DIASTOLIC DYSFUNCTION AND HEART FAILURE

PHYSIOLOGY, PATHOLOGY, HISTORICAL FEATURES
AND
CLINICAL PERSPECTIVE

2nd Virtual Symposium on Heart Failure

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OBJECTIVES

- This lecture is designed to give the participant a broad perspective on the intellectual development of the concept of “diastolic heart failure” . We will discuss many of the observations leading up to current understandings of this disorder.

The reader/listener should also

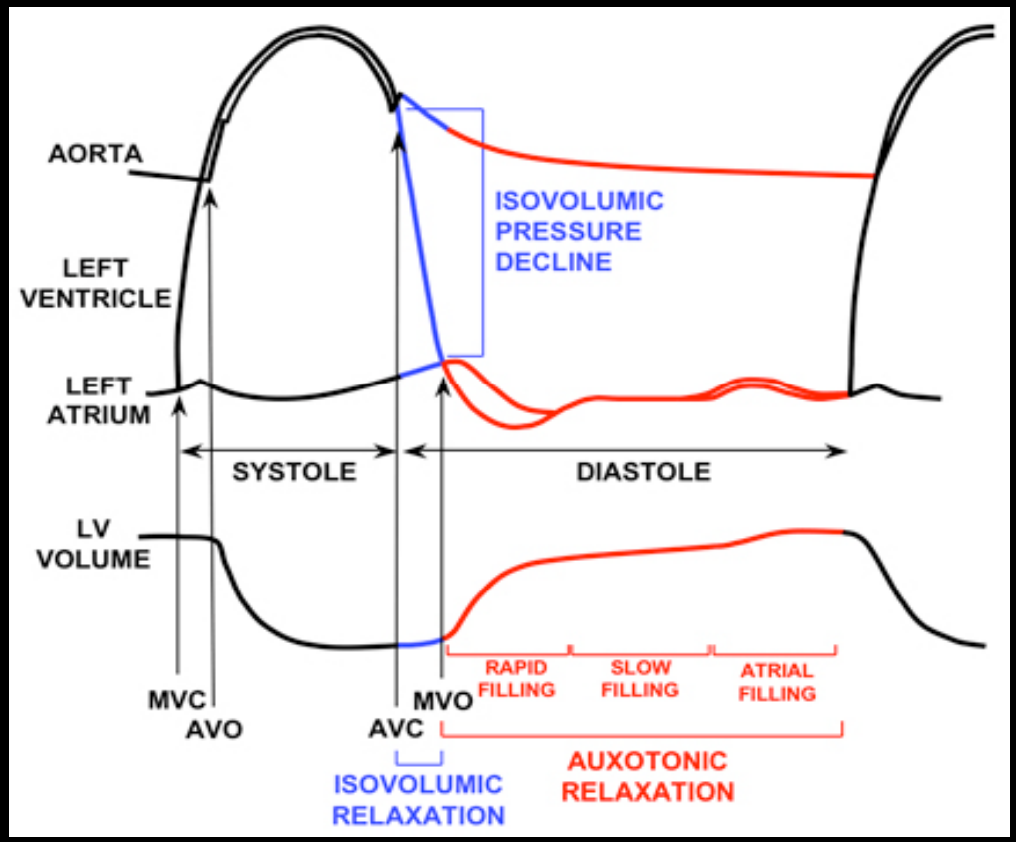
- 1) gain an understanding of the historical investigations into this disorder
- 2) obtain insight into the underlying causes for the development of diastolic dysfunction and heart failure with preserved ventricular function.
- 3) understand the diagnostic approach, epidemiology and prognosis of this disorder

Disclaimer: Your lecturer has had the privilege of witnessing and participating in many of the investigations described in this study. This presentation is a personal view of the history and the interpretation of the current status. There are many other contributors to this “story” that may have been omitted due to the limitations imposed on time and space.

TERMINOLOGY

- Diastolic Dysfunction
  - Alteration in active relaxation and/or passive elastic properties of the LV or other cardiac chambers that results in elevated pressures.
- Diastolic Heart Failure
  - Signs/symptoms of heart failure (congestion) with normal ventricular function/size. Findings of abnormal diastolic function helpful but not necessary.
- Systolic Heart Failure
  - Signs/symptoms of heart failure with abnormal ventricular function/size.

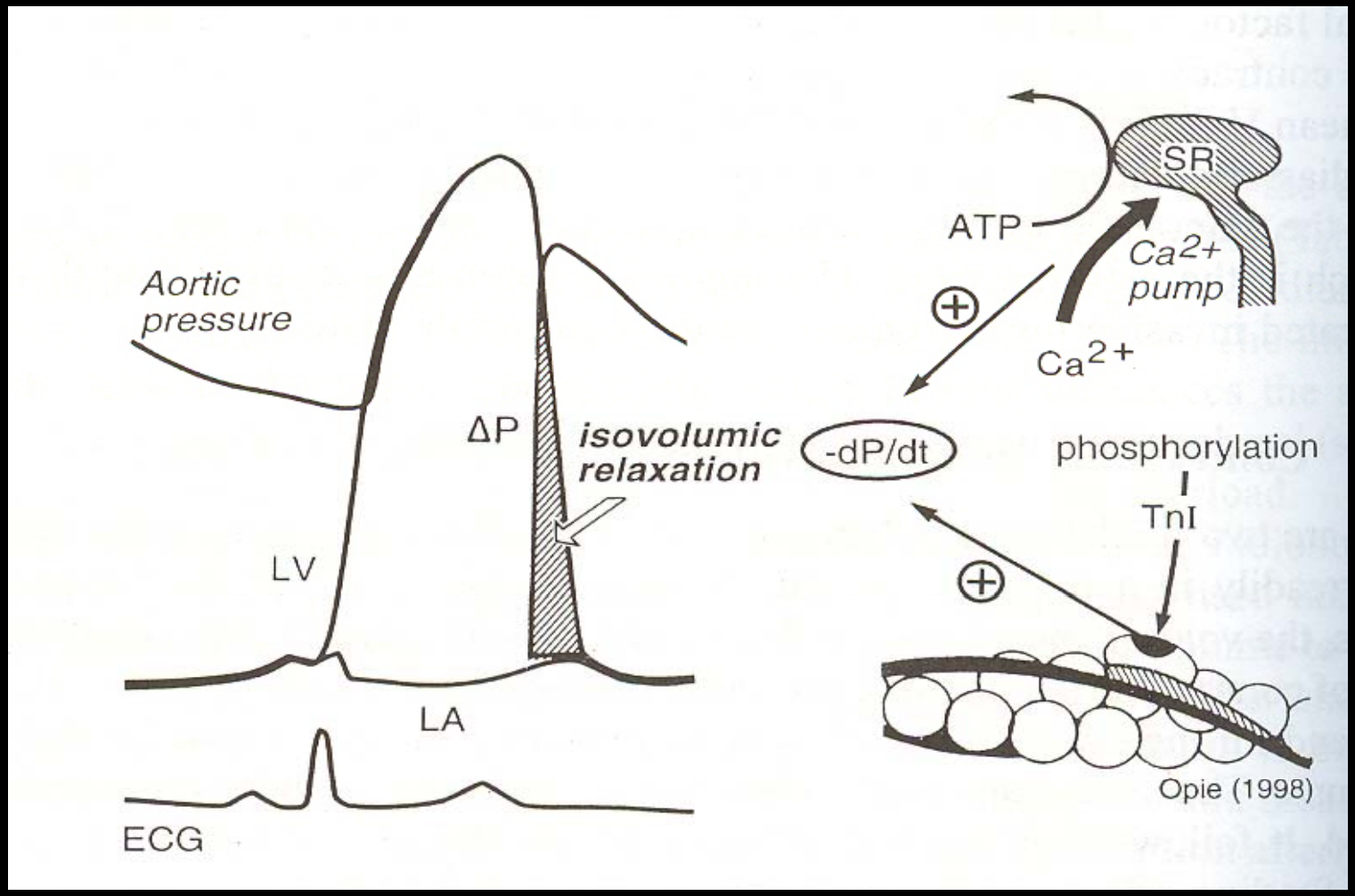
Phases of Diastole



>>A brief review of left ventricular diastolic physiology is presented. Diastole begins with the relaxation of the contracted left ventricle associated with a rapid fall in left ventricular pressures. At mitral valve opening (MVO), there is rapid filling of the left ventricle.
As left ventricular and left atrial pressures equalize, there is a negligible change in the left ventricular volume. With the onset of atrial systole, there is a late contribution (about 20%) to ventricular filling.

ACTIVE RELAXATION

EARLY--- ISOVOLUMIC--- and *ENERGY DEPENDENT*

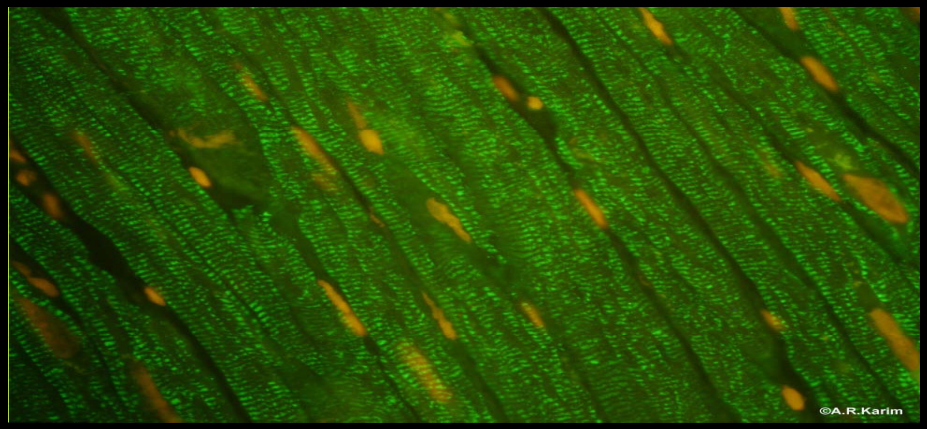


>>In order for relaxation to take place, calcium must move out of the cytosol. It is normally taken up by the sarcoplasmic reticulum. This process is strongly energy dependent and very susceptible to the lack of oxygen. With ischemia, active relaxation as well as contraction is immediately affected.

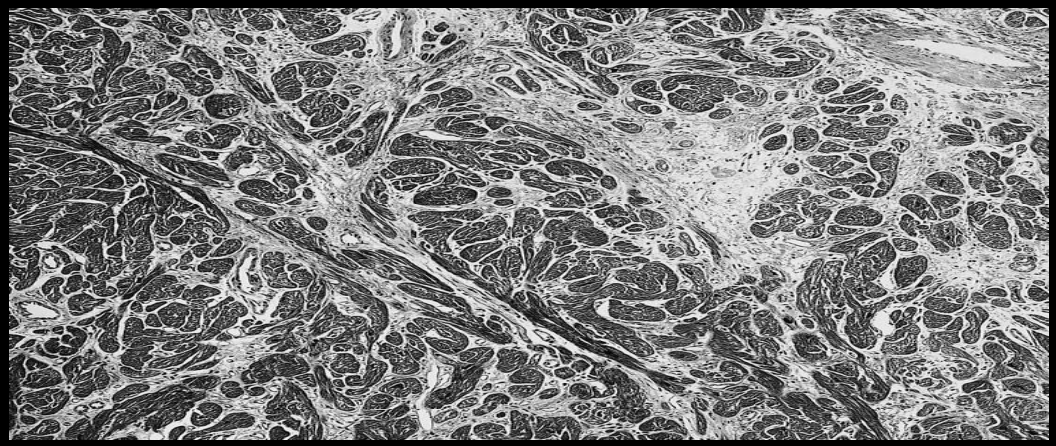
Abnormal Interstitial Collagen Deposition and Hypertrophy

Producing a Chronic State of Diminished Distendibility

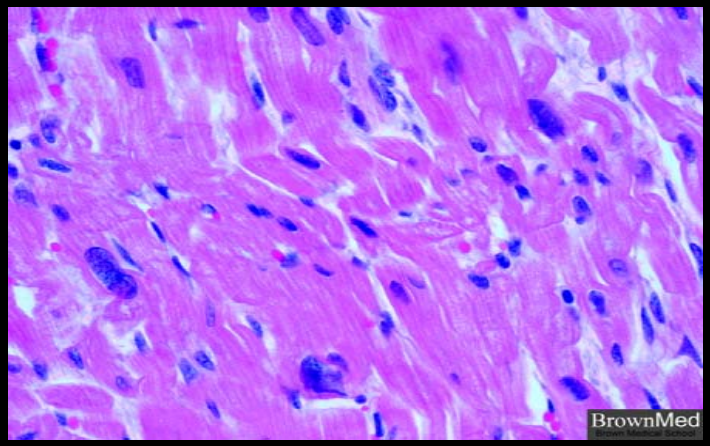
Normal Myocardium



Fibrosis



Hypertrophy



>> On this slide, significant pathologic changes are demonstrated that are typical of the other factors that may influence diastolic relaxation. The viscoelastic properties of the fibrotic or hypertrophied myocardium primarily influence the distensibility of the left ventricle in late diastole.

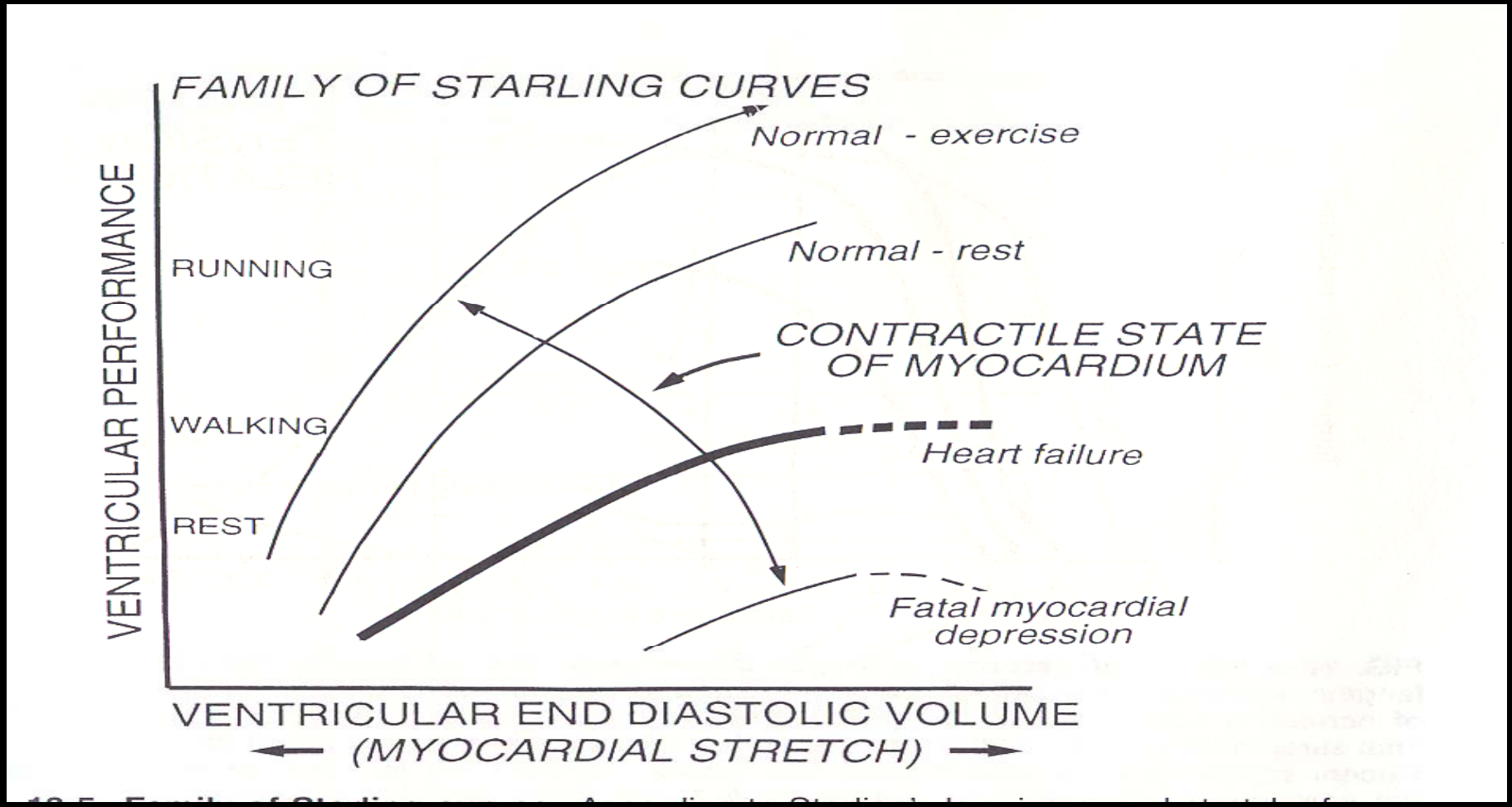
“In the Olden Days”

- 1940-1965: Experimental heart failure studies, produced by volume overload, was associated with increased LV diastolic pressures and flat or declining CO. Therefore, increased LVDP became a surrogate for heart failure.

- 1955-65 Early Catheterization studies: Most patients studied had rheumatic and congenital heart disease with heart failure. They frequently had elevated LV diastolic pressures. This observation supported the concept that increased LV diastolic pressures was an appropriate marker for heart failure.

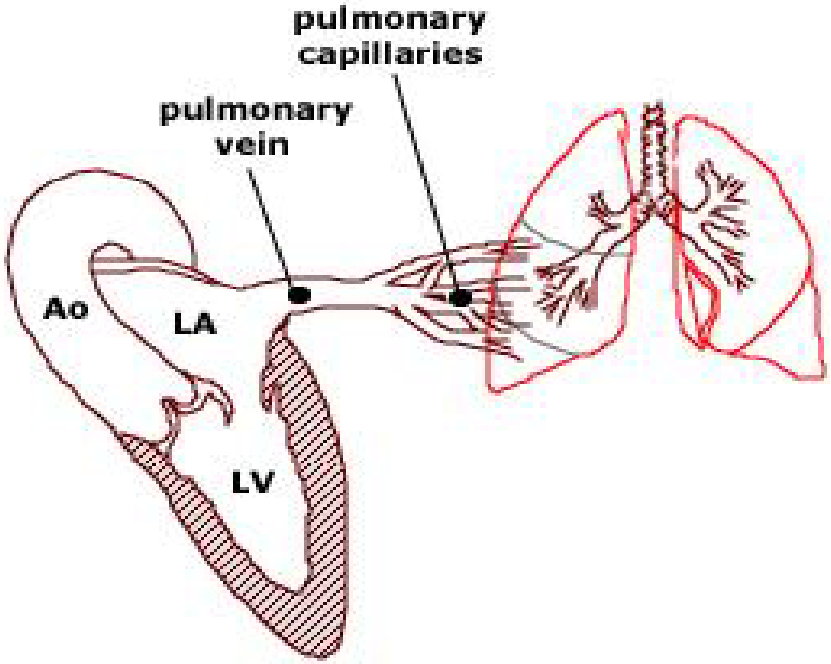
- 1955-65: Dr. Robert Case (St. Luke’s Experimental Lab in NYC) was among several who demonstrated that experimental animals with induced global Ischemia developed increased LV diastolic pressures and declining cardiac output. The increased LV diastolic pressures were equated with heart failure. In the context of global LV ischemia, this was probably an accurate conclusion

Heart failure = Declining CO and Increasing filling (diastolic) pressures



>>This slide exemplifies the early concept of heart failure as determined in experimental animal isolated heart preparations. Cardiologists substituted LV diastolic pressure for LV volumes because of the greater ease of measuring pressure rather than volumes. All heart failure at that time was a failure of contraction properties.

Elevated Left Ventricular Diastolic Pressure Results in Pulmonary Congestion



PCWP 3-12 mm Hg=normal
12-25 mm Hg=elevated
>25 mm Hg=pulmonary edema

>>This slide demonstrates the equalization of pressures in diastole. During the diastasis period of diastole, all pressures are equal between the left ventricle, left atrium, pulmonary veins and the pulmonary capillaries. Temporary or persistent increase of the pulmonary pressures over 25 mmHg can result in the development of pulmonary edema.

Newer Ideas !

•1963 Dr. Eugene Braunwald authored an editorial in the American J of Medicine, commenting on the marked increases of left ventricular diastolic pressures their team had observed in hypertrophied hearts, and aortic stenosis without evidence of clinical heart failure. He concluded that the elevated LV end-diastolic pressure was in these patients was due to an alteration in the pressure-volume relationship or compliance of the left ventricle. Under these circumstances, the left ventricular pressure was not a reliable indicator of heart failure.

Exercise-Induced Ischemia and Ventricular Hemodynamics

Weiner, Dwyer and Cox Circ 1968

Tabl

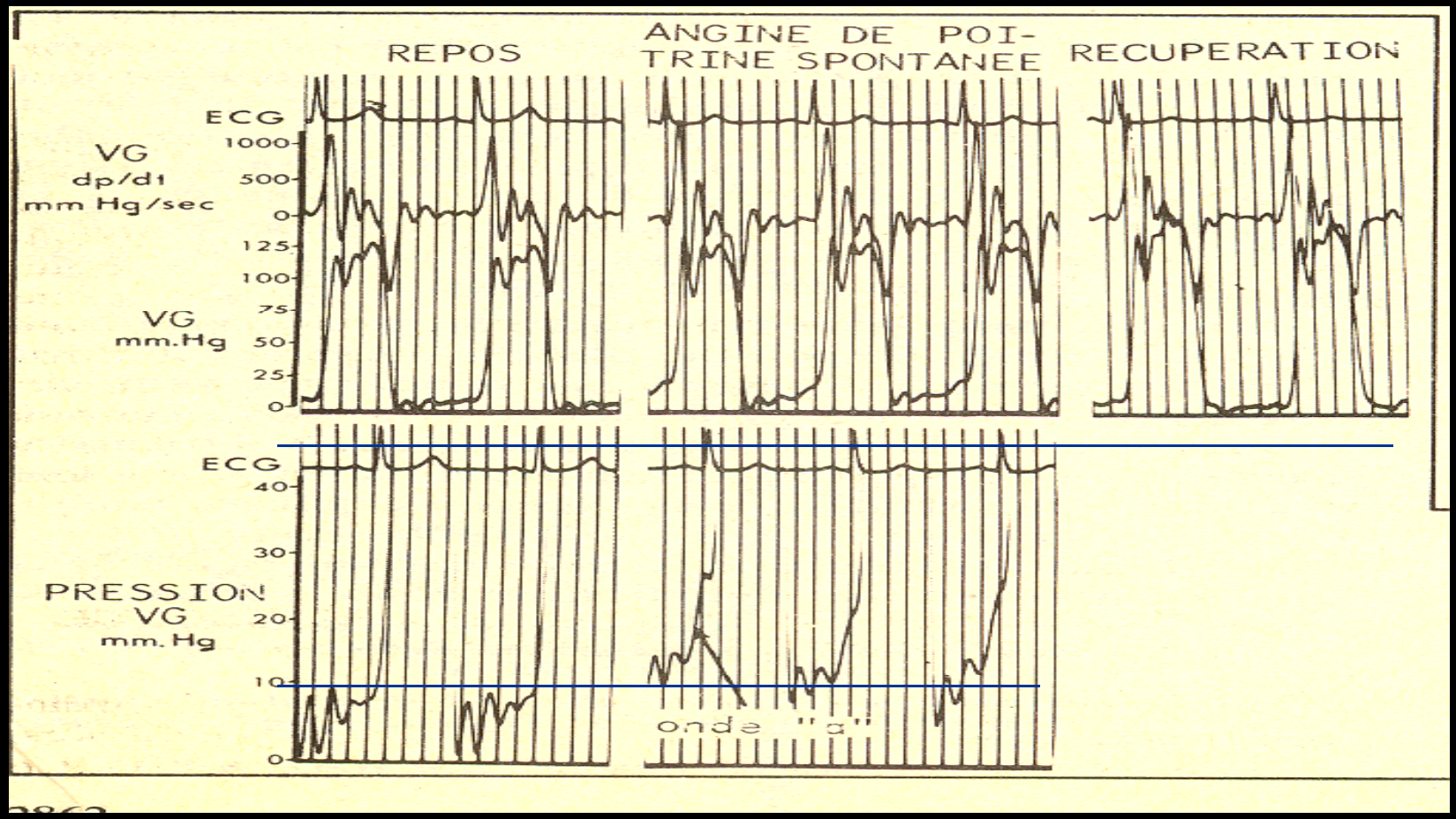
Response to Exercise in Patients with Angina Pectoris

Subject (BSA)	Time	ECG ST depr.	Angina	HR	LVSP	LVEDP	LV dp/dt
M.D.	Rest	0.0	0	67	145	12	1080
(1.8)	1′	0.5	0	105	200	22	2000
	2′	0.5	0	108	200	32	2080
	3′	1.0	0	108	200	30	2080
	4′	2.0	2	105	200	30	2520
	5′	2.0	3	105	200	—	—
	7′ p̄	0.0	0	75	110	—	—
W.F.	Rest	0.0	0	65	145	12	1000
(2.1)	1′	0.0	0	80	160	23	1000
	2′	0.0	0	90	180	28	1240
	3′	0.5	0	96	180	30	1240
	4′	0.5	1	102	178	32	1280
	5′	1.0	2	105	160	30	1320
	6′	1.5	3	110	165	40	—
	3′ p̄	1.5	0	80	160	20	1280
J.L.	Rest	0.0	0	76	110	10	1596
(1.93)	1′	—	0	100	140	22	1764
	2′	—	0	110	140	25	1932
	3′	0.5	1	115	140	30	2352
	4′	0.5	2	115	150	35	2352
	5′	0.5	4	115	150	35	—
	6′	0.5	3	115	150	—	—
	3′ p̄	0.0	0	88	120	13	2352

>> This slide demonstrates several examples of hemodynamic measurements in patients with exercise-induced ischemia. This led to a suspicion of a concept that dynamic alterations in LV relaxation (increased LV diastolic pressures) occur secondary to ischemia. Note changes in the LVEDP during exercise- induced angina

SPONTANEOUS ANGINA

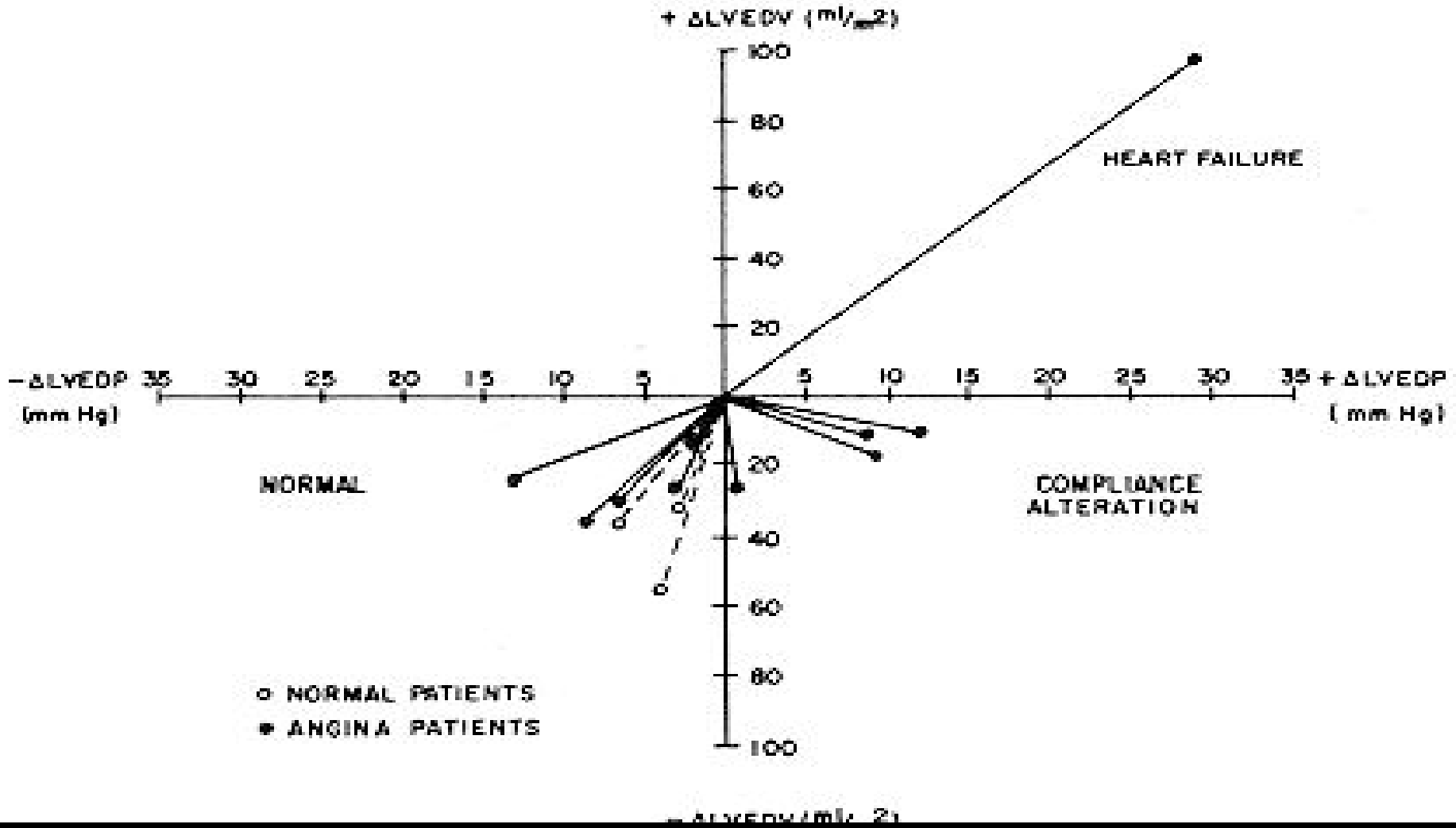
EFFECT ON LEFT VENTRICULAR DIASTOLIC PRESSURE



>> This slide demonstrates the same type of changes in diastolic pressure (10 to 25 mmHg) during spontaneous angina during a cardiac catheterization. This observation was unencumbered by the heart rate and blood pressure changes seen with exercise. The elevated diastolic pressures were not associated with markers of hear failure i.e.. declining blood pressure or increasing heart rate. In addition, we observed no change in the recorded LV dp/dt. (personal observation)

CHANGES IN LV DIASTOLIC PRESSURE AND VOLUME

DURING ANGINA -- INDUCED BY ATRIAL PACING



>> In this study, we induced angina by atrial pacing. Four patients demonstrated that "diastolic pressures increased with a decline in LV volume. These changes were immediately reversed with cessation of ischemia." The increase in the diastolic pressure of the LV was consistent with temporary and acute alterations in the compliance characteristics of the left ventricle.

DWYER CIRC 1970

Regional Contractile Properties Are Also Immediately Affected by Ischemia

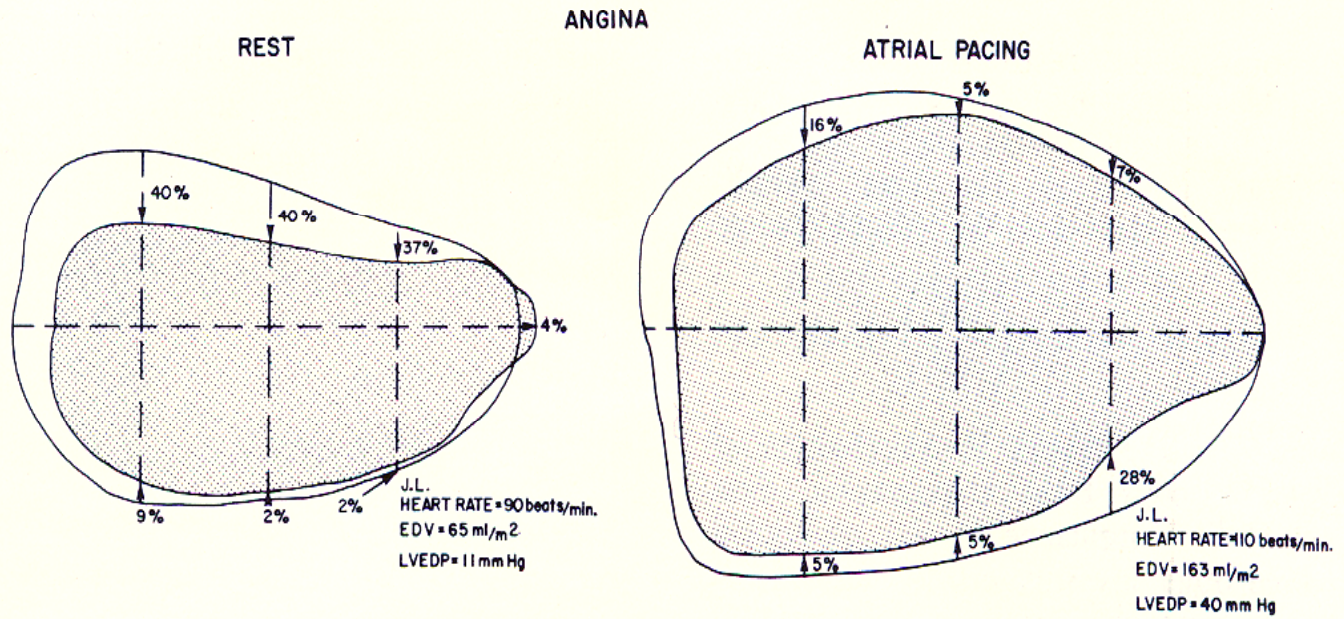


Figure 3

A patient who developed overt heart failure during angina. Angina has resulted in a marked increase in end-diastolic pressure and a fall in stroke work.

>> In the same study, one patient demonstrated severe abnormalities of contraction along with severely increased diastolic pressure and volume. These findings were more consistent with the acute development of heart failure , as we classically view it. Such a change might clinically be associated with acute pulmonary edema.

Interest in Pulmonary Edema with Acute MI in Patients with Normal Ejection Fraction

•**1983** Warnowitz et al: Described pulmonary edema in acute MI with normal ejection fraction **(>45%).** CIRC (**but reported a I yr. 25% mortality**)

•**1984** Dwyer, Greenberg & Steinberg – Described the natural history of patients (MPIP) with pulmonary congestion following an acute MI. AJC

Pulm. Congestion:	**30% had EF > 50%**	**1 yr mortality =15%**
No Pulm. Congestion:	**43% had EF > 50%**	**1 yr mortality = 3%**

>> These reports represent the increasing awareness that pulmonary edema occurs in the presence of a normal left ventricular (EF > 50%).
These clinical studies tie closely to the earlier observations that ischemia could cause contraction and relaxation abnormalities, leading to pulmonary edema, that could resolve as rapidly as it appeared.
The occurrence of pulmonary edema in patients with normal LV function, generally signaled that a substantial amount of left ventricular myocardium was at risk. This appears to be confirmed by the high 1 year mortality.

Surgical Treatment of Recurrent Pulmonary Edema in Patients with Coronary Disease and Normal Ejection Fraction

- The next slide depicts four case reports of patients with known coronary disease and preserved left ventricular function who developed recurrent pulmonary edema. Attempts at medical treatment were quite aggressive but unsuccessful. The clinical episodes of pulmonary edema were essentially aborted after reconstitution of coronary blood flow with coronary by pass surgery.

NEJM 1985

MEDICAL INTELLIGENCE

CORONARY REVASCULARIZATION FOR RECURRENT PULMONARY EDEMA IN ELDERLY PATIENTS WITH ISCHEMIC HEART DISEASE AND PRESERVED VENTRICULAR FUNCTION

RICHARD KUNIS, M.D., HENRY GREENBERG, M.D., CHIN BOR YEOH, M.D., OSCAR B. GARFEIN, M.D., ANTHONY J. PEPE, M.D., BRUCE H. PINKERNELL, M.D., MARK V. SHERRID, M.D., AND EDWARD M. DWYER, JR., M.D.

EF=48%

EF=76%

EF=79%

EF=67%

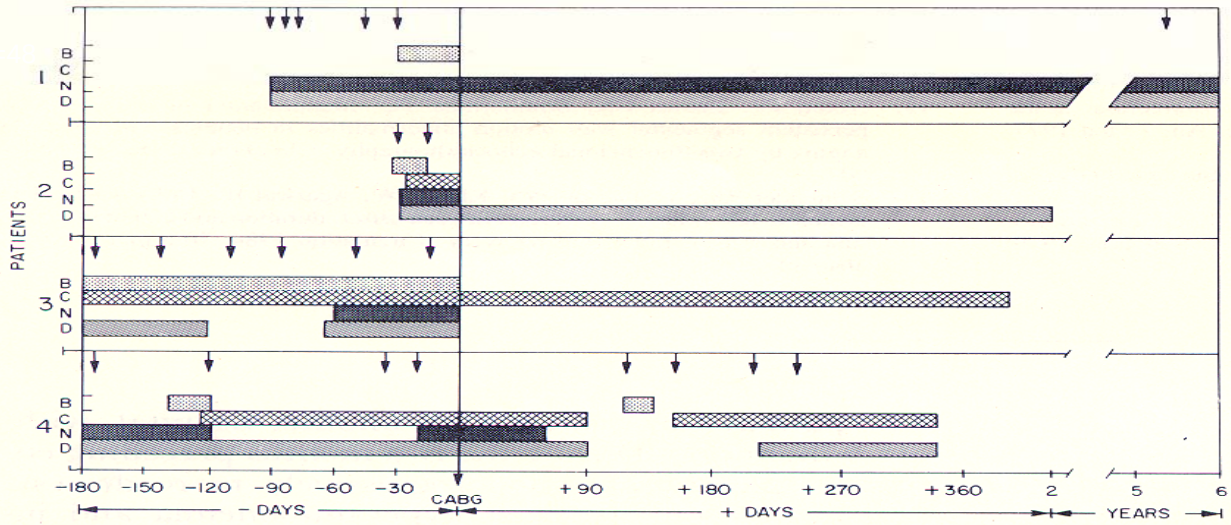


Figure 1. Chronological Display of Recurrent Episodes of Acute Pulmonary Edema (Arrows) and Antianginal and Diuretic Therapy before and after Coronary Artery Bypass Grafting (CABG) in Four Patients.

B denotes beta-adrenergic–blocking drugs, C calcium channel–blocking drugs, N oral nitrates, and D diuretic agents.

The Effect of an Acute Increase/Decrease in Arterial Blood Pressure on LV Diastolic Pressure

ANGIOTENSIN II Infusion & Blockade

1992 Katayama et al Jpn Circ J

With Angiotensin infusion, ABP increased from 137 to 170 mmHg and LVEDP increased from 13 to 20 mmHg

1994 Clarkson et al Clin Sci

Angiotensin Infusion produced dose related prolongation of IVRT

1999 Oki et al J Am Soc Echo

Angiotensin Infusion in normal subjects increased BP 30% and significantly decreased LV relaxation indicators.

1978 Turini et al Arch Int Pharmacodyn Ther

Angiotensin II blockade in congestive heart failure.

A decline in mean arterial pressure from 95 to 86 mm Hg

accompanied by a reduction in LV filling pressure from 19 to 11 mm Hg

>> These studies have demonstrated that increasing left ventricular load , such as seen with marked increases in systolic blood pressure, is associated with increasing LV diastolic pressures through alterations in relaxation of the LV.

These findings are consistent with the clinical observations of acute pulmonary edema in hypertensive patients who have severe elevations of blood pressure. The usual clinical observation is that effective treatment results from control of systolic pressures.

Assessment of Diastolic Function

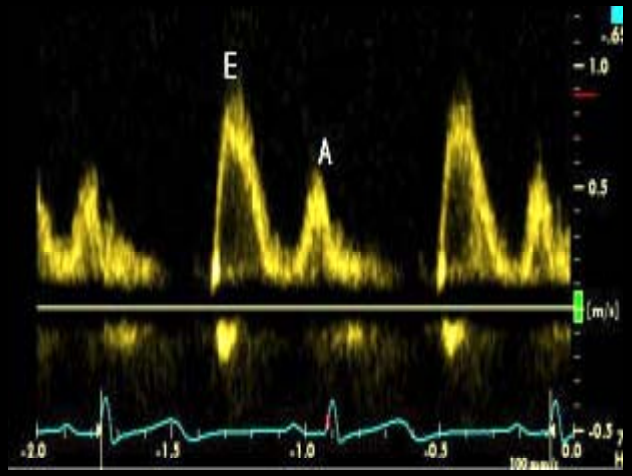
•1975-2007 Non invasive techniques (2D Echocardiogram) were developed that evaluated LV ejection fraction, diastolic volume, wall thickness, mass, and regional wall motion.

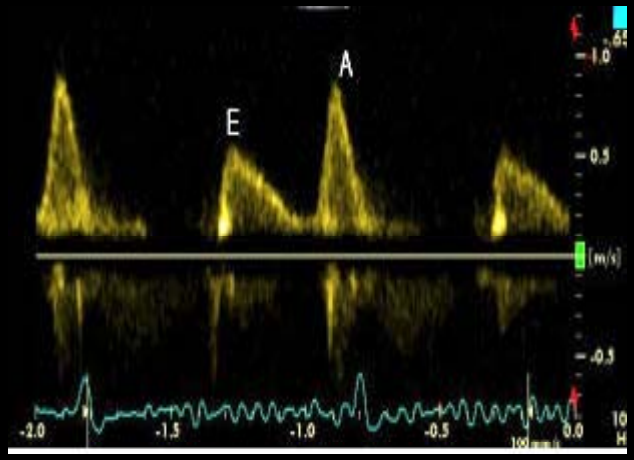
Echocardiogram *** (under stable/rest setting)**

Doppler studies can now detail flow patterns from the left atrium into the LV

E/A flow mitral velocity ratio: In Diastolic dysfunction, E declines and A increases (see below)

Newer techniques: Pulmonary venous flow velocity and Tissue Doppler





Cardiac Catheterization **continues to be the "gold standard" but is limited by the invasive nature of the study. Techniques used are :**

***Research method*: Tau = Time during the isovolumetric relaxation period for LV pressure to fall 2/3 of the initial pressure in diastole.**

***Clinical method*: Normal heart size and contraction pattern with elevated LV end diastolic pressure (normal =12 mmHg). Greater specificity when >16 mmHg used as "abnormal".**

MOST COMMON CAUSES OF DIASTOLIC DYSFUNCTION with NORMAL EF

ACUTE/ TRANSIENT - affecting early relaxation

- **Ischemia**
- **Acute Hypertension**

CHRONIC – affecting early relaxation

- **Hypertrophy**

CHRONIC/ ? REVERSIBLE - affecting later stages of diastole altering distensibility of the LV

- **Chronic myocardial Infarction with replacement fibrosis**
- **Chronic Hypertension with interstitial fibrosis & hypertrophy**
- **Diabetes and Obesity**
- **Aortic Stenosis & IHSS**
- **Idiopathic Hypertrophic Cardiomyopathy**

>> In this slide we depict the disorders that impact diastolic function through their effect on early relaxation or on the viscoelastic properties of the LV.
These disorders may eventually lead to diastolic heart failure.
The most common diseases associated with diastolic heart failure are on these lists.

Symptoms at Onset of Diastolic Heart Failure

Table 2. Presenting Symptoms and Signs of Heart Failure.

Variable	Reduced Ejection Fraction (<40%) (N=1570)	Preserved Ejection Fraction (>50%) (N=880)	P Value
	no. (%)		
Symptoms			
Acute pulmonary edema	332 (21.1)	152 (17.3)	0.02
Dyspnea or shortness of breath	1511 (96.2)	835 (94.9)	0.11
Chest pain	399 (25.4)	212 (24.1)	0.47
Orthopnea	729 (46.4)	374 (42.5)	0.06
Syncope	27 (1.7)	10 (1.1)	0.26
Paroxysmal nocturnal dyspnea	473 (30.1)	220 (25.0)	0.007
Signs			
Bilateral ankle edema	888 (56.6)	581 (66.0)	<.001
Wheezing	302 (19.2)	173 (19.7)	0.80
Neck-vein distention	962 (61.3)	506 (57.5)	0.07
Crackles or rales on lung examination	1324 (84.3)	743 (84.4)	0.95
Hepatojugular reflux	119 (7.6)	69 (7.8)	0.82
Hepatomegaly	81 (5.2)	38 (4.3)	0.35
Presence of S3	196 (12.5)	74 (8.4)	0.002
Presence of S4	80 (5.1)	33 (3.8)	0.13
Chest radiographic signs			
Pulmonary edema	814 (51.8)	414 (47.0)	0.02
Pleural effusion	716 (45.6)	360 (40.9)	0.03

>>Nothing too surprising here! The clinical presentations of heart failure are similar, regardless of the ejection fraction

Bhatia et al. NEJM 2006

TRIGGERS TO HEART FAILURE IN PATIENTS WITH PRESERVED LV FUNCTION

- **Ischemia**
- **Hypertension (>200 mmHg)**
- **Volume overload**
  - Increased salt & water intake
  - Chronic renal disease
  - Iatrogenic (procedure or surgery related)
- **Tachycardia**
- **Atrial Fibrillation with and without rapid VR**

>>These triggers are self explanatory.
The blood pressure and heart rate, as triggers, are best assessed from emergency room or ambulance records.

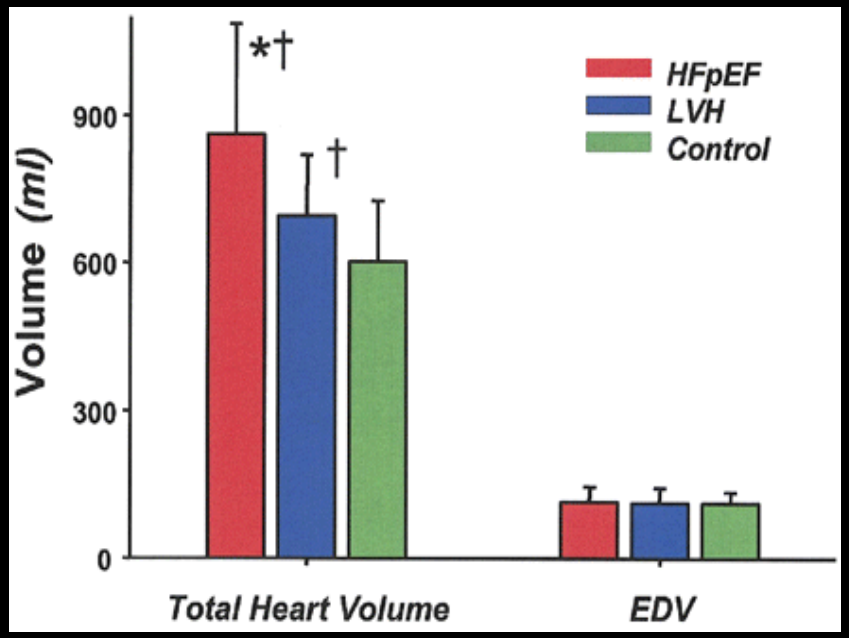
Who Develops Diastolic Heart Failure?
Hospitalizations in NYC and Minneapolis

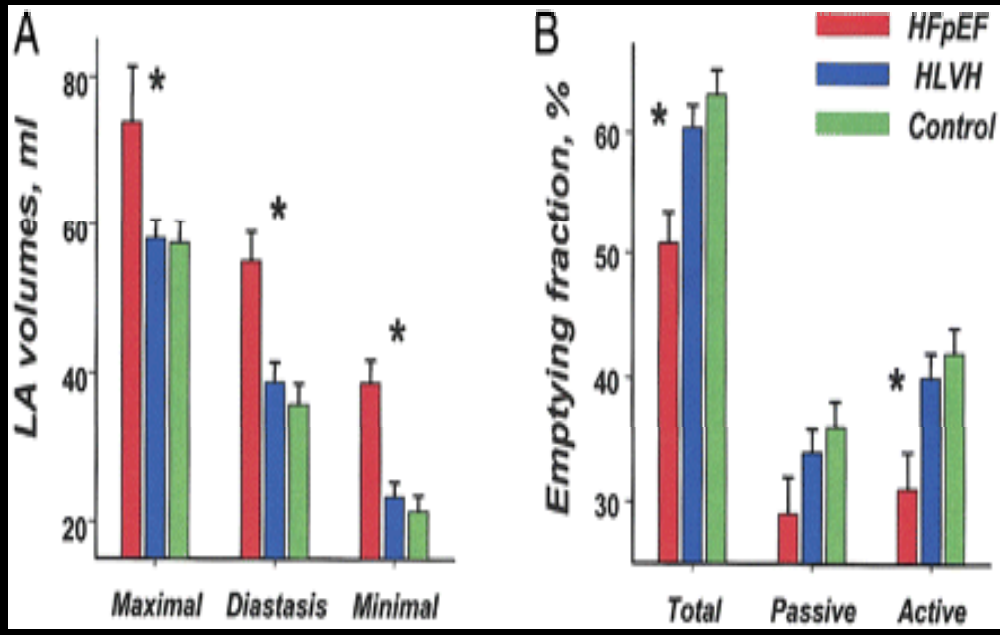
Klapholz et al 2004 JACC **Owan et al 2006 NEJM**	Total (NYC) 619	Total (Minn) 2167
Age (yrs)*	72 ± 14	74 ± 14
Gender (male)	28%	44%
History of hypertension	78%	63%
Systolic BP (mm Hg, on presentation)	160 ± 35	-
Diastolic BP (mm Hg, on presentation)	84 ± 20	-
Diabetes mellitus	46%	33%
Coronary artery disease	43%	53%
History of COPD or asthma	25%	-
Obesity (BMI>30)	46%	41%

>> Diastolic heart failure is dominated by the elderly, hypertensive, diabetic, obese patient with a clinical history of coronary disease. A limitation of the demographics of these studies is that neither study confirmed coronary artery disease status by arteriography or stress test.

Differences between Diastolic Dysfunction and Diastolic Heart Failure

Melenovsky et al JACC 2007



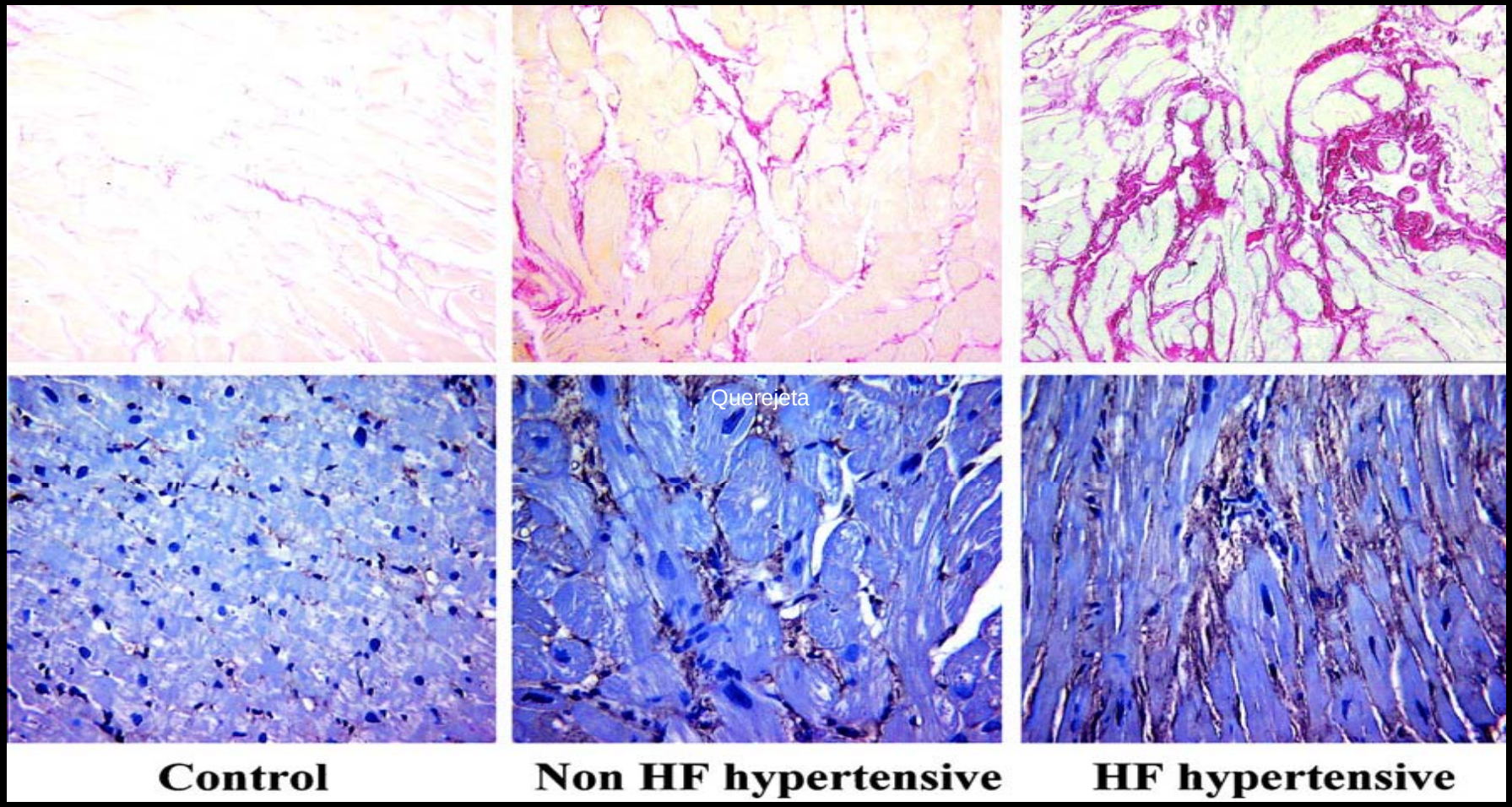


HFpEF = Heart failure with preserved ejection fraction
LVH = Patients with LVH but no heart failure
Control =Normal patients without LVH or heart failure

HFHFp

>> In the patients who developed heart failure, the increased total heart volume (note red bar in left panel) is primarily related to the increase in LA volume (note red bar in right panel). The authors state that "the results suggest that atrial function may be a key compensatory mechanism countering evolution of HFpEF, and they highlight the diagnostic utility of atrial failure as a marker of the disease. "

Diastolic Dysfunction to Diastolic Heart failure
Increase of Collagen Deposition



Querejeta et al CIRC 2004 Increased Collagen Type I Synthesis in Patients With Heart Failure of Hypertensive Origin

>>Their findings suggest that an excess of cardiac collagen type I synthesis and deposition may be involved in the enhancement of myocardial fibrosis that accompanies the development of heart failure in patients with hypertensive heart disease.

Prognosis of Diastolic Heart Failure

The next four slides will depict studies that examine the survival of patients with diastolic dysfunction and the survival of patients with heart failure with a normal ejection fraction.

The prognosis of these patients are strongly influenced by the percentage of patients with coronary artery disease. Other important variables are age and the percentage of patients with co-existing diseases such as diabetes, hypertension, obesity and other vascular diseases.

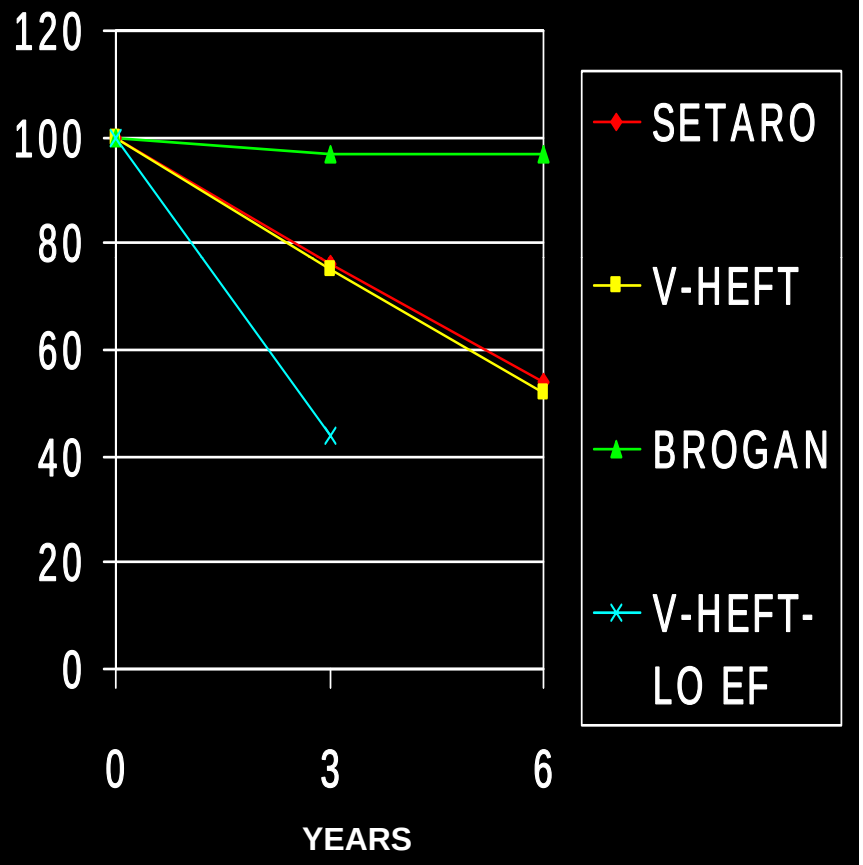
Most studies have examined all-cause mortality and causes of death, are not detailed. Since patients with diastolic heart failure have severe co-morbidities, deaths due to renal, cerebral vascular disease, & thrombo-emboli are common and unrelated to the cardiac disorder. Studies of population of patients with a mean age over 70 years would expectedly carry higher mortality rates than another study with a mean age of 60 years.

Demographic differences in the % of coronary artery disease patients, age and co-morbidities will account for much of the variances in the survival of diastolic heart failure patients as found in the published studies. These variances have created some "controversy" As to the prognosis of heart failure with preserved ejection fraction.

Additional controversies surround the comparison of survival rates in patients with systolic heart failure to the survival in patients with diastolic heart failure. Most studies have shown mortality rates for patients with systolic heart failure at 15-20 % per year. The mix of heart failure class would obviously influence the mortality. But given all the mortality data from systolic heart failure studies, it appears that the mortality in systolic heart failure is about double that seen in most studies of heart failure with preserved ejection fraction.

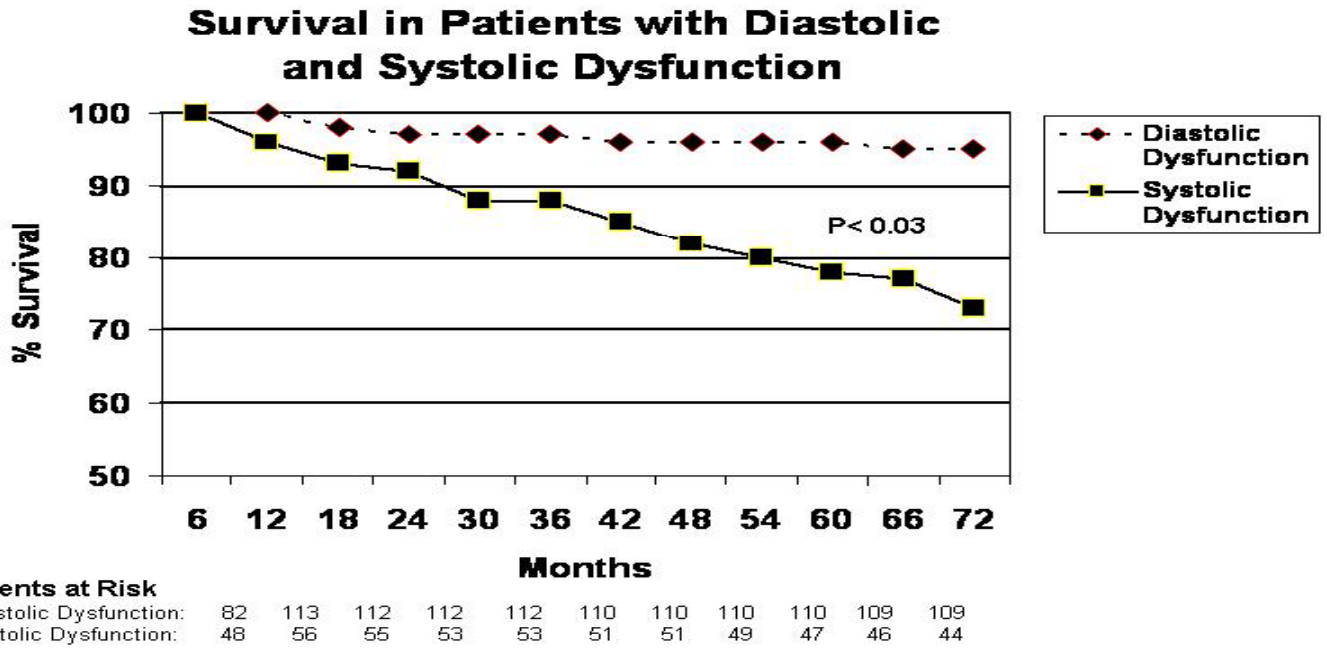
MORTALITY IN DIASTOLIC DYSFUNCTION and DIASTOLIC HEART FAILURE

- **SETARO et al 1992; AJC**
  - 52 pts WITH CHF & INTACT SYSTOLIC FUNCTION
  - F/U 7 YRS
  - 50% CAD; 31% HTN
- **COHN et al 1990; CIRC (V-HEFT)**
  - 83 pts WITH CHF & INTACT SYSTOLIC FUNCTION
  - F/U 5 YRS
  - 27% CAD; 53% HTN
- **BROGAN et al 1992;AJM**
  - 51 pts Diastolic dysfunction; no HF
  - F/U 6 YRS
  - NO CAD



>> These are the early small, long term follow up studies. Two studies have heart failure and preserved ventricular function with Coronary disease patients included. The average annual mortality is 7%for HF patients and near 1% for patients with diastolic dysfunction and without heart failure. These results are similar to later studies. It is noteworthy that the mortality in V-HEFT patients with systolic HF was 20%/year.

PROGNOSIS OF DIASTOLIC DYSFUNCTION without HEART FAILURE & NORMAL CORONARY ARTERIES



Mortality <1%/yr.

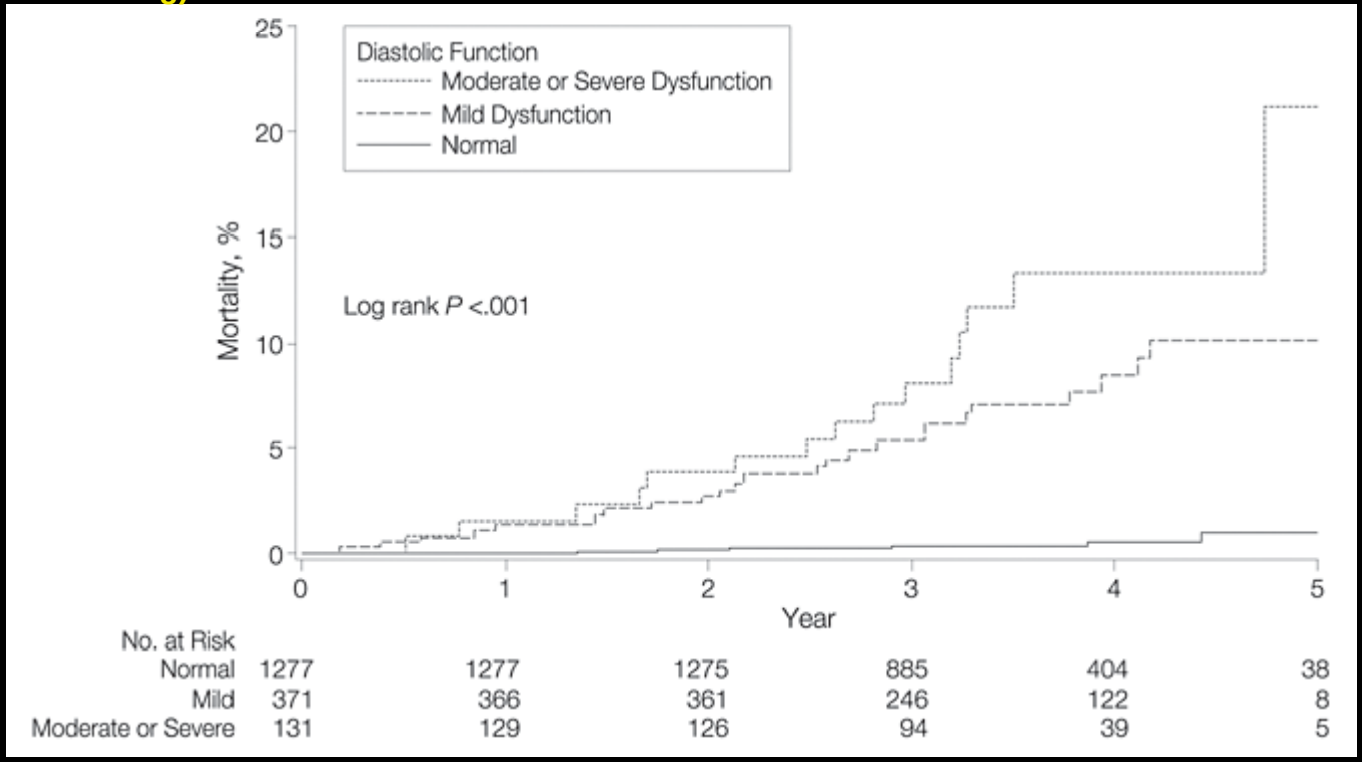
>> This study looks at mortality in patients with diastolic dysfunction without heart failure. Coronary artery disease was excluded by coronary arteriography. Mortality approximated that of the general population at that age group. In the systolic dysfunction group, only 27% had heart failure.

Mean Age = 58 years
Gender = 56% female

BRADY & DWYER 2006 Clin Card

Mortality in Diastolic Dysfunction without Heart Failure

Redfield et al JAMA 2003
(Outpatient setting)



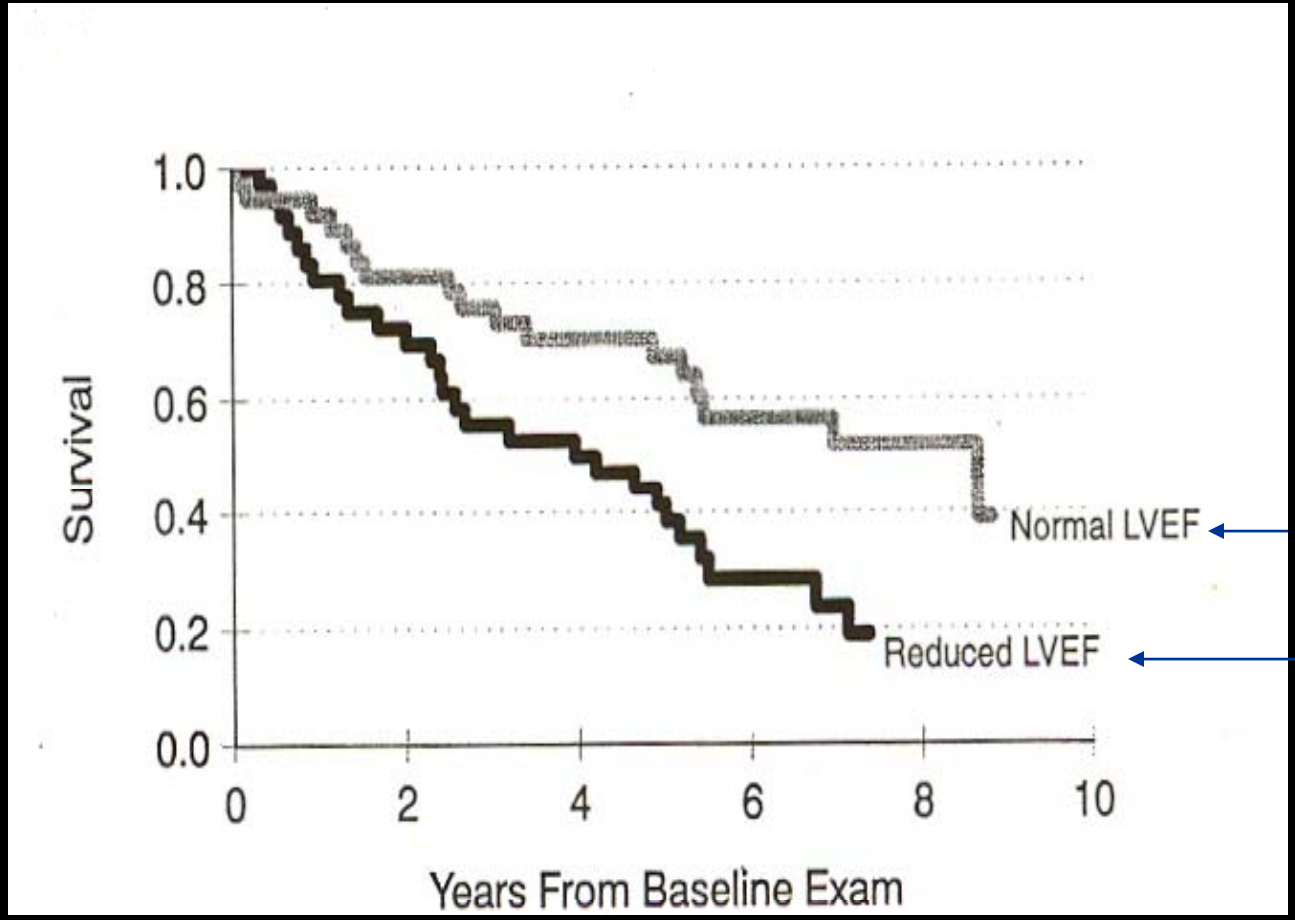
Mortality =2%/yr.

>> This is a similar study of patients with diastolic dysfunction without heart failure. Coronary disease was present but at a relatively low 20%. The mortality was slightly higher at 2% per year.
The slightly higher mortality rate was probably due to the presence of coronary disease.

5% MI; 20%CAD

Mean Age = 63 years
Gender = 50% female

FRAMINGHAM STUDY
Chronic Heart Failure Diagnosis



57% CAD
Mortality=7%/yr.

72% CAD

>> An earlier study from an outpatient setting. A typical mortality was observed in the normal Ejection fraction group. The group with heart failure and reduced ejection fraction had a much steeper mortality curve. Both groups had a very high rate of coronary disease.

Mean age = 73 years
Gender = 65% female

VASAN JACC 1999

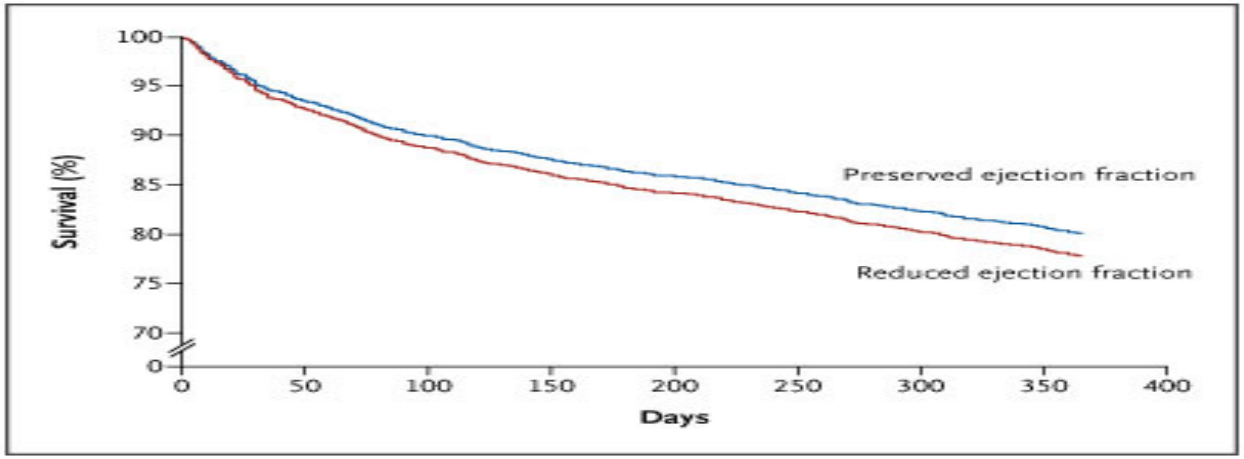
Outcome of Heart Failure with Preserved Ejection Fraction in a Population-Based Study

(Discharged from the Hospital with a Diagnosis of CHF)

Bhatia et al.
NEJM 2006

Table 1. Characteristics of Patients.*

Characteristic	Reduced Ejection Fraction (<40%) (N=1570)	Preserved Ejection Fraction (>50%) (N=8
Mean LVEF — %	25.9	62.4
Age — yr	71.8 ± 12	75.4 ± 11.51
Male sex — no. (%)	983 (62.6)	302 (34.3)
Coronary artery disease or ischemia — no. (%)	764 (48.7)	312 (35.5)
Hypertension — no. (%)	772 (49.2)	485 (55.1)
Hyperlipidemia — no. (%)	350 (22.3)	136 (15.5)
Diabetes — no. (%)	611 (38.9)	279 (31.7)



22%/yr.

>> This study is at considerable variance from other studies that have examined the mortality of patients with heart failure and normal ejection fraction. The authors found a 22% mortality in the first year for that group. This is 3 times the mortality found in other studies. The causes of death were not detailed. Mortality in the systolic HF group is consistent with most other studies.

TREATMENT OF DIASTOLIC HEART FAILURE

CHRONIC

- **Standard management of underlying disorder(s) i.e.. Ischemic issues, hypertension, diabetes and Obesity.**
- **Greater emphasis on maintaining sinus rhythm in patients with paroxysmal atrial fibrillation. Control of heart rate with beta-blockade**
- **In hypertrophic and/or fibrotic disorders, including Hypertension, Diabetes and Obesity, consider**
  ACE inhibitors, Spironalactone & beta-blockers to promote regression of LV mass and prevention of further fibrosis.

ACUTE

- **Control Ischemia**
- **Control BP**
- **Control HR**
- **Reduce Central volume --- NTG, Morphine, Diuretics**

SUMMARY

- Diastolic Heart failure is common (30-40% of HF admissions)
- There is an important role of ischemia and elevated blood pressure in the management of acute and chronic diastolic heart failure.
- Prognosis is heavily influenced by the presence of coronary disease, co-morbidities, and the age of the patient.
- Advances will probably rely on further understanding of causes of abnormal collagen metabolism in the hypertrophy remodeling process and our ability to reverse or control that process.