CARDIOMYOPATHY

By:

Dr. Muriithi Nyamu
Physician/ Cardiologist

Cardiomyopathies

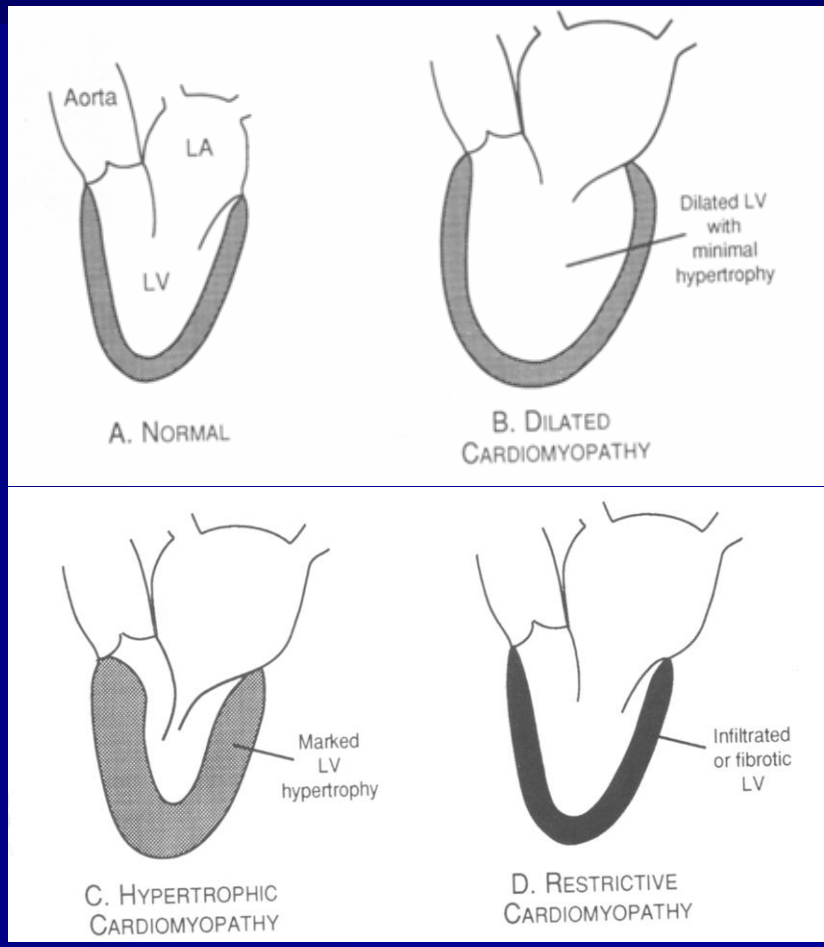
- Definition: diseases of heart muscle
- 1980 WHO: unknown causes
  - Not clinically relevant
- 1995 WHO: "diseases of the myocardium associated with cardiac dysfunction "
  - pathophysiology
  - each with multiple etiologies

Cardiomyopathy

WHO Classification

anatomy & physiology of the LV

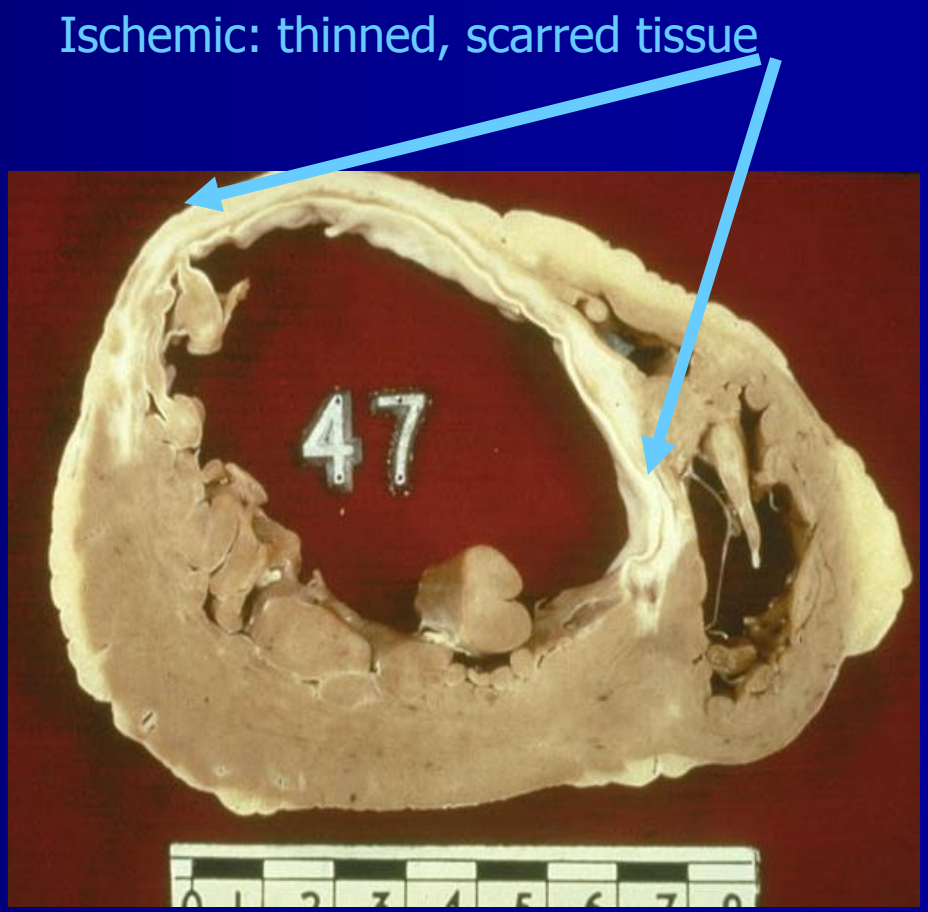
1. Dilated
   - Enlarged
   - Systolic dysfunction
2. Hypertrophic
   - Thickened
   - Diastolic dysfunction
3. Restrictive
   - Diastolic dysfunction
4. Arrhythmogenic RV dysplasia
   - Fibrofatty replacement
5. Unclassified
   - Fibroelastosis
   - LV noncompaction



Circ 93:841, 1996

CM: Specific Etiologies

- Ischemic
- Valvular
- Hypertensive
- Inflammatory
- Metabolic
- Inherited
- Toxic reactions
- Peripartum



Dilated Cardiomyopathy

- Dilation *and* impaired contraction of ventricles:
  - Reduced *systolic* function with or without heart failure
  - Characterized by myocyte damage
  - Multiple etiologies with similar resultant pathophysiology

- Majority of cases are **idiopathic**
  - incidence of idiopathic dilated CM 5-8/100,000
  - incidence likely higher due to mild, asymptomatic cases
  - 3X more prevalent among males and African-Americans

DCM: Etiology

Ischemic
Valvular
Hypertensive
Familial
Idiopathic
Inflammatory
- **Infectious**
  - **Viral – picornovirus, Cox B, CMV, HIV**
  - **Ricketsial - Lyme Disease**
  - **Parasitic - Chagas' Disease, Toxoplasmosis**
- **Non-infectious**
  - **Collagen Vascular Disease (SLE, RA)**
  - **Peripartum**

Toxic
- **Alcohol, Anthracyclins (adriamycin), Cocaine**

Metabolic
- **Endocrine –thyroid dz, pheochromocytoma, DM, acromegaly,**

Nutritional
- **Thiamine, selenium, carnitine**

Neuromuscular (Duchene's Muscular Dystrophy--x-linked)

DCM: Infectious

Acute viral myocarditis

- Coxasackie B or echovirus
- Self-limited infection in young people
- Mechanism?:
  - Myocyte cell death and fibrosis
  - Immune mediated injury
  - BUT:
    - No change with immunosuppressive drugs

DCM: toxic

Alcoholic cardiomyopathy

- Chronic use
- Reversible with abstinence
- Mechanism?:
  - Myocyte cell death and fibrosis
  - Directly inhibits:
    - mitochondrial oxidative phosphorylation
    - Fatty acid oxidation

DCM: inherited

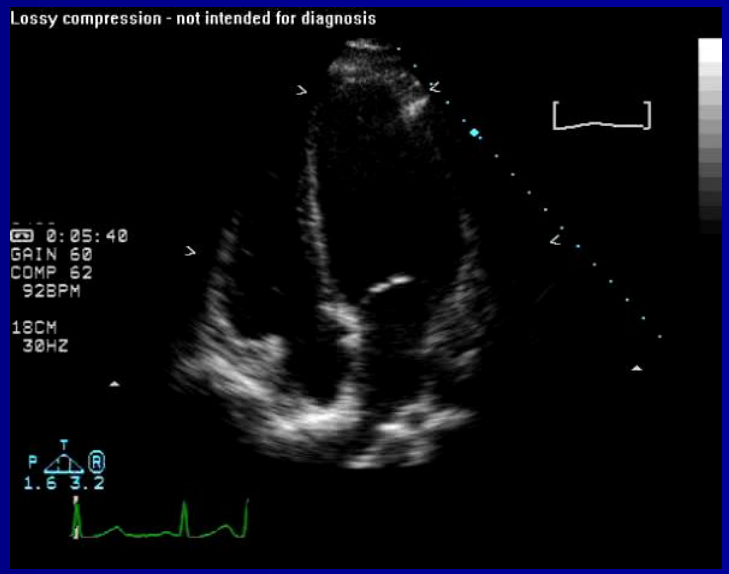
Familial cardiomyopathy

- 30% of 'idiopathic'
- Inheritance patterns
  - Autosommal dom/rec, x-linked, mitochondrial
- Associated phenotypes:
  - Skeletal muscle abn, neurologic, auditory
- Mechanism:
  - Abnormalities in:
    - Energy production
    - Contractile force generation
  - Specific genes coding for:
    - Myosin, actin, dystophin…

DCM: Peripartum

Diagnostic Criteria

- 1 mo pre, 5 mos post
- Echo: LV dysfunction
  - LVEF < 45%
  - LVEDD > 2.7 cm/m2
- Epidemiology/Etiology
- 1:4000 women
    - JAMA 2000;283:1183
- Proposed mechanisms:
  - Inflammatory Cytokines:
    - TNFa, IL6, Fas/AP01
      - JACC 2000 35(3):701.



MECHANISMS IN HEART FAILURE

Ischemic injury
Myocardial disease
Genetics

Neurohormones
Cytokines
Oxidative stress

Altered molecular expression
Ultrastructural changes
Myocyte hypertrophy
Myocyte contractile dysfunction
Apoptosis
Fibroblast proliferation
Collagen deposition
Ventricular remodeling

Hemodynamic Derangement
Clinical Heart Failure
Arrhythmia

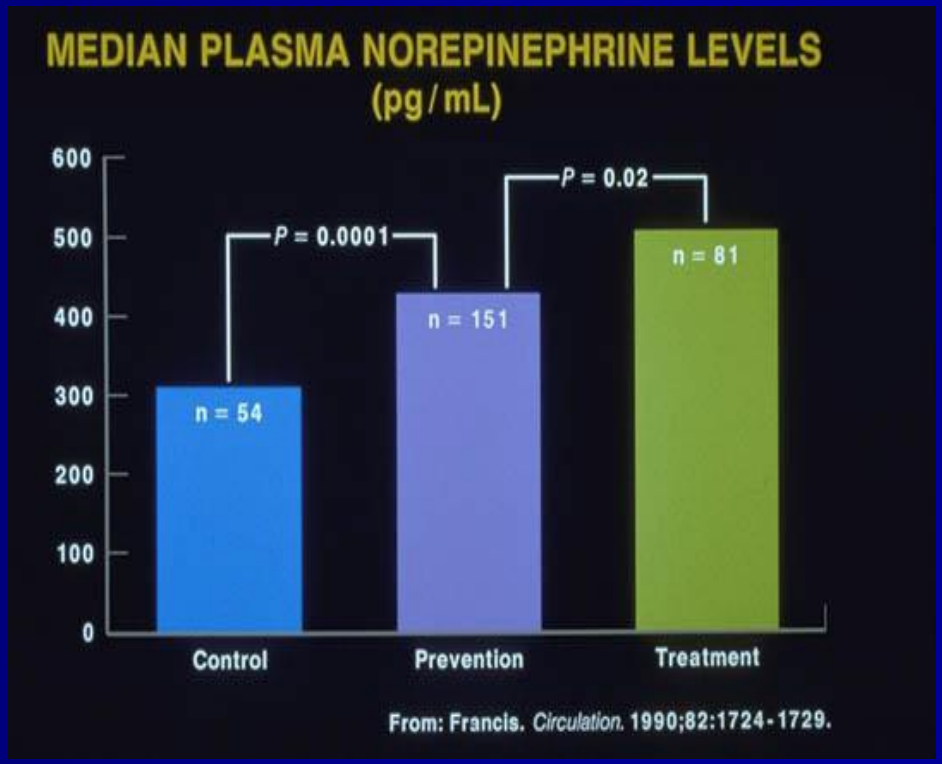
Pathophysiology

- Initial Compensation for impaired myocyte contractility:
  - Frank-Starling mechanism
  - Neurohumoral activation
  - ↑ intravascular volume

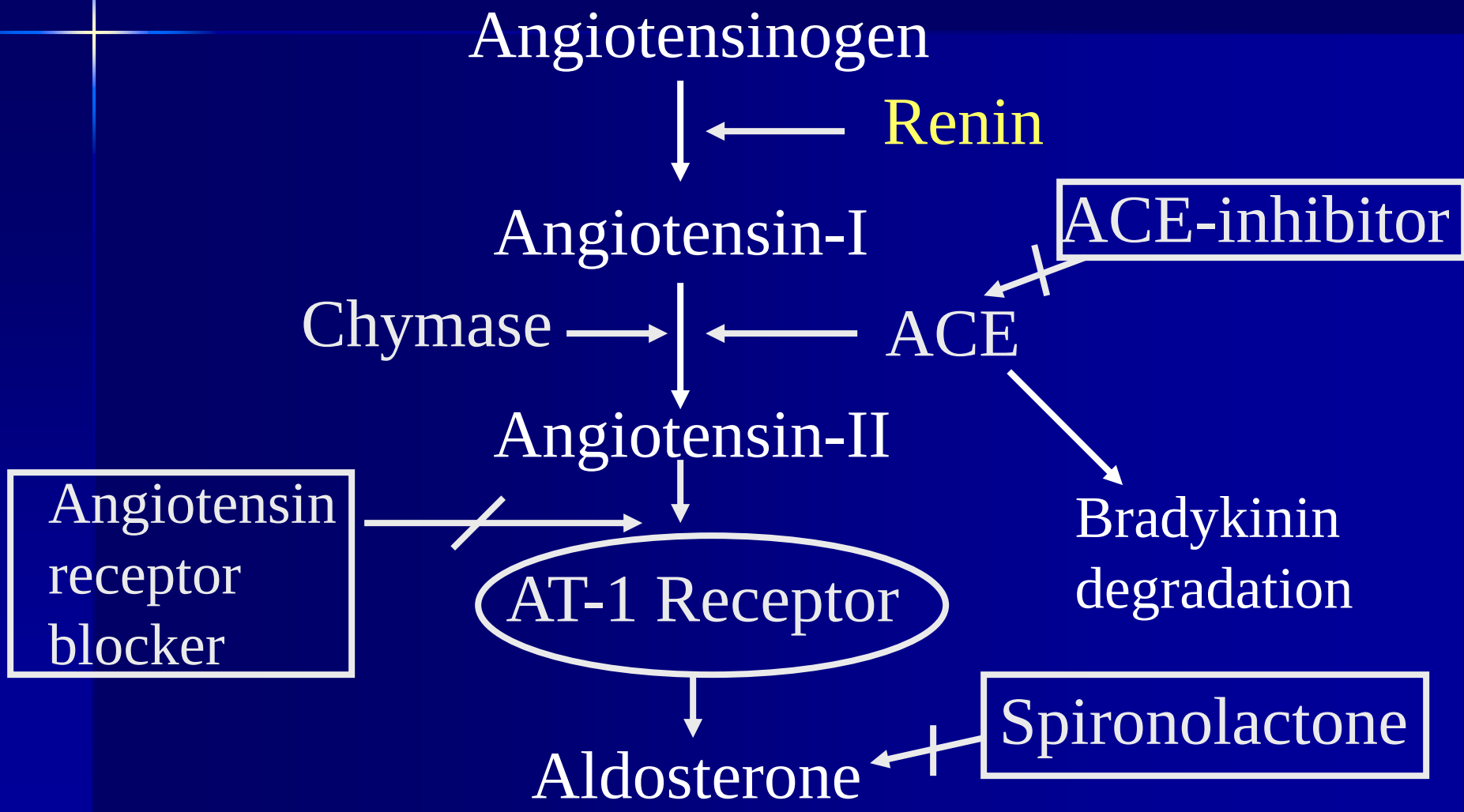
- Eventual decompensation
  - ventricular remodeling
  - myocyte death/apoptosis
  - valvular regurgitation

Pathophysiology: Neurohumoral

- Adrenergic nervous system
- Renin-angiotensin-aldosterone axis
- Vasopressin
- Natriuretic peptides
- Endothelin



Renin-Angiotensin-Aldosterone Pathways



Angiotensin-II Effects

- Vasoconstriction
- Aldosterone production
- Myocyte hypertrophy
- Fibroblast proliferation
- Collagen deposition
- Apoptosis
- Pro-thrombotic
- Pro-oxidant
- Adrenergic stimulation
- Endothelial dysfunction

The Kidney in Heart Failure

- Reduced renal blood flow
- Reduced glomerular filtration rate
- Increased renin production
- Increased tubular sodium reabsorption
- Increased free water retention (vasopressin)

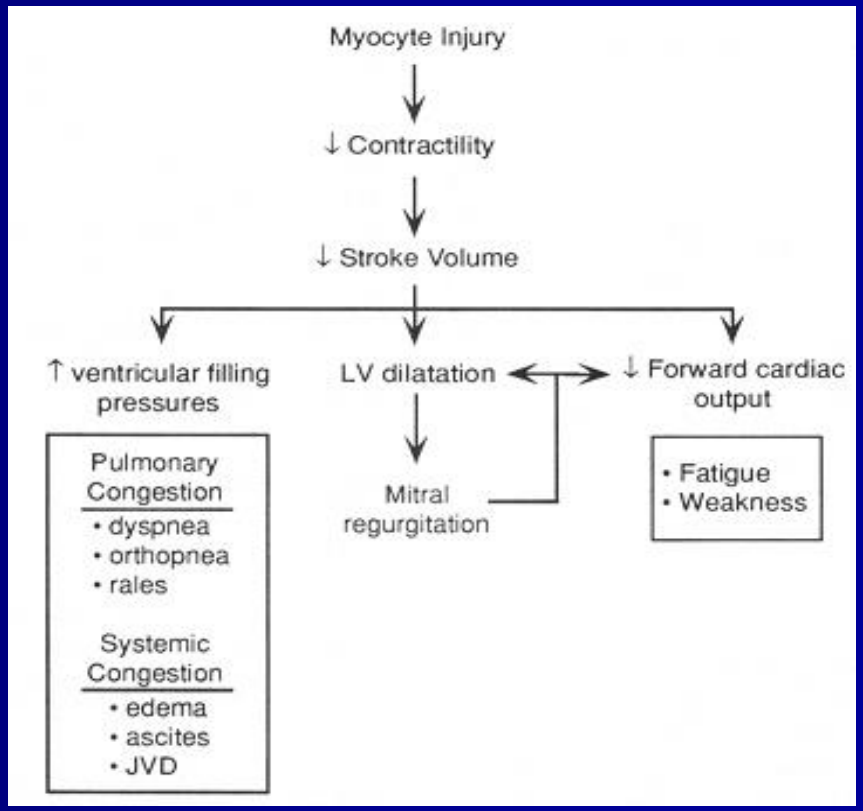
Clinical Findings

Biventricular Congestive Heart Failure

-Low forward Cardiac Output
-fatigue, lightheadedness, hypotension

-Pulmonary Congestion
-Dyspnea,
-orthopnea, & PND

-Systemic Congestion
-Edema
-Ascites
-Weight gain



Physical Exam

Decreased C.O.
- Tachycardia
- ↓ BP and pulse pressure
- cool extremities (vasoconstriction)
- Pulsus Alternans (end-stage)

Pulmonary venous congestion:
- rales
- pleural effusions

Cardiac:
- laterally displaced PMI
- S3 (acutely)
- mitral regurgitation murmur

Systemic congestion
- ↑ JVD
- hepatosplenomegaly
- ascites
- peripheral edema

Diagnostic Studies

CXR -enlarged cardiac silhouette,
vascular redistribution interstitial edema,
pleural effusions

EKG –normal
tachycardia, atrial and ventricular
enlargement, LBBB, RBBB, Q-waves

Blood Tests
(ANA,RF, Fe^{2+}, TFT's,ferritin,)

Echocardiography
LV size, wall thickness function
valve dz, pressures

Cardiac Catheterization
hemodynamics
LVEF
angiography

Endomyocardial Biopsy

Criteria for NYHA Functional Classification

Class 1: No limitation of physical activity.
Ordinary physical activity w/o fatigue, palpitation, or dyspnea.

Class 2: Slight limitation of physical activity. Comfortable at rest, but symptoms w/ ordinary physical activity

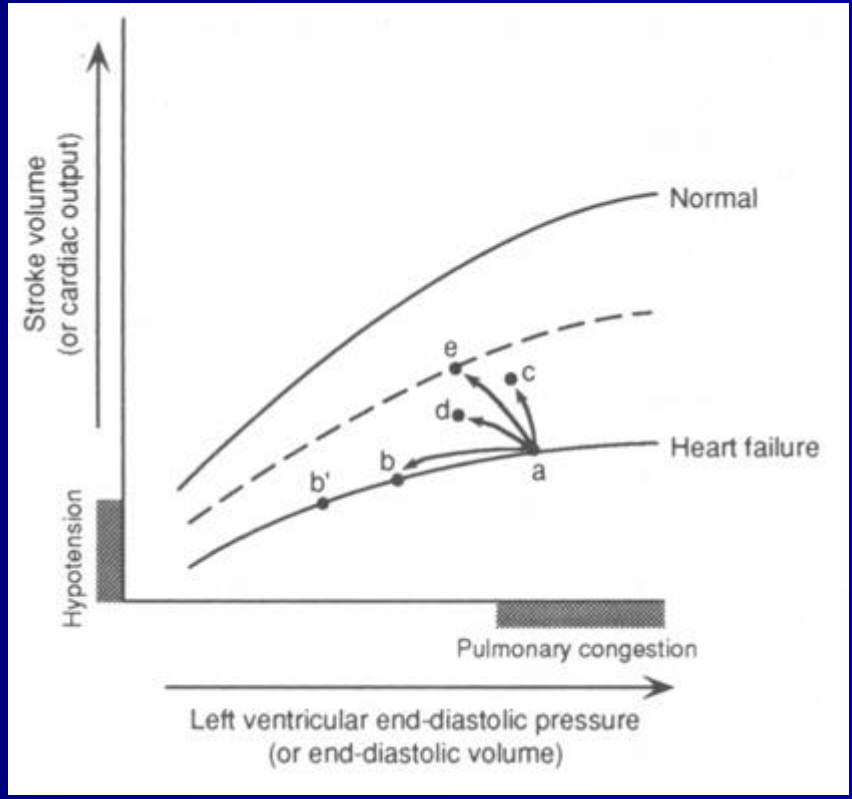
Class 3: Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.

Class 4: Unable to carry out any physical activity without discomfort. Symptoms include cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

***J Cardiac Failure* 1999;5:357-382**

Aim of Treatment

- Preload reduction
  - Diuretics
  - venodilators
- Vasodilators
  - ACEI
- Inotropes
  - Acutely
  - Chronically
    - mortality



Vasodilator Agents in Heart Failure

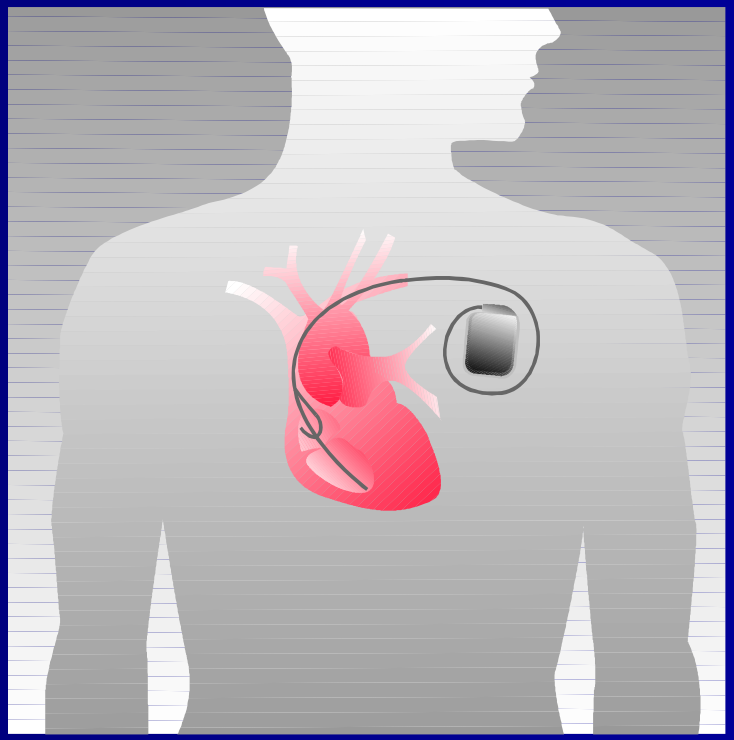
Drug	Mechanism	Action	Use
Nitroglycerin and long-acting nitrates*	Direct via nitric oxide	Veno / arterioloar	Hemodynamic; anti-ischemic; long term
Nitroprusside	Direct via nitric oxide	Arteriolar > venodilation	Hemodynamic
Hydralazine*	Direct	Arteriolar	?long term*
ACE inhibitors#	Reduced A-II Incr. bradykinin	Veno / arterioloar	Long-term

*Hydralazine and a long-nitrate shown to reduce mortality long-term

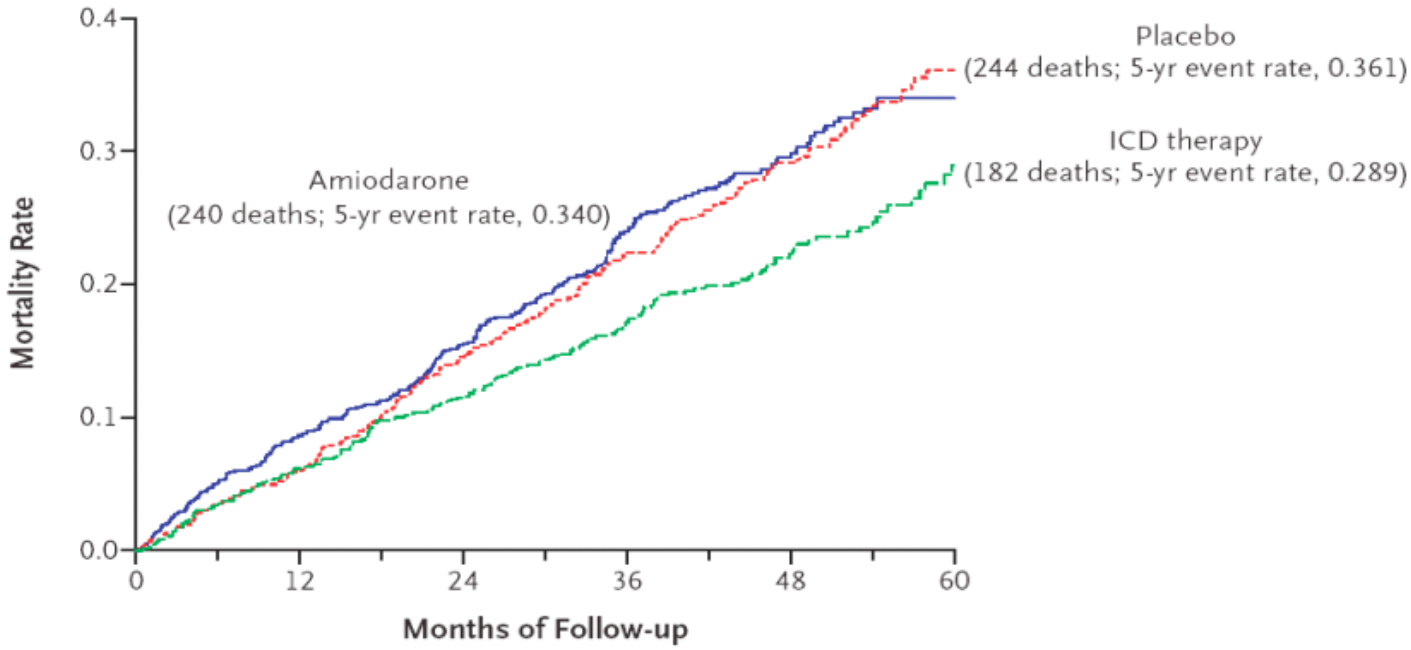
Other actions (aside from vasodilation) likely to be important

CRT: Cardiac Resynchronization Therapy

1. Improved hemodynamics
   - Increased CO
   - Reduced LV filling pressures
   - Reduced sympathetic activity
   - Increased systolic function w/o MVO2
2. Reverse LV remodeling/architecture
   - Decreased LVES/ED volumes
   - Increased LVEF
     - Circ ’02, JACC ’02, JACC ’02, NEJM’02



Anti-arrhythmic drugs, ICD placebo and Death

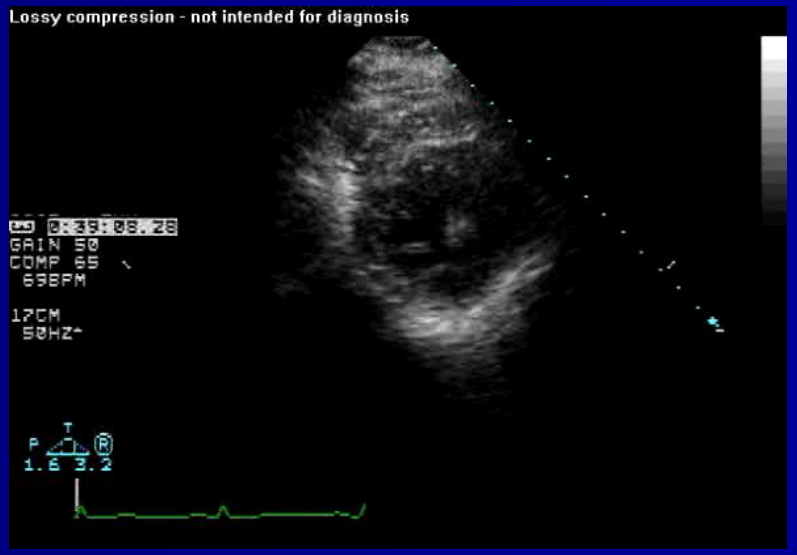


Bardy G et al.
NEJM 2005; 352:3

Sudden Cardiac Death
SCD-HeFT
Heart Failure Trial

Diastolic Dysfunction

- 40-50% of pts w/ CHF have nml LVEF
  - Vasan JACC '99
  - Grossman Circ '00
- Prevalence:
  - increases with age
  - higher in women
- Etiology: HTN & LVH
- Diagnosis:
  - MV& PV Doppler
  - TDI, Color m-mode



Hypertrophic Cardiomyopathy

Left ventricular hypertrophy not due to pressure overload
Hypertrpohy is variable in both severity and location:
- -asymmetric septal hypertrophy
- -symmetric (non-obstructive)
- -apical hypertrophy

Vigorous systolic function, but impaired diastolic function
- impaired relaxation of ventricles
- elevated diastolic pressures

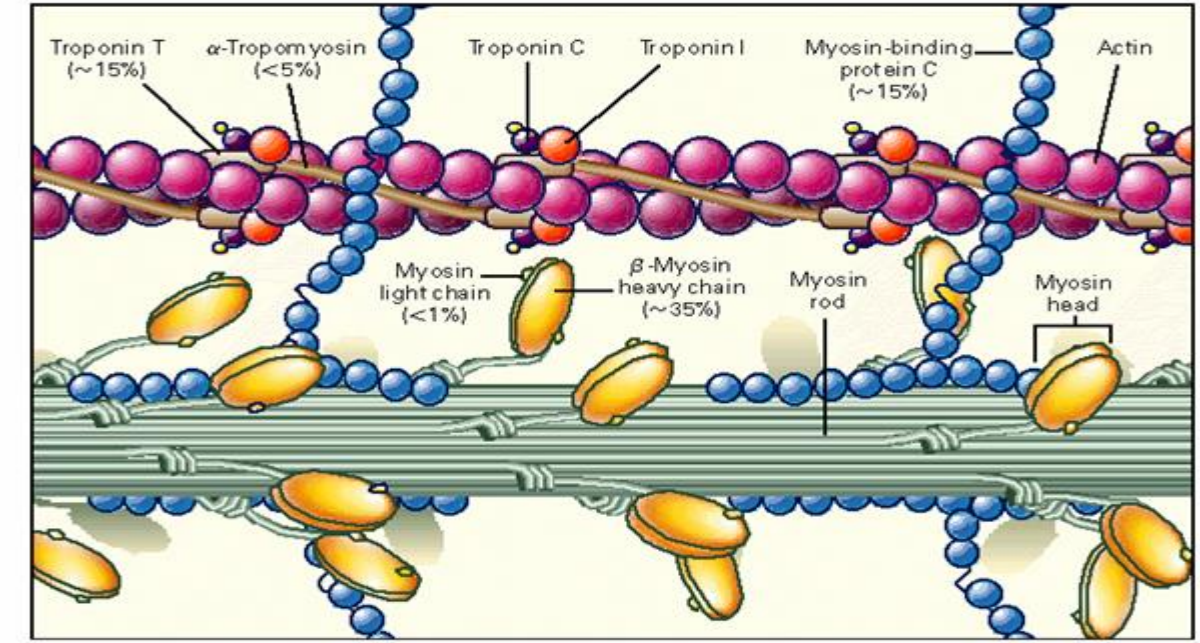
prevalence as high as 1/500 in general population
- mortality in selected populations 4-6% (institutional)
- probably more favorable (≤1%)

Etiology

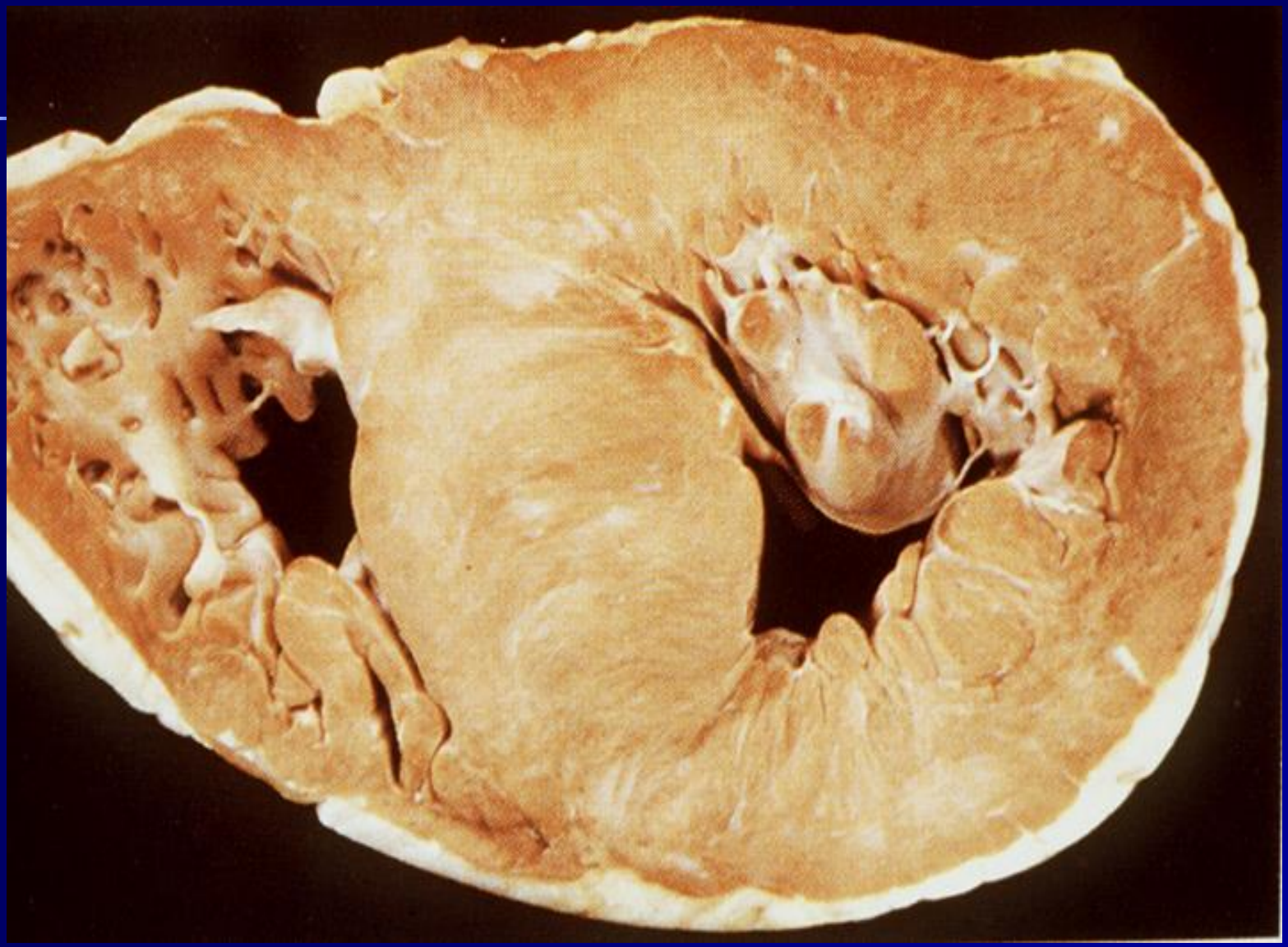
Familial in ~ 55% of cases with autosomal dominant transmission
Mutations in one of 4 genes encoding proteins of cardiac sarcomere
account for majority of familial cases

β-MHC
cardiac troponin T
myosin binding protein C
α-tropomyosin

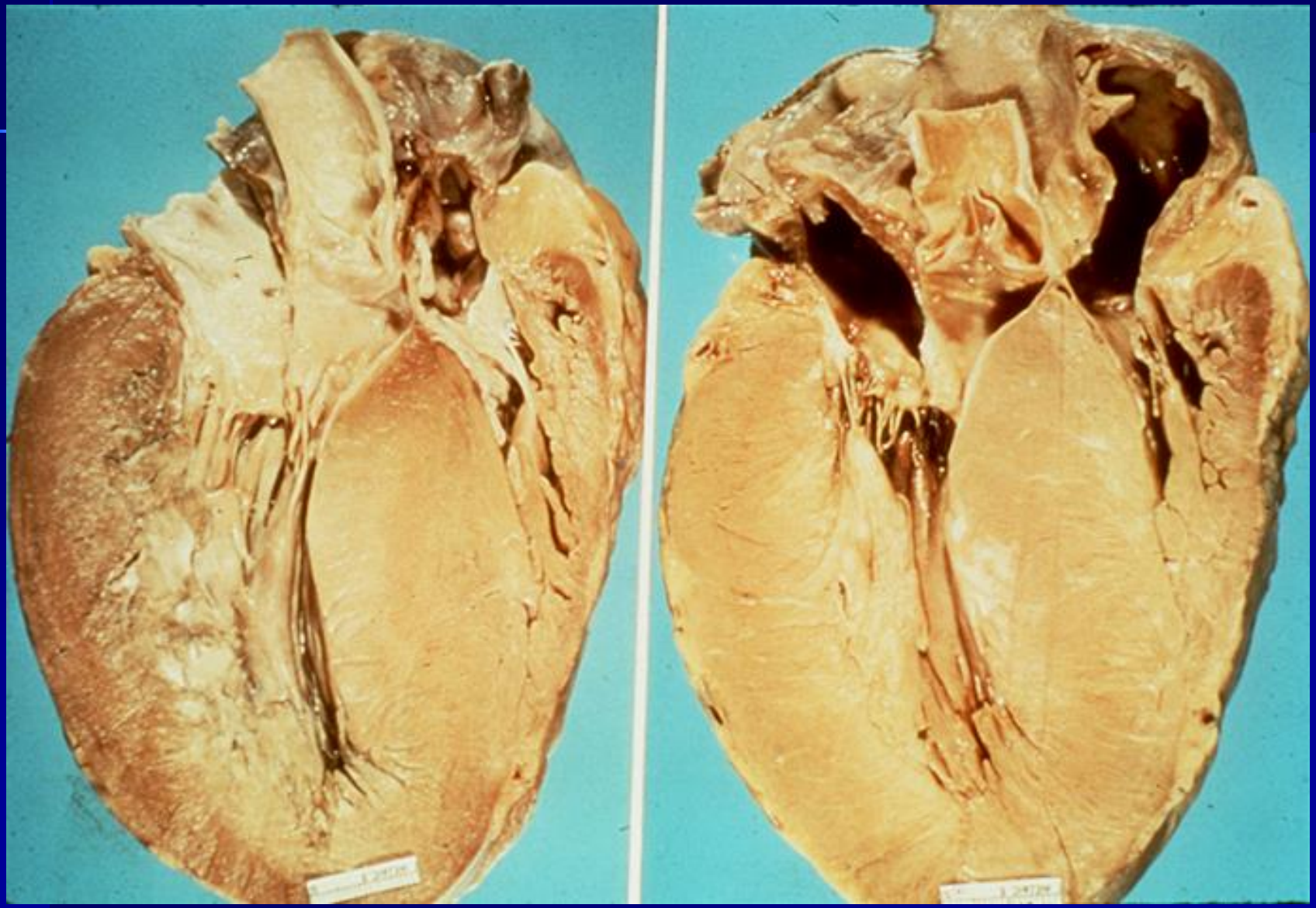
Remainder are spontaneous mutations.

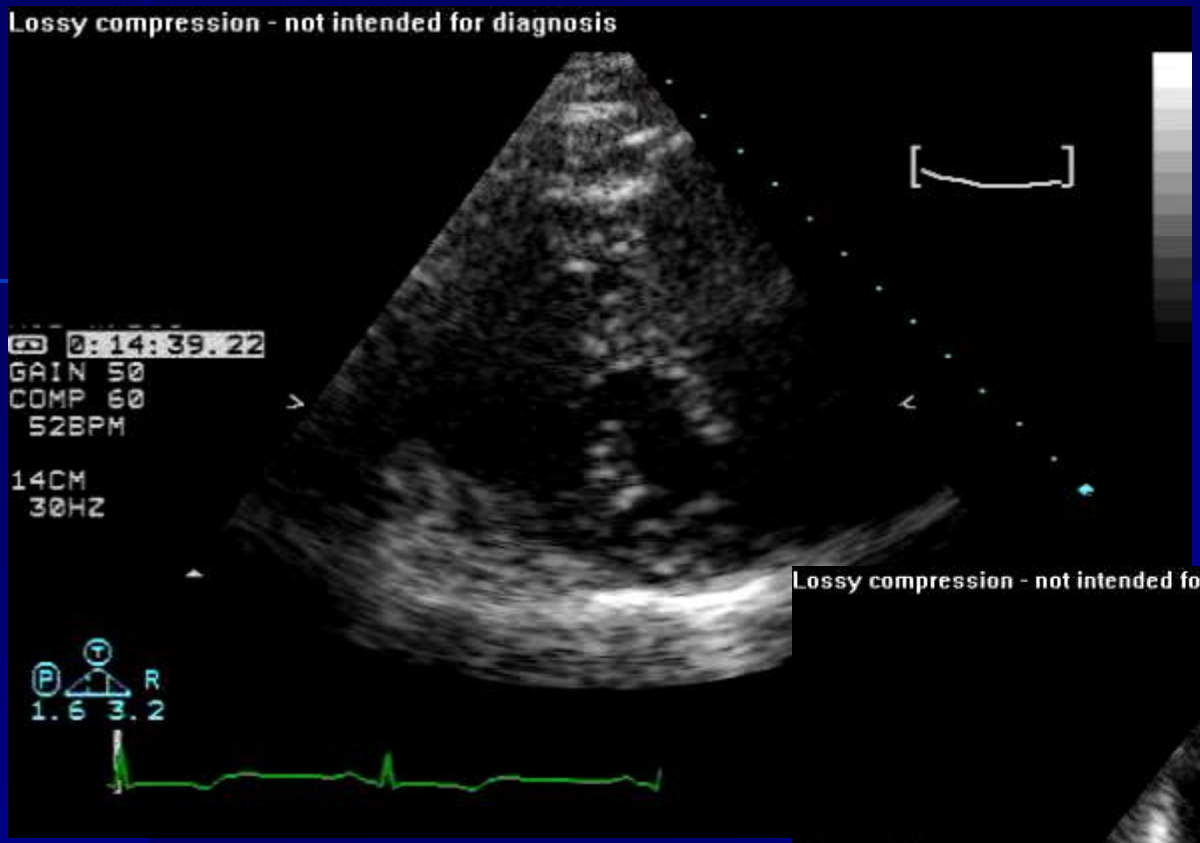


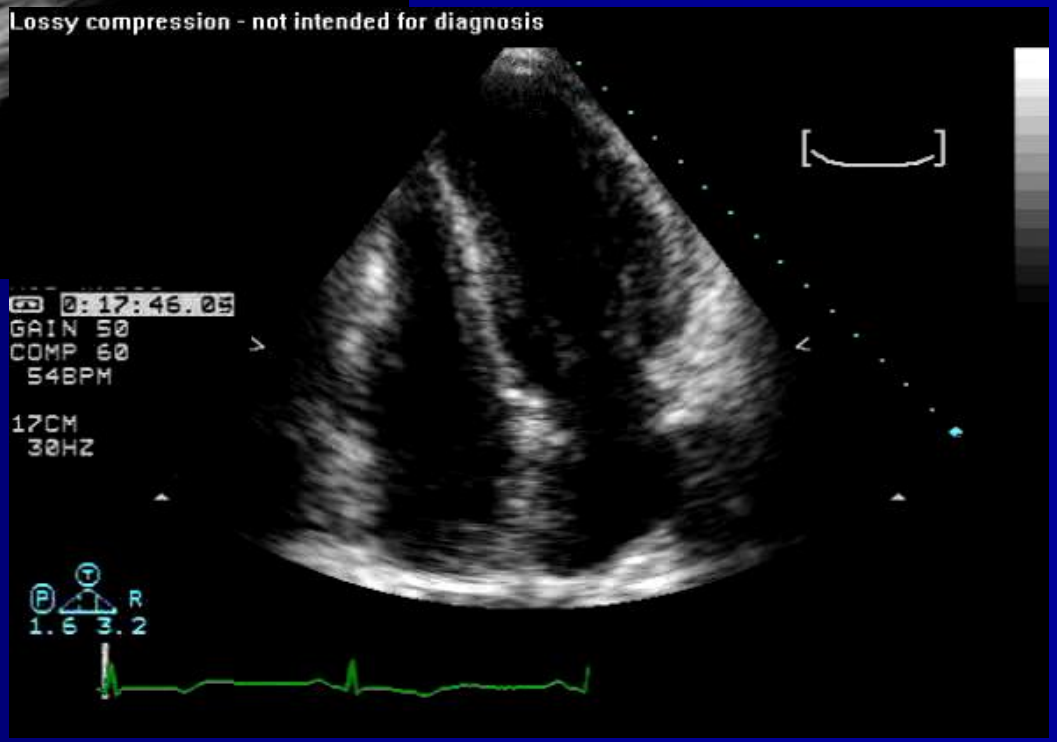
Hypertrophic Cardiomyopathy



Hypertrophic Cardiomyopathy

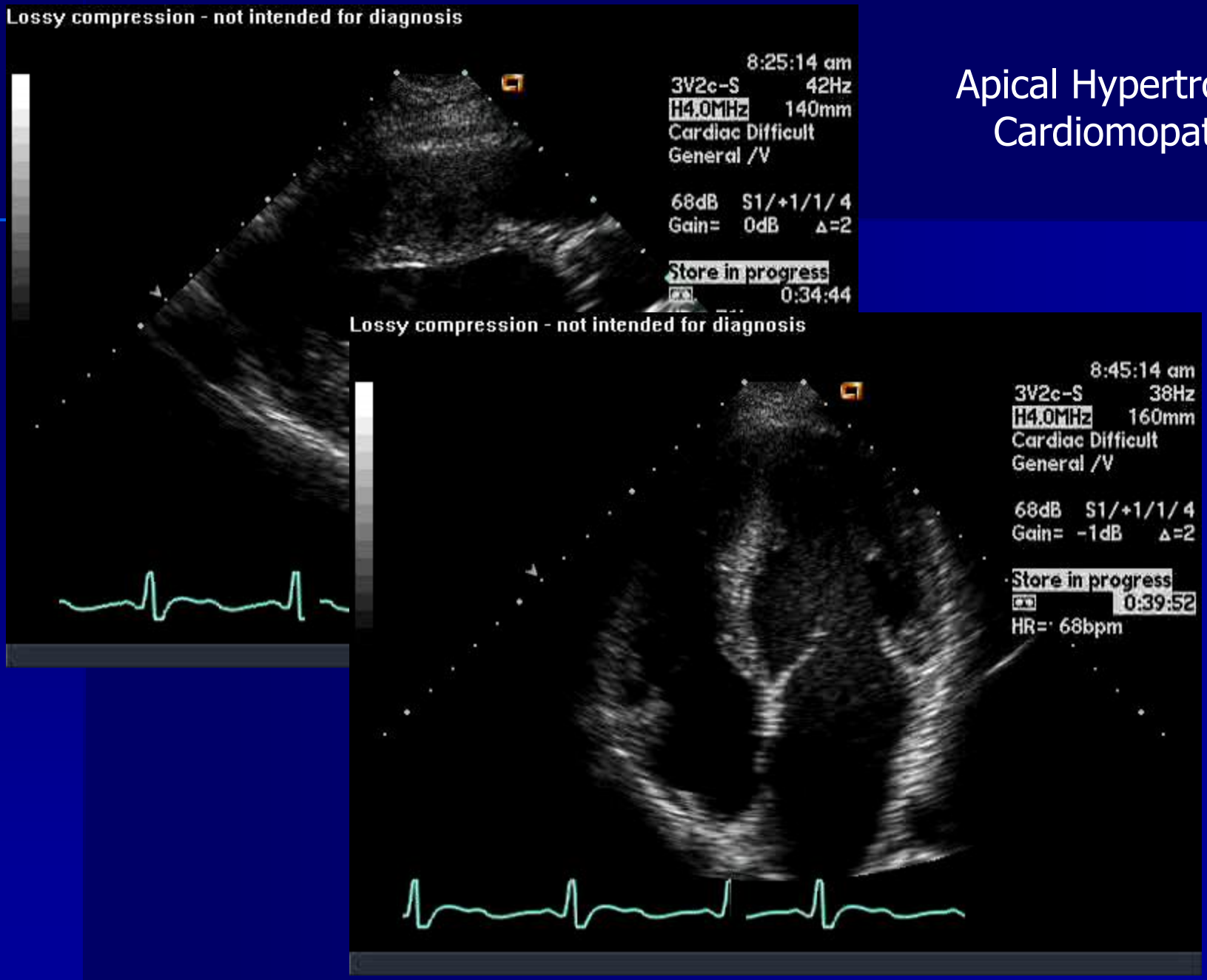




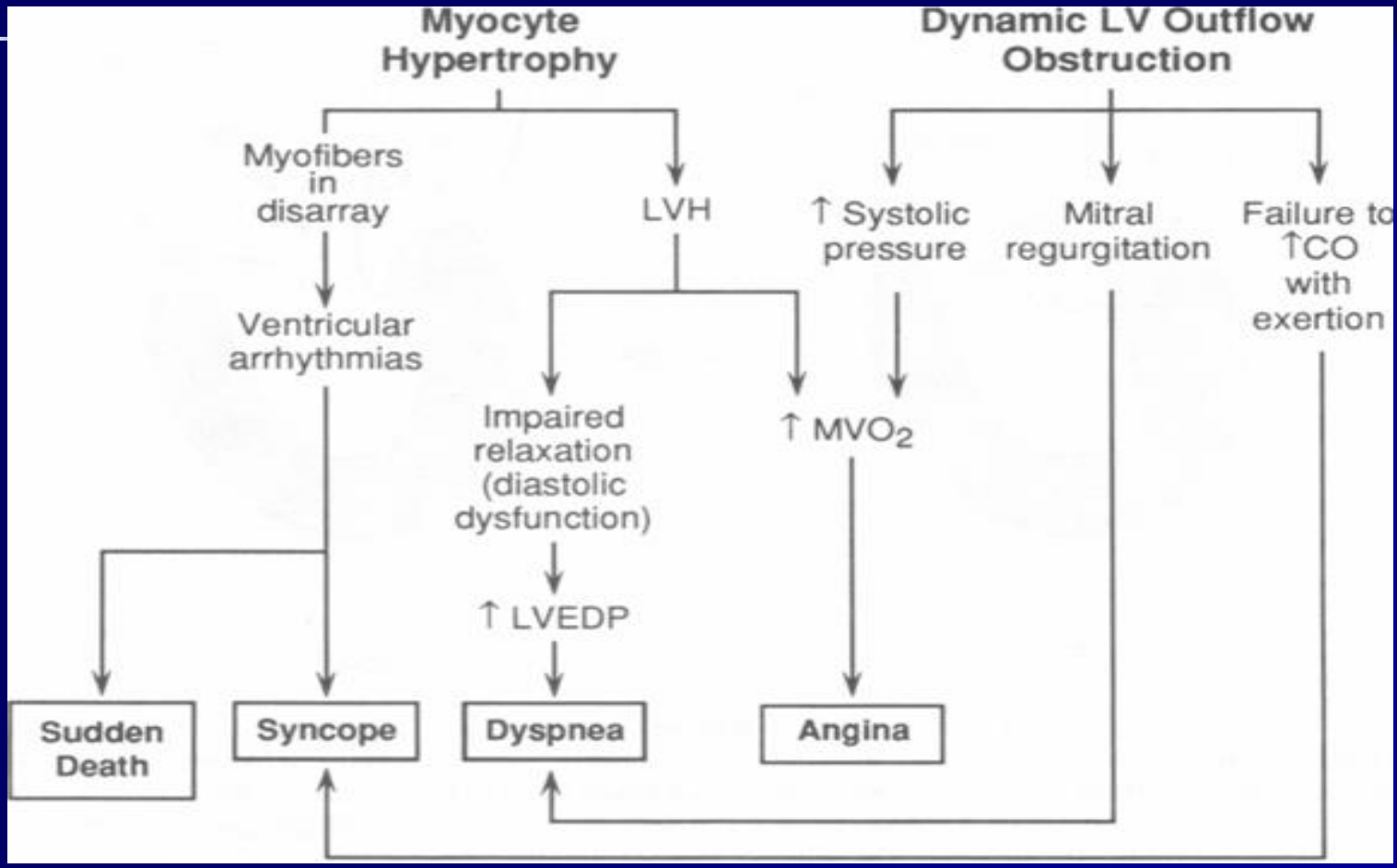


Hypertrophic cardiomyopathy

Apical Hypertrophic Cardiomopathy



Pathophysiology



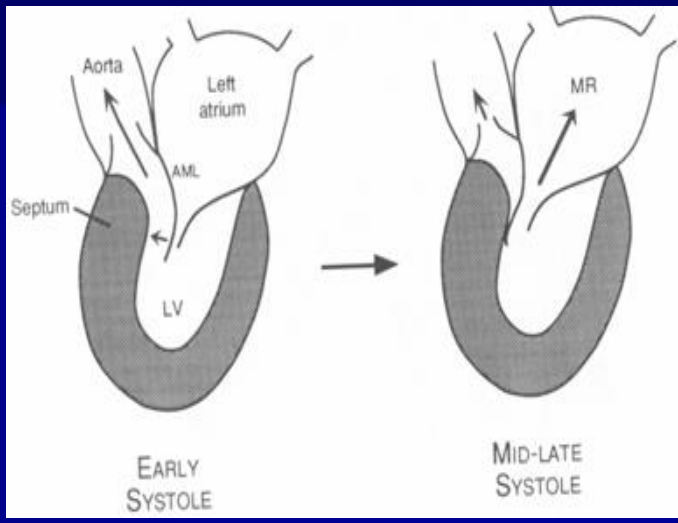
HCM with outflow obstruction

Dynamic LVOT obstruction (may not be present at rest)

SAM (systolic anterior motion of mitral valve)

LVOT Obstruction ⇒ LVOT gradient
⇒ ↑wall stress ⇒ ↑MVO2 ⇒ ischemia/angina

↑ LVOT gradient: ↑ HR (DFP), ↓preload (LVEDV),
↓ afterload(BP).
↓ LVOT gradient: ↑ BP (Afterload), ↑ LVEDV(preload)



Symptoms of dyspnea and angina more related to diastolic dysfunction than to outflow tract obstruction

Syncope: LVOT obstruction (failure to increase CO during exercise or after vasodilatory stress) or arrhythmia.

Physical Exam

Bisferiens pulse ("spike and dome")
S4 gallop
Crescendo/Descrescendo systolic ejection murmur

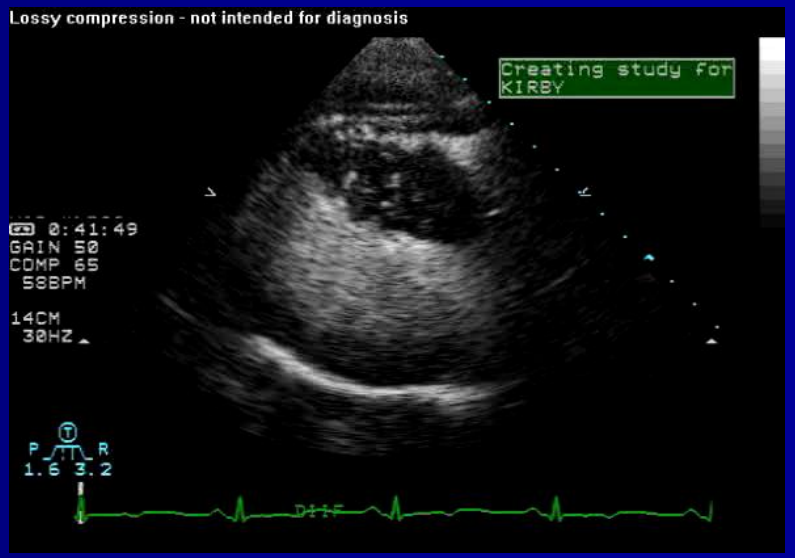
HOCM vs. Valvular AS

	Intensity of murmur	
	HOCM	AS
Valsalva (↓preload, ↓ afterload)	↑	↓
Squatting (↑ preload, ↑ afterload)	↓	↑
Standing (↓preload, ↓ afterload)	↑	↓

Holosystolic apical blowing murmur of mitral regurgitation

Diagnostic Studies

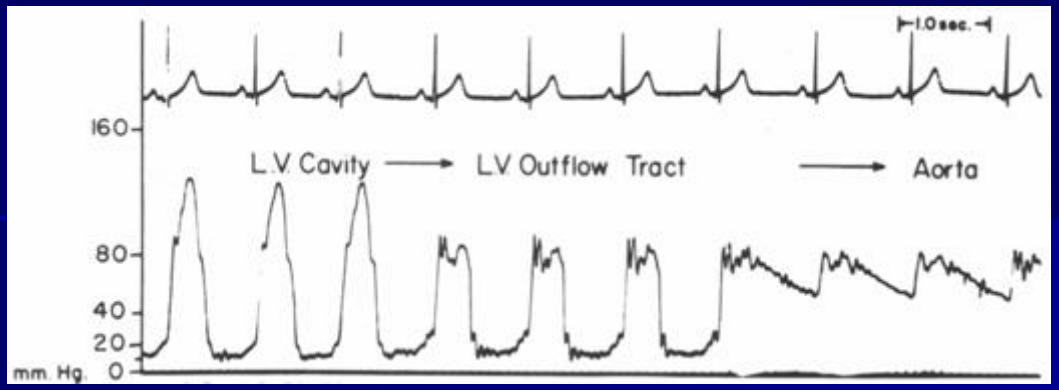
- EKG
  - NSR
  - LVH
  - septal Q waves
- 2D-Echocardiography
  - LVH; septum >1.4x free wall
  - LVOT gradient by Doppler
  - Systolic anterior motion of the mitral valeregurgitation
- Cardiac Catheterization
  - LVOT gradient and pullback
  - provocative maneuvers
  - Brockenbrough phen



HCM-ASH using contrast

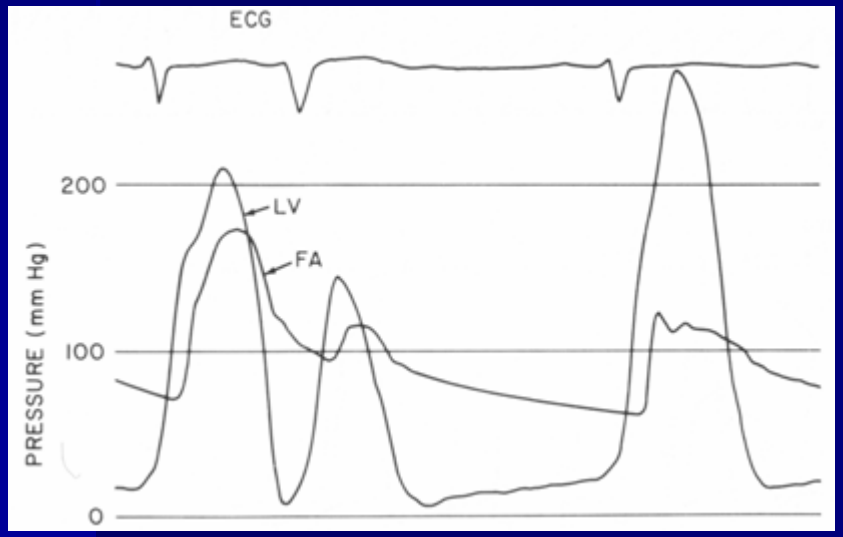
Cardiac Catheterization

LV pullback



Brockenbrough-Braunwald Sign

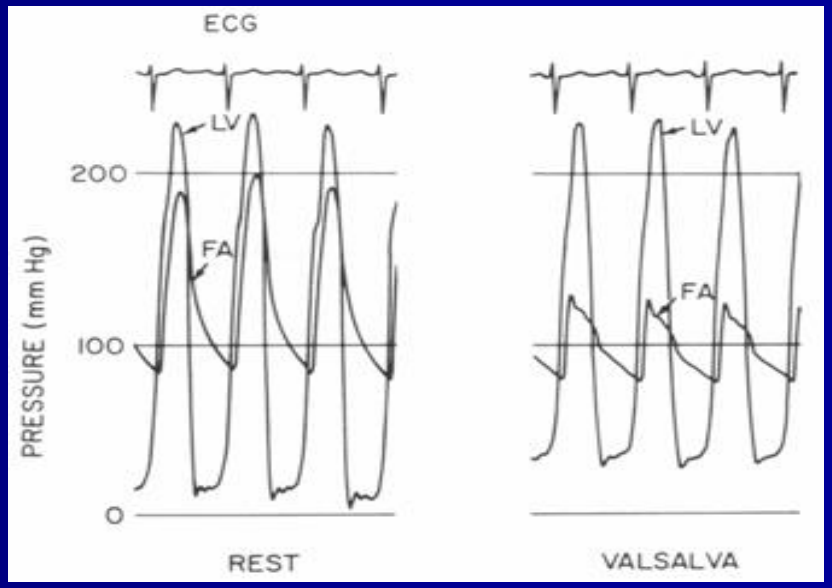
failure of aortic pulse pressure to rise post PVC



Provocative maneuvers:

Valsalva

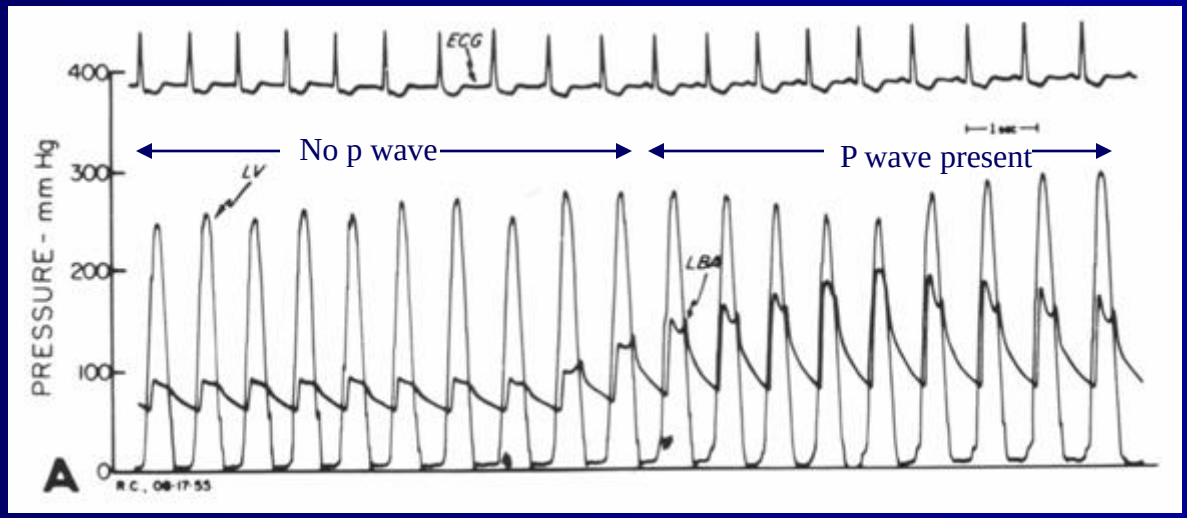
amyl nitrate inhalation



Atrial Fibrillation

Acute A. Fib is poorly tolerated -Acute Pulmonary Edema and Shock
Chronic a fib - Fatigue, dyspnea and angina

Rapid HR - decreased time for diastolic filling and LV relaxation
Loss of atrial "Kick" – decreased LV filling
- decreased SV and increased outflow tract obstruction



Rate slowing with β-blockers and Ca2+ channel blockers
Digitalis is relatively contra-indicated- positive inotrope
DC Cardioversion

Treatment

For symptomatic benefit

β-blockers

↓ mvO2

↓ gradient (exercise)

arrythmias

Calcium Channel blockers

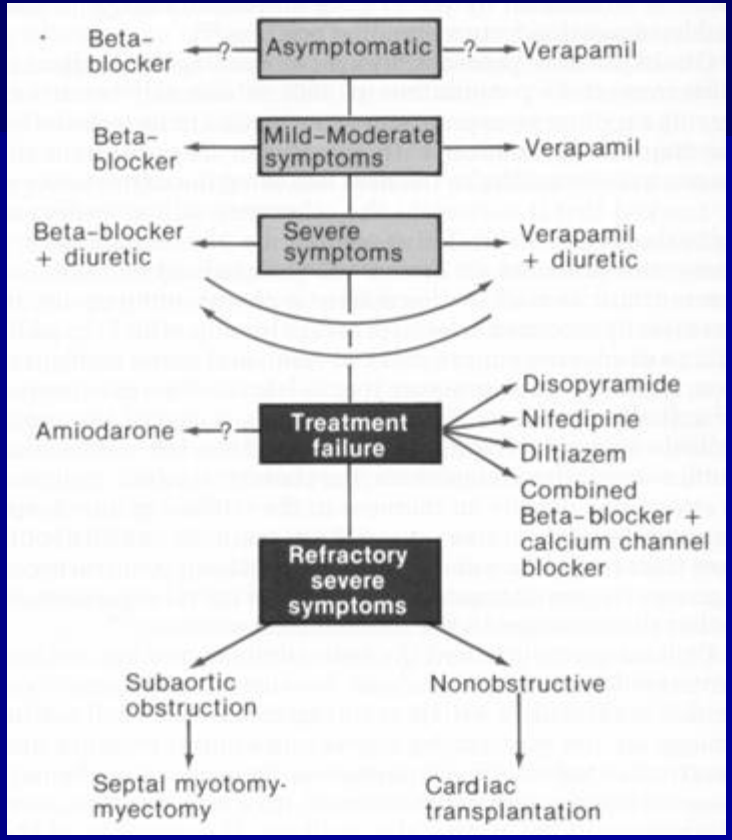
Anti-arrhythmics

afib

amiodorone

Disopyramide

AICD for sudden death



antibiotic prophylaxis for endocarditis

No therapy has been shown to improve mortality

HCM: Surgical Treatment

For severe symptoms with large outflow gradient (>50mmHg)
Does not prevent Sudden Cardiac Death

Myomyectomy
- removal of small portion of upper IV septum
- +/- mitral valve replacement
- 5 year symptomatic benefit in ~ 70% of patients

Dual Camber (DDD pacemaker) pacing
- decreases LVOT gradient (by~25%)
- randomized trials have shown little longterm benefit
- possible favorable morphologic changes

ETOH septal ablation

AICD to prevent sudden death

Hypertrophic CM

- Most common cause of death in young people.
- The magnitude of left ventricular hypertrophy is directly correlated to the risk of SCD.
- Young pts with extreme hypertrophy and few or no symptoms are at substantial long-term risk of SCD.

.

Spirito P. *N Engl J Med.* 1997;336:775-785.
Maron BJ. *N Engl J Med*. 2000;342:365-373.

Prognosis

Sudden Death 2-4%/year in adults
4-6% in children/adolescents

AICD for: survivors of SCD with Vfib
episodes of Sustained VT
pts with family hx of SCD in young family members
High risk mutation (TnT, Arg403Gln)

Predictors of adverse prognosis:

- early age of diagnosis
- familial form with SCD in 1st degree relative
- history of syncope
- ischemia
- presence of ventricular arrhythmias on Holter (EPS)

EPS

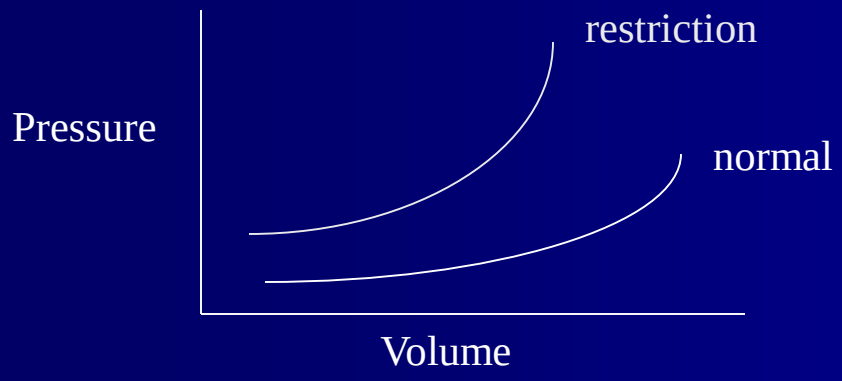
Amiodorone (low dose)

Prophylactic AICD?

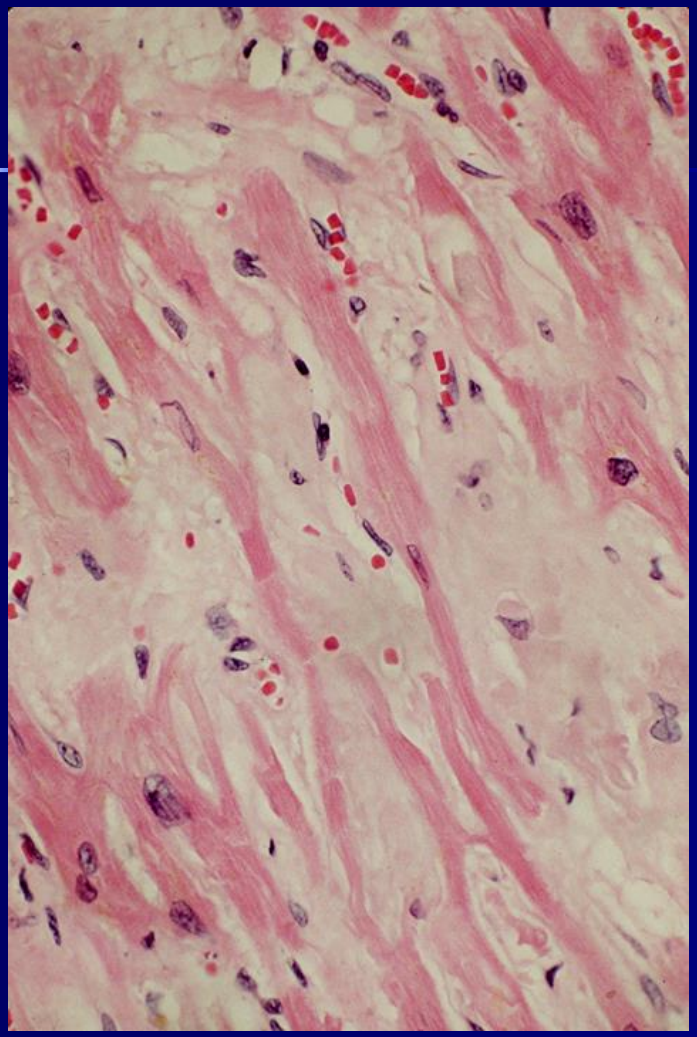
Restrictive Cardiomyopathy

Characterized by:

- impaired ventricular filling due to an abnormally stiff (rigid) ventricle
- normal systolic function (early on in disease)
- intraventricular pressure rises precipitously with small increases in volume



Causes : infiltration of myocardium by abnormal substance
fibrosis or scarring of endocardium



Amyloid infiltrative CM

TABLE 4. CAUSES OF RESTRICTIVE CARDIOMYOPATHY.

Myocardial

Noninfiltrative disorders
- Idiopathic disease
- Familial disease
- Hypertrophy
- Scleroderma
- Diabetes mellitus
- Pseudoxanthoma elasticum

Infiltrative disorders
- Amyloidosis
- Sarcoidosis
- Gaucher's disease
- Hurler's syndrome
- Fatty infiltration

Storage disorders
- Hemochromatosis
- Fabry's disease
- Glycogen storage disease

Endomyocardial

Endomyocardial fibrosis
Hypereosinophilic (Löffler's) syndrome
Carcinoid syndrome
Metastatic cancer
Exposure to radiation
Toxins
Anthracycline (doxorubicin or daunorubicin)
Serotonin
Methysergide
Ergotamine
Mercurial agents
Busulfan

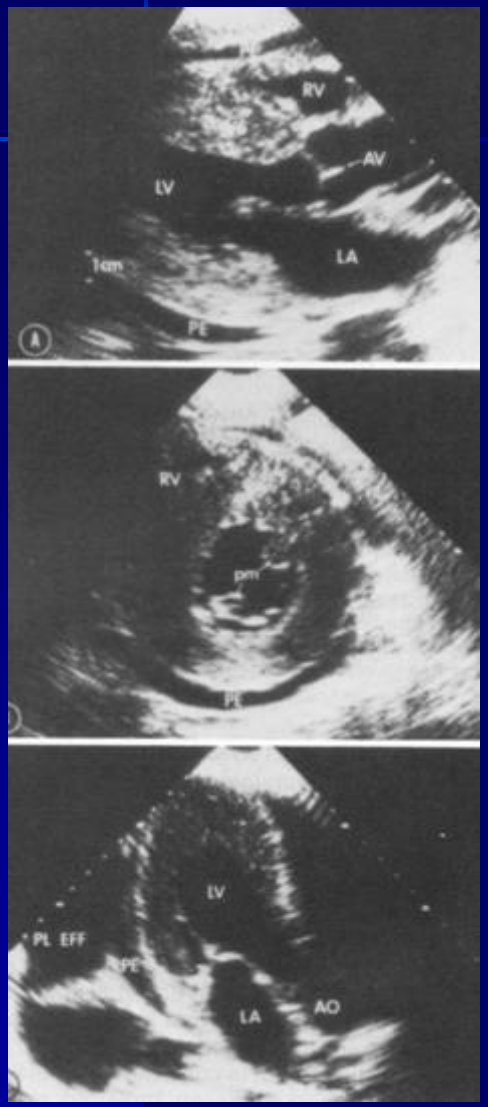
Amyloidosis

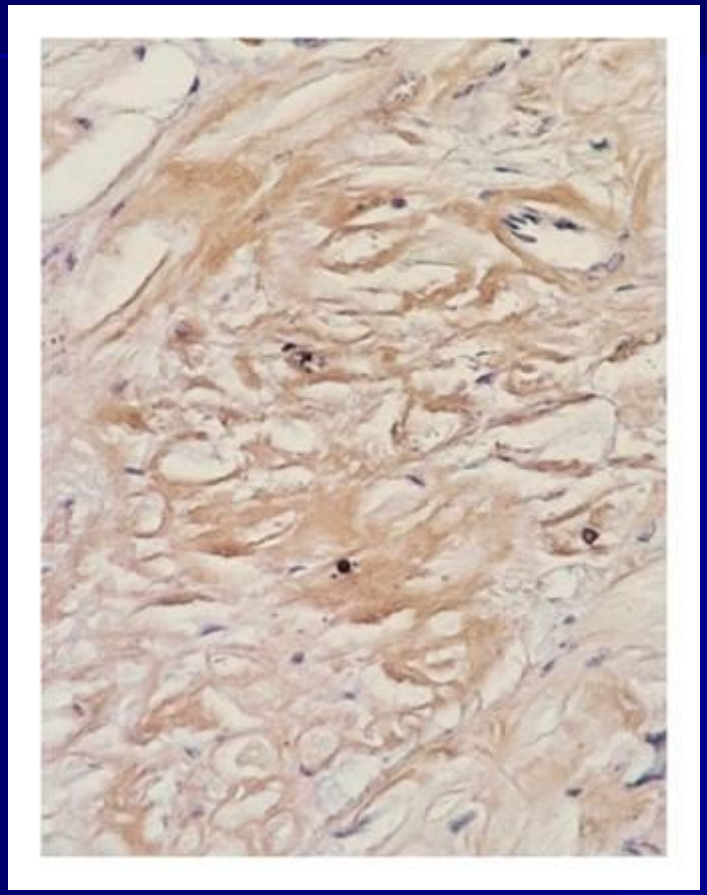
Primary Amyloidosis
- immunoglobulin light chains -- multiple myeloma

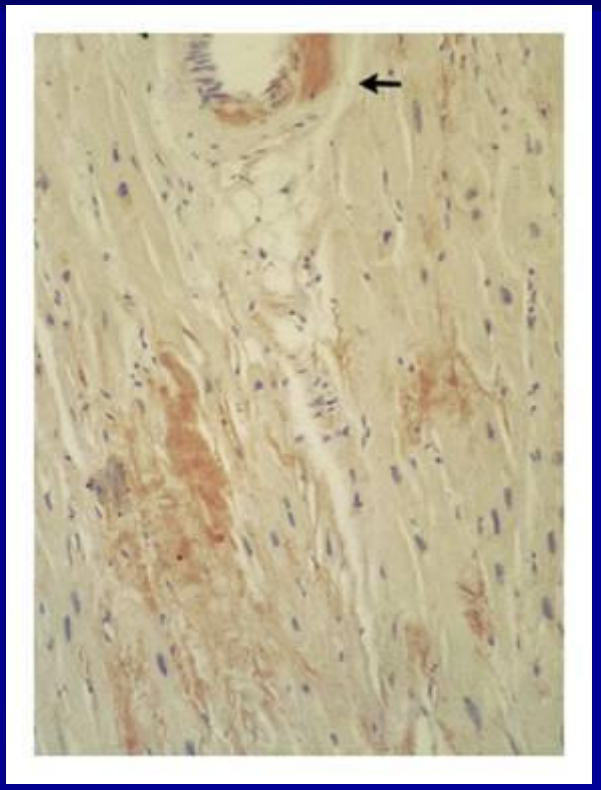
Secondary Amyloidosis
- deposition of protein other than immunoglobulin
  - senile
  - familial
  - chronic inflammatory process

restriction caused by replacement of normal myocardial contractile elements by infiltrative interstitial deposits

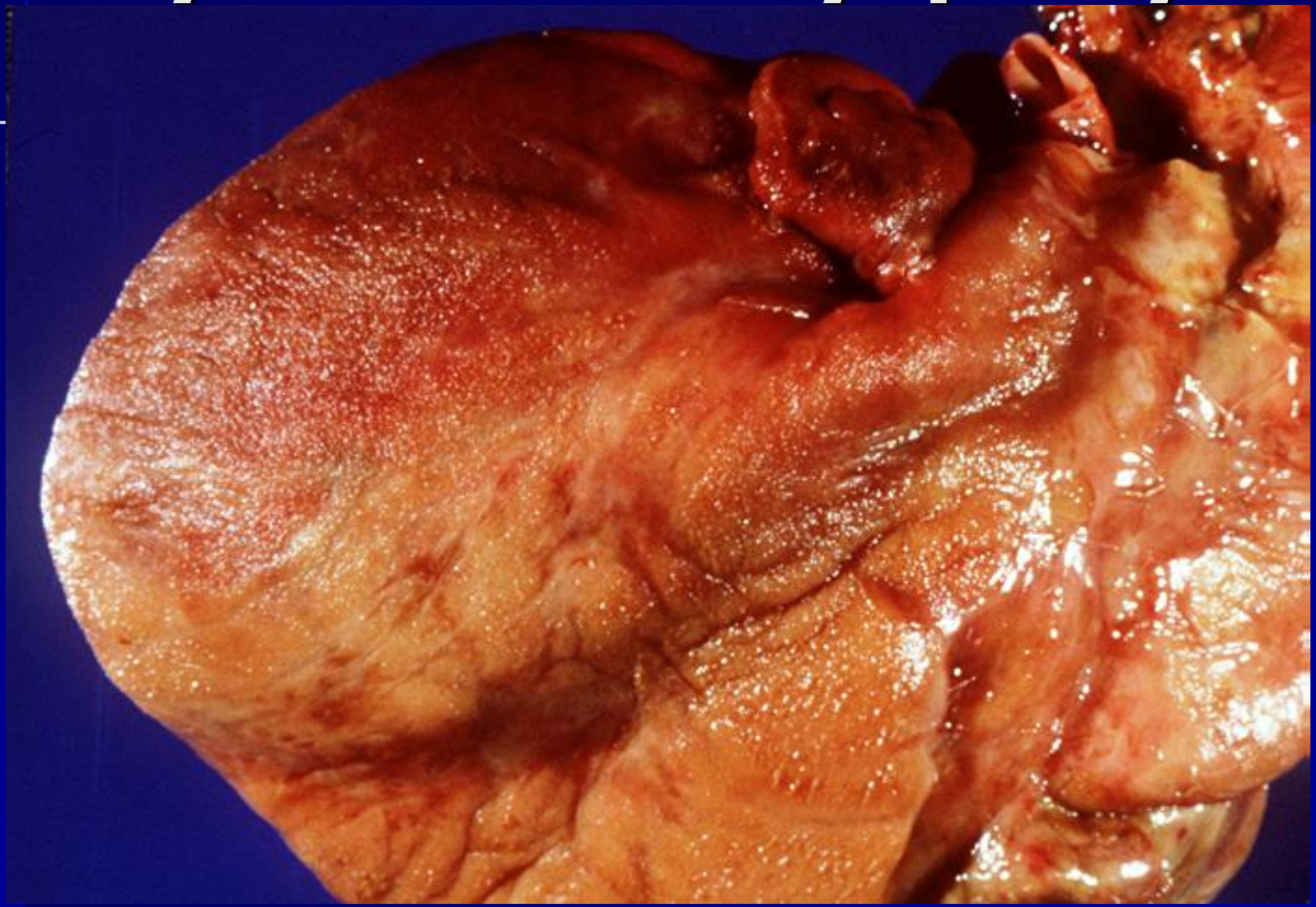
Amyloidosis



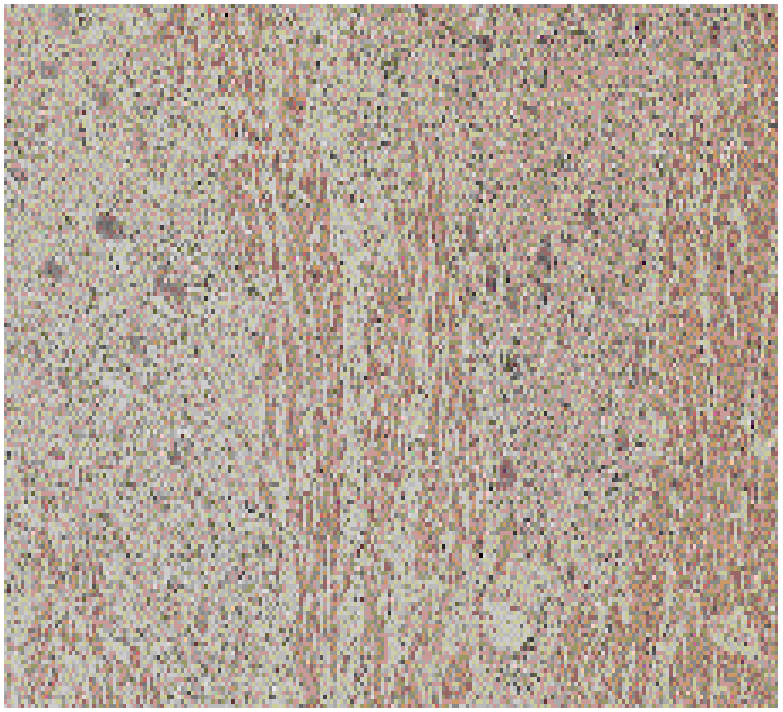




Amyloid Cardiomyopathy



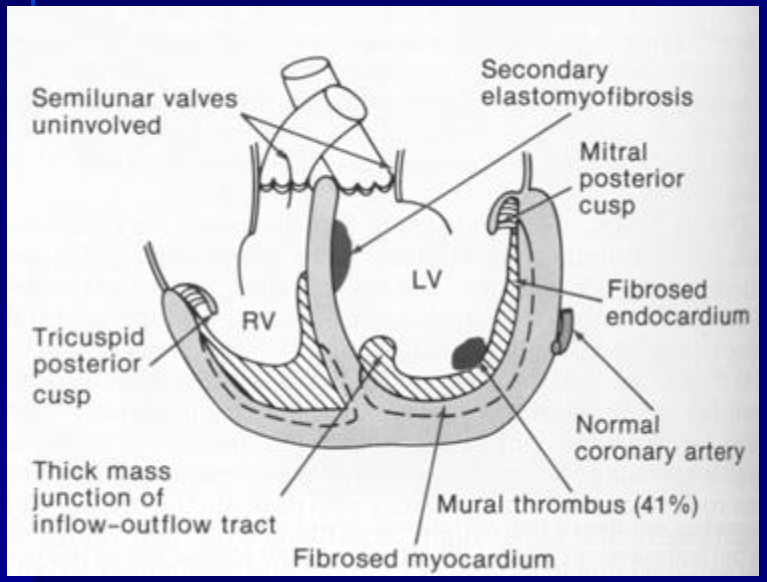
Sarcoidosis

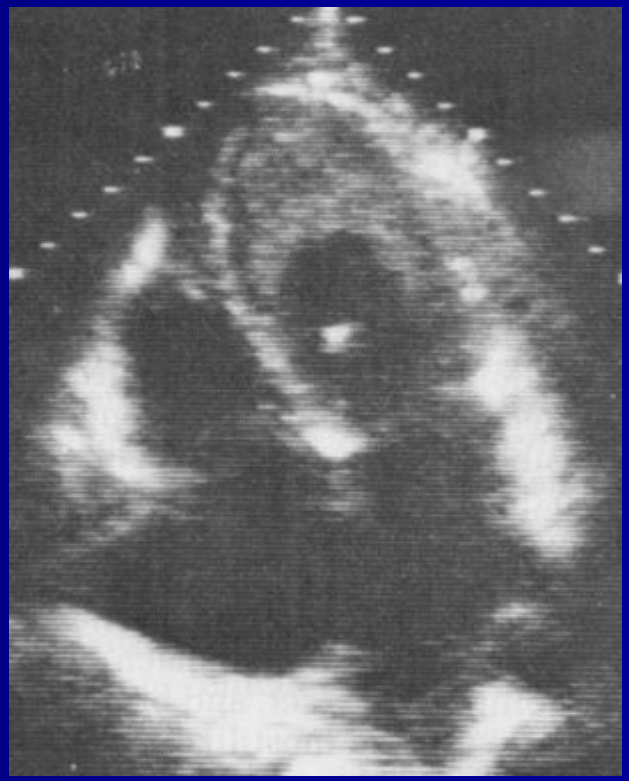


Restriction
Conduction System Disease
Ventricular Arrhythmias
(Sudden Cardiac Death)

Endomyocardial Fibrosis

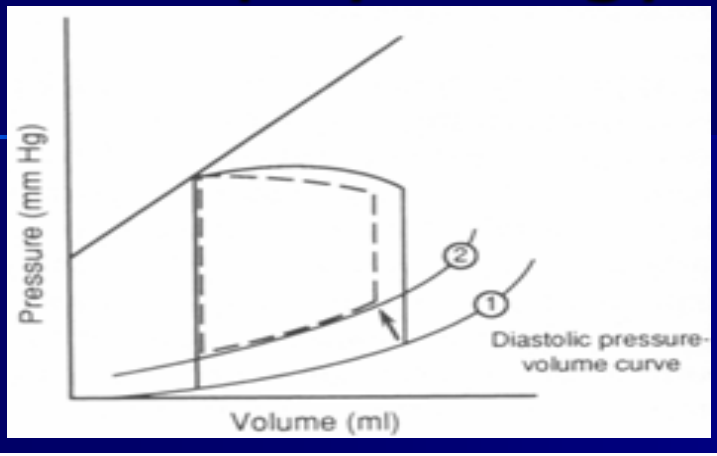
Endemic in parts of Africa, India, South and Central America, Asia
15-25% of cardiac deaths in equatorial Africa
hypereosinophilic syndrome (Loffler's endocarditis)

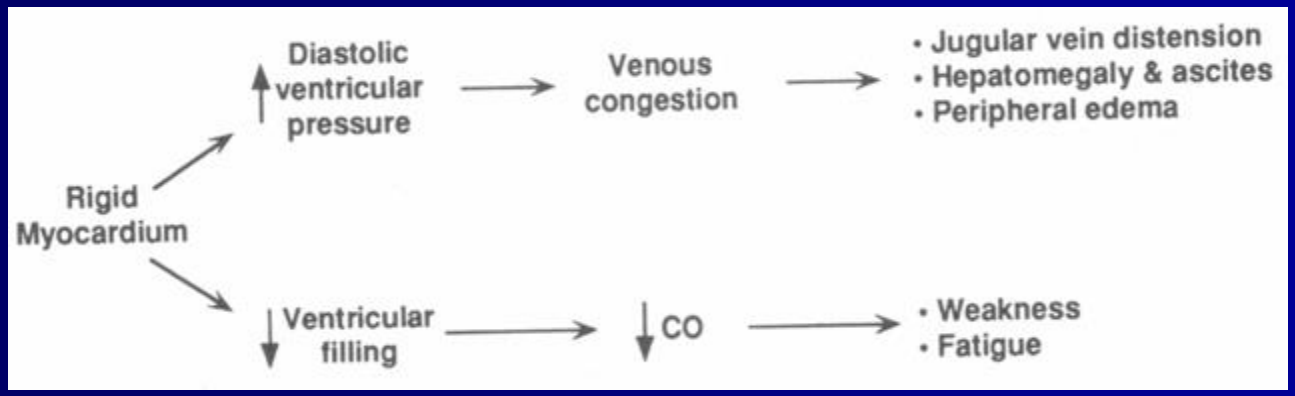




Thickening of basal inferior wall
endocardial deposition of thrombus
apical obliteration
mitral regurgitation
80-90% die within 1-2 years

Pathophysiology of Restriction





Elevated systemic and pulmonary venous pressures
right and left sided congestion
reduced ventricular cavity size with ↓SV and ↓CO

Clinical Findings

Right > Left heart failure

- Dyspnea
- Orthopnea/PND
- Peripheral edema
- Ascites/Hepatomegaly

Fatigue/ ↓exercise tolerance

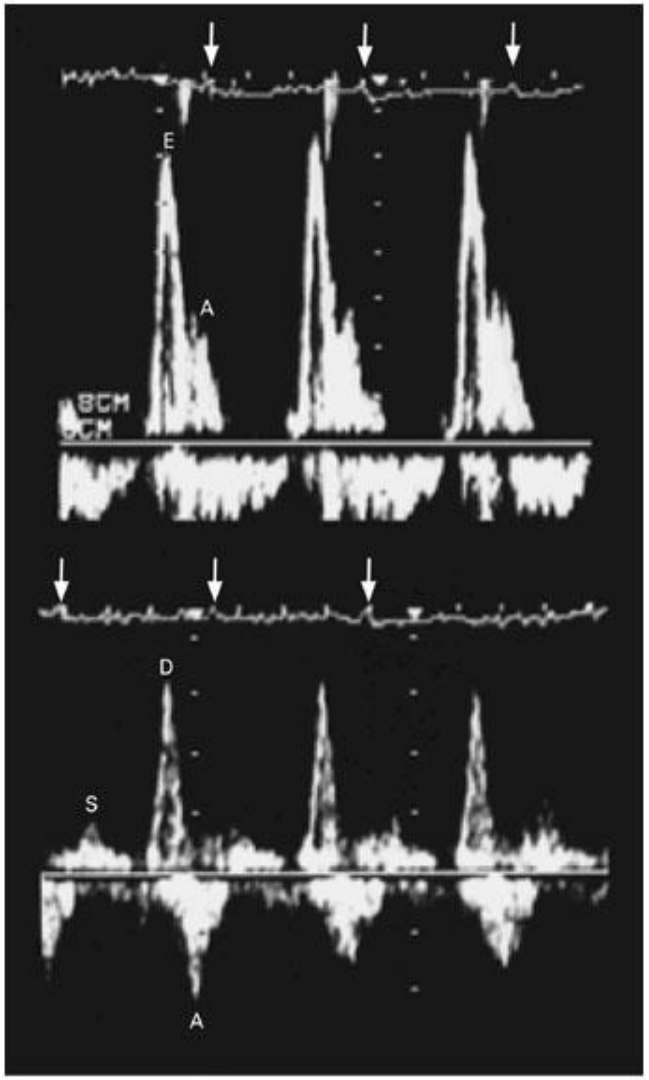
Clinically mimics constrictive Pericarditis

Diagnostic Studies

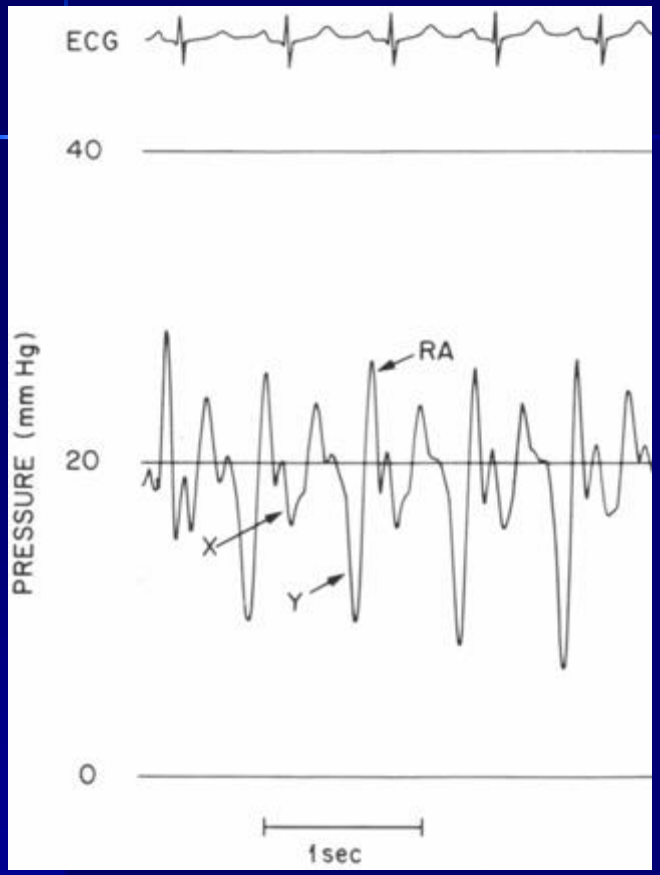
2D-Echo/Doppler-
- mitral in-flow velocity
- rapid early diastolic filling

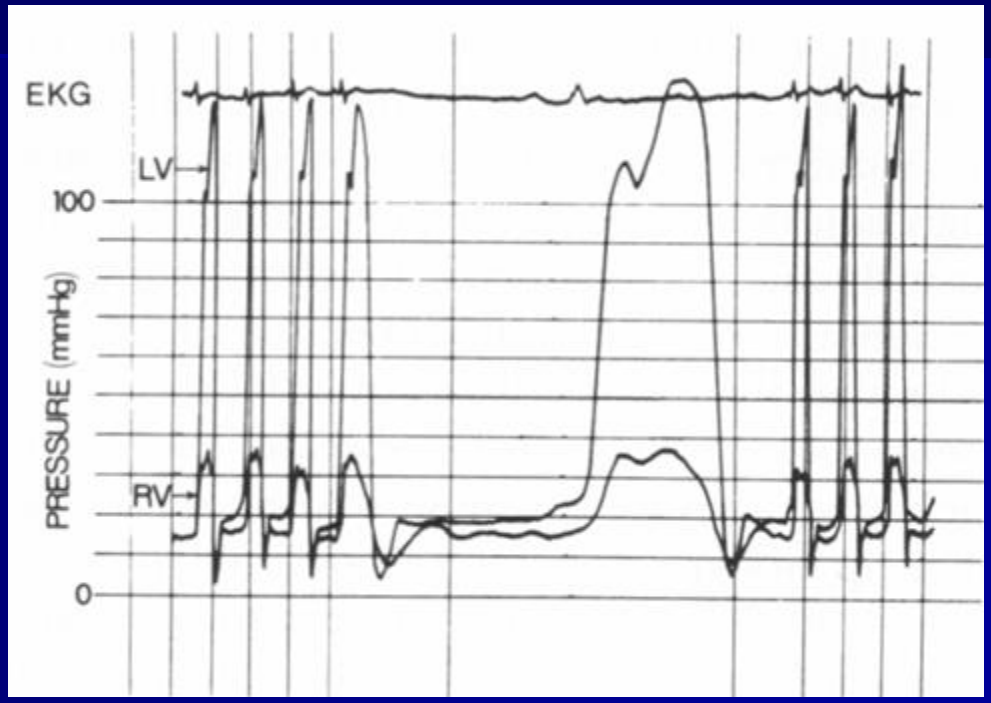
Catheterization –
- diastolic pressure equilibration
- restrictive vs constrictive hemodynamics

Endomyocardial biopsy-
- definite Dx of restrictive pathology



Cardiac Catheterization





Prominent y descent
rapid atrial emptying

"dip and plateau"
rapid ventricular filling

then abrupt cessation of blood flow due to non-compliant myocardium

Constriction vs. Restrictive CM

TABLE 2. THE DIFFERENTIAL DIAGNOSIS OF RESTRICTIVE CARDIOMYOPATHY AND CONSTRICTIVE PERICARDITIS.*

TYPE OF EVALUATION	RESTRICTIVE CARDIOMYOPATHY	CONSTRICTIVE PERICARDITIS
Physical examination	Kussmaul's sign may be present Apical impulse may be prominent S3 may be present, rarely S4 Regurgitant murmurs common	Kussmaul's sign usually present Apical impulse usually not palpable Pericardial knock may be present Regurgitant murmurs uncommon
Electrocardiography	Low voltage (especially in amyloidosis), pseudoinfarction, left-axis deviation, atrial fibrillation, conduction disturbances common	Low voltage (<50 percent)
Echocardiography	Increased wall thickness (especially thickened interatrial septum in amyloidosis) Thickened cardiac valves (amyloidosis) Granular sparkling texture (amyloid)	Normal wall thickness Pericardial thickening may be seen Prominent early diastolic filling with abrupt displacement of interventricular septum
Doppler studies	Decreased RV and LV velocities with inspiration Inspiratory augmentation of hepatic-vein diastolic flow reversal Mitral and tricuspid regurgitation common	Increased RV systolic velocity and decreased LV systolic velocity with inspiration Expiratory augmentation of hepatic-vein diastolic flow reversal
Cardiac catheterization	LVEDP often >5 mm Hg greater than RVEDP, but may be identical	RVEDP and LVEDP usually equal RV systolic pressure <50 mm Hg RVEDP >one third of RV systolic pressure
Endomyocardial biopsy	May reveal specific cause of restrictive cardiomyopathy	May be normal or show nonspecific myocyte hypertrophy or myocardial fibrosis
CT/MRI	Pericardium usually normal	Pericardium may be thickened

*LV denotes left ventricular, RV right ventricular, LVEDP left ventricular end-diastolic pressure, RVEDP right ventricular end-diastolic pressure, CT computed tomography, and MRI magnetic resonance imaging.

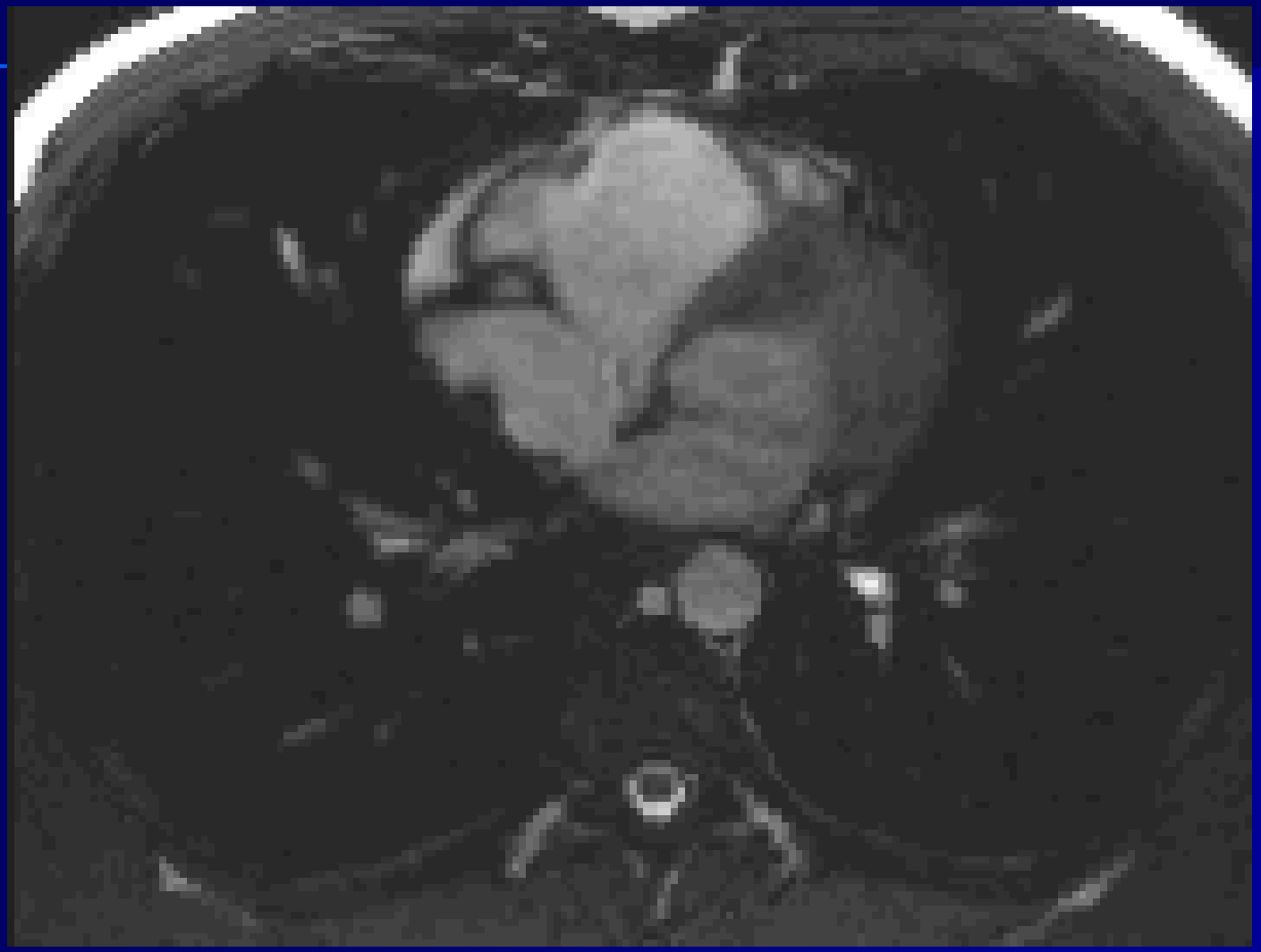
Treatment

- Treat underlying cause
  - r/o constriction which is treatable (restriction poor prognosis)
  - amyloid (melphalan/prednisone/colchicine)
  - Endomyocardial Fibrosis (steroids, cytotoxic drugs, MVR)
  - Hemochromatosis (chelation, phlebotomy)
  - Sarcoidosis (steroids)
- Diuretics
  - For congestive symptoms, but $\downarrow$ LV/RV filling $\Rightarrow \downarrow$ CO
- Digoxin (avoid in amyloidosis)
- Antiarrhythmics for afib
  - amiodorone
- Pacemaker for conduction system disease
- Anticoagulation for thrombus (esp in atrial appendages)

Arrhythmogenic RV Dysplasia

- Myocardium of RV free wall replaced:
  - Fibrofatty tissue
  - Regional wall motion/function is reduced
- Ventricular arrhythmias
  - SCD in young

MRI: RV Dysplasia



LV Noncompaction

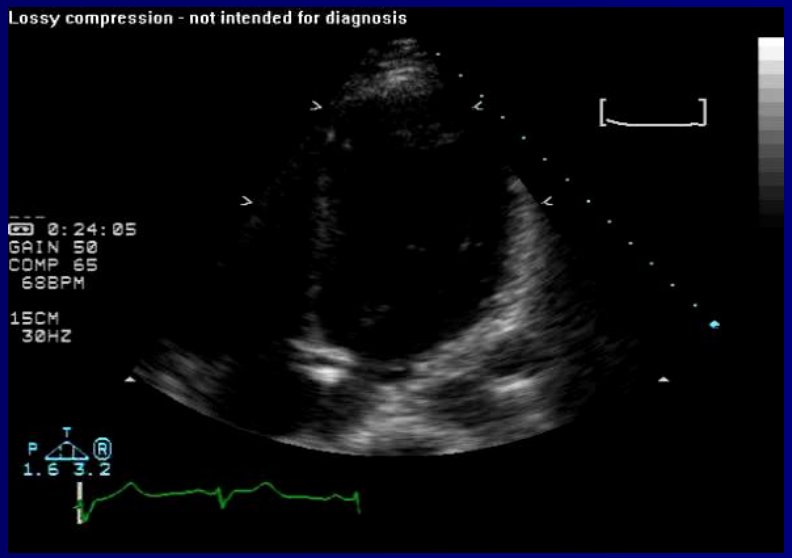
Diagnostic Criteria

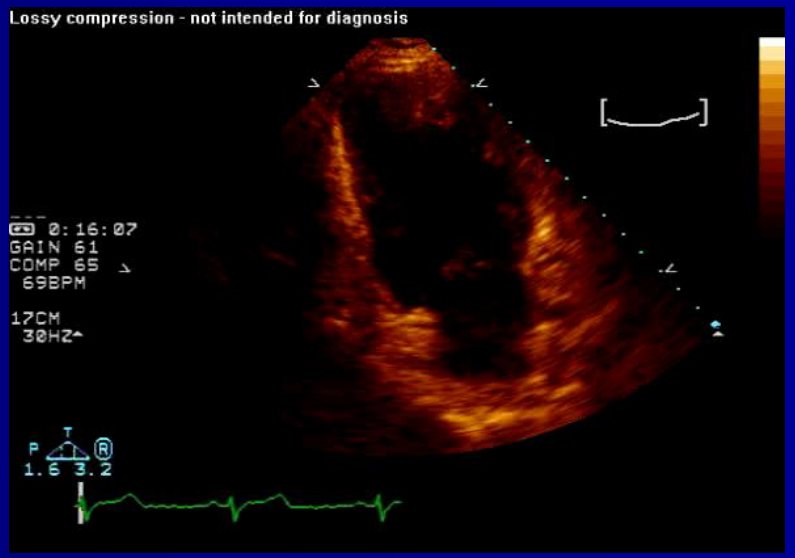
- Prominent trabeculations, deep recesses in LV apex
- Thin compact epicardium, thickened endocardium
  - Stollberger C, JASE '04
- Other phenotypic findings

Prognosis and Treatment

- Increased risk of CHF, VT/SCD, thrombosis
  - Oechslin EN, JACC '00
- Hereditary risk
  - Screening of offspring
- Pregnancy: case report

Echo: LV Noncompaction





Cardiomyopathy

WHO Classification

anatomy & physiology of the LV

1. Dilated
   - Enlarged
   - Systolic dysfunction
2. Hypertrophic
   - Thickened
   - Diastolic dysfunction
3. Restrictive
   - Myocardial stiffness
   - Diastolic dysfunction
4. Arrhythmogenic RV dysplasia
   - Fibrofatty replacement
5. Unclassified
   - Fibroelastosis
   - LV noncompaction