Myocardial Diseases: The Cardiomyopathies

Mat Maurer and Charles Marboe

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 cardiomyopathy 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 endomyocardial biopsy for diagnosis.
6. Identify gross anatomic and histologic correlates of the major types of cardiomyopathy.
Definition and Classification

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

Historical Timeline

- 1980: WHO / ISFC
- 1995: Functional (Dilated, Hypertrophic, Unclassified)
- 2006: Genetic (Primary, Secondary)

Etiologies

• Ischemic cardiomyopathy
• Valvular cardiomyopathy
• Hypertensive cardiomyopathy
• Inflammatory cardiomyopathy
• Metabolic cardiomyopathy
• General system disease
• Muscular dystrophies.
• Neuromuscular disorders.
• Sensitivity and toxic reactions.
• Peripartal cardiomyopathy
Define the Etiology:
For Treatment and Prognosis

WHO Classification

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

# Functional / Morphologic Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
<th>Sample Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilated</td>
<td>Dilated left/both ventricle(s) with impaired contraction</td>
<td>Ischemic, idiopathic, familial, viral, alcoholic, toxic, valvular</td>
</tr>
<tr>
<td>Hypertrophic</td>
<td>Left and/or right ventricular hypertrophy</td>
<td>Familial with autosomal dominant inheritance</td>
</tr>
<tr>
<td>Restrictive</td>
<td>Restrictive filling and reduced diastolic filling of one/both ventricles, Normal/near normal systolic function</td>
<td>Idiopathic, amyloidosis, endomyocardial fibrosis</td>
</tr>
</tbody>
</table>
## ARVD vs. Unclassified

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<thead>
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<th>Type</th>
<th>Definition</th>
<th>Sample Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARVD</td>
<td>Genetic, muscular disorder of the right ventricle is replaced by fat and fibrosis, and causes abnormal heart rhythm</td>
<td>ARVD</td>
</tr>
<tr>
<td>Unclassified</td>
<td>Genetic disorder, known as &quot;spongiform cardiomyopathy&quot; in which embryonically the myocardium fails to regress.</td>
<td>Non-compaction</td>
</tr>
</tbody>
</table>

## Dilated vs. Hypertrophic vs. Restrictive

- **Normal Heart**
  - Heart chambers relax and fill, then contract and pump.

- **Heart with Dilated Cardiomyopathy**
  - Left ventricle
  - Right ventricle
  - Muscle fibers have stretched.
  - Heart chamber enlarges.

- **Heart with Hypertrophic Cardiomyopathy**
  - Growth and arrangement of muscle fibers are abnormal.
  - Heart walls thicker, especially in the left ventricle.

- **Heart with Restrictive Cardiomyopathy**
  - Ventricle walls stiffen and lose flexibility.
Morphologic Summary

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

Diagnostic Tests

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

Normal Echocardiogram
Normal Echocardiogram

Normal MRI
Right & Left Heart Catheterization

Left Heart Catheterization

Right Heart Catheterization
Endomyocardial Biopsy

Diagnoses made by Endomyocardial Bx

1. Myocarditis
   - Giant Cell
   - CMV
   - Toxoplasmosis
   - Chagas disease
   - Rheumatic
   - Lyme

2. Infiltrative
   - Amyloid
   - Sarcoid
   - Hemochromatosis
   - Hypereosinophilic
   - Tumors

3. Toxins
   - Doxorubicin
   - Radiation Injury

4. Genetic
   - Infiltrative
   - Glycogen Storage
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

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
- Abdomen: 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

Case #1 (DCM): Primary Mechanism
Decreased Contractility
Myocarditis

Inflammatory infiltrate in the myocardium associated with myocyte damage

Myocarditis
Myocarditis

Inflammatory infiltrate in the myocardium associated with myocyte damage

Myocarditis

Giant cell myocarditis
Diagnoses of Dilated Cardiomyopathies made by Endomyocardial Bx

1. Myocarditis
   - Giant Cell
   - CMV
   - Toxoplasmosis
   - Chagas disease
   - Rheumatic
   - Lyme

2. Infiltrative
   - Amyloid
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   - Hypereosinophilic
   - Tumors

3. Toxins
   - Doxorubicin
   - Radiation Injury

4. Genetic
   - Infiltrative
   - Glycogen Storage

Chagas Disease:

American trypanosomiasis

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

Life cycle

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

*Trypanosoma cruzi*

Amastigotes

ACUTE RHEUMATIC FEVER

- Immune response
- Lymph node
- B lymphocytes
- Antinuclear antibodies
- Blood vessel
- ACUTE RHEUMATIC HEART DISEASE
- CROSS-REACTIONS
- Vegetations
- Myocardial fibrous body
- Fibrous pericarditis
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

Sarcoid granulomas with extensive fibrosis
36 year old woman with restrictive hemodynamics and liver disease
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.
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/m².
4. Little or no inflammation.
5. End stage: myocyte hypertrophy and interstitial fibrosis

Anthracycline toxicity: Cytoplasmic vacuoles (Masson trichrome stain)
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.
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
PAS stain

PAS after diastase digestion

Polyglucosan bodies
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): 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): 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 electrophesis - small monoclonal protein
- Serum lambda light chains = 23 mg/dl, Kappa = 4.1 mg/dl, ratio = 4.5

Case#2(RCM): Chest X-Ray
Case #2 (RCM): Chest X-Ray

Case #2 (RCM): EKG
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):
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): 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
Cardiac Amyloidosis

Nodular deposits of amyloid in the myocardium.
Diffuse deposits of amyloid around individual myocytes.

Amyloid deposits are birefringent when the Congo Red stain is viewed with polarized light.
Amyloid infiltration of epicardial fat

Involvement of fat and blood vessel (vein)
These amyloid deposits are reactive by immunoperoxidase staining for Kappa light chains.

Cardiac Amyloid: Electron microscopy is the most sensitive means of diagnosis.
AMYLOID: 7-10 nanometer fibrils haphazardly arranged.

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): 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): 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): Chest X-Ray
HCM: Pathology

Trichrome stain: Myocyte disarray in HCM

Normal Myocardium
HCM vs. Normal

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

HCM: Obstruction and Mitral Regurgitation
Presentation of HCM

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
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

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.

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
## HCM Sarcomere Genes

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

### 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
Causes of Sudden Death in Young Athletes

HCM

- Can be asymmetric
- Wall thickness: > 15 mm
- LA: > 40 mm
- LVEDD: < 45 mm
- Diastolic function: always abnormal

Athletic heart

- Concentric & regresses
- < 15 mm
- < 40 mm
- > 45 mm
- 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%

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
Risk Stratification in HCM

- Major risk factors
  - Primary prevention
    - LV thickness ≥30 mm
    - ABPR
    - NSVT
    - Unexplained syncope
    - Family history of SCD
  - Secondary prevention
    - Prior ventricular fibrillation or Sustained ventricular tachycardia
    - ICU

<table>
<thead>
<tr>
<th>Major risk factors</th>
<th>Estimated 8 year survival from SCD</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>95%</td>
<td>Unless otherwise indicated, unlikely that ICD warranted</td>
</tr>
<tr>
<td>1</td>
<td>92%</td>
<td>ICD reasonable, but decision needs to be made on an individual basis</td>
</tr>
<tr>
<td>≥2</td>
<td>82%</td>
<td>High-risk cohort, should receive ICD as primary prevention</td>
</tr>
</tbody>
</table>

Management of HCM

- Overall Population With Hypertrophic Cardiomyopathy (HCM)
  - Genetic-Positive Phenotype-Negative
  - Nonischemic Follow-up
  - None or Mild Symptoms
    - No Treatment or Drug Therapy
  - High Risk of Sudden Death
    - Implantable Cardioverter-Defibrillator
  - Atrial Fibrillation
    - Pharmacological Rate Control
    - Cardioversion Antiarrhythmia
  - Drug-Resistant Heart Failure Symptoms
  - Drug Therapy
  - Progressive Heart Failure Symptoms

- Alternatives to Surgery
  - Heart Transplantation
  - Ventricular Septal Myectomy

- Nonobstructive HCM (Restrictive or Hypokinetic)

- Obstructing HCM (Rest or Provocative)
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.

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): Chest X-Ray
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): Ventricular Tachycardia
Case #4 (ARVD): MRI

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

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>MAJOR CRITERIA</th>
<th>MINOR CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structural or functional abnormalities</strong></td>
<td>Severe dilatation of the right ventricle with mild or no left ventricular impairment</td>
<td>Mild global right ventricular dilatation with a normal left ventricle</td>
</tr>
<tr>
<td></td>
<td>Localized right ventricular aneurysms (akinetically dyskinetic areas of diastolic bulging)</td>
<td>Mild segmental dilatation of the right ventricle or regional right ventricular hypokinesia</td>
</tr>
<tr>
<td></td>
<td>Severe segmental dilatation of the RV</td>
<td></td>
</tr>
<tr>
<td><strong>Tissue characterization</strong></td>
<td>Infiltration of RV by fat, with presence of surviving strands of cardiomyocytes</td>
<td></td>
</tr>
<tr>
<td><strong>ECG repolarization abnormalities</strong></td>
<td>Inverted T waves in the right precordial leads (V1-V3) in patients age 12 years or older</td>
<td></td>
</tr>
<tr>
<td><strong>ECG depolarization or conduction abnormalities</strong></td>
<td>Epsilon waves in V1, V2, or V3</td>
<td>Late potentials in signal-averaged electrophysiology</td>
</tr>
<tr>
<td></td>
<td>Infiltrated prolongation (&gt;=110 ms) of the QRS complex in precordial leads (V1, V2, or V3)</td>
<td></td>
</tr>
</tbody>
</table>

### ARVC: Diagnostic Criteria

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

Biologic Basis/Genetics

<table>
<thead>
<tr>
<th>SYMBOL</th>
<th>GENE NAME</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSC2</td>
<td>Desmocollin 2</td>
</tr>
<tr>
<td>DSP</td>
<td>Desmoplakin</td>
</tr>
<tr>
<td>DSG2</td>
<td>Desmoglein 2</td>
</tr>
<tr>
<td>PIP2</td>
<td>Plakophilin 2</td>
</tr>
<tr>
<td>RYR2</td>
<td>Ryanodine receptor 2</td>
</tr>
<tr>
<td>JUP</td>
<td>Plakoglobin</td>
</tr>
<tr>
<td>TMEM43</td>
<td>Transmembrane protein 43</td>
</tr>
</tbody>
</table>
Arrhythmogenic Right Ventricular Dysplasia (ARVD)
Extensive fatty replacement of myocardium; extending from the epicardium toward the endocardium.
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 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

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

**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)
Clinical Manifestations

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced exercise tolerance</td>
<td>JVP/ HJ reflux</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>Rales / Pleural effusions</td>
</tr>
<tr>
<td>Congestion / Fluid Retention</td>
<td>Gallops (S3 and S4)</td>
</tr>
<tr>
<td>Difficulty in sleeping</td>
<td>Hepatomegaly / Ascites</td>
</tr>
<tr>
<td>- Orthopnea</td>
<td>Edema</td>
</tr>
<tr>
<td>- PND</td>
<td>Cool Extremities</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Pulses Alternans / Bifid Pulse</td>
</tr>
</tbody>
</table>

Signs of Heart Failure
Goals of Treatment

1. Identification and correction of underlying condition causing heart failure.
2. Elimination of acute precipitating cause of symptoms.
4. Improve long term survival.

Treatment by Stage
Ventricular Remodeling

Pharmacologic Treatment

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

Epicardium

Compact myocardium

Non-compact myocardium

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

**Case #2: Right Heart Catheterization:**

**Pulmonary Artery Pressure**

**Snapshot:** PCW : 40/51/44

**Snapshot:** PA : 58/36/46
Case #2: Right Heart Catheterization:
LV - PCWP Pressures

Types of Cardiac Amyloid

<table>
<thead>
<tr>
<th>Amyloidosis Type</th>
<th>Protein</th>
<th>Cardiac Involvement</th>
<th>Median Survival, mo</th>
<th>Extracardiac Manifestations</th>
<th>Diagnostic Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary (AL)</td>
<td>Light</td>
<td>22% - 34%</td>
<td>2-5 mo (2 mo heart failure present at diagnosis)</td>
<td>Renal failure, proteinuria, hyperviscosity, autonomic dysfunction, macroglossa, purpura, neuropathy, cardiac tunnel syndrome</td>
<td>SPCR, UPER</td>
</tr>
<tr>
<td>Hereditary (ATTR)</td>
<td>Mutant TTR</td>
<td>Variable</td>
<td>70</td>
<td>Severe neuropathy, autonomic dysfunction, renal failure, blindness</td>
<td>ATTR, electron microscopy, serum TTR isoelectric focusing, restriction fragment length polymorphism analysis</td>
</tr>
</tbody>
</table>

Hemodynamic Subtypes of HCM

Types of HCM
Hypertrophic Cardiomyopathy

Sarcomeric Protein Mutations

Non-Sarcomeric Mutations

~ 11 Genes--- or more?
> 400 mutations

Storage Diseases

AMP-Kinase (PRKAG2)

Lamp2 (Danon)

Fabry Disease

EKG: HCM

Fig. 5. ECG of patient with apical hypertrophic cardiomyopathy variant with deeply inverted T waves in chest leads V2, V3 and limb leads II, III, and aVL.
Echocardiogram of HCM

Cardiac Catheterization of HCM
Brockenbrough Sign
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.

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: 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

Supplemental Case: Echocardiogram
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?

Endomyocardial Biopsy in IDCM

Normal

DCM: Myocyte hypertrophy with interstitial fibrosis
Endomyocardial Biopsy in IDCM

Myocyte hypertrophy
(very enlarged and irregular nuclei)

Decreased Contractility