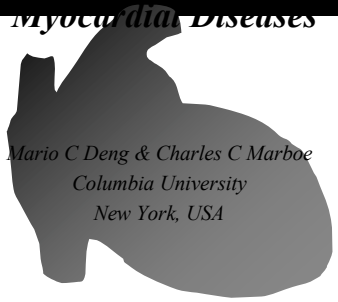
Myocardial Diseases



Mario C Deng & Charles C Marboe
Columbia University
New York, USA

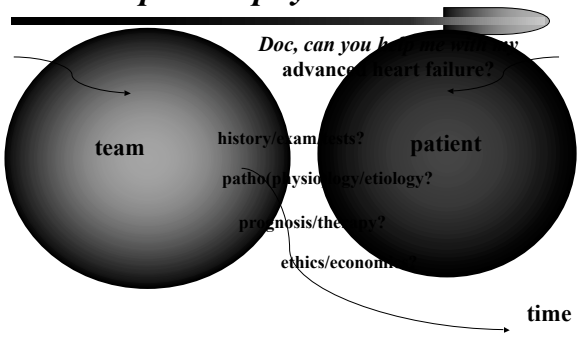
context

- **Cardiac cycle**
- **Valvular heart diseases**
- **Ischemic heart diseases**
- **Congenital heart diseases**
- **Myocardial diseases**

objectives

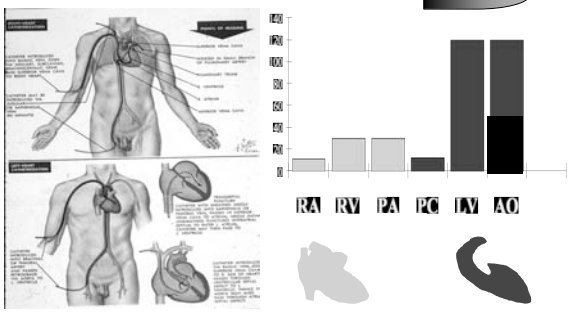
- **classify myocardial diseases into three major phenotypes**
- **describe their clinical presentation during the initial encounter**
- **delineate the diagnostic process and the role of different tests**
- **interpret these results in the context of pathophysiology**
- **employ the stages of heart failure to delineate therapeutic steps**

patient-physican encounter

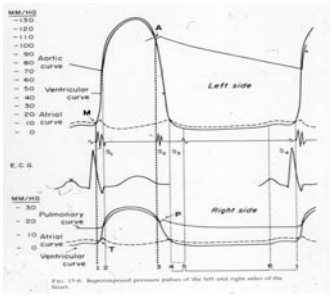


advanced heart failure

right & left heart catheter

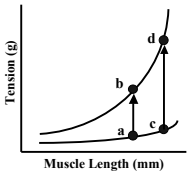


cardiac cycle - ECG & pressures



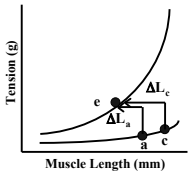
cardiac muscle function

Preload



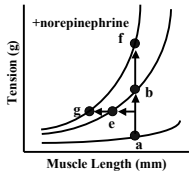
•The length of a cardiac muscle fiber prior to the onset of contraction.
•Frank Starling

Afterload



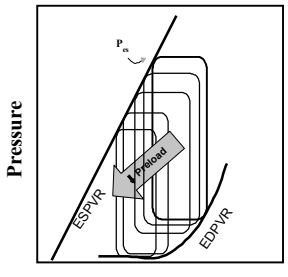
•The force against which a cardiac muscle fiber must shorten.
•Isotonic Contraction

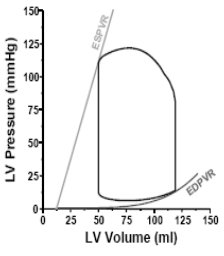
Contractility



•The force of contraction independent of preload and afterload.
•Inotropic State

the pressure volume loop





http://www.columbia.edu/itc/hs/medical/heartsim/

AHF pathophysiology & therapy

adrenergic system
renin-angiotensin
endothelin system

natriuretic
cytokine system
growth hormone

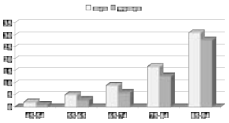
+ organ failure -
+ cachexia -
+ congestion -
+ hypoperfusion -

+ afterload -
+ preload -
+ contractility -
+ heart rate -
+ remodeling -
+ ischemia -
+ arrhythmia -

Medical Center

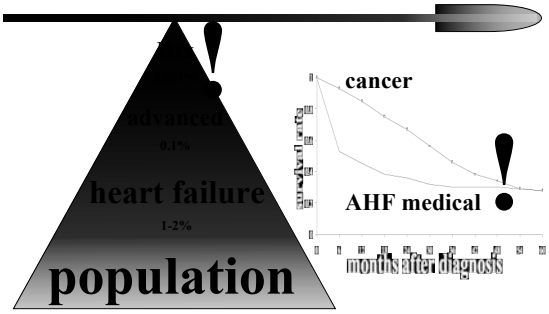
age, sex & heart failure

Average annual incidence/1000



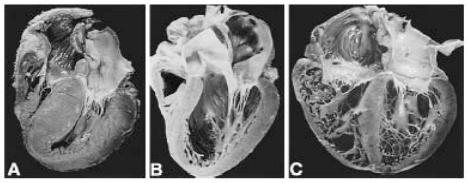
Kannel et al. Br Heart J 1994;72:53

epidemiology

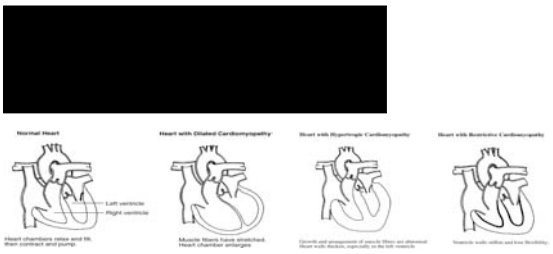


macroscopic pathology

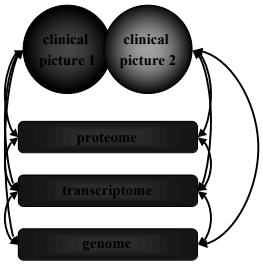
hypertrophic cardiomyopathy | **normal** | **dilated cardiomyopathy**



cardiomyopathy phenotypes



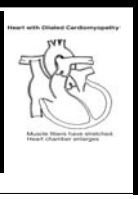
systems biology strategy



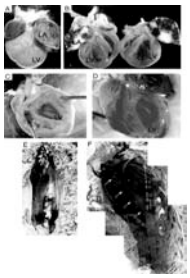
- level distinction
- relationships within levels
- relationships between levels
- iterative strategy

Health Sciences Building

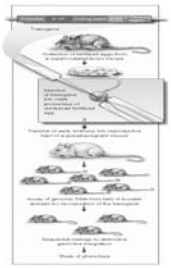
cardiomypathy phenotypes



transgenic animals



Cardiac Compartment-specific Overexpression of a Modified Retinoic Acid Receptor Produces Dilated Cardiomyopathy and Congestive Heart Failure in Transgenic Mice



Colbert CM...Robbins J

Shuldiner AR. NEJM 1996;334:653

specific cardiomyopathies

- Ischemic
- Valvular
- Hypertensive
- Inflammatory (Idiopathic, Autoimmune, Infectious)
- Metabolic (Endocrine, Amyloid)
- General system Disease (Connective Tissue Disorders)
- Muscular Dystrophies
- Neuromuscular Disorders
- Sensitivity and Toxic Reactions
- Peripartum

ischemic dilated cardiomyopathy

team patient

initial presentation

- 55 y male
- married, 2 kids
- large anterolat wall AMI
- 10/31/04 Impella pump
- 11/03/04 HeartMate I MCSD
- evaluation for heart transplant
- 2/17/05 heart transplant

follow-up

- stable post-transplant course
- back to work and normal life

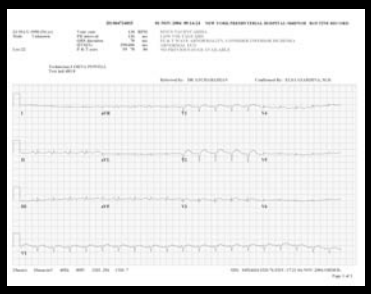
teaching points

- benefits of hi-tech medicine

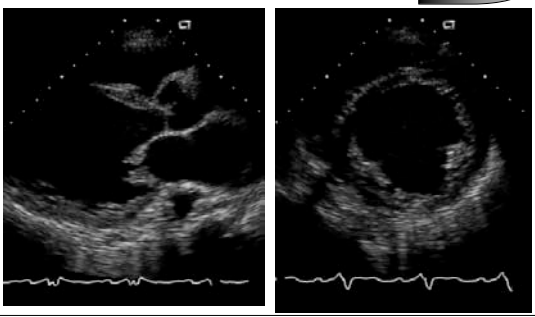
GE #4734815 *1950 m

team patient

team patient



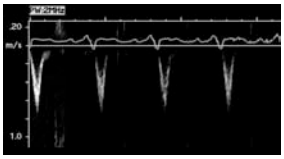
DCM TTE - parasternal axis

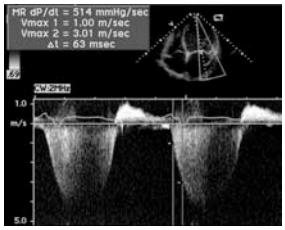


DCM TTE – apical 2/4 chamber view

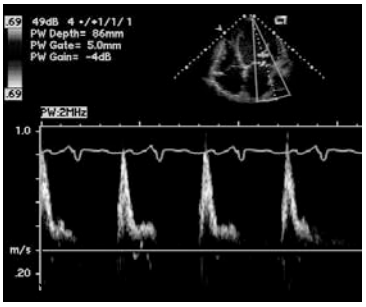
DCM TTE – AV/MV velocity

Calculated CO= 2.1 L/min
Tei index 0.85

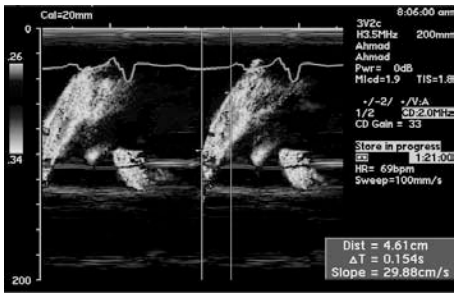




DCM TTE – E deceleration time

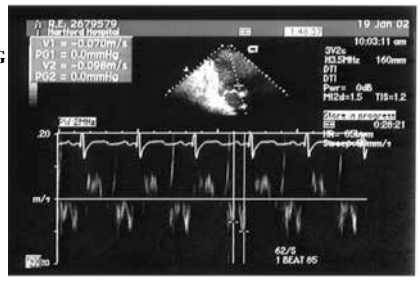


DCM TTE – early mitral flow

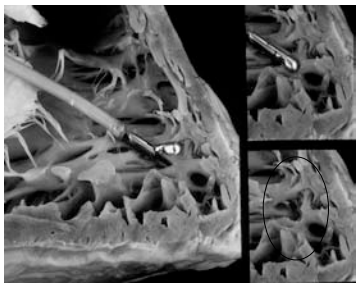


DCM TTE – PA pressure

E/prop vel = 2.7
E/Ea = 16
PASP= 56mmHG



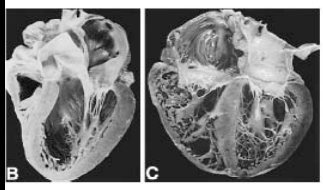
endomyocardial biopsy



macroscopic pathology

normal

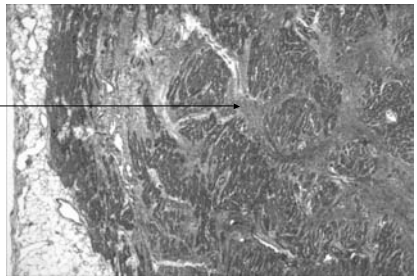
dilated cardiomyopathy



idiopathic dilated cardiomyopathy

Masson trichrome stain

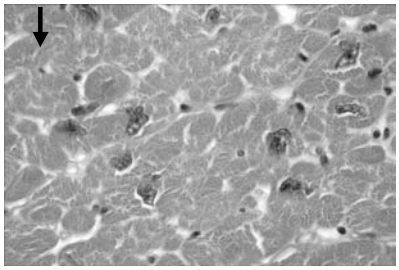
extensive interstitial fibrosis (blue) with myocytes in red and epicardial fat/pericardium to the left



idiopathic dilated cardiomyopathy

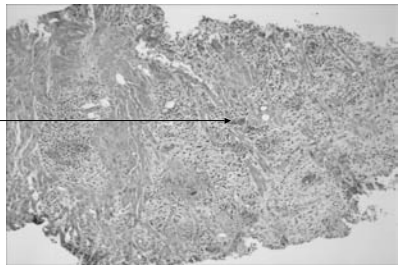
Hematoxylin & eosin stain:

Myocyte hypertrophy (very enlarged and irregular nuclei)



myocarditis

inflammatory infiltrate in the myocardium associated with myocyte damage



myocarditis

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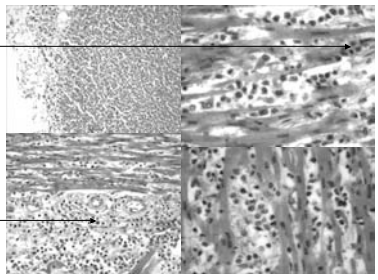
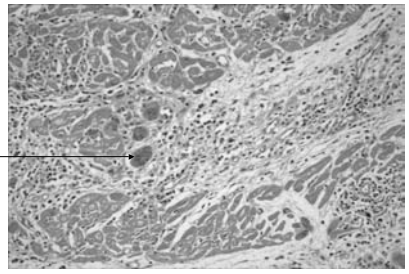
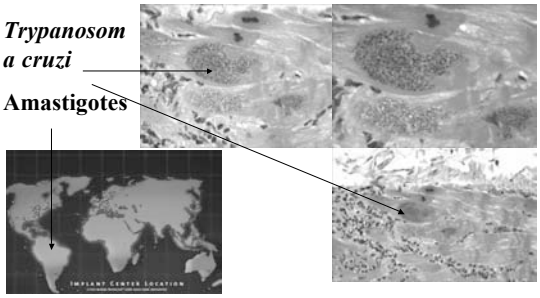


giant cell myocarditis



chagas disease

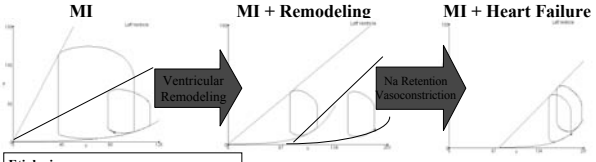


College of Physicians & Surgeons

dilated cardiomyopathy

- **pathology**
  - **enlargement of all four chambers, mild hypertrophy, interstitial fibrosis**
- **pathophysiology**
  - **Frank-Starling mechanism, neurohormonal activation, myocardial remodeling**
- **etiology**
  - **genetic, infectious, inflammatory, toxic, metabolic, neuromuscular**

decreased contractility

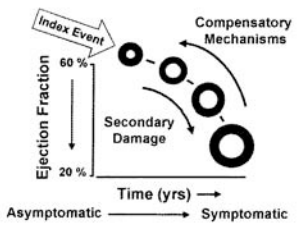


Etiologies

- Ischemic Cardiomyopathy
  - Myocardial Infarction
  - Myocardial Ischemia
- Myocarditis
- Toxins
  - Anthracycline
  - Alcohol
  - Cocaine

Parameter	Normal	MI	MI + Remodeling	MI + HF
BP (mm Hg)	124/81	68/46	68/45	80/50
SV (ml)	61	35	34	38
Cardiac Output (L/min)	3.7	2.1	2.0	2.3
PCWP (mm Hg)	10	16	18	33

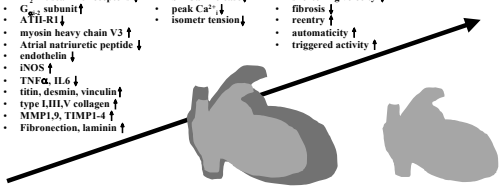
heart failure & remodeling



Mann DL et al. Circulation 1999;100:999-1008

transcriptome>proteome>phenotype

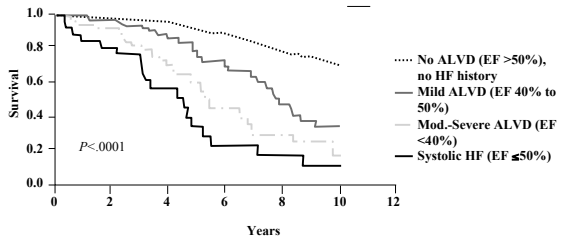
- **gene**
  - Ca++-, K+-channel↑↓
  - Na+/H+ antiporter↑
  - SERCA2 ↓
  - Phospholamban ↓
  - Ryanodine receptor ↓
  - β_1-adrenoceptors ↓
  - M_2 muscarinic receptors ↓
  - $G_{\alpha i-2}$ subunit↑
  - ATII-R1↓
  - myosin heavy chain V3 ↑
  - Atrial natriuretic peptide ↓
  - endothelin ↓
  - iNOS ↑
  - TNFα, IL6 ↓
  - titin, desmin, vinculin↑
  - type I,III,V collagen ↑
  - MMP1,9, TIMP1-4 ↑
  - Fibronection, laminin ↑
- **cell**
  - cell size ↓
  - cell # ↑
  - cell nucleus # ↑
  - DNA repair ↑
  - mitochondr mass ↑
  - apoptosis ↓
  - SR Ca^{2+} release↓
  - peak Ca^{2+}↓
  - isometr tension↓
- **organ**
  - cardiac mass ↓
  - LVEDP ↓
  - LVEDV ↓
  - wall stress ↑
  - ejection fraction↓
  - force-time integral ↓
  - shortening velocity ↓
  - fibrosis ↓
  - reentry ↑
  - automaticity ↑
  - triggered activity ↑
- **organism**
  - neurohormoes ↓
  - cytokines ↓
  - oxygen uptake ↑
  - body weight ↓
  - endothelial function ↓
  - immune competence ↑



dilated cardiomyopathy

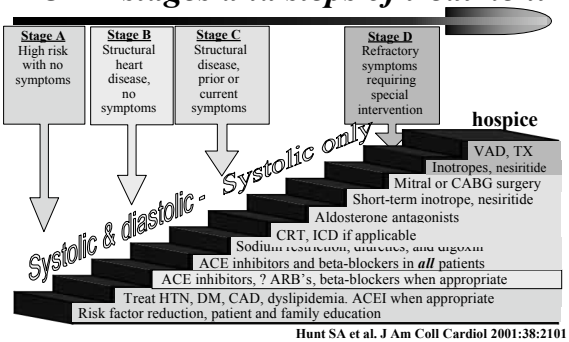
- **prognosis**
  - 1-year survival 10-90%, 5-year survival 50%
  - Improved with active therapy
- **therapy**
  - underlying cause, relief of congestion, augmentation of cardiac output, prevention of arrhythmias and thromboemboli

Framingham Study - mortality



Wang TJ et al. Circulation. 2003;108:977

CHF stages and steps of treatment



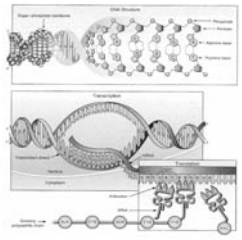
Hunt SA et al. J Am Coll Cardiol 2001:38:2101

cardiomyopathy phenotypes

[redacted]

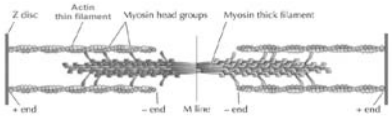
hypertrophic cardiomyopathy genetics

- **autosomal dominant trait**
  - **2/3 of patients have family history**
  - **more than 200 mutations in 10 genes encoding contractile sarcomeric proteins**
  - **two genes for non-sarcomeric proteins and mitochondrial genome**



Rosenthal N. NEJM 1994;331:39

HCM mutation frequencies



Gene	Chromosome	Frequency, %	Number of Mutations
βMHC	14q1	35–50	>50
MYBP-C	11q11	15–20	>15
Cardiac troponin T	1q3	15–20	>20
α-tropomyosin	15q2	<5	3
Cardiac troponin I	19q13	<1	3
MLC-1	3p	<1	2
MLC-2	12q	<1	2
α-Cardiac actin	15q11	?	2
Titin	2q31	?	?
Unknown	7q3	?	?

hypertrophic cardiomyopathy

team patient

initial presentation

- 44 y female
- heart murmur since childhood
- married ,4 kids
- 3/6/06 mitral valve repair & myectomy
- 3/8/06 mitral valvle replacement
- complicated postoperative course

follow-up

- good longterm recovery

teaching points

- HOCM surgically challenging

AJ #5015860 *1962 f

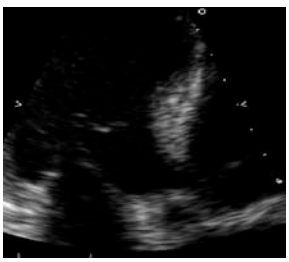
hypertrophic cardiomyopathy

- **history**
  - **sudden death during vigorous exercise 1/500, suncope, angina, dyspnea**
- **physical exam**
  - **S4, systolic murmur (LVOT obstruction – increased by Valsalva, MR)**
- **diagnostic tests**
  - **X-ray**
  - **ECG (LAH, LVH)**
  - **Echocardiogram (asymmetric hypertrophy)**
  - **Catheterization (LVOT gradient)**
  - **Genetic testing**

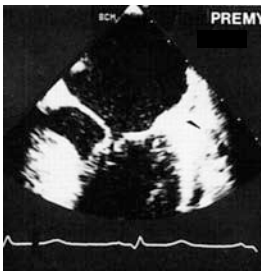
HCM TTE - parasternal axis

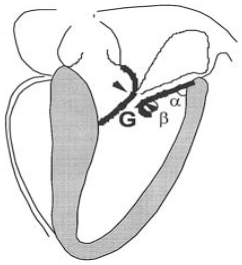
HCM TTE– apical view

HCM TTE– mitral regurgitation



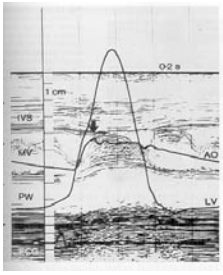
HCM TTE– SAM & malcoaptation





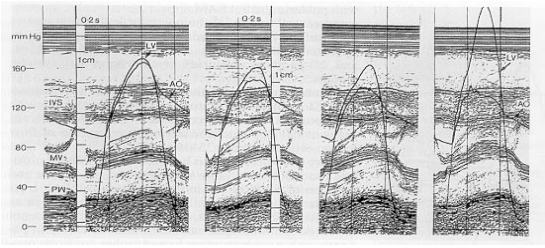
Grigg LE, Wigle ED, Rakowski H. J Am Coll Cardiol 20:42, 1992

HCM TTE– SAM & obstruction



Pollick C, Rakowski H, Wigle ED. Circulation 66:1087, 1982

HCM TTE– LVOT obstruction



Pollick C, Rakowski H, Wigle ED. Circulation 69:43, 1984

cardiomyopathy phenotypes

[redacted]

amyloidosis cardiomyopathy

PRIMARY: amyloid light chain (AL)
lambda: kappa = 2:1
SECONDARY: serum amyloid A (AA)
SENILE CARDIAC: (SCA); transthyretin
FAMILIAL: autosomal dominant with mutations in transthyretin, gelsolin, apolipoprotein A-I, lysozyme, or fibrinogen genes.

iron storage disorders

- **Iron overload – Hemosiderosis – following multiple blood transfusions.**
- **Hereditary Hemochromatosis**
  Autosomal recessive
  ***HFE* gene on chromosome 6**
  Increased intestinal absorption of dietary iron

restrictive cardiomyopathy

team patient

initial presentation

- 51 y male
- banker,2 kids
- rapidly progressive heart failure
- heart transplant evaluation
- heart transplantation 2003
- autologous stem cell transplantation (CAMP9)

follow-up

- sucessful post-heart/stemcell transplant course

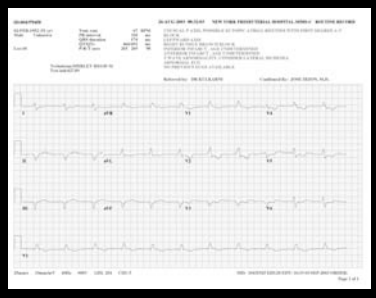
teaching points

- amyloid-related cardiomyopathy DD challenging

LD #4379458 *1952 m

team patient

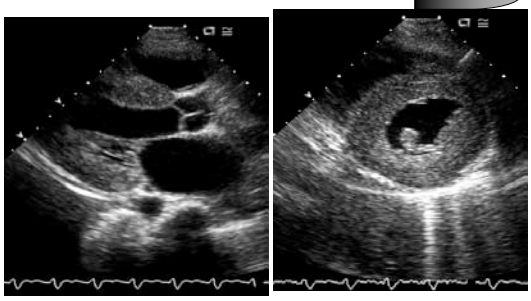
team patient



restrictive cardiomyopathy

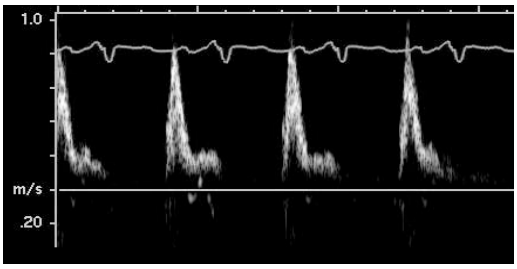
- **history**
  - Fatigue, exercise tolerance ↓
- **physical exam**
  - rales, neck veins ↑, ascites, peripheral edema, KUSSMAUL SIGN
- **diagnostic tests**
  - Xray: normal sized heart, congestion
  - ECG: ST/T-changes, a-fib, AB-block, BBB
  - echocardiography
  - endomyocardial bipsy

RCM TTE– parasternal view



RCM TTE– apical view

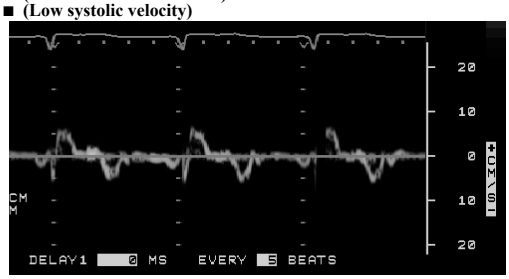
RCM TTE– restrictive mitral filling



Decel time= 102 msec

RCM TTE– tissue doppler

- **Abnormally low E'**
- **(Atrial mechanical failure)**
- **(Low systolic velocity)**



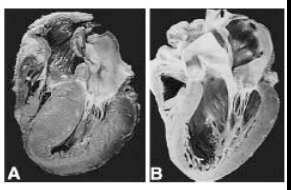
RCM TTE– tissue doppler

Impaired relaxation- reduced propagation velocity

macroscopic pathology

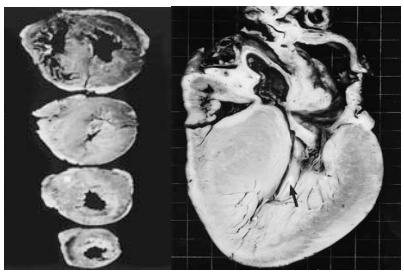
hypertrophic cardiomyopathy

normal



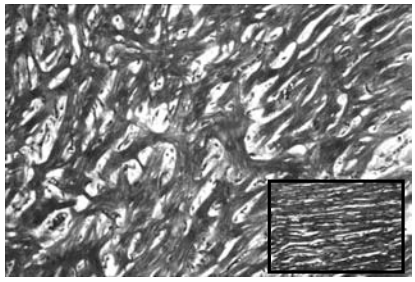
macroscopic pathology

concentric hypertrophy



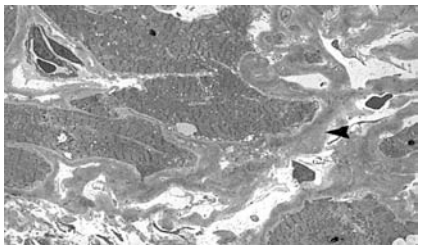
microscopic pathology HCM

myocyte disarray



microscopic pathology amyloid

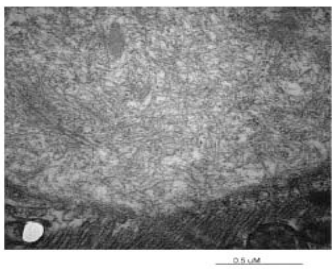
Amyloid encircling a myocyte (original magnification, x1890)



Mudhar, H S et al. J Clin Pathol 2001;54:321-325

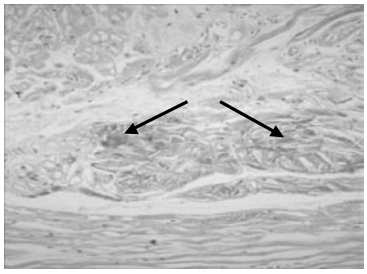
microscopic pathology amyloid

Amyloid: 7-10 nm fibrils haphazardly arranged



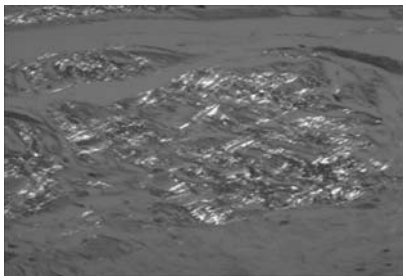
microscopic pathology amyloid

Congo Red stain of amyloid deposits in the heart

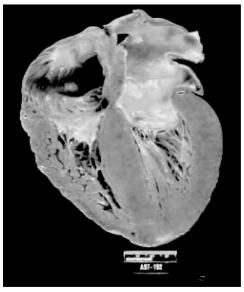


microscopic pathology amyloid

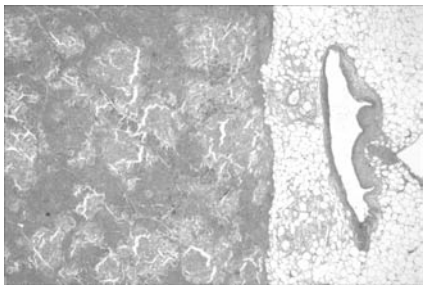
Congo Red stain under polarized light: Amyloid deposits are birefringent.



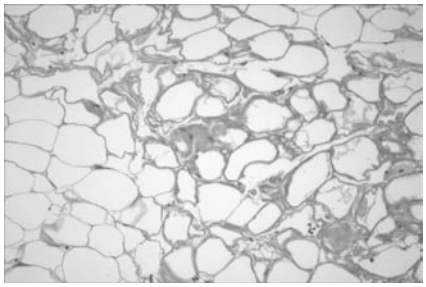
macroscopic pathology amyloid



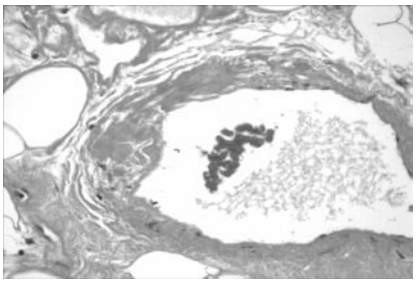
microscopic pathology amyloid



microscopic pathology amyloid



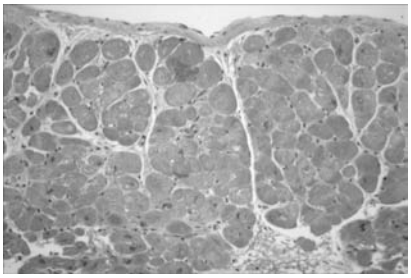
microscopic pathology amyloid



iron storage disease

Endomyocardial Biopsy:

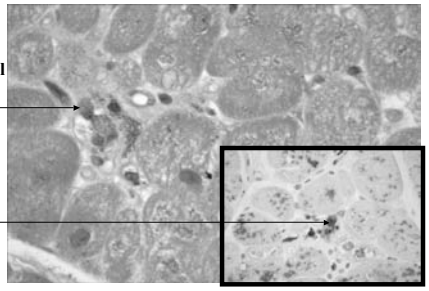
Iron storage disease in the heart



iron storage disease

Iron deposits in myocytes and interstitial macrophages

Prussian Blue stain: Iron is blue



hypertrophic cardiomyopathy

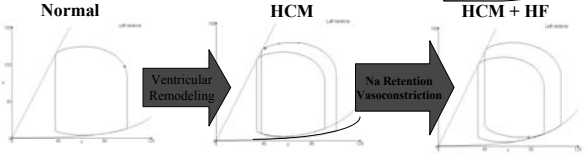
- **pathology**
  - **asymmetric septal hypertrophy, myocardiac fibers in disarray, compensatory hypertrophy and fibroblast proliferation**
- **pathophysiology**
  - **compliance and relaxation reduced , dynamic LV outflow tract obstruction, abnormal motion of the anterior mitral leaflet**
- **etiology**
  - **sarcomere complex mutations (b-myosin heavy chain, cardiac trop T, myosin-binding protein C (automal dominant mechanism)**

restrictive cardiomyopathy

- **pathology**
  - **abnormally rigid ventricles (not necessarily hypertrophied), endocardial fibrosis or scarring or myocardial infiltration**
- **pathophysiology**
  - **upward shilt of passive ventricular filling curve > elevated pulmonary and systemic venous pressures**
  - **reduced cavity size > stroke volume/cardiac output ↓**
- **etiology**
  - **infitrative: amyloidosis, sarcoidosis**
  - **storage disease: hemochromatosis, glycogen storage diseases**
  - **endocardial fibrosis**
  - **hypereosinophilic syndrome**
  - **metastatic tumors**
  - **radiation therapy**
  - **noninfiltrative: scleroderma, idiopathic**

decreased filling

Normal **HCM** **HCM + HF**

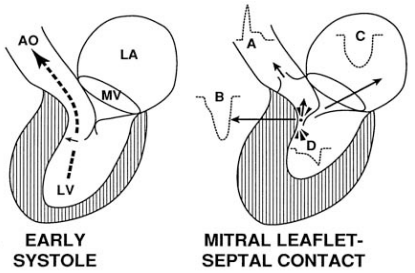


Etiologies

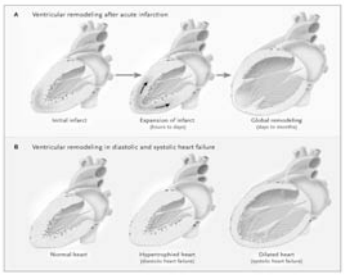
- Mitral Stenosis
- Constriction
- Restrictive Cardiomypoathy
- Cardiac Tamponade
- Hypertrophic Cardiomyopathy
- Infiltrative Cardiomyopathy

Parameter	Normal	HCM	HCM + HF
BP (mm Hg)	124/81	112/74	131/87
SV (ml)	61	57	66
Cardiac Output (L/min)	3.7	3.4	4.0
PCWP (mm Hg)	10	12	27

LV outflow tract obstruction



ventricular remodeling



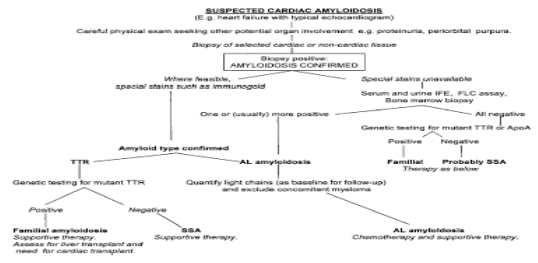
hypertrophic cardiomyopathy

- **prognosis**
  - **dependent on mutation**
  - **Sudden death 4-6% per year (children), 2-4% (adults)**
- **therapy**
  - **AVOID strenuous exercise**
  - **B-blockers (myocardial oxygen demand↓, LVOT gradient ↓)**
  - **CA-channel antagonists**
  - **amiodarone (a-fib)**
  - **antibiotic prophylaxis**
  - **Defibrillator (patient with elevated risk)**
  - **dual chamber PM**
  - **Septal ablation with ethanol**
  - **myomectomy**

restrictive cardiomyopathy

- **prognosis**
  - **Very poor prognosis**
- **therapy**
  - **salt restriction**
  - **diuretics (cautious use)**
  - **Maintainance of SR**
  - **Intravavitary thrombus: anticoagulation**

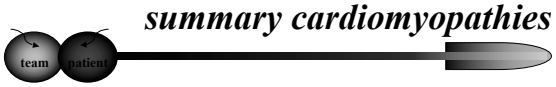
amyloidosis management



Heart-liver transplantation? **Heart-autologous BM transplantation?**

Entrance

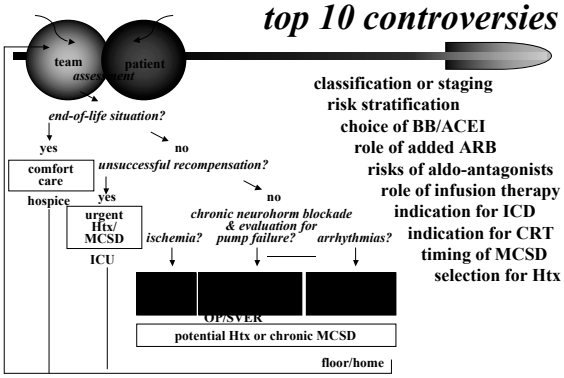
summary cardiomyopathies



phenotype	*dilated*	*hypertrophic*	*restrictive*
history	left heart failure	SOB, cP, syncope	right heart failure
physical exam	S3, S4, MR	S4, valsalva+ murmur	Kussmaul sign
chest Xray	LV enlargement, PVH	LA enlargement	PVH
ECG	SR↑, ST/T, IC abnorm	LVH	low volt, AV cond↓
echo	chamber dilat, regurg	asymm LVH, SAM	LV wall ↑, LVEF ok
cardiac catheter	CAD?, RA/PC↑, CO↓	compl↓, LVOT grad	RA/PC↑,square root
biopsy	r/o myocarditis	DD restrctive	r/o infitrative
therapy	systolic HF guidelines	BB, CA, cave volume	systemic approach

Braunwald E. Heart Disease (4th Ed). Saunders, Philadelpia

top 10 controversies



classification or staging
risk stratification
choice of BB/ACEI
role of added ARB
risks of aldo-antagonists
role of infusion therapy
indication for ICD
indication for CRT
timing of MCSD
selection for Htx