and a decrease in EF. Is it possible that these individuals with HFPEF are somehow protected from dilation and remodeling and does gender, hypertrophy, or diabetes play a critical role in modifying the disease of HF? There is also some belief that diastolic dysfunction may proceed to systolic dysfunction over time and that both entities are the extreme manifestations of one syndrome. (21) Adding even more to the mystery of HFPEF are those individuals who have evidence of diastolic dysfunction on Echo but have no clinical symptoms of HF. It is also believed that some degree of diastolic dysfunction is a part of the normal aging process and is not always accompanied by the clinical syndrome of HF. (16)

The usual diagnostic tool for diagnosing diastolic dysfunction is a 2 D Echo with Doppler. The person with diastolic dysfunction has LVH, increased wall thickness, and a high ratio of mass to volume. They have normal or near-normal end-diastolic volumes and a high ratio of wall thickness to chamber radius. (19,22) In diastolic dysfunction, LVH is usually concentric and the myocytes exhibit an increased diameter, presenting as wider and thicker. They also have an increase in collagen content and increased continuity of the fibrillar components of the extracellular matrix. (19,22). In contrast, those individuals with HFREF have an increase in end-diastolic volume, little increase in wall thickness, and a substantial decrease in the ratio of mass to volume and thickness radius. (19 22) The myocytes in HFREF exhibit eccentric remodeling and appear elongated in appearance. There is also degradation and disruption of the fibrillar collagen. (19,22) Individuals with diastolic dysfunction also have enlarged left atriums

and this is one of the key Echocardiographic findings in diastolic dysfunction along with LVH. (22)

Another method commonly used to describe diastolic dysfunction through Echo is the E to A ratio. Diastole is an active energy-requiring process in which the heart relaxes immediately after contraction, vigorously filling the ventricular cavity with blood. (16) There are four phases of diastole. The first phase is isovolumetric relaxation and occurs as calcium is sequestered into the SERCA pump deactivating the actin--myosin bridges. (17) This produces a suction effect that facilitates early ventricular filling. This phase begins with closure of the aortic valve and lasts until the mitral valve opens. As discussed previously, this phase can be affected by ischemia, as less energy is available to run the SERCA pump. The second phase begins with the opening of the mitral valve and passive ventricular filling begins. Filling is dependent on the pressure gradient between the left atrium and the left ventricle as well as the viscoelastic properties of the myocardium. (17) Factors that affect this process are chronic hypertension leading to LVH and fibrosis. The third phase is referred to as diastasis and is a period of low flow across the mitral valve. This occurs as the pressure between the left atrium and left ventricle equalizes. The fourth phase begins with atrial contraction, which creates an active pressure gradient between the left atrium and left ventricle again and facilitates further filling of the left ventricle. (17) The E wave indicates the velocity of blood flow during early diastolic filling across the mitral valve in phase two. The A wave indicates atrial contraction in phase four and represents late ventricular filling. These two velocities are measured and an E/A ratio are calculated. A normal E to A ratio is 1.5 with the E wave normally being larger. In early diastolic dysfunction, this relationship reverses, as the ventricle takes longer to relax because of the passive stiffness. The E to A ratio becomes less than one. (16, 17) Often times this is referred to as E to A reversal on an Echo report. As diastolic dysfunction worsens and LV compliance is reduced, the LA pressure increases and restores the LA-LV pressure gradient to its normal range. (16,17) This paradoxical normalization of the E/A ratio is referred to as pseudonormalization. Even though the pressure gradient has returned to normal both the pressures in the LA and LV are higher than normal and therefore creates a tall but more narrow E wave. (16,17) In those individuals with severe diastolic dysfunction the LA fails and LV filling occurs primarily in early diastole. The LA produces low-velocity A waves creating an E/A ratio greater than 2.0. This is referred to as a restrictive pattern and indicates a worsening prognosis. (16) There are several factors however, that can affect the E and A wave velocities including blood volume, mitral valve function and anatomy, and atrial fibrillation. (17)

The increased ventricular stiffness seen in diastolic HF causes these patients to be very vulnerable to the development of pulmonary edema. These individuals tend to decompensate very quickly and often present with symptoms of pulmonary edema. Increased stiffness of the LV dictates the association of very small changes in volume with large changes in LV diastolic pressure. Pulmonary edema is the direct consequence of increased passive chamber stiffness; the ventricle is unable to accept venous return adequately without high diastolic pressures; forcing the blood back into the pulmonary vessels. (11) This helps explain why these patients are so vulnerable to small changes in

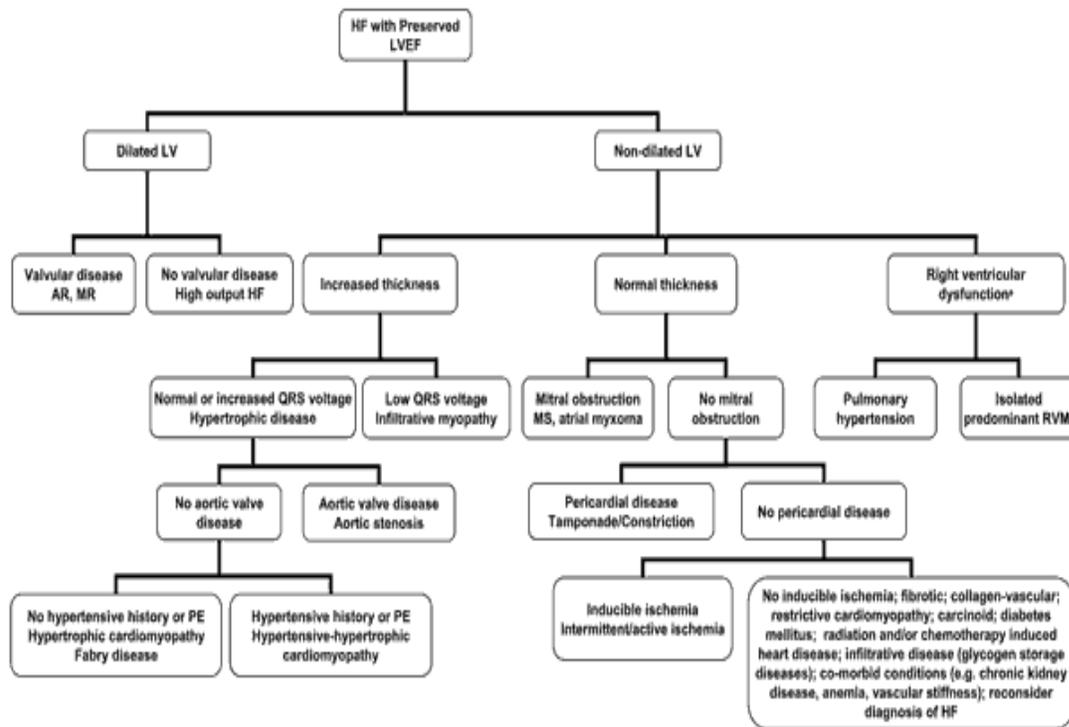
fluid balance and why they are more susceptible to hypertensive crisis. Because of this lack of ventricular compliance, these individuals are more likely to have serious consequences when they are nonadherent with medications or sodium restrictions. This ventricular stiffening also makes them more vulnerable to dramatic shifts in blood pressure (BP) with vasodilation and vasoconstriction. This may make these individuals prone to hypotension with overly aggressive diuresis or vasodilation (18)

Another common manifestation of HFPEF that occurs because of diastolic dysfunction is decreased exercise tolerance. With diastolic dysfunction, the ability to use the Frank-Starling mechanism is limited because diastolic stiffness prevents the increase in LV end-diastolic volume that normally accompanies exercise. (23) The stroke volume fails to rise, and patients experience dyspnea and fatigue. There is also an exaggerated rise in BP in response to exercise that increases LV load and in turn further impairs myocardial relaxation and filling. (23) Tachycardia and increased venous return produce a sharp rise in ventricular filling pressures, which also contributes to increased symptoms. (24) Even though these individuals have a normal EF, they still have a decrease in cardiac output with exercise. The capacity to augment cardiac output during exercise is limited making them very susceptible to exercise induced dyspnea. Two of these reasons include; increased left ventricular diastolic and pulmonary venous pressure causing a reduction in lung compliance, thus increasing the work of breathing; and an inadequate cardiac output during exercise leading to fatigue of the legs and of the accessory muscles of respiration. (17)

These patients with diastolic dysfunction are also at an increased risk for atrial fibrillation. As the end-diastolic pressures raise, this causes the atrium to distend and increases the stress on the left atrium, which may lead to atrial fibrillation. (25) What further complicates this process is that these patients are very vulnerable to tachycardia, which may occur with atrial fibrillation. Tachycardia decreases LV filling and coronary perfusion times, increases myocardial oxygen consumption, and causes incomplete relaxation, thus worsening HFPEF. (25) Atrial fibrillation also worsens diastolic dysfunction due to the loss of the atrial kick. Maurer et al (26) list three features common in all patients with HFNEF: high resting LV end-diastolic pressure, reduced exercise capacity, and propensity for pulmonary edema.

The diagnosis of HFPEF is usually made in the individual with clinical symptoms of HF and preserved EF which is defined as an EF > 40%, 45%, or 50%. According to the ACC/AHA guidelines, a definitive diagnosis is made when the rate of ventricular relaxation is slowed. This physiological abnormality is characteristically associated with the finding of an elevated LV filling pressure in a patient with normal LV volumes and contractility and the absence of valvular heart disease. (5) The HFSA guidelines define HFPEF in a similar manner with a potential presentation of LVH and concentric remodeling as a part of the diagnosis. (6) The most common causes of diastolic dysfunction in the individual with HFPEF are hypertension, diabetes, ischemia, and aging. Other less common causes of diastolic dysfunction need to be ruled out. Some of these causes include infiltrative diseases such as amyloidosis and sarcoidosis, non-infiltrative diseases such as idiopathic and hypertrophic cardiomyopathies, and

pericardial disorders such constrictive pericarditis or pericardial effusion (5,6). The HFSA guidelines have an algorithm for the diagnosis of HFPEF. (6)



LVEF = left ventricular ejection fraction; HF = heart failure;
 QRS = electrocardiographic ventricular depolarization; AR = aortic Regurgitation; MR = mitral regurgitation; MS = mitral stenosis;
 RVMI = right ventricular myocardial infarction; PE = pulmonary embolism

*Some patients with right ventricular dysfunction have LV dysfunction due to ventricular interaction

Currently there is limited data on effective treatments for those individuals with HFPEF. There have been three clinical trials examining the role of ACEI/ARB in treating HFPEF. The Perindopril in Elderly People with Chronic Heart Failure study (PEP-CHF) was a randomized, double-blind, international, multicenter trial that compared perindopril (target dose of 4mg) to placebo in patients 70 years of age or older who had evidence of clinical HF with relatively preserved EF ($\geq 40\%$) and echocardiographic evidence of diastolic dysfunction. The study randomized 850 patients and the mean follow-up was 26 months. The primary end point was the composite of all-cause mortality or unplanned HF-related hospitalization. The primary end point did not vary in the two groups.(27) Perindopril did improve the secondary end points of 6-minute walk distance and New York Heart Association (NHYA) class. (27)

A second trial that included patients with HFPEF was the CHARM-Preserved trial. This trial was a multicenter, double-blind international trial examining the role of Candesartan (target dose 32 mg) in HFPEF. The investigators randomly assigned 3023

patients to either Candesartan 32mg daily or a placebo. Patients were followed for a mean of 36 months. The primary endpoints were CV death or admission to the hospital for HF. The results of the study showed that there was no difference in mortality between the two groups but there was a modest (14%) decrease in HF hospitalizations. (9) The investigators also examined nonfatal MI and stroke, both of which were similar between the two groups. (9)

A third completed trial examining the treatment of HFPEF is the Irbesartan in Patients with HF and Preserved EF (I-PRESERVE). This randomized, placebo-controlled trial enrolled 4128 patients aged ≥ 60 , in New York Heart Association Class II-IV, with an EF $\geq 45\%$. The trial compared the effects of Irbesartan 300mg with placebo. The participants were followed for a median of 49.5 months. The primary endpoints were all-cause mortality or protocol specific cardiovascular hospitalizations for nonfatal MI, stroke, worsening HF, unstable angina, or dysrhythmia. Secondary outcomes were the components of the primary outcome, a composite HF outcome, a change in the total score on the Minnesota Living with HF scale at 6 months, a change in the plasma level of NT-proBNP at 6 months, a composite vascular-event outcome and death from Cardiovascular (CV) causes. (28) There were no significant differences in the primary endpoints between the two groups of subjects. (28) The study also found no treatment benefit in any group and no significant difference in secondary endpoints such as CV death, HF death/HF hospitalizations, six-minute walk test, NT-pro-BNP, and quality of life. (28) It is important to mention that in this trial a high percentage of participants were already receiving ACEIs and spironolactone. The authors speculated that the treatment of a large proportion of patients with multiple inhibitors of the RAAS might have left little room for further benefit from the addition of an angiotensin-receptor blocker. (28) The results of these trials are disappointing and leave more speculation as to the exact etiology of HFPEF. It is possible that HFPEF does not appear to involve neurohormonal activation as a critical pathophysiologic mechanism in the same way that HFREF does.

Two other trials are currently in process to examine medications to treat HFPEF. Treatment of Preserved Cardiac function heart failure with an Aldosterone antagonist TOPCAT is studying the effects of spironolactone versus placebo in patients with HFPEF. The Evaluating the Effectiveness of Sildenafil at Improving Health Outcomes and Exercise Ability in People with Diastolic Heart Failure (RELAX) study is examining the benefit of the phosphodiesterase-5 inhibitors sildenafil. It will be interesting to learn the results of these two trials.

Unfortunately, there is very little research to support specific medications or therapies in the treatment of HFPEF. The ACC/AHA guidelines suggest that without clinical trials for guidance, treating HFPEF should be based on the control of physiological factors such as blood pressure, heart rate, blood volume, and myocardial ischemia, all of which are known to affect ventricular relaxation (5)

ACC/AHA Recommendations include the following:

Class I recommendations

1. Control of systolic and diastolic BP in accordance with published guidelines
2. Control of ventricular rate if in atrial fibrillation
3. Use of diuretics to control pulmonary congestion and peripheral edema.

Class IIa recommendations

1. Coronary revascularization in whom symptomatic or demonstrable myocardial ischemia is judge to be having an adverse effect on cardiac function

Class IIb recommendations

1. Restoration of sinus rhythm in patients with atrial fibrillation
2. Use of ACEIs, ARBs, beta blockers, or calcium channel blockers in patients with controlled hypertension
3. Usefulness of digoxin to minimize the symptoms of HFPEF is not well established.

HFSA Guidelines include the following: (6)

1. Careful attention to differential diagnosis to distinguish among a variety of cardiac disorders, because treatments may differ.
2. Evaluation for ischemic heart disease and inducible myocardial ischemia.
3. Blood pressure monitoring
4. Counseling on the use of a low-sodium diet
5. Diuretic use in those patients with clinical evidence of volume overload; using either a thiazide or loop diuretic. Excessive diuresis, which may lead to orthostatic changes in blood pressure and worsening renal function, should be avoided
6. In the absence of other specific indications for these drugs, ARBs or ACE inhibitors may be considered
7. ACE inhibitors should be considered in all patients with HFPEF who have symptomatic atherosclerotic CV disease or diabetes and one additional risk factor. In patients who meet these criteria but are intolerant to ACE inhibitors, ARBS should be considered.
8. Beta blocker treatment is recommended in patients with HFPEF who have prior MI, hypertension, or atrial fibrillation requiring control of ventricular rate.
9. Calcium channel blockers should be considered in patients with HFPEF who have atrial fibrillation requiring control of ventricular rate and intolerance to beta blockers. In those patients, diltiazem or verapamil should be considered, CCBs should also be considered for those with symptom-limiting angina, and hypertension
10. Measures to restore and maintain sinus rhythm may be considered in patients who have symptomatic atrial flutter-fibrillation.

Even though there are not definitive therapies, from clinical trials supporting the use of specific medications in the treatment of HFPEF, there are strong recommendations from the ACC/AHA and HFSA to treat the comorbidities most commonly associated with HFPEF. These comorbidites include hypertension, diabetes, CAD, atrial fibrillation,

and chronic kidney disease. Clinical practice guidelines based on randomized controlled trials do exist and provide evidence for preventing and treating these comorbidities. As one author stated, "the message is clear: treat now by treating comorbidities; even though it is important to continue to search for specific treatments for HFPEF we should not hesitate to treat what we know". (29)

The importance of good BP management is essential in treating individuals with HFPEF. The selection of antihypertensive medications should be based on current guidelines and tailored to each individual's comorbid conditions. The RAAS is involved in many processes associated with HF, such as hypertension, LVH, myocardial fibrosis, and vascular dysfunction. Using ACEIs or ARBs seems to be a very logical choice for treating patients with HFPEF who have hypertension and other comorbidities such as CAD and Diabetes. The use of aldosterone blockers may be useful for those with hypertension or following a MI. Whether beta blockers have a beneficial effect in HFPEF has yet to be studied. Again, using them in patients who have another indication seems important and beta blockers should be used in persons who have a history of a myocardial infarction or for rate control in atrial fibrillation. With the emerging data on chronotropic incompetence in diastolic dysfunction the use of beta blockers or non-dihydropyridine calcium channel blockers may not be the best choice unless they have other indications for their use such as rate control in those individuals with atrial fibrillation. The dihydropyridine calcium channel blockers may be useful in those individuals with hypertension or angina. Currently however, there are no studies examining the effects of calcium channel blockers for those individuals with HFPEF. Diuretics should be used when volume overload is an issue. However, it is important to avoid dehydration since these individuals are vulnerable to hypotension associated with volume depletion.

An important aspect of BP management is education regarding lifestyle changes. Encouraging daily exercise, weight loss, and restricting sodium intake to 2000mg or less per day are some lifestyle changes that can assist in lowering BP. Education regarding medication adherence should also be stressed. In practice with patients emphasize how vulnerable they are to volume overload and try to explain the correlation between sodium intake and volume overload. A retrospective study to determine whether controlling Systolic Blood Pressure (SBP), pulse pressure, and heart rate in the outpatient setting would result in decreased hospital utilization in patients with HFPEF was conducted. The authors reviewed 140 charts and found that those patients with a SBP < 140, pulse pressure < 65, and heart rate between 55-70 eighty percent of the time had a significant decrease in hospital utilization than those individuals who did not meet the above parameters. (30) The study also found that when outpatient clinic visits were missed there was a significant increase in hospital utilization. Even though the study had several limitations, it showed the importance of BP and heart rate control in those patients with HFPEF.

Diabetes is another very significant comorbidity in individuals with HFPEF. It is very important to assist and encourage these individuals to control their diabetes. Nurses can play an important role in assessing what these individuals know about their diabetes

and give them information on tools and resources for better diabetes management. Another important comorbidity that should be addressed in individuals with HFPEF is sleep disordered breathing. With the noted link between sleep disordered breathing and hypertension, diabetes, and obesity these individuals should be screened. Nurses can also play a very important role in helping these individuals improve their adherence in the treatment of sleep disordered breathing.

Exercise training may also improve symptoms in patients with HFPEF and could be beneficial in terms of functional capacity, weight loss, and treating comorbid conditions such as hypertension and diabetes. There have not been any large-scale trials evaluating the benefits of exercise in individuals with HFPEF, but there have been some smaller studies showing the benefit of exercise. In a study by Grewal et al (31), they found that diastolic dysfunction was strongly and inversely associated with exercise capacity in a group of patients with HFPEF and no signs of ischemia. Takemoto et al (32) compared exercise-trained athletes with matched sedentary individuals, found that echocardiographic indices of diastolic function were significantly different between the two groups, and suggested that LV diastolic dysfunction associated with aging is less pronounced in exercise-trained individuals. In one evaluation of exercise, elderly women with NHHA class II or III and an EF greater than 45% were randomized to a 12-week home-based exercise program or no intervention. Women assigned to the exercise program had significant improvement in the 6-minute walk test and in quality of life as measured by the Living with Heart Failure Questionnaire and the Geriatric Depression Scale. (33) Additional research is needed in this area as well.

In summary, at least half of patients with HF have a normal EF. They are likely to be older, more likely to be female, and usually have a significant history of hypertension and other comorbidities such as atrial fibrillation and diabetes. These individuals have similar clinical symptoms and morbidity as those patients with HFREF. They have poor exercise tolerance, which affects their ability to perform usual activities and affects quality of life. These patients are also at increased risk for pulmonary edema and very sensitive to changes in their volume status. Very little research guides the most effective way to treat HFPEF so treatments are aimed at controlling the contributing factors like hypertension, Diabetes, and ischemia. As investigators continue to study the pathophysiology of HFPEF, understanding of this process will hopefully improve and provide focused direction of how to treat this type of HF with the development of new clinical practice guidelines. As our population continues to age, it is likely the numbers of patients with HFPEF will continue to increase. Nurse can play a significant role in helping these patients manage their chronic condition and assist them in understanding the disease itself and making the lifestyle changes necessary to manage HFPEF.

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