Myocardial Diseases

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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-physician encounter

Doc, can you help me with my advanced heart failure?

history/exam/tests?

patho(physio)logy/etiology?

prognosis/therapy?

ethics/economics?
advanced heart failure

- low ejection fraction
- cardiac dilatation
- ventricular arrhythmia
- inotrope requirement
- chronic hyponatremia
- organ dysfunction
- severe symptoms
- frequent hospitalization

right & left heart catheter
**cardiac cycle - ECG & pressures**

- **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

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**cardiac muscle function**

**Preload**

**Afterload**

**Contractility**

- ECG
- Pressures
- Muscular function
- Length of a cardiac muscle fiber prior to the onset of contraction.
- Frank Starling
- Force against which a cardiac muscle fiber must shorten.
- Isotonic Contraction
- Force of contraction independent of preload and afterload.
- Inotropic State

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*Fig. 15-6. Superimposed pressure pulses of the left and right sides of the heart.*
the pressure volume loop

AHF pathophysiology & therapy

- adrenergic system
- renin-angiotensin
- endothelin system
- natriuretic system
- cytokine system
- growth hormone

+ organ failure -
+ cachexia -
+ congestion -
+ hypoperfusion -
+ afterload -
+ preload -
+ contractility -
+ heart rate -
+ remodeling -
+ ischemia -
+ arrhythmia -
age, sex & heart failure

**Epidemiology**

- Htx: 0.001%
- Advanced: 0.1%
- Heart failure: 1-2%
- Population

**Survival Rate**

- Cancer
- AHF medical

**Macroscopic Pathology**

- Hypertrophic cardiomyopathy
- Normal
- Dilated cardiomyopathy

![Images of heart samples](A, B, C)
cardiomyopathy phenotypes

- dilated cardiomyopathy
- hypertrophic cardiomyopathy
- restrictive cardiomyopathy

systems biology strategy

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

- dilated cardiomyopathy
- hypertrophic cardiomyopathy
- restrictive cardiomyopathy
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**

**initial presentation**
- 55 y male
- married, 2 kids
- large anterolat wall AMI
- 10/31/04 Impella pump
- 11/03/04 HeartMate 1 MCSD
- evaluation for heart transplant
- 2/17/05 heart transplant

**teaching points**
- benefits of hi-tech medicine

**follow-up**
- stable post-transplant course
- back to work and normal life

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**Xray ischemic cardiomyopathy**

**team**

**patient**

X-ray image: ischemic cardiomyopathy

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GE #4734815 *1950 m


**ECG ischemic cardiomyopathy**

![ECG ischemic cardiomyopathy image]

**DCM TTE - parasternal axis**

![DCM TTE - parasternal axis image]
DCM TTE – apical 2/4 chamber view

Calculated CO = 2.1 L/min
Tei index 0.85

DCM TTE – AV/MV velocity

Calculated CO = 2.1 L/min
Tei index 0.85
**DCM TTE – E deceleration time**

Decel time = 102 msec

**DCM TTE – early mitral flow**

Dist = 4.61 cm
Δt = 0.154 s
Slope = 29.88 cm/s
DCM TTE – PA pressure

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

endomyocardial biopsy
**NYPH - South West View**

**macroscopic pathology**

- normal cardiomyopathy
- dilated cardiomyopathy

![Image of heart tissue samples](image.png)
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

inflammatory infiltrate in the myocardium associated with myocyte damage
giant cell myocarditis

- Multinucleated giant cells

chagas disease

- Trypanosoma cruzi
- Amastigotes
dilated cardiomyopathy

- **pathology**
  - enlargement of all four chambers, mild hypertrophy, interstitial fibrosis

- **pathophysiology**
  - Frank-Starling mechanism, neurohormonal activation, myocardial remodeling

- **etiologic**
  - genetic, infectious, inflammatory, toxic, metabolic, neuromuscular
decreased contractility

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>MI</th>
<th>MI + Remodeling</th>
<th>MI + HF</th>
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<td>124/81</td>
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<td>Cardiac Output (L/min)</td>
<td>3.7</td>
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<td>PCWP (mm Hg)</td>
<td>10</td>
<td>16</td>
<td>18</td>
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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-adrenoceptors↓
  - M1, muscarinic receptors↓
  - Gs, subunit↑
  - ATII-R↓
  - myosin heavy chain V3↑
  - Atrial natriuretic peptide↓
  - endothelin↓
  - iNOS↓
  - TNFα, IL6↓
  - titin, desmin, vinculin↑
  - type I, III, V collagen↑
  - MMP1, 9, TIMP1-4↑
  - Filronectin, laminin↑

- **cell**
  - cell size↓
  - cell #↑
  - cell nucleus #↑
  - DNA repair↓
  - mitochondrial mass↑
  - apoptosis↓
  - SR Ca2+ release↓
  - peak Ca2+↓
  - isometric tension↓

- **organ**
  - cardiac mass↓
  - LVEDP↓
  - LVEDV↓
  - wall stress↑
  - ejection fraction↓
  - force-time integral↓
  - shortening velocity↓
  - fibrosis↓
  - reentry↑
  - automaticity↑
  - triggered activity↑

- **organism**
  - neurohormones↓
  - cytokines↓
  - oxygen uptake↑
  - body weight↑
  - endothelial function↓
  - immune competence↑

transcriptome > proteome > phenotype

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**


- No ALVD (EF >50%), no HF history
- Mild ALVD (EF 40% to 50%)
- Mod.-Severe ALVD (EF <40%)
- Systolic HF (EF ≤50%)

**CHF stages and steps of treatment**

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

- **Stage A**: High risk with no symptoms
- **Stage B**: Structural heart disease, no symptoms
- **Stage C**: Structural disease, prior or current symptoms
- **Stage D**: Refractory symptoms requiring special intervention
- **Hospice**: VAD, TX
  - Inotropes, nesiritide
  - Mitral or CABG surgery
  - Short-term inotrope, nesiritide
  - Aldosterone antagonists
  - CRT, ICD if applicable
  - Sodium restriction, diuretics, and angiotensin
  - ACE inhibitors and beta-blockers in all patients
  - ACE inhibitors, ARB’s, beta-blockers when appropriate
  - Treat HTN, DM, CAD, dyslipidemia. ACEI when appropriate
  - Risk factor reduction, patient and family education

**Systolic & diastolic**
cardiomyopathy phenotypes

- dilated cardiomyopathy
- hypertrophic cardiomyopathy
- restrictive cardiomyopathy
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

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<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Frequency, %</th>
<th>Number of Mutations</th>
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<td>bMHC</td>
<td>14q1</td>
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<tr>
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<td>1p13</td>
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<td>Cardiac troponin T</td>
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<tr>
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<td>3p</td>
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<td>Titin</td>
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<tr>
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<td>7q3</td>
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**hypertrophic cardiomyopathy**

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

**teaching points**
- HOCM surgically challenging

**follow-up**
- good longterm recovery

**Xray hypertrophic cardiomyopathy**
ECG hypertrophic cardiomyopathy

- history
  - sudden death during vigorous exercise 1/500, syncpe, 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

**cardiomyopathy phenotypes**

- dilated cardiomyopathy
- hypertrophic cardiomyopathy
- restrictive cardiomyopathy

**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

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

**Teaching points**
- Amyloid-related cardiomyopathy DD challenging

**Follow-up**
- Successful post-heart/stemcell transplant course

LD #4379458 *1952 m
Xray restrictive cardiomyopathy

ECG restrictive cardiomyopathy
**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 biopsy

**RCM TTE—parasternal view**
RCM TTE – apical view

Decel time = 102 msec

RCM TTE – restrictive mitral filling

Decel time = 102 msec
Abnormally low E' (Atrial mechanical failure) (Low systolic velocity)

RCM TTE – tissue doppler
Impaired relaxation - reduced propagation velocity

RCM TTE – tissue doppler

Impaired relaxation - reduced propagation velocity
macroscopic pathology

hypertrophic cardiomyopathy  normal
**macroscopic pathology**

concentric hypertrophy

**microscopic pathology HCM**

myocyte disarray
Amyloid encircling a myocyte (original magnification, x1890)

Amyloid: 7-10 nm fibrils haphazardly arranged

Congo Red stain of amyloid deposits in the heart

Congo Red stain of amyloid deposits in the heart show birefringent deposits under polarized light.

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

microscopic pathology amyloid
microscopic pathology amyloid
Endomyocardial Biopsy:
Iron storage disease in the heart

Iron deposits in myocytes and interstitial macrophages

Prussian Blue stain: Iron is blue
hypertrophic cardiomyopathy

- **pathology**
  - asymmetric septal hypertrophy, myocardial 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 T, myosin-binding protein C (autosomal dominant mechanism)
restrictive cardiomyopathy

- **pathology**
  - abnormally rigid ventricles (not necessarily hypertrophied), endocardial fibrosis or scarring or myocardial infiltration

- **pathophysiology**
  - upward shift of passive ventricular filling curve > elevated pulmonary and systemic venous pressures
  - reduced cavity size > stroke volume/cardiac output

- **etiology**
  - infiltrative: amyloidosis, sarcoidosis
  - storage disease: hemochromatosis, glycogen storage diseases
  - endocardial fibrosis
  - hyperesinophilic syndrome
  - metastatic tumors
  - radiation therapy
  - noninfiltrative: scleroderma, idiopathic

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decreased filling

**Etiologies**
- Mitral Stenosis
- Constriction
- Restrictive Cardiomyopathy
- Cardiac Tamponade
- Hypertrophic Cardiomyopathy
- Infiltrative Cardiomyopathy

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<td>57</td>
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<td>4.0</td>
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<td>PCWP (mm Hg)</td>
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<td>12</td>
<td>27</td>
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</table>
LV outflow tract obstruction

EARLY SYSTOLE

MITRAL LEAFLET-SEPTAL CONTACT

ventricular remodeling

A Ventricular remodeling after acute infarction

Initial infarct

Expansion of infarct

(Global remodeling)

B Ventricular remodeling in diastolic and systolic heart failure

Normal heart

Hypertrophied heart

(Dilated heart)

(Dilated heart)
**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?
**summary cardiomyopathies**

<table>
<thead>
<tr>
<th>phenotype</th>
<th>dilated</th>
<th>hypertrophic</th>
<th>restrictive</th>
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<tbody>
<tr>
<td>history</td>
<td>left heart failure</td>
<td>SOB, cP, syncope</td>
<td>right heart failure</td>
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<td>physical exam</td>
<td>S3, S4, MR</td>
<td>S4, valsalva+ murmur</td>
<td>Kussmaul sign</td>
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<td>chest Xray</td>
<td>LV enlargement, PVH</td>
<td>LA enlargement</td>
<td>PVH</td>
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<tr>
<td>ECG</td>
<td>SR↑, ST/T, IC abnorm</td>
<td>LVH</td>
<td>low volt, AV cond↓</td>
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<td>echo</td>
<td>chamber dilat, regurg</td>
<td>asmm LVH, SAM</td>
<td>LV wall ↑, LVEF ok</td>
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<td>cardiac catheter</td>
<td>CAD?, RA/PC↑, CO↓</td>
<td>compl↓, LVOT grad</td>
<td>RA/PC↑, square root</td>
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<td>therapy</td>
<td>systolic HF guidelines</td>
<td>BB, CA, cave volume</td>
<td>systemic approach</td>
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Braunwald E. Heart Disease (4th Ed). Saunders, Philadelphia

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**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
timing of MCSD
selection for Htx

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

classification or staging
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selection for Htx
Columbia University Medical Center

- Teaching
- Patient Care
- Care