Cardiomyopathy: 
Etiology and Diagnosis

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UTHSCSA and STVHCS
Cardiomyopathy – Morphologic Categories

- Dilated
- Hypertrophic
- Restrictive

Braunwald’s Heart Dz, 8th ed, 2008; p. 1739.
- **Physiologic response:**
  - Hypertrophy (FHCM)
  - Dilation (familial DCM, diffuse loss of myocytes and fibrosis)
  - Both

- **Clinical disorders:**
  - HCM
  - DCM
  - Restr CM

*Response of the Heart to Genetic Disorders*

Dilated Cardiomyopathies

- Familial/genetic
- Viral/immune
- Alcohol/toxic
- Unknown

Braunwald’s Heart Dz, 8th ed, 2008; p. 1740.
Restrictive Cardiomyopathies

- Idiopathic
- Infiltrative

Braunwald’s Heart Dz, 8th ed, 2008; p. 1740.
Cardiomyopathy Etiologic Categories
Specific Cardiomyopathies

- Ischemic
- Valvular
- Hypertensive
- Inflammatory - myocarditis
- Metabolic
- General systemic disease
- Muscular Dystrophies
- Neuromuscular disorders
- Sensitivity and Toxic reactions
- Peripartum cardiomyopathy

Braunwald’s Heart Dz, 8th ed, 2008; p. 1740.
Metabolic Cardio-myopathies

• Endocrine Abnormalities
• Glycogen storage disease
• Deficiencies (hypokalemia)
• Nutritional disorders

Braunwald’s Heart Dz, 8th ed, 2008; p. 1740.
<table>
<thead>
<tr>
<th>General Systemic Cardio-myopathies</th>
<th>Muscular Dystrophies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connective tissue diseases</td>
<td>Duchenne/Becker muscular dystrophy</td>
</tr>
<tr>
<td>Infiltrative diseases</td>
<td>Myotonic dystrophy</td>
</tr>
<tr>
<td>– Sarcoidosis</td>
<td>Emery-Dreifuss muscular dystrophy</td>
</tr>
<tr>
<td>– Leukemia</td>
<td></td>
</tr>
</tbody>
</table>

Braunwald’s Heart Dz, 8th ed, 2008; p. 1740, 2142.
## Neuro-muscular Disorders

- Friedreich’s ataxia
- Noonan syndrome
- Lentiginosis

## Sensitivity and Toxic Reactions

- Alcohol
- Catecholamine
- Anthracyclines
- Irradiation
- Others

Braunwald’s Heart Dz, 8th ed, 2008; p. 1740.
Cardiomyopathy: Unifying Hypothesis

HCM

- Direct Genetic Mutation
  - β-MHC
  - αTM
  - cTnT
  - MBP-C
  - ELC
  - RLC
  - TnI
  - Actin

SARCOMERE

- Calcineurin
- Ox-Phos
- Mitochondria
- SR
- Metabolic
- Cascade Effect

DCM

- Direct Genetic Mutation
  - MLP
  - Vinculin
  - CVB
  - Actin
  - DAG
  - Metavinculin
  - Desmin
  - Dystrophin

CYTOSKELETON

- Ox-Phos
- Drugs
- Metabolic
- Cascade Effect

Hurst, 10th Ed, 2001, p. 1800
This hypothesis breaks down many places.
Update: Familial HCM

- Cause: always genetic in adults
- Some inherited, some *de novo* mutation
- Single-gene disorder
- Autosomal-dominant
- 11 genes, each for a sarcomeric protein
- Over 600 mutations, most single-point missense mutation
There are 15 classes of myosins

There are 15 classes of myosins.
Myosin

Blue spheres: HCM mutations
Red spheres: DCM mutations
Light blue spheres: HCM

ATP binding site

Essential myosin light chain

Myosin binding site

Regulatory myosin light chain

Braunwald’s Heart Disease, 8th ed, p. 116, 2008.
Update: Familial HCM - 2

- HCM is the most common cause of SCD in the young
- Prevalence: 1 in 500
- Symptoms: dyspnea, then chest pain, then syncope/presyncope/SCD
- Murmurs: midsystolic LV ejection murmur and mitral regurgitation, characteristic response to maneuvers
- ECG often with LVH
- Echocardiography is confirmatory IVS >1.3cm without other cause

Roberts R, Sigwart U. Circulation 2001;104:2113
Update: Familial HCM - 3

- Dominant mode of inheritance indicates that the abnormal protein poisons the effect of the normal protein.
- Basic science studies: mutations in the contractile apparatus impair contractility and induce release of growth factors and stimulate hypertrophy and fibrosis, with sarcomere disarray as the hallmark of the phenotype.

Roberts R, Sigwart U. Circulation 2001;104:2113
### TABLE 10-1: Gene Mutations in Cardiac Hypertrophy

<table>
<thead>
<tr>
<th>Locus</th>
<th>Symbol</th>
<th>Name</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>1q32</td>
<td>TNNT2</td>
<td>Cardiac troponin T</td>
<td>Sarcomere</td>
</tr>
<tr>
<td>2q31</td>
<td>TTN</td>
<td>Titin</td>
<td>Sarcomere</td>
</tr>
<tr>
<td>3p21</td>
<td>MYL3</td>
<td>Essential myosin light chain</td>
<td>Sarcomere</td>
</tr>
<tr>
<td>3p21-p14</td>
<td>TNNC1</td>
<td>Cardiac troponin C</td>
<td>Sarcomere</td>
</tr>
<tr>
<td>11p11.2</td>
<td>MYBP3</td>
<td>Cardiac myosin binding protein C</td>
<td>Sarcomere</td>
</tr>
<tr>
<td>12q23-q24</td>
<td>MYL2</td>
<td>Regulatory myosin light chain</td>
<td>Sarcomere</td>
</tr>
<tr>
<td>14q12</td>
<td>MYH7</td>
<td>Beta-myosin heavy chain</td>
<td>Sarcomere</td>
</tr>
<tr>
<td>14q12</td>
<td>MYH6</td>
<td>Alpha-myosin heavy chain</td>
<td>Sarcomere</td>
</tr>
<tr>
<td>15q14</td>
<td>ACTC</td>
<td>Cardiac actin</td>
<td>Sarcomere</td>
</tr>
<tr>
<td>15q22</td>
<td>TPM1</td>
<td>Alpha-tropomyosin</td>
<td>Sarcomere</td>
</tr>
<tr>
<td>19p13,2</td>
<td>TNNI3</td>
<td>Cardiac troponin I</td>
<td>Sarcomere</td>
</tr>
<tr>
<td>7q36</td>
<td>PRKAG2</td>
<td>Protein kinase, AMP-activated</td>
<td>Metabolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>noncatalytic, gamma-2</td>
<td></td>
</tr>
<tr>
<td>Xq22</td>
<td>GLA</td>
<td>Alpha-galactosidase A</td>
<td>Lysosome, metabolism</td>
</tr>
<tr>
<td>Xq24</td>
<td>LAMP2</td>
<td>Lysosome-associated membrane</td>
<td>Lysosome, metabolism</td>
</tr>
</tbody>
</table>

*AMP = adenosine monophosphate.*

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Genetics of HCM

Troponin T (~15%)
α-Tropomyosin (<5%)

Myosin light chain (<1%)

β-Myosin heavy chain (~35%)

Myosin rod

Myosin head

Actin

Myosin-binding protein C (~15%)

Colucci WS et al. Atlas of Heart Failure 2nd ed. 1999
Endocrinopathies

- Acromegaly – LVH and DCM
- Cushing – LVH and DCM
  - Carney complex: LA myxoma and pigmented skin lesions, genetic 17Q2
- Hyperthyroidism – afib beta blocker
- Hypothyroidism – effusion
- Pheo – HF
Glycogen Storage Diseases

Pompe’s disease (glycogenosis type 2 = GSDII = acid maltase deficiency = MIM 232300; chromosome 17q23-25, the GAA gene): acid alpha-1,4 glucosidase deficiency, recessive, HCM phenotype, usually die by age 2, striking LVH voltage and CHF, lysosomal-associated membrane protein-1 (LAMP-1) levels elevated … Enzyme replacement therapy with human recombinant alglucosidase alpha is possible.
Danon’s Disease

These have pre-excitation

X-linked lysosome-associated membrane protein

LAMP2

PRKAG2 mutations can also produce HCM

Metabolic Disorders Producing HCM - 2

- **Beckwith-Wiedermann Syndrome**: often dominant, error on Chromosome 11, multiple anomalies, hemihypertrophy or hemihyperplasia and macroglossia and susceptibility to tumors, esp Wilms, and HCM (not usually a prominent part of the syndrome)
Metabolic Disorders Producing HCM - 3

- **Leopard Syndrome**: lentigenes, ECG conduction defects, ocular hypertelorism, pulmonic valve stenosis, abnormality of genitalia, retardation of growth, deafness, sensorineural (HCM and endocardial fibroelastosis), molecular and genetic abnormality unknown.

- Rarely, cardiomyopathy or complex CHD may be present (Braunwald’s 8th ed, p. 1571).
Truncal or mucosal pigmented spots or larger café-au-lait spots; hypertelorism; deafness (low set ears) – each of these 3 had HCM

Friedrich’s Ataxia: most common (1:50,000) hereditary spinal cerebellar degeneration; recessive, 50-90% have cardiac disease, HCM, rarely DCM, arrhythmias, 90% with inverted or biphasic T in inferior and left chest leads, AFL or AF common, concentric LVH, reduced protein – frataxin in mitochondrial membranes for iron homeostasis and respiratory function leading to mitochondrial dysfunction, poor oxidative stress response and apoptosis (9q13-31.1) Gene has too many GAA repeats in intron 1 (66-500)

Braunwald’s Heart Disease, 8th ed. 2008. p. 2145.
Friedrich’s Ataxia

28-yo man with LAE and LVH

Myofibril dysarray is not common in FA

SCD not so common

Braunwald’s Heart Disease, 8th ed. 2008. p. 2145.
Friedrich’s Ataxia

12-yo boy with severe ataxia, systolic function is normal

Friedrich’s Ataxia

17 yo who progressed from normal to DCM – marked connective tissue replacement

Braunwald’s Heart Disease, 8th ed. 2008. p. 2146.
Friedrich’s Ataxia

34 yo man with widespread ST-T changes

Braunwald’s Heart Disease, 8th ed. 2008. p. 2146.
Friedrich’s Ataxia

- **Treatment**: idebenone therapy (a free radical scavenger) may be helpful, may decrease wall thickness, and may improve EF if depressed, does not appear to improve neurological outcomes

- Death usually from neurologic respiratory failure or infection in 30s or 40s.

Dilated Cardiomyopathies

- Idiopathic dilated cardiomyopathy
- X-Linked dilated cardiomyopathy
- X-Linked cardioskeletal myopathy (Barth Syndrome)
- Familial arrhythmogenic RV dysplasia
Cytoskeletal Proteins Involved in DCM

Hurst, 10th Ed, 2001, p. 1799
Cytoskeletal Proteins Involved in DCM

MLP(CRP-3): muscle LIM protein, regulates muscle differentiation. 2 adjacent Zinc fingers, dimerize, serve both mechanical and signaling functions

Lin-11, Isl-1, Mec-3, insulin binding protein and regulatory protein

CREB:
Cyclic AMP response element binding protein, a nuclear transcription factor

Leiden JM. NEJM 1997; 337:1080
Cysteine-Rich Protein (CRP1)

A: N terminal

B: C terminal

Residue 65 is largely responsible for alpha-actinin binding, and alpha-actinin is a cross-linker of cytoskeletal actin.

Cytoskeletal Proteins Involved in DCM

MLP – muscle LIM protein

Nature Med
1999;5:267
**Dystrophin**

427 kDa

- **Black** – actin-binding domains
- **White** – rod domain with spectrin-like repeats
- **Gray** – Carboxy terminal domain bind dysgroglycan, along with cysteine-rich

- **H1-H4** – hinge segments available to proteolytic cleavage

**Badorff C et al.**

Dystrophin Glycoprotein Complex

**Basal Lamina:**
collagen types I and IV, heparin sulfate proteoglycan, entactin, fibronectin, and laminin. *Laminin* is a heterotrimer composed of alpha, beta, and gamma chains held together by disulfide bonds. *Merosin* is the collective name for laminins that share a common alpha2 chain. alpha-Dystroglycan binds to laminin.

Cecil Textbook of Medicine 2000, fig 505-1
Dystrophin Glycoprotein Complex
Familial DCM

- Accounts for 30% of idiopathic DCM
- Gene defects
  - **Lamin A/C**, esp A, on Chromosome 1 (like Emery-Dreyfuss muscular dystrophy), structural protein of nuclear membrane
  - **Actin** (located in domain that is immobilized and attached to the Z-band or intercalated disc, transmitting, not generating force)
  - **Desmin** (protein transmits force and other signals to the cytoplasm and nucleus from the sarcomere – it spans from Z-band to nuclear membrane and elsewhere)
  - **Dystrophin** (in Duchenne muscular dystrophy, intracellular)
  - **Alpha dystroglycan** on the extracellular surface
  - **Alpha-sarcoglycan** in the membrane
TABLE 64–5  List of Molecular Defects in Familial Dilated Cardiomyopathy (FDC)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autosomal Dominant FDC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTC</td>
<td>Cardiac action</td>
<td>sarcomeric protein; muscle contraction</td>
</tr>
<tr>
<td>DES</td>
<td>Desmin</td>
<td>dystrophin-associated glycoprotein complex; transduces contractile forces</td>
</tr>
<tr>
<td>SGCD</td>
<td>δ-Sarcoglycan</td>
<td>dystrophin-associated glycoprotein complex; transduces contractile forces</td>
</tr>
<tr>
<td>MYH7</td>
<td>β-Myosin heavy chain</td>
<td>sarcomeric protein; muscle contraction</td>
</tr>
<tr>
<td>TNNT2</td>
<td>Cardiac troponin T</td>
<td>sarcomeric protein; muscle contraction</td>
</tr>
<tr>
<td>TPM1</td>
<td>α-Tropomyosin</td>
<td>sarcomeric protein; muscle contraction</td>
</tr>
<tr>
<td>TTN</td>
<td>Titin</td>
<td>sarcomere structure/extensible scaffold for other proteins</td>
</tr>
<tr>
<td>VCL</td>
<td>Metavinculin</td>
<td>sarcomere structure; intercalated discs</td>
</tr>
<tr>
<td>MYBPC</td>
<td>Myosin-binding protein C</td>
<td>sarcomeric protein; muscle contraction</td>
</tr>
<tr>
<td>MLP/CSR3</td>
<td>Muscle LIM protein</td>
<td>sarcomere stretch; sensor/Z discs</td>
</tr>
<tr>
<td>ACTN2</td>
<td>α-Actinin-2</td>
<td>sarcomere structure; anchor for myofibrillar actin</td>
</tr>
<tr>
<td>PLN</td>
<td>Phospholamban</td>
<td>sarcoplasmic reticulum Ca$^{2+}$ regulator; inhibits SERCA2 pump</td>
</tr>
<tr>
<td>ZASP/LBD3</td>
<td>Cypher/LIM binding domain 3</td>
<td>cytoskeletal assembly; involved in targeting and clustering of membrane proteins</td>
</tr>
<tr>
<td>MYH6</td>
<td>α-Myosin heavy chain</td>
<td>sarcomeric protein; muscle contraction</td>
</tr>
<tr>
<td>ABCC</td>
<td>SUR2A</td>
<td>regulatory subunit of Kir6.2, an inwardly rectifying cardiac K$_{ATP}$ channel</td>
</tr>
<tr>
<td>LMNA</td>
<td>Lamin A/C</td>
<td>inner leaflet, nuclear membrane protein; confers stability to nuclear membrane; gene expression</td>
</tr>
<tr>
<td><strong>X-linked FDC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMD</td>
<td>Dystrophin</td>
<td>primary component of dystrophin-associated glycoprotein complex; transduces contractile forces</td>
</tr>
<tr>
<td>TAZ/G4.5</td>
<td>Tafazzin</td>
<td>unknown</td>
</tr>
<tr>
<td><strong>Recessive FDC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNN13</td>
<td>cardiac troponin I</td>
<td>sarcomeric protein, muscle contraction</td>
</tr>
</tbody>
</table>

Effects of Muscular Dystrophy

Dystrophin deficiency and α-sarcoglycan deficiency

- Acute membrane damages
  - Dendritic cell and mast cell infiltration and activation

- Ca\(^{2+}\) influx

- Deficiency of associated proteins
  - Defect of myofiber-ECM link, defect of synapse stabilization

- Mitochondrial function and energy metabolism

- De-differentiation

- Failure of regeneration
  - α-Cardiac actin, Versican, OSF-2
  - ERK6

- Toxic bystander effects

- Necrosis

- Loss of Ca\(^{2+}\) homeostasis, macrophage infiltration

- Immune responses, tissue remodeling, connective tissue changes

- C3, PLA\(_2\)S

- Alternative lineages

- Embryonic myosin heavy chain

Non-cell autonomous

Cell autonomous

TRENSIS in Pharmacological Sciences
**Limb-Girdle Dystrophies**

<table>
<thead>
<tr>
<th>Type</th>
<th>Protein product</th>
<th>Genetic loci</th>
<th>Age at onset</th>
<th>Unique features</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Myotilin</td>
<td>5q31</td>
<td>18–35 y</td>
<td>Dysarthria</td>
</tr>
<tr>
<td>IB</td>
<td>?</td>
<td>1q11–21</td>
<td>4–38 y</td>
<td>Cardiac involvement</td>
</tr>
<tr>
<td>IC</td>
<td>Caveolin 3</td>
<td>3q25</td>
<td>~ 5 y</td>
<td>Cramping, calf hypertrophy</td>
</tr>
<tr>
<td>IIA</td>
<td>Calpain-3</td>
<td>15q15.1–15.3</td>
<td>2nd decade</td>
<td>Shoulder girdle atrophy</td>
</tr>
<tr>
<td>IIB</td>
<td>Dysferlin</td>
<td>2p13</td>
<td>Late teens</td>
<td>Markedly elevated CPK</td>
</tr>
<tr>
<td>IIC</td>
<td>γ-Sarcoglycan</td>
<td>13q13</td>
<td>3–15 y</td>
<td>Asymptomatic scapular winging, calf hypertrophy</td>
</tr>
<tr>
<td>IID</td>
<td>a-Sarcoglycan</td>
<td>17q12–21.33</td>
<td>3–15 y</td>
<td>Same as γ-sarcoglycan</td>
</tr>
<tr>
<td>IIE</td>
<td>b-Sarcoglycan</td>
<td>4q12</td>
<td>Mean, 7.6 y</td>
<td>Early loss of ambulation</td>
</tr>
<tr>
<td>IIF</td>
<td>d-Sarcoglycan</td>
<td>5q33–34</td>
<td>4–10 y</td>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>IIG</td>
<td>Telethonin</td>
<td>17q11–12</td>
<td>2nd decade</td>
<td>Proximal upper extremities more involved, rimmed vacuoles</td>
</tr>
<tr>
<td>IIH</td>
<td>?</td>
<td>9q31–33</td>
<td>8–27 y</td>
<td>Facial muscle weakness</td>
</tr>
</tbody>
</table>

CPK, creatine phosphokinas.
X-Linked DCM (XLCM)

• Worse in men, fibrosis worst in posterior wall
• Dystrophin locus at Xp21 (same gene as for Duchenne and Becker muscular dystrophy), with defect at N-terminal end and rod portion, and also alpha dystroglycan was reduced
• Destabilization of muscle membrane
• CHF, ventricular arrhythmias, transplant
X-Linked Cardioskeletal Myopathy

- Barth syndrome
- Recessive: DCM with endocardial fibroelastosis, neutropenia, skeletal myopathy
- Males die in infancy, females unaffected
- Mitochondrial problems, locus Xq28, gene G4.5, protein tafazzin (function unclear), also causes isolated LV noncompaction and dilated HCM
Familial Arrhythmogenic RV Dysplasia (ARVD)

- Often the first symptom is SCD
- There is no definitive diagnostic standard, RV biopsy often false negative (abnormality moves from epicardium to endocardium)
- No common gene (chromosomes 1, 2, 14, 17, 3, 10 implicated in different families)
- MRI and Echo and ECG (T inversion in V1-3, late potentials, ventricular arrhythmia with LBBB pattern) helpful in diagnosis
Restrictive Cardiomyopathies

- Most common is amyloid, mutations in the transthyretin gene and protein
- Mucopolysaccharidoses
  - 7 types
    - Hurler’s Syndrome
    - Hunter’s Syndrome
    - Morquio’s Disease
    - Maroteaux-Lamy Disease
  - deficient in lysosomal enzymes that degrade glycosaminoglycans, leading to their accumulation
  - Multiple system involvement
  - Diagnose by culturing skin fibroblasts or leukocytes and assessing enzyme activity

Subsequent slides
Amyloid Heart Disease

- An infiltrative disease, along with sarcoid and Gaucher’s.
- Group of diseases with beta-pleated sheet extracellular protein deposit (insoluble, impervious to proteolytic digestion)
  - **Primary** systemic (AL): monoclonal immunoglobulin spike in 80% (MM light chain)
  - **Secondary** (AA): nonimmunoglobulin (TB, Rheum Arth)
  - Senile
  - Familial (transthyretin, >50-80 mutants), homotetramer 55kDa,
Human Transthyretin Tetramer

Blue – extended inner beta sheet
Red – outer beta sheet
Yellow – lone helix
Green – loops, that contribute to the tetramer formation

Hamilton JA et al. Cellular and Molecular Life Sciences 2001;58:1491
Transthyretin Dimer

Red – aromatic residues between the extended beta-sheets

Hamilton JA et al. *Cellular and Molecular Life Sciences* 2001;58:1491
Hurler’s Syndrome

- MPS-I, autosomal recessive, 22q11, 1:40,000, alpha-iduronidase (IDUA) deficiency – degrades heparan and dermatan sulfate, so these are elevated in urine (mucopolysacchariduria)

- Clinical subtypes:
  - severe (MPS-IH, Hurler, CAD, AS, MR/MS, HCM, EFE, death usually <10yo),
  - intermediate (MPS-IH-S, Hurler-Scheie, onset in teens),
  - mild (MPS-IS, Scheie, AR, nl lifespan)

- Treatment: allogeneic bone marrow transplant
Hunter’s Syndrome

- Xq26-Xq28, 1:30,000, iduronate sulfatase, excess dermatan and heparan sulfate in urine
- MI in childhood, most die before 20yo
- Wide clinical variability, depending on type of genetic mutation
Morquio’s Disease

- MPS-IVA, recessive, 16q24, deficient N-acetyl-galactosamine-6-sulfatase, excess urinary keratan sulfate and chondroitin 6-sulfate
- Prototypical chondroosteodystrophy, spondyloepiphyseal dysplasia, short-trunk dwarfism, normal intelligence
- Cardiac disease in 2nd decade, aortic valve disease, regurgitation
Maroteaux-Lamy Disease

- Syndrome, 5q13-q14, deficient arylsulfatase B, degrades dermatan sulfate and chondroitin 4-sulfate
- DCM and aortic or mitral stenosis or insufficiency
- Variable manifestations, and cardiac manifestations are usually after neurologic problems, usually by adolescence
- Treatment: Bone marrow transplantation
Muscular Dystrophies with Cardiac Involvement

- Duchenne Muscular Dystrophy (DMD)
- Becker’s Muscular Dystrophy (BMD)
- Emery-Dreifuss Muscular Dystrophy (EDMD)
- Myotonic Dystrophy (Steinert’s disease)
- Limb-girdle muscular dystrophy (DAG’s)
- Fascioscapulohumeral Dystrophy
- Nemaline Myopathy
- Endocardial Fibroelastosis (EFE)
Duchenne Muscular Dystrophy (DMD) - 1

- 1:3,300 male births, 1/3 are spontaneous mutations, pseudohypertrophy calves
- Female carriers may (~8%) have mild or moderate slowly progressive myopathy
• Heart commonly involved: 25% of deaths are cardiac
  – DCM with fibrosis mainly in posterobasal and lateral walls, mitral prolapse (post-med pap musc dysfunction), and conduction abnormality, large R and R/S in V1, deep narrow Q in lateral leads
  – LAE on ECG may be conduction problem
  – AFB, PFB, atrial flutter, IVCD, pacing not usually necessary
Duchenne Muscular Dystrophy

Braunwald fig 71-3, from Perloff. Posterobasal necrosis/fibrosis
X-linked Duchenne Muscular Dystrophy

- Exaggerated lumbar lordosis
- Calf pseudohypertrophy (fat accum streaky Xray)
- Shortened Achilles tendon
- Hypertrophy/pseudohypertrophy of deltoid and pectoralis major
- Also trapezius

Paul and Juhl, 1998 Fig 10-8
Braunwald 2001, Fig 71-1. From Perloff JK
ECG in DMD

Half of the cardiac deaths are sudden

Braunwald 2001, fig 71-4 from Fisch C
Becker’s Muscular Dystrophy (BMD)

- 1:25,000, Dystrophin abnormality like DMD but less severe and later onset, with survival to middle age, muscle abnormality identical pattern to DMD
- Heart involved in 80%, DCM, CHF, conduction abnormalities, MR from annular dilation
Becker’s MD

Braunwald 2001 fig 71-5
Emery-Dreifuss Muscular Dystrophy (EDMD)

- Xq28 gene that makes emerin, Chromosome 1 defect in lamin A/C; Relatively rare, no pseudohypertrophy, DCM is common, variable severity, AV block, commonly need pacemaker
- Some have DCM and no peripheral disease
Myotonic Dystrophy (Steinert’s Disease, DM) - 1

- 19q13.3 encoding myotonin protein kinase (DMPK), a serine-threonine protein kinase, excessive triplet repeats in the gene of CTG, usually with >100 repeats (CTG expansion size, nl <37) to produce disease

- Most common form of inherited muscular dystrophy in adults (1:8000, more in French Canadians, less in African blacks), autosomal dominant, ties up a CUG-binding protein (CUG-BP), has “anticipation”
Myotonic Dystrophy (Steinert’s Disease, DM) - 1

• Serious cardiac complications: fibrosis and fatty infiltration, common conduction abnormalities, SCD, bradycardia, prolonged PR and progression to CHB, VD, DCM may occur, less than diastolic dysfunction
Myotonic Dystrophy: Histology

- Fatty infiltration of AVN in 57 yo man
- Focal replacement fibrosis and atrophy in 48 yo woman

- Risk of progression of AV block with anesthesia is significant

Braunwald 2001 Fig 71-8
From Nguyen HH. JACC 1988
36-year-old, 1 year apart

Braunwald 2001 Fig 71-9
Fascioscapulohumeral Dystrophy

- 4q35, gene unknown, eponym Landouzy-Dejerine MD, 2 clinical types, one autosomal dominant around 10 yo, one is infantile
- Cardiac problems are generally mild. Progressive atrial dysfunction with atrial paralysis (?EDMD), sinus bradycardia, junctional escape rhythm, AV block, and atrium is unresponsive to electrical stimulation, also may have atrial flutter or atrial tachycardia

Braunwald 2001 Fig 71-10   From Perloff JK
Nemaline Myopathy

- Probably autosomal dominant, mutation in alpha-actin gene (ACTA1), or TPM3 encoding alpha-tropomyosin slow, or NEB encoding nebulin
- ACTA1 also causes actin myopathy with excessive thin filaments
- Conduction abnormalities and cardiac dilatation are unusual, with nemaline rods in the myocardium
- Z-band material – alpha-actinin

Robbins, 1998, fig 29-12
Endocardial Fibroelastosis

• Autosomal dominant or recessive or X-linked, now a rare disease, since MMR vaccination, may have been due to mumps intrauterine
Model of Cardiac Ventricular Cell, with Ion Channels and Pumps
Circles indicate beta adrenergic augmentation

18 Currents in a Cardiac Ventricular Cell:

INa indicates fast sodium current; 
ICa(L), calcium current through L-type calcium channels; 
ICa(T) calcium current through T-type calcium channels; 
IKr, fast component of delayed rectifier potassium current; 
IKs, slow component of delayed rectifier potassium current; 
IK1, inward rectifier potassium current; 
IKp, plateau potassium current; 
IK(ATP), ATP-sensitive potassium current; 
INaK, sodium-potassium pump current; 
INaCa, sodium-calcium exchange current; 
Ip(Ca), calcium pump in sarcolemma; 
INa,b, sodium background current; 
ICa,b, calcium background current; 
Ins(Ca), nonspecific calcium-activated current; 
Iup, calcium uptake from myoplasm to network sarcoplasmic reticulum (NSR); 
Irel, calcium release from junctional sarcoplasmic reticulum (JSR); 
Ileak, calcium leakage from NSR to myoplasm; and 
Itr, calcium translocation from NSR to JSR. 
Calmodulin, troponin, and calsequestrin are calcium buffers.

<table>
<thead>
<tr>
<th>Current</th>
<th>Probable clone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na$^+$ current</td>
<td>SCN5A (hH1)*</td>
</tr>
<tr>
<td>L-type Ca$^{2+}$ current</td>
<td>dihydropyridine receptor*</td>
</tr>
<tr>
<td>T-type Ca$^{2+}$ current</td>
<td></td>
</tr>
<tr>
<td>Na$^+$-Ca$^{2+}$ exchange</td>
<td>Na$^+$-Ca$^{2+}$ exchanger</td>
</tr>
<tr>
<td>I$_{TO1}$ (4-AP-sensitive)</td>
<td>Kv1.2, 1.4, 1.5, 2.1 +/- 4.2/3*</td>
</tr>
<tr>
<td>I$_{TO2}$ (Ca$^{2+}$-activated)</td>
<td></td>
</tr>
<tr>
<td>I$_{KS}$</td>
<td>KvLQT1 + IsK (minK)</td>
</tr>
<tr>
<td>I$_{Kr}$</td>
<td>HERG</td>
</tr>
<tr>
<td>I$_{Kur}$</td>
<td>possibly Kv1.5*</td>
</tr>
<tr>
<td>I$_{Cl}$ or / $K_p$</td>
<td>CFTR (Cl), TWIK/ORK1 (K) family</td>
</tr>
<tr>
<td>Inward rectifiers</td>
<td>Kir2 (I$<em>{K1}$), Kir3.1+3.4 (I$</em>{K-Ach}$); Kir6+SUR (I$_{K-ATP}$)</td>
</tr>
<tr>
<td>I$_f$ (pacemaker current)</td>
<td></td>
</tr>
</tbody>
</table>

* subunits also identified
Pore-forming K+ channel subunits in man and rodent. grey box=heart

Interactive Processes in a Cell

Congenital QT Prolongation

• Diagnostic Criteria:
  – Asymptomatic patient, QTc>470msec
  – OR: Male with QTc>440 or female with QTc>460 PLUS:
    • Stress-related syncope
    • Torsade de pointes
    • Family history of early (<35yo) SCD
  – These criteria are neither totally sensitive or specific

Congenital QT Prolongation

- **Romano-Ward**: autosomal dominant, no deafness
- **Jervell and Lange-Nielson**: autosomal recessive, with deafness (KVLQT1 and minK also control inner ear endolymph homeostasis)
- These 2 syndromes are disturbances in the same genes and channels, except Jervell and Lange-Nielson patients are homozygous, and the Romano-Ward patients are heterozygous with variable penetrance
# Types of Congenital Prolonged QT interval

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQTS1 (most common)*</td>
<td>KvLQT1</td>
<td>11p15.5</td>
<td>↓Iks (alpha subunit)</td>
</tr>
<tr>
<td>LQTS2</td>
<td>HERG</td>
<td>7q35-q36</td>
<td>↓Ikr</td>
</tr>
<tr>
<td>LQTS3 (rare)</td>
<td>SCN5A</td>
<td>3p21-p23</td>
<td>↑late INa</td>
</tr>
<tr>
<td>LQTS4</td>
<td>?</td>
<td>4q25-q27</td>
<td>?</td>
</tr>
<tr>
<td>LQTS5 (rare)*</td>
<td>minK (KCNE1)</td>
<td>21q22.1-q22</td>
<td>↓Iks (ancillary subunit)</td>
</tr>
<tr>
<td>LQTS6</td>
<td>MiRP1 (KCNE2)</td>
<td>21q22.1-q22</td>
<td>↓Ikr</td>
</tr>
</tbody>
</table>

* Jervell and Lange-Nielson as well as Romano-Ward
LQTS2: Ikr

LQTS3: late INa

LQTS1

LQTS5

Iks

Adrenergic Effects in Congenital Prolonged QT interval

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Pharm Mimic</th>
<th>↑QT/↑TDR</th>
<th>Isoproterenol, +Propranolol</th>
<th>Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQTS1</td>
<td>chromanol 293B</td>
<td>+/-</td>
<td>↑/↑, n/n</td>
<td>↓Iks</td>
</tr>
<tr>
<td>LQTS2</td>
<td>dofetalide, E-4031, d-sotalol</td>
<td>+/-</td>
<td>↑/↑↓, n/n</td>
<td>↓Ikr</td>
</tr>
<tr>
<td>LQTS3</td>
<td>anthopleurin A, ATX-II</td>
<td>+++/++</td>
<td>↓/↓, n/n</td>
<td>↑late INa</td>
</tr>
</tbody>
</table>

Experimentally: beta-blockade totally suppresses Tdp in LQT1, partially suppresses TdP in LQT2, and may provoke TdP in LQT3

Shimizu, J Am Coll Cardiol 2000;35:778-86
Mutations in LQTS Genes

• Each gene has multiple types of abnormalities, some are hot spots

• Modifier genes?: identical gene defects have variability in clinical features

• Modification of channel function:
  – Related to specific amino acid defect
  – KvLQT1, KCNE1 and HERG lose function
  – SCN5A gains function (defective inactivation)
Clinical Correlation in Congenital LQTS

- Manifestations
  - LQTS1: trigger of exercise
  - LQTS3: trigger with sleep or rest, shorten QT with exercise
  - LQTS2: both rest and exercise

- Management
  - Beta-blocker is first choice therapy
  - LQT3 usually improve with mexiletine
  - LQT2 may improve with mexiletine
ECG manifestations of LQTS

- Vary with genotype

Type 1

Type 2

Type 3

Circ, Dec 5, 2000… Wilde and Roden p 2797, Zhang et al, p.2849
Type 1

Circ, Dec 5, 2000... Wilde and Roden p 2797, Zhang et al, p.2849
Type 2

Circ, Dec 5, 2000... Wilde and Roden p 2797, Zhang et al, p.2849
Type 3

Circ, Dec 5, 2000… Wilde and Roden p 2797, Zhang et al, p.2849
References:


• Sandoe, Sigurd, Arrhythmia - A guide to clinical electrocardiology Publishing Partners Verlags GmbH 1991


• Wilde et al. Circulation 2000;102:2799-2801
Defects of Metabolism Causing Cardiomyopathy

- Carnitine deficiency
- Medium chain Acyl-CoA Dehydrogenase (MCAD) deficiency
- Long/Very long chain Acyl-CoA Dehydrogenase (LCAD/VLCAD) deficiency
- Fabry’s disease
- Homocysteinuria
- Mitochondrial cardiomyopathies
- Connective tissue disorders
- Primary rhythm/conduction disorders
- Congenital heart disease c/s genetic syndromes
Homocystinuria

- Autosomal Recessive, 1:75,000, 21q22.3, cystathionine beta-synthase (CBS) deficient, elevated serum methionine and elevated urine homocystine
- Homozygous: marfanoid habitus, arterial and venous thrombosis (activation of factor V, inhibition of protein C and decreased AT-III), medial degeneration of the aorta and intimal hyperplasia and fibrosis
- 13-47% respond to pyridoxine
- May occur from Vit B6 or B12 or folate deficiency
- Mechanism: induction of cyclin A gene, inducing VSMC proliferation

Note: article on post PCI improved outcomes in folate admin; NEJM Nov 29, 200
Mitochondrial DNA

Gray – 7 subunits of complex I (ND)
Black – 3 subunits of cytochrome c oxidase (COX), 12S and 16S ribosomal RNA (rRNA)
Dark gray – Cytochrome b
Gray – 2 subunits of ATP synthetase (ATPase 6 and 8)
White – 22 tRNA’s

Boxed information: known point mutations associated with cardiomyopathy

Human mtDNA
16,569 bp, 37 genes

Hirano M et al. Curr Opin Cardiol 2001; 16:201
Mitochondrial DNA

Santorelli FM et al. Am Heart J 2001; 141:E1
http://www.gen.emory.edu/mitomap.html
A Commonly Affected mt-tRNA, \((\text{Ile})\)

Santorelli FM et al.  
Am Heart J 2001; 141:E1
Generation of ATP

(A.) Glycolysis
- Glucose → Pyruvate → Lactate
  - Promotes Glycogenesis
  - Carbohydrates
  - Dichloroacetate

(B.) Fatty Acid Oxidation
- Fatty Acids → Acylcarnitine
  - Promotes Fatty Acid Oxidation
    - Carnitine deficiency
    - MCAD/LCAD deficiency
    - Deficiencies of CPTI/II
    - Carnitine Translocase deficiencies

(C.) Oxidative Phosphorylation
- From glycolysis and tricarboxylic acid cycle
- From β-fatty acid oxidation

Clay AS et al. Chest 2001;120:634
Ragged Red Fibers in Mitochondrial Disease

Gomori’s trichrome

Abnormal mitochondria give a blotchy red appearance to the fiber, initially subsarcolemmal, then throughout fiber

Clay AS et al. Chest 2001;120:634
Ragged Red Fibers in Mitochondrial Disease

Gomori’s trichrome

Abnormal mitochondria give a blotchy red appearance to the fiber, initially subsarcolemmal, then throughout fiber

EM: mitochondria show “parking lot” inclusions

Robbins 1998, fig 29-13
Diagnostic Workup in Suspected Mitochondrial Disease

Clay AS et al. Chest 2001;120:634
Mitochondrial DNA Defects

• mtDNA is in 2-10 copies/organelle, and multiple organelles/cell, 200 mutations identified so far, maternal transmission

• Tissues with high oxidative phosphorylation demand are more affected by problems: kidney, retina, brain, muscle, heart

• Most have heteroplasmy, mix of mutant and normal mitochondria correlation with severity of phenotype, often brain and muscle disturbances

• Cardiac problems more with respiratory chain defects
Mitochondrial DNA

Point mutations in structural and protein-coding genes are indicated inside the circle, with the clinical phenotype and the nucleotide position of the mutation. The thick arc indicates the position of the most common single deletion, which is 5 kb in length, and the thin arcs outside the circle indicate the multiple deletions. MERRF, myoclonic epilepsy with ragged red fibers; MELAS, the syndrome of mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes; LHON, Leber's hereditary optic neuropathy; NARP, neuropathy, ataxia, and retinitis pigmentosa; Leigh, maternally inherited Leigh's disease.

Harrison's Principles of Internal Medicine, fig 67-1
Kearns-Sayre Syndrome (KSS)

- Ptosis, chronic progressive external ophthalmoplegia, retinal pigmentation, cardiac conduction defects (20% pts have cardiac involvement, prolonged H-V), DCM, hearing loss, limb weakness, DM, hypoparathyroid

- Deletion esp tRNA leu in mtDNA

Braunwald 2001, fig 71-15
MERRF Syndrome

• MERRF: myoclonic epilepsy with ragged-red muscle fibers, tRNA-Lys: seizures, ataxia, HCM, complex I and IV abnormality

MELAS Syndrome

• MELAS: mitochondrial encephalopathy, lactic acidosis, stroke-like episodes, can have ragged-red fibers, exercise intolerance, HCM, DCM, usually complex I abnormality, tRNA-Leu
# CONTIGUOUS GENE SYNDROMES

<table>
<thead>
<tr>
<th>Syndromes with Cardiovascular Involvement</th>
<th>Region</th>
<th>Locus</th>
<th>Cardiovascular Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriohepatic dysplasia</td>
<td>AHD</td>
<td>del 20p11.23-p12.2</td>
<td>Peripheral pulmonic stenosis/hypoplasia</td>
</tr>
<tr>
<td>Cat-eye syndrome</td>
<td>CES</td>
<td>dup22q11</td>
<td>Total anomalous pulmonary venous return</td>
</tr>
<tr>
<td>DiGeorge sequence</td>
<td>DGS</td>
<td>del 22q11</td>
<td>Truncus arteriosus, right aortic arch, TOF, PDA</td>
</tr>
<tr>
<td>Miller-Dieker syndrome</td>
<td>MDS</td>
<td>del 17p13</td>
<td>PDA ± complex anomalies</td>
</tr>
<tr>
<td>Prader-Willi syndrome and</td>
<td>PWS/AS</td>
<td>del 15q12(pat)</td>
<td>Cor pulmonale (secondary to obesity central apnea)</td>
</tr>
<tr>
<td>WAGR syndrome tumor</td>
<td></td>
<td>del 11p13</td>
<td>Hypertension (secondary to Wilms tumor)</td>
</tr>
</tbody>
</table>

# Syndromes Without Frequent Cardiovascular Involvement

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Region</th>
<th>Locus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angelman syndrome</td>
<td></td>
<td>del 15q12 (mat)</td>
</tr>
<tr>
<td>Smith-Magenis syndrome</td>
<td></td>
<td>del 17p11.2</td>
</tr>
</tbody>
</table>

Braunwald 2001 Table 56-1
## Physiology of Sensation During Exercise

<table>
<thead>
<tr>
<th>System</th>
<th>Process</th>
<th>Sensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Motor command</td>
<td>Effort</td>
</tr>
<tr>
<td>Nerve</td>
<td>Excitation–contraction (Na⁺–K⁺)</td>
<td>Weakness</td>
</tr>
<tr>
<td></td>
<td>Cross-bridge formation (Ca²⁺)</td>
<td></td>
</tr>
<tr>
<td>Muscle</td>
<td>Power output (ATP → ADP)</td>
<td>Tension</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Glycogen + ADP → ATP + Lactate + H⁺</td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Glycogen + ADP + O₂ → ATP + CO₂</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FFA + ADP + O₂ → ATP + CO₂</td>
<td></td>
</tr>
<tr>
<td>Circulation</td>
<td>Blood flow</td>
<td></td>
</tr>
<tr>
<td>Lungs</td>
<td>Ventilation</td>
<td></td>
</tr>
</tbody>
</table>

Jones NL et al. NEJM 2000; 343:632.
Major Metabolic Pathways During Exercise

Jones NL et al. NEJM 2000; 343:632