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
Doc, can you help me with my 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

the pressure volume loop

http://www.columbia.edu/itc/hs/medical/heartsim/
**AHF pathophysiology & therapy**

- adrenergic system
- renin-angiotensin
- endothelin system
- growth hormone
- + hypoperfusion -
- + congestion -
- + organ failure -
- + cachexia -
- natriuretic system
- + afterload -
- + preload -
- + contractility -
- + heart rate -
- + remodeling -
- + ischemia -
- + arrhythmia -
- + remodeling -
- + contractility -
- + heart rate -
- + ischemia -
- + arrhythmia -

**Medical Center**

**age, sex & heart failure**

*Average annual incidence/1000*

**epidemiology**

- advanced cancer
- heart failure
- population

**macroscopic pathology**

- hypertrophic cardiomyopathy
- normal
- dilated cardiomyopathy

**cardiomyopathy phenotypes**
systems biology strategy

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

clinical picture 1

clinical picture 2

proteome

transcriptome

genome

NYPH

Hammer Health Sciences Building

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 anterolateral wall AMI
- 10/31/04 Impella pump
- 11/03/04 HeartMate 1 MCSD
- Evaluation for heart transplant
- 2/17/05 heart transplant
- Stable post-transplant course
- Back to work and normal life

Teaching points
- Benefits of hi-tech medicine

follow-up
- Holter post-transplant course
- Back to work and normal life

GE 44754815 *1950 m
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

stable post-transplant course

back to work and normal life

initial presentation

follow-up

benefits of hi-tech medicine

teaching points

ECG ischemic cardiomyopathy

GE #4734815 *1950 m

DCM TTE - parasternal axis
DCM TTE – apical 2/4 chamber view

DCM TTE – AV/MV velocity

Calculated CO = 2.1 L/min
Tei index 0.85

DCM TTE – E deceleration time
DCM TTE – early mitral flow

DCM TTE – PA pressure

endomyocardial biopsy
massocopic pathology

normal  dilated cardiomyopathy

idiopathic dilated cardiomyopathy

Masson trichrome stain
extensive interstitial fibrosis (blue) with myocytes in red and epicardial fat/pericardium to the left
**idiopathic dilated cardiomyopathy**

Hematoxylin & eosin stain:
Myocyte hypertrophy (very enlarged and irregular nuclei)

**myocarditis**

Inflammatory infiltrate in the myocardium associated with myocyte damage
**giant cell myocarditis**

Multinucleated giant cells

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**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

- **etiology**
  - genetic, infectious, inflammatory, toxic, metabolic, neuromuscular

**decreased contractility**

<table>
<thead>
<tr>
<th>Etiologies</th>
<th>Parameter</th>
<th>Normal</th>
<th>MI</th>
<th>MI + Remodeling</th>
<th>MI + HF</th>
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</thead>
<tbody>
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<td>Ischemic Cardiomyopathy</td>
<td>PCWP (mm Hg)</td>
<td>3.7</td>
<td>2.1</td>
<td>2.0</td>
<td>2.3</td>
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<td>– Myocardial Infarction</td>
<td>SV (ml)</td>
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<td>Toxins</td>
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<tr>
<td>– Anthracline</td>
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<td>– Alcohol</td>
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<tr>
<td>– Cocaine</td>
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<td>Myocarditis</td>
<td>Cardiac Output (L/min)</td>
<td>10</td>
<td>16</td>
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<td>13</td>
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<td>– Alcohol</td>
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<td>– Cocaine</td>
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</tbody>
</table>

**heart failure & remodeling**

Mann DL et al. *Circulation* 1999;100:995-1008
transcriptome > proteome > phenotype

- gene
  - Ca++-, K+-channel
  - Na+/H+ antiporter
  - SERCA2
  - Phospholamban
  - Ryanodine receptor
  - β1-adrenoceptors
  - M2 muscarinic receptors
  - Gαi-2 subunit
  - ATII-R1
  - myosin heavy chain V3
  - Atrial natriuretic peptide
  - endothelin
  - iNOS
  - TNF-α, IL6
  - titin, desmin, vinculin
  - type I, III, V collagen
  - MMP1, 9, TIMP1-4
  - Fibronection, laminin

- cell
  - cell size
  - cell nucleus
  - DNA repair
  - mitochondrion mass
  - apoptosis

- organ
  - cardiac mass
  - LVEDP
  - LVEDV
  - wall stress
  - ejection fraction
  - shortening velocity
  - fibrosis

- organism
  - 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

CHF stages and steps of treatment

Stage A
High risk with no symptoms

Stage B
Structural heart disease, no symptoms

Stage C
Structural disease, prior or current symptoms

Stage D
Refactory symptoms requiring special intervention

Risk factor reduction, patient and family education
Treat HTN, DM, CAD, dyslipidemia. ACEI when appropriate
ACE inhibitors, ARB's, beta-blockers when appropriate
ACE inhibitors and beta-blockers in all patients

Aldosterone antagonists
Sodium restriction, diuretics, and digoxin

Short-term inotrope, nesiritide
Mitral or CABG surgery

Inotropes, nesiritide
CRT, ICD if applicable

VAD, TX
Bumetanide, mexiletine


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

HCM mutation frequencies

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<tr>
<th>Gene</th>
<th>Occurrence</th>
<th>Frequency %</th>
<th>Number of Mutations</th>
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<td>MYH7</td>
<td>10%</td>
<td>5–10%</td>
<td>&gt; 0.0</td>
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<tr>
<td>MYBPC3</td>
<td>40%</td>
<td>20–30%</td>
<td>= 0.0</td>
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<tr>
<td>Desmin</td>
<td>19%</td>
<td>= 0.0</td>
<td>= 0.0</td>
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<tr>
<td>Na/K ATPase</td>
<td>19%</td>
<td>= 0.0</td>
<td>= 0.0</td>
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<tr>
<td>Titin</td>
<td>10%</td>
<td>&gt; 0.0</td>
<td>= 0.0</td>
</tr>
<tr>
<td>MLC-1 C</td>
<td>5%</td>
<td>&gt; 0.0</td>
<td>= 0.0</td>
</tr>
<tr>
<td>MLC-2 C</td>
<td>5%</td>
<td>&gt; 0.0</td>
<td>= 0.0</td>
</tr>
<tr>
<td>Troponin C</td>
<td>5%</td>
<td>&gt; 0.0</td>
<td>= 0.0</td>
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<tr>
<td>Troponin A</td>
<td>5%</td>
<td>&gt; 0.0</td>
<td>= 0.0</td>
</tr>
<tr>
<td>Troponin T</td>
<td>5%</td>
<td>&gt; 0.0</td>
<td>= 0.0</td>
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</tbody>
</table>

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

- follow-up
  - good long-term recovery

- teaching points
  - HCM medically challenging
hypertrophic cardiomyopathy

- history
  - sudden death during vigorous exertion, syncope, angina, dyspnea

- physical exam
  - S4, systolic murmur (LVOT obstruction - increased by Valsalva, MR)

- diagnostic tests
  - X-ray
  - ECG (LBBB, LVH)
  - Echocardiogram (asymmetric hypertrophy)
  - Catheterization (LVOT gradient)
  - Genetic testing
**HCM TTE – SAM & malcoaptation**

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

**HCM TTE – SAM & obstruction**


**HCM TTE – LVOT obstruction**

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 yo male
- Banker, kids
- Rapidly progressive heart failure
- Heart transplant evaluation
- Heart transplantation: BLS
- Autologous stem cell transplantation (CAMP9)

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

Teaching points
- Amyloid-related cardiomyopathy: DD
- Restrictive cardiomyopathy: Xray
- ECG restrictive cardiomyopathy

LD #4379458 *1952 m
restrictive cardiomyopathy

- history
  - Fatigue, exercise tolerance ↓

- physical exam
  - rales, neck veins ↑, ascites, peripheral edema, KUSMAUL SIGN

- diagnostic tests
  - Xray: normal sized heart, congestion
  - ECG: ST-T changes, atrial fibrillation, BBB
  - echocardiography
  - endomyocardial biopsy

RCM TTE – parasternal view

RCM TTE – apical view
**RCM TTE – restrictive mitral filling**

Decel time = 102 msec

**RCM TTE – tissue doppler**

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

**RCM TTE – tissue doppler**

Impaired relaxation - reduced propagation velocity
**Hypertrophic Cardiomyopathy**

- Normal

**Concentric Hypertrophy**

- Macroscopic pathology

**Microscopic Pathology HCM**

- Myocyte disarray

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**Microscopic Pathology Amyloid**

- Amyloid encircling a myocyte (original magnification, x1890)

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**Microscopic Pathology Amyloid**

- Amyloid: 7-10 nm fibrils haphazardly arranged
Congo Red stain of amyloid deposits in the heart.

Amyloid deposits are birefringent.

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

Macroscopic pathology amyloid.
**iron storage disease**

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, compensated
    or unmasked dilatation

- pathophysiology
  - compliance and relaxation reduced, dynamic LV outflow tract obstruction,
    abnormal motion of the anterior mitral leaflet

- etiology
  - sarcomere abnormalities (myosin heavy chain, cardiac trop T, myosin-
    binding protein C, familial 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

decreased filling

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Normal</th>
<th>HCM</th>
<th>HCM + HF</th>
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</thead>
<tbody>
<tr>
<td>Mitral Stenosis</td>
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<tr>
<td>Constriction</td>
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<tr>
<td>Restrictive Cardiomyopathy</td>
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<tr>
<td>Cardiac Tamponade</td>
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<tr>
<td>Hypertrophic</td>
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<tr>
<td>Cardiomyopathy</td>
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<tr>
<td>Infilitrative Cardiomyopathy</td>
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<th>Parameter</th>
<th>Normal</th>
<th>HCM</th>
<th>HCM + HF</th>
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<tr>
<td>BP (mm Hg)</td>
<td>120/80</td>
<td>110/70</td>
<td>110/80</td>
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<tr>
<td>Cardiac Output (L/min)</td>
<td>3.7</td>
<td>3.4</td>
<td>4.0</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>10</td>
<td>12</td>
<td>12</td>
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</table>
LV outflow tract obstruction

- Early systole
- Mitral leaflet-septal contact

Ventricular remodeling

Hypertrophic cardiomyopathy

- Prognosis
  - Depends 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
  - Septal ablation with ethanol
  - Septal ablation with alcohol
  - Myomectomy
restrictive cardiomyopathy

- **prognosis**
  - Very poor prognosis

- **therapy**
  - Salt restriction
  - Diuretics (cautious use)
  - Maintenance of SR
  - Intraventricular 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>S0R, cP, syncope</td>
<td>Right heart failure</td>
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<tr>
<td>Physical Exam</td>
<td>S3, S4, MR</td>
<td>S4, valsalva+ murmur</td>
<td>Kussmaul sign</td>
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<tr>
<td>Chest X-ray</td>
<td>LV enlargement, PVL</td>
<td>LA enlargement</td>
<td>PVH</td>
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<tr>
<td>ECG</td>
<td>SR+, ST-T, ic abnormal</td>
<td>LVH</td>
<td>Low volt, AV cond</td>
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<td>Echo</td>
<td>Chamber dilat, regurg</td>
<td>Asymm LVH, SAM</td>
<td>RA/PC↑, square root</td>
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<tr>
<td>Biopsy</td>
<td>Cad, RA/PC↑, CO↓</td>
<td>Comp, LVOT grad</td>
<td>RA/PC↑, square root</td>
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<td>Therapy</td>
<td>R/o myocarditis</td>
<td>DiD restrictive</td>
<td>R/o infiltrative</td>
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<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
- Indication for CRT
- Timing of MCSD
- Selection for Htx

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No successful recompensation?

End-of-life situation?

Yes

Unsuccessful recompensation?

No

Chronic renal failure & evaluation for ischemia?

Yes

Pump failure?, arrhythmias?

No

Cardiac catheter

Yes

Potential Htx or chronic MCSD

ICU

Floor/home

Columbia University Medical Center

Teaching

Patient care

Research