Physiology

Heart and Circulation

Functions of the Circulatory System

- Transportation:
  - Respiratory:
    - Transport O_2 and CO_2.
  - Nutritive:
    - Carry absorbed digestion products to liver and to tissues.
  - Excretory:
    - Carry metabolic wastes to kidneys to be excreted.

Functions of the Circulatory System (continued)

- Regulation:
  - Hormonal:
    - Carry hormones to target tissues to produce their effects.
  - Temperature:
    - Divert blood to cool or warm the body.
  - Protection:
    - Blood clotting.
  - Immune:
    - Leukocytes, cytokines and complement act against pathogens.

Components of Circulatory System

- Cardiovascular System (CV):
  - Heart:
    - Pumping action creates pressure head needed to push blood through vessels.
  - Blood vessels:
    - Permits blood flow from heart to cells and back to the heart.
      - Arteries, arterioles, capillaries, venules, veins.
- Lymphatic System:
  - Lymphatic vessels transport interstitial fluid.
    - Lymph nodes cleanse lymph prior to return in venous blood.

Composition of Blood

- Plasma:
  - Straw-colored liquid.
    - Consists of H_2O and dissolved solutes.
      - Ions, metabolites, hormones, antibodies.
        - Na^+ is the major solute of the plasma.
- Plasma proteins:
  - Constitute 7-9% of plasma.
    - Albumin:
      - Accounts for 60-80% of plasma proteins.
      - Provides the colloid osmotic pressure needed to draw H_2O from interstitial fluid to capillaries.
        - Maintains blood pressure.

Composition of the Blood (continued)

- Plasma proteins (continued):
  - Globulins:
    - α globulin:
      - Transport lipids and fat soluble vitamins.
    - β globulin:
      - Transport lipids and fat soluble vitamins.
    - γ globulin:
      - Antibodies that function in immunity.
  - Fibrinogen:
    - Constitutes 4% of plasma proteins.
    - Important clotting factor.
      - Converted into fibrin during the clotting process.

Composition of the Blood (continued)

- Serum:
  - Fluid from clotted blood.
    - Does not contain fibrinogen.
- Plasma volume:
  - Number of regulatory mechanisms in the body maintain homeostasis of plasma volume.
    - Osmoreceptors.
    - ADH.
    - Renin-angiotensin-aldosterone system.

Erythrocytes

- Flattened biconcave discs.
- Provide increased surface area through which gas can diffuse.
- Lack nuclei and mitochondria.
  - Half-life ~ 120 days.
- Each RBC contains 280 million hemoglobin with 4 heme chains (contain iron).
- Removed from circulation by phagocytic cells in liver, spleen, and bone marrow.

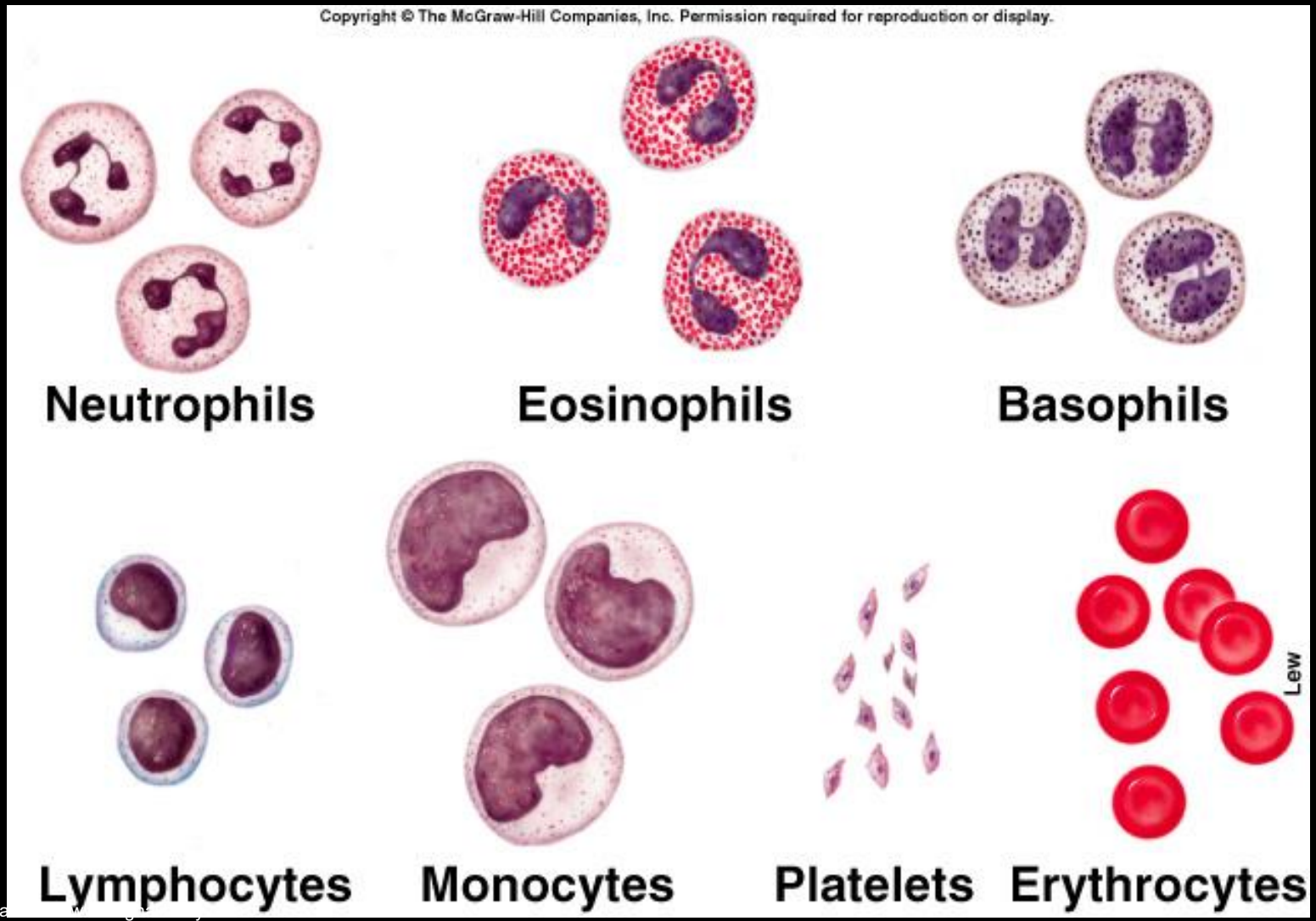
Leukocytes

- Contain nuclei and mitochondria.
- Move in amoeboid fashion.
  - Can squeeze through capillary walls (diapedesis).
- Almost invisible, so named after their staining properties.
  - Granular leukocytes:
    - Help detoxify foreign substances.
      - Release heparin.
  - Agranular leukocytes:
    - Phagocytic.
      - Produce antibodies.

Platelets (thrombocytes)

- Smallest of formed elements.
  - Are fragments of megakaryocytes.
  - Lack nuclei.
- Capable of amoeboid movement.
- Important in blood clotting:
  - Constitute most of the mass of the clot.
  - Release serotonin to vasoconstrict and reduce blood flow to area.
- Secrete growth factors:
  - Maintain the integrity of blood vessel wall.
- Survive 5-9 days.

Blood Cells and Platelets



Hematopoiesis

- Undifferentiated cells gradually differentiate to become stem cells, that form blood cells.
- Occurs in myeloid tissue (bone marrow of long bones) and lymphoid tissue.
- 2 types of hematopoiesis:
  - Erythropoiesis:
    - Formation of RBCs.
  - Leukopoiesis:
    - Formation of WBCs.

Erythropoiesis

- Active process.
  - 2.5 million RBCs are produced every second.
- Primary regulator is erythropoietin.
  - Binds to membrane receptors of cells that will become erythroblasts.
  - Erythroblasts transform into normoblasts.
  - Normoblasts lose their nuclei to become reticulocytes.
  - Reticulocytes change into mature RBCs.
    - Stimulates cell division.
- Old RBCs are destroyed in spleen and liver.
  - Iron recycled back to myeloid tissue to be reused in hemoglobin production.
- Need iron, vitamin B_{12} and folic acid for synthesis.

Leukopoiesis

- Cytokines stimulate different types and stages of WBC production.
- Multipotent growth factor-1, interleukin-1, and interleukin-3:
  - Stimulate development of different types of WBC cells.
- Granulocyte-colony stimulating factor (G-CSF):
  - Stimulates development of neutrophils.
- Granulocyte-monocyte colony stimulating factor (GM-CSF):
  - Simulates development of monocytes and eosinophils.

RBC Antigens and Blood Typing

- Each person's blood type determines which antigens are present on their RBC surface.
- Major group of antigens of RBCs is the ABO system:

Type A:
Only A antigens present.

Type B:
Only B antigens present.

Type AB:
Both A and B antigens present.

Type O:
Neither A or B antigens present.

RBC Antigens and Blood Typing (continued)

- **Each person inherits 2 genes that control the production of ABO groups.**

Type A:
May have inherited A gene from each parent.
May have inherited A gene from one parent and O gene from the other.

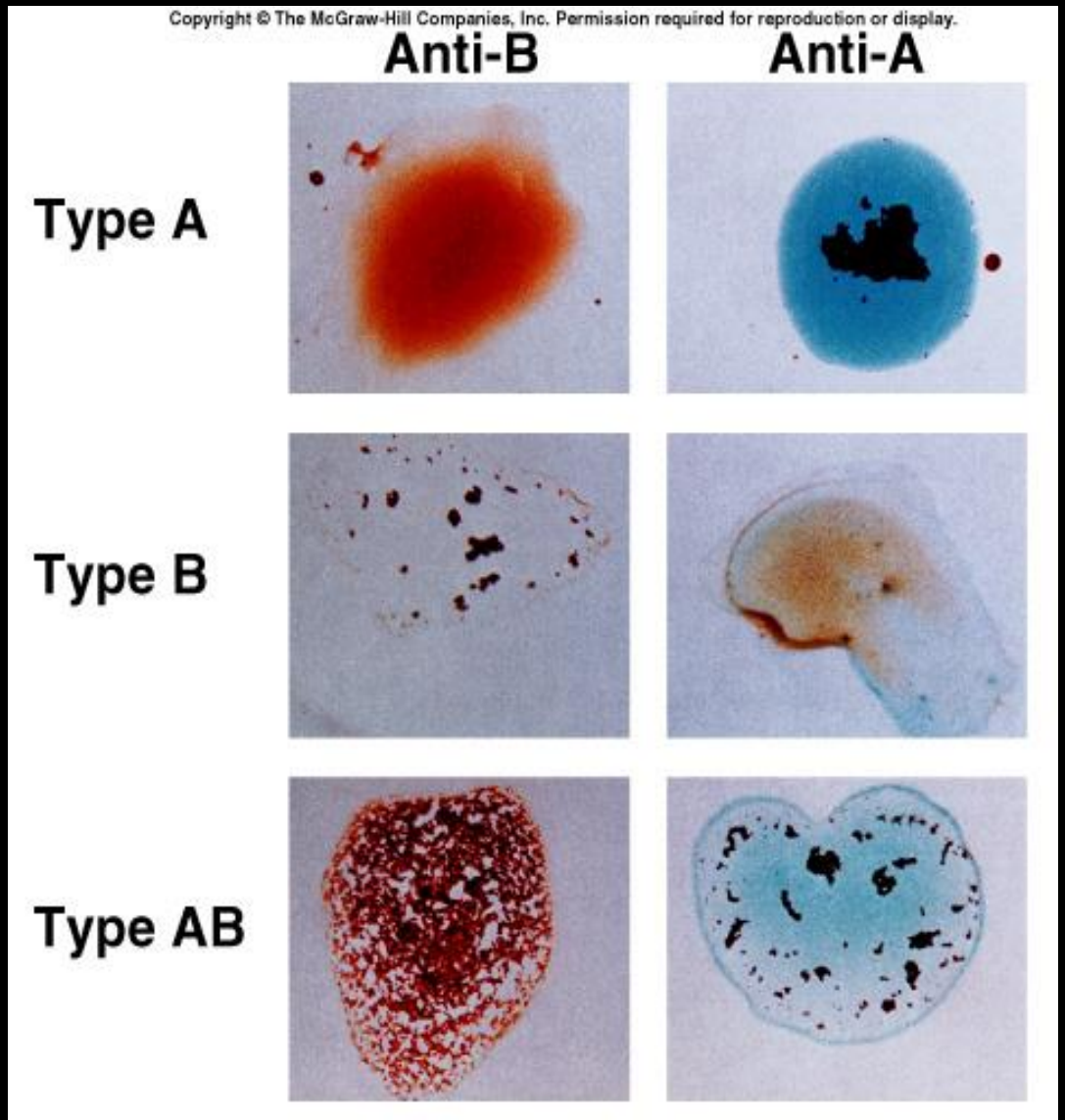
Type B:
May have inherited B gene from each parent.
May have inherited B gene from one parent and O gene from the other parent.

Type AB:
Inherited the A gene from one parent and the B gene from the other parent.

Type O:
Inherited O gene from each parent.

Transfusion Reactions

- If blood types do not match, the recipient's antibodies attach to donor's RBCs and agglutinate.
- Type O:
  - Universal donor:
    - Lack A and B antigens.
    - Recipient's antibodies cannot agglutinate the donor's RBCs.
- Type AB:
  - Universal recipient:
    - Lack the anti-A and anti-B antibodies.
  - Cannot agglutinate donor's RBCs.



Rh Factor

- Another group of antigens found on RBCs.
- Rh positive:
  - Has Rho(D) antigens.
- Rh negative:
  - Does not have Rho(D) antigens.
- Significant when Rh- mother gives birth to Rh+ baby.
  - At birth, mother may become exposed to Rh+ blood of fetus.
    - Mother at subsequent pregnancies may produce antibodies against the Rh factor.
- Erythroblastosis fetalis:
  - Rh- mother produces antibodies, which cross placenta.
    - Hemolysis of Rh+ RBCs in the fetus.

Blood Clotting

- Function of platelets:
  - Platelets normally repelled away from endothelial lining by prostacyclin (prostaglandin).
    - Do not want to clot normal vessels.
- Damage to the endothelium wall:
  - Exposes subendothelial tissue to the blood.

Blood Clotting (continued)

- Platelet release reaction:
  - Endothelial cells secrete von Willebrand factor to cause platelets to adhere to collagen.
  - When platelets stick to collagen, they degranulate as platelet secretory granules:
    - Release ADP, serotonin and thromboxane A_2.
      - Serotonin and thromboxane A_2 stimulate vasoconstriction.
      - ADP and thromboxane A_2 make other platelets "sticky."
        - Platelets adhere to collagen.
        - Stimulates the platelet release reaction.
    - Produce platelet plug.
      - Strengthened by activation of plasma clotting factors.

Blood Clotting (continued)

- Platelet plug strengthened by fibrin.
- Clot reaction:
  - Contraction of the platelet mass forms a more compact plug.
  - Conversion of fibrinogen to fibrin occurs.
- Conversion of fibrinogen to fibrin:
  - Intrinsic Pathway:
    - Initiated by exposure of blood to a negatively charged surface (collagen).
      - This activates factor XII (protease), which activates other clotting factors.
    - Ca^{2+} and phospholipids convert prothrombin to thrombin.
      - Thrombin converts fibrinogen to fibrin.
        - Produces meshwork of insoluble fibrin polymers.

Blood Clotting (continued)

- Extrinsic pathway:
  - Thromboplastin is not a part of the blood, so called extrinsic pathway.
  - Damaged tissue releases thromboplastin.
    - Thromboplastin initiates a short cut to formation of fibrin.

Blood Clotting (continued)

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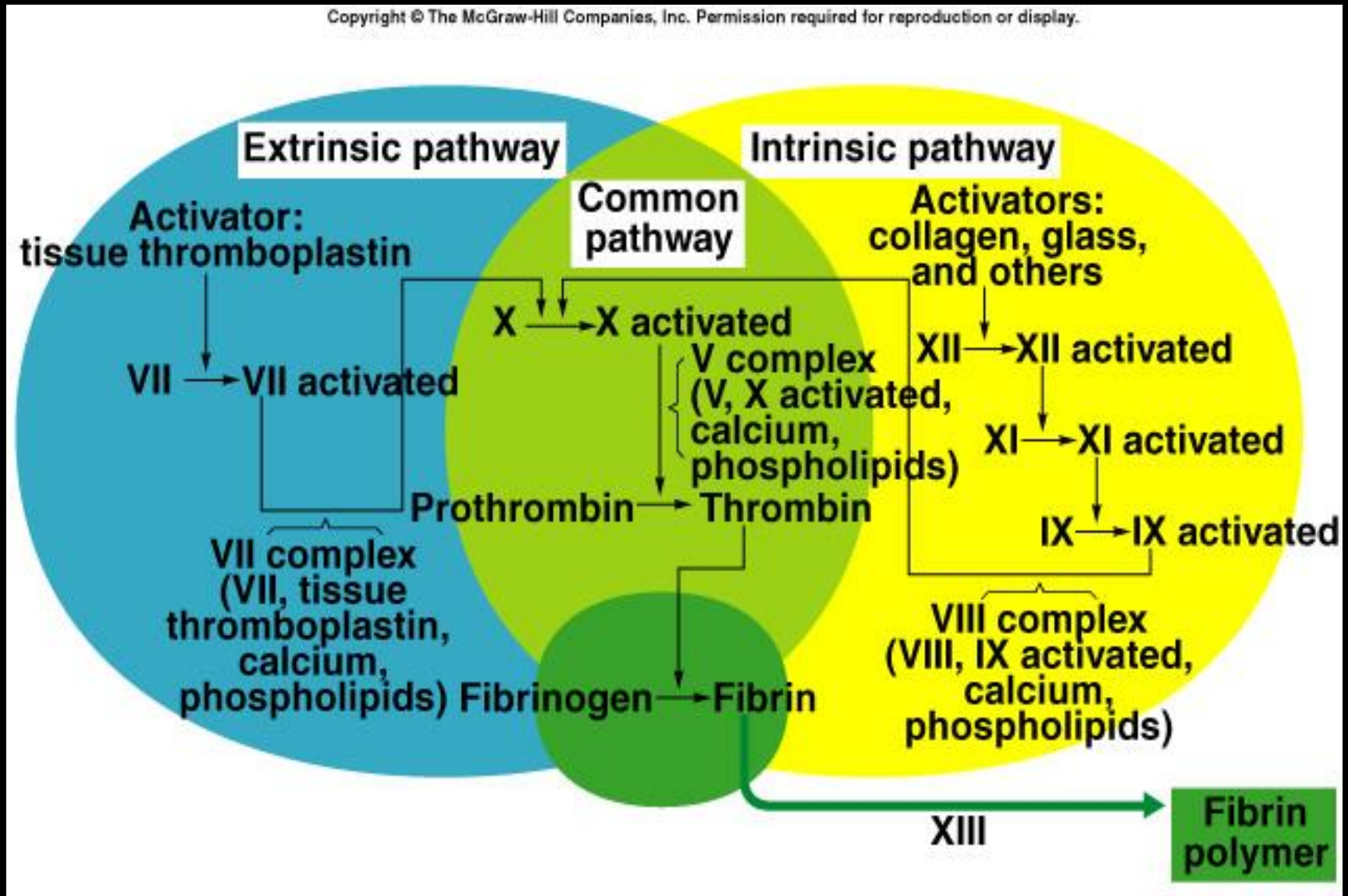
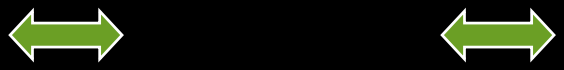


Dissolution of Clots

- Activated factor XII converts an inactive molecule into the active form (kallikrein).
  - Kallikrein converts plasminogen to plasmin.
- Plasmin is an enzyme that digests the fibrin.
  - Clot dissolution occurs.
- Anticoagulants:
  - Heparin:
    - Activates antithrombin III.
  - Coumarin:
    - Inhibits cellular activation of vitamin K.

Acid-Base Balance in the Blood

- Blood pH is maintained within a narrow range by lungs and kidneys.
- Normal pH of blood is 7.35 to 7.45.
- Some H^+ is derived from carbonic acid.
- $H_2O + Co_2 \quad H_2Co_3 \quad H^+ + HCo_3^-$



Acid-Base Balance in the Blood (continued)

- Types of acids in the body:
  - Volatile acids:
    - Can leave solution and enter the atmosphere as a gas.
      - Carbonic acid.

$$H_2O + CO_2 \quad H_2CO_3 \quad H^+ + HCO_3^-$$

  - Nonvolatile acids:
    - Acids that do not leave solution.
      - Byproducts of aerobic metabolism, during anaerobic metabolism and during starvation.
      - Sulfuric and phosphoric acid.

Buffer Systems

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- Provide or remove H^+ and stabilize the pH.
- Include weak acids that can donate H^+ and weak bases that can absorb H^+.
- HCO_3^- is the major buffer in the plasma.
- $H^+ + HCO_3^- \rightleftharpoons H_2CO_3$
- Under normal conditions excessive H^+ is eliminated in the urine. 

Acid Base Disorders

- Respiratory acidosis:
  - Hypoventilation.
    - Accumulation of CO_2.
      - pH decreases.
- Respiratory alkalosis:
  - Hyperventilation.
    - Excessive loss of CO_2.
      - pH increases.

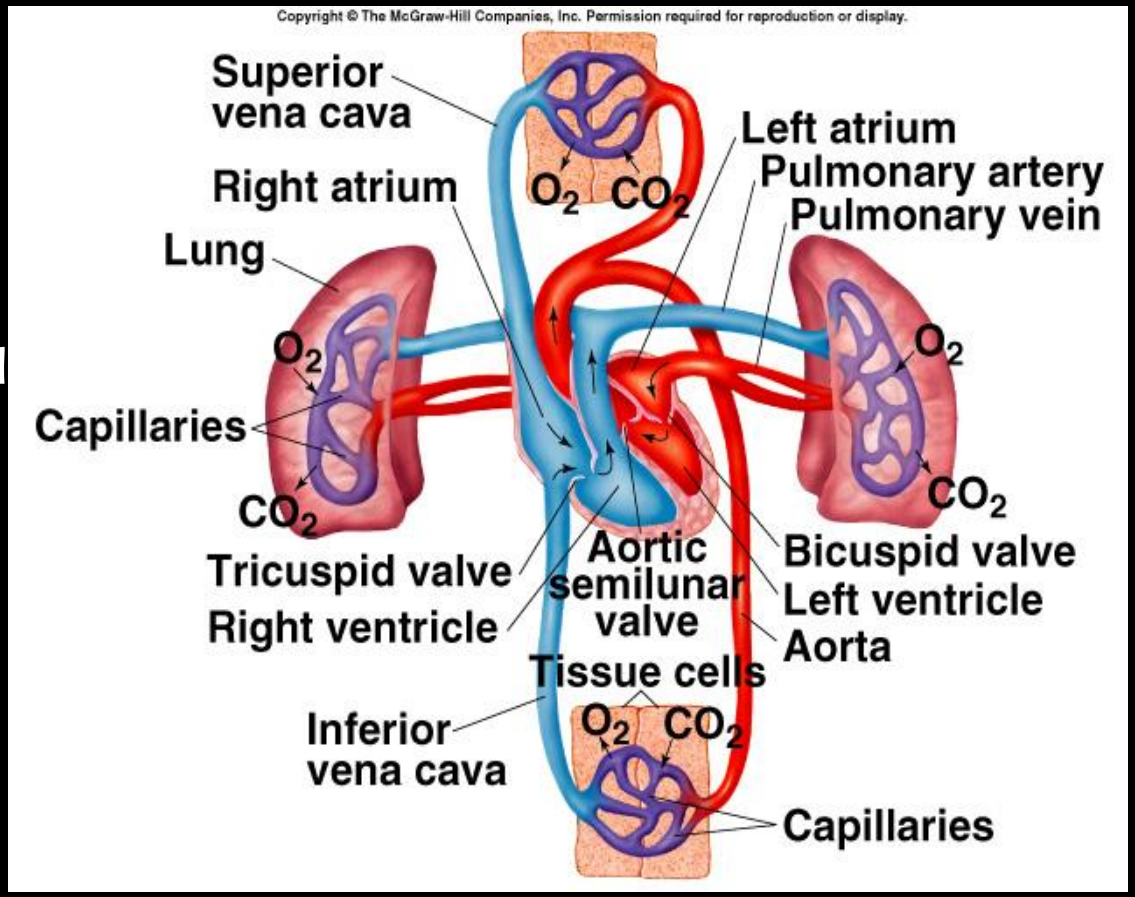
- Metabolic acidosis:
  - Gain of fixed acid or loss of HCO_3^-.
    - Plasma HCO_3^- decreases.
      - pH decreases.
- Metabolic alkalosis:
  - Loss of fixed acid or gain of HCO_3^-.
    - Plasma HCO_3^- increases.
      - pH increases.

pH

- Normal pH is obtained when the ratio of HCO_3^- to CO_2 is 20:1.
- Henderson-Hasselbalch equation:
- $pH = 6.1 + \log = \frac{[HCO_3^-]}{[0.03P_{Co2}]}$

Pulmonary and Systemic Circulations

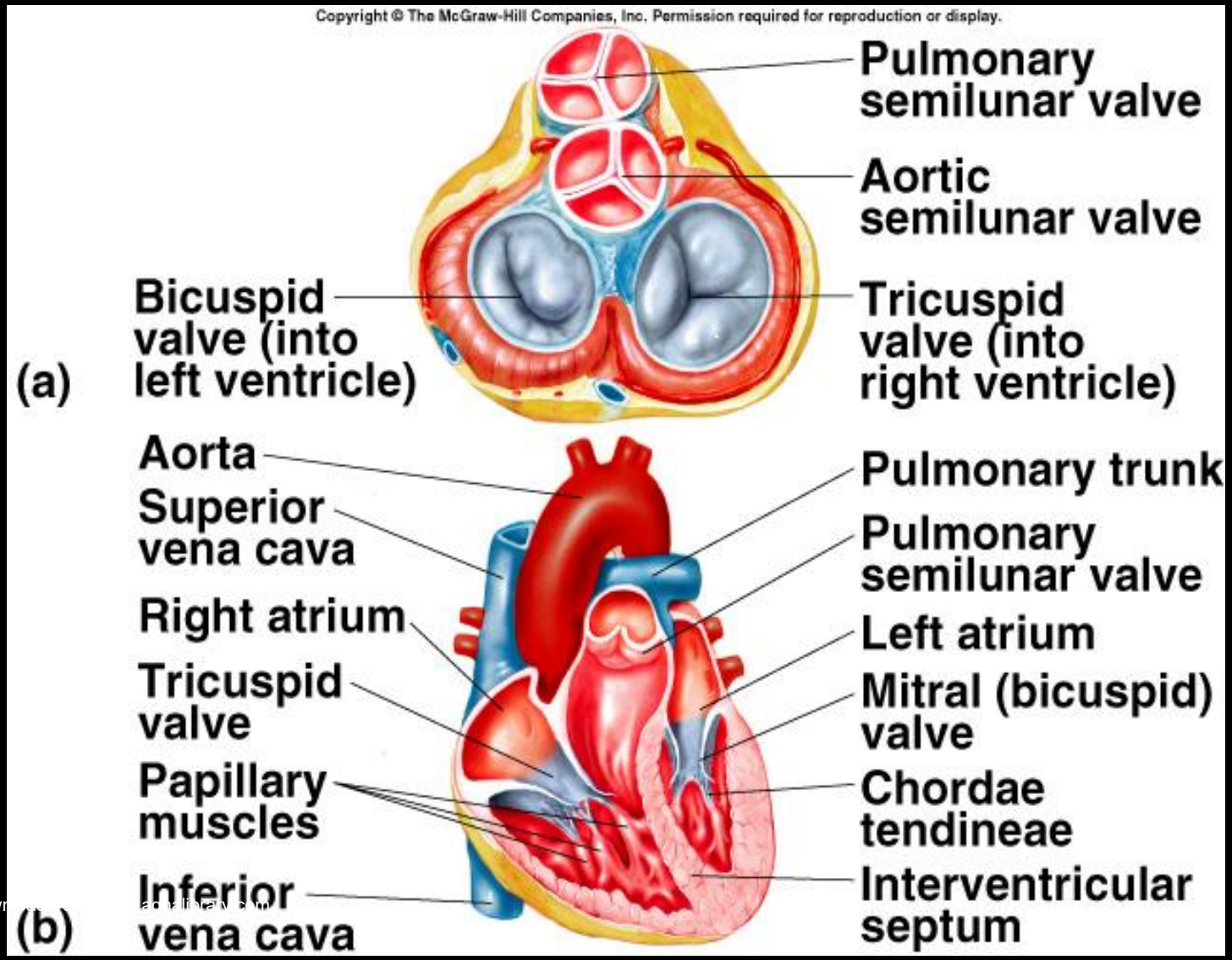
- Pulmonary circulation:
  - Path of blood from right ventricle through the lungs and back to the heart.
- Systemic circulation:
  - Oxygen-rich blood pumped to all organ systems to supply nutrients.
- Rate of blood flow through systemic circulation = flow rate through pulmonary circulation.



Atrioventricular and Semilunar Valves

- Atria and ventricles are separated into 2 functional units by a sheet of connective tissue by AV (atrioventricular) valves.
  - One way valves.
  - Allow blood to flow from atria into the ventricles.
- At the origin of the pulmonary artery and aorta are semilunar valves.
  - One way valves.
  - Open during ventricular contraction.
- Opening and closing of valves occur as a result of pressure differences.

Atrioventricular and Semilunar Valves



Cardiac Cycle

- Refers to the repeating pattern of contraction and relaxation of the heart.
  - Systole:
    - Phase of contraction.
  - Diastole:
    - Phase of relaxation.
  - End-diastolic volume (EDV):
    - Total volume of blood in the ventricles at the end of diastole.
  - Stroke volume (SV):
    - Amount of blood ejected from ventricles during systole.
  - End-systolic volume (ESV):
    - Amount of blood left in the ventricles at the end of systole.

Cardiac Cycle (continued)

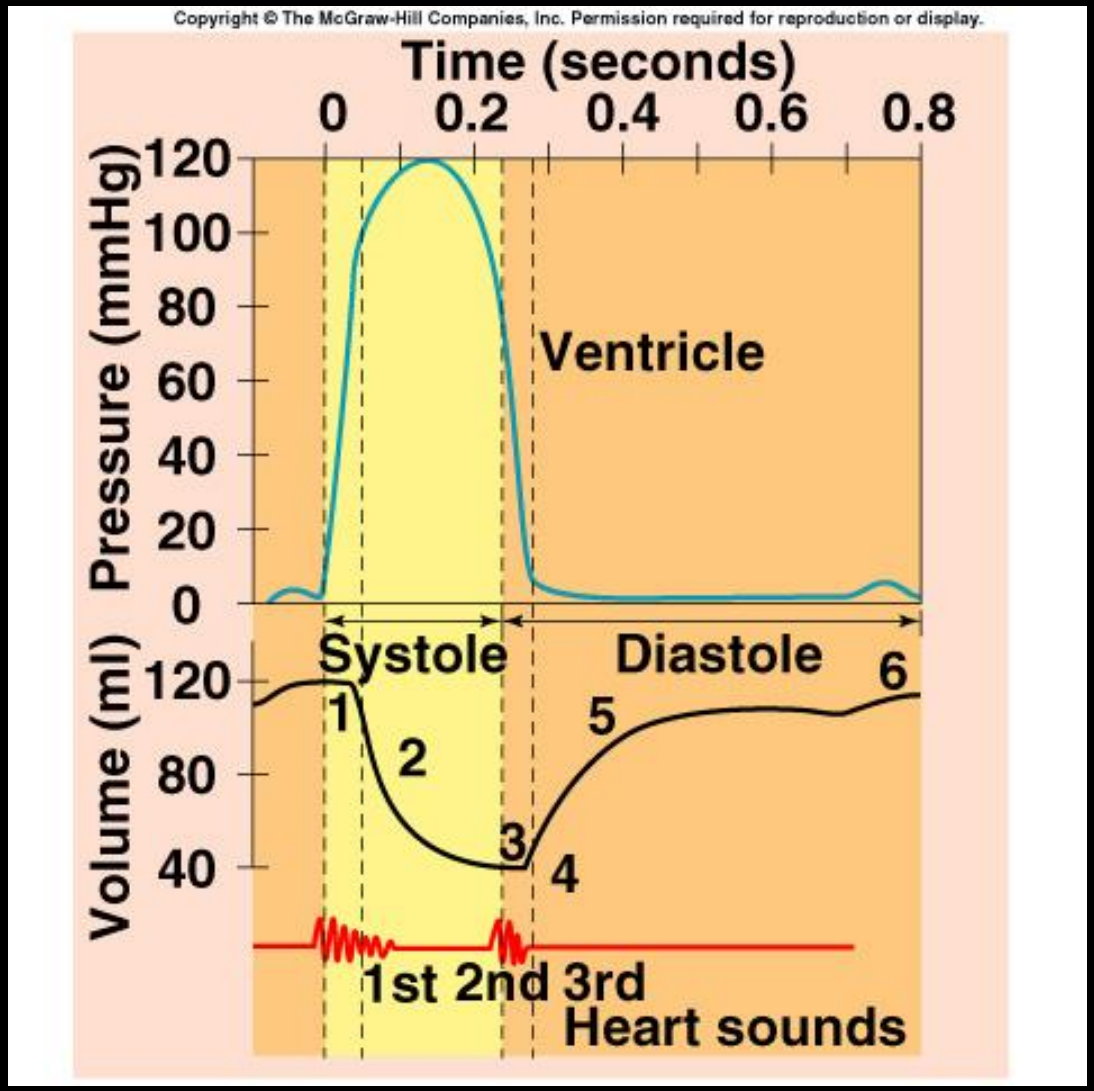
- Step 1: Isovolumetric contraction:
  - QRS just occurred.
  - Contraction of the ventricle causes ventricular pressure to rise above atrial pressure.
    - AV valves close.
  - Ventricular pressure is less than aortic pressure.
    - Semilunar valves are closed.
      - Volume of blood in ventricle is EDV.
- Step 2: Ejection:
  - Contraction of the ventricle causes ventricular pressure to rise above aortic pressure.
    - Semilunar valves open.
  - Ventricular pressure is greater than atrial pressure.
    - AV valves are closed.
      - Volume of blood ejected: SV.

Cardiac Cycle (continued)

- Step 3: T wave occurs:
  - Ventricular pressure drops below aortic pressure.
- Step 4: Isovolumetric relaxation:
  - Back pressure causes semilunar valves to close.
    - AV valves are still closed.
      - Volume of blood in the ventricle: ESV.
- Step 5: Rapid filling of ventricles:
  - Ventricular pressure decreases below atrial pressure.
    - AV valves open.
      - Rapid ventricular filling occurs.

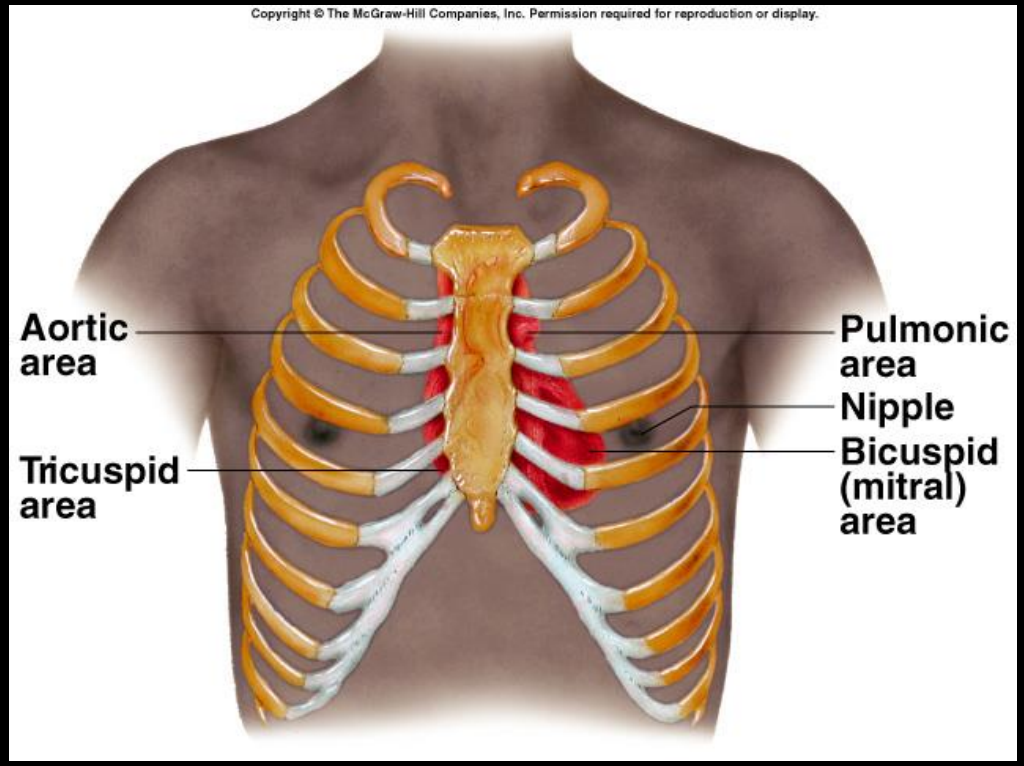
Cardiac Cycle (continued)

- Step 6: Atrial systole:
  - P wave occurs.
  - Atrial contraction.
    - Push 10-30% more blood into the ventricle.



Heart Sounds

- Closing of the AV and semilunar valves.
- Lub (first sound):
  - Produced by closing of the AV valves during isovolumetric contraction.
- Dub (second sound):
  - Produced by closing of the semilunar valves when pressure in the ventricles falls below pressure in the arteries.

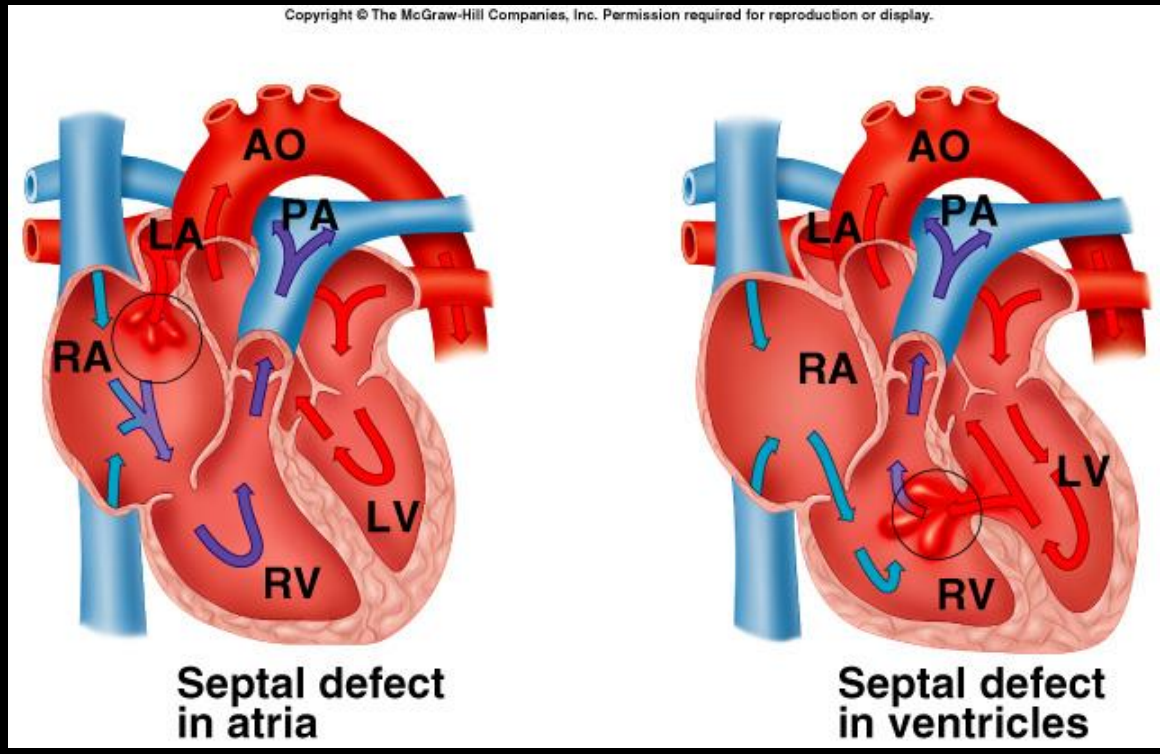


Heart Murmurs

- Abnormal heart sounds produced by abnormal patterns of blood flow in the heart.
- Defective heart valves:
  - Valves become damaged by antibodies made in response to an infection, or congenital defects.
- Mitral stenosis:
  - Mitral valve becomes thickened and calcified.
    - Impairs blood flow from left atrium to left ventricle.
    - Accumulation of blood in left ventricle may cause pulmonary HTN.
- Incompetent valves:
  - Damage to papillary muscles.
    - Valves do not close properly.
      - Murmurs produced as blood regurgitates through valve flaps.

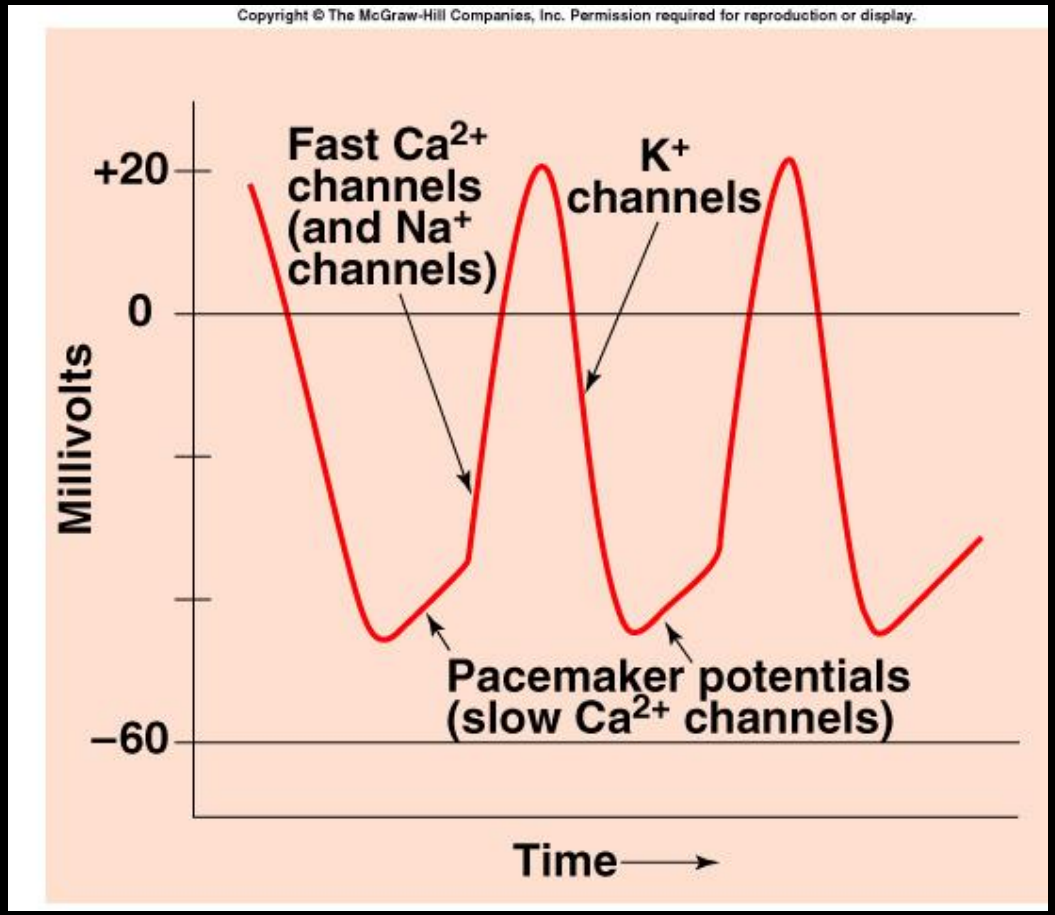
Heart Murmurs

- Septal defects:
  - Usually congenital.
    - Holes in septum between the left and right sides of the heart.
    - May occur either in interatrial or interventricular septum.
  - Blood passes from left to right.



Electrical Activity of the Heart

- SA node:
  - Demonstrates automaticity:
    - Functions as the pacemaker.
  - Spontaneous depolarization (pacemaker potential):
    - Spontaneous diffusion caused by diffusion of Ca^{2+} through slow Ca^{2+} channels.
      - Cells do not maintain a stable RMP.



Pacemaker AP

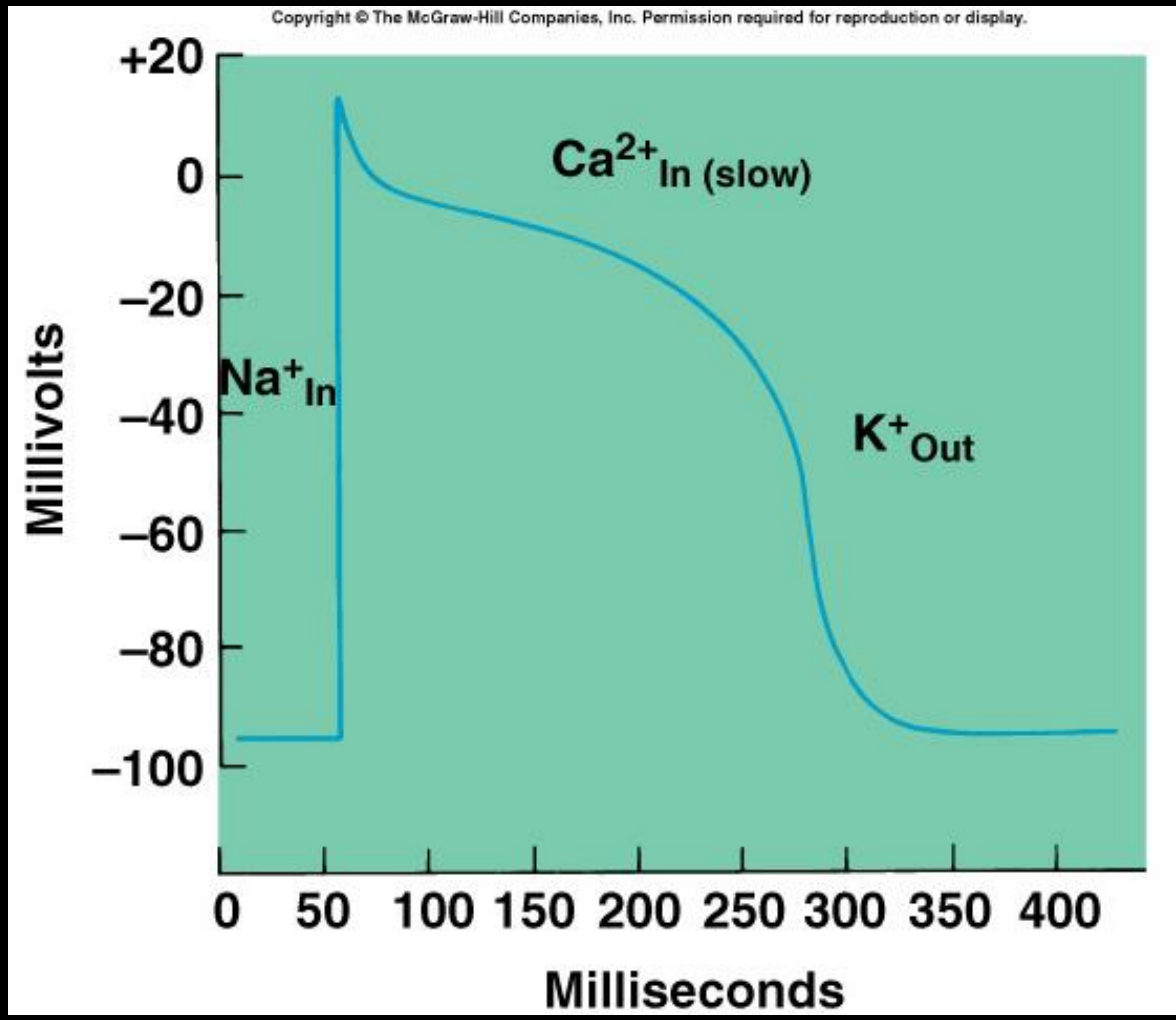
- Depolarization:
  - VG fast Ca^{2+} channels open.
    - Ca^{2+} diffuses inward.
  - Opening of VG Na^{+} channels may also contribute to the upshoot phase of the AP.
- Repolarization:
  - VG K^{+} channels open.
    - K^{+} diffuses outward.
- Ectopic pacemaker:
  - Pacemaker other than SA node:
    - If APs from SA node are prevented from reaching these areas, these cells will generate pacemaker potentials.

Myocardial APs

- Majority of myocardial cells have a RMP of –90 mV.
- SA node spreads APs to myocardial cells.
  - When myocardial cell reaches threshold, these cells depolarize.
- Rapid upshoot occurs:
  - VG Na^+ channels open.
    - Inward diffusion of Na^+.
- Plateau phase:
  - Rapid reversal in membrane polarity to –15 mV.
    - VG slow Ca^{2+} channels open.
      - Slow inward flow of Ca^{2+} balances outflow of K^+.

Myocardial APs (continued)

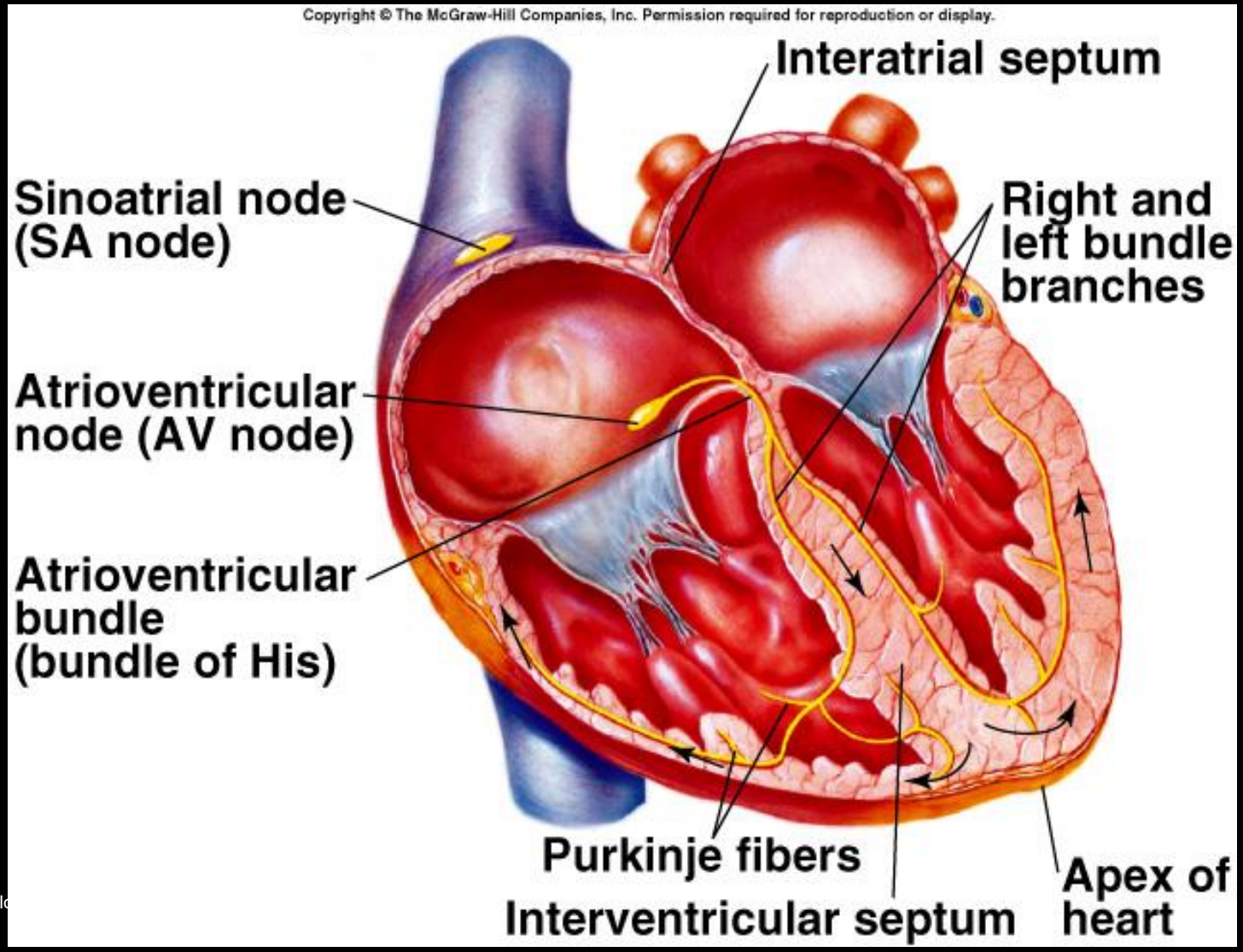
- Rapid repolarization:
  - VG K^+ channels open.
  - Rapid outward diffusion of K^+.



Conducting Tissues of the Heart

- APs spread through myocardial cells through gap junctions.
- Impulses cannot spread to ventricles directly because of fibrous tissue.
- Conduction pathway:
  - SA node.
  - AV node.
  - Bundle of His.
  - Purkinje fibers.
- Stimulation of Purkinje fibers cause both ventricles to contract simultaneously.

Conducting Tissues of the Heart (continued)

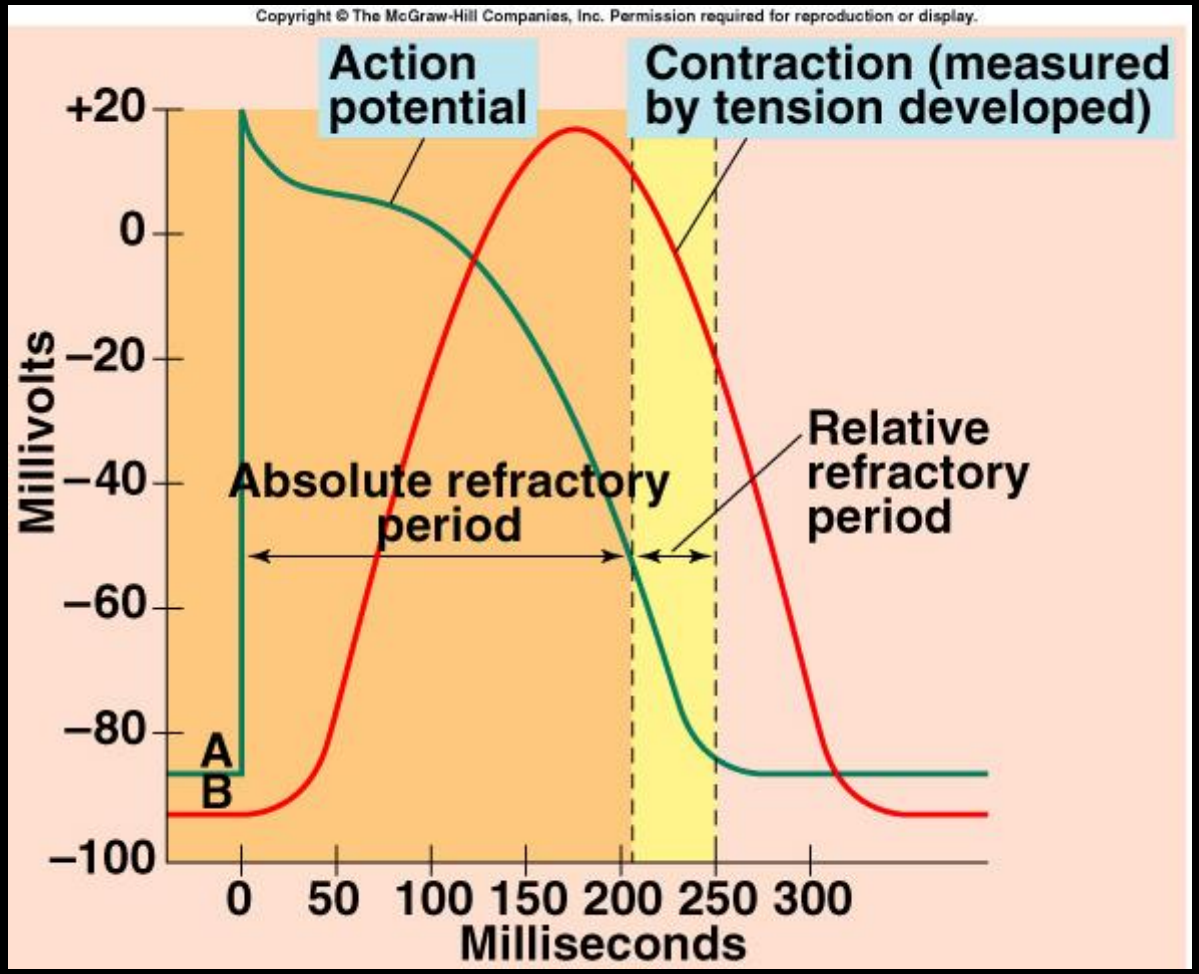


Conduction of Impulse

- APs from SA node spread quickly at rate of 0.8 - 1.0 m/sec.
- Time delay occurs as impulses pass through AV node.
  - Slow conduction of 0.03 – 0.05 m/sec.
- Impulse conduction increases as spread to Purkinje fibers at a velocity of 5.0 m/sec.
  - Ventricular contraction begins 0.1–0.2 sec. after contraction of the atria.

Refractory Periods

- Heart contracts as syncytium.
- Contraction lasts almost 300 msec.
- Refractory periods last almost as long as contraction.
- Myocardial muscle cannot be stimulated to contract again until it has relaxed.
  - Summation cannot occur.



Excitation-Contraction Coupling in Heart Muscle

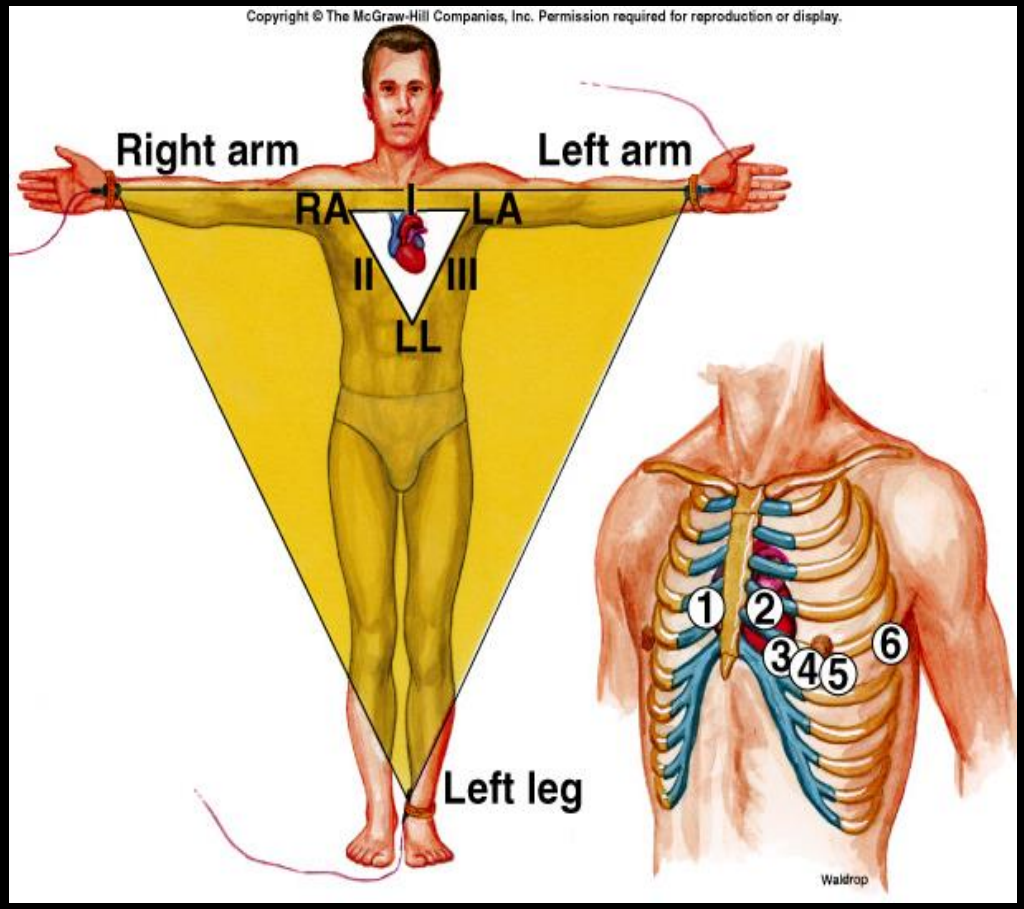
- Depolarization of myocardial cell stimulates opening of VG Ca^{2+} channels in sarcolema.
  - Ca^{2+} diffuses down gradient into cell.
    - Stimulates opening of Ca^{2+}-release channels in SR.
  - Ca^{2+} binds to troponin and stimulates contraction (same mechanisms as in skeletal muscle).
- During repolarization Ca^{2+} actively transported out of the cell via a Na^{+}-Ca^{2+}- exchanger.

Electrocardiogram (ECG/EKG)

- The body is a good conductor of electricity.
  - Tissue fluids have a high [ions] that move in response to potential differences.
- Electrocardiogram:
  - Measure of the **electrical activity** of the heart per unit time.
    - Potential differences generated by heart are conducted to body surface where they can be recorded on electrodes on the skin.
- Does **NOT** measure the flow of blood through the heart.

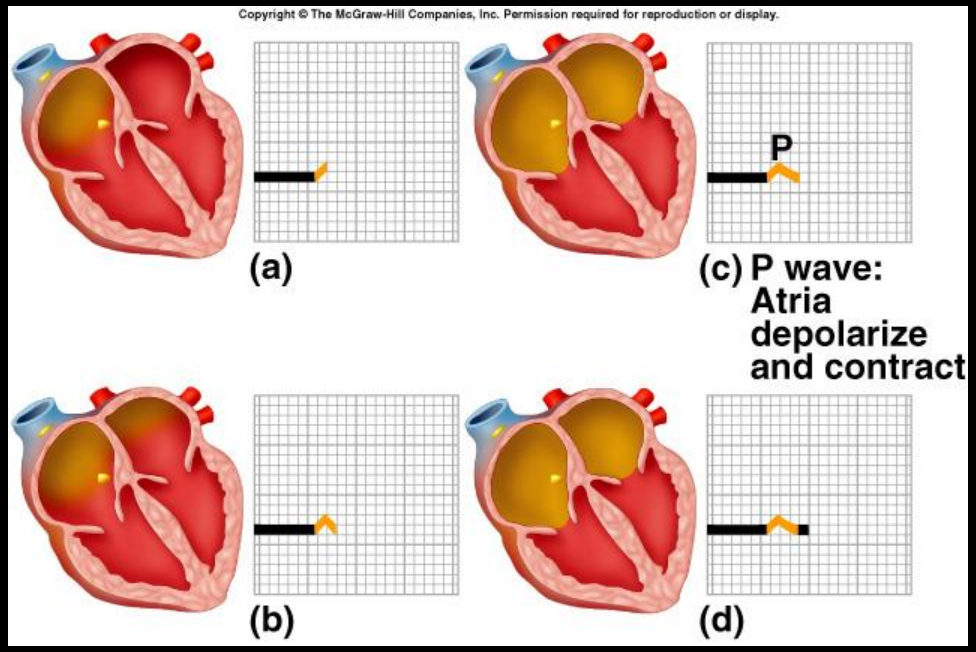
ECG Leads

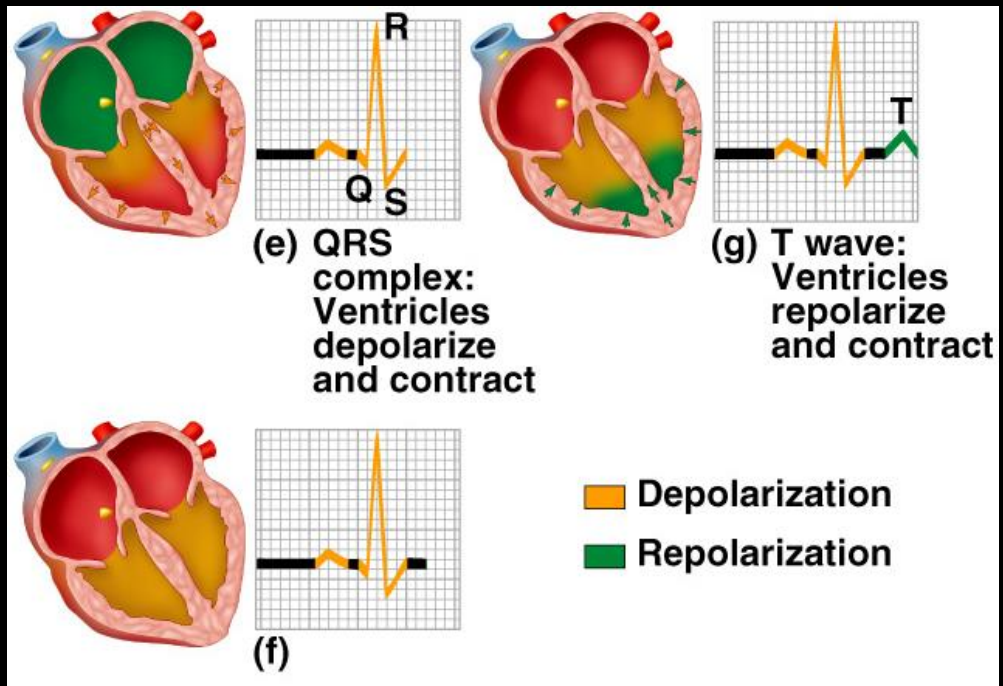
- Bipolar leads:
  - Record voltage between electrodes placed on wrists and legs.
  - Right leg is ground.
- Unipolar leads:
  - Voltage is recorded between a single "exploratory electrode" placed on body and an electrode built into the electrocardiograph.
  - Placed on right arm, left arm, left leg, and chest.
    - Allow to view the changing pattern of electrical activity from different perspectives.



ECG

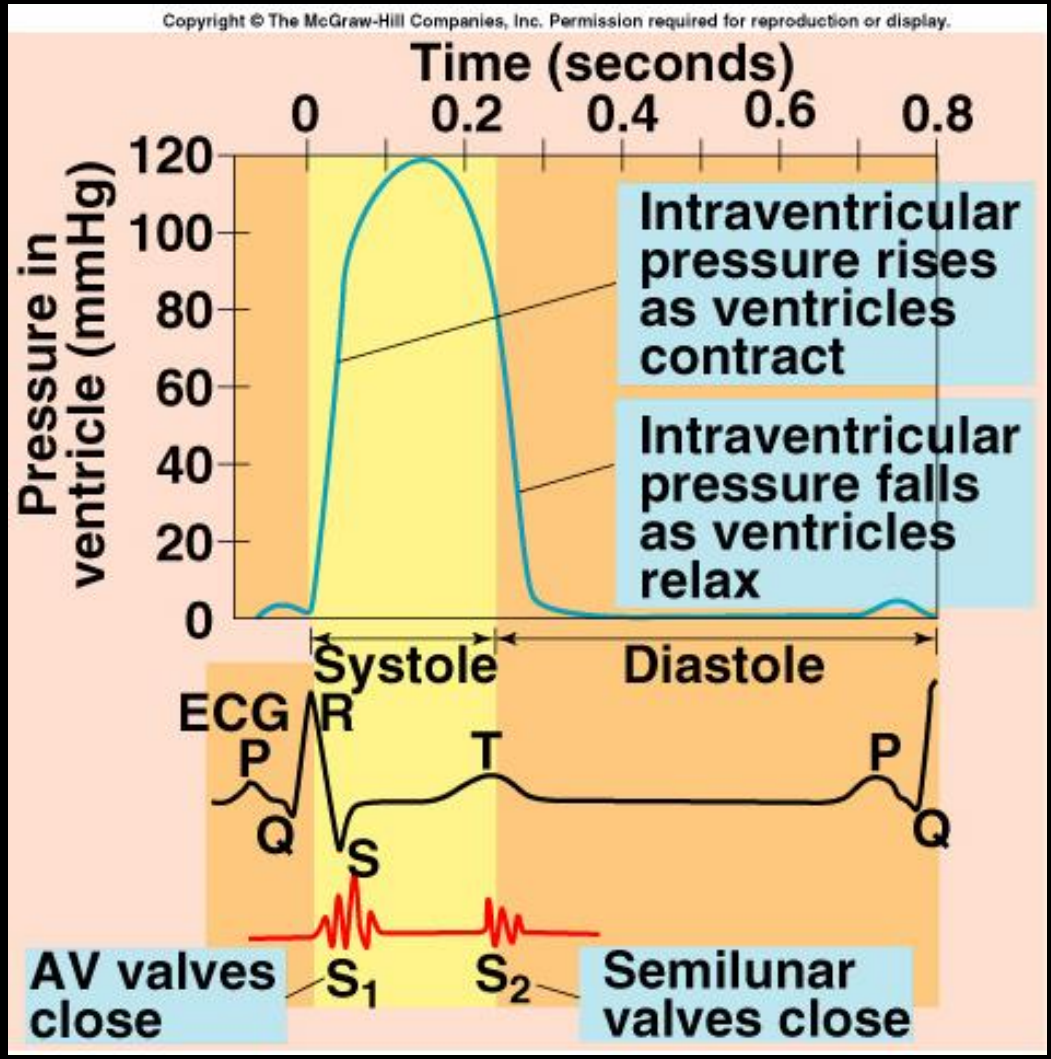
- P wave:
  - Atrial depolarization.
- QRS complex:
  - Ventricular depolarization.
  - Atrial repolarization.
- T wave:
  - Ventricular repolarization.





Correlation of ECG with Heart Sounds

- First heart sound:
  - Produced immediately after QRS wave.
  - Rise of intraventricular pressure causes AV valves to close.
- Second heart sound:
  - Produced after T wave begins.
  - Fall in intraventricular pressure causes semilunar valves to close.



Systemic Circulation

- Arteries.
- Arterioles.
- Capillaries.
- Venules.
- Veins.

- Role is to direct the flow of blood from the heart to the capillaries, and back to the heart.

Blood Vessels

- Walls composed of 3 “tunics:”
  - Tunica externa:
    - Outer layer comprised of connective tissue.
  - Tunica media:
    - Middle layer composed of smooth muscle.
  - Tunica interna:
    - Innermost simple squamous endothelium.
    - Basement membrane.
    - Layer of elastin.

Blood Vessels (continued)

- Elastic arteries:
  - Numerous layers of elastin fibers between smooth muscle.
    - Expand when the pressure of the blood rises.
      - Act as recoil system when ventricles relax.
- Muscular arteries:
  - Are less elastic and have a thicker layer of smooth muscle.
  - Diameter changes slightly as BP raises and falls.
- Arterioles:
  - Contain highest % smooth muscle.
    - Greatest pressure drop.
    - Greatest resistance to flow.

Blood Vessels (continued)

- Most of the blood volume is contained in the venous system.
  - Venules:
    - Formed when capillaries unite.
      - Very porous.
  - Veins:
    - Contain little smooth muscle or elastin.
      - Capacitance vessels (blood reservoirs).
    - Contain 1-way valves that ensure blood flow to the heart.
- Skeletal muscle pump and contraction of diaphragm:
  - Aid in venous blood return of blood to the heart.

Types of Capillaries

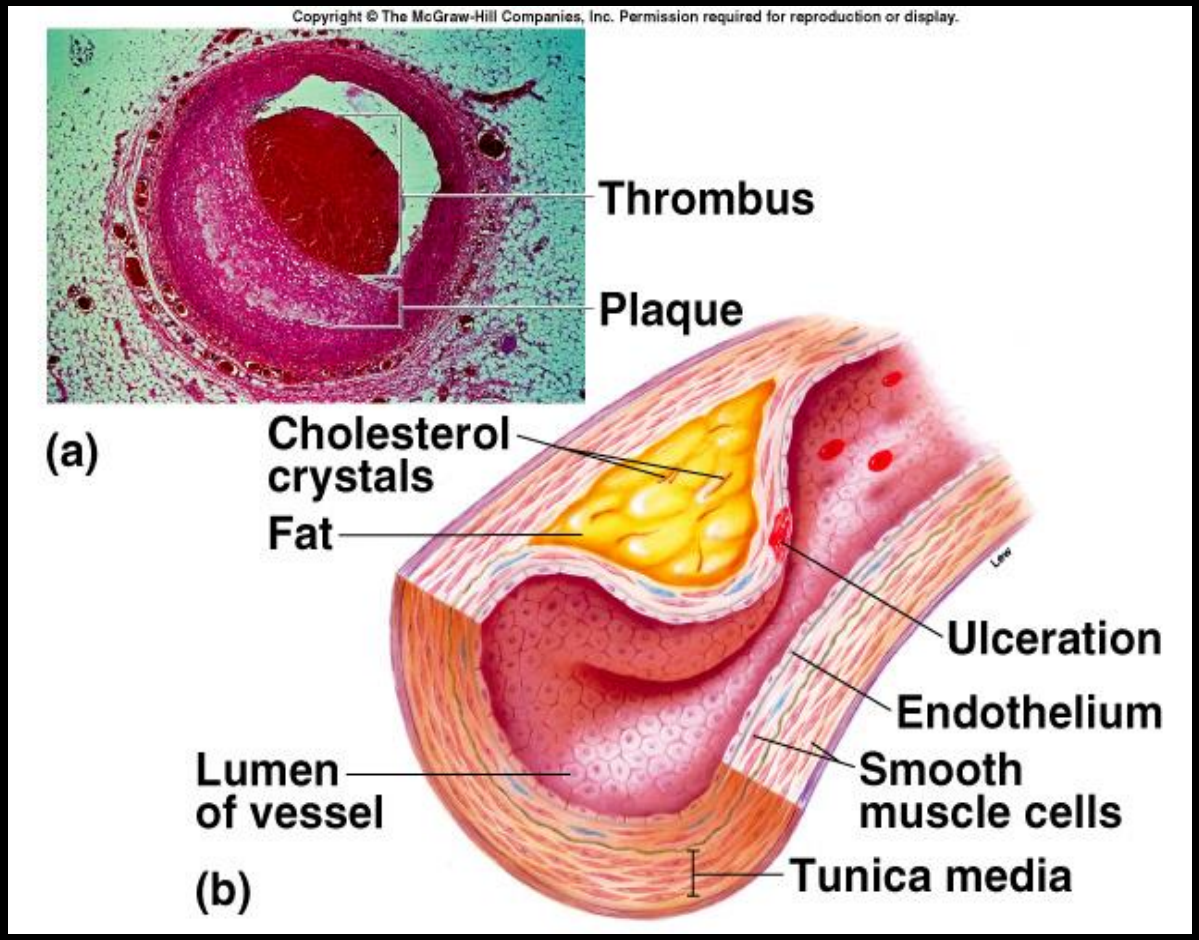
- Capillaries:
  - Smallest blood vessels.
    - 1 endothelial cell thick.
      - Provide direct access to cells.
        - Permits exchange of nutrients and wastes.
  - Continuous:
    - Adjacent endothelial cells tightly joined together.
      - Intercellular channels that permit passage of molecules (other than proteins) between capillary blood and tissue fluid.
        - Muscle, lungs, and adipose tissue.
  - Fenestrated:
    - Wide intercellular pores.
      - Provides greater permeability.
        - Kidneys, endocrine glands, and intestines.
  - Discontinuous (sinusoidal):
    - Have large, leaky capillaries.
      - Liver, spleen, and bone marrow.

Atherosclerosis

- Most common form of arteriosclerosis (hardening of the arteries).
- Mechanism of plaque production:
  - Begins as a result of damage to endothelial cell wall.
    - HTN, smoking, high cholesterol, and diabetes.
  - Cytokines are secreted by endothelium; platelets, macrophages, and lymphocytes.
    - Attract more monocytes and lymphocytes.

Atherosclerosis (continued)

- Monocytes become macrophages.
  - Engulf lipids and transform into foam cells.
- Smooth muscle cells synthesize connective tissue proteins.
  - Smooth muscle cells migrate to tunica interna, and proliferate forming fibrous plaques.



Cholesterol and Plasma Lipoproteins

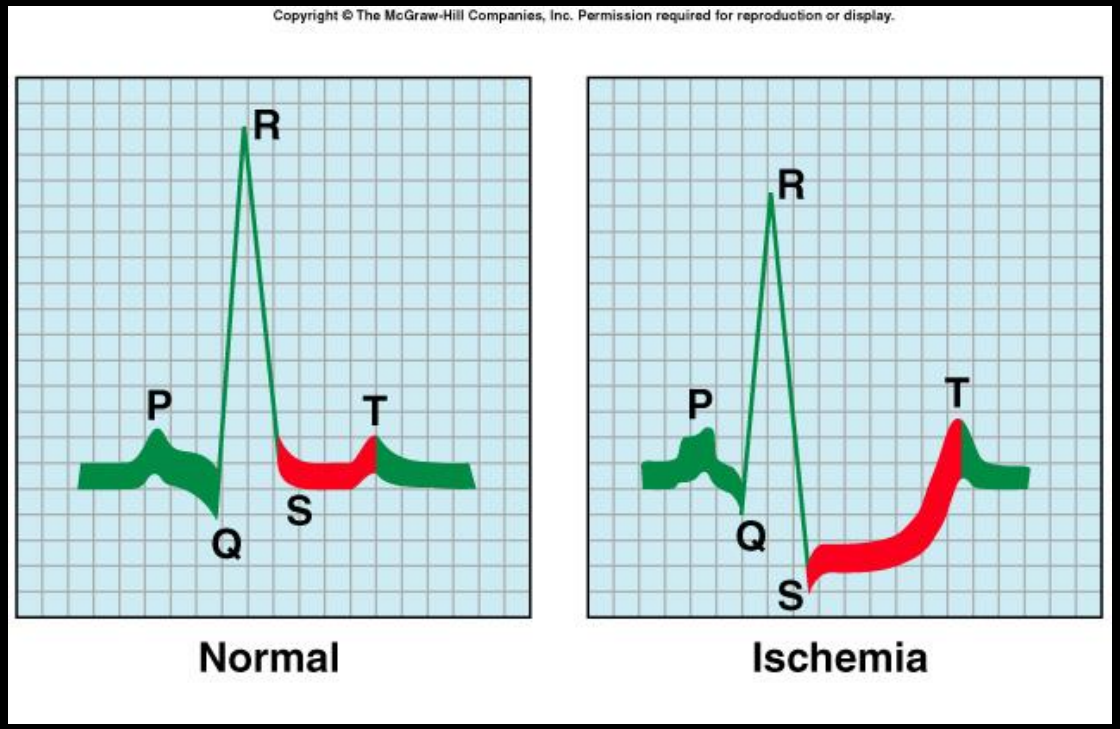
- High blood cholesterol associated with risk of atherosclerosis.
- Lipids are carried in the blood attached to protein carriers.
- Cholesterol is carried to the arteries by LDLs (low-density lipoproteins).
  - LDLs are produced in the liver.
    - LDLs are small protein-coated droplets of cholesterol, neutral fat, free fatty acids, and phospholipids.

Cholesterol and Plasma Lipoproteins
(continued)

- Cells in various organs contain receptors for proteins in LDL.
  - LDL protein attaches to receptors.
    - The cell engulfs the LDL and utilizes cholesterol for different purposes.
    - LDL is oxidized and contributes to:
      - Endothelial cell injury.
      - Migration of monocytes and lymphocytes to tunica interna.
      - Conversion of monocytes to macrophages.
  - Excessive cholesterol is released from the cells.
    - Travel in the blood as HDLs (high-density lipoproteins), and removed by the liver.
      - Artery walls do not have receptors for HDL.

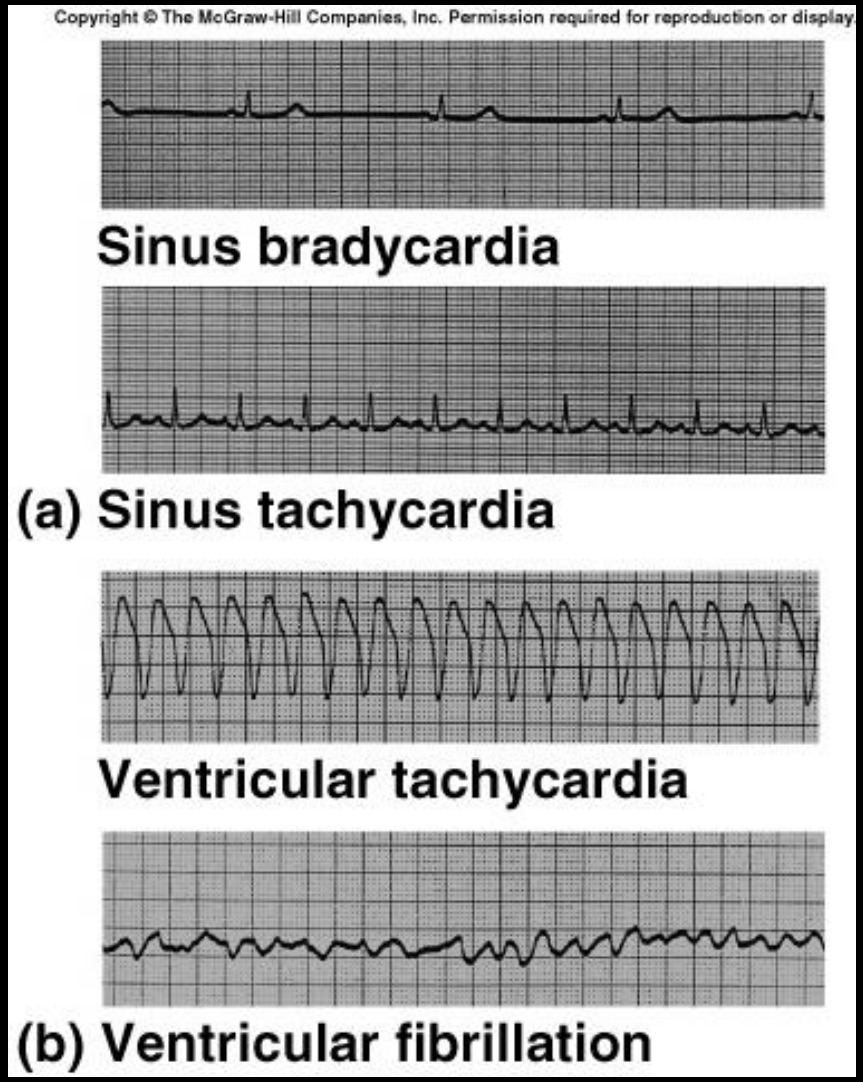
Ischemic Heart Disease

- Ischemia:
  - Oxygen supply to tissue is deficient.
    - Most common cause is atherosclerosis of coronary arteries.
  - Increased [lactic acid] produced by anaerobic respiration.
- Angina pectoris:
  - Substernal pain.
- Myocardial infarction (MI):
  - Changes in T segment of ECG.
  - Increased CPK and LDH.



Arrhythmias Detected on ECG

- Arrhythmias:
  - Abnormal heart rhythms.
- Flutter:
  - Extremely rapid rates of excitation and contraction of atria or ventricles.
    - Atrial flutter degenerates into atrial fibrillation.
- Fibrillation:
  - Contractions of different groups of myocardial cells at different times.
    - Coordination of pumping impossible.
      - Ventricular fibrillation is life-threatening.

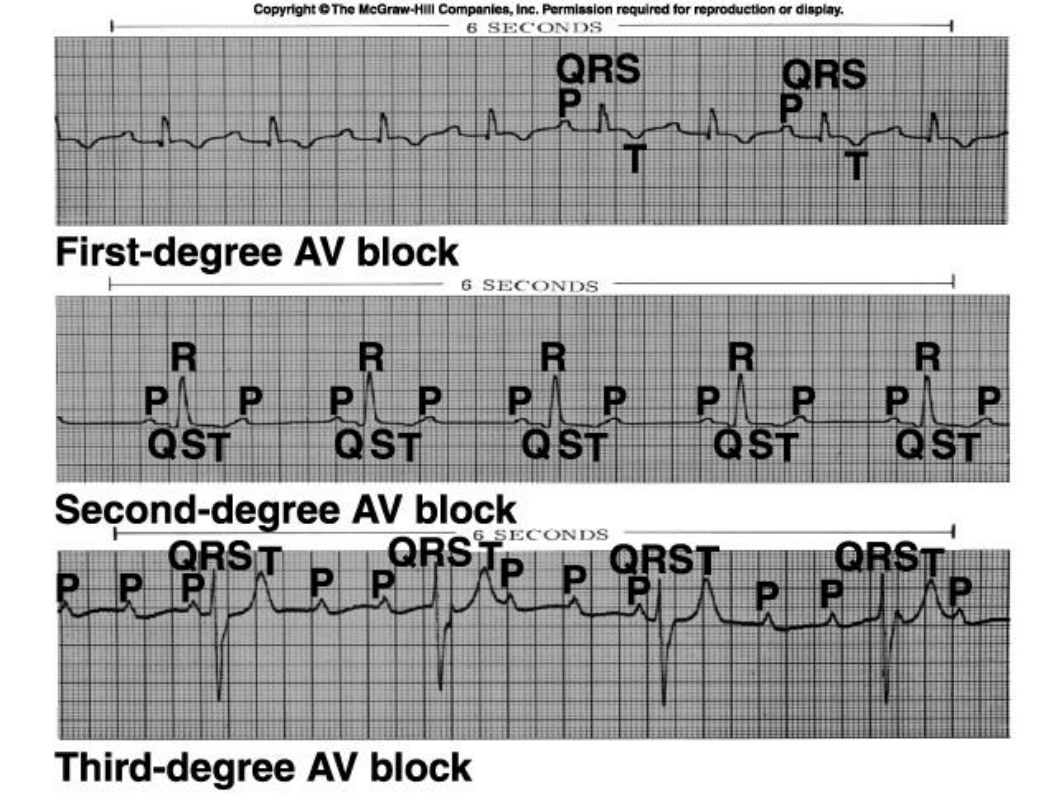


Arrhythmias Detected on ECG (continued)

- Bradycardia:
  - HR slower < 60 beats/min.
- Tachycardia:
  - HR > 100 beats/min.
- First–degree AV nodal block:
  - Rate of impulse conduction through AV node exceeds 0.2 sec.
    - P-R interval.
- Second-degree AV nodal block:
  - AV node is damaged so that only 1 out of 2-4 atrial APs can pass to the ventricles.
    - P wave without QRS.

Arrhythmias Detected on ECG (continued)

- Third-degree (complete) AV nodal block:
  - None of the atrial waves can pass through the AV node.
  - Ventricles paced by ectopic pacemaker.

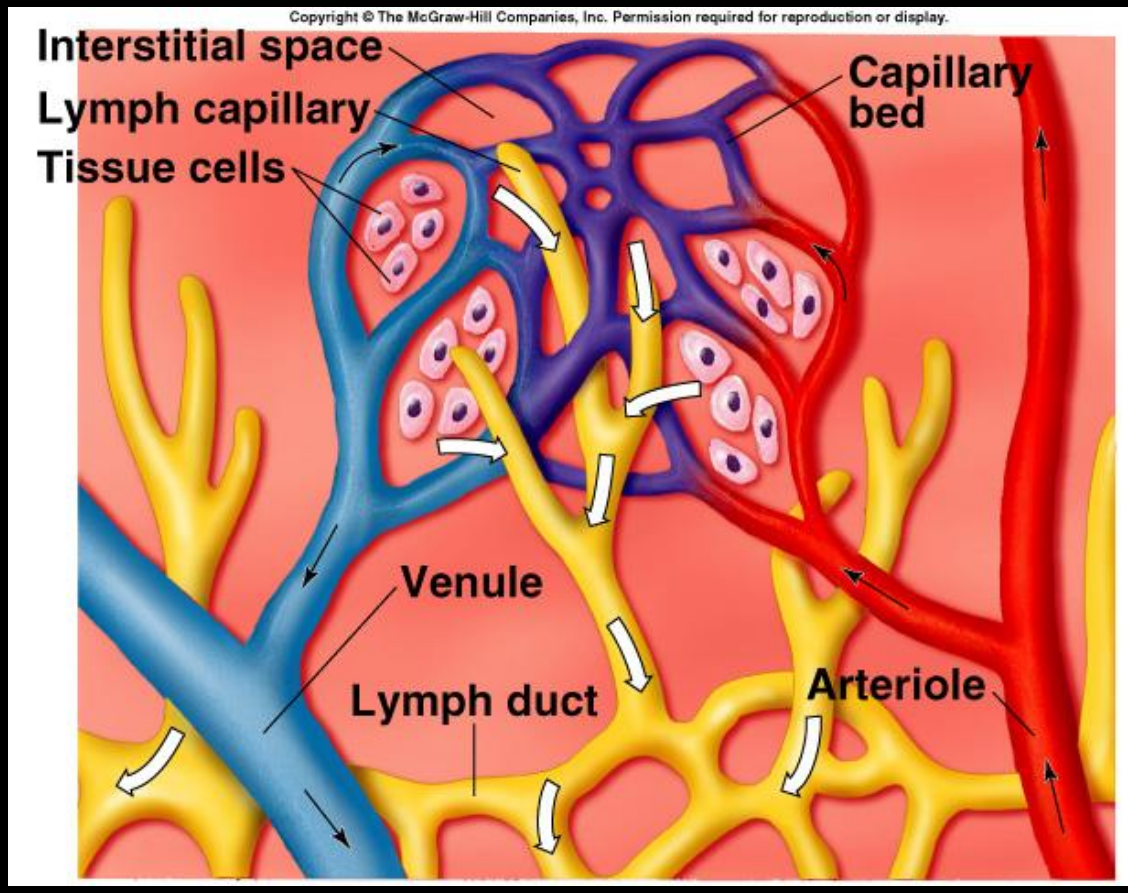


Lymphatic System

- 3 basic functions:
  - Transports interstitial (tissue) fluid back to the blood.
  - Transports absorbed fat from small intestine to the blood.
  - Helps provide immunological defenses against pathogens.

Lymphatic System (continued)

- Lymphatic capillaries:
  - Closed-end tubules that form vast networks in intercellular spaces.
- Lymph:
  - Fluid that enters the lymphatic capillaries.
    - Lymph carried from lymph capillaries, to lymph ducts, and then to lymph nodes.
  - Lymph nodes filter the lymph before returning it to the veins.



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