Myocardial Diseases: The Cardiomyopathies

Mat Maurer and Charles Marboe

Etiologies

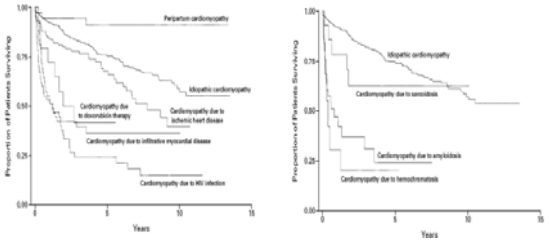
- Ischemic cardiomyopathy
- Valvular cardiomyopathy
- Hypertensive cardiomyopathy.
- Inflammatory cardiomyopathy
- Metabolic cardiomyopathy
- General system disease
- Muscular dystrophies.
- Neuromuscular disorders.
- Sensitivity and toxic reactions.
- Peripartal cardiomyopathy

Objectives

At the conclusion of this seminar, learners will be able to:

1. Define the term cardiomyopathy and be able to classify myocardial diseases into major types.
2. Be able to link pathophysiologic mechanism(s) with each type of cardiomyopathy.
3. Delineate physical exam findings in patients with cardiomyopathy.
4. Understand basic tests (EKG, CXR, Echo, Cardiac Catheterization) that are employed to diagnose a cardiomoypathy and be able to define results for a particular type of cardiomyopathy
5. Delineate conditions that cause reversible cardiomyopathies and those that may require an endomyoycardial biopsy for diagnosis.
6. Identify gross anatomic and histologic correlates of the major types of cardiomyopathy.

Define the Etiology:
For Treatment and Prognosis

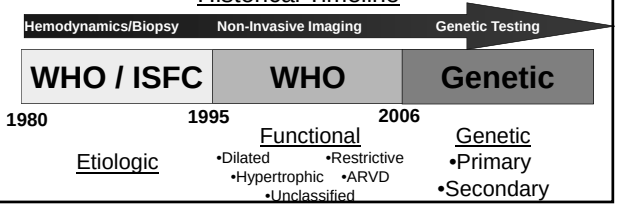


N Engl J Med. 2000 Apr 13;342(15):1077-84.

Definition and Classification

- Cardiomyopathy, literally means "heart muscle disease"
- A classification serves to bridge the gap between ignorance and knowledge

Historical Timeline

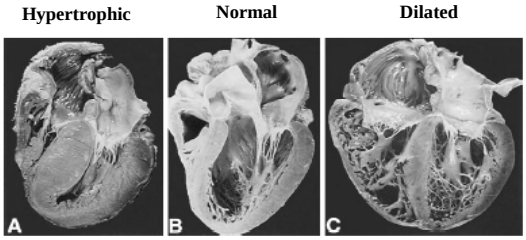


WHO Classification

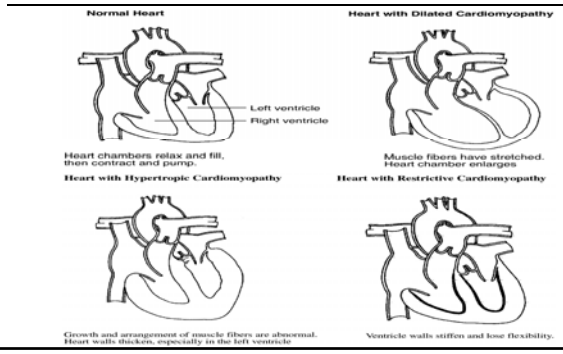
Functional Classification

1. Dilated Cardiomyopathy
2. Hypertrophic cardiomyopathy
3. Restrictive Cardiomyopathy
4. RV Dysplasia
5. Unclassified (Obliterative)

Functional / Morphologic Classification



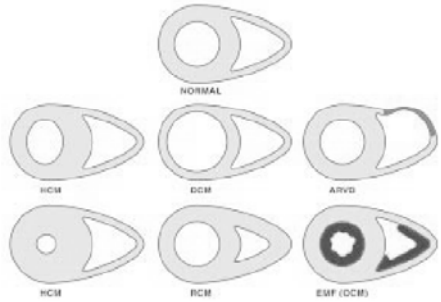
Dilated vs. Hypertrophic vs. Restrictive



Dilated vs. Hypertrophic vs. Restrictive

Type	Definition	Sample Etiologies
Dilated	Dilated left/both ventricle(s) with impaired contraction	Ischemic, idiopathic, familial, viral, alcoholic, toxic, valvular
Hypertrophic	Left and/or right ventricular hypertrophy	Familial with autosomal dominant inheritance
Restrictive	Restrictive filling and reduced diastolic filling of one/both ventricles, Normal/near normal systolic function	Idiopathic, amyloidosis, endomyocardial fibrosis

Morphologic Summary

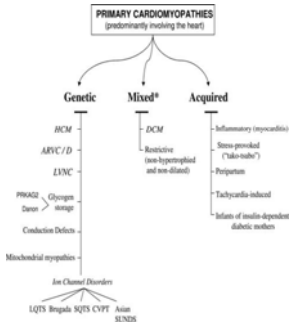


ARVD vs. Unclassified

Type	Definition	Sample Etiologies
ARVD	Genetic, muscular disorder of the right ventricle is replaced by fat and fibrosis, and causes abnormal heart rhythm	ARVD
Unclassified	Genetic disorder, known as "spongiform cardiomyopathy" in which embyonically the myocardium fails to is regress.	Non-compaction

Genetic Classification

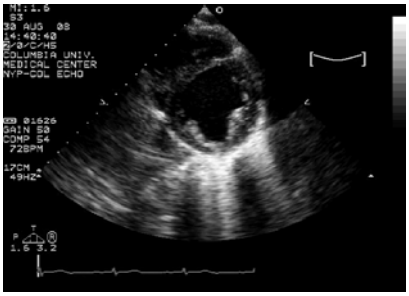
- Primary
  - Can be genetic, nongenetic or acquired
  - Solely or predominantly confined to heart muscle and are relatively few in number
- Secondary
  - Pathological myocardial involvement as part of a large number and variety of generalized systemic (multi-organ) disorders



Secondary

- Infiltrative
- Storage
- Toxicity
- Endomyocardial
- Inflammatory
- Endocrine
- Cardiofacial
- Neuromuscular/Neurologic
- Autoimmune/Collagen

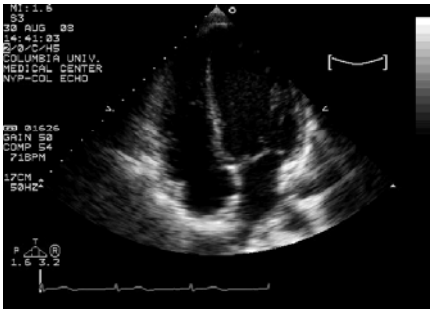
Normal Echocardiogram



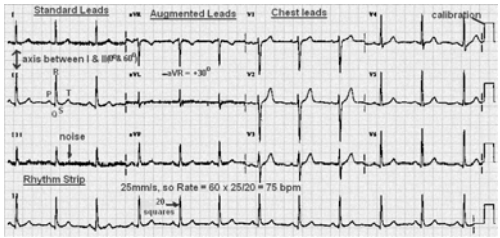
Diagnostic Tests

- Chest X ray
- EKG
- Echocardiogram
- Blood tests: Na, BUN, Creatinine, BNP
- Exercise tests
- MRI
- Cardiac catheterization
- Endomyocardial Biopsy

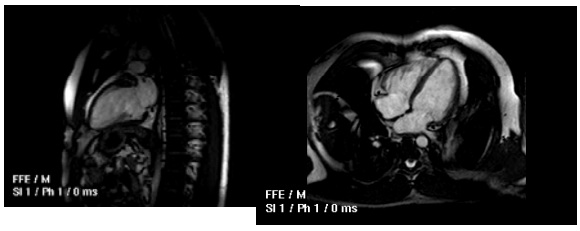
Normal Echocardiogram

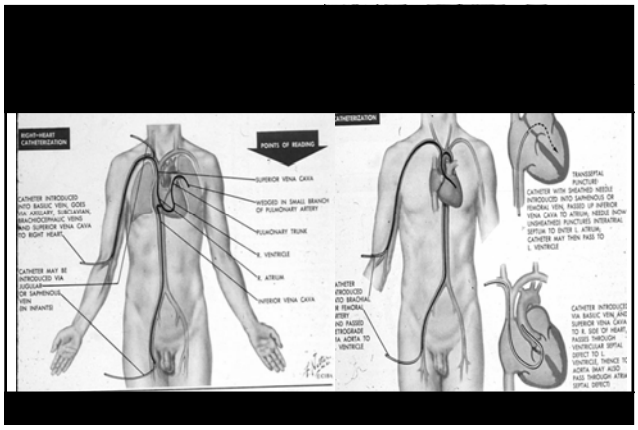


EKG



Normal MRI





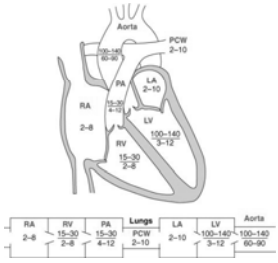
Diagnoses made by Endomyocardial Bx

1. **Myocarditis**
   - **Giant Cell**
   - **CMV**
   - **Toxoplamosis**
   - **Chagas disease**
   - **Rheumatic**
   - **Lyme**
2. **Infiltrative**
   Amyloid
   Sarcoid
   Hemochromatosis
   Hypereosinophilic
   Tumors
- **3. Toxins**
  - **Doxorubicin**
  - **Radiation Injury**

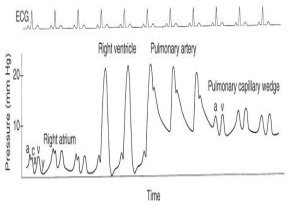
4. Genetic
Infiltrative
Glycogen Storage

Right & Left heart Catheterization

Left Heart Catheterization



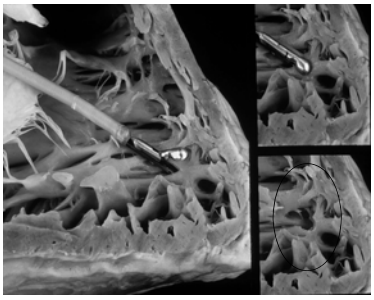
Right Heart Catheterization



Potentially Reversible Dilated Cardiomyopathies

- **Ischemic with viable myocardium**
- **Uncorrected Valvular Disease**
- **Inflammatory**
  - Viral
  - Toxo
  - Lyme
- **Toxic**
  - Alcohol
  - Cocaine
  - Cobalt
- **Hypersensitivity**
- **Endocrine**
  - Hyperthyroidism
  - Pheochromocytoma
- **Metabolic**
  - HypoCa, HypoP
  - Uremia
  - Carnitine
- **Nutritional**
  - Selenium, Thiamine
- **Infiltrative**
  - Hemochromatosis
  - Sarcoidosis

Endomyocardial Biopsy

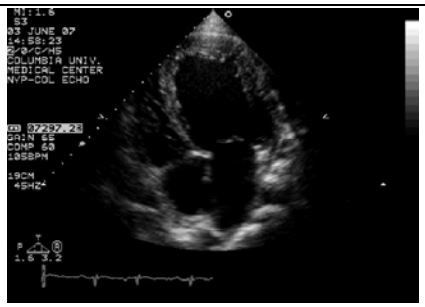


Case #1 (DCM): History

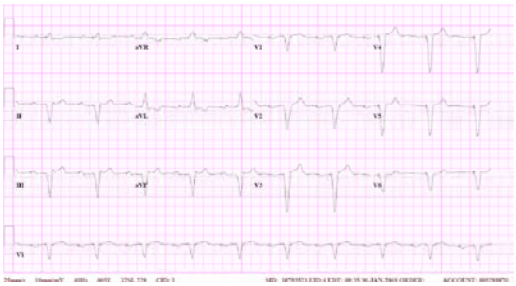
- 56-year old female
- Recent URI about 3 weeks
- Progressive effort intolerance
- Increasing shortness of breath and fatigue
- Admitted to the hospital

Case #1 (DCM): Physical Exam

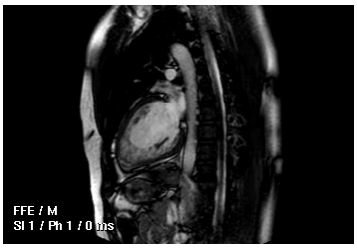
- Well-developed, well-nourished female
- 5 feet 10 inches, weighed 188 pounds.
- BP = 100/70 mmHg, P= 70 bpm, RR =26.
- Skin: warm
- Neck: JVP at 8 cm with prominent “v” wave.
- Cardiac: Regular cardiac rhythm with a S3 gallop but non-displaced PMI
- Lungs: crackles at bases
- Adbomen: soft, nontender without organomegaly
- Ext: No edema.

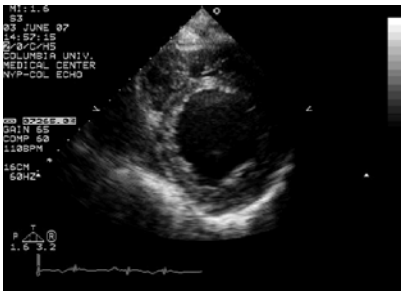


Case #1 (DCM): EKG

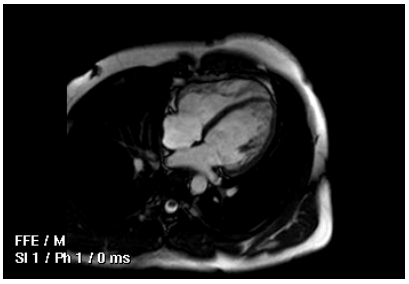


Case #1 (DCM): MRI





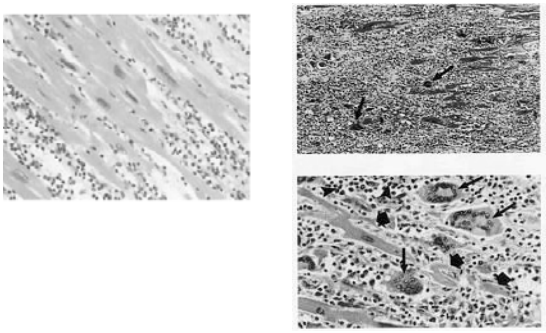
Case #1(DCM):MRI



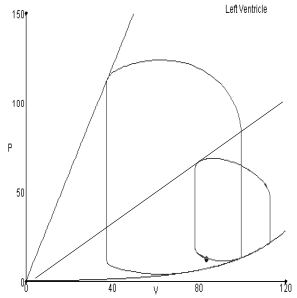
Case #1 (DCM): Catherization and Bx

- Catheterization
  - Right atrial pressure = 18
  - Pulmonary artery pressure= 43/29
  - Pulmonary wedge pressure =27
  - Cardiac output of 3.6 L/min
  - Cardiac index 1.8 L/min/m2
- Biopsy was performed

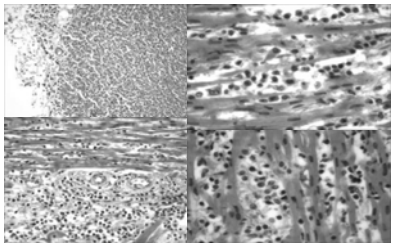
Myocarditis



Case #1 (DCM): Primary Mechanism Decreased Contractility

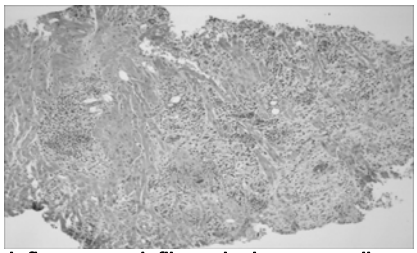


Myocarditis



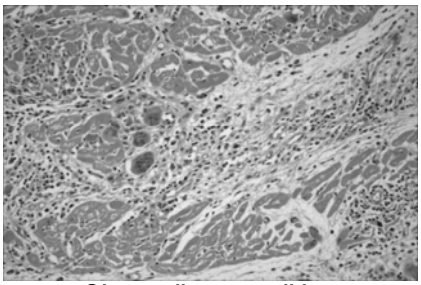
Inflammatory infiltrate in the myocardium associated with myocyte damage

Myocarditis



Inflammatory infiltrate in the myocardium associated with myocyte damage

Myocarditis



Giant cell myocarditits

Diagnoses of Dilated Cardiomyopathies made by Endomyocardial Bx

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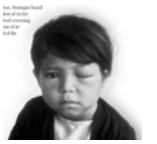
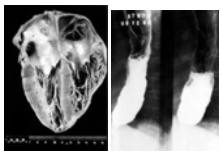
   - **Chagas disease**
   - **Rheumatic**
   - **Lyme**
2. **Infiltrative**
   Amyloid
   Sarcoid
   Hemochromatosis
   Hypereosinophilic
   Tumors
- **3. Toxins**
  - **Doxorubicin**
  - **Radiation Injury**

4. **Genetic**
   Infiltrative
   Glycogen Storage

Chagas Disease:
Clinical Manifestations

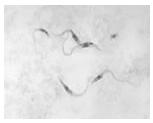
- Acute stage:
  - Usually occurs unnoticed
  - Fever, fatigue, body aches, headache, rash, loss of appetite, diarrhea, and vomiting.
  - Signs: mild enlargement of liver/spleen, swollen glands, and local swelling (a chagoma, Romaña's sign)
- Chronic stage:
  - The symptomatic chronic stage affects the digestive system and heart.
  - Cardiomyopathy, which causes heart rhythm abnormalities and can result in sudden death.
  - 1/3 develop digestive system damage (megacolon and mega esophagus),





Chagas Disease:
American trypanosomiasis

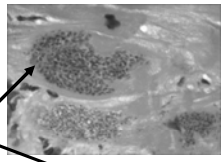
- Most common cause of heart failure worldwide
- Caused by the protozoan *Trypanosoma cruzi*.
- Insect vector

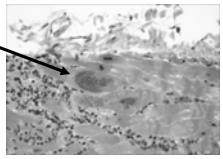


Chagas Disease *chagas disease*

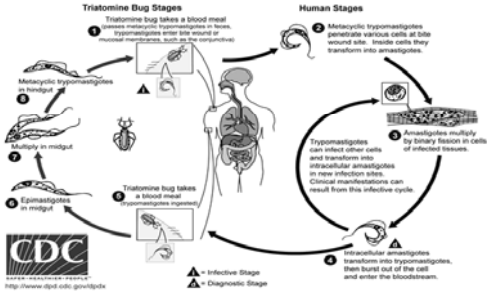
Trypanosoma cruzi

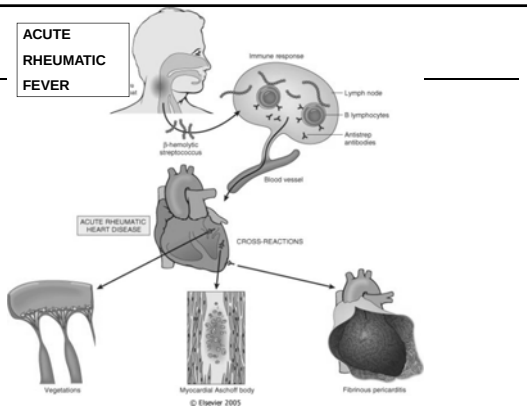
Amastigotes

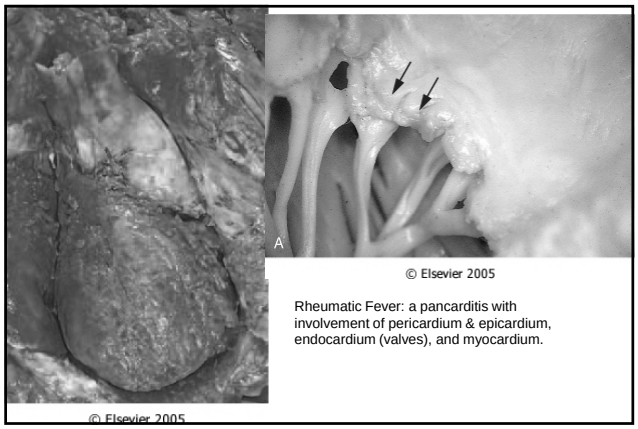




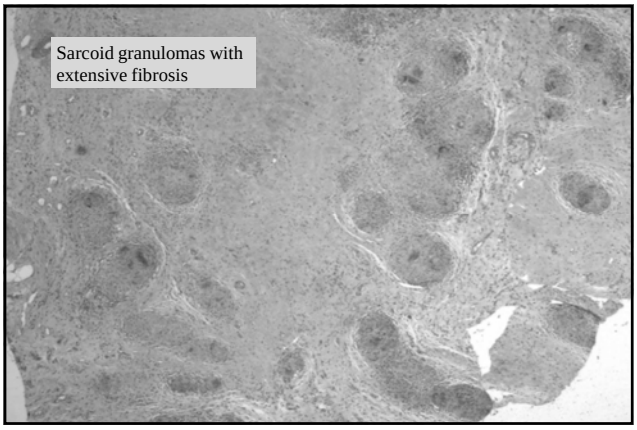
Chagas Disease
Life cycle





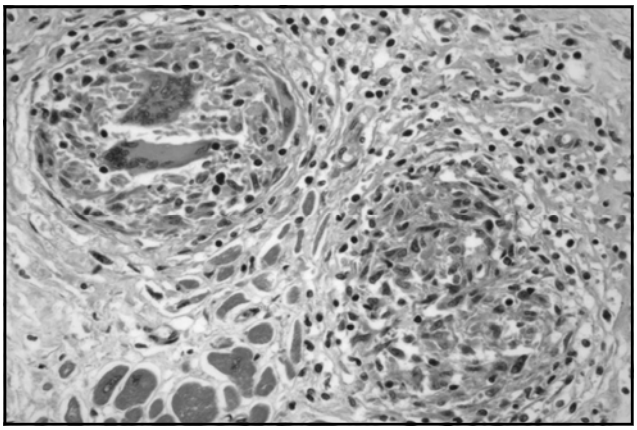


Rheumatic Fever: a pancarditis with involvement of pericardium & epicardium, endocardium (valves), and myocardium.



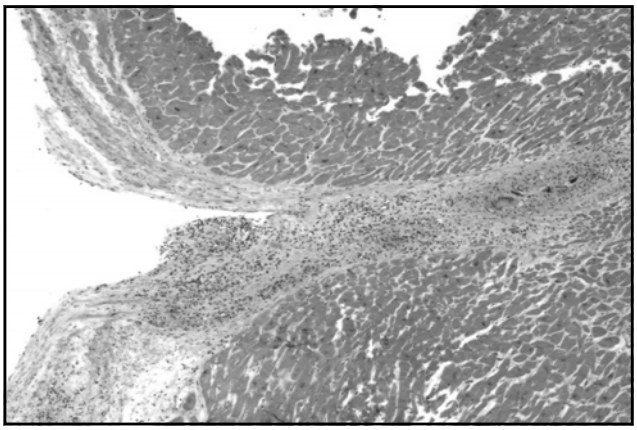
Rheumatic Fever:

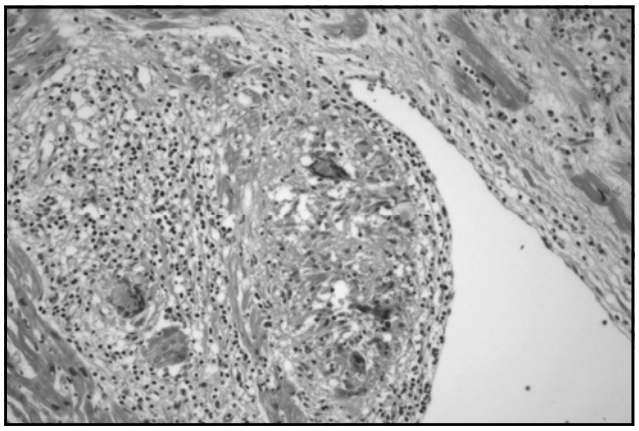
Myocardial involvement with an Aschoff body – a cardiac 'granuloma.'

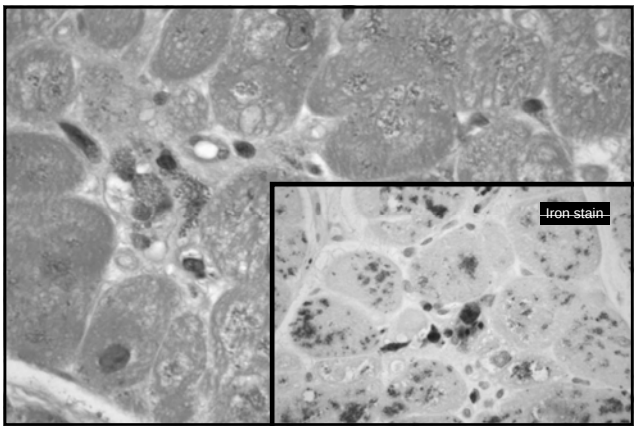


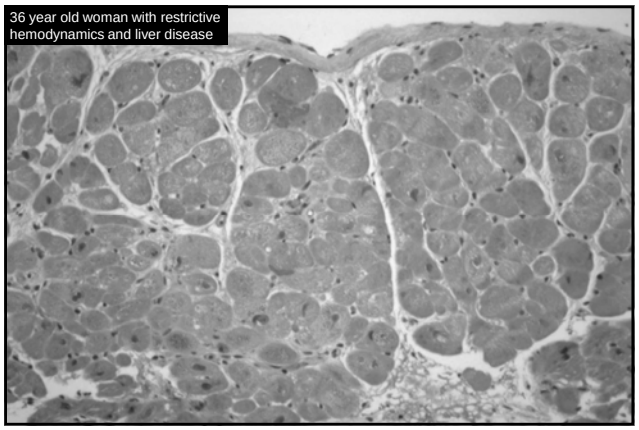
Infiltrative Disorders

- Amyloid
- Sarcoid - a granulomatous disease
- Hemochromatosis
- Hypereosinophilic Syndrome
- Tumors



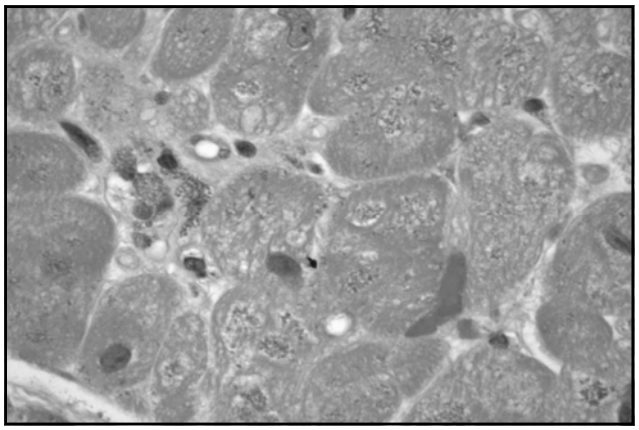






Toxins

- Anthracycline-derivatives such as Doxorubicin
- Radiation injury
- Alcohol (no specific features for diagnosis by biopsy)



Anthracycline Cardiotoxicity

1. **Acute, within days:** EKG changes, LV dysfunction is usually transient and reversible.
2. **Late-onset:** ventricular dysfunction and arrhythmias; irradiation increases risk.
3. **Dilated cardiomyopathy:** cumulative, dose dependent, irreversible, progressive.

Overall incidence of severe CHF is 2-3%.

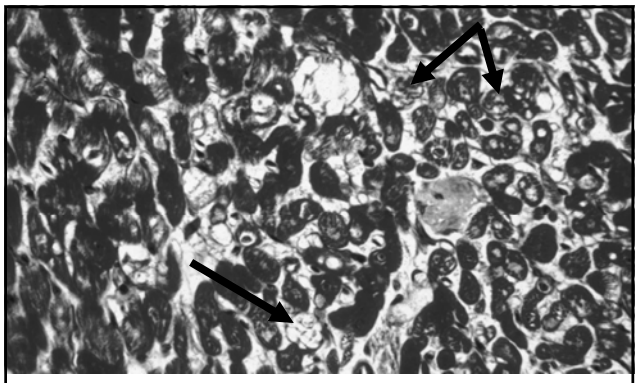
Anthracycline Cardiotoxicity

Pathology

1. Cytoplasmic vacuolation (dilated sarcoplasmic reticulum).
2. Myofibrillar degeneration (loss of myofibrils)
3. Seen in almost all patients receiving doses of > 240 mg/m^2.
4. Little or no inflammation.
5. End stage: myocyte hypertrophy and interstitial fibrosis

Glycogen storage disease type IV (Andersen disease)

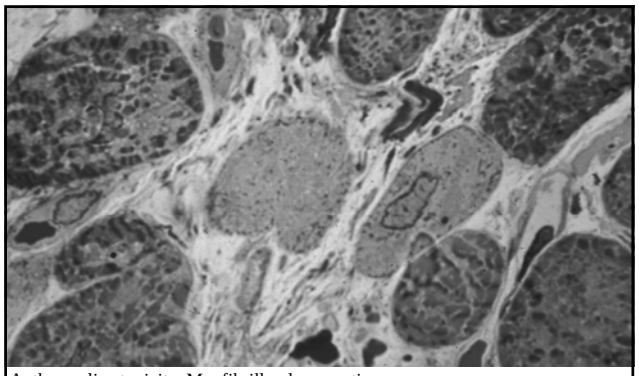
- Autosomal Recessive
- Deficiency of glycogen branching enzyme (GBE1; 1,4-1,6-glucan: 1,4-glucan 6-glycosyl transferase); chr. 3p14
- Abnormal glycogen (polyglucosan) accumulates in tissues
- The clinical presentations are extremely heterogeneous.



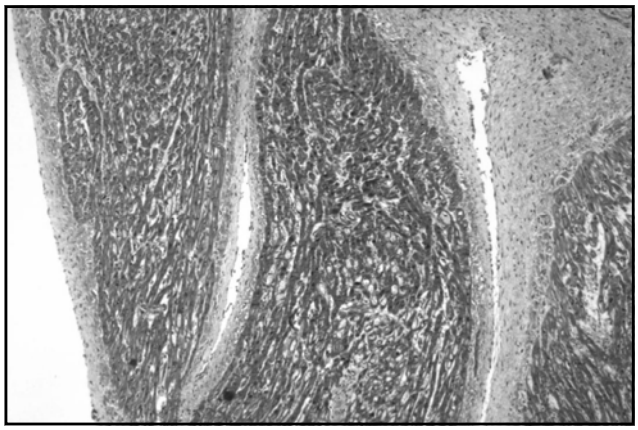
Anthracycline toxicity: Cytoplasmic vacuoles
(Masson trichrome stain)

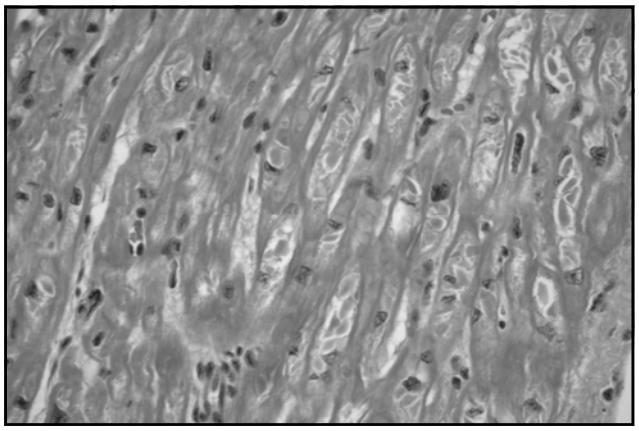
Glycogen storage disease type IV (Andersen disease)

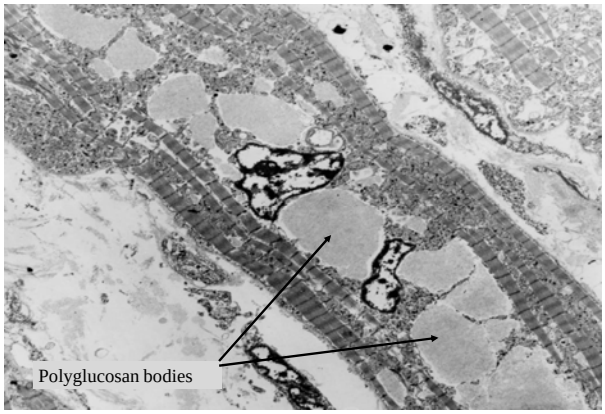
- Classic: rapidly progressive liver failure
- Non-progressive hepatic form
- Fatal neonatal neuromuscular disease
- Multisystem: skeletal, cardiac, nerve and liver

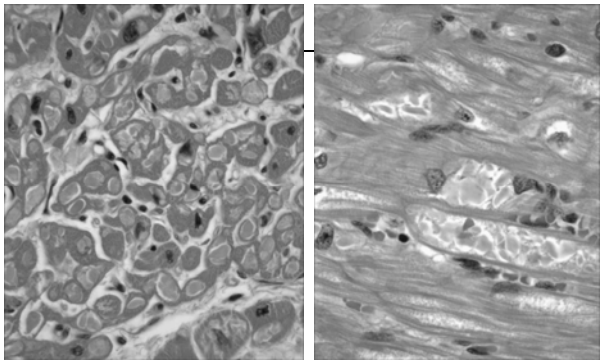


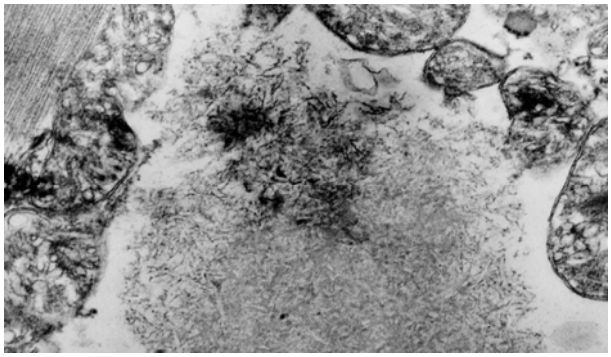
Anthracycline toxicity: Myofibrillar degeneration
(1 micron section/toluidine blue stain)

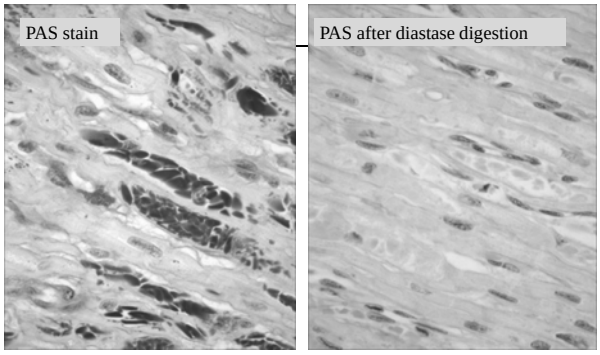












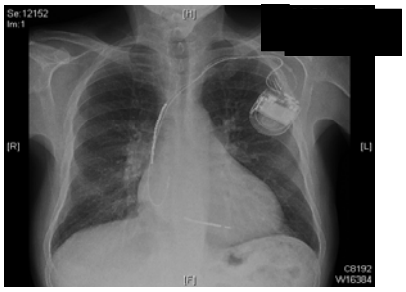
Part Two

Break Time!!!!

Case #2 (RCM): History

- 53 year old male with progressive shortness of breath
- PMHx: HTN, DM, and hypercholesterolemia
- Unlimited exercise tolerance until 6 weeks ago
- Initially SOB on severe exertion and w/ stairs
- Progressed over 6 weeks to minimal exertion
- Symptoms: two pillow orthopnea, frequent paroxysmal nocturnal dyspnea, increasing lower extremity edema and abdominal distention, early satiety and 25 pound weight gain and tight clothes
- NYHA Class III

Case#2(RCM):Chest X-Ray

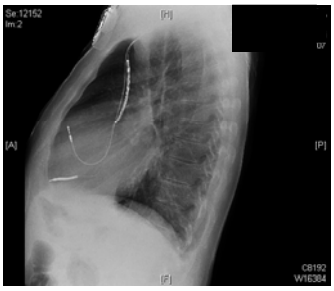


Case #2 (RCM): Physical Exam

BP=90/60 HR=104 RR=22 T=98.6° SaO2=100%

- Gen: WD/WN, in NAD
- Skin: multiple echymosis
- HEENT: NC/AT; EOMI; PERRL, macroglossia
- Neck: elevated JVP to 12cm with rapid x and y descent
- Chest: Bilateral basilar rales
- Heart: PMI in 5th intercostal space, RRR, S1 + S2, S4,
- Abd: distended, NT; +BS, liver 2 finger breaths below CM and 14 cm in span.
- Ext: 2+ LE edema bilaterally to calf

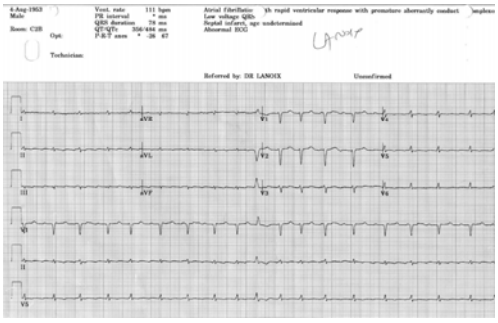
Case#2(RCM):Chest X-Ray

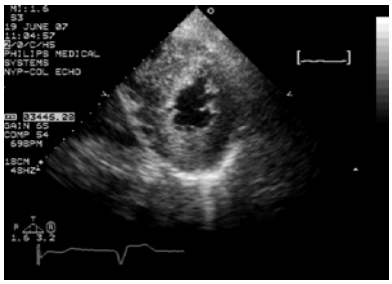


Case #2 (RCM): Laboratory Data

- Hemoglobin /Hematocrit = 11 / 33
- Blood urea nitrogen 47 mg/dl, Creatinine = 1.4 mg/dl
- B- type naturetic peptide = 875 pg/ml
- Troponin I = 0.2
- 24 hour urine protein 527 mg/dl
- Serum protein electropheisis - small monoclonal protein
- Serum lamba light chains = 23 mg/dl, Kappa = 4.1 mg/dl, ratio = 4.5

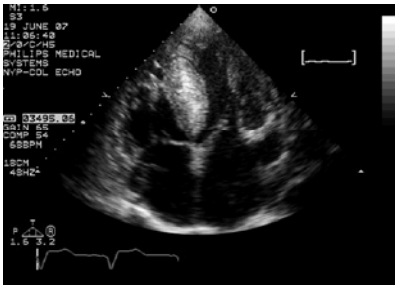
Case #2 (RCM): EKG





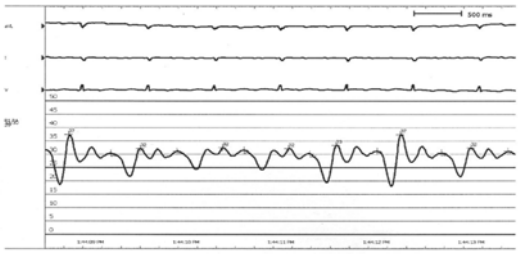
Case #2 (RCM): Pressure Measurements

- Right Atrium = 30 mmHg
- Right Ventricle = 60/30 mmHg
- Pulmonary Artery = 60/35 mmHg
- Pulmonary Wedge = 35 mmHg
- Left Ventricle = 127/30 mmHg
- Aorta = 127/88 mm Hg
- Cardiac Output = 2.4 L/min
- Cardiac Index = 1.2 L/min/m2



Case #2 (RCM) Right Heart Catheterization:

Right Atrial Pressure

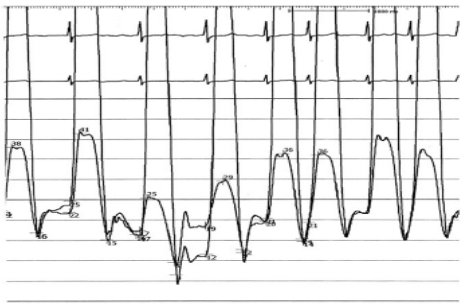


Case #2 (RCM): Cardiac Catheterization

- Left dominant circulation
- Left Main = no disease
- RCA = mild diffuse disease
- LAD = proximal 40% stenosis
  middle 40% stenosis
- LCx = mild diffuse disease
- Left ventricular function low normal
- Mild mitral regurgitation

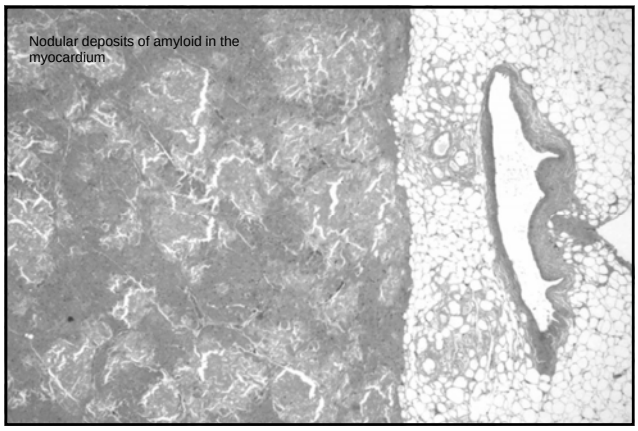
Case #2 (RCM): Catheterization:

LV - RV Pressures



What is the Primary Pathophysiologic Mechanism?

1. Increased Blood Volume (Excessive Preload)
2. Increased Resistant to Blood Flow (Excessive Afterload)
3. Decreased contractility
4. Decreased Filling



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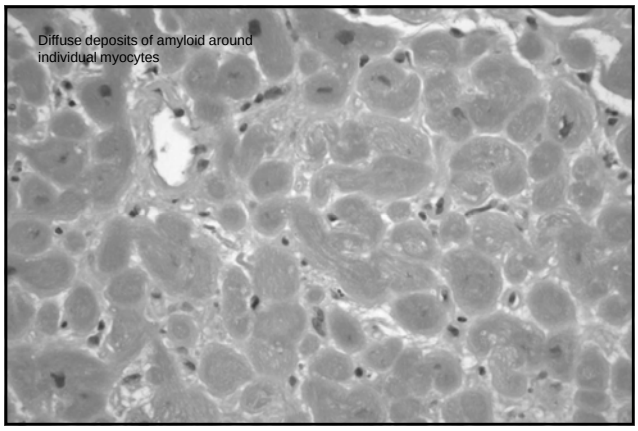
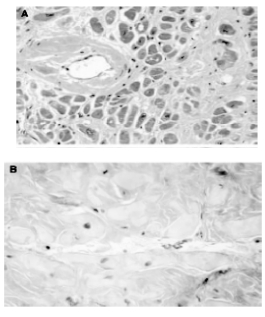
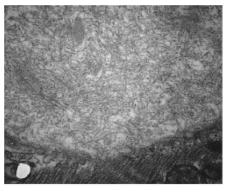
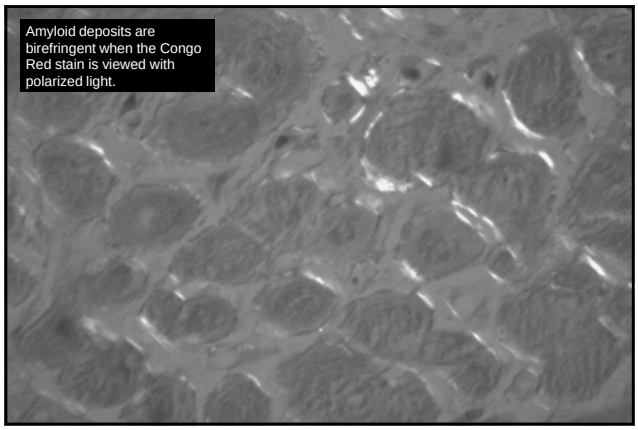
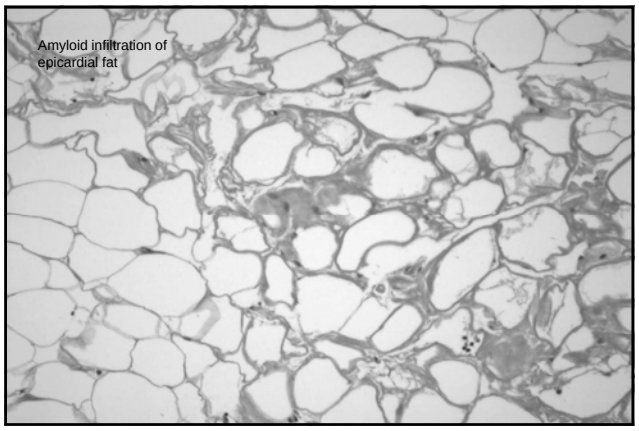


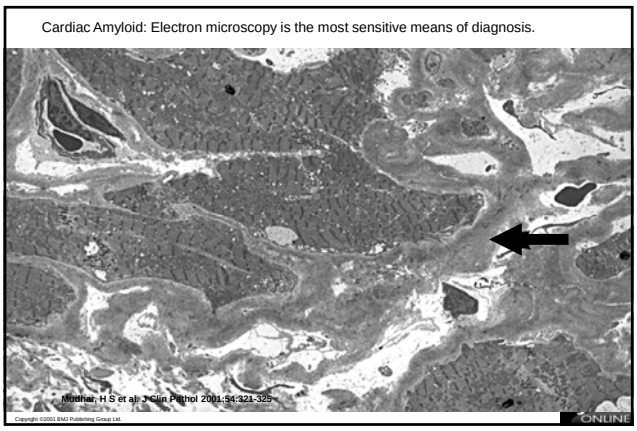
Cardiac Amyloidosis

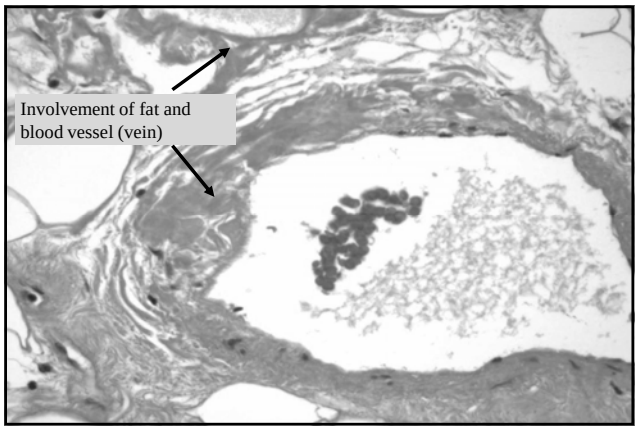


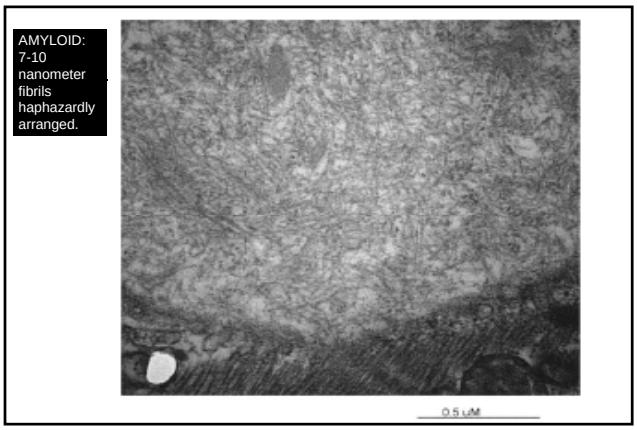


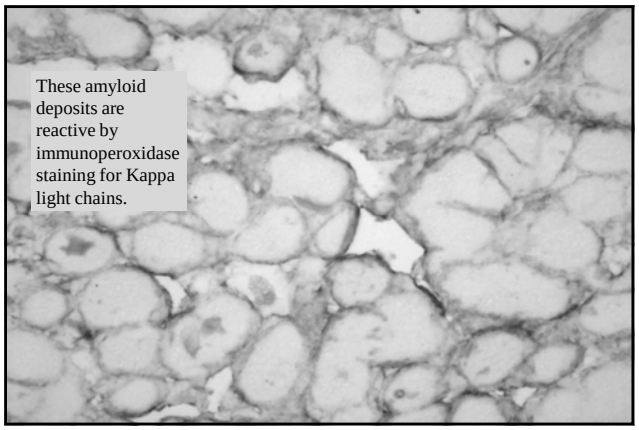


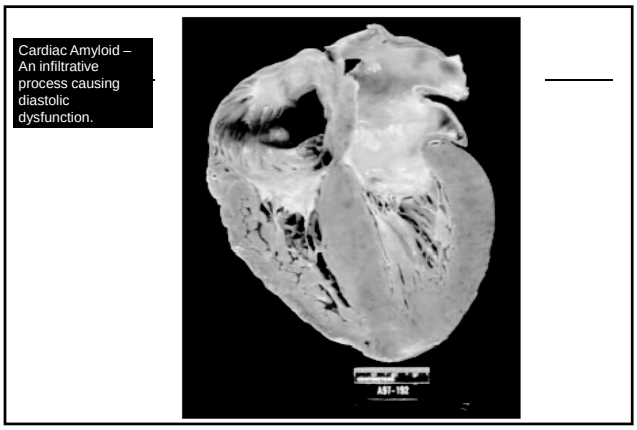

Amyloid infiltration of epicardial fat


Cardiac Amyloid: Electron microscopy is the most sensitive means of diagnosis.
Mudhar, H S et al. J Clin Pathol 2001;54:321-325
Copyright ©2001 BMJ Publishing Group Ltd.
ONLINE


Involvement of fat and blood vessel (vein)


AMYLOID: 7-10 nanometer fibrils haphazardly arranged.
0.5 uM

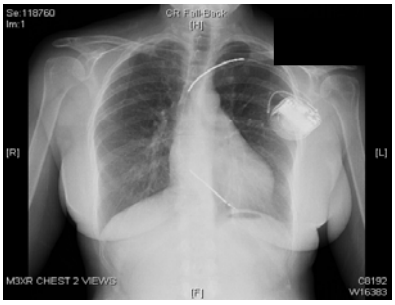

These amyloid deposits are reactive by immunoperoxidase staining for Kappa light chains.


Cardiac Amyloid – An infiltrative process causing diastolic dysfunction.

Case #3 (HCM): History

- 26 year old male
- Presents with episode of syncope
- No history of heart disease
- Family history of uncle and grandmother with premature death in 40-50's

Case#3(HCM):Chest X-Ray

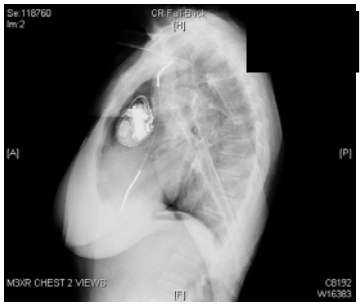


Case #3 (HCM): Physical Exam

BP = 90/70 P = 60 RR = 18 T= 37°

- Gen: WD/WN, in NAD
- Neck: JVP to 8cm with prominent "v" wave
- Chest: clear lung fields
- Heart: PMI in 5th intercostal space, midclavicular line, RRR, S1 + S2, S4, III/IV holosystolic murmur at apex radiating to axilla
- Abd: mildr right upper quadrant tenderness, liver 14 cm in span.
- Ext: trace ankle edema

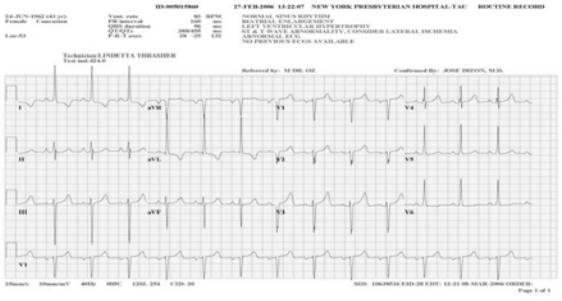
Case#3(HCM):Chest X-Ray

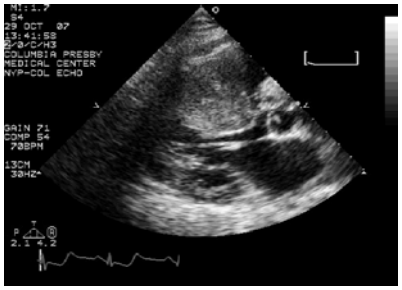


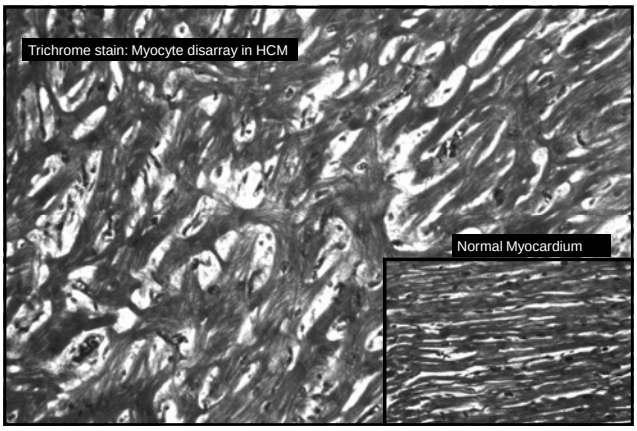
Case #3 (HCM): Laboratory Testing

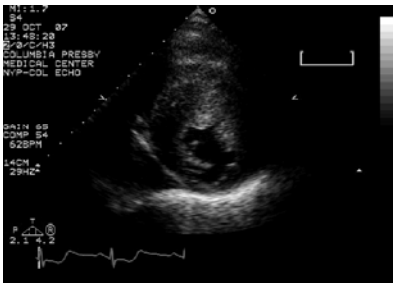
- White blood count = 6.5
- Hemoglobin /Hematocrit = 13 / 39
- Sodium = 135
- Blood urea nitrogen 20 mg/dl, Creatinine = 1.0 mg/dl
- B- type naturetic peptide = 227 pg/ml

Case #3 (HCM): EKG

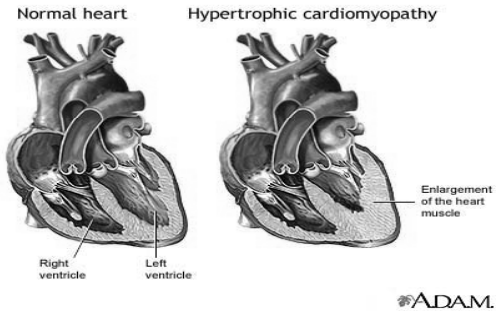




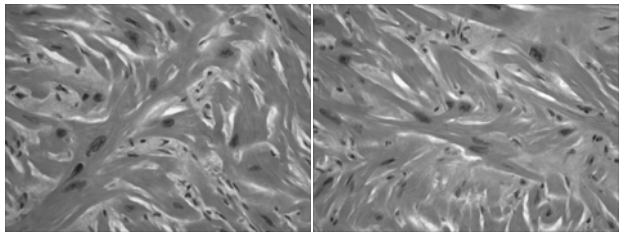




HCM vs. Normal



HCM: Pathology



Who Does HCM affect?

- 1 in 500 people (most common genetic cardiovascular disease)
  - Incidence is about 0.2% to 0.5% of general population.
- An estimated 600,000 to 1.5 million Americans have HCM.
- HCM can present at anytime in any age of life
- Most people are not aware they have HCM because symptoms can go unnoticed and most people with the disease live healthy, normal lives

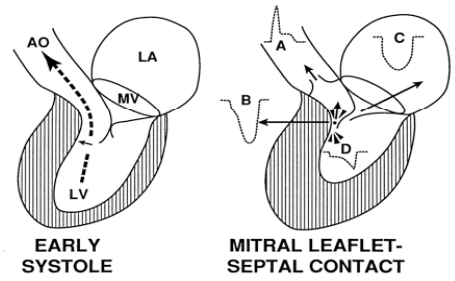
Pathophysiology of HCM

- Systole
  - dynamic outflow tract gradient
- Diastole
  - impaired diastolic filling, ↑ filling pressure
- Myocardial ischemia
  - ↑ muscle mass, filling pressure, O2 demand
  - ↓ vasodilator reserve, capillary density
  - abnormal intramural coronary arteries
  - systolic compression of arteries
- Mitral Regurgitation
- Arrhythmias

Symptoms of HCM

- Chest pain
- Fainting, especially during exercise
- Light-headedness or dizziness, especially after activity or exercise
- Palpitations
- Shortness of breath
- Fatigue, reduced activity tolerance
- Shortness of breath
- Heart failure

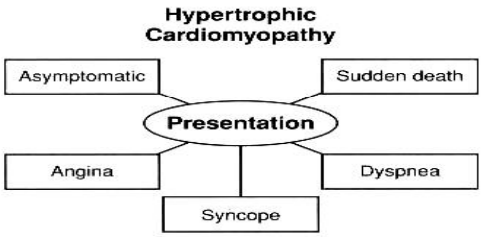
HCM: Obstruction and Mitral Regurgitation



Clinical Manifestation of HCM

- Asymptomatic, echocardiographic finding
- Symptomatic
  - dyspnea in 90%
  - angina pectoris in 75%
  - fatigue, pre-syncope
  - syncope ↑ risk of SCD in children and adolescents
  - palpitation, PND, CHF, dizziness less frequent

Presentation of HCM

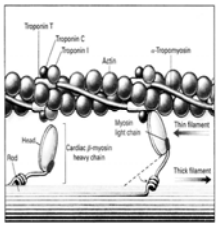


Physical exam in HCM

- Apex localized, sustained
- Palpable S4
- Tripple ripple
- Prominent “a” wave
- Rapid upstroke carotid pulse, “jerky” bifid (spike-and-dome pulse)
- Harsh systolic ejection murmur across entire precordium → apex & heart base
- MR: separate murmur: severity of MR related to degree of outflow obstruction

Genetics of HCM

- First discovered in the 1950s
- Autosomal dominant trait
  - Mutations in genes that encode one of the sarcomere proteins including
  - >400 mutations in these genes.
  - Frequency
    - 45% of mutations occur in β myosin heavy chain gene
    - 35% involve cardiac myosin binding protein C gene.



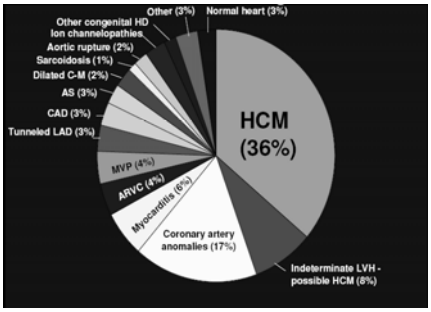
Other Causes of Left Ventricular Hypertrophy

- Clinical mimics
  - Glycogen storage,
  - Amyloid
- Genetic
  - Noonan's
- Exaggerated physiologic response
  - Afro-Caribbean hypertension
  - Old age hypertrophy
  - Athlete's heart

HCM - Genetics

- Autosomal dominant disease
- Males and females equally affected.
- 50% of the offspring of affected individuals will be at risk for inheriting the gene and developing disease
- In any one family, all members have the same mutation
- Onset of clinical symptoms is delayed until adolescence or early adulthood
- Clinical features somewhat predictive of sudden death
- Certain mutations are highly predictive **of sudden death**

Causes of Sudden Death in Young Athletes



HCM Sarcomere Genes

Gene Symbol (s)	Gene Name	Disease Phenotype	Frequency in Patients with HCM
MYH7	β - Myosin heavy chain	Mild or severe HCM; DCM; non-compaction CM; hyalin body myopathy	25 - 35%
MYBPC3	Cardiac myosin-binding protein C	Expression similar to MYH7, late-onset	20 – 30%
TNNT2	Cardiac troponin T	Mild hypertrophy, sudden death; DCM	5-15%
TNNI3	Cardiac troponin I	HCM Extreme intrafamilial heterogeneity, no sudden death without severe disease; Restrictive Cardiomyopathy; increased wall thickness	< 5%
TPM1	Tropomyosin 1 α	HCM and DCM; Variable prognosis, sudden death;	< 5%
ACTC	α Cardiac actin 1	Atypical hypertrophy; Atrial septal defect; DCM hereditary idiopathic dilated cardiomyopathy; hypertrophic cardiomyopathy-11;	Rare
MYL3	Essential myosin light chain 3	Skeletal myopathy	Rare
MYL2	Regulatory myosin light chain 2	Skeletal myopathy	< 5%
TNNC1	Troponin C	HCM	Rare

Differential Diagnosis Between HCM and Althlete's Heart

HCM	Athletic heart
• Can be asymmetric	• Concentric & regresses
• Wall thickness: > 15 mm	• < 15 mm
• LA: > 40 mm	• < 40 mm
• LVEDD : < 45 mm	• > 45 mm
• Diastolic function: always abnormal	• Normal

Natural History/Prognosis of HCM

- Annual mortality 3% in referral centers, probably closer to 1% for all patients
- Risk of SCD higher in children may be as high as 6% per year
  - Majority have progressive hypertrophy
  - Adults - 2-3% SCD per year
  - Adolescents - 4-6% SCD per year
  - Infants (less than 1 yr old), mortality = 50%
- Clinical deterioration usually is slow
- Progression to DCM occurs in 10-15%

Management of HCM

Risk Factors for Sudden Death in HCM

- Massive LVH (e.g > 30 mm)
- Family history of sudden death
- Unexplained/recurrent syncope
- Nonsustained VT (Holter Monitoring)
- Drop in blood pressure during exercise

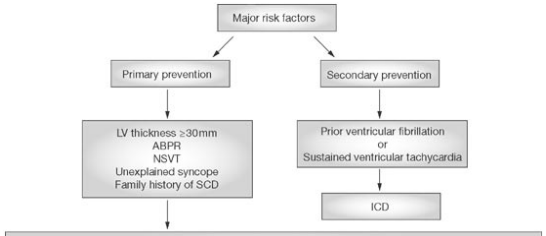
•? Genetic mutations prone to SCD

Br Heart J 1994; 72:S13

Case #4 (ARVD): History

- 48 year old male with recurrent syncope and mild-moderate shortness of breath
- PMHx: None
- Family History: Father, uncle has sudden cardiac death
- Recurrent syncope over last 5-10 years, with episodes notable occurring during physical exertion (e.g. playing tennis)
- Successfully resuscitated during one of these episodes.
- Currently NYHA Class II
- Had extensive evaluation including following.

Risk Stratification in HCM



Major risk factors	Estimated 6 year survival from SCD[a]	Recommendation
0	95%	Unless otherwise indicated, unlikely that ICD warranted
1	93%	ICD reasonable, but decision needs to be made on an individual basis
≥2	82%	High-risk cohort, should receive ICD as primary prevention

Case #4 (ARVD): Physical Exam

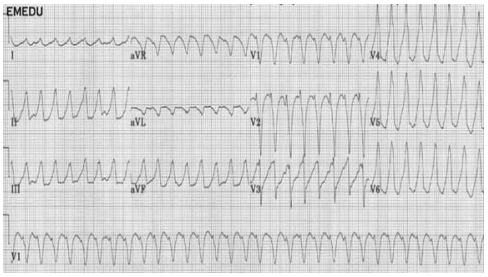
BP=100/70 HR=60 RR=16 T=98.6° SaO2=100%

- Gen: WD/WN, in NAD
- Skin: warm
- HEENT: NC/AT; EOMI; PERRL
- Neck: elevated JVP to 12cm with rapid large v wave
- Chest: clear to auscultation
- Heart: PMI in 5th intercostal space, RRR, S1 + S2, RV heave in subxypophoid space, RVS3
- Abd: NT; +BS, liver 2 finger breaths below CM, 14 cm in span and pulsatile
- Ext: 1+ lower exremity edema bilaterally to calf, prominent varicose veins

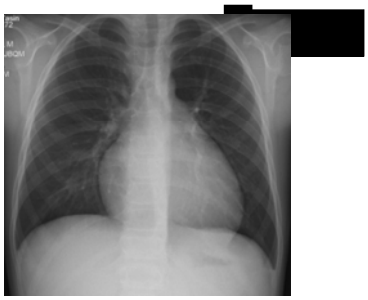
Case #4 (ARVD): Laboratory Data

- Hemoglobin /Hematocrit = 12 / 36
- Blood urea nitrogen 42 mg/dl, Creatinine = 1.4 mg/dl
- Total bilirubin = 2.2, Direct billirubin 0.6
- Alkaline Phosphataste 124, GGTP = 450
- B- type natriuretic peptide = 875 pg/ml
- Troponin I = <0.02

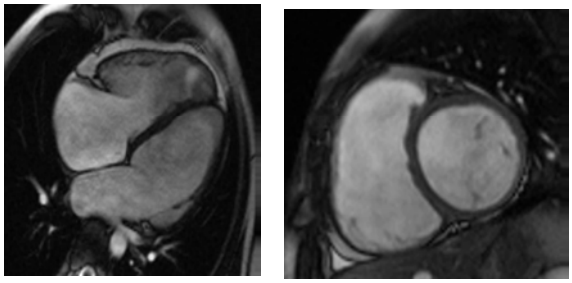
Case #4 (ARVD): Ventricular Tachycardia



Case#4(ARVD):Chest X-Ray

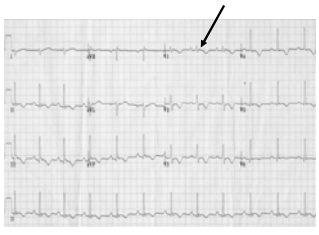


Case #4 (ARVD): MRI



Case #4 (ARVD): EKG

- Incomplete or complete RBBB
- Inverted T waves in the anterior precordial leads
- Localized prolongation of the QRS complex in leads V1 and V2
- Epsilon waves visible as sharp discrete deflections at the terminal portion of the QRS complex in the anterior precordial leads



Case #4 (ARVD): Cardiac Catheterization

- Left dominant circulation
- Left Main = no disease
- RCA = proximal 20% stenosis
- LAD = no disease
- LCx = mild diffuse disease
- Left ventricular function low normal
- No mitral regurgitation

- Right Atrium = 12 mmHg
- Right Ventricle = 30/12 mmHg
- Pulmonary Artery = 30/14 mmHg
- Pulmonary Wedge = 12 mmHg
- Left Ventricle = 100/10 mmHg
- Aorta = 104/72 mm Hg
- Cardiac Output = 3.4 L/min
- Cardiac Index = 2.4 L/min/m2

ARVC: Diagnostic Criteria

CATEGORY	MAJOR CRITERIA	MINOR CRITERIA
Structural or functional abnormalities	• Severe dilatation and reduction in the right ventricular ejection fraction, with mild or no left ventricular impairment • Localized right ventricular aneurysms (akinetic dyskinetic areas of diastolic bulging) • Severe segmental dilatation of the RV	• Mild global right ventricular dilatation or ejection fraction reduction, with a normal left ventricle • Mild segmental dilation of the right ventricle; or • Regional right ventricular hypokinesia
Tissue characterization	Infiltration of RV by fat, with presence of surviving strands of cardiomyocytes	
ECG repolarization abnormalities		Inverted T waves in the right precordial leads (V2–V3 in patients above age 12 years in the absence of a right bundle branch block)
ECG depolarization or conduction abnormalities	• Epsilon waves in V1, V2, or V3 • Localized prolongation (>110 ms) of the QRS complex in precordial leads (V1, V2, or V3)	Late potentials in signal-averaged electrocardiography

Biologic Basis/Genetics

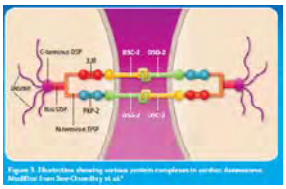


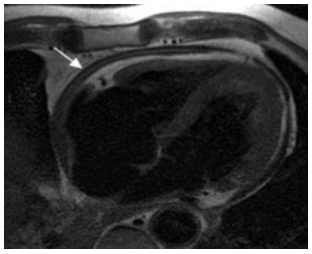
TABLE 2: Genes associated with ARVC

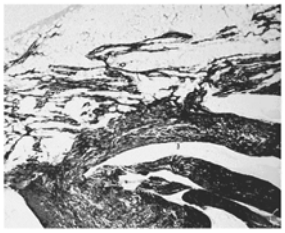
SYMBOL	GENE NAME
DSC2	Desmocollin 2
DSP	Desmoplakin
DSG2	Desmoglein 2
PKP2	Plakophilin 2
RYR2	Ryanodine receptor 2
JUP	Plakoglobin
TMEM43	Transmembrane protein 43

ARVC: Diagnostic Criteria

CATEGORY	MAJOR CRITERIA	MINOR CRITERIA
Arrhythmias		• Left bundle branch block (LBBB) VT (sustained or nonsustained) on ECG Holter monitoring or exercise testing • Frequent ventricular premature contractions or VPCs (>1000 per 24 h) on Holter
Family history	Familial disease confirmed by biopsy or autopsy	• Family history of premature sudden death (<35 y) caused by suspected ARVC • Family history of clinical diagnosis based on current criteria

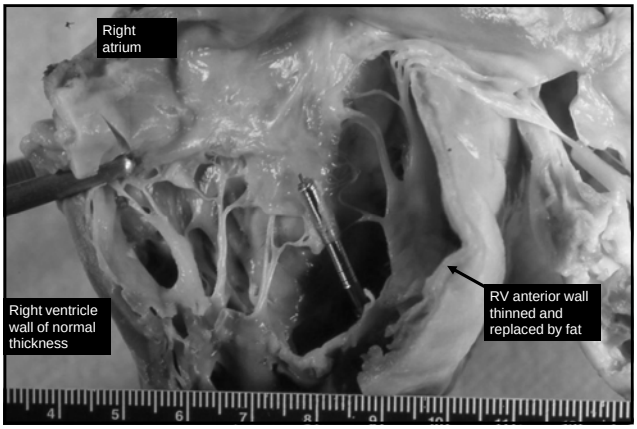
Arrhythmogenic Right Ventricular Dysplasia (ARVD)

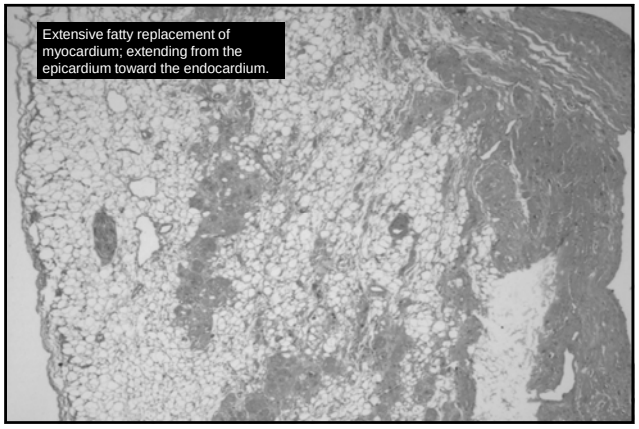




Arrhythmogenic Cardiomyopathy: Genetics

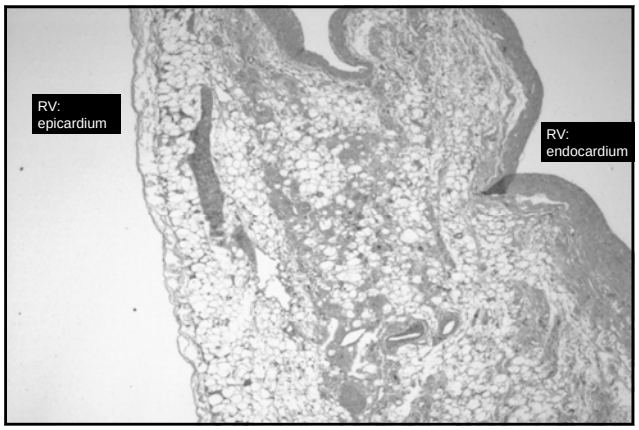
- ~50% are familial with Autosomal Dominant transmission.
- Eight genetic loci identified
- Four genes identified:
  - Ryanodine receptor – calcium release channel (RyR2)
  - Plakoglobin (JUP) – cytoskeletal/adherens-junction protein
  - Desmoplakin (DSM) – desmosomal protein
  - Desmin-related myopathy ARVD7
  - Laminin? ARVD5





Arrhythmogenic RV Cardiomyopathy: Epidemiology

- Estimated incidence of 1 in 10,000 in US
- Rare cause of sudden death in US (~3%)
- Male predominance
- Increased incidence in some areas
  - In northern Italy, it is an important cause of sudden death accounting for 13 - 20% of all cases



Arrhythmogenic Cardiomyopathy

EKG:
- QRS prolongation > 110 msec;
- T wave inversion V2-3;
- Ventricular arrhythmias with LBBB;
- Frequent extrasystoles (>1000/24 hours).

Cardiac MRI:
- Assess ventricle thickness, contractile function, fatty infiltration.

Echocardiography
- Dilation of the RV and outflow tract.
- Reduced global or regional EF

Venticulography
- Can be helpful in making diagnosis,
- Measure LV filling pressures and cardiac output.

Arrhythmogenic Cardiomyopathy: Clinical Manifestations

Family history of sudden death or VT

Presents with ventricular arrhythmias
- Frequent ectopic ventricular beats with LBBB morphology
- Repetitive extraventricular beats
- Nonsustained VT

Syncope

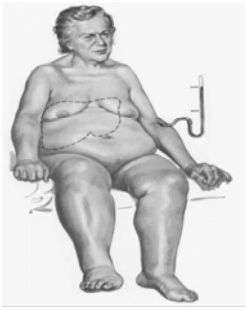
Congestive heart failure

Arrhythmogenic Cardiomyopathy Risk Factors for Sudden Death

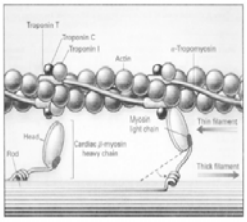
- History of cardiac arrest or syncope
- Markedly abnormal late potentials on EKG
- Marked RV dilation
- Motion abnormalities on echo or angio
- LV involvement or dilation
- Locus 1q42.43 (ryanodine receptor – ARVD2)

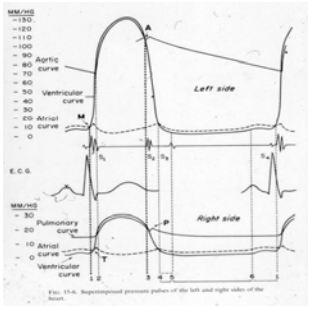
Supplemental Materials

Signs of Heart Failure



Physiology –
From Muscle to Chamber Function





Goals of Treatment

1. Identification and correction of underlying condition causing heart failure.
2. Elimination of acute precipitating cause of symptoms.
3. Modulation of neurohormonal response to prevent progression of disease.
4. Improve long term survival.

Clinical Manifestations

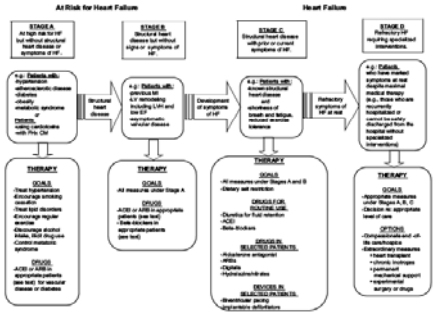
Symptoms

- Reduced exercise tolerance
- Shortness of breath
- Congestion / Fluid Retention
- Difficulty in sleeping
  - Orthopnea
  - PND
- Weight loss

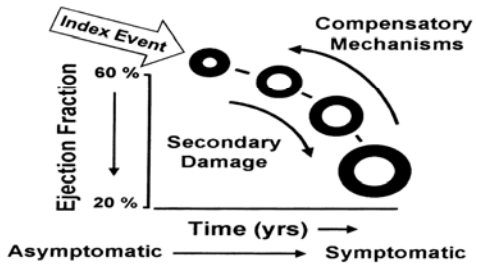
Signs

- JVP/ HJ reflux
- Rales / Pleural effusions
- Gallops (S3 and S4)
- Hepatomegaly / Ascites
- Edema
- Cool Extremities
- Pulses Alternans / Bifid Pulse

Treatment by Stage

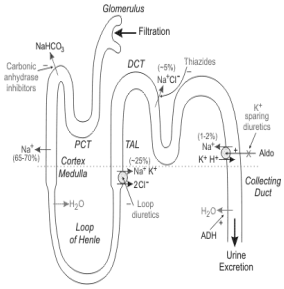


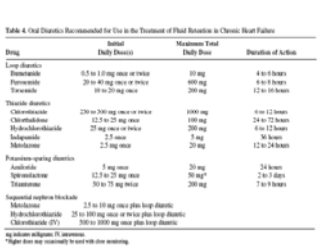
Ventricular Remodeling



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

Diuretics for Heart Failure

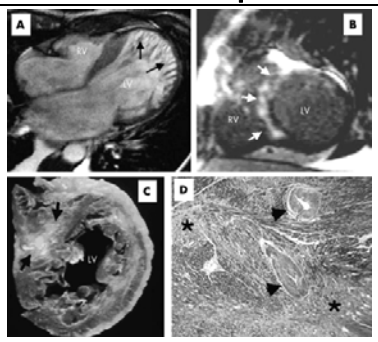




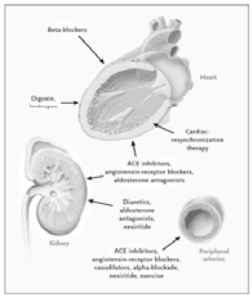
Pharmacologic Treatment

- ACE Inhibitors
- Beta Blockers
- Diuretics
- Angiotensin Receptor Antagonists
- Digoxin
- Vasodilators
- Inotropes

LV Non-Compaction



Nuerohormonal Antagonism



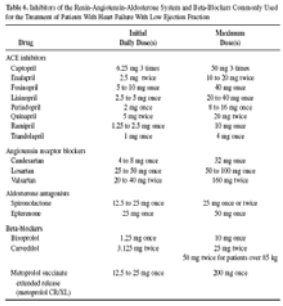
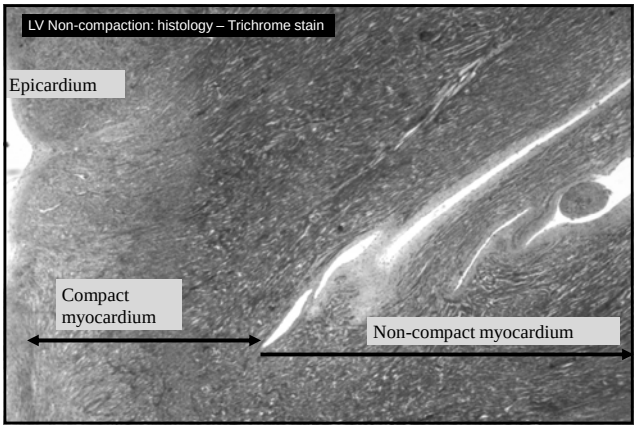


Table 6. Inhibitors of the Renin-Angiotensin-Aldosterone System and Beta-Blockers Commonly Used for the Treatment of Patients With Heart Failure With Low Ejection Fraction

Drug	Initial Daily Dose(s)	Maximum Dose(s)
ACE inhibitors		
Captopril	6.25 mg 3 times	50 mg 3 times
Enalapril	2.5 mg twice	10 to 20 mg twice
Fosinopril	5 to 10 mg once	40 mg once
Lisinopril	2.5 to 5 mg once	20 to 40 mg once
Perindopril	2 mg once	8 to 16 mg once
Quinapril	5 mg twice	20 mg twice
Ramipril	1.25 to 2.5 mg once	10 mg once
Trandolapril	1 mg once	4 mg once
Angiotensin receptor blockers		
Candesartan	4 to 8 mg once	32 mg once
Losartan	25 to 50 mg once	50 to 100 mg once
Valsartan	20 to 40 mg twice	160 mg twice
Aldosterone antagonists		
Spironolactone	12.5 to 25 mg once	25 mg once or twice
Eplerenone	25 mg once	50 mg once
Beta-blockers		
Bisoprolol	1.25 mg once	10 mg once
Carvedilol	3.125 mg twice	25 mg twice 50 mg twice for patients over 85 kg
Metoprolol succinate extended release (metoprolol CR/XL)	12.5 to 25 mg once	200 mg once

LV Non-compaction: histology – Trichrome stain



Noncompaction of the ventricular myocardium

- "Persistence of spongy myocardium"
- Depressed ventricular function, normal LV volume, increased LVEDP, systemic embolism, ventricular arrhythmias
- May be isolated – or -

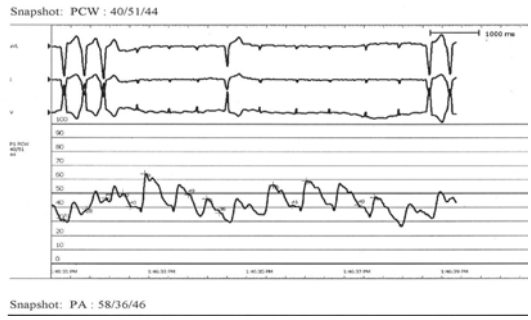
  associated with other anomalies: Pulmonary atresia with intact septum; AS (bicuspid); cardiac fibroma; anomalous coronary arteries; common ventricle

Types of Cardiac Amyloid

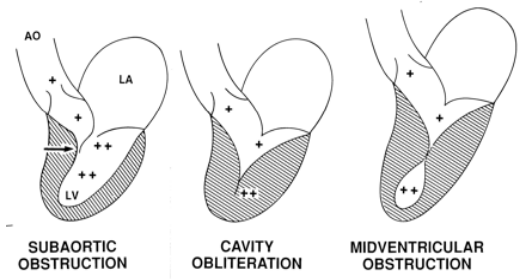
Table. Classification of the Subtypes of Cardiac Amyloidosis

Amyloidosis Type	Protein	Cardiac Involvement	Median Survival, mo	Extracardiac Manifestations	Diagnostic Testing
Primary (AL)	Light chain	22%-34%	13 (4 mo if heart failure present at diagnosis)	Renal failure, proteinuria, hepatomegaly, autonomic dysfunction, macroglossia, purpura, neuropathy, carpal tunnel syndrome	SPEP, UPEP, bone marrow biopsy tissue analysis revealing plasma cell dyscrasia, κ and λ light-chain antiserum staining
Hereditary (ATTR)	Mutant TTR	Variable	70	Severe neuropathy, autonomic dysfunction, renal failure, blindness	ATTR antiserum staining, serum TTR isoelectric focusing, restriction fragment length polymorphism analysis
Senile systemic (ATTR)	TTR	Common	75	Diffuse organ involvement	ATTR antiserum staining

Arch Intern Med. 2006 Sep 25;166(17):1805-13.

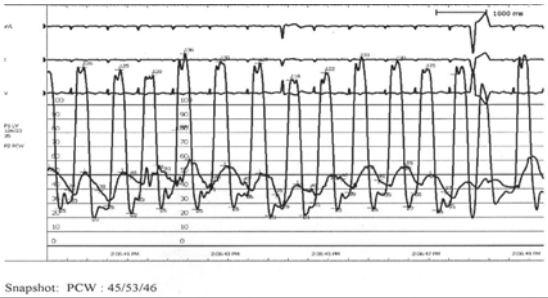


Hemodynamic Subtypes of HCM

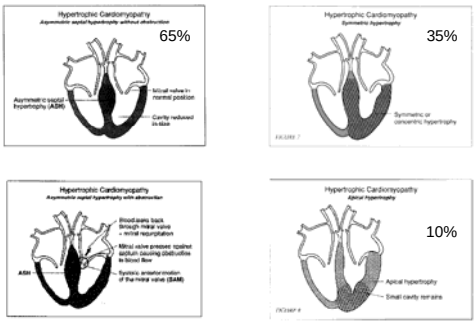


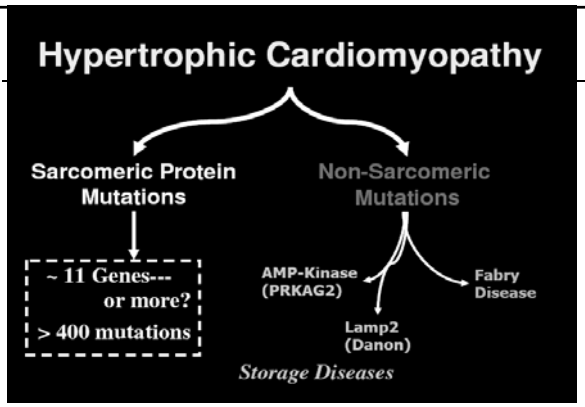
Case #2: Right Heart Catheterization:

LV - PCWP Pressures



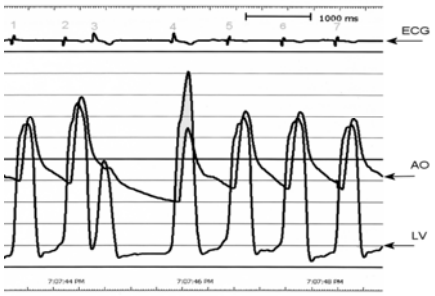
Types of HCM





Cardiac Catheterization of HCM

Brockenbrough Sign



EKG: HCM

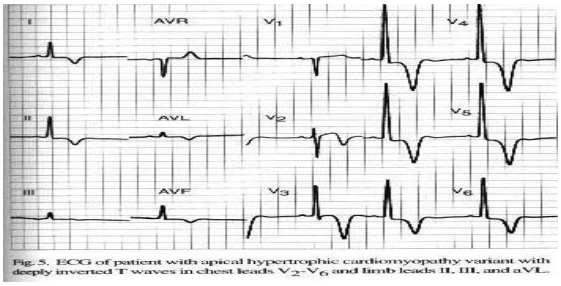


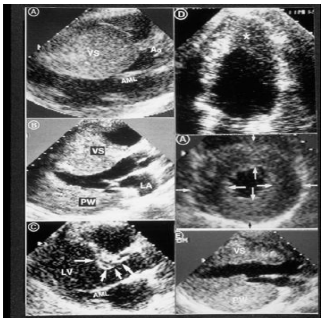
Fig. 5. ECG of patient with apical hypertrophic cardiomyopathy variant with deeply inverted T waves in chest leads V_2-V_6 and limb leads II, III, and aVL.

Supplemental Case: Physical Exam

BP = 160/90, HR = 94, RR = 22, T = 98.9°

- Well developed, well nourished
- Mild - moderately short of breath
- JVD at 15 cm, with a large "v" wave
- Decreased breath sounds at both bases with overlying rales 1/3 up bilaterally
- PMI displaced laterally and inferiorly, regular cardiac rhythm, S3 gallop, III/IV holosystolic murmur
- Soft, with mild RUQ tenderness, liver 2 cm below costal margin,
- 2+ pitting edema to ankles.

Echocardiogram of HCM

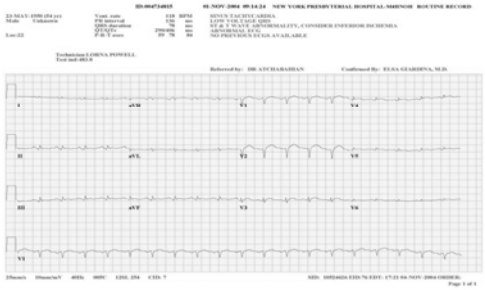


Supplemental Case: Laboratory Data

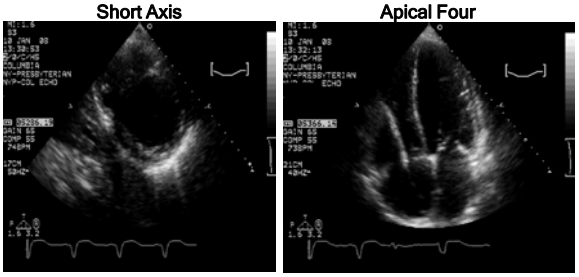
Laboratory analysis showed:

- Hemoglobin of 12.4 gm/dl, hematocrit of 37%
- Serum sodium = 136 meq/L
- BUN = 36 mg/dl
- Creatinine = 1.4 mg/dl
- B-type naturetic peptide = 670 pg/ml

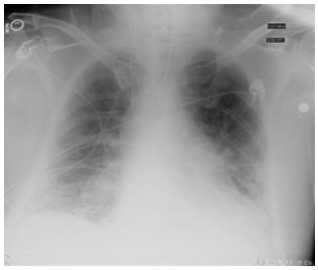
Supplemental Case: EKG



Supplemental Case: Echocardiogram



Supplemental Case: CXR



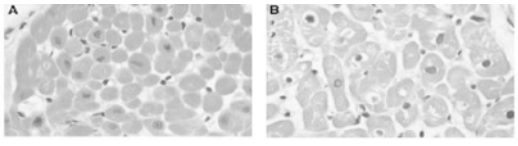
Questions

1. What class of cardiomyopathy (DCM, RCM, HCM) does this patient have?
2. What is the primary pathophysiologic mechanism of heart failure?
3. What is the utility of endomyocardial biopsy?

Supplemental Case: History

- 53 year old African American male
- History of HTN for at least 15 years and Diabetes for 10 years
- Now presents with:
  - Exertional intolerance
  - Increasing abdominal girth
  - Peripheral edema
  - Nightly paroxysmal nocturnal dyspnea

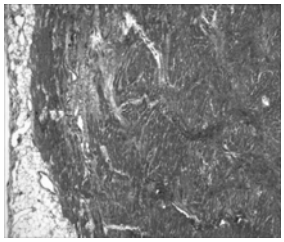
Endomyocardial Biopsy in IDCM

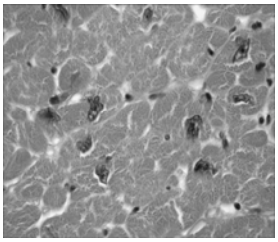


Normal

DCM: Myocyte hypertrophy with interstitial fibrosis

Endomyocardial Biopsy in IDCM





Myocyte hypertrophy (very enlarged and irregular nuclei)

Decreased Contractility