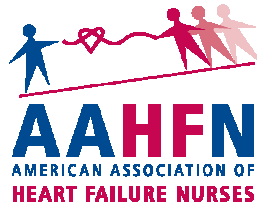


Heart Failure with a Normal Ejection Fraction



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Introduction

Heart Failure (HF) is a growing epidemic in the United States. It is estimated that at least five million individuals currently are diagnosed with HF and over 550,000 new diagnoses will be made each year. (1) It is the number one cause of hospital admissions in individuals over the age of 65. (1) The type of HF that is most familiar is systolic HF (SHF), which occurs when the left ventricle is dilated and enlarged with poor systolic function. In this type of HF the ejection fraction (EF) is usually defined as less than 40%. However, in recent years it has been discovered that about 50% of the patients who have clinical symptoms of HF actually have a normal or preserved ejection fraction. This is usually defined as an EF equal to or greater than 50%, although some studies have used 40% or 45% as the cut off. 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) This has helped to spur the interest in describing the pathophysiology and the best treatment for individuals with this type of HF. As nurses caring for patients with HF it becomes clear that nursing must also develop an understanding of the prevalent clinical characteristics, pathophysiology, and treatment of HF with a normal ejection fraction (HFNEF). The purpose of this article is to examine all four of these concepts as they relate to HFNEF.

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 began to study the pathophysiology of HF with a normal ejection fraction (HFNEF) in more depth it became less clear whether everyone who has HFNEF actually has diastolic dysfunction. Therefore, the name diastolic HF has been changed to HFNEF or HF with preserved LV function. Brutsaert explains that the term diastolic heart failure (DHF) implies precise understanding of the mechanisms that would apply to all patients with HFNEF. (4) However, he believes this pathophysiology is not completely understood nor is it clear that all patients have the same disease. If it continues to be referred to as DHF then perhaps some important discoveries may be missed regarding the treatment of this disease. (4)

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Description

The Heart Failure Society of America (HFSA) published guidelines for the treatment of HF in 2006. HFNEF is described as a clinical syndrome with numerous possible causative or comorbid conditions.(5) The left ventricle is characterized by hypertrophy, increased extracellular matrix, and abnormal calcium handling with delayed relaxation. They also state that the diagnosis of HFNEF can be made when there is a combination of clinical symptoms of HF and the findings of preserved or relatively preserved LVEF using an imaging method.(5) A similar definition is found in the 2005 ACC/AHA practice guidelines. These guidelines state that HFNEF is typically diagnosed in a patient who has the usual clinical signs and symptoms of HF and is shown to have a normal LVEF and no valvular abnormalities on echocardiography. (6)

Prevalence

One study that reported the high prevalence of HFNEF was a retrospective analysis done over a 15 year time 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 analysis showed that the prevalence of HFNEF 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 HFNEF were older, more likely to be a female, had a higher mean body-mass index, were more likely to be obese, and had lower than normal Hemoglobin levels. The patients in this study also had a higher incidence of hypertension and atrial fibrillation but had less Coronary Artery Disease (CAD) and valvular disease. The study also found that the prevalence of HFNEF increased over time. In the first 5 years 38% of the patient admissions had HFNEF, the second five years the percentage increased to 47%, and the last five years the percentage increased to 54%. It was found that survival rates for those individuals with HFNEF were slightly higher than those with reduced EF. In addition, the survival rates increased over the 15 years for those patients with reduced EF but did not improve for those with HFNEF. A second study was conducted using Olmsted County residents who had incident or prevalent HF to determine EF measurement, diastolic function and BNP in community residents with HF. This was a prospective study in which patients were enrolled over a two-year time frame. There were 556 total patients with 55% of them having HFNEF. (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 HFNEF. In the OPTIMIZE-HF registry 51% of the 41,000 patients had an EF greater than 40%. In both sets of data the patients with HFNEF were older, with an average age of 73.9 and 75.1 respectively. There was also a higher percentage of women with HFNEF in both registries, and a lower percentage of African Americans. In both registries the incidence of Coronary Artery Disease or previous history of Myocardial Infarction was less in those patients with HFNEF. Hypertension or a history of hypertension was significantly higher in

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both groups who had HFNEF. (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 HFNEF. (2) Also IV agents including vasodilators, nesiritide, and inotropes were used less frequently. At discharge the use of other standard HF medications was less except for the use of diuretics. Presentation characteristics and LOS were the same for both groups of Left Ventricular Systolic Dysfunction (LVSD) and HFNEF. In-hospital mortality and ICU management was significantly less in those patients with HFNEF. Similar data was observed in the OPTIMIZE-HF registry with those patients who had HFNEF receiving less standard HF medications, such as ACE inhibitors, aldosterone inhibitors, and beta-blockers, on admission and at discharge. Mortality rates were significantly higher in those hospitalized with LV systolic dysfunction. However, LOS, rehospitalization rates, and unadjusted all-cause mortality at 60 and 90 days were the same between those patients with LVSD and HFNEF.

By looking at this data we can begin to develop a profile of those patients with HFNEF. These individuals will be older, more likely to be women, and have many comorbidities such as hypertension, atrial fibrillation, diabetes, and obesity. It is clear that the morbidity and clinical presentations are very similar to those patients with systolic HF. Armed with all this data nursing must move forward to help determine what the best treatment and care is for these individuals. Unfortunately, the majority of the randomized clinical trials examining the treatment of HF have been aimed at individuals with an abnormal EF, thus excluding those with HFNEF.

Pathophysiology of HFNEF

The pathophysiology of HFNEF is currently evolving as scientists and cardiologists attempt to answer the question of what exactly causes HF with a normal EF. The main question is whether or not all patients with HFNEF (excluding those with valvular disease) truly have diastolic dysfunction or whether there are other mechanisms causing the symptoms of HF. There are some individuals who have the clinical symptoms of HF but don't seem to have any underlying myocardial disorder. At the opposite end are a few cases in which diastolic dysfunction is the known cause of the symptoms, such as restrictive cardiomyopathy, hypertrophic cardiomyopathy and the infiltrating cardiomyopathies such as amyloidosis. (6) There are a few studies that explored the pathophysiology in patients with HFNEF. In these studies the majority of subjects had some degree of diastolic dysfunction. (8, 9,10) After reviewing these studies it seems that diastolic dysfunction is indeed present in most patients with HFNEF and until there is definite evidence to prove otherwise it is important for nurses to understand the concept of diastolic dysfunction. Some degree of diastolic dysfunction is present in the majority of patients I see in my clinical setting who are admitted with decompensated HF but have a normal EF.

The two main mechanisms in diastolic dysfunction are abnormal relaxation and passive stiffness (11, 12). Diastolic HF occurs when the ventricular chamber is unable to

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accept an adequate blood volume during diastole, at normal diastolic pressures, and at volumes sufficient to maintain an appropriate stroke volume. The ACC/AHA guidelines define 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. (6)

Active relaxation requires energy and occurs in a series of energy consuming steps. (12) It begins at the end of contraction and occurs during isovolumetric relaxation and early ventricular filling. (12) One of the mechanisms necessary for relaxation to occur is the sarcoplasmic reticulum calcium ATP-ase (SERCA) pump which removes calcium from the cytosol. (12,13) Decreased levels or activity of SERCA can decrease the removal of calcium from the cytosol which impairs relaxation of the ventricles. There are several factors that can affect the SERCA pump. Some of these factors include ischemia, left ventricular hypertrophy (LVH), Aortic Stenosis, advanced age, and hypothyroidism. (13) 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. (12, 13)

The other mechanism present in diastolic dysfunction is passive stiffness. This mechanism returns the myocardium to its resting force and length. End-diastolic pressures are higher and the end-diastolic volume is lower when passive stiffness is present. (12) This stiffness tends to increase with age due to diffuse fibrosis. (11) It is also increased in patients with focal scar or aneurysms following a MI. (11) There is also some thought that the combination of LVH and high diastolic ventricular pressure may 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. (13)

The usual diagnostic tool for diagnosing diastolic dysfunction is an Echo. The patient with diastolic dysfunction tends to have increased mass of the left ventricle along with elevated LV end-diastolic pressure. In diastolic dysfunction the LVH that is present is usually concentric whereas in systolic HF the LVH tends to be eccentric. (14) Another method used to determine diastolic dysfunction is the E to A ratio. The E wave indicates the velocity of blood flow during early diastolic filling across the mitral valve. The A wave indicates atrial contraction. A normal E to A ratio is 1.5 with the E wave 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 1 in early diastolic dysfunction. (15) Often times this is referred to as E to A reversal on an Echo report. As diastolic dysfunction worsens and LV filling pressures rise, LV filling occurs primarily during early diastole because the pressure at end-diastole is so high that atrial contraction contributes to less LV filling than normal. (15) In this case, the E to A ratio rises above two. This is referred to as a restrictive pattern and usually indicates a poor prognosis. The

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patient with diastolic dysfunction often has a dilated left atrium as well due to the high end-diastolic pressures. In a presentation given by Dr. Zile at HFSA in 2006 he described the changes associated with diastolic dysfunction as changes in mass without changes in volume. He demonstrated this through a picture of the myocyte in diastolic dysfunction. The myocyte in diastolic dysfunction is much wider and thicker as a result of the hypertrophy. He also stressed the importance at looking at the left atrium and stated that the size of the left atrium is the Hgb A1C of diastolic dysfunction.

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. (9) This helps explain why these patients are so vulnerable to small changes in fluid balance.

A second explanation of this is also very descriptive of what happens when diastolic dysfunction is present. As a result of decreased relaxation and increased stiffness the curve for LVDP in relation to volume is shifted upward and to the left, chamber compliance is reduced, the time of filling is altered, and the diastolic pressure is elevated. (16) Under these circumstances, a relatively small increase in central blood volume or an increase in venous tone, arterial stiffness, or both can cause a substantial increase in left atrial and pulmonary venous pressures which may result in pulmonary edema. (16)

Another common manifestation of HFNEF that occurs as a result 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. (17) During exercise diastolic pressure increases. 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. (17) 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 for two reasons. The first reason is related to the increased left ventricular diastolic and pulmonary venous pressure, which cause a reduction in lung compliance, thus increasing the work of breathing. (16) The second reason for the exercise intolerance is an inadequate cardiac output during exercise, which can lead to fatigue of the legs and of the accessory muscles of respiration. (16) In my clinical practice I find this to be a common finding among those patients with HFNEF.

There is also some thought now that LVH is associated with the activation of the renin-angiotensin-aldosterone system (RAAS) which causes sodium and water retention. (13) It is also thought that the RAAS increases collagen and is therefore associated with increased ventricular stiffness. (17) It becomes clear after reading about the

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pathophysiology of HFNEF that health care professionals must do a better job of treating and managing hypertension. It seems that many of the factors that affect myocardial relaxation and passive stiffness are made worse by hypertension. Hypertension causes LVH and increased connective tissue content both of which decrease cardiac compliance. As the ventricle thickens the blood flow can't keep up since there's no increase in blood vessels, which leads to fibrosis. Myocyte hypertrophy increases interstitium and cellular matrix which also leads to fibrosis. It seems we are again faced with a vicious circle of events, similar to what we see in individuals with SHF.

These patients with diastolic dysfunction are also at an increased risk for atrial fibrillation. As the end-diastolic pressures increase this causes the atrium to distend and become stressed. (15) This of course may lead to atrial fibrillation. 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. (15) Atrial fibrillation also worsens diastolic dysfunction due to the loss of the atrial kick. Maurer et al (18) list three features common in all patients with HFNEF; these consist of a high resting LV end-diastolic pressure, reduced exercise capacity, and propensity for pulmonary edema.

One final point of interest is that most patients with SHF also have some measure of diastolic dysfunction, often times severe. (8,10,11,14) This leads to several unanswered questions, such as why these patients with HFNEF do not dilate and progress into the so-called remodeling typical of chronic HF. (4) Is it possible that they are somehow protected from dilation and remodeling and does gender, hypertrophy, or diabetes play a critical role in modifying the disease of HF? (4) Another theory proposed by Brutsart, which hasn't been clinically proven, is that subtle systolic dysfunction is not evident by measurement of EF but is sufficient to induce a neurohormonal response, leading to the clinical symptoms of HF. Finally the question is asked whether HFNEF is a stage on the progression to SHF. (4) It is hoped that over the next few years these questions will be answered.

Comparison of SHF and HFNEF

There are several differences and similarities between the two types of HF. The clinical signs and symptoms certainly seem to be similar and it would be difficult to determine which type of HF an individual has just based on their symptoms. It also appears that morbidity is similar between the two types. Mortality rates have varied with the registry data showing lower mortalities in those individuals with HFNEF. (2, 3) However, some of non-registry data shows us that the mortality rates are similar between the two groups. (7, 8) The difference in mortality rates between the two groups is still controversial but we know that mortality rates are higher in both groups compared to controls. (10, 16) The typical patient with HFNEF will be older, more likely a female, and have a history of hypertension, or diabetes when compared to those with SHF. The person with HFNEF is also more likely to present with symptoms of pulmonary edema.

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Kitzman, et al. (19) compared three groups of subjects to see if there were differences between those with LVSD, HFNEF, and age-matched healthy controls. He 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 LVSD. Levels of norepinephrine, BNP, and ANP were significantly elevated compared to the control group. However, ANP and BNP were significantly higher in the LVSD group compared to those with HFNEF. Finally, quality of life scores were lower than controls in both groups. This study helps us to see that patients with HFNEF have similar symptoms and issues as those patients with LVSD. It may also assist us in knowing that the treatment of both types of HF might be very similar.

Treatment of HFNEF

Currently there have been only two randomized clinical trial looking at the treatment of HFNEF. The first trial was the CHARM-Preserved trial. (20) In this trial the investigators randomly assigned 3023 patients to either Candesartan 32mg daily or a placebo. They followed the patients 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. The investigators also examined nonfatal MI and stroke, both of which were similar between the two groups.

The second clinical trial was recently completed in 2008. This trial enrolled 4128 patients aged ≥ 60 , in New York Heart Association Class II-IV, with an EF $> 45\%$. The trial, named the I-PRESERVE trial, compared the effects of Irbesartan 300mg with placebo. (21) 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, HF, unstable angina, or dysrhythmia. There were no significant differences in the primary endpoints between the two groups of subjects. 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. There was a significant difference with the Irbesartan group having serious hyperkalemia. (21) This second study demonstrating the lack of treatment benefit with an ARB is frustrating and leaves continued questions as to the best way to treat patients with HFNEF.

Another clinical trial is the TOPCAT or Treatment of Preserved Cardiac Function HF with an Aldosterone Antagonist. The targeted completion date for this trial is in 2011 and the goal is 4500 patients followed for two years.

Unfortunately, there is very little to go on in determining how to best treat HFNEF. The ACC/AHA guidelines suggest that without clinical trials for guidance, treating HFNEF 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.

Class I recommendations from the ACC/AHA are

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

Class IIa recommendations suggest

1. Coronary revascularization if myocardial ischemia is felt to be contributing to the alterations in cardiac function.

Class IIb suggest

1. restoration of sinus rhythm in patients with atrial fibrillation
2. use of ACEIs, ARBs, beta blockers, or calcium channel blockers to control hypertension
3. usefulness of digoxin to minimize the symptoms of HFNEF is not well established.

The guidelines from the HFSA are very similar, with the exception of adding counseling on a low-sodium diet as one of their recommendations.

In an article by Zile (17) he suggests treating HFNEF using three steps. The first step is to target symptom reduction by decreasing pulmonary venous congestion. This can be done by decreasing left ventricular volume, maintaining synchronous atrial contraction (SR), and increasing the duration of diastole by reducing heart rate. Other treatments that might be effective at decreasing pulmonary venous congestion are diuretics, and sodium and fluid restriction. He also suggests nitrates to decrease central blood volume and finally suggests blunting of neurohormonal activation with the use of ACEIs and ARBs. The second step is to target the pathology that caused the HFNEF by treating hypertension, diabetes, and ischemia. The third step is to target the underlying mechanisms that are altered by the disease process such as exercise intolerance. For this he suggests using beta-blockers, or calcium channel blockers.

Most authors mention ACEIs or ARBs as a good selection for treatment of HFNEF and hypertension, especially in those patients who also have diabetes since both agents have been found to be renal protective, especially ARBs (5, 6, 15, 17, 22). ACEIs are also identified as the preferred agent to use for stroke prevention (23). Beta-blockers are recommended for their benefit of lowering BP and improving exercise tolerance. If the patient has a history of previous MI then the use of a beta-blocker is even more important and highly recommended (5, 6, 15, 17, 22). Calcium channel blockers are used for their effect on lowering blood pressure and improving exercise tolerance (5, 6, 15, 17, 22). Calcium channel blockers may also be used for rate control in atrial fibrillation or in patients experiencing angina. Diuretics are recommended especially when volume overload is present (5, 6, 15, 17, 22).

The importance of good BP management seems essential in treating these individuals. An important aspect of BP management that is often overlooked 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 compliance is also necessary. It is also important for these individuals to monitor their weight daily and report sudden weight gain and other symptoms

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of fluid overload to their physician right away. However, knowing that the majority of these patients are older some of these lifestyle changes can be very difficult. When educating patients with HFNEF an explanation of their vulnerability to fluid volume changes should be included. The consequences of consuming large amounts of sodium and fluids should also be explained and linked to the changes they might see in their fluid volume status and symptoms.

None of the references I reviewed for this article discussed the treatment of diabetes in those individuals with HFNEF. Since this is such a common comorbidity associated with HFNEF I feel it's very important to assist and encourage these individuals to tightly control their diabetes. It should be assessed whether they need further education to manage their diabetes. Another factor that bears mentioning here is sleep disordered breathing. With the link between sleep disordered breathing and hypertension it seems it would be important to assess these individuals for the possibility that they might have sleep disordered breathing.

Summary

In summary, it is known that at least half of our 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 like atrial fibrillation and diabetes. It is also known that they have similar clinical symptoms and morbidity as those patients with LVSD. They have poor exercise tolerance, which affects their ability to do many of their usual activities. They are also at increased risk for pulmonary edema and are very sensitive to changes in their volume status. There appear to be many factors that impair the ability of the ventricle to relax and increase the ventricle's passive stiffness, many of which are chronic. There is very little research out there that tells us the most effective way to treat HFNEF so the treatments we have are aimed at controlling the factors that caused the problem in the first place like hypertension, diabetes, and ischemia. As investigators continue to study the pathophysiology of HFNEF our understanding of this process will hopefully improve and guide us in the right direction of how to treat this type of HF. Hopefully in the future, clinical practice guidelines for treating HFNEF will be developed. As our population continues to age it is likely the numbers of patients with HFNEF will continue to increase. The nurses' role in helping these patients manage this chronic disease is very important, as we assist them in understanding the disease itself and assist them in making the lifestyle changes necessary to manage this disease.

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