Integrated Cardiovascular and Immune System Notes for Week 1
January 9, 2015

ANATOMY

CV system -- modeled like water flow in a fish tank…

Qs -- How is need to energy regulated? What designates the pump's activity? What is the driving force of water returning to the "replenisher"? How is the pump regulated? What are the characteristics of the pipe? Where does regulatory information come from? Are changes localized or general? How do the valves facilitate unidirectional flow? What happens if characteristics of the liquid change?

Thoracic Cage

- Borders
  - rib cadge
  - diaphragm (inferior thoracic process; esophagus, inferior vena cava, and descending aorta pass through)
  - superior thoracic aperture (manubrium, 1st rib, T1)
  - spinal column
  - Inferior thoracic aperture (xiphoid process, costal margin, 12th rib, T12)
- Contents
  - Heart
    - Apex -- mostly composed of the left ventricle
    - Base -- mostly composed of the left atrium
    - Fibrous skeleton -- gives the myocardium something to hang onto, designates valves
    - Grooves -- house vascular structure and coronary sinus
      - Atrioventricular groove (coronary sulcus)
      - Inter ventricular groove
  - Lungs
  - Sympathetic nerves (sympathetic chain)
  - Parasympathetic nerves
  - Autonomic plexuses
    - Cardiac
    - Pulmonary
  - Phrenic nerve (C3-5) -- innervates diaphragm, somatic, pair
  - Somatic nerves (intercostal n) -- in-between ribs
- Functions -- protection, resist lung recoil, upper limb attachment, and muscle attachment
- Mediastinum -- space in the thorax that includes everything except the lungs, divided b/t T4-T5
  - Superior
  - Inferior
    - Anterior
    - Posterior
    - Middle -- heart

Blood flow through the heart

Deoxygenated blood from systemic circulation goes into the heart via the superior/ inferior vena cava into the right atrium, then into the right ventricle, into the

pulmonary artery to pulmonary circulation… oxygenated blood leaves the lungs and flows into the left atrium via pulmonary veins, then into the left ventricle, and finally back into systemic circulation via the aorta.

Pericardium and Pericardial Cavity
- Fibrous pericardium -- keeps the heart from getting too big
- Formation -- the heart tube folds into the serous pericardium and then forms single heart tube
- Visceral layer -- stuck to the surface of the heart, comes with some adipose
  - Epicardium = visceral layer + adipose
- Parietal layer -- stuck to the fibrous pericardium
  - Blends into the tunica adventitia of great vessels
- Pericardial cavity -- does not contain the heart! Contains a little fluid and a little air
- Paricardiophrenic ligament -- holds heart to diaphragm
- Sternopericardial ligament -- holds heart to sternum`

Pathologies
- Pulmonary embolism -- a clot that breaks free and blocks pathways in the lungs
- Left-sided heart failure -- leads to high pulmonary blood pressure and edema
- Aortic aneurysm -- expansion of the vessel wall, tends to press on other structures or rupture
- Pericarditis -- infections, inflammation of pericardium
- Effusion -- filling pericardial cavity with fluid
  - Heart compression
- Prolapsed valve -- the inability of the papillary muscles to hold the valves closed during systole
- Calcific aortic stenosis -- the valve will not open all the way during diastole
- Mitral valves regurgitation -- the valve doesn't stay closed during systole
- Prolapse -- valves fall out of place

Heart Valves
- Atrioventricular valves -- between ventricles and atria
  - Tricuspid -- right side
  - Bicuspid (Mitral) -- left side
  - Connected to papillary muscle via tendinous cords (chordae tendinae)
  - Close when ventricular pressure increases
- Semilunar valves -- between ventricles and outflow
  - Aortic
    - holes distal to the aortic valve that feeds the coronary arteries
  - Pulmonary
  - Each has 3 cusps with no tendinous cords or papillary muscles
  - Close when ventricular pressure falls
- Diastole -- relaxation
- Systole -- contraction

Coronary Vessels
- Deep to the visceral layer of the serous pericardium
- Right coronary artery -- sits in coronary groove
  - Sinuatrial nodal branch -- serves the sinuatrial node (pacemaker); 60%

Anterior/posterior AV branch
Marginal branch
Posterior interventricular branch

Left coronary artery --
Circumflex branch -- in coronary sulcus
Anterior interventricular branch (Left Anterior Descending; widow maker) -- gives blood to the left ventricle
Sinuatrial nodal branch (40%)

Coronary sinus -- drains into the right atria
Great cardiac vein
Middle cardiac vein
Small cardiac vein
Smallest cardiac veins (Thesbesian veins) -- direct drainage into the right atrium

Conduction System of the Heart

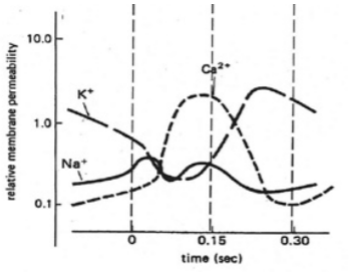
SA node -- through atria to AV node
Pacemaker
Necessary for regulation of HB (sympathetic and parasympathetic innervation)

AV node -- from atria to ventricles in membranous part of IVS via AV bundle (bundle of Hiss)
Right and left bundles within muscular IVS (interventricular septum) -- through ventricles via subendocardial branches (Purkinje fibers)

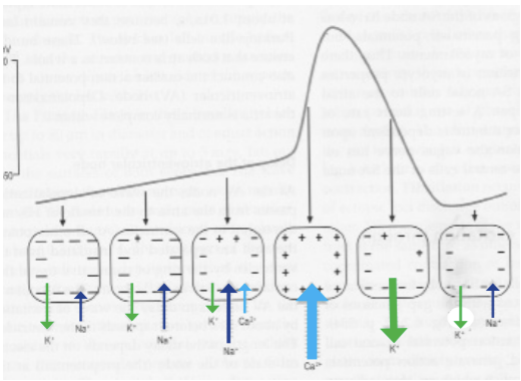
PHYSIOLOGY

Our functional heart model is based on a piston-pump (like one found in a vehicle engine or a bicycle air pump)
"stroke" is equivalent to "contraction"
The frequency of contraction is controlled by the main pacemaker cell (SA node) and driven by electrical gradients

Permeability changes as such:
O seconds -- [K^+] decreases and [Ca^{2+}] increases to make the membrane potential less negative, approaching action potential
15 seconds -- [K^+] decreases and [Ca^{2+}] decreases to make the membrane potential more negative, repolarizing
30 seconds -- [K^+] decreases and [Ca^{2+}] increases to make the membrane potential less negative, coming back to resting potential (pacemaker potential in pacemaker cell)



The resulting curve looks like this:



Pacemaker cell contractions are self-initiated, but the rate of contraction can be affected by hormones and neurotransmitters.
Sympathetic influence increases the rate of the rise of pacemaker potential by

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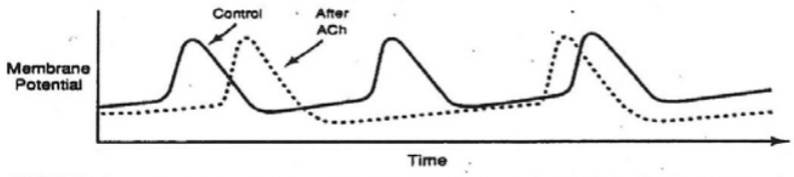
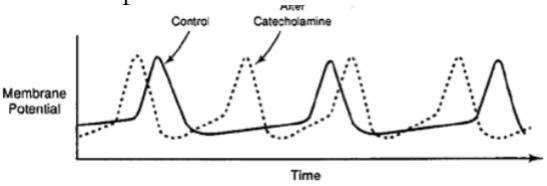
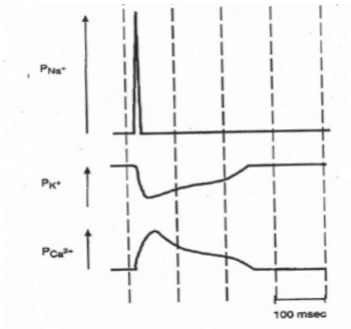
stimulating the increase in the amount of open K^+ channels open



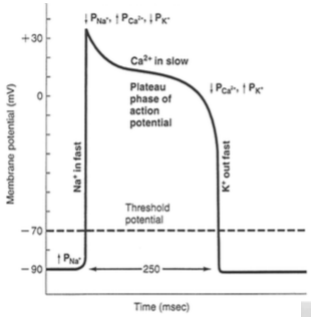
Parasympathetic influence decreases the rate of the rise of pacemaker potential by stimulating the increase in the amount of ligand gated Ca^{2+} channels open



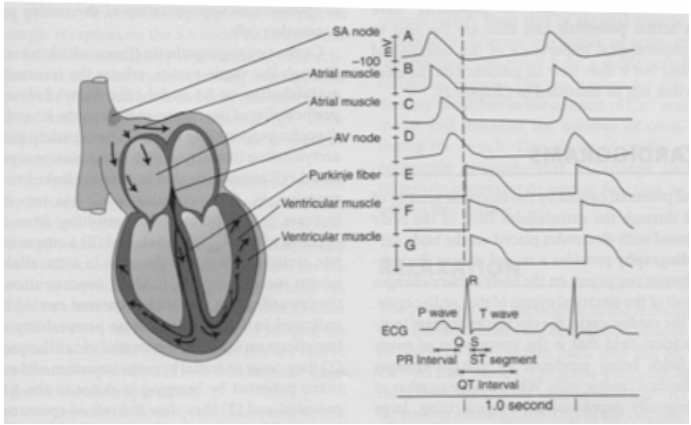
Relative Permeability



The bottom of the arrow represents 0 permeability. Note the appearance of voltage-gated time-inactivation channels associated with the rapid influx and outflow of Na+. After the first 50 seconds or so, the K^+ permeability (P_K) increases and Ca^{2+} permeability (P_{Ca}) decreases, the cell repolarizes.



Phase 0 -- resting potential; P_{Na} increases
Phase 1 -- Na+ gates open quickly (time-inactivation gates)
Phase 2 -- decrease in P_{Na} and P_K, increase in P_{Ca}
Phase 3 -- Ca^{2+} in slow
Phase 4 -- decrease in P_{Ca}; increase in P_K



ase 5 -- K^+ out fast

An ECG is a look at the sum of the contraction cycle throughout the heart.

Mechanical Properties

Contraction -- heart pumps

How is cardiac muscle similar to skeletal muscle?

Striations -- presence of a sarcomere

Na/K-ATPase

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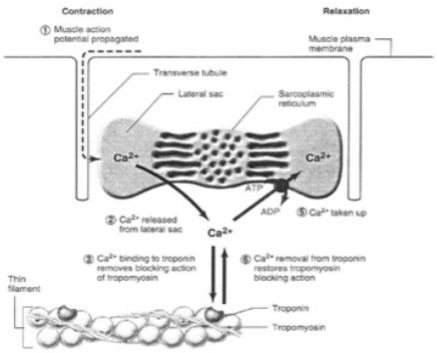
Sarcomere shortening
Calcium is stored in and released from the sarcoplasmic reticulum
Calcium is pumped into the sarcoplasmic reticulum against the gradient using an ATP-pump

Skeletal Muscle



How is it different?
Calcium mediated calcium release from the sarcomere
More types of calcium channels
Small single cells
Ca release is not enough to engage all troponin -- partial engagement of muscle (needs to come in wither more or faster)
Action potential includes the movement of Ca^{2+} into the cell
Contraction occurs during the action potential
Calcium is pumped back into the extracellular fluid (a Na/Ca antiporter powered by Na/K ATPase)
They cannot experience tetany -- you cannot stimulate another action potential until the previous is done based on a voltage-reset mechanism
Increase in muscle length increases the force of contraction (Starling's law of the heart)

Cardiac Muscle

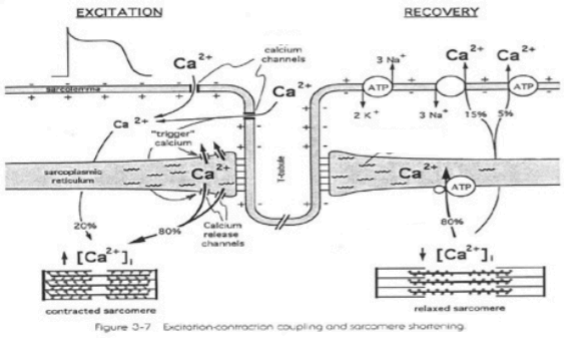


Figure 3-7 Excitation-contraction coupling and sarcomere shortening.

Cardiac Output -- volume ejected per unit of time (V per min)
HR x SV = CO
HR is dependent on the pacemaker cell rate and autonomic stimulation
CO is dependent on the venous return and preload

BIOCHEMISTRY
Fuel Utilization in Cardiac Muscle (Learning Objectives)

1) Describe fuel utilization in cardiac muscle in normal (non-ischemic) conditions. (part C on page 887; part A on page 891; figures 23.1 and 47.5)

Main fuel -- fatty acids used aerobically, 60-80%
Rest is lactate and glucose (with high insulin spike following a high carbohydrate meal)
Regulation -- AMP levels: AMP protein kinase>> (+) malonyl Co A Decarboxylase (decrease [malonyl CoA]) and (-) Acetyl CoA carboxylase (increase [malonyl CoA])
Increase in [malonyl CoA] decreases the use of FA as fuel by inhibiting CAT1

Lipid Transport in the Blood (Learning Objectives)

1) Describe the release of fatty acids from adipocytes and the transport of the fatty acids through the blood during fasting and exercise:
Describe the mechanism by which glucagon causes activation of hormone-sensitive lipase in the fasting state. Describe the mechanism by which epinephrine causes activation of hormone-sensitive lipase both in the fasting state and during exercise.

- Glucagon -- stimulates the adenylate cyclase > ^[cAMP] > stimulates PKA > phosphorylates hormone-sensitive lipase to activation > hydrolysis of ester bonds in fat/TAG molecules > albumin (made in the liver) transports the FA through the blood to muscle cells and glycerol goes to the liver for gluconeogenesis; NOT ADRENERGIC RECEPTORS
  - Glucagon levels rise during the fasting state
  - Made by alpha cells of the pancreas
- Epinephrine -- acts similarly to glucagon, it interacts with a different receptor, both are heptahelical (crosses the membrane seven times and makes a helix in the membrane) receptors which interact with hetreotrimeric (three different subunits) G-proteins (able to bind GTP/GDP) which activates a membrane-associated enzyme (i.e. adenylate cyclase); interacts with adrenergic receptors
  - Epinephrine levels rise during exercise
- Albumin is the protein that transports endogenous FA through the blood stream

Describe the reactions catalyzed by hormone-sensitive lipase (HSL) and other lipases. Name the type of linkages that are hydrolyzed in lipolysis. Describe the fates of the glycerol and fatty acids that result. Describe the role played by albumin in the transport of the fatty acids. (from part E on page 184 through part 2 on page 186; part 2 on page 488 and top of page 489; part C on pages 489-490; Section V on pages 611-612; part B on page 417 through part 1 on page 417; figures 7.9, 11.10, 11.17, 11.18, and 36.10)

- Hormone sensitive lipase catalyses the hydrolysis of TAGs in to FAs

2) Describe the delivery of fatty acids by lipoproteins in the fed state:
a) Describe the generalized structure of a lipoprotein. (figure 32.8)

- Amphipathic molecules in the surface layer
  - Proteins
  - Phospholipids (monolayer)
  - Cholesterol
- Core of mainly nonpolar lipids
  - TAG
  - Cholesterol esters

b) Describe the sources, functions, and fates of lipoproteins in the fed state. (Section IV on page 26)

- Chylomicrons and VLDLs transport exogenous FA
- Deliver to (cardiac) muscle cells and adipose cells

c) Describe the synthesis of chylomicrons, their transport of dietary (exogenous) triacylglycerols, and their delivery of fatty acids to adipose tissue and muscle

(including cardiac muscle) after a fatty meal. (part C on pages 22-23; Sections IV and V on pages 591-593; figures 32.3, 32.10, and 32.13)

Chylomicrons are synthesized in enterocytes

They travel through lymphatic vessels (thoracic duct) before they get to the blood stream (left subclavian vein)

Fat molecules in core: dietary (exogenous) TAGs

Increased by high fat meals

Turn into remnants as they interact with subsequent interactions with LPL

Deliver cholesterol to liver via chylomicron remnant receptors (Apo E)

Get endocytosed

Liver uses cholesterol to make bile salts

d) Describe the synthesis of very low density lipoproteins (VLDLs), their transport of endogenous triacylglycerols, and their delivery of fatty acids to adipose tissue and muscle (including cardiac muscle) after a high carbohydrate meal. (Sections II and III on pages 608-609; figures 33.2 and 33.19)

VLDLs come from liver cells

Fat molecules in core: endogenous TAGs

Increased by a high carbohydrate meal

Turn into LDL and HDL with subsequent interactions with LPL

e) Describe the locations of lipoprotein lipase, and the reaction that it catalyzes. (figures 32.13 and 33.2)

Lipoprotein lipases (LPL) -- catalyze the hydrolysis of TAGs from lipoproteins

FA travels quickly into adipocytes and myocytes

Resulting glycerol goes to liver for gluconeogenesis

In capillary walls near muscle cells and adipose cells (synthesized by those cells)

Activated by apoprotein C2 on the surface of the lipoprotein

f) Describe the sources and functions of the following apoproteins: apo A1, apo B48, apo B100, apo C2, apo C3, and apo E. (the part about apoproteins just below the middle of page 639; table 34.3 on page 640)

Apo A1 -- activates LCAT, part of HDL

Apo B48 -- assembly/ secretion of chylomicrons

Apo B100 -- see table

Apo C2 -- activator of lipoprotein lipase

Apo C3 -- see table

Apo E -- see table

3) Describe the delivery of cholesterol by lipoprotein remnants: (Section VI through part C on pages 639-642)

a) Describe the conversion of chylomicrons into chylomicron remnants. Describe the fate of chylomicron remnants, the location of chylomicron remnant receptors, and the role of apo E in this process. (Section VI through part A on pages 639-641; figure 32.13)

Chylomicrons turn into chylomicron remnants through subsequent interactions with LPL. The FA goes to muscle cells and adipose cells and the glycerol goes to the liver.

b) Describe the conversion of VLDLs into LDLs. Describe the fate of LDLs, the location of LDL receptors, and the role of apo B-100 and apo E in this process. (parts B and C on pages 641-642; figure 34.14)

LDL -- taken up by hepatocytes (to make bile salts) and steroid hormone-producing cells take them up (Apo B100 and Apo E help them interact with LDL receptors)

c) Describe the regulation of the expression of the gene coding for LDL receptors. Describe the biochemical basis and clinical consequences of familial hypercholesterolemia. (from Section VII through Section VIII part A on pages 645-648; figures 34.18 and 34.4 A)

The gene that codes for LDL receptors is SRE and it recycles receptors
What if one or more of the genes that code for LDL receptors, on chromosome 19, is mutated? Hypercholesterolemia, which increases atherosclerotic activity

4) Describe the role of antioxidants in the prevention of atherosclerosis. (part C on page 642; part C on pages 648-649; Section IX on pages 649-650; figures 34.14, 34.21, and 34.22)

If LDLs stay in the blood too long, they are likely oxidized and taken up by scavenger receptors. Macrophages combine with oxidized LDLs to become foam cells that go into the subendotheilial cells to form atherosclerotic plaques
HDLs and antioxidants can prevent the reactions that lead to atherosclerosis.

5) Reverse Cholesterol Transport:

a) Identify the source of HDLs. (parts 1 and 2 on page 642)

HDLs are from liver cells

b) Describe the function of HDLs in reverse cholesterol transport. Describe the reaction catalyzed by lecithin : cholesterol acyltransferase (LCAT) and its importance in this process. Describe the role of apo A1 in this process. <u>Draw schematics for the structure of a lecithin and the structure of a cholesterol ester.</u> (part 3 on pages 642-644; figures 34.16 and 34.15)

Lecithin (phospholipid) in the surface layer of HDLs
LCAT -- catalyzes the transfer of an acyl group from a lecithin reactant to a cholesterol reactant (creating a cholesterol ester, which absorbs into the core of an HDL)

c) Describe the interactions between HDLs and other lipoproteins in circulation. Describe the fate of HDLs.(parts 4 and 5 on pages 644-645; figures 34.16 and 34.17)

The HDLs will transfer cholesterols to LDLs,VLDLs, and chylomicrons. While VLDLs et al will give TAGs to HDLs.

<u>Suggested Review Questions</u>: #4 on page 69; #5 on page 436; #2 on page 492; #1 on page 596; #4 and #5 on page 662.