BACKGROUND AND CLINICAL PRESENTATION

- Goals and Objectives
  - Review the normal myocyte and causes of cardiac dysfunction
  - Clinical presentation of Myopathies, “Sick Hearts”

- Don’t forget that definition of Acquired
BACKGROUND AND CLINICAL PRESENTATION

- No disclosures
- Pictures and images
Myopathy
- Disease of the muscle
- myo- Greek μυο "muscle" + –pathy Greek pathos "suffering"

Cardiomyopathy
- A disease of the heart muscle contributing to the disruption of normal cardiac function – weakening of the heart muscle
- THE REALLY SICK HEART
  - The myofibril
  - Electrolyte exchange
  - Energy use in the heart
How the Heart works
CARDIAC MECHANICS

- Part of the larger system
CARDIAC MECHANICS - MYOFIBRIL
CARDIAC MECHANICS - PROTEINS
CARDIAC MECHANICS – ELECTROLYTES
CARDIAC MECHANICS – ENERGY

**Energy Production**

- **Normoxia**
  - Glucose + ADP + P_i → ATP
  - ATP → ADP + P_i + H^+
  - Glycolysis
  - Lactate + H^+
  - pH decreases

- **Anoxia**
  - ATP
  - Glycolysis
  - Lactate + H^+
  - pH decreases

- **Mitochondria**
  - CO_2 + H_2O
  - O_2
  - ATP
  - ADP
  - P_i

- **ATP Synthase**
  - F_0 F_1
  - Cristae

**Cardiac Mechanics**

- ATP → ADP + P_i + H^+
- Glycolysis
- Lactate + H^+
- pH decreases
- Ca^{2+} and Mg^{2+} ↑

**Additional Components**

- Anoxia
- Many soluble metabolic intermediates
- Ribosomes
- Porin channels
1. Myosin heads hydrolyze ATP and become reoriented and energized.

2. Myosin heads bind to actin, forming crossbridges.

3. Myosin heads rotate toward center of the sarcomere (power stroke).

4. As myosin heads bind ATP, the crossbridges detach from actin.

Contraction cycle continues if ATP is available and Ca^{2+} level in the sarcoplasm is high.
- Not enough energy
- Energy use is bad
- The mechanical components don’t work correctly
PHYSIOLOGY

- Mechanics translate to physiology
- Oxygen delivery to tissue
- Energy delivery to tissue
- Clear products of metabolism
SICK HEARTS

- Extrinsic vs Intrinsic
- Anatomic/structural abnormalities
  - Ischemia
    - Low oxygen
    - Low power/substrate delivery to the heart muscle
- Cardiomyopathy - Disease of the heart muscle
- Arrhythmia
THE SICK HEART – STRUCTURAL ABNORMALITIES

- Obstructive lesions
STRUCTURAL ABNORMALITIES

- Ischemic lesions
THE SICK HEART – DILATED CARDIOMYOPATHY
DILATED CARDIOMYOPATHY
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Mitochondrial β-Oxidation spiral

- LCHAD (α, α)
- LCEH
- Long-chain 2-eneoyl-CoA hydratase
- Long-chain 3-hydroxyacyl-CoA dehydrogenase
- Long-chain 3-ketoacyl-CoA thiolase
- Matrix enzymes
  - NAD
  - FAD
  - CoA-SH
  - 3-Ketoacyl-CoA thiolase

FAD

Acyl-CoA-Dehydrogenase

LCAD (C8-C18)
MCAD (C4-C12)
SCAD (C4-C6)

DH

2-Enoyl-CoA-Hydratase

2-Enoyl-CoA

3-Hydroxyacyl-CoA

3-Hydroxy-Acyl-CoA-Dehydrogenase

SCHAD (about 6 C-atoms)
LCHAD (C12-C16)

Ketoacyl-CoA

Saturated acyl-CoA (Cn-2)

Acetyl-CoA
Dilated Cardiomyopathy
Initial Work-Up

- Chest X-ray
- EKG
- Urine:
  - Organic Acids including 3-methylglutaconic acid, lactate
  - Urinalysis
  - Amino Acids
- Blood for:
  - Lactic Acids
  - Pyruvate
  - Chem 7, Magnesium, Calcium
  - Selenium
  - CBC d/p
  - CPK(MM, MB, total)
  - Troponin I
  - Liver Function Tests
  - Acylcarnitine profile
  - Cholesterol
  - Thyroid Function Tests
  - ESR
  - Viral PCR/serologies
    - CMV, EBV, ADENOVIRUS, ENTEROVIRUS
    - Amino Acids
    - Serum
    - BNP
- Echocardiogram
- Holter
- Treadmill
- Blood for cell lines:
  - Gene mutation analysis
  - Mitochondrial genome analysis
  - Cytogenetics
- Skeletal Muscle Biopsy:
  - Histology
  - EM
  - Mitochondrial respiratory chain analysis, acyl-CoA DH analysis
- Endomyocardial Biopsy:
  - Histology
  - EM
  - PCR for Viral Genome
  - Mitochondrial respiratory chain analysis
- Tracheal aspirate for viral PCR panel
- Family History:
  - Echocardiograms of 1º relatives
  - Prenatal History
THE SICK HEART - MYOCARDITIS

- Inflammation of the heart muscle
- Presentation variable – arrhythmia, myopathy
- Systemic, “localized”
MYOCARDITIS

Normal heart

Myocardium (heart muscle)

Myocarditis causes the heart muscle to become thick and swollen
MYOCARDITIS

Infection

Viral
Coxsackie
Echovirus
Epstein-Barr
Cytomegalovirus
Influenza
Adenovirus
Rubella
Varicella
Herpes
Mumps
Hepatitis
Polio
HIV (?)
Variolax
Rabies
Arbovirus
Mycoplasma

Noninfectious
Cardiotoxins
Catecholamines
Anthrax
Cocaine

Neocarzinostatin

Initial Insult
(Viral Infection)

Cross-Reactive Antigen

Acute Injury

Cellular and Humoral Response

Biochemical Effects

Chamber Dilation, Myocardial Fibrosis and Failure

(From Brown, CA, AM J MED, 99: 31.)
MYOCARDITIS
Acute Myocarditis

- Viral infection
  - Myocyte necrosis
  - Macrophage activation
    - Cytokine expression
      - Interleukin-1
      - Interleukin-2
      - Tumor necrosis factor
      - Interferon-γ

Subacute Myocarditis

- Infiltrating mononuclear cells
  - Natural killer cells
  - Perforin
  - Nitric oxide
  - Cytotoxic T lymphocytes
  - B lymphocytes
  - Neutralizing antibodies

Chronic Myocarditis

- Fibrosis
- Cardiac dilatation
- Heart failure

Time Course of Experimental Viral Myocarditis in Mice. Adapted from Kawai with the permission of the publisher. The timeline is not to scale.
MYOCARDITIS
Clinical outcomes of acute myocarditis in childhood
K J Lee, B W McCrindle, D J Bohn, G J Wilson, G P Taylor, R M Freedom, J F Smallhorn, L N Benson
MYOCARDITIS

Dilated Cardiomyopathy
Initial Work-Up

- Chest X-ray
- EKG
- Urine
  - Organic Acids including 3-methylglutaconic acid, lactate
  - Urinalysis
  - Amino Acids
- Blood for:
  - Lactic Acid
  - Pyruvate
  - Chem 7, Calcium
  - Selenium
  - CBC d/p
  - CPK(MN, Troponin
  - Liver Fur
  - Acylcarnitine
  - Cholesterol...
  - Thyroid Function Tests
- Echocardiogram
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Viral PCR/serologies
- CMV, EBV, PARVO, ADENOVIRUS, ENTEROVIRUS

ESR

URINALYSIS:
- Organic Acids including 3-methylglutaconic acid, lactate
- Urinalysis
- Amino Acids

BLOOD FOR:
- Lactic Acid
- Pyruvate
- Chem 7, Calcium
- Selenium
- CBC d/p
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THE SICK HEART – HYPERTROPHIC CARDIOMYOPATHY
HYPERTROPHIC CARDIOMYOPATHY

- The big picture

Hypertrophic Cardiomyopathy

- Normal Heart
- Hypertrophied Heart
HYPERTROPHIC CARDIOMYOPATHY

Blood leaks back through mitral valve = mitral regurgitation

Mitral valve presses against septum causing obstruction to blood flow

Normal muscle structure

Myocardial disarray

Hypertrophic Cardiomyopathy

1g3: cTnT

11p11.2: MYBPC3

3p: MELC

14q11: beta MHC

12q23-24.3: MFLC

16q2 alpha TM

Systolic anterior motion of the mitral valve (SAM)
HYPERTROPHIC CARDIOMYOPATHY
HYPERTROPHIC CARDIOMYOPATHY

- Poor cardiac output
HYPERTROPHIC CARDIOMYOPATHY

- Arrhythmias
HYPERTROPHIC CARDIOMYOPATHY

- Infants less than 1 year
- 1 % per year
- 4-6% risk of sudden cardiac death
- Early detection with lifestyle changes
THE SICK HEART - ARRHYTHMIA

- Arrhythmogenic myopathy
- Primary rhythm disorders
Restrictive Cardiomyopathy
Sepsis, acidosis, etc
CARDIOMYOPATHIES

- Multiple disorders cause a Really Sick Heart
- “Acquired”
- Multiple effects of these disorders
- Variable presentation
A neonate is prepared for discharge from the hospital. He was the product of uncomplicated pregnancy.

At day #3 of life, he is noted to the breathing fast and hard. He has “Ashen.”

Pulse oxymetry is normal in his right upper extremity and absent in his lower extremity.

This patient has a really sick heart.
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A 6-month-old infant has had difficulty feeding that has progressed over the past week. He presents to his pediatrician and is noted to be breathing 80 times per minute.

He is diaphoretic. There are retractions. He has no febrile illness. His pulses are very weak. His heart rate is 140 when he is at rest.

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A 7-year-old had an upper respiratory infection about 10 days ago. The runny nose has resolved, but his illness continues to “linger.”

He is unable to hold down fluids. He has had no diarrhea. His mother is concerned because his skin has appeared gray.

He presents to the emergency room weak and is noted to have a heart rate of 130.

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- This patient has a really sick heart.
A teenager was playing football. When running across the field, he suddenly collapsed to the ground.

Wide QRS tachycardia was noted.

By history, he had a viral gastrointestinal infection about a week ago but he had "completely recovered."

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A fatigued 14 year old has been loosing weight without trying.

On exam she has a heart rate of 135. An ECG demonstrates an abnormal axis to the P wave with a rate of 135.

She has a rate of 135 for most of the 24 hour period on a 24 hour ambulatory ECG.

This young lady has a really sick heart.
ECTOPIC ATRIAL TACHYCARDIA

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- On exam she has a heart rate of 135. An ECG demonstrates an abnormal axis to the P wave with a rate of 135.
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Evaluation included an ECG with inverted T waves in II, III and AVF.

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Thank you