Heart Failure with Preserved Ejection Fraction:
Is there a passage between Scylla and Charybdis?

VLYSSE passe le destroit de Scylla & de Carybde, où six de ses gens sont deuorez par des Dragons: puis se faict lier au mats du nauire, afin d'euiter les charmes des Sereines. C'est vn tesmoignage, *Que les dangers sont touſiours preſents, où les entrepriſes ſe trouuent grandes, & qu'il faut que le corps ſe giſant ſoy-meſme pour vaincre les volupitez, & les autres paſſions de l'ame.*

Internal Medicine Grand Rounds
UT Southwestern Medical Center
February 15, 2008

David W. Markham, M.D.
Assistant Professor of Medicine
Division of Cardiology
Heart Failure / Transplant Program

Introduction and Scope of the Problem

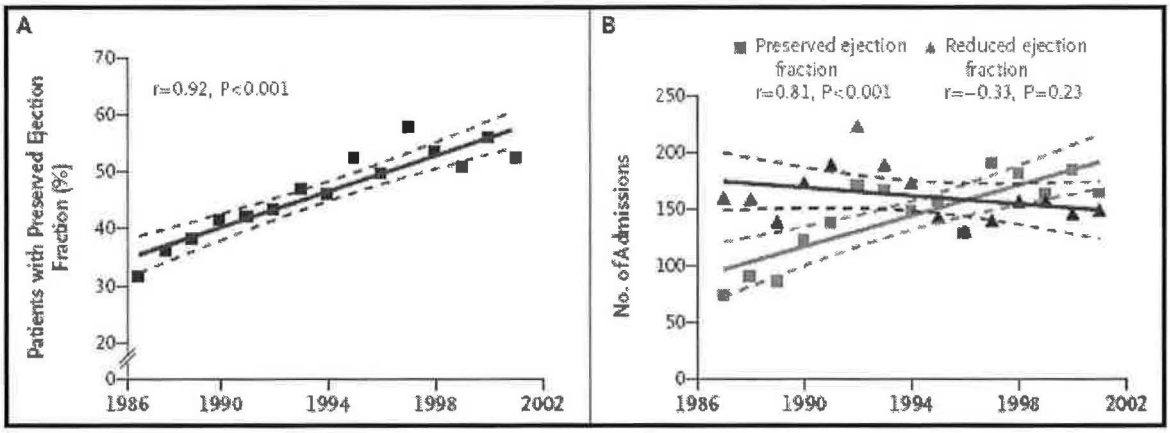
Heart failure is classically considered a syndrome that occurs in the setting of a reduced ejection fraction (systolic dysfunction) and cardiac dilation. Heart failure with preserved ejection fraction (HFPEF), also know as "diastolic heart failure", is a patho-physiologically distinct syndrome from HF 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. Indeed, many times it does seem like we are often between Scylla and Charybdis when it comes to HFPEF.

Currently there are about 5 million Americans with HF, and approximately 500,000 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%. 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 1), 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 1: 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]



The Question of Diagnosis: Does HFPEF exist?

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. 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]

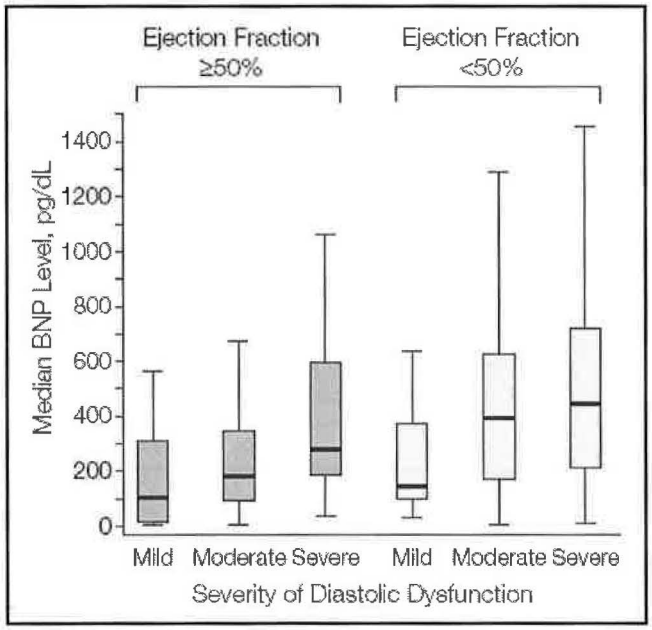


Figure 2: Median brain natriuretic peptide (BNP) levels by EF [10]

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. Then, we will delve further into the controversy.

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.

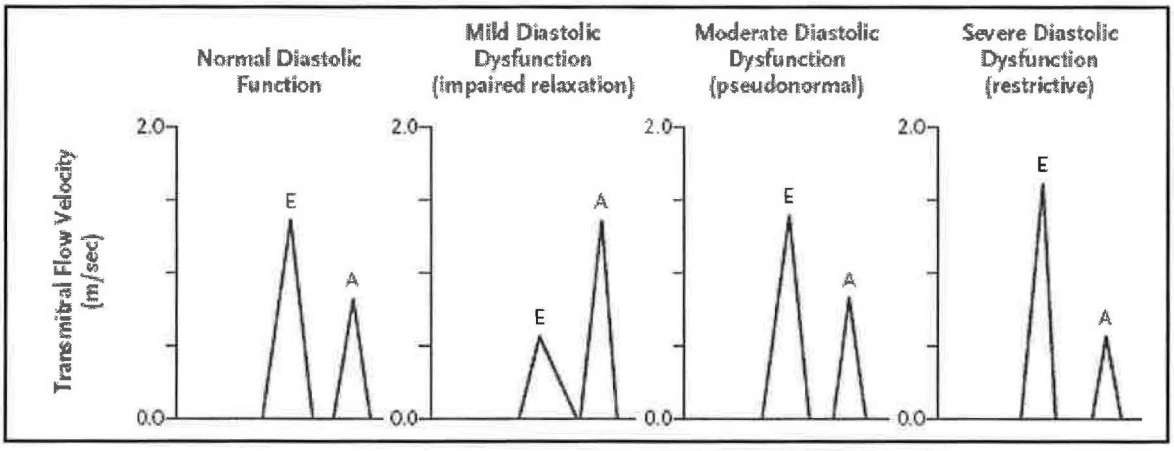
Tables 3 and 4: The Framingham Criteria for HF and The European Criteria for HFPEF

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 of mildly reduced LV function with normal chamber size (EF >45%)
3. Abnormal LV relaxation, filling, diastolic stiffness

Let us now define diastolic dysfunction, a key point in understanding much of the data in HFPEF. 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 3).

Figure 3: 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 4).

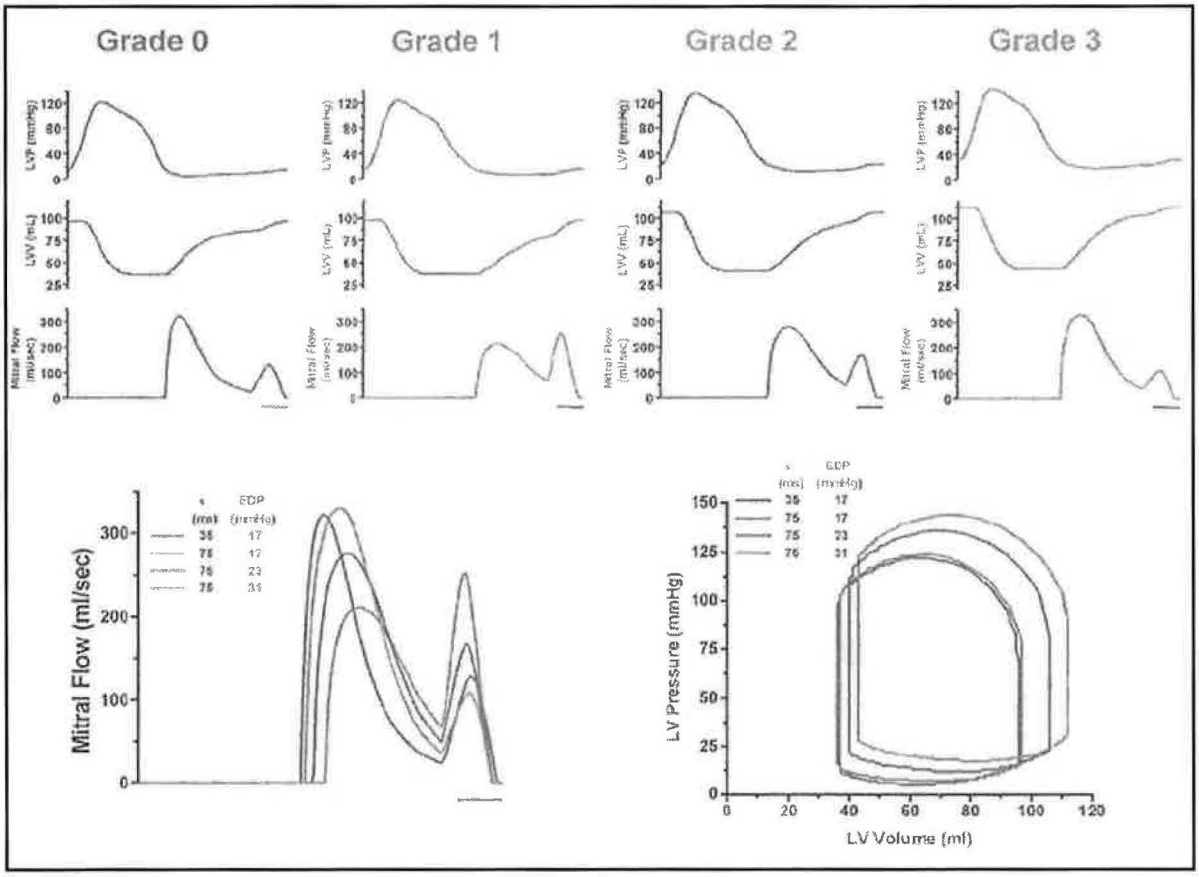


Figure 4: Echocardiographic Doppler grades of diastolic function based on mitral inflow patterns.[19] There is no shift in the end-diastolic pressure volume relationship (bottom right), indicating that changes in Doppler filling patterns can be independent of alterations in the intrinsic passive diastolic 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.

Pressure volume analysis 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 5).

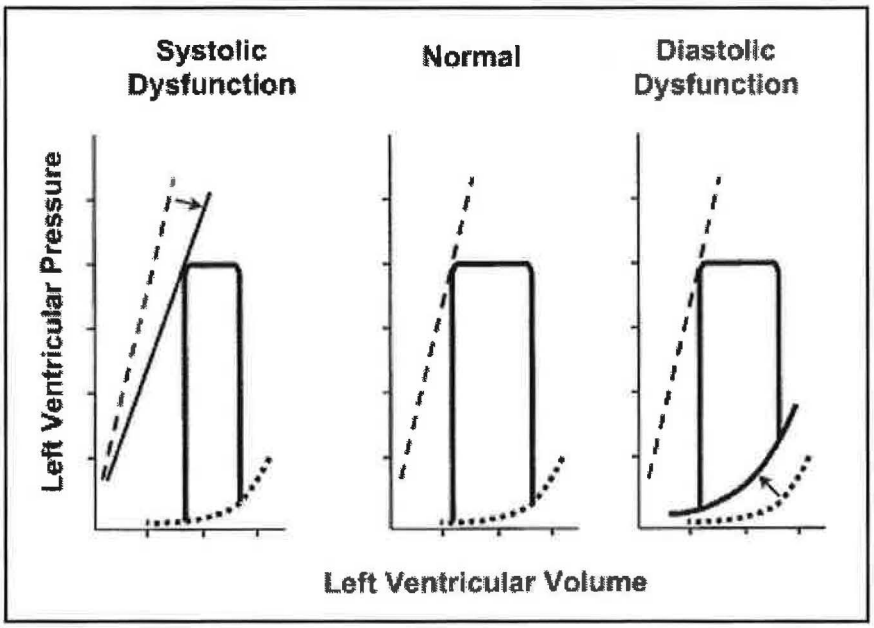


Figure 5: Pressure volume loops [21]

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 6). 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.

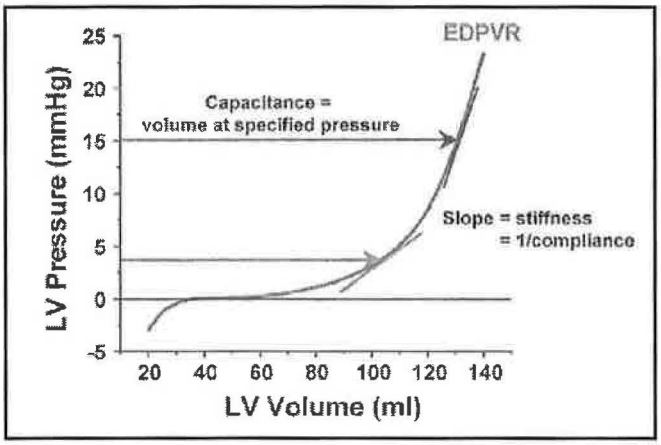


Figure 6: LV stiffness increases with pressure and is nonlinear [19]

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 7). 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.

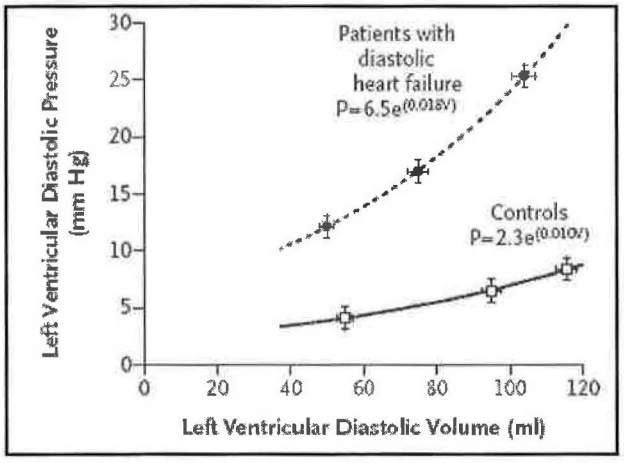


Figure 7: Diastolic pressure volume relation in patients with HFPEF and controls [22]

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 8 shows that EDPVR from patients with HFPEF can be shifted to the left or right.[25]

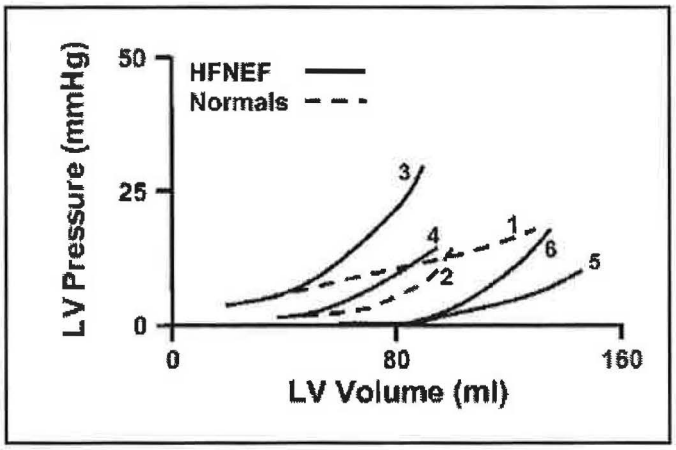


Figure 8: Examples of the EDPVR from various patients with HFPEF and normal controls [25]

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 9).[26]

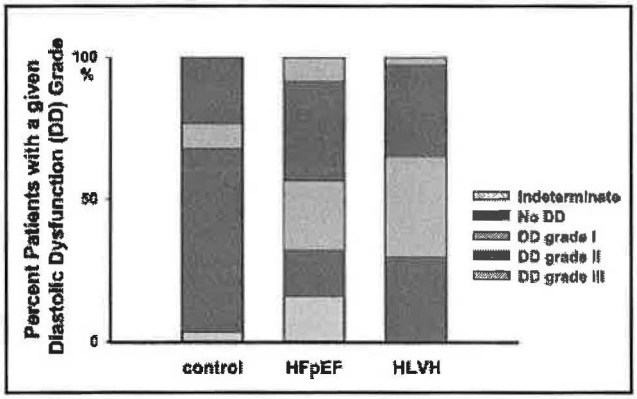


Figure 9: Comparison of diastolic dysfunction grades between HFPEF, hypertensive LVH (HLVH), and controls [26]

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 10) compared to a number of other measures.

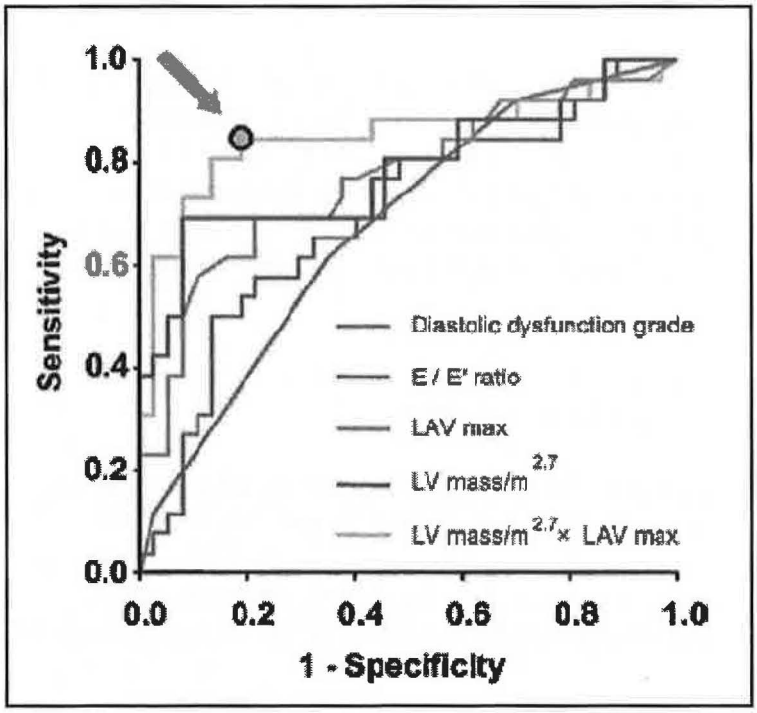


Figure 10: ROC analysis for prediction of HFPEF [26]

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 11). This theory is borne from animal[28] and human data.

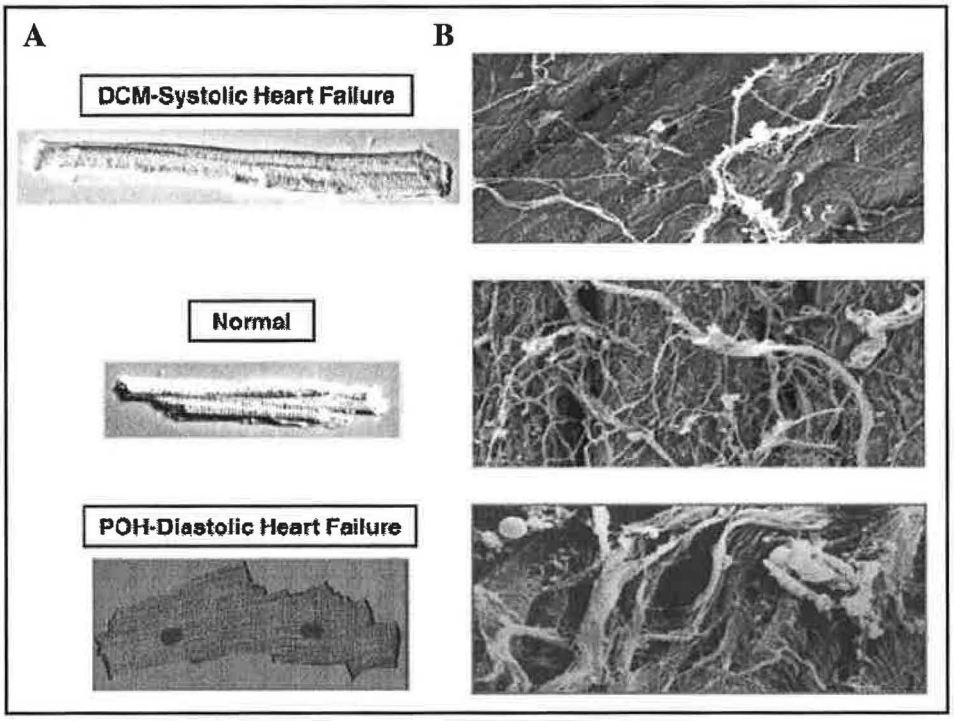


Figure 11: A) Isolated cardiomyocytes from animal models of DCM, normal, and pressure overload hypertrophy (POH), and B) Scanning electron micrographs from each model. In DCM, there is decreased collagen. In POH, there is increased collagen.[28]

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 12).

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

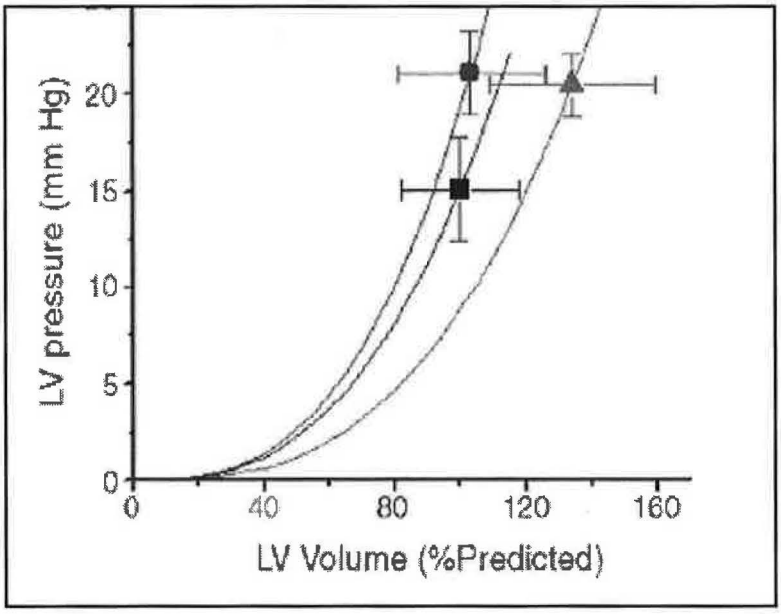


Figure 12: Group averaged PV point and estimated EDPVR for nonhypertensive HFPEF (left), controls (middle), and hypertensive HFPEF (right) [8]

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]).

The Question of 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).

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. There is currently no data to support or refute this, so the debate continues.

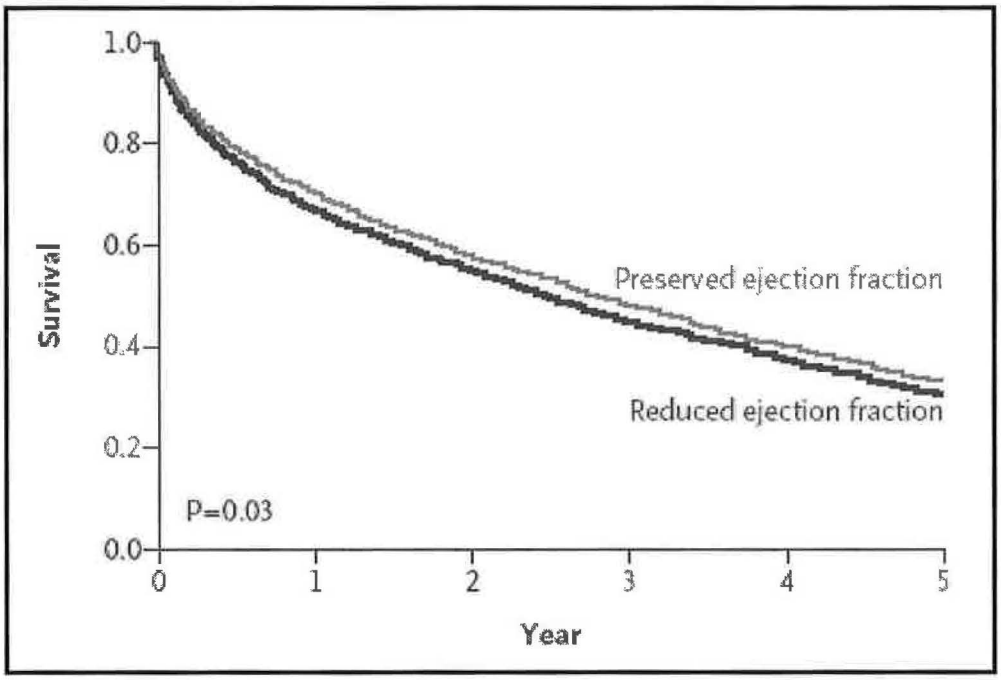


Figure 13: Prognosis in HFPEF and HF with Reduced EF [6]

The Question of Treatment

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 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 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).

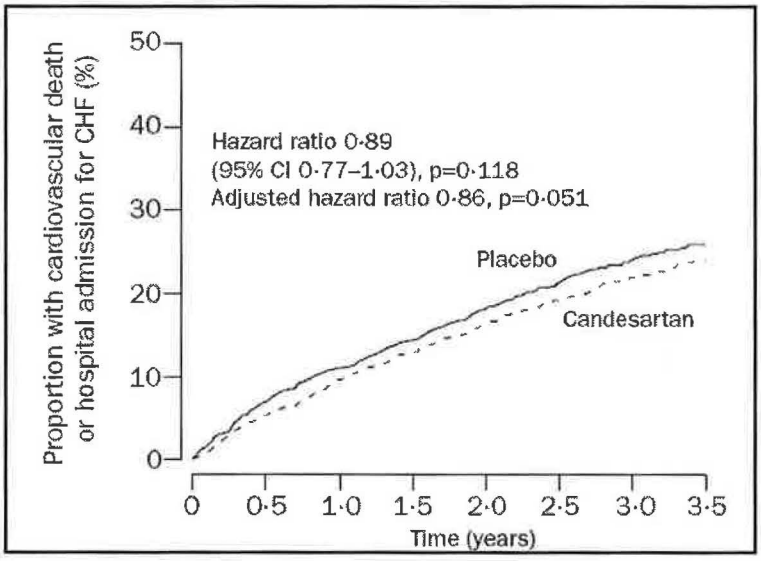


Figure 14:
CV Death or HF hospitalization in CHARM-Preserved [35]

The 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 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.

Ongoing Trials

The I-PRESERVE Trial is currently underway.[38] The trial was initiated in 2002, and the results should be available in 2008. The trial has enrolled 4128 patients with HFPEF, and they are randomized to irbesartan (an angiotensin receptor blocker) or placebo. Enrollees must have age > 60 years old, symptoms of HF, and EF >45%. 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 endpoint is combined all-cause mortality and HF hospitalization.

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.

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
Ongoing Studies				
I-PRESERVE	irbesartan	4128	EF>45%, Age>60, NYHA II-IV	Mortality, HF hospitalization
TOPCAT	spironolactone	≈ 4000	EF>45%, Age>50, clinical HF	Mortality, HF hospitalization

The Question of Where To Go From Here

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.

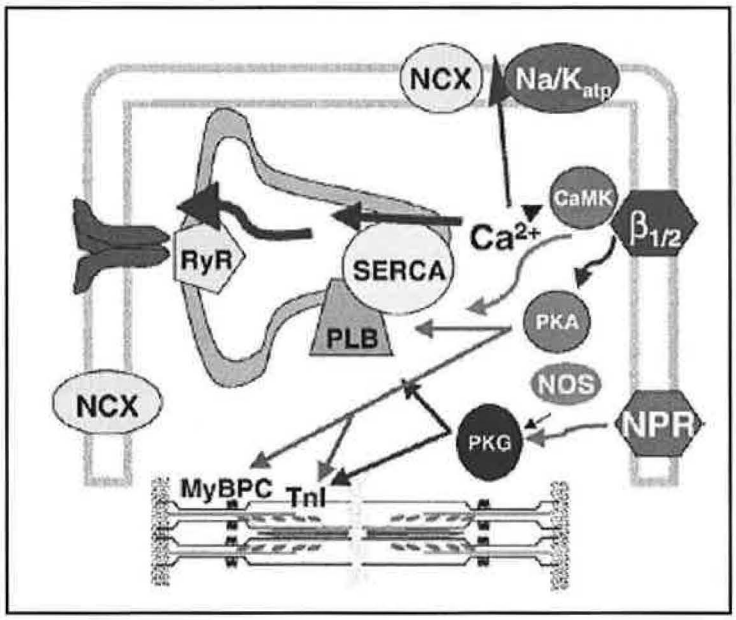


Figure 15: Molecular mechanisms of calcium handling [39]

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 by stimulating 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] Few data are currently available on the use of this drug in humans.

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).

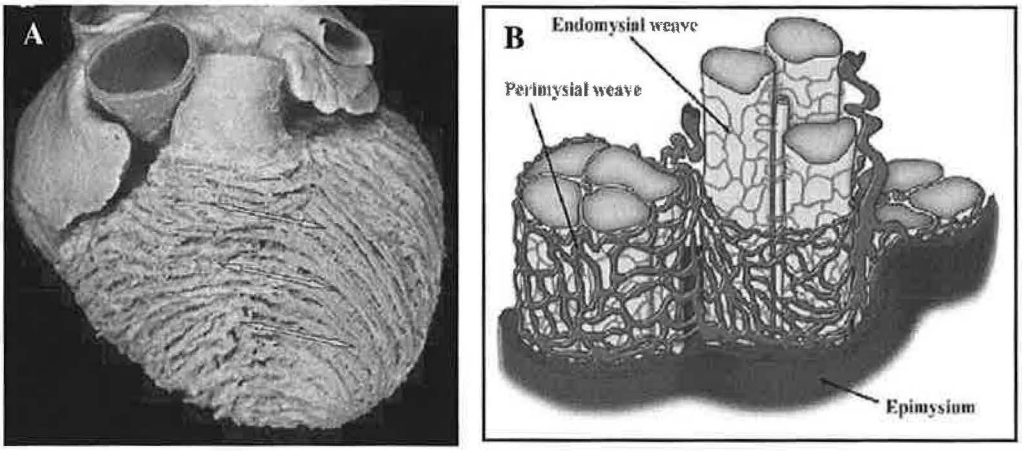


Figure 16: The extracellular matrix of the heart. A) Normal heart with epimysial component removed, emphasizing the myofibers and their perimysial covering. B) Fibrous matrix of the heart. [45]

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).

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

7) Tough choices lie ahead

References

1. Hunt SA. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *Journal of the American College of Cardiology.* 2005;46(6):e1-e82.
2. Owan TE, Redfield MM. Epidemiology of Diastolic Heart Failure. *Progress in Cardiovascular Diseases.* 2005;47(5):320-332.
3. Yancy CW, Lopatin M, Stevenson LW, et al. Clinical Presentation, Management, and In-Hospital Outcomes of Patients Admitted With Acute Decompensated Heart Failure With Preserved Systolic Function: A Report From the Acute Decompensated Heart Failure National Registry (ADHERE) Database. *Journal of the American College of Cardiology.* 2006;47(1):76-84.
4. Heart Failure Society of A. Section 11: Evaluation and Management of Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction. *Journal of Cardiac Failure.* 2006;12(1):e80-e85.
5. Bhatia RS, Tu JV, Lee DS, et al. Outcome of Heart Failure with Preserved Ejection Fraction in a Population-Based Study. *N Engl J Med.* July 20, 2006 2006;355(3):260-269.
6. Owan TE, Hodge DO, Herges RM, et al. Trends in Prevalence and Outcome of Heart Failure with Preserved Ejection Fraction. *N Engl J Med.* July 20, 2006 2006;355(3):251-259.
7. Yturralde RF, Gaasch WH. Diagnostic Criteria for Diastolic Heart Failure. *Progress in Cardiovascular Diseases.* 2005;47(5):314-319.
8. Maurer MS, Kronzon I, Burkhoff D. Ventricular Pump Function in Heart Failure with Normal Ejection Fraction: Insights from Pressure-Volume Measurements. *Progress in Cardiovascular Diseases.* 2006;49(3):182-195.
9. Maisel AS, McCord J, Nowak RM, et al. Bedside B-Type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction: Results from the Breathing Not Properly Multinational Study. *J Am Coll Cardiol.* June 4, 2003 2003;41(11):2010-2017.
10. Bursi F, Weston SA, Redfield MM, et al. Systolic and Diastolic Heart Failure in the Community. *JAMA.* November 8, 2006 2006;296(18):2209-2216.
11. Wei T, Zeng C, Chen L, et al. Systolic and diastolic heart failure are associated with different plasma levels of B-type natriuretic peptide. *International Journal of Clinical Practice.* 2005;59(8):891-894.
12. McKee PA CW, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *New England Journal of Medicine.* 1971;285(26):1441-1446.
13. Carlson KJ LD, Goroll AH, Leahy M, Johnson RA. An analysis of physicians' reasons for prescribing long-term digitalis therapy in outpatients. *J Chronic Dis.* 1985;38(9):733-739.
14. Paulus WJ, Tschope C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left

ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J.* October 2, 2007 2007;28(20):2539-2550.

15. Vasan RS, Levy D. Defining Diastolic Heart Failure : A Call for Standardized Diagnostic Criteria. *Circulation.* May 2, 2000 2000;101(17):2118-2121.
16. Zile MR, Gaasch WH, Carroll JD, et al. Heart Failure With a Normal Ejection Fraction: Is Measurement of Diastolic Function Necessary to Make the Diagnosis of Diastolic Heart Failure? *Circulation.* August 14, 2001 2001;104(7):779-782.
17. Aurigemma GP, Gaasch WH. Diastolic Heart Failure. *N Engl J Med.* September 9, 2004 2004;351(11):1097-1105.
18. Maurer MS, Burkhoff D, Fried LP, et al. Ventricular Structure and Function in Hypertensive Participants With Heart Failure and a Normal Ejection Fraction: The Cardiovascular Health Study. *Journal of the American College of Cardiology.* 2007;49(9):972-981.
19. Maurer MS, Spevack D, Burkhoff D, et al. Diastolic dysfunction: Can it be diagnosed by Doppler echocardiography? *Journal of the American College of Cardiology.* 2004;44(8):1543-1549.
20. Scalia GM, Greenberg NL, McCarthy PM, et al. Noninvasive Assessment of the Ventricular Relaxation Time Constant ({tau}) in Humans by Doppler Echocardiography. *Circulation.* January 7, 1997 1997;95(1):151-155.
21. Zile MR, Baicu CF, Bonnema DD. Diastolic Heart Failure: Definitions and Terminology. *Progress in Cardiovascular Diseases.* 2005;47(5):307-313.
22. Zile MR, Baicu CF, Gaasch WH. Diastolic Heart Failure -- Abnormalities in Active Relaxation and Passive Stiffness of the Left Ventricle. *N Engl J Med.* May 6, 2004 2004;350(19):1953-1959.
23. Kass DA, Wolff MR, Ting C-T, et al. Diastolic Compliance of Hypertrophied Ventricle Is Not Acutely Altered by Pharmacologic Agents Influencing Active Processes. *Ann Intern Med.* September 15, 1993 1993;119(6):466-473.
24. Kawaguchi M, Hay I, Fetics B, et al. Combined Ventricular Systolic and Arterial Stiffening in Patients With Heart Failure and Preserved Ejection Fraction: Implications for Systolic and Diastolic Reserve Limitations. *Circulation.* February 11, 2003 2003;107(5):714-720.
25. Burkhoff D, Maurer MS, Packer M. Heart Failure With a Normal Ejection Fraction: Is It Really a Disorder of Diastolic Function? *Circulation.* February 11, 2003 2003;107(5):656-658.
26. Melenovsky V, Borlaug BA, Rosen B, et al. Cardiovascular Features of Heart Failure With Preserved Ejection Fraction Versus Nonfailing Hypertensive Left Ventricular Hypertrophy in the Urban Baltimore Community: The Role of Atrial Remodeling/Dysfunction. *Journal of the American College of Cardiology.* 2007;49(2):198-207.
27. Zile MR, LeWinter MM. Left Ventricular End-Diastolic Volume Is Normal in Patients With Heart Failure and a Normal Ejection Fraction: A Renewed Consensus in Diastolic Heart Failure. *Journal of the American College of Cardiology.* 2007;49(9):982-985.

28. Aurigemma GP, Zile MR, Gaasch WH. Contractile Behavior of the Left Ventricle in Diastolic Heart Failure: With Emphasis on Regional Systolic Function. *Circulation.* January 17, 2006 2006;113(2):296-304.
29. Maurer MS, King DL, El-Khoury Rumbarger L, et al. Left Heart Failure With a Normal Ejection Fraction: Identification of Different Pathophysiologic Mechanisms. *Journal of Cardiac Failure.* 2005;11(3):177-187.
30. Redfield MM, Jacobsen SJ, Borlaug BA, et al. Age- and Gender-Related Ventricular-Vascular Stiffening: A Community-Based Study. *Circulation.* October 11, 2005 2005;112(15):2254-2262.
31. Balmain S, Padmanabhan N, Ferrell WR, et al. Differences in arterial compliance, microvascular function and venous capacitance between patients with heart failure and either preserved or reduced left ventricular systolic function. *European Journal of Heart Failure.* 2007;9(9):865-871.
32. O'Connor CM, Carson PE, Miller AB, et al. Effect of amlodipine on mode of death among patients with advanced heart failure in the praise trial. *The American Journal of Cardiology.* 1998;82(7):881-887.
33. Saxon LA, Bristow MR, Boehmer J, et al. Predictors of Sudden Cardiac Death and Appropriate Shock in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial. *Circulation.* December 19, 2006 2006;114(25):2766-2772.
34. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): Developed in Collaboration With the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: Endorsed by the Heart Rhythm Society. *Circulation.* September 20, 2005 2005;112(12):e154-235.
35. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *The Lancet.* 2003;362(9386):777-781.
36. Shibata MC, Flather MD, Bohm M, et al. Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS).: Rationale and design. *International Journal of Cardiology.* 2002;86(1):77-85.
37. Cleland JGF, Tendera M, Adamus J, et al. Perindopril for elderly people with chronic heart failure: the PEP-CHF study. *European Journal of Heart Failure.* 1999;1(3):211-217.
38. Carson P, Massie BM, McKelvie R, et al. The Irbesartan in Heart Failure With Preserved Systolic Function (I-PRESERVE) Trial: Rationale and Design. *Journal of Cardiac Failure.* 2005;11(8):576-585.
39. Borlaug BA, Kass DA. Mechanisms of Diastolic Dysfunction in Heart Failure. *Trends in Cardiovascular Medicine.* 2006;16(8):273-279.
40. Miyamoto MI, del Monte F, Schmidt U, et al. Adenoviral gene transfer of SERCA2a improves left-ventricular function in aortic-banded rats in transition to

heart failure. *Proceedings of the National Academy of Sciences.* January 18, 2000 2000;97(2):793-798.

41. Hoshijima M, Ikeda Y, Iwanaga Y, et al. Chronic suppression of heart-failure progression by a pseudophosphorylated mutant of phospholamban via in vivo cardiac rAAV gene delivery. *Nat Med.* 2002;8(8):864-871.
42. Mattera GG, Lo Giudice P, Loi FMP, et al. Istaroxime: A New Luso-Inotropic Agent for Heart Failure. *The American Journal of Cardiology.* 2007;99(2, Supplement 1):S33-S40.
43. Rocchetti M, Besana A, Mostacciuolo G, et al. Diverse Toxicity Associated with Cardiac Na+/K+ Pump Inhibition: Evaluation of Electrophysiological Mechanisms. *J Pharmacol Exp Ther.* May 1, 2003 2003;305(2):765-771.
44. Rocchetti M, Besana A, Mostacciuolo G, et al. Modulation of Sarcoplasmic Reticulum Function by Na+/K+ Pump Inhibitors with Different Toxicity: Digoxin and PST2744 [(E,Z)-3-((2-Aminoethoxy)imino)androstane-6,17-dione Hydrochloride]. *J Pharmacol Exp Ther.* April 1, 2005 2005;313(1):207-215.
45. Anderson RH, Ho SY, Redmann K, et al. The anatomical arrangement of the myocardial cells making up the ventricular mass. *European Journal of Cardio-Thoracic Surgery.* 2005;28(4):517-525.
46. Wu Y, Bell SP, Trombitas K, et al. Changes in Titin Isoform Expression in Pacing-Induced Cardiac Failure Give Rise to Increased Passive Muscle Stiffness. *Circulation.* September 10, 2002 2002;106(11):1384-1389.
47. MacKenna DA, Omens JH, McCulloch AD, et al. Contribution of collagen matrix to passive left ventricular mechanics in isolated rat hearts. *Am J Physiol Heart Circ Physiol.* March 1, 1994 1994;266(3):H1007-1018.
48. Baicu CF, Stroud JD, Livesay VA, et al. Changes in extracellular collagen matrix alter myocardial systolic performance. *Am J Physiol Heart Circ Physiol.* January 1, 2003 2003;284(1):H122-132.
49. Brower GL, Janicki JS. Contribution of ventricular remodeling to pathogenesis of heart failure in rats. *Am J Physiol Heart Circ Physiol.* February 1, 2001 2001;280(2):H674-683.
50. Senzaki H, Paolocci N, Gluzband YA, et al. {beta}-Blockade Prevents Sustained Metalloproteinase Activation and Diastolic Stiffening Induced by Angiotensin II Combined With Evolving Cardiac Dysfunction. *Circ Res.* April 14, 2000 2000;86(7):807-815.
51. Herrmann KL, McCulloch AD, Omens JH. Glycated collagen cross-linking alters cardiac mechanics in volume-overload hypertrophy. *Am J Physiol Heart Circ Physiol.* April 1, 2003 2003;284(4):H1277-1284.
52. Asif M, Egan J, Vasan S, et al. An advanced glycation endproduct cross-link breaker can reverse age-related increases in myocardial stiffness. *Proceedings of the National Academy of Sciences.* March 14, 2000 2000;97(6):2809-2813.
53. Kass DA, Shapiro EP, Kawaguchi M, et al. Improved Arterial Compliance by a Novel Advanced Glycation End-Product Crosslink Breaker. *Circulation.* September 25, 2001 2001;104(13):1464-1470.
54. Little WC, Zile MR, Kitzman DW, et al. The Effect of Alagebrium Chloride (ALT-711), a Novel Glucose Cross-Link Breaker, in the Treatment of Elderly

Patients With Diastolic Heart Failure. *Journal of Cardiac Failure.* 2005;11(3):191-195.