Heart Failure with Preserved Ejection Fraction: The New Devil in the Pandemic

Internal Medicine Grand Rounds
UT Southwestern Medical Center

Farhana Kazi, M.D.
Assistant Professor of Medicine
Division of Cardiology

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Introduction and Scope of the Problem

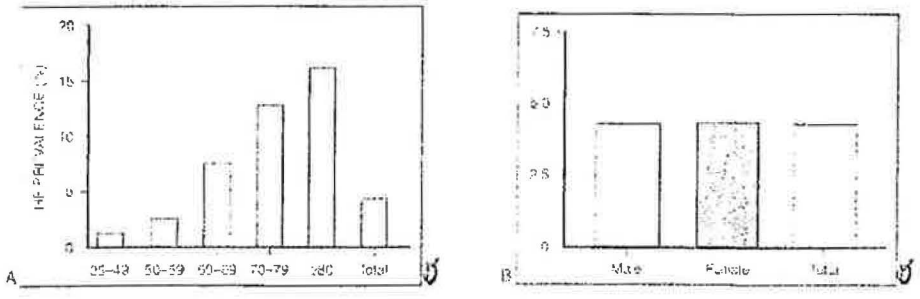
Until the last two decades, the possibility that large numbers of patients with heart failure (HF) might have a normal ejection fraction was not considered. As numerous studies have now demonstrated, heart failure with a normal ejection fraction (HFPEF) is very common, why it was not previously recognized is unclear. It may be that HFPEF was always common but that the cardiology community failed to recognize it. It is also possible that the prevalence of HFPEF has increased over time, leading to more widespread recognition.

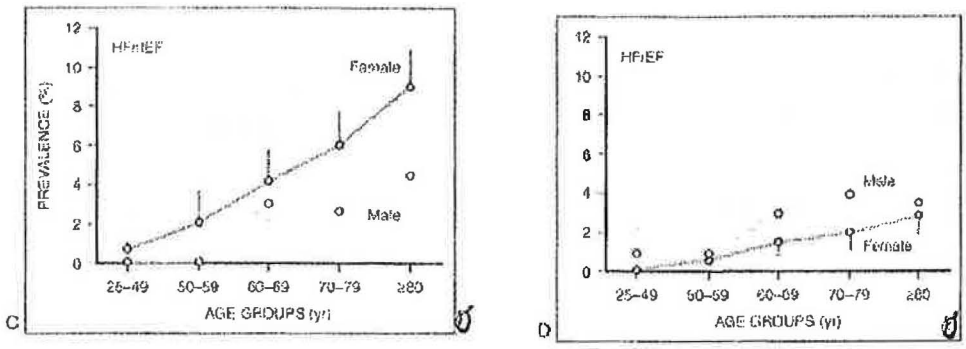
Heart failure is classically considered a syndrome that occurs in the setting of a reduced ejection fraction (systolic dysfunction) and cardiac dilation. Heart failure with preserved ejection fraction (HFPEF), also known as "diastolic heart failure", is a patho-physiologically distinct syndrome from HF with systolic dysfunction. This syndrome is difficult to study, and much debate continues about its etiology, diagnosis, and treatment. This review will describe some of the controversies that remain in our understanding of this highly prevalent and morbid disorder. I want to emphasize that our understanding of this syndrome is incomplete and will continue to evolve as the field advances.

Epidemiology

Currently there are about 6 million Americans with HF, and approximately 550,000 new cases per year.[1] The growing numbers of HF have been described as an "epidemic."[2] Recent data suggest that as many as 50% of patients admitted for HF have normal EF, usually defined as an EF greater than 40-50%.

Thirteen epidemiological studies have defined the prevalence of HFPEF in various HF populations and have documented a prevalence of 50 to 55 percent. Importantly, the prevalence of HFPEF among patients with HF varies dramatically with age and gender.[55] The prevalence of HF increases with age (fig 1-A) and is similar in men and women (fig1-B). The prevalence of HF with a depressed EF increases with age but is more common in men than in women at any age (fig 1-D), whereas the prevalence of HFPEF increases even more dramatically with age (more than HF with a reduced EF) and is much more common in women than in men at any age (fig 1-C). More data are needed concerning variation in the prevalence of HFPEF in different regional and ethnic groups.
Figure 1





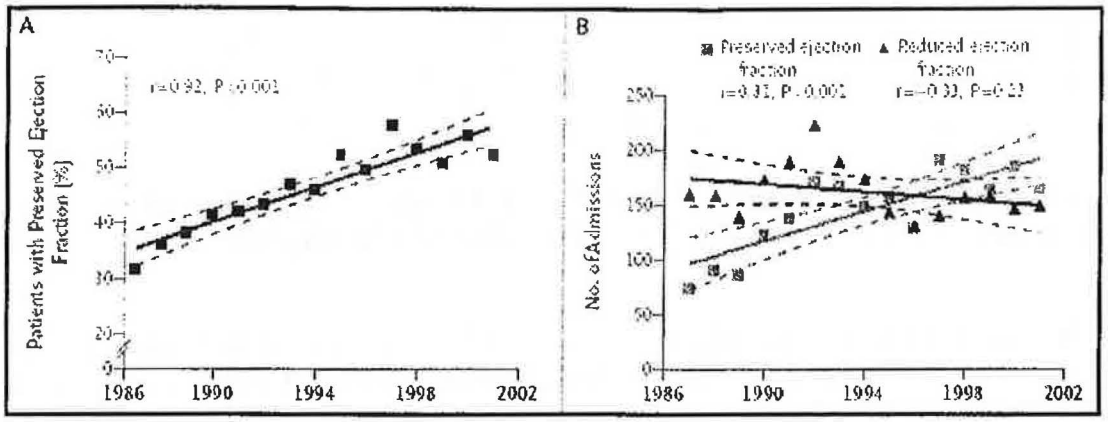
Modified from Ceia F, Fonseca C, Mota T, et al: Prevalence of chronic heart failure in Southwestern Europe: The EPICA study. Eur J Heart Fail 4:531, 2002.

The most recent data on the epidemiology of HFPEF come from the ADHERE registry.[3] In the ADHERE registry, more than 100,000 hospitalizations for HF were analyzed in the United States. Patients with HFPEF were more likely to be women, older, and hypertensive when compared to HF with systolic dysfunction. They were also less likely to have had a prior myocardial infarction (Table 1). The average age range of patients with HFPEF is about 73-79 years old, and 61-76% are women.[4] As mentioned, many patients with HFPEF (> 90% in some studies) have a history of hypertension (HTN). In other studies from Ontario, Canada (the EFFECT dataset)[5] and Olmstead County,[6] similar demographic results were reported. It is important to note that the prevalence of HFPEF is increasing (Figure 2), while the prevalence of HF with systolic dysfunction appears to be constant.

Table 1: Demographic Data from the ADHERE registry of HFPEF [3]

Characteristic	**Preserved EF (n=26,322)**	**Reduced EF (n=25,865)**	**P value**
Age (yrs)	73.9	69.8	< 0.0001
Women (%)	62	40	< 0.0001
African American (%)	17	22	< 0.0001
Hypertension (%)	77	69	< 0.0001
CAD (%)	50	59	< 0.0001
Diabetes (%)	45	40	< 0.0001
Renal Insufficiency (%)	26	26	0.98

Figure 2: Trends in the prevalence of HFPEF. A) Increase in percentage of patients with HFPEF during the time of the study. B) Number of admission for HFPEF increased during the study, while admissions for HF with reduced EF did not change.[6]



Diagnosis

It should be noted that HFPEF and HF with systolic dysfunction are clinically indistinguishable. The history, physical, ECG, and chest X-ray are not usually helpful in differentiating HFPEF and systolic dysfunction.[7] It is not until a symptomatic patient is imaged that it is possible to accurately define the EF (figure 3).

Figure 3

Figure 4. The signs and symptoms of systolic and isolated diastolic heart failure are similar. Patients typically present with exertional dyspnea, paroxysmal nocturnal dyspnea, orthopnea, jugular venous distention, crackles, a displaced apical impulse, and extra heart sounds S_3 and S_4. (Adapted from Echeverria et al, 1983)

Thus, a variety of illnesses can present with the appearance of HFPEF, because diagnosis is made by excluding a reduced EF (i.e. not by ruling in disease). Table 2 lists some of these diseases.

Table 2

Heart Failure with Preserved Ejection Fraction: Differential Diagnosis and Contributing Factors
Restrictive cardiomyopathy
Infiltrative cardiomyopathy (Amyloid, hemochromatosis)
Hypertrophic cardiomyopathy
Hypertensive heart disease
Chronic renal dysfunction
Salt/Water abnormality
Anemia
Obesity
Excessive vasoconstriction
RV Infarct
Primary RV failure
Arrhythmogenic RV dysplasia
ASD
Tamponade
Constrictive pericarditis
Atrial myxoma
Valvular stenosis or regurgitation
*Adapted from Prog CV Dis, 2006,49(3) 2006:182-195 [8]

Brain natriuretic peptide (BNP) levels are also not helpful in determining LV function, although BNP levels typically are slightly less in HFPEF (Figure 2).[9-11]

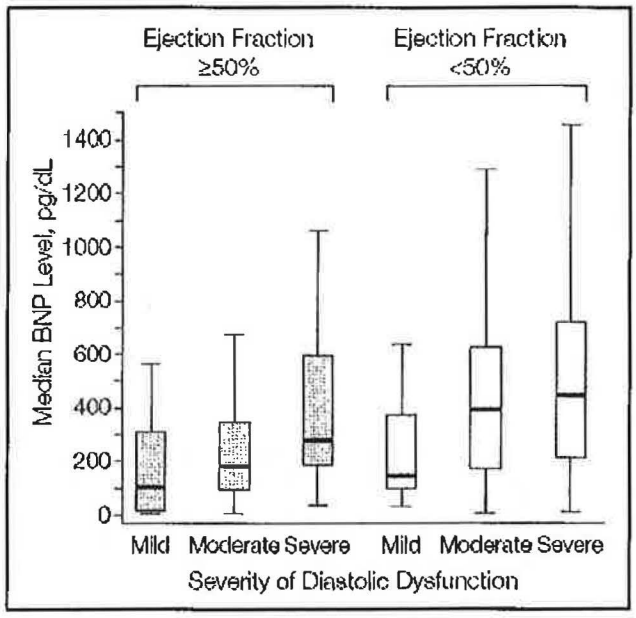


Figure 2: Median brain natriuretic peptide (BNP) levels by EF [10]

Although HFPEF is probably related to a wide variety of problems (i.e. aging, hypertension, diabetes, etc.), the syndrome is usually explained on the basis of a single abnormality: abnormal stiffness and relaxation of the LV, typically related to concentric hypertrophy. This may or may not be true. To explore this dilemma it is important to first describe the diagnostic criteria for HFPEF with regard to relaxation and stiffness.

Several criteria's have been suggested to standardize the diagnosis of HFPEF. Framingham criteria (Table 3) and Boston criteria have been developed to assist with the clinical diagnosis of general HF.[12, 13] These criteria rely on symptoms (orthopnea, dyspnea at rest or with exertion, paroxysmal nocturnal dyspnea) and other clinical criteria (jugular venous distension, rales, S3, hepatojugular reflux, edema, pleural effusion, tachycardia, etc.). The Framingham and Boston criteria are mainly used in HF with systolic dysfunction. For HFPEF, there exist several criteria that build on these scales. The first is the European criteria (Table 4), which is based on "signs and symptoms of HF" (Framingham and Boston), abnormal LV relaxation from echocardiography or catheterization, and normal LV function (defined as EF > 45% and LVEDV < 102 ml/m2).[14] The Vasan and Levy criteria also state that there should be reliable evidence of HF, normal EF (>50% within 72 hours of HF event), and LV diastolic dysfunction (DD).[15] The development of the Zile criteria hypothesized that diastolic dysfunction was not necessary to diagnose HFPEF.[16] In this study, 63/63 patients had evidence of DD. The conclusion was that DD was not necessary to diagnose HFPEF if the patient had evidence of LV hypertrophy. In short, there exists no generally accepted single definition for HFPEF, particularly with regard to EF cutoff and timing of imaging.

Tables 3 and 4: The Framingham Criteria for HF and The European Criteria for HFPEF

Framingham Criteria for Heart Failure
Major Criteria PND or Orthopnea Neck vein distension Rales Cardiomegaly Acute pulmonary edema S3 gallop Increased venous pressure > 16cm of water Circulation time >25s Hepatojugular reflux
Minor Criteria Ankle edema Night cough DOE Hepatomegaly Pleural effusion Vital capacity decrease by 1/3 Tachycardia
Major or Minor Criteria Weight loss >4.5 kg in 5 days in response to treatment

European Criteria for HFPEF
1. Signs and symptoms of CHF: DOE, pulmonary edema, rales, peak VO2 < 25 mL/kg/min
2. Normal or mildly reduced LV function with normal chamber size (EF>45%)
3. Abnormal LV relaxation, filling, diastolic stiffness

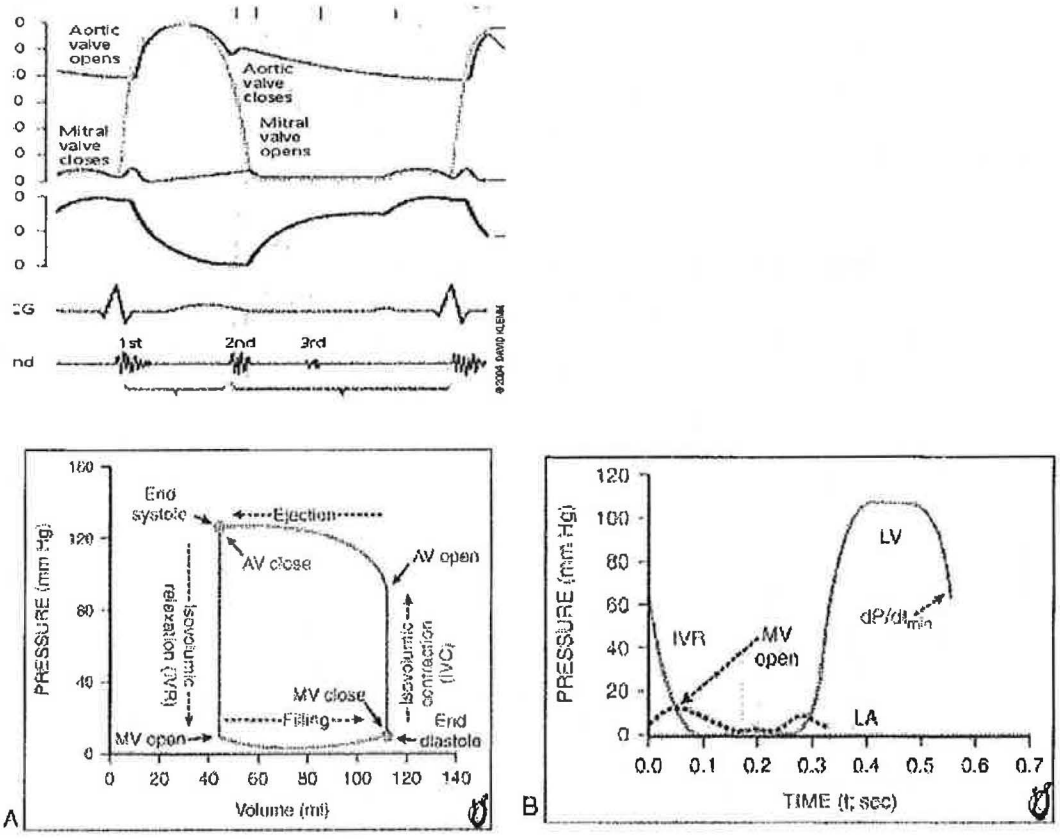
Assessment of Diastolic Function and Dysfunction

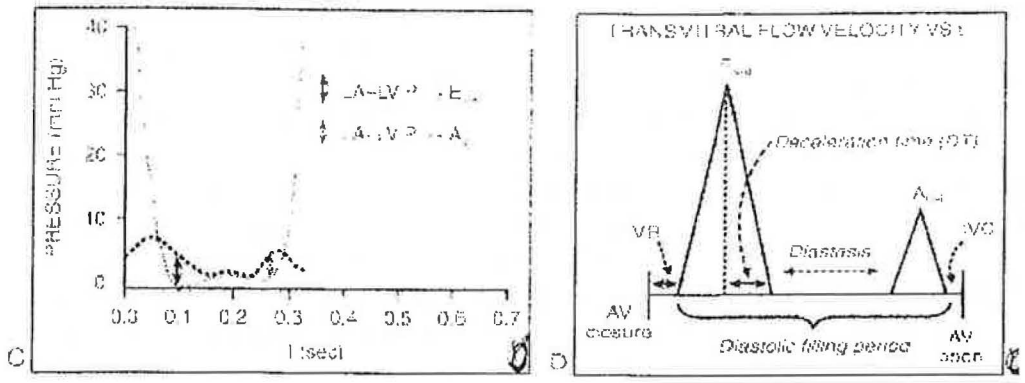
Understanding of the pathophysiologic mechanisms in HFPEF mandates a clear understanding of LV diastolic and systolic function and the manner in which LV

function is influenced by volume status, which together with LV geometry determines preload, and of the arterial system, which together with LV geometry affects afterload. Although abnormal diastolic function has long been hypothesized to be the primary factor responsible for hemodynamic perturbations and symptoms in HFPEF, only recently have studies proved this hypothesis by studying diastolic function in patients with HFPEF and relevant control populations (see later). Because LV structure and function are altered by age, gender, and cardiovascular disease in the absence of HF, it is important to understand how LV structure and function differ between persons with HFPEF and elderly persons with cardiovascular disease but no HF. Whereas abnormal diastolic function plays a key role in HFPEF, other mechanisms also contribute to the pathophysiologic process in many patients.

Let us now define diastolic dysfunction, a key point in understanding much of the data in HFPEF. Diastole is conventionally described by four phases: isovolumic relaxation, rapid filling, diastasis, and atrial systole (late diastolic filling) as seen in Figure 3

Figure 3

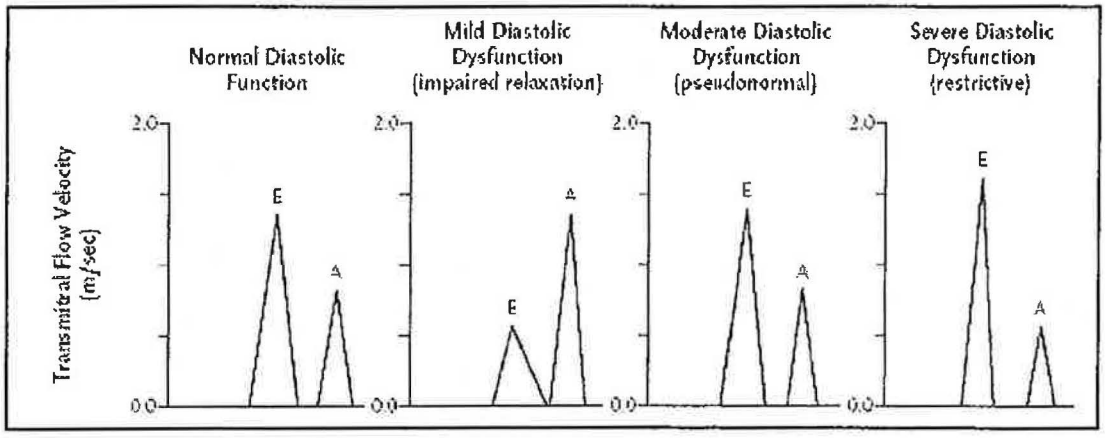




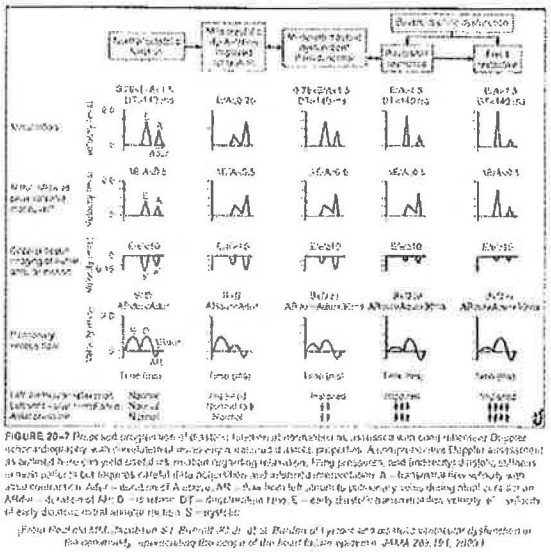
Non-invasive evaluation of diastolic function continues to play a critical role in furthering our understanding of diastole, improving the diagnosis of diastolic dysfunction, evaluating left ventricular filling pressures, and providing important prognostic information for patients with heart failure. Echocardiography, cardiovascular magnetic resonance, and nuclear cardiology each provide important tools for evaluating diastolic performance.

Diastolic dysfunction, as assessed by Doppler echocardiogram, continues to be utilized widely. In normal sinus rhythm, diastolic flow from the left atrium to the LV has two components: 1) the E wave – early diastolic filling, and 2) the A wave – late filling /atrial contraction (Figure 4).

Figure 4: Mitral inflow patterns assessed by echocardiography [17]



Alterations in the waveforms of these velocities provide insight into diastolic properties of the LV. However, these measurements are known to be highly dependent on loading conditions and may be reflective of the increased LV filling pressures seen in HFPEF.



Data from the Cardiovascular Health Study (CHS) showed that E/A ratios were higher in patients with HFPEF compared to those with HTN without HF.[18] It is argued, however, that Doppler measures of filling dynamics do not adequately measure the intrinsic diastolic chamber properties of the ventricle, which are typically and most accurately assessed by pressure volume analysis.[19] Data demonstrate that Doppler grades of DD do correlate with increased LA pressure but not with abnormalities on pressure volume analysis.[19] Doppler studies by echocardiogram probably reflect integrative characteristics and lack true specificity in HFPEF (Figure 5).

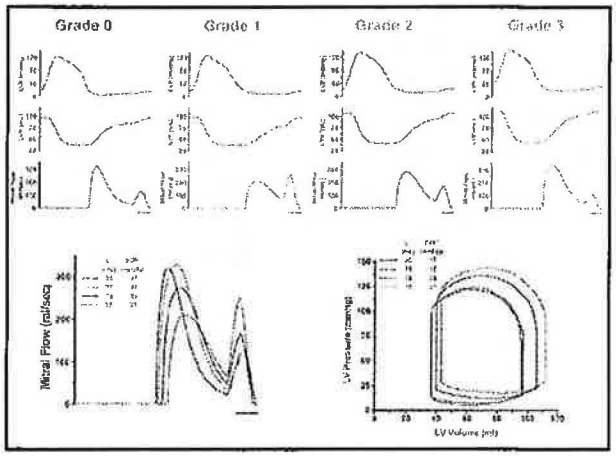


Figure 5: Echocardiographic Doppler grades of diastolic function based on mitral inflow patterns.[19] There is no shift in the end-diastolic pressure volume relationship (bottom right), indicating that changes in Doppler filling patterns can be independent of alterations in the intrinsic passive diastolic properties of the left ventricle.

Other echocardiographic and catheterization data can be obtained to measure the active relaxation component of diastole. One is the echocardiographic determination of tau (τ).[20] Tau is determined by fitting a monoexponential curve to the isovolumic period of the ventricular pressure curve. Essentially, tau is the time it takes for LV pressure to drop by two thirds. Tau prolongation occurs when isovolumic relaxation is slowed. Another assessment of relaxation can be obtained via cardiac catheterization by measuring the peak instantaneous rate of LV pressure decline, but this requires a high fidelity micromanometer. However, no index of relaxation is specific for the intrinsic properties of the LV unless loading is held constant. This is a difficult problem, but can be done by altering afterload either mechanically or pharmacologically. The preload must also be taken into account, making these assessments difficult and complicated.

Evaluation of diastolic function can also be performed by CMRI. Mitral valve inflow velocities, early deceleration time, and pulmonary vein flow velocities are diastolic parameters that can be measured by phase-contrast CMRI. Cardiac magnetic resonance imaging steady-state gradient echo can evaluate functional dimensions for time-volume curves; and myocardial tagging can assess ventricular diastolic "untwisting," which may be important for improved pathophysiologic understanding. Studies have compared echocardiography and CMRI for diagnosing diastolic dysfunction in small patient groups with similar results. Cardiac magnetic resonance imaging can now provide clinically relevant data regarding the underlying cause of diastolic dysfunction and offers promise to gain mechanistic insights for therapeutic strategy development and clinical trial planning.

Pressure volume analysis however, remains the best way to measure the diastolic properties (stiffness) of the LV, but these invasive studies are not trivial and are only accurately performed in a small number of centers. The main debate in this area is whether an abnormality truly exists in the end diastolic pressure volume relationship (EDPVR). In systolic dysfunction, compared to the normal heart, the end systolic pressure volume relationship (ESPVR) is displaced downward and to the right. This signifies the depressed contractility of this disease state. However, in HFPEF some investigators believe that that the primary abnormality of the condition is an upward and leftward shift of the end diastolic pressure volume relationship (EDPVR) (Figure 6).

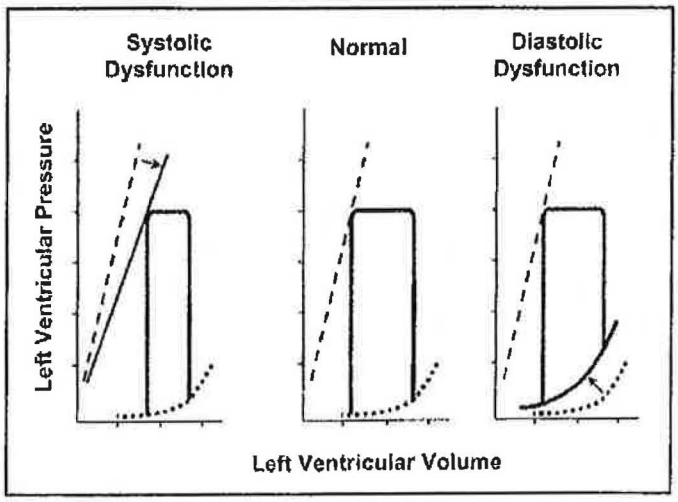


Figure 6: Pressure volume loops [21]

The EDPVR is largely determined by passive factors (i.e. myocardial mass, extracellular matrix, and chamber geometry) of the LV. Stiffness is typically defined by the slope of the EDVPR at a given volume (dP/dV), and compliance is the mathematical reciprocal of stiffness. Stiffness increases in relationship to the filling pressure, so it is certainly not linear (Figure 7). This is important because stiffness and capacitance change over a range of filling pressures, again making assessment of DD difficult and complex. When the EDPVR is abnormal, it suggests that higher filling pressures are necessary to fill the LV.

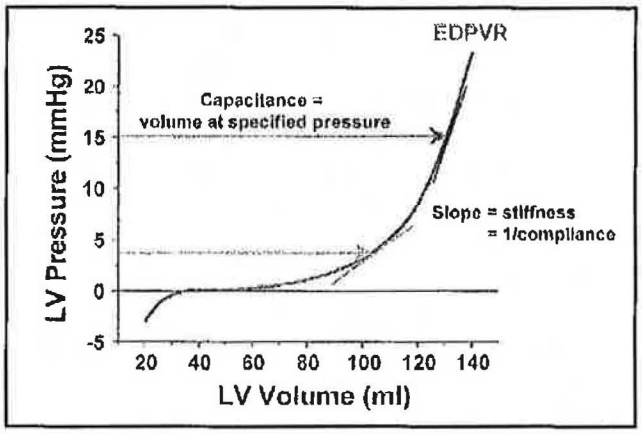


Figure 7: LV stiffness increases with pressure and is nonlinear [19]

With regard to the importance of the EDPVR, one school of thought believes that significant abnormalities in relaxation and stiffness exist in HFPEF. Their argument is based on an important study of 47 patients with HFPEF who were carefully assessed by cardiac catheterization and echocardiogram. These results showed that tau was prolonged, the EDPVR was shifted upward and leftward, and the LV passive-stiffness constant was increased.[22] This study used highly complex calculations of passive diastolic stiffness using end diastolic pressure and volume, pre-A diastolic pressure and volume, and volume at minimal diastolic pressure. These values were used to generate a corrected LV diastolic pressure and a corrected passive-stiffness constant. The data demonstrate a significant increase in the passive stiffness of LV in HFPEF (Figure 8). The authors go on to postulate that exercise intolerance in HFPEF (another major source of controversy) is explained by 1) diastolic dysfunction that leads to increased LV filling pressures during activity, and 2) a stiff, non-compliant LV that cannot fully utilize the Frank-Starling mechanism.

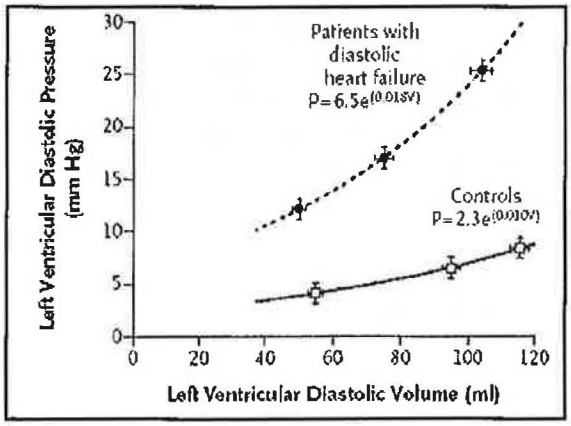


Figure 8: Diastolic pressure volume relation in patients with HFPEF and controls [22]

There are those who believe differently regarding DD. The other school of thought believes that significant abnormalities in relaxation and stiffness do not exist in HFPEF. They argue that HFPEF is not due to a single underlying pathophysiological mechanism. They argue that studies of HFPEF need to be done on a population of people that is representative – older women and not young men, such as in the previous study. They point to data showing that tau is similarly increased in many types of myocardial hypertrophy and is not known to be correlated with induction of symptomatic HF.[23] Most outstandingly, this school also points to data showing that in some patients with HFPEF there is actually a downward and rightward shift of the EDPVR, suggesting that the findings of abnormal stiffness and relaxation may not apply to most patients and may apparently be abnormal only because of inability to correct for preload.

When correcting for preload, Kawaguchi et al showed that volumes of patients with HFPEF may be shifted either upward or downward, that tau was within the normal range, and that these patients dramatically increased preload during exercise with little change in EDPVR and with marked prolongation of the time constant of relaxation (τ).[24] Figure 9 shows that EDPVR from patients with HFPEF can be shifted to the left or right.

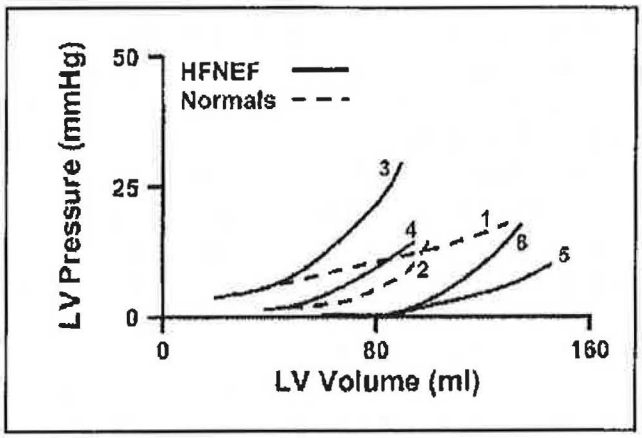


Figure 9: Examples of the EDPVR from various patients with HFPEF and normal controls [24]

The interpretation of this data is that the abnormalities of stiffness and relaxation may be the result, rather than the cause, of elevated filling pressures. This can possibly be explained by increased ventriculo-vascular stiffness, as measured by effective arterial elastance (E_A) and end systolic elastance (E_{ES}) (see below). Thus, this group of investigators argues that diastolic dysfunction may not be the universal underlying mechanism for HFPEF. Let us now go further into the debate and examine what can explain these discrepancies.

The Question of Etiology: Why some patients and not others?

In other words, why do some patients with echocardiographic features of DD have HF and others do not? It is possible that the array of contributing factors (see Table 2), which are heterogeneous in nature, do not lead to one disease called HFPEF. Thus, the controversy in this area of HFPEF study proceeds from the previous debate on the existence of DD and involves whether or not patients with HFPEF have specific features that distinguish them as a group.

An important study from Baltimore compared patients of similar age, gender, and race for different CV characteristics. One group had HFPEF and a second group had asymptomatic LV hypertrophy (termed hypertensive LVH group – HLVH). The control group consisted of normotensive subjects without LVH. The study was designed to assess what characteristics are special in those with HFPEF and what perhaps leads HFPEF subjects to develop symptoms. The study showed that the two groups had significant overlap in DD grades (Figure 10).[26]

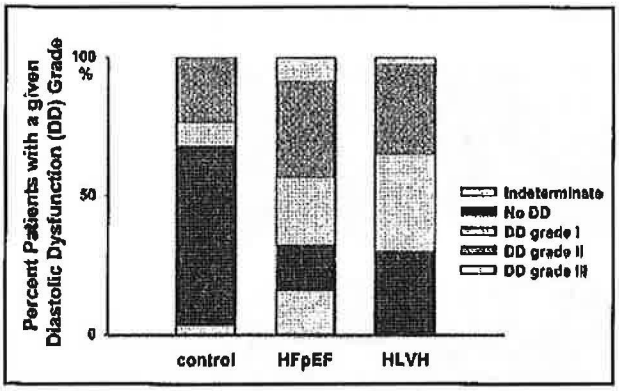


Figure 10: Comparison of diastolic dysfunction grades between HFPEF, hypertensive LVH (HLVH), and controls [26]

Subjects with HFPEF had more LV hypertrophy, higher left atrial volumes, lower atrial emptying fractions, and more frequent coronary artery disease. There was no single vascular or conventional LV diastolic or systolic feature that was predictive of HFPEF. The product of LV mass index (LVMI) and left atrial volumes (LAV_{MAX}) showed the best discrimination by ROC analysis (Figure 11) compared to a number of other measures.

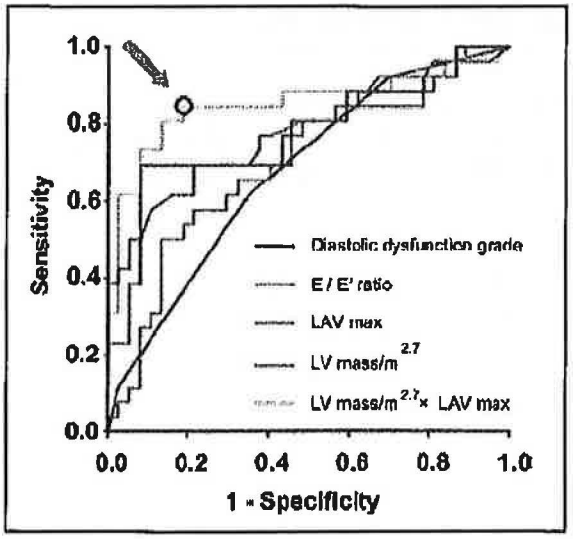


Figure 11: ROC analysis for prediction of HFPEF [26]

The authors speculate that LA abnormalities may be related to exposure to chronically elevated pressures, higher filling pressures during exercise, or the presence of CAD, diabetes, renal dysfunction, or obesity. These diseases could lead to neurohormonal activation, fluid retention, or other direct effects causing atrial damage. Importantly, in this study there was no significant difference between patients with HFPEF and HLVH with regard to LV volume (EDV). However, there is much controversy regarding whether patients with HFPEF have increased or decreased LV volumes. Let us explore this issue further and revisit the two schools of thought.

The school of pro-DD and "abnormal EDPVR" claims that patients with HFPEF have small hearts.[27] They rely on the premise that hypertrophy is at the core of the process and the result is LV volume reduction, cellular hypertrophy, and increased fibrosis (Figure 12). This theory is borne from animal[28] and human data.

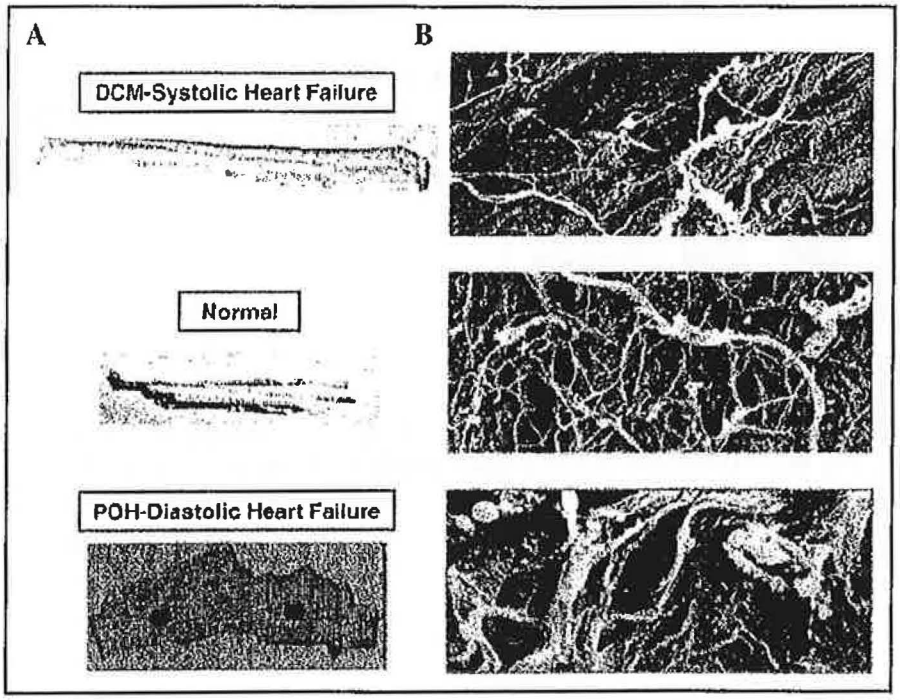


Figure 12: A) Isolated cardiomyocytes from animal models of DCM, normal, and pressure overload hypertrophy (POH), and B) Scanning electron micrographs from each model. In DCM, there is decreased collagen. In POH, there is increased collagen.[28]

They also argue that 2-D echo measurement of volume has been validated and that contractility in HFPEF is normal or increased. Obviously, the measurement of volume is quite important in these studies because careful assessment requires plotting an accurate pressure volume curve.

The other school – those who believe that DD does not explain the syndrome – support the hypothesis that LV volumes can be increased in HFPEF. To support this hypothesis, a study was performed using 3-D echo to measure LV volume and mass.[29] Non-invasive techniques were used to measure LV diastolic properties. The study population included 99 normotensive controls, 35 patients with HFPEF with hypertension, and 11 patients with nonhypertensive HFPEF. The results suggested that patients with HFPEF without a history of hypertension have LV volumes similar to controls. However, this group did have an elevated EDP and an upward shifted EDPVR. In contrast, the group with HFPEF and a history of hypertension had increased LV volumes and rightward-shifted EDPVR, thus potentially implicating increased blood volume in this group (Table 5 and Figure 13).

Parameter	Controls	Nonhypertensive HFPEF	Hypertensive HFPEF
End Diastolic Volume (EDV)	95 ± 21	98 ± 25	118 ± 29 *
End Systolic Volume (ESV)	40 ± 10	49 ± 14	54 ± 14 *

Table 5: LV volumes in subgroups of patients with HFPEF [8]
* P < 0.05 vs. controls and nonhypertensive HFPEF

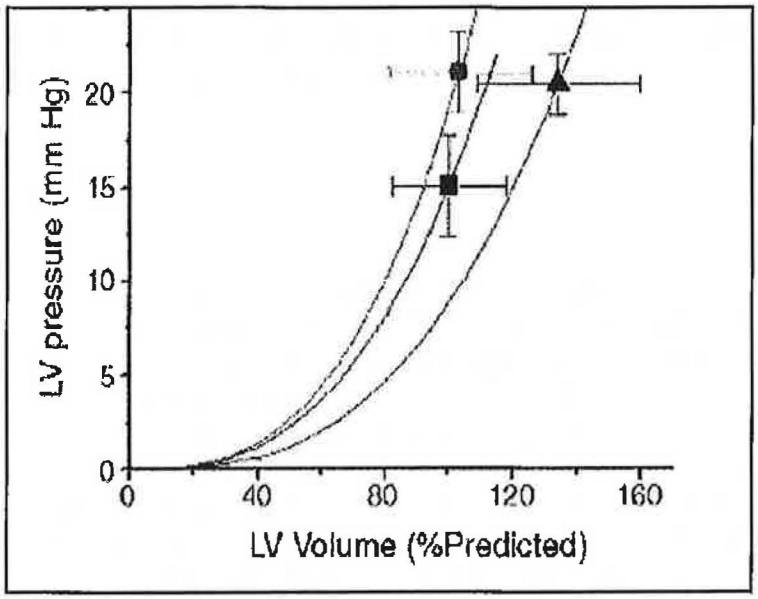


Figure 13: Group averaged PV point and estimated EDPVR for nonhypertensive HFPEF (left), controls (middle), and hypertensive HFPEF (right) [8]

Indeed, some studies further suggest that there may be increased blood volume in HFPEF,[29] possibly leading from subtle abnormalities in systolic function that results in neurohormonal activation and salt and water retention. To further bolster the argument for increased volumes, the group points to data from the CHS showing that the average

LV diastolic dimension and stroke volume was increased in the HFPEF group compared to healthy and hypertensive controls.[18]

These investigators further demonstrated that subjects with hypertension and HFPEF have higher end systolic elastance (E_{ES}) and arterial elastance (E_A) compared to nonhypertensive HFPEF patients.[29] End systolic elastance is a complicated calculation involving stroke volume, blood pressure, and duration of isovolumic contraction and ejection. Each is determined by echocardiography. Arterial elastance is a lumped index of vascular hemodynamic load related mostly to total peripheral resistance and heart rate. E_{ES} and E_A are known to increase with aging and are increased more in elderly women than men.[30] The subjects with the highest measured end systolic elastance were generally short, non-obese, elderly women with longstanding HTN. Volumes were significantly lower in the hypertensive HFPEF group compared to the nonhypertensive HFPEF group. This adds further weight to their argument that HFPEF is a heterogeneous disorder with clinically distinguishable subgroups. Importantly, they criticize the assessment of volume by using only 2-D echo and state that accurate assessment of volume requires 3-dimensional imaging.

To summarize, one school believes that DD is the primary cause of HFPEF, with abnormalities of LV wall thickening and small volumes. The other school believes that the problem is heterogeneous (HFPEF patients have both small and large volumes) with important effects related to extracardiac abnormalities (i.e. abnormal ventriculo-vascular coupling [31]).

Prognosis in HFPEF

Data from the ADHERE registry suggest that the in-hospital mortality for systolic dysfunction is slightly higher than HFPEF (3.9% vs. 2.8%; p=0.005).[3] When adjusting for the mortality difference by gender, race, and eight other mortality risk factors, the difference was still significant. In the EFFECT study, the unadjusted and adjusted mortality rates at 30 days and 1 year were not significantly different between the two groups. Also, the rates of readmission did not differ. From the Olmstead county study, HFPEF had slightly higher 5 year survival (65% vs. 68%; p=0.03), but evaluation of the outcomes over time showed improvement with systolic dysfunction but not with HFPEF. Thus, it appears that the mortality is not dramatically different for HFPEF when evaluating these data *in toto* (Figure 13).

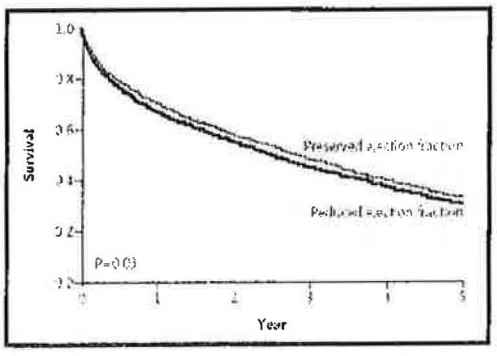
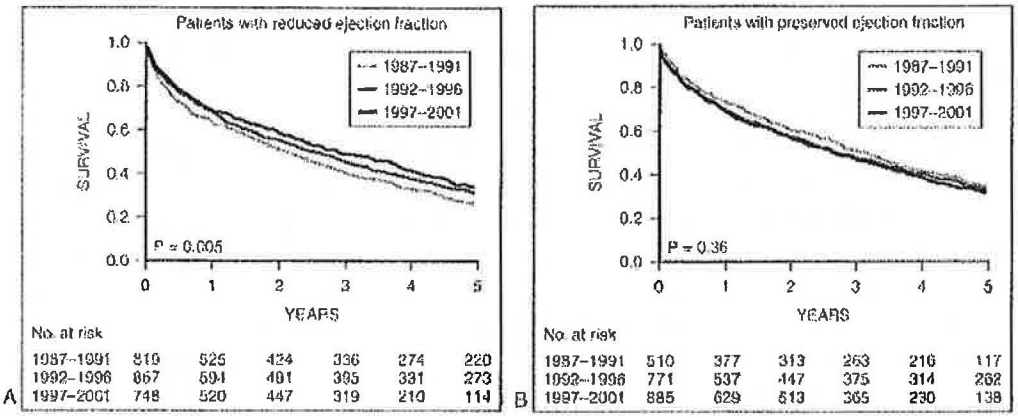
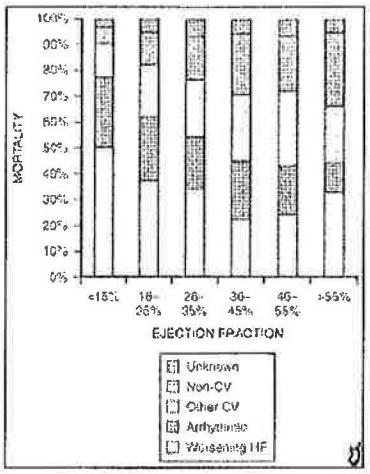


Figure 13: Prognosis in HFPEF and HF with Reduced EF [6]



There are few detailed data on the mode of death in HFPEF. It is known, for instance, that in NYHA class II patients with systolic dysfunction 64% of deaths are due to sudden death and only 12% from pump failure.[32, 33] However, in NYHA class IV patients with systolic dysfunction, the numbers are reversed. 56% of deaths are from pump failure and 33% die from sudden death. These data are lacking in HFPEF. Most data presented in recent studies are derived from searches of death databases and not from careful adjudication of actual cause of death. One existing hypothesis is that patients with HFPEF have a low incidence of pump failure, and cause of death is related to the co-morbidities that frequently afflict this population: coronary artery disease (CAD), renal dysfunction, stroke, and diabetes (Figure 14).



(From Curtis JP, Sokol SI, Wang Y, et al: The association of left ventricular ejection fraction, mortality, and cause of death in stable outpatients with heart failure. J Am Coll Cardiol 42:736, 2003.)

Treatment

In general, the management of HFPEF has two objectives. The first is to treat the presenting syndrome of HF—relieve resting or exercise-associated venous congestion and eliminate precipitating factors. The second is to reverse the factors responsible for diastolic dysfunction or other perturbations that lead to HFPEF. Both nonpharmacologic and pharmacologic strategies may be used to achieve these objectives. Present treatment strategies for HFPEF are largely based on assumptions of

its pathophysiologic mechanisms and on extrapolations from proven strategies used in HF with a reduced EF.

In systolic HF, several pharmacological therapies are known to improve morbidity and/or mortality (ACE-inhibitors, beta-blockers, aldosterone antagonists, diuretics, digoxin, and combination isosorbide/hydralazine). These data are derived from well-designed clinical trials going back 20-30 years. For HFPEF, there is a major paucity of clinical trial data. There exist no proven therapies for this morbid, mortal, and highly prevalent disease. Also, guidelines are greatly lacking. These deficiencies are mostly because of our lack of clear targets for intervention and uncertainty in the etiology. Some guidelines[34] and many anecdotal recommendations rely on the following:

1) Volume management/filling pressure reduction with diuretics
2) Fluid and salt restriction
3) Aggressive management of hypertension
4) Prevention of myocardial ischemia; revascularization when reasonable
5) Maintenance of sinus rhythm; avoidance of tachycardia

Again, data from the ADHERE database show that practice patterns of medication prescription differ significantly between those with systolic dysfunction and HFPEF (Table 6). However, these practice patterns are based on virtually no proven trial data. Let us review the previous trial data in HFPEF.

Medication	HFPEF	Systolic HF	P value
Diuretic	79.5	83.7	<0.0001
ACE Inhibitor	47.7	61.5	<0.0001
ARB	13.2	11.0	<0.0001
ACE or ARB	58.9	71.3	<0.0001
Beta-blocker	52.2	62.6	<0.0001
Digoxin	21.1	44.1	<0.0001
Spironolactone	10.6	24.7	<0.0001

Table 6: Medication use in HFPEF and Systolic HF [3]

Completed Trials

The Digitalis Investigation Group (DIG) trial included a small subgroup of patients with HFPEF. In the HFPEF group, digoxin did not alter the primary endpoint of HF hospitalization or cardiovascular mortality but did reduce HF hospitalizations.[56] Unfortunately, total cardiovascular hospitalizations were not reduced because of an increased rate of admissions for unstable angina, which completely negated the beneficial effect of reduced HF hospitalizations.

The CHARM-Preserved Trial (Candesartan in Heart Failure – Assessment of Reduction in Mortality and Morbidity) compared 3023 HFPEF patients who were randomized to either placebo or Candesartan (the angiotensin receptor blocker).[35] The patients were followed for 36.6 months, and the combined endpoint was CV death and HF hospitalization. The trial did not show a statistically significant difference between the two groups (p=0.12), but fewer patients on candesartan were hospitalized (230 vs. 279, p=0.017) (Figure 14).

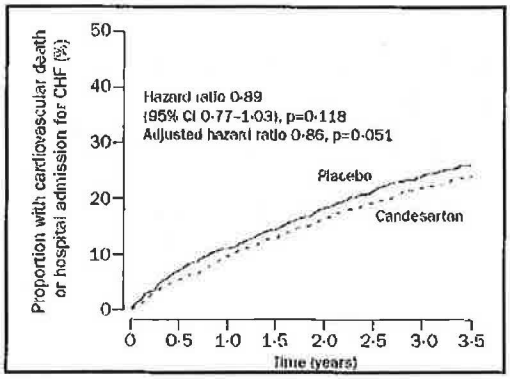


Figure 14:
CV Death or HF hospitalization in CHARM-Preserved [35]

The I-PRESERVE trial tested the angiotensin receptor blocker irbesartan in 4128 patients who were at least 60 years of age and had New York Heart Association Class II- IV HF and an EF of at least 45%. [57] %. The demographics of the study population is different from CHARM with more women (60% vs. 40%), higher hypertensive HF (63% vs. 23%, and less CAD (25% vs. 56%). The study population is also older than CHARM (72 years vs. 67 years). The primary composite outcome was death from any cause or hospitalization for a cardiovascular cause (HF, myocardial infarction, unstable angina, arrhythmia, or stroke). Secondary outcomes included death from HF or hospitalization for HF, death from any cause and from cardiovascular causes, and quality of life. Irbesartan had no effect on any of the pre specified outcome measures (Figure 15).

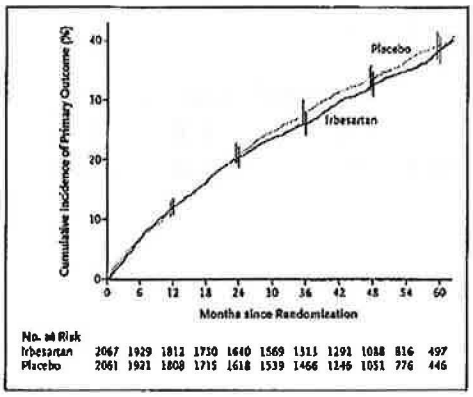


Figure 15: Death form any cause and hospitalization for HF.

The PEP-CHF Trial (Perindopril for Elderly Persons with Chronic Heart Failure) was designed to study the effects of an ACE-inhibitor in an elderly population (age > 70) with HFPEF.[37] 850 patients were randomized to either perindopril or placebo. The primary endpoint was all-cause mortality and HF hospitalization in 1 year. The primary endpoint at 1 year was significantly different between the groups (p=0.055, but this was mainly driven by reduction of hospitalization in the ACE-inhibitor group. During the entire follow up (2.1 years) no endpoint was statistically significant.

The SENIORS Trial (The Study Effects of Nebivolol Intervention on Outcomes and Rehospitalizations in Seniors with Heart Failure) tested this novel, selective beta-1 adrenoreceptor blocker with additional vasodilator properties in 2128 patients with HF and age greater than 70.[36] Patients did not specifically have HFPEF, but some patients (20%) had an EF > 45%. Nebivolol significantly reduced death or hospitalization (p=0.039) in the study, but in a subgroup analysis of the patients with EF>35% there was no significant difference in benefit.

The Hong Kong diastolic heart failure study[58] randomized 150 patients with HFnlEF (EF > 45%) to diuretics alone, diuretics plus irbesartan, or diuretics plus ramipril. Quality of life assessment, 6-minute walk test, and Doppler echocardiography were performed at baseline and at 12, 24, and 52 weeks. The quality of life score and 6-minute walk test increased similarly, and hospitalizations were similar in all three groups. Modest improvements in Doppler systolic and diastolic indices and NT-proBNP levels were seen only in the irbesartan and ramipril groups.

Ongoing Trials

The TOPCAT trial (Treatment of Preserved Cardiac Function in Heart Failure with an Aldosterone Antagonist) is also ongoing at this time. The study design is similar to I-PRESERVE, except the intervention is spironolactone (15mg/day titrated to 45mg/day) vs. placebo. The expected completion date is early 2011.

A number of other ongoing clinical trials in HFPEF are testing novel treatment strategies, including (but not limited to) endothelin antagonists, sildenafil (RELAX trial), atrial pacing (RESET trial), and baroreflex control devices (Rheos diastolic heart failure trial). (See www.clinicaltrials.gov.)

Table 7: Clinical Trials in HFPEF

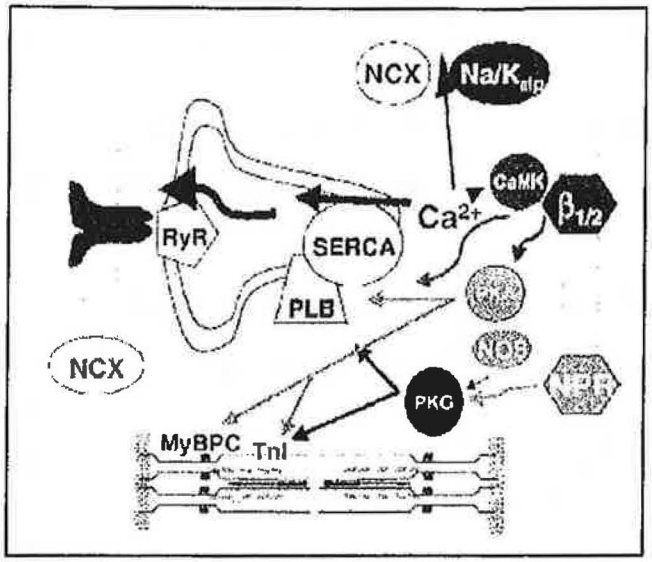
Trial	Study Drug	N	Entry Criteria	Primary Endpoint
Completed Studies				
CHARM-Preserved	candesartan	3023	EF>40%, NYHA II-IV	CV death, HF hospitalization
SENIORS	nebivolol	2128	Age>70, EF<35%, HF hospitalization with 6 mo	Mortality, CV hospitalization
PEP-HF	perindopril	850	Age>70, HF diagnosis	Mortality, HF hospitalization
I-PRESERVE	irbesartan	4128	EF>45%, Age>60, NYHA II-IV	Mortality, HF hospitalization
The HongKong Diastolic Heart Failure Study	Diuretics Diuretics+Ramipril Diuretics+Irbesartan	150	EF > 45%	Quality of life assessment, 6-minute walk test, and Doppler echocardiography
Ongoing Studies				
TOPCAT	spironolactone	≈ 4000	EF>45%, Age>50, clinical HF	Mortality, HF hospitalization

Future Directions

What else lies in future for the treatment of HFPEF? What new targets might become important? We must first examine some of the molecular and cellular mechanisms of HFPEF. Novel therapeutic agents may permit new opportunities to effect myocardial relaxation and stiffness. Two novel therapies will be discussed: 1) Istaroxime (PST2744), and 2) Alagebrium (ALT-711).

In the heart, contraction ceases and tension is released when Ca^{2+} dissociates from troponin C and is sequestered into the sarcoplasmic reticulum (via the sarcoplasmic reticulum Ca-ATPase 2a – SERCA 2a) and cytosol (via the sodium/calcium exchanger – NCX) (Figure 15). Thus, ATP is required for detachment of the actin-myosin cross-bridges.

Figure 15: Molecular mechanisms of calcium handling [39]



SERCA 2a expression and activity decline in HF, and gene transfer studies involving SERCA 2a and phospholamban (reducing inhibition of SERCA 2a) improve the rate of LV relaxation.[40, 41] Efforts are ongoing to target this system in the human heart. A novel agent that is currently in phase II trials may be promising. Istaroxime (PST2744) is an agent that inhibits sodium/potassium ATPase activity and stimulates SERCA 2a.[42] This action prevents Ca^{2+} accumulation and promotes myocardial relaxation (lusitropism). Istaroxime is unrelated to cardiac glycosides but does have inotropic qualities. Also, unlike other positive inotropic agents, it does not seem to have proarrhythmic effects. The mechanism by which this agent does not promote arrhythmias is unclear, although electrophysiologic studies in a guinea pig model suggest that it suppresses inward calcium transients related to the genesis of delayed afterdepolarizations.[43, 44] In HORIZON-HF trial120 patients with EF < 35% with acute heart failure decompensation were randomized to a continuous 6-hour infusion of 1 of 3 doses of istaroxime or placebo. At end of infusion istaroxime patients had a lower PCWP, increase in SBP and decreased diastolic stiffness.

With regard to myocardial stiffness, it may be possible to intervene at the level of the collagen network that surrounds myocytes and capillaries. An extensive array of endomysial, perimysial, and epimysial fibers form a matrix around muscle bundles and lie adjacent to the epicardium and endocardium (Figure 16).

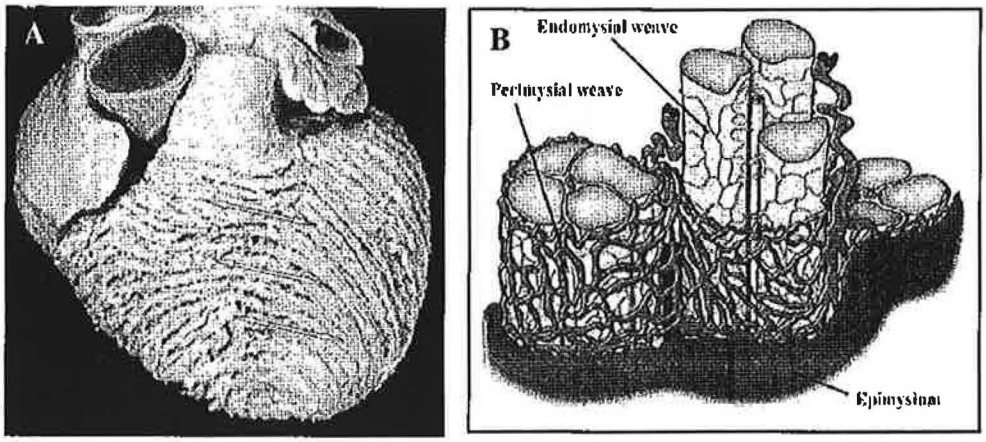


Figure 16: The extracellular matrix of the heart. A) Normal heart with epimysial component removed, emphasizing the myofibers and their perimysial covering. B) Fibrous matrix of the heart. [45]

These fibers are important in diastolic tension and ventricular compliance.[46] Some data in animal models suggest that collagenase perfusion and breakdown of perimysial fibers promotes a rightward shift in the EDPVR.[47] Other studies have used plasmin, oxidized glutathione, and hydroxyproline with similar results.[48, 49] However, there remains a significant debate on whether stiffness and collagen content are related in humans. For example, some believe that it is the quality, not the quantity, of collagen deposition in the heart that is most related to stiffness. This may be related to the type of cross-linking in the cardiac extracellular matrix.

In a dog model of DD using 48 hours of tachycardia pacing and administration of angiotensin II, there were poor correlations between collagen synthesis and LV stiffness.[50] However, matrix metalloproteinase (MMP) activation was significant. These data suggest that the extracellular matrix in HF is under complex control, and there are perhaps effects of MMPs on other components of the matrix that lead to edema, altered cross-linking, irregular myocyte arrangement, and increased diastolic stiffness. Again, it may be that qualitative changes are most important in diastolic stiffness.

Another component of this extracellular system involves advanced glycation endproducts (AGE). With age, HTN, and diabetes, AGE accumulate on proteins such as collagen and elastin to promote increased vascular and cardiac stiffness. In a volume-overload model that did not alter total collagen composition, cross-links between AGE and collagen correlated with stiffening of the LV.[51] Importantly, a novel cross-link breaker was fed to aged dogs. This agent was shown to increase ventricular compliance, giving possible credence for tests in humans with HFPEF to reduce cardiac stiffness. In this study, LV diastolic stiffness improved by 40% after treatment for one month.[52]

Indeed, this drug (ALT-711 or Alagebrium) has now been tested in humans. One multicenter trial in older patients and increased arterial stiffness (pulse pressure > 60 mmHg), ALT-711 significantly lowered pulse pressure and improved total arterial compliance.[53] In a study of 23 patients with HFPEF, ALT-711 was given over 16 weeks, and multiple CV measures were performed before and after treatment.[54] New

York Heart Association class improved, but maximal exercise tolerance did not. There were improvements in LV mass and aortic stiffness during the study, and early diastolic mitral annular velocity increased (p=0.045).

Currently there are two trials evaluating ALT-711 in HFPEF. The BENEFICIAL study is a double-blind, placebo controlled, randomized trial evaluating the primary outcome of aerobic capacity (Peak VO2) during exercise testing. 100 patients will receive placebo or study drug for 9 months. The DIAMOND study will test ALT-711 in elderly patients with HFPEF for 16 weeks. This pilot study will assess improvement in aortic distensibility, exercise tolerance, and quality of life. Thus, it is not yet known whether this agent will prove effective in HFPEF, but early data is promising.

In summary, molecular and cellular targets are emerging that may be important in the treatment of the acutely ill or chronically debilitated patient with HFPEF. In addition, other agents may be developed to attack other aspects of this complicated pathophysiological process (i.e. myocyte hypertrophy via Rho-kinase or phophodiesterase 5 inhibition).

Current Therapeutic Recommendations

Current recommendations for treatment of patients with HFPEF are as outlined above.[2,3] In addition, it is important to treat other contributing comorbidities and risk factors aggressively, such as diabetes, hyperlipidemia, renal dysfunction, and renal vascular disease. One retrospective study has shown that statin use, but not the use of beta blockers, ACE inhibitors, or calcium channel blockers, is associated with improved survival in patients with HFPEF.[58] Until more clinical trials are performed in patients with HFPEF, the empiric nature of therapeutic recommendations and their uncertain benefit must be recognized.

Conclusions

1) HFPEF is difficult to define and characterize

2) Accurate assessment of diastole requires nontrivial, invasive measurements

3) Much debate continues on the interpretation of clinical, hemodynamic, and structural abnormalities

4) No effective treatments exist

5) Novel therapeutic targets are emerging

6) Much work is yet to be done, and this is certainly an area where creative thinking is wanted

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