Case 3: Path of the Heart

Block 4 Module 2

COMPONENTS OF THE VASCULATURE

ARTERIES	ARTERIOLES	CAPILLARIES	VENULES	VEINS
• A series of vessels that transport blood away from the heart by branching into vessels of smaller and smaller diameter, eventually branching into capillaries to supply all regions of the body with oxygenated blood • Have smaller diameter than their venous counterparts • Are thick-walled and under high pressure • The blood volume contained in arteries is called the stressed volume	• Are the smallest branches of the arteries with a diameter of less than 0.1 mm • The width of the wall is approximately equal to the diameter of its lumen • The endothelium of the tunica intima is supported by a thin subendothelial connective tissue layer consisting of type III collagen and a few elastic fibers embedded in ground substance • A thin, fenestrated internal elastic lamina is absent in small and terminal arterioles but present in larger arterioles. • Do not have external elastic lamina • In small arterioles, the tunica media is composed of a single smooth muscle cell layer that completely encircles the endothelial cells. • In larger arterioles, the tunica media consists of 2-3 layers of smooth muscle cells. • The tunica adventitia is scant and is represented by fibroelastic connective tissue housing a few fibroblast • Are the site of highest resistance in the CVS • Have a smooth muscle wall that is extensively innervated by autonomic fibers • Arteriolar resistance is regulated by the autonomic nervous system	• Have the largest total cross-sectional and surface area. • The smallest blood vessels, approximately 50 um in length with a diameter of 8-10 um. • Are formed by a single layer of squamous endothelial cells rolled into a tube, with the long axis of these cells lying in the same direction as the blood flow • The cytoplasm contains a Golgi complex, a few mitochondria, some rough endoplasmic reticulum (RER), and free ribosomes • Intermediate filaments located around the perinuclear zone vary in filament composition. These filaments (desmin and vimentin) provide structural support to the endothelial cells, but the significance of their variation is unclear. • The large number of pinocytotic vesicles associated with the entire plasmalemma is an identifying characteristic of capillaries • The external surfaces of the endothelial cells are surrounded by a basal lamina secreted by the endothelial cells • Endothelial cells are joined together by fasciae occludentes, or tight junctions • Are the site of exchange of nutrients, water, and gases	• Their walls are similar to but larger than capillaries, with a thin endothelium surrounded by reticular fibers and pericytes but larger venules possess smooth muscle cells instead of pericytes. • The endothelial cells of venules located in certain lymphoid organs are cuboidal rather than squamous and are called high – endothelial venules. ○ These function in lymphocytic recognition and segregation by type-specific receptors on their luminal surface, ensuring that specific lymphocytes migrate into the proper regions of the lymphoid parenchyma. • Are innervated by autonomic fibers.	• Large veins include the vena cavae and the pulmonary, portal, renal, internal jugular, iliac, and azygos veins • Progressively merge to form large veins, eventually, the venae cavae (inferior and superior), to return blood to the heart from the extremities, head, liver, and body wall • Contain the highest proportion of the blood in the CVS. • The blood volume contained in the veins is called unstressed volume

LAYERS OF THE ARTERY

- **Tunica Intima**
  - innermost layer made up of:

Endothelium	• Composed of a single layer of flattened squamous epithelial cells, which form a tube lining the lumen of the vessel • Endothelial cells not only provide an exceptionally smooth surface but also function in secreting types II, IV, and V collagens, lamin, endothelin, nitric oxide, and Von Willebrand factor. • Also possess membrane-bound enzymes, such as angiotensin- converting enzyme (ACE), which cleaves angiotensin I to generate angiotensin II, as well as enzymes that inactivate bradykinin, serotonin, prostaglandins, thrombin, and norepinephrine. • They also bind lipoprotein lipase, the enzyme that degrades lipoproteins. • Von Willebrand factor facilitates the coagulation of platelets during clot formation and is stored only in arteries
Subendothelial Layer	• Lies immediately beneath the endothelial cells • Composed of loose connective tissue and a few scattered smooth muscle cells, both arranged longitudinally
Internal Elastic Lamina	• ·Especially well developed in muscular arteries • Marks the boundary between the tunica intima and tunica media • Composed of elastin, which is a fenestrated sheet that permits the diffusion of substances into the deeper regions of the arterial wall to nourish the cells there.

- **Tunica Media**
  - The thickest layer of the vessel wall
  - Composed of mostly helically arranged smooth muscle cells
  - Interspersed within the layers of smooth muscles are some elastic fibers, type II collagen, and proteoglycans
  - External elastic lamina is present in larger muscular arteries which is more delicate than the internal elastic lamina and separates the tunica media from the overlying tunica adventitia
  - Capillaries and postcapillary venules do not have a tunica media, in these small vessels pericytes replace the tunica media
- **Tunica Adventitia**
  - The outermost layer of the blood vessel wall, blends into the surrounding connective tissue
  - Composed mostly of fibroblasts, type I collagen fibers and longitudinally oriented elastic fibers.

LAYERS OF THE VEIN

- Greater diameter than arteries
- Diameter increase at each convergence while arterial diameter continue to decrease at each branching
- Larger lumen, slit-like in appearance
- Walls are thinner and less elastic than arterial wall
- The 3 layers lack distinct boundaries particularly the boundaries between the tunica intima and the tunica media
- Only a few major vessels (such as pulmonary veins) have a well-developed smooth muscle layer and most large veins are without a tunica media; in its place is a well-developed tunica adventitia, an exception are the superficial veins of the legs, which have a well-defined muscular wall, perhaps to resist the distension caused by gravity.
- The muscular and elastic layers are not well developed but the connective tissue components are more pronounced than in arteries
- The thickest layer is the tunica adventitia and in large veins, this layer contain many elastic fibers, abundant collagen fibers, and vasa vasorum whereas the inferior vena cava has longitudinally arranged smooth muscle cells in its adventitia
- Veins with little or no smooth muscle in their walls are found in the retina, meninges, placenta, and penis.
- Have valves (medium vein) that function to prevent backflow of blood

DIFFERENTIATING THE FEATURES OF ARTERIES AND VEINS

	ARTERIES	VEINS
Overall diameter	• Lesser	• Greater
Thickness of the Wall and Shape of Lumen	• Thicker • More elastic and less likely to collapse after death • Lumen is more regular	• Thinner • Less elastic that's why it collapses during death • Lumen is slit-like or irregular in shape
Diameter of lumen in relation to the thickness of the wall	• Lesser than the thickness of the wall except in large arteries • The smaller the artery the thicker the wall is compared to the size of lumen	• Relatively thin wall and relatively larger lumen
Three coats	• Well demarcated and distinguishable from each other	• More loosely constructed that's why the 3 coats lack distinct boundaries
Internal elastic lamina	• Present and well developed in medium sized arteries	• Present only in large veins
Thickest coat	• Tunica media	• Tunica adventitia
Muscle and Tissue	• More of smooth muscles and elastic tissue	• Lesser amount of smooth muscles and elastic fibers • More connective tissues
Valves	• Absent	• Present especially in the lower extremities (medium veins)
Vasa vasorum	• Fewer and prominent in tunica media and tunica adventitia of elastic artery	• More prevalent in the walls (Tunica adventitia of large veins)
Blood Content	• Because of agonal contraction at the moment of death, it is usually empty • Internal elastic membrane appears scalloped	• Because of weaker agonal contraction the lumen may contain blood

TYPES OF ARTERIES AND THEIR CHARACTERISTICS

ARTERY	TUNICA INTIMA	TUNICA MEDIA	TUNICA ADVENTITIA
1. Elastic Artery (conducting) e.g. Aorta	• Endothelium with Weibel-Palade bodies, basal lamina, subendothelial layer, incomplete internal elastic lamina	• 40 to 70 striated elastic membranes • Smooth muscle cells interspersed between elastic membranes • Thin external elastic lamina • Vasa vasorum in outer half	• Thin layer of fibroelastic connective tissue • Vasa vasorum • Lymphatic vessels • Nerve fibers
2. Muscular Artery (distributing) e.g. Femoral Artery	• Endothelium with Weibel-Palade bodies, basal lamina, subendothelial layer, thick internal elastic lamina	• Up to 40 layers of smooth muscle cells • Thick external elastic lamina	• Thin layer of fibroelastic connective tissue • Vasa vasorum not very prominent • Lymphatic vessels • Nerve fibers
3. Arteriole	• Endothelium with Weibel-Palade bodies, basal lamina, subendothelial layer not very prominent, some elastic fibers instead of defined internal elastic lamina	• One or two layers of smooth muscle cless	• Loose connective tissue • Nerve fibers
4. Metarteriole	• Endothelium, Basal Lamina	• Smooth muscle cells form Precapillary sphincter	• Sparse • Loose connective tissue

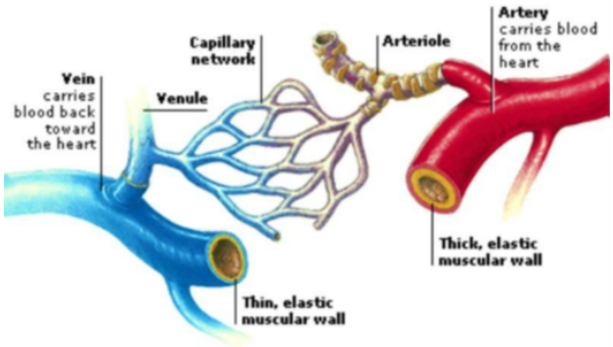
TYPES OF VEINS AND THEIR CHARACTERISTICS

VEINS	TUNICA INTIMA	TUNICA MEDIA	TUNICA ADVENTITIA
1. Large Veins	• **Endothelium:** basal lamina, valves in some, subendothelial connective tissue	• Connective tissue: smooth muscle cells	• Smooth muscle cells oriented in longitudinal bundles: cardiac muscle cells near their entry into the heart; collagen layers with fibroblasts
2. Medium and Small veins	• **Endothelium:** basal lamina, valves in some, subendothelial connective tissue	• Reticular and elastic fibers, some smooth muscle cells	• Collagen layers with fibroblasts
3. Venules	• **Endothelium**: basal lamina (pericytes, postcapillary venules)	• Sparse connective tissue and a few smooth muscle cells	• Some collagen and a few fibroblasts

CAPILLARIES

- The smallest blood vessels
- Composed of a single layer of squamous endothelial cells
- The large number of pinocytotic vesicles associated with the entire plasmalemma is an identifying characteristic of capillaries.
  - These vesicles may be in singular array, two singles may be fused together, or several vesicles may be fused, forming a transient channel
- The external surface of the endothelial cells are surrounded by a basal lamina.
- Pericytes are located along the outside of the capillaries and small venules, and appear to be surrounding them.
  - Pericytes share the basal lamina of the endothelial cells.

1.Continuous capillaries	• Have no pores/fenestrae in their walls • Present in muscle, nervous, and connective tissues, whereas in the brain tissue they are classified as modified continuous capillaries. • The intercellular junctions between their endothelial cells are a type of fasciae occludentes, which prevent passage of many molecules. • Substances such as amino acids, glucose, nucleosides, and purines move across the capillary wall via carrier-mediated transport
2. Fenestrated capillaries	• Have pores (fenestrae) in their walls that are covered by pore diaphragm. • Found in the pancreas, intestines and endocrine glands. • The pores are bridged by an ultrathin diaphragm. • These pore-diaphragm complexes are located in clusters, thus, most of the endothelial wall of the fenestrated capillary is without fenestrae – an exception is the renal glomerulus, composed of fenestrated capillaries that lack diaphragm
3. Sinusodial capillaries	• May possess discontinuous endothelial cells and basal lamina and many contain many large fenestrae without diaphragms, enhancing exchange between blood and tissue. • Because of their location, sinusoidal capillaries have an enlarged diameter of 30 - 40 um. • Are lined by endothelium • The vascular channels in certain organs of the body, including the bone marrow, liver, spleen, lymphoid organs, and certain endocrine glands are called sinusoids, irregular blood pools, or channels that conform to the shape of the structure in which they are located



STRUCTURAL CHARACTERISTICS OF THE VASCULAR SYSTEM AND THEIR FUNCTIONAL SIGNIFICANCE

CAPACITIES, PERCENTAGE DISTRIBUTION OF BLOOD IN THE VASCULAR TREE

Capacitance (Compliance)

- Describes the distensibility of blood vessels
- Can be expressed by the following equation: C= V/P
  - C- capacitance (ml/mmHg)
  - V- volume (ml)
  - P- pressure (mmHg)
- Is directly proportional to volume and inversely proportional to pressure.
- Is much greater for veins than arteries.
  - As a result, more blood volume is contained in the veins (unstressed volume) than in the arteries (stressed volume)
- Changes in the capacitance of the veins produce changes in unstressed volume.
  - For example, a decrease in venous capacitance decreases the unstressed volume and increase stressed volume by shifting blood from the veins to the arteries.
- Capacitance of the arteries decreases as a person ages; therefore, the arteries becomes less distensible.

VELOCITY OF BLOOD FLOW AND CROSS-SECTIONAL AREA

- Can be expressed by the following equation:
  - V = Q/A
    - V - velocity (cm/sec)
    - Q - Blood flow (ml/min)
    - A - cross-sectional area (cm2)
- Velocity is directly proportional to blood flow and inversely proportional to the cross-sectional area at any level of the CVS.
- For example, blood velocity is higher in the aorta (small cross-sectional area) than in the sum of all the capillaries (large cross-sectional area).
- The lower velocity of blood flow in the capillaries optimizes the exchange of substances across the capillary wall.
- Blood flow:
  - Can be expressed by the following equation:

$$Q = \Delta P / R \quad \text{or} \quad \text{Cardiac output} = \frac{\text{Mean arterial pressure} - \text{right atrial pressure}}{\text{Total peripheral resistance (TPR)}}$$

Q – Flow - cardiac output (ml/min)
ΔP – pressure gradient - pressure gradient (mmHg)
R – resistance - total peripheral resistance (mmHg / ml/min)

- The equation for blood flow (or cardiac output) is analogous to Ohm's law for electrical circuits (I = V / R), where blood flow is analogous to current and pressure is analogous to voltage.
- The pressure gradient (AP) drives blood flow.
  - It is the pressure difference (P1-P2) between the two ends of the vessel.
- Thus, blood flows from high pressure to low pressure, and flow is inversely proportional to the resistance of the blood vessels.

RESISTANCE

- Is directly proportional to the viscosity of the blood.
  - For example, increasing viscosity by increasing hematocrit will increase resistance and decrease flow.
- Is directly proportional to length of vessel.
- Is inversely proportional to the fourth power of the vessel radius.
  - This is a powerful relationship.
  - For example, if blood vessel radius decreases by a factor of 2, then resistance will increase by a factor of 16 (24) and flow will therefore decrease by a factor of 16.

Resistance in Parallel or Series:

- **Parallel Resistance**
  - is illustrated by the systemic circulation: each organ is supplied by an artery that branches off the aorta. The total resistance of this parallel arrangement is expressed in the following equation:

$$\frac{1}{R_{total}} = \frac{1}{R_a} + \frac{1}{R_b} + \cdots\cdots \frac{1}{R_n}$$

R_a, R_b, & R_n are the resistance of the renal, hepatic, and ....arteries, respectively. The total resistance is less than the resistance of any of the individual arteries.

- **Series Resistance**
  - Is illustrated by the arrangement of blood vessels within a given organ. Each organ is supplied by a large artery, smaller arteries, then arterioles, capillaries, and veins arranged in series.
  - The total resistance is the sum of the individual resistance, as expressed in the ff equation:

R total = R artery + R arterioles + R capillaries

POISEUILLE'S EQUATION

- Poiseuille equation - gives factors that change the resistance of blood vessels

$$R = \frac{8nl}{\pi r^4}$$

R – resistance
n - viscosity of blood
l – length of blood vessel
r^4 – radius of blood vessel to the 4th power

DIFFERENCE BETWEEN LAMINAR & TURBULENT FLOW

- **Laminar Flow**
  - Blood flows at a steady rate through a long, smooth vessel, it flows in streamlines, with each layer of blood remaining the same distance from the wall. The central portion of the blood stays in the center of the vessel.
- **Turbulent Flow**
  - Blood flowing in all directions in the vessel and continually mixing within the vessel.
- Laminar flow is streamlined (in a straight line), turbulent flow is not.

CAUSES OF TURBULENT BLOOD FLOW

- High blood flow velocity
- Obstruction in a vessel
- Sharp turn
- Rough surface
- Eddy currents - adds to friction

FACTORS AFFECTING TURBULENT FLOW

- Velocity of Blood flow (v) - cm/s
- Diameter of Blood vessel (d)
- Viscosity of Blood (n) + density (p) (poise)
- Formula:

$$Re = \frac{v \bullet d}{n/p}$$

REYNOLD'S EQUATION

- Reynold's number predicts whether blood flow will be laminar or turbulent
- **Reynold's Equation**
  - Re (Reynold's no.) = measure of the tendency for turbulence to occur
    - Re > 200 - 400 : turbulent flow at branches of vessels
    - Re > 2000 : turbulence even in straight smooth vessel
  - When Reynold's number is increased, there is a greater tendency for turbulence, which causes audible vibrations called bruits. Reynolds number (and therefore turbulence) is increased by the following factors:
    - ↓ blood viscosity (e.g. ↓ hematocrit, anemia)
    - ↑ blood velocity (e.g. narrowing of a vessel)

FLOW CONTINUITY EQUATION

Velocity of blood flow and cross-sectional area

- Can be expressed by the flow continuity equation:
  - v = Q/A
    - v - velocity (cm/sec)
    - Q - Blood flow (ml/min)
    - A - cross-sectional area (cm2)
- Velocity is directly proportional to blood flow and inversely proportional to the cross-sectional area at any level of the CVS.
- For example, blood velocity is higher in the aorta (small cross-sectional area) than in the sum of all the capillaries (large cross-sectional area).
- The lower velocity of blood flow in the capillaries optimizes the exchange of substances across the capillary wall.

BERNOULLI'S PRINCIPLE

- The greater the velocity of flow in a vessel, the lower the lateral pressure distending its wall.
- Clinical Significance:
  - When a vessel is narrowed by a pathologic process such as an arteriosclerotic plaque, the lateral pressure at the constriction is decreased and the narrowing tends to maintain itself.

LAW OF LAPLACE

- Law of Laplace states that tension is proportional to radius.
- The smaller the radius of a blood vessel, the lower the tension in the wall necessary to balance the distending pressure.
- Clinical Significance:
  - A dilated heart must do more work than a non-dilated heart. When the radius of a cardiac chamber is increased, a greater tension must be developed in the myocardium to produce any given pressure.

MECHANISM OF CRITICAL CLOSING PRESSURE IN BLOOD VESSELS AND THE FACTORS AFFECTING IT

- When pressure in a small blood vessel is reduced, a point is reached at which there is no flow of blood even though the pressure is not zero. The pressure at which flow ceases is called the critical closing pressure.
- This is in part a manifestation of the fact that it takes some pressure to force red cells through capillaries which have smaller diameter than the red cells.
- Also, the vessels are surrounded by tissues that exert a small but definite pressure on the vessels and when the intraluminal pressure falls below the tissue pressure, the vessels collapse

CASE 4
VENOUS PRESSURE AND FLOW

Definition of Terms

Central venous pressure (Right atrial pressure)
- Pressure in the right atrium

Peripheral venous pressure
- Pressure in the peripheral veins

Mean circulatory filling pressure
- Without blood flow, the pressures everywhere in the circulation become equal after a minute or so. This equilibrated pressure level is called mean circulatory filling pressure.

Venous return
- The quantity of blood flowing from the veins into the right atrium each minute.

Methods for Measuring Venous Pressure

- **Clinical Estimation of Venous Pressure**
  - Venous pressure can be estimated by simply observing the degree of distention of the peripheral veins, especially of the neck veins.
  - For example, in the sitting position, the neck veins are never distended in the normal, quietly resting person. However, when the right atrial pressure increases to as much as +10 mm Hg, the lower veins of the neck begin to protrude and, at +15 mm Hg atrial pressure, all the veins in the neck become distended.
- **Direct Measurement of Venous Pressure and Right Atrial Pressure**
  - Venous pressure can be measured easily by inserting a needle directly into a vein and connecting it to a pressure recorder.
  - The only means whereby right atrial pressure can be measured accurately is by inserting a catheter through the peripheral veins and into the right atrium. Pressures measured through such central venous catheters are often used in some types of hospitalized cardiac patients to provide a constant assessment of the heart-pumping ability.

Principle regarding Venous Pressure and Flow

- Blood from all the systemic veins flows into the **right atrium.** Therefore, the pressure in the right atrium is called the **central venous pressure**.
- **Right atrial pressure** is regulated by a balance between (1) the ability of the heart to pump blood out of the right atrium and ventricle into the lungs and (2) the tendency for blood to flow from the peripheral veins into the right atrium.
- If the right heart is pumping strongly, the right atrial pressure decreases. Conversely, weakness of the heart elevates the right atrial pressure. Any effect that causes rapid inflow of blood into the right atrium from the peripheral veins elevates the right atrial pressure.
- **Factors that can increase venous return and thereby increase the right atrial pressure are as follows:**
  - Increased blood volume
  - Increased large vessel tone throughout the body with resultant
  - increased peripheral venous pressures
  - Dilation of the arterioles, which decreases the peripheral resistance and allows rapid flow of blood from the arteries into the veins.
  - Positive pressure breathing
  - Straining
  - Heart failure
- **Factors that decrease central venous pressure (right atrial pressure):**
  - Negative pressure breathing
  - Shock
- The same factors that regulate right atrial pressure also contribute to the regulation of cardiac output because the amount of blood pumped by the heart depends on both the ability of the heart to pump and the tendency for blood to flow into the heart from the peripheral vessels.
- The normal right atrial pressure is about **0 mm Hg**, which is equal to the atmospheric pressure around the body. It can increase to **20 to 30 mm Hg** under very abnormal conditions, such as the following: (1) serious heart failure; or (2) after massive transfusion of blood, which greatly increases the total blood volume and causes excessive quantities of blood to attempt to flow into the heart from the peripheral vessels.
- The lower limit to the right atrial pressure is usually about **-3 to -5 mmHg** below atmospheric pressure, which is also the pressure in the chest cavity that surrounds the heart. The right atrial pressure approaches these low values when the heart pumps with exceptional vigor or when blood flow into the heart from the peripheral vessels is greatly depressed, such as after severe hemorrhage.

Effects of the following on venous pressure and flow

- **Venous resistance to flow**
  - Large veins have so little resistance to blood flow when they are distended that the resistance then is almost zero.
  - However, most of the large veins that enter the thorax are compressed at many points by the surrounding tissues, so that blood flow is impeded at these points. For example, the veins from the arms are compressed by their sharp angulations over the first rib. Also, the pressure in the neck veins often falls so low that the atmospheric pressure on the outside of the neck causes these veins to collapse. Finally, veins coursing through the abdomen are often compressed by different organs and by the intra-abdominal pressure, so they usually are at least partially collapsed to an ovoid or slit-like state. For these reasons, the large veins do usually offer some resistance to blood flow, and thus the pressure in the more peripheral small veins in a person lying down is usually +4 to +6 mmHg greater than the right atrial pressure.
- **Factors that tend to collapse the veins entering the thorax:**
  - Atmospheric pressure collapse in neck
  - Rib collapse
  - Axillary collapse
  - Intrathoracic pressure = -4 mm Hg
  - Abdominal pressure collapse

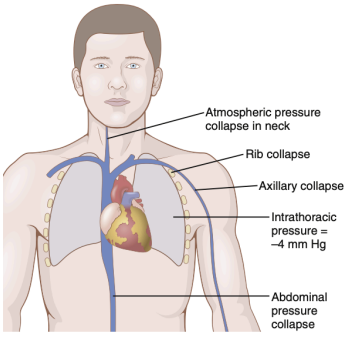


Figure 15-9. Compression points that tend to collapse the veins entering the thorax.

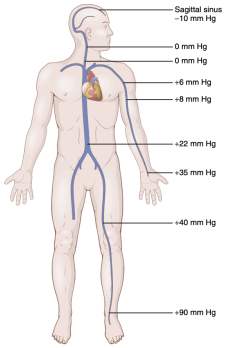


Figure 15-10. Effect of gravitational pressure on the venous pressures throughout the body in the standing person.

- **Posture**
  - Gravitational pressure also occurs in the vascular system because of the weight of the blood in the vessels.

- When a person is **standing**, the pressure in the right atrium remains about **0 mm Hg** because the heart pumps any excess blood that attempts to accumulate at this point into the arteries. However, in an adult who is standing absolutely still, the pressure in the **veins of the feet** is about **+90 mm Hg** simply because of the gravitational weight of the blood in the veins between the heart and the feet. The venous pressures at other levels of the body are proportionately between 0 and 90 mm Hg.
- In the **arm veins**, the pressure at the level of the top rib is usually about **+6 mm Hg** because of compression of the subclavian vein as it passes over this rib.
  - The gravitational pressure down the length of the arm is then determined by the distance below the level of this rib. Thus, if the gravitational difference between the level of the rib and the hand is +29 mm Hg, this gravitational pressure is added to the +6 mm Hg pressure caused by compression of the vein as it crosses the rib, making a total of +35 mm Hg pressure in the veins of the hand.
- The **neck veins** of a person standing upright collapse almost completely all the way to the skull because of atmospheric pressure on the outside of the neck. This collapse causes the pressure in these veins to remain at **zero** along their entire extent.
  - Any tendency for the pressure to rise above this level opens the veins and allows the pressure to fall back to zero because of flow of the blood.
  - Conversely, any tendency for the neck vein pressure to fall below zero collapses the veins still more, which further increases their resistance and again returns the pressure back to zero.
- The **veins inside the skull**, on the other hand, are in a chamber (the skull cavity) that cannot collapse. Consequently, negative pressure can exist in the dural sinuses of the head; in the standing position, the venous pressure in the sagittal sinus at the top of the brain is about **-10 mmHg** because of the hydrostatic “suction” between the top of the skull and the base of the skull.
  - Therefore, if the sagittal sinus is opened during surgery, air can be sucked immediately into the venous system; the air may even pass downward to cause air embolism in the heart and death.

- **Cardiac Contraction**
  - Atrial pressure drops sharply during the ejection phase of the ventricular systole because the atrioventricular valves are pulled downward, increasing the capacity of the atria.
    - This action sucks blood into the atria from the great veins.
    - The sucking of the blood into the atria during systole contributes appreciably to the venous return, especially at rapid heart rates.
  - Close to the heart, venous flow becomes pulsatile.
    - When the heart rate is slow, two periods of peak flow are detectable, one during **ventricular systole**, due to pulling down of the atrioventricular valves, and one in **early diastole**, during the period of rapid ventricular filling.
- **Thoraco-Abdominal Pump (Respiratory Pump)**
  - The respiratory pump works in the following manner:
    - When you inhale, the diaphragm is pulled downward and the rib cage expands, which lowers pressure in the thoracic cavity and raises pressure in the abdominal cavity.
      - This action creates a pressure gradient that promotes movement of blood from abdominal veins to the central veins located in the thoracic cavity. The drop in venous pressure during inspiration aids venous return.
    - When you exhale, the thoracic pressure rises and abdominal pressure falls.
      - This creates a pressure gradient that would tend to favor the backward movement of blood from the central veins to the abdominal veins, but such backward flow is prevented by the closure of the valves in the abdominal veins.
      - Instead, the rise in thoracic pressure drives the forward movement of blood from the central veins to the heart, thereby, promoting increased end-diastolic volume and cardiac output.
  - Skeletal muscle pump (Venous pump)
    - The peripheral veins contain one-way valves that allow blood to flow forward the heart but prevent it from flowing backward.
    - When skeletal muscles contract, they press against veins traveling between them, which raises the pressure of blood within them. This increased pressure forces the more distal valves to close, preventing blood from flowing backward, and forces the more proximal valves to open, allowing blood to flow toward the heart.
    - When the muscles relax and the pressure drops, backflow is prevented by closure of one-way valves in the veins.
    - By alternately contracting and relaxing, muscles act as “pumps” or “auxiliary hearts” that help drive blood toward the central veins, which raises central venous pressure.
      - For this reason, any exercise that involves rhythmic muscle contractions, such as walking, or running, promotes an increase in venous return, increased stroke volume, and increased cardiac output.
  - Venomotor tone
  - The activity of vasoconstrictor neurons of the sympathetic nervous system triggers increased contractile activity in venous smooth muscle, with a resulting rise in tension referred to as venomotor tone.
  - An increase in venomotor tone has two effects:
    - Constriction of veins raises the pressure of blood within them, which forces blood to return to the heart and briefly increases stroke volume.
    - Increased wall tension reduces venous compliance which raises central venous pressure and produces a sustained increase in stroke volume.
  - Therefore, an increase in venomotor tone promotes a rise in cardiac output and mean arterial pressure. Changes in venomotor tone are important components of the reflexes that regulate arterial pressure.
- Venous valves
  - Were it not for valves in the veins, the gravitational pressure effect would cause the venous pressure in the feet to always be about +90 mm Hg in a standing adult.
    - However, every time the legs move, the muscles tighten and compress the veins in or adjacent to the muscles, which squeezes the blood out of the veins.
    - However, the valves in the veins are arranged so that the direction of venous blood flow can only be toward the heart.
    - Consequently, every time a person moves the legs or even tenses the leg muscles, a certain amount of

venous blood is propelled toward the heart. This pumping system is known as the venous pump or muscle pump, and it is efficient enough that under ordinary circumstances, the venous pressure in the feet of a walking adult remains less than +20 mm Hg.

- The valves of the venous system may become "incompetent" or even be destroyed when the veins have been overstretched by excess venous pressure lasting weeks or months, which can occur in pregnancy or when a person stands most of the time.
- Stretching the veins increases their cross-sectional areas, but the leaflets of the valves do not increase in size. Therefore, the leaflets of the valves no longer close completely.
  - With this lack of complete closure, the pressure in the veins of the legs increases greatly because of failure of the venous pump, which further increases the sizes of the veins and finally destroys the function of the valves entirely.
  - Thus, the person develops what are called varicose veins, which are characterized by large bulbous protrusions of the veins beneath the skin of the entire leg, particularly the lower leg.

Functional relationship between cardiac output and central venous pressure (right atrial pressure)

- Cardiac and vascular function curves- are simultaneous plots of cardiac output and venous return as a function of right atrial pressure or end-diastolic volume.
- The cardiac function (cardiac output) curve
  - Depicts the Frank-Starling relationship for the ventricle.
  - Is a characteristic of the heart itself.
  - Shows that cardiac output is a function of end-diastolic volume- a consequence of the length-tension relationship in cardiac muscle fibers. Remember that changes in end-diastolic volume are a major mechanism for altering cardiac output.

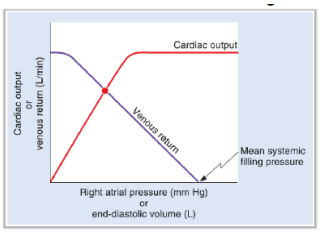


FIGURE 3.11. Simultaneous plots of the cardiac and vascular function curves. The curves cross at the equilibrium point for the cardiovascular system.

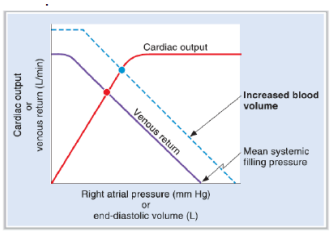


FIGURE 3.12. Effect of increased blood volume on the mean systemic filling pressure, vascular function curve, cardiac output, and right atrial pressure.

- The vascular function (venous return) curve
  - Depicts the relationship between blood flow through the vascular system (or venous return) and right atrial pressure.
  - Defines the changes in central venous pressure that are caused by changes in cardiac output.
  - Is entirely independent of the characteristics of the heart.
  - Mean systemic filling pressure
    - The point at which the vascular function curve intersects the x-axis.
    - Equals right atrial pressure when there is "no flow" in the cardiovascular system.
    - It is measured when the heart is stopped experimentally. Under these conditions, cardiac output and venous return are zero, and pressure is equal throughout the cardiovascular system.
    - When the right atrial pressure rises to equal the mean systemic filling pressure, there is no longer any pressure difference between the peripheral vessels and the right atrium. There can no longer be any flow from any peripheral vessels back to the atrium. However, when the right atrial pressure falls progressively lower than the mean systemic filling pressure, the flow to the heart increases proportionately. The greater the difference between the mean systemic filling pressure and the right atrial pressure, the greater the venous return.
    - The difference between these two pressures is called pressure gradient for venous return.
    - Mean systemic filling pressure is increased by an increase in blood volume or by a decrease in venous capacitance (where blood is shifted from the veins to the arteries).
      - An increase in mean systemic filling pressure is reflected in a shift of the vascular function curve to the right.
    - Mean systemic filling pressure is decreased by a decrease in blood volume or by an increase in venous capacitance (where blood is shifted from the arteries to the veins).
      - A decrease in mean systemic filling pressure is reflected in a shift of the vascular function curve to the left.
- Slope of the venous return curve
  - It is determined by the resistance of the arterioles.
  - A clockwise rotation of the venous return curve indicates a decrease in total peripheral resistance (TPR). When TPR is decreased for a given right atrial pressure, there is an increase in venous return (i.e., vasodilation of the arterioles "allows" more blood to flow from the arteries to the veins and back to the heart).
  - A counterclockwise rotation of the venous return curve indicates an increase in TPR. When TPR is increased for a given right atrial pressure, there is a decrease in venous return to the heart (i.e., vasoconstriction of the arterioles decreases blood flow from the arteries to the veins and back to the heart).

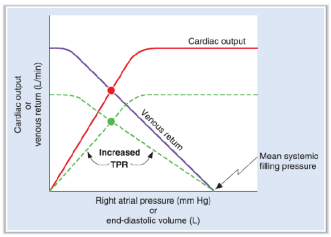


FIGURE 3.13. Effect of increased total peripheral resistance (TPR) on the cardiac and vascular function curves and on cardiac output.

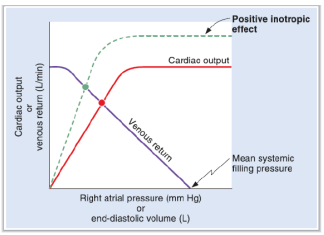


FIGURE 3.14. Effect of a positive inotropic agent on the cardiac function curve, cardiac output, and right atrial pressure.

- Combining Cardiac Output and Venous Return Curves
  - When cardiac output and venous return are simultaneously plotted as a function of right atrial pressure, they intersect at a single value of right atrial pressure.
  - The point at which the two curves intersect is the **equilibrium**, or **steady-state point**. Equilibrium occurs when cardiac output equals venous return.
  - Cardiac output can be changed by altering the cardiac output curve, the venous return curve, or both curves simultaneously. The superimposed curves can be used to predict the direction and magnitude of changes in cardiac output and the corresponding values of right atrial pressure.
  - **Inotropic agents change the cardiac output curve**
    - **Positive inotropic agents** (e.g., cardiac glycosides, digitalis) produce increased contractility and increased cardiac output.
      - The equilibrium, or intersection, point shifts to a higher cardiac output and a correspondingly lower right atrial pressure.
      - Right atrial pressure decreases because more blood is ejected from the heart on each beat (increased stroke volume).
    - **Negative inotropic agents** produce decreased contractility and decreased cardiac output.
  - Changes in blood volume or venous capacitance change the venous return curve

- **Increases in blood volume** or **decreases in venous capacitance** increase mean systemic filling pressure, shifting the venous return curve to the right in a parallel fashion. A new equilibrium, or intersection point is established at which both **cardiac output** and **right atrial pressure** are **increased**.
- **Decreases in blood volume** (e.g., hemorrhage) or **increases in venous capacitance** have the opposite effect- decreased mean systemic filling pressure and a shift of the venous return curve to the left in a parallel fashion. A new equilibrium point is established at which both **cardiac output** and **right atrial pressure** are **decreased**.

- **Changes in TPR change both the cardiac output and the venous return curves.**
  - Changes in TPR alter both curves simultaneously; therefore, the responses are more complicated than those noted in the previous examples.
  - **Increasing TPR** causes a **decrease** in both **cardiac output** and **venous return**.
    - A **counterclockwise rotation of the venous return curve** occurs. Increased TPR results in decreased venous return as blood is retained on the arterial side.
    - A **downward shift of the cardiac output curve** is caused by the increased aortic pressure (increased afterload) as the heart pumps against a higher pressure.
    - As a result of these simultaneous changes, a new equilibrium point is established at which both **cardiac output** and **venous return** are **decreased**, but right atrial pressure is unchanged.
  - **Decreasing TPR** causes an **increase** in both **cardiac output** and **venous return**.
    - A **clockwise rotation of the venous return curve** occurs. Decreased TPR results in increased venous return as more blood is allowed to flow back to the heart from the arterial side.
    - An **upward shift of the cardiac output curve** is caused by the decreased aortic pressure (decreased afterload) as the heart pumps against a lower pressure.
    - As a result of these simultaneous changes, a new equilibrium point is established at which both **cardiac output** and **venous return** are **increased**, but right atrial pressure is unchanged.

DYNAMICS OF THE MICROCIRCULATION

Structure of Capillary Bed

- Metarterioles branch into the capillary beds. At the junction of the arterioles and capillaries is a smooth muscle band called the **precapillary sphincter**.
- True capillaries do not have smooth muscle; they consist of a single layer of **endothelial cells** surrounded by a basement membrane.
- **Clefts (pores)** between the endothelial cells allow passage of water-soluble substances. The clefts represent a very small fraction of the surface area (<0.1 %).
- Blood flow through the capillaries is regulated by contraction and relaxation of the arterioles and the precapillary sphincters.

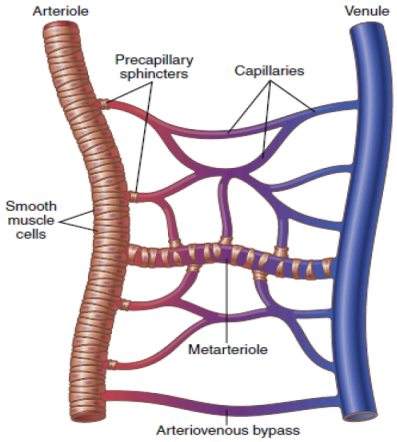


Figure 16-1. Components of the microcirculation.

Substances that can cross the capillary wall and the mechanisms involved in their passage across the capillary wall

- **Lipid-soluble substances**
  - Cross the membranes of the capillary endothelial cells by **simple diffusion.**
  - Include **O2** and **CO2**.
- **Small water-soluble substances**
  - Cross via the water-filled clefts between the endothelial cells.
  - Include **water, glucose,** and **amino acids**.
  - Generally, protein molecules are too large to pass freely through the clefts.
  - In the **brain**, the clefts between endothelial cells are exceptionally tight **(blood-brain barrier).**
  - In the **liver** and **intestine**, the clefts are exceptionally wide and allow passage of protein. These capillaries are called **sinusoids**.
- **Large water-soluble substances**
  - Can cross by **pinocytosis**.

Factors that influence transcapillary movement (Starling Hypothesis) and how they maintain normal fluid movement

- The Starling equation

$$J_v = K_f\left[(P_c - P_i) - (\pi_c - \pi_i)\right]$$

where:
J_v = fluid movement (mL/min)
K_f = hydraulic conductance (mL/min·mm Hg)
P_c = capillary hydrostatic pressure (mm Hg)
P_i = interstitial hydrostatic pressure (mm Hg)
π_c = capillary oncotic pressure (mm Hg)
π_i = interstitial oncotic pressure (mm Hg)

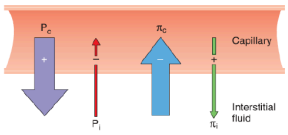


FIGURE 3.18 Starling forces across the capillary wall. + *sign* = favors filtration; − *sign* = opposes filtration; P_c = capillary hydrostatic pressure; P_i = interstitial hydrostatic pressure; π_c = capillary oncotic pressure; π_i = interstitial oncotic pressure.

- **Jv** is **fluid flow**.
  - When **Jv is positive**, there is net fluid movement out of the capillary **(filtration)**.
  - When **Jv is negative**, there is net fluid movement into the capillary **(absorption)**.
- **Kf** is the **filtration coefficient**.
  - It is the hydraulic conductance (**water permeability**) of the capillary wall.
- **Pc** is **capillary hydrostatic pressure**.

- An increase in Pc **favors filtration** out of the capillary.
- Pc is determined by arterial and venous pressures and resistances.
- An increase in either arterial or venous pressure produces an increase in Pc; increases in venous pressure have a greater effect on Pc.
- Pc is higher at the arteriolar end of the capillary than at the venous end (except in glomerular capillaries, where it is nearly constant).

- **Pi** is **interstitial fluid hydrostatic pressure**.
  - An increase in Pi **opposes filtration** out of the capillary.
  - It is normally close to 0 mm Hg (or it is slightly negative).
- π**c** is **capillary oncotic** or **colloid osmotic pressure**.
  - An increase in πc **opposes filtration** out of the capillary.
  - πc is increased by increases in the protein concentration in the blood (e.g., dehydration).
  - πc is decreased by decreases in the protein concentration in the blood (e.g., nephrotic syndrome, protein malnutrition, liver failure).
  - Small solutes do not contribute to πc.
- π**i** is **interstitial fluid oncotic pressure**.
  - An increase in πi **favors filtration** out of the capillary.
  - πi is dependent on the protein concentration of the interstitial fluid, which is normally quite low because very little protein is filtered.

Factors that increase filtration

- ↑**Pc**- caused by increased arterial pressure, increased venous pressure, arteriolar dilation, and venous constriction
- ↓**Pi**
- ↓ π**c-** caused by decreased protein concentration in the blood
- ↑ π**i**- caused by inadequate lymphatic function

FACTORS THAT CONTROL BLOOD FLOW AND THE MECHANISM INVOLVED

Local (Intrinsic) Control

- **Examples of local control**
  - **Autoregulation**
    - Blood flow to an organ remains constant over a wide range of perfusion pressures.
    - Organs that exhibit autoregulation are the heart, brain, and kidney.
    - For example, if perfusion pressure to the heart is suddenly decreased, compensatory vasodilation of the arterioles will occur to maintain a constant flow
  - **Active hyperemia**
    - Blood flow to an organ is proportional to its metabolic activity.
    - For example, if metabolic activity in skeletal muscle increases as a result of strenuous exercise, blood flow to the muscle will increase proportionately to meet metabolic demands.
  - **Reactive hyperemia**
    - Is an increase in blood flow to an organ that occurs after a period of occlusion of flow.
    - The longer the period of occlusion is, the greater the increase in blood flow is above pre-occlusion levels.
- **Mechanisms that explain local control of blood flow**
  - **Myogenic hypothesis**
    - Explains autoregulation, but not active or reactive hyperemia
    - Is based on the observation that vascular smooth muscle contracts when it is stretched.
    - For example, if perfusion pressure to an organ suddenly increases, the arteriolar smooth muscle will be stretched and will contract. The resulting vasoconstriction will maintain a constant flow (without vasoconstriction, blood flow would increase as a result of the increased pressure).
  - **Metabolic hypothesis**
    - Is based on the observation that the tissue supply of O2 is matched to the tissue demand for O2.
    - Vasodilator metabolites are produced as a result of metabolic activity in tissue. These vasodilators are CO2, H+, K+, lactate, and adenosine.
    - Examples of active hyperemia:
      - √ If the metabolic activity of a tissue increases (e.g., strenuous exercise), both the demand for O2 and the production of vasodilator metabolites increase. These metabolites cause arteriolar vasodilation, increased blood flow, and increased O2 delivery to the tissue to meet demand.
      - √ If blood flow to an organ suddenly increases as a result of a spontaneous increase in arterial pressure, then more O2 is provided for metabolic activity. At the same time, the increased flow "washes out" vasodilator metabolites. As a result of this "washout," arteriolar vasoconstriction occurs, resistance increases, and blood flow is decreased to normal.

Humoral (Extrinsic) Control of blood flow

- **Sympathetic innervation of vascular smooth muscle**
  - Increases in sympathetic tone cause vasoconstriction.
  - Decreases in sympathetic tone cause vasodilation.
  - The density of sympathetic innervation varies widely among tissues. Skin has the greatest innervation, whereas coronary, pulmonary, and cerebral vessels have little innervation.
- **Other vasoactive hormones**
  - **Histamine**
    - Causes arteriolar dilation and venous constriction.
    - The combined effects of arteriolar dilation and venous constriction cause increased Pc and increased filtration out of the capillaries, resulting in local edema.
    - Is released in response to tissue trauma.
  - **Bradykinin**
    - Causes arteriolar dilation and venous constriction.
    - Produces increased filtration out of the capillaries (similar to histamine) and causes local edema.
  - Serotonin (5-hydroxytryptamine)
    - Causes **arteriolar constriction** and is released in response to blood vessel damage to help prevent blood loss.
    - Has been implicated in the vascular spasms of **migraine headaches**
  - Prostaglandins
    - **Prostacyclin** is a vasodilator in several vascular beds.
    - **E-series prostaglandins** are vasodilators.
    - **F-series prostaglandins** are vasoconstrictors.
    - **Thromboxane A2** is a vasoconstrictor.

Coronary circulation

- Is controlled almost entirely by **local metabolic factors**.
- Exhibits autoregulation.
- Exhibits active and reactive hyperemia.
- The most important local metabolic factors: **hypoxia** and **adenosine**.

- For example, increases in myocardial contractility are accompanied by an increased demand for O2. To meet this demand, compensatory vasodilation of coronary vessels occurs and, accordingly, both blood flow and O2 delivery to the contracting heart muscle increase (active hyperemia).
- During **systole**, mechanical compression of the coronary vessels reduces blood flow. After the period of occlusion, blood flow increases to repay the O2 debt (reactive hyperemia).
- Sympathetic nerves play a minor role.

LYMPHATICS

Functions

- The lymphatic system represents an accessory route through which fluid can flow from the interstitial spaces into the blood.
- Most importantly, the lymphatics can carry proteins and large particulate matter away from the tissue spaces, neither of which can be removed by absorption directly into the blood capillaries. This return of proteins to the blood from the interstitial spaces is an essential function, without which we would die within about 24 hours.

Functional Anatomy

Types of lymphatic vessels

- Initial lymphatics – lack valves and smooth muscle in their walls
  - They are found in regions such as the intestine or skeletal muscle.
  - Tissue fluid enters them through loose junctions between the endothelial cells that form their walls.
  - The fluid in them apparently is massaged by muscle contractions of the organs and contraction of arterioles and venules, with which they are often associated.
  - They drain into the collecting lymphatics
- Collecting lymphatics – have valves and smooth muscle in their walls and contract in a peristaltic manner, propelling the lymph along the vessels.
  - Flow in the collecting lymphatics is further aided by movements of skeletal muscle, the negative intrathoracic pressure during inspiration, and the suction effect of high velocity flow of blood in the veins in which the lymphatics terminate. However, the contractions are the principal factor propelling the lymph.

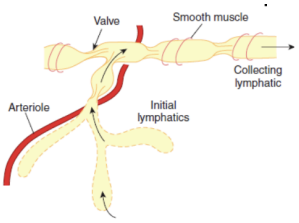


FIGURE 31–32 Schematic of the lymphatic system. Initial lymphatics are highly permeable structures without smooth muscle or valves. Unidirectional flow is accomplished in the collecting lymphatics, which appear like a string of beads due to the regular valves. Lymphatics are often close to blood vessels, whose contractions also encourage flow in the lymphatic system.

Lymph channels in the body

- Almost all tissues of the body have special lymph channels that drain excess fluid directly from the interstitial spaces. The exceptions include the superficial portions of the skin, central nervous system, endomysium of muscles, and bones.
  - However, even these tissues have minute interstitial channels called **prelymphatics** through which interstitial fluid can flow; this fluid eventually empties into lymphatic vessels or, in the case of the brain, into the cerebrospinal fluid and then directly back into the blood.
- Essentially all the lymph vessels from the lower part of the body eventually empty into the **thoracic duct**, which in turn empties into the blood venous system at the juncture of the **left internal jugular vein** and **left subclavian vein**.

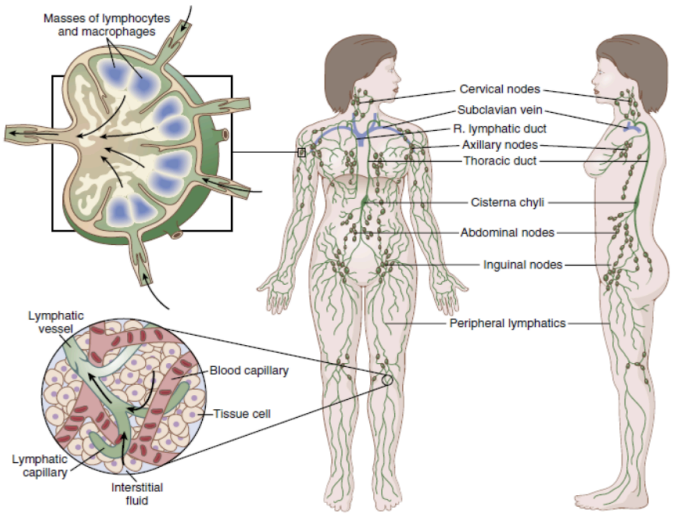


Figure 16-6. The lymphatic system.

- Lymph from the **left side of the head**, **left arm**, and **parts of the chest region** also enters the thoracic duct before it empties into the veins.
- Lymph from the **right side of the neck and head**, **right arm**, and **parts of the right thorax** enters the right lymph duct (much smaller than the thoracic duct), which empties into the blood venous system at the juncture of the right subclavian vein and internal jugular vein.
- **Terminal Lymphatic Capillaries and Their Permeability.**
  - Most of the fluid filtering from the **arterial ends** of blood capillaries flows among the cells and finally is reabsorbed back into the **venous ends** of the blood capillaries but, on average, about 1/10th of the fluid instead enters the **lymphatic capillaries** and returns to the blood through the lymphatic system rather than through the venous capillaries.
- The total quantity of all this lymph is normally only **2 to 3 L/day**.
- The fluid that returns to the circulation by way of the lymphatics is extremely important because substances of high molecular weight, such as proteins, cannot be absorbed from the tissues in any other way, although they can enter the lymphatic capillaries almost unimpeded. The reason for this mechanism is a special structure of the lymphatic capillaries, demonstrated in Figure 16-7.
  - This figure shows the endothelial cells of the lymphatic capillary attached by **anchoring filaments** to the surrounding connective tissue.
  - At the junctions of adjacent endothelial cells, the edge of one endothelial cell overlaps the edge of the adjacent cell in such a way that the overlapping edge is free to flap inward, thus forming a minute valve that opens to the interior of the lymphatic capillary.
  - Interstitial fluid, along with its suspended particles, can push the valve open and flow directly into the lymphatic capillary. However, this fluid has difficulty leaving the capillary once it has entered because any backflow closes the flap valve. Thus, the lymphatics have valves at the very tips of the terminal lymphatic capillaries, as well as valves along their larger vessels, up to the point where they empty into the blood circulation.

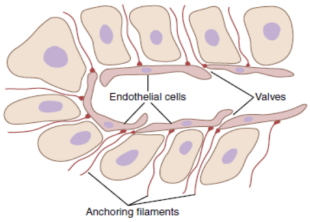


Figure 16-7. Special structure of the lymphatic capillaries that permits passage of substances of high molecular weight into the lymph.

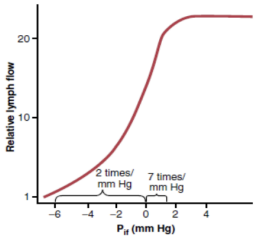


Figure 16-8. Relationship between interstitial fluid pressure and lymph flow in the leg of a dog. Note that lymph flow reaches a maximum when the interstitial pressure (P_{if}) rises slightly above atmospheric pressure (0 mm Hg). (*Courtesy Dr. Harry Gibson and Dr. Aubrey Taylor.*)

Formation of Lymph

- Lymph is derived from interstitial fluid that flows into the lymphatics. Therefore, lymph as it first enters the terminal lymphatics has almost the same composition as the interstitial fluid.
- The protein concentration in the interstitial fluid of most tissues averages about **2 g/dL**, and the protein concentration of lymph flowing from these tissues is near this value.
- Lymph formed in the liver has a protein concentration as high as **6 g/dL**, and lymph formed in the intestines has a protein concentration as high as **3 to 4 g/dL**.
    - Because about two thirds of all lymph normally is derived from the liver and intestines, the thoracic duct lymph, which is a mixture of lymph from all areas of the body, usually has a protein concentration of **3 to 5 g/dL**.
- The lymphatic system is also one of the major routes for absorption of nutrients from the gastrointestinal tract, especially for absorption of virtually all fats in food.
    - After a fatty meal, thoracic duct lymph sometimes contains as much as 1% to 2% fat.
- Finally, even large particles, such as bacteria, can push their way between the endothelial cells of the lymphatic capillaries and in this way enter the lymph. As the lymph passes through the lymph nodes, these particles are almost entirely removed and destroyed.

Rate of Lymph Flow

- About **100 mL/hr** of lymph flows through the thoracic duct of a resting human, and approximately another **20 mL** flows into the circulation each hour through other channels, making a total estimated lymph flow of about **120 mL/hr** or **2 to 3 L/day**.
- **Factors that determine the rate of lymph flow**
    - **Interstitial fluid pressure**
      Figure 16-8 shows the effect of different levels of interstitial fluid hydrostatic pressure on lymph flow, as measured in animals.
    - Note that normal lymph flow is very little at interstitial fluid pressures more negative than the normal value of **-6 mm Hg**. Then, as the pressure rises to **0 mm Hg** (**atmospheric pressure**), flow increases more than 20-fold.
    - Therefore, any factor that increases interstitial fluid pressure also increases lymph flow if the lymph vessels are functioning normally. Such factors include the following:
        - Elevated capillary hydrostatic pressure
        - Decreased plasma colloid osmotic pressure
        - Increased interstitial fluid colloid osmotic pressure
        - Increased permeability of the capillaries
    - All these factors favor net fluid movement into the interstitium, thus increasing interstitial fluid volume, interstitial fluid pressure, and lymph flow all at the same time.
    - However, note in Figure 16-8 that when the interstitial fluid hydrostatic pressure becomes 1 or 2 mm Hg greater than atmospheric pressure (>0 mm Hg), lymph flow fails to rise any further at still higher pressures. This results from the fact that the increasing tissue pressure not only increases entry of fluid into the lymphatic capillaries, but also compresses the outside surfaces of the larger lymphatics, thus impeding lymph flow.
    - At the higher pressures, these two factors balance each other, so lymph flow reaches a maximum flow rate. This maximum flow rate is illustrated by the upper level plateau in Figure 16-8.
- **Lymphatic pump-** increases lymph flow
    - Valves exist in all lymph channels. Figure 16-9 shows typical valves for collecting lymphatics into which the lymphatic capillaries empty.
    - Videos of exposed lymph vessels in animals and in humans have shown that when a collecting lymphatic or larger lymph vessel becomes **stretched with fluid**, the smooth muscle in the wall of the vessel automatically contracts.
        - Furthermore, each segment of the lymph vessel between successive valves functions as a separate automatic pump. That is, even slight filling of a segment causes it to contract, and the fluid is pumped through the next valve into the next lymphatic segment.
        - This fluid fills the subsequent segment and a few seconds later it also contracts, with the process continuing all along the lymph vessel until the fluid is finally emptied into the blood circulation.
- In a very large lymph vessel, such as the thoracic duct, this lymphatic pump can generate pressure as high as **50 to 100 mm Hg**.
- **Pumping Caused by External Intermittent Compression of the Lymphatics**
    - In addition to the pumping caused by intrinsic intermittent contraction of the lymph vessel walls, any external factor that intermittently compresses the lymph vessel can also cause pumping. In order of their importance, such factors are as follows:
        - Contraction of surrounding skeletal muscles
        - Movement of the parts of the body
        - Pulsations of arteries adjacent to the lymphatics
        - Compression of the tissues by objects outside the body
    - The lymphatic pump becomes very active during exercise, often increasing lymph flow 10-to 30-fold. Conversely, during periods of rest, lymph flow is sluggish (almost zero).

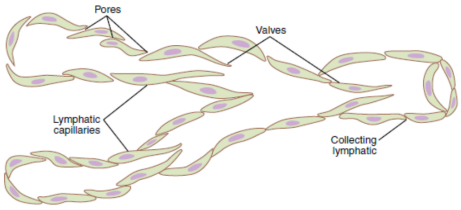


Figure 16-9. Structure of lymphatic capillaries and a collecting lymphatic, with the lymphatic valves also shown.

- **Lymphatic capillary pump**
    - The terminal lymphatic capillary is also capable of pumping lymph, in addition to the pumping by the larger lymph vessels.
    - The **anchoring filaments** on the walls of the lymphatic capillaries tightly adhere to the surrounding tissue cells.
        - Therefore,each time excess fluid enters the tissue and causes the tissue to swell, the anchoring filaments pull on the wall of the lymphatic capillary, and fluid flows into the terminal lymphatic capillary through the junctions between the endothelial cells.
        - Then, when the tissue is compressed, the pressure inside the capillary increases and causes the overlapping edges of the endothelial cells to close like valves. Therefore, the pressure pushes the lymph forward into the collecting lymphatic instead of backward through the cell junctions.

- The lymphatic capillary endothelial cells also contain a few contractile **actomyosin filaments**.
  - In some animal tissues (e.g., a bat wing), these filaments have been observed to cause rhythmical contraction of the lymphatic capillaries in the same rhythmic way that many of the small blood vessels and larger lymphatic vessels contract.
  - Therefore,it is probable that at least part of lymph pumping results from lymph capillary endothelial cell contraction in addition to contraction of the larger muscular lymphatics.

Summary of Factors that Determine Lymph Flow

- From the previous discussion, one can see that the two primary factors that determine lymph flow are (1) the **interstitial fluid pressure** and (2) the **activity of the lymphatic pump**.
- Therefore, one can state that, roughly, the rate of lymph flow is determined by the product of interstitial fluid pressure times the activity of the lymphatic pump.

Other Important Roles of the Lymphatic System

- **Lymphatic System Plays a Key Role in Controlling Interstitial Fluid Protein Concentration, Volume, and Pressure**
  - It is already clear that the lymphatic system functions as an overflow mechanism to return excess proteins and excess fluid volume from the tissue spaces to the circulation.
  - Therefore, the lymphatic system also plays a central role in controlling the following: (1) **concentration of proteins in the interstitial fluids**; (2) **volume of interstitial fluid**; and (3) **interstitial fluid pressure**. Here is an explanation of how these factors interact.

1. Remember that **small amounts of proteins leak continuously** out of the **blood capillaries** into the interstitium.
   a. Only minute amounts, if any, of the leaked proteins return to the circulation by way of the venous ends of the blood capillaries.
   b. Therefore, these proteins tend to accumulate in the interstitial fluid, which in turn increases the colloid osmotic pressure of the interstitial fluids.
2. The **increasing colloid osmotic pressure** in the interstitial fluid shifts the balance of forces at the blood capillary membranes in favor of fluid filtration into the interstitium.
   a. Therefore, in effect, fluid is translocated osmotically outward through the capillary wall by the proteins and into the interstitium, thus increasing both interstitial fluid volume and interstitial fluid pressure.
3. The **increasing interstitial fluid pressure** greatly increases the rate of lymph flow, which carries away the excess interstitial fluid volume and excess protein that has accumulated in the spaces.

- Thus, once the interstitial fluid protein concentration reaches a certain level and causes comparable increases in interstitial fluid volume and pressure, the return of protein and fluid by way of the lymphatic system becomes great enough to balance the rate of leakage of these into the interstitium from the blood capillaries.
  - Therefore, the quantitative values of all these factors reach a steady state, and they remain balanced at these steady state levels until some factor changes the rate of leakage of proteins and fluid from the blood capillaries.
- **Significance of Negative Interstitial Fluid Pressure for Holding Body Tissues Together**
  - Traditionally, it has been assumed that the different tissues of the body are held together entirely by **connective tissue fibers**.
  - However, connective tissue fibers are very weak or even absent at many places in the body, particularly at points where tissues slide over one another (e.g., skin sliding over the back of the hand or over the face). Yet, even at these places, the tissues are held together by the **negative interstitial fluid pressure**, which is actually a partial vacuum.
  - When the tissues lose their negative pressure, fluid accumulates in the spaces, and the condition known as **edema** occurs.

REGULATION OF ARTERIAL BLOOD PRESSURE

- **Blood pressure -** the force exerted by the blood against any unit area of the vessel wall.
  - When one says that pressure in a vessel is 50 mmHg, one means that the force exerted is sufficient to push a column of mercury against gravity up to a level 50 mm high.
- **Systolic pressure-** is the highest arterial pressure during a cardiac cycle.
  - This occurs when the heart contracts and blood is ejected into the arterial system.
- **Diastolic pressure-** is the lowest arterial pressure during a cardiac cycle.
  - This occurs when the heart is relaxed and blood is being returned to the heart via the veins.
- **Mean arterial pressure-** The mean arterial pressure is the average of the arterial pressures measured millisecond by millisecond over a period of time.
  - It is not equal to the average of the systolic and diastolic pressures because at normal heart rates, a greater fraction of the cardiac cycle is spent in diastole than in systole. Thus, the arterial pressure remains closer to diastolic pressure than to systolic pressure during the greater part of the cardiac cycle.
  - At the usual heart rate, the mean arterial pressure is determined about 60% by the diastolic pressure and 40% by the systolic pressure.

$$Mean\ Arterial\ Pressure = DP + \frac{1}{3}(SP - DP)$$

$$MAP = DP + \frac{(SP-DP)}{3} \rightarrow \frac{3DP+SP-DP}{3} \rightarrow \boldsymbol{Mean\ Arterial\ Pressure} = \frac{\boldsymbol{2DP+SP}}{3}$$

  - Nearer the diastolic pressure than to the systolic pressure during the greater part of the cardiac cycle.
- **Pulse pressure-** is the difference between systolic and diastolic pressures, which is about 40 mmHg.
  - Factors that affect pulse pressure:
    1. The **stroke volume output** of the heart
    2. The **compliance (total distensibility)** of the arterial tree
    3. The **character of ejection** from the heart during systole.
    - The first two are major factors while the third is a less important factor.
  - However, the most important determinant of pulse pressure is **stroke volume**.
    - As blood is ejected from the left ventricle into the arterial system, systolic pressure increases dramatically because of the relatively low capacitance of the arteries.
    - Since diastolic pressure remains unchanged during ventricular systole, the pulse pressure increases to the same extent as does systolic pressure.
  - Decreases in capacitance, such as those that occur with the aging process, cause the pulse pressure to increase.
- **Characteristics of the pulse** and **Proper technique of taking the pulse in various peripheral areas** (refer to CASE 3)
- **Proper technique in taking the blood pressure**
  - **Palpatory method**
    - The systolic pressure can be determined by inflating an arm cuff and then letting the pressure fall and determining the pressure at which the radial pulse first becomes palpable.
    - The pressures obtained by this method are usually 2-5 mmHg lower than those measured by the auscultatory method.
  - **Auscultatory method**
    - An inflatable cuff attached to a mercury monometer (**sphygmomanometer**) is wrapped around the arm and a stethoscope is placed over the brachial artery at the elbow.
    - When the cuff pressure is great enough to close the artery during part of the arterial pressure cycle, a sound is heard with each pulsation. These sounds are called **Korotkoff sounds**, which are believed to be caused mainly by blood jetting through the partly occluded vessel (turbulent flow in the brachial artery).
    - The cuff pressure at which the sounds are first heard is the **systolic pressure**. The **diastolic pressure** correlates best with the pressure at which the sound disappears.
    - More sensitive and more precise method for measuring systolic pressure.
    - Also permits the diastolic pressure to be estimated.
- **Normal blood pressure range for adults according to JNC 8**
  - The blood pressure in the brachial artery in young adults in the sitting or lying position at rest is approximately < 120/80 mmHg.
    - Systolic BP: **< 120 mmHg**
    - Diastolic BP: **< 80 mmHg**

Blood Pressure Classification for Adults—JNC 7, American Society of Hypertension

Category	Systolic (mm Hg)	Diastolic (mm Hg)
Normal	<120	<80
Prehypertension	120–139	80–89
Stage 1 hypertension		
Age ≥18 to <60 yrs	140–159	90–99
Age ≥60 yrs[a]	150–159	90–99
Stage 2 hypertension	≥160	≥100
If diabetes or renal disease (including age ≥60 yrs)	<140	<90

[a]The American Society of Hypertension raises this cutoff to age ≥80 years.

Sources: Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community: A statement by the American Society of Hypertension and the International Society of Hypertension. *J Clin Hypertens.* 2014;16:14; Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure—The JNC 7 Report. *JAMA.* 2003;289:2560. Available at http://www.nhlbi.nih.gov/health-pro/guidelines/current/

Age ≥60 years	Systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥90 mm Hg (strong recommendation)
Age <60 years	Systolic blood pressure ≥140 mm Hg (expert opinion) Diastolic blood pressure ≥90 mm Hg (strong recommendation)
Age >18 years with chronic kidney disease or diabetes	Systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg (expert opinion)

Source: James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA.* 2014;311:507.

- **BP Classification for Adult Filipinos**

TABLE 1 Blood pressure classification for adult filipinos

Category	Blood pressure range
Normal BP	< 120/80 mm Hg
Borderline BP	120–139/ 80–89 mm Hg
Hypertension	≥140/90 mm Hg

- **Limitations of BP reading**
  - **Cuffs that are too short or too narrow** may give falsely high readings.
    - Using a regular-size cuff on an obese arm may lead to a false diagnosis of hypertension.
    - A loose cuff or a bladder that balloons outside the cuff leads to falsely high readings.
  - **Position of the arm is below the mid chest level** so the brachial artery is below heart level resulting in a falsely high blood pressure.
    - The patient's own effort to support the arm may raise the blood pressure.
  - An **unrecognized auscultatory gap** may lead to serious underestimation of systolic pressure or overestimation of diastolic pressure.
- **Effects of changes in cardiac output and total peripheral resistance on arterial blood pressure and pulse pressure**
  - Normal total peripheral resistance (TPR) = Normal cardiac output (CO)
    - ↑**TPR =** ↓CO.
    - ↓**TPR =** ↑CO, ↑↓ pulse pressure, ↓ arterial pressure
    - ↓**CO =** ↓arterial pressure
- **Effect of the following physiologic factors on the blood pressure:**
  - **Age**
    - In apparently healthy humans, both the systolic and the diastolic pressures increase with age.
    - An important cause of the systolic pressure rise is decreased distensibility of the arteries; at the same level of cardiac output, the systolic pressure is higher in old subjects than in young ones because there is less increase in the volume of the arterial system during systole to accommodate the same amount of blood.
  - **Emotion**
    - Increases the cardiac output and it may be difficult to obtain a truly resting blood pressure in an excited or tense individual.
    - Because of nervousness, about 20% of hypertensive patients have higher blood pressure in the doctor's office than during their normal daytime activity (white coat hypertension).
  - **Exercise**
    - The same brain activity that sends motor signals to the peripheral muscles to exercise also sends simultaneous signals into the autonomic nervous centers of the brain to excite circulatory activity, causing venous constriction, increased heart rate, and increased contractility of the heart; all these changes acting together increase the arterial pressure even above normal which in turn forces more blood flow through the active muscles.
  - **Body position (posture)**
    - Changes in gravitational forces
    - The following changes occur when an individual moves from a supine position to a standing position:

1. **When a person stands**, a significant volume of blood pools in the lower extremities because of the high compliance of the veins. (Muscular activity would prevent this pooling.)
2. **As a result of venous pooling** and **increased local venous pressure**, capillary hydrostatic pressure (Pc) in the legs increases and fluid is filtered into the interstitium. If net filtration of fluid exceeds the ability of the lymphatics to return it to the circulation, edema will occur.
3. **Venous return decreases.** As a result of the decrease in venous return, both stroke volume and cardiac output decrease (Frank-Starling relationship).
4. **Initially, arterial pressure decreases** because of the reduction in cardiac output. If cerebral blood pressure becomes low enough, fainting may occur.
5. **Compensatory mechanisms** will attempt to increase blood pressure to normal.
   - The **carotid sinus baroreceptors** respond to the decrease in arterial pressure by decreasing the firing rate of the carotid sinus nerves.
   - A coordinated response from the **vasomotor center** then increases sympathetic outflow to the heart and blood vessels and decreases parasympathetic outflow to the heart.
   - As a result, heart rate, contractility, TPR, and venous return increase, and blood pressure increases toward normal.
6. **Orthostatic hypotension** (fainting or light-headedness on standing) may occur in individuals whose baroreceptor reflex mechanism is impaired (e.g., individuals treated with sympatholytic agents) or who are volume depleted

table 3.4 Summary of Responses to Standing

Parameter	Initial Response to Standing	Compensatory Response
Arterial blood pressure	↓	↑ (toward normal)
Heart rate	—	↑
Cardiac output	↓	↑ (toward normal)
Stroke volume	↓	↑ (toward normal)
TPR	—	↑
Central venous pressure	↓	↑ (toward normal)

TPR = total peripheral resistance.

- **Mechanisms involved in the regulation of blood pressure in reference to:**
  - **Neural control**
    - The most important mechanisms for regulating arterial pressure are a fast, neurally-mediated baroreceptor mechanism and a slower, hormonally regulated renin-angiotensin-aldosterone mechanism.
    - **Baroreceptor reflex**
      - Includes **fast, neural mechanisms.**
      - Is a negative feedback system that is responsible for the minute-to-minute regulation of arterial blood pressure.
      - Baroreceptors are stretch receptors located within the walls of the carotid sinus near the bifurcation of the common carotid arteries.
      - Steps in the baroreceptor reflex (Figure 3.16)
        1. A **decrease in arterial pressure** decreases stretch on the walls of the carotid sinus.
           - ✓ Because the baroreceptors are most sensitive to **changes in arterial pressure**, rapidly decreasing arterial pressure produces the greatest response.
           - ✓ Additional baroreceptors in the **aortic arch** respond to increases, but not to decreases, in arterial pressure.

2. Decreased stretch **decreases the firing rate of the carotid sinus nerve** [Hering nerve, cranial nerve (CN) IX], which carries information to the vasomotor center in the brainstem.
3. The **set point for mean arterial pressure** in the vasomotor center is about 100 mm Hg. Therefore, if mean arterial pressure is less than 100 mm Hg, a series of autonomic responses is coordinated by the vasomotor center. These changes will attempt to increase blood pressure toward normal.
4. The **responses of the vasomotor center** to a decrease in mean arterial blood pressure are coordinated to increase the arterial pressure back to 100 mm Hg. The responses are **decreased parasympathetic (vagal) outflow to the heart and increased sympathetic outflow to the heart and blood vessels.**
   - ❖ The following four effects attempt to increase the arterial pressure back toward normal:
     - ➢ ↑**heart rate**, resulting from decreased parasympathetic tone and increased sympathetic tone to the SA node of the heart.
     - ➢ ↑**contractility and stroke volume**, resulting from increased sympathetic tone to the heart.
       - ✓ Together with the increase in heart rate, the increases in contractility and stroke volume produce an increase in cardiac output that increases arterial pressure.
     - ➢ ↑**vasoconstriction of arterioles**, resulting from the increased sympathetic outflow. As a result, TPR and arterial pressure will increase.
     - ➢ ↑**vasoconstriction of veins (venoconstriction)**, resulting from the increased sympathetic outflow. Constriction of the veins causes a decrease in unstressed volume and an increase in venous return to the heart. The increase in venous return causes an increase in cardiac output by the Frank-Starling mechanism.

   - ❖ Example of baroreceptor reflex: response to **acute blood loss**

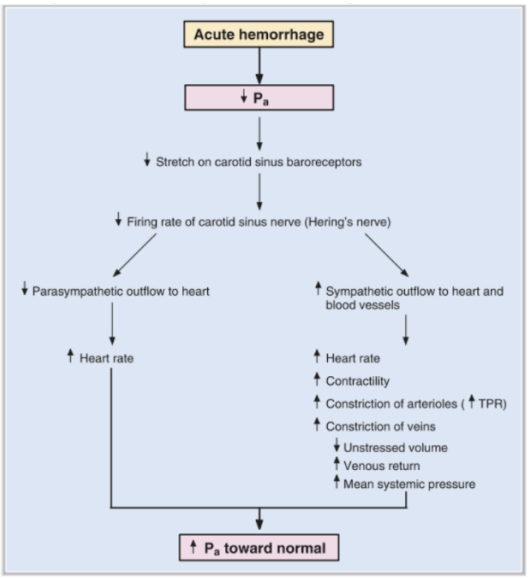


FIGURE 3.16. Role of the baroreceptor reflex in the cardiovascular response to hemorrhage. P_a = mean arterial pressure; TPR = total peripheral resistance.

   - ❖ Example of the baroreceptor mechanism: **Valsalva maneuver**
     - ➢ The integrity of the baroreceptor mechanism can be tested with the Valsalva maneuver (i.e., expiring against a closed glottis).
     - ➢ Expiring against a closed glottis causes an increase in intrathoracic pressure, which decreases venous return.
     - ➢ The decrease in venous return causes a decrease in cardiac output and arterial pressure (Pa).
     - ➢ If the baroreceptor reflex is intact, the decrease in Pa is sensed by the baroreceptors, leading to an increase in sympathetic outflow to the heart and blood vessels. In the test, an increase in heart rate would be noted.
     - ➢ When the person stops the maneuver, there is a rebound increase in venous return, cardiac output, and Pa. The increase in Pa is sensed by the baroreceptors, which direct a decrease in heart rate.

- ○ **Hormonal control including autocoids**
  - ■ **Renin-angiotensin-aldosterone system**
    - ❖ Is a slow, hormonal mechanism.
    - ❖ Is used in long-term blood pressure regulation by adjustment of blood volume.
    - ❖ **Renin** is an enzyme. **Angiotensin I** is inactive.
    - ❖ **Angiotensin II** is physiologically active.
    - ❖ **Angiotensin II** is degraded by **angiotensinase**. One of the peptide fragments, **angiotensin III**, has some of the biologic activity of angiotensin II.
    - ❖ **Steps in the renin-angiotensin-aldosterone system**
      1. A **decrease in renal perfusion pressure** causes the **juxtaglomerular cells** of the afferent arteriole to secrete **renin**.
      2. Renin is an enzyme that catalyzes the conversion of angiotensinogen to **angiotensin I** in **plasma**.
      3. **Angiotensin-converting enzyme (ACE)** catalyzes the conversion of angiotensin I to **angiotensin II**, primarily in the **lungs**.
      - ➢ **ACE inhibitors** (e.g., captopril) block the conversion of angiotensin I to angiotensin II and, therefore, decrease blood pressure.
      - ➢ **Angiotensin receptor (AT1) antagonists** (e.g., losartan) block the action of angiotensin II at its receptor and decrease blood pressure.
      4. **Angiotensin II** has 4 effects:
      - ➢ It stimulates the synthesis and secretion of aldosterone by the adrenal cortex.
        - ★ Aldosterone increases **Na+ reabsorption** by the renal distal tubule, thereby increasing extracellular fluid (ECF) volume, blood volume, and arterial pressure.
        - ★ This action of aldosterone is **slow** because it requires new protein synthesis.
      - ➢ It increases **Na+-H+ exchange** in the proximal convoluted tubule.
        - ★ This action of angiotensin II directly increases Na+ reabsorption, complementing the indirect stimulation of Na+ reabsorption via aldosterone.
        - ★ This action of angiotensin II leads to contraction alkalosis.
      - ➢ It **increases thirst** and therefore water intake
      - ➢ It causes **vasoconstriction of the arterioles**, thereby increasing TPR and arterial pressure.
    - ❖ Example: **response of the renin-angiotensin-aldosterone system to acute blood loss**

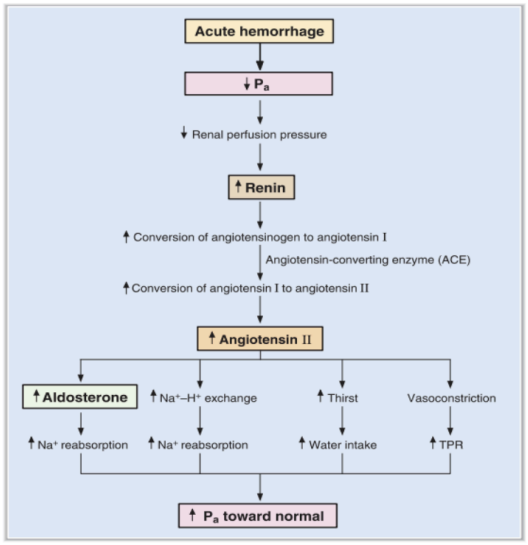


FIGURE 3.17. Role of the renin–angiotensin–aldosterone system in the cardiovascular response to hemorrhage. P_a = mean arterial pressure; TPR = total peripheral resistance.

- **Autoregulation or local control**
  - Cerebral ischemia
    - When the brain is ischemic, the partial pressure of carbon dioxide (Pco2) in brain tissue increases.
    - Chemoreceptors in the vasomotor center respond by **increasing sympathetic outflow** to the heart and blood vessels.
      - Constriction of arterioles causes intense **peripheral vasoconstriction** and increased TPR. Blood flow to other organs (e.g., kidneys) is significantly reduced in an attempt to preserve blood flow to the brain.
      - **Mean arterial pressure** can increase to life-threatening levels.
    - The **Cushing reaction** is an example of the response to cerebral ischemia. Increases in intracranial pressure cause compression of the cerebral blood vessels, leading to cerebral ischemia and increased cerebral Pco2. The vasomotor center directs an increase in sympathetic outflow to the heart and blood vessels, which causes a profound increase in arterial pressure.
  - **Chemoreceptors in the carotid and aortic bodies**
    - Are located near the bifurcation of the common carotid arteries and along the aortic arch.
    - Have very high rates of O2 consumption and are very sensitive to decreases in the partial pressure of oxygen (Po2).
    - **Decreases in Po_2** activate vasomotor centers that produce vasoconstriction, an increase in TPR, and an increase in arterial pressure.
  - **Vasopressin [antidiuretic hormone (ADH)]**
    - Is involved in the regulation of blood pressure in response to hemorrhage, but not in minute-to-minute regulation of normal blood pressure.
    - Atrial receptors respond to a decrease in blood volume (or blood pressure) and cause the release of vasopressin from the posterior pituitary.
    - Vasopressin has two effects that tend to increase blood pressure toward normal:
      - It is a **potent vasoconstrictor** that increases TPR by activating **V_1 receptors** on the arterioles.
      - It **increases water reabsorption** by the renal distal tubule and collecting ducts by activating **V_2 receptors**.
  - **Atrial natriuretic peptide (ANP)**
    - Is released from the atria in response to an increase in blood volume and atrial pressure.
    - Causes **relaxation of vascular smooth muscle**, dilation of arterioles, and decreased TPR.
    - Causes **increased excretion of Na+ and water** by the kidney, which reduces blood volume and attempts to bring arterial pressure down to normal.
    - Inhibits **renin secretion**.

HEMODYNAMICS OF CIRCULATION

Dynamics

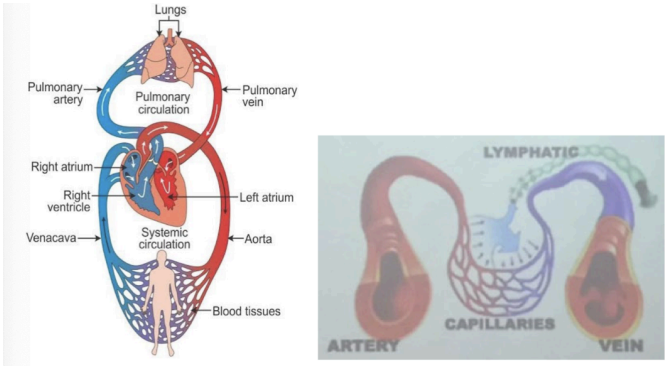
- Refers to the movement of bodies and the action of force.

Hemodynamics

- Is the movement of blood. It is the process by which the blood goes around the circulation, including the forces that affect its movement.

THE HEART, ARTERIES, CAPILLARIES, VEINS, AND LYMPHATICS

- The **circulatory system** observes the needs of the tissues in the body.
- That is to transport nutrients, hormones or transmitters to the metabolizing tissue and to remove the waste products for disposal.
- All this is to maintain the most favorable environment for tissues.
    - That means that the removal of waste and delivery of oxygen and nutrients is so that the tissues can work in the most favorable way possible.
    - So that means that each and every single cell of the body is connected to the circulatory system.



- To do this circulatory system requires **conduits,** the blood vessels to the body and to the lungs. That means that there are two circulations in the body — **pulmonary and systemic** — and from the lungs and the body back to the heart itself.
- And we also need the interface for the actual exchange of nutrients and waste takes place, and that is the **capillaries**.
- And of course, we need the pump that will keep the whole thing going. That's the **heart**.
- Then there is the **lymphatic system**.
    - In simplest terms, there are a series of blind-ended tubes that wrap around each and every living tissue of the body each and every step, and their purpose is to assist in the removal of excess fluid, transport fats, and support immune function.
    - They're just an **accessory**.
- This means that all the components of the circulatory system, from the afferent vessels, to the pump, to the efferent vessels, are programmed for one purpose and one purpose only, to deliver the oxygen rich blood towards the organs while extracting waste and carbon dioxide for excretion.
- The circulatory system is as its name implies a circuit.
    - That means it's a closed loop.
    - It is composed of the conduits to and from the central pump, and the conduits are arteries, veins, and the veins to the accessory — the lymphatics — and the capillaries between artery and vein that handle the exchange in nutrients and waste.
    - So that means that, since it's a closed loop at any given time, the amount of blood in one part of the loop is the same as the amount of blood in any other part of the loop.
    - That's how it is if it's normal.

COMMON STRUCTURE OF THE CONDUITS OF THE VASCULAR TREE

- The conduits are arteries, veins, and lymphatics.
    - The lymphatics and capillaries are **unilayered** (only have one layer), otherwise the veins and arteries have a common structure composed of 3 layers.

(1) Connective Tissue | Tunica Adventitia

- The outermost connective tissue layer for support and protection of the blood vessel.
- In large blood vessels, they also have their own blood vessels supplying that big blood vessel, which are called **vasa vasorum**, and they also have nerves which are called **vasa nervorum**.

(2) Smooth Muscle | Tunica Media

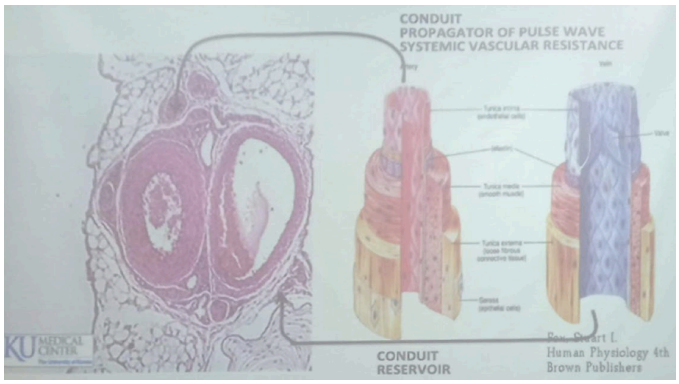
- The second layer that is responsible for constriction (the ability of the blood vessel to recoil).

(3) Endothelium | Tunica Intima

- The innermost layer
- It has 2 important structures, the **internal** and **external elastic membrane**.
    - These are important because they are found in large blood vessels for the purpose of elasticity or recoil.

ENDOTHELIUM

- Consisting of endothelial cells, it is the thinnest type of membrane.
- It is also the most genetically stable, that means that it does not change and mutate but it renews itself every 100 days.
- The endothelium is the largest organ (in the old days we thought it was the liver or the skin) spread in one layer thick.
    - It has approximately 6 tennis courts.
- It is composed of a single layer of **endothelial cells**, followed by **basement membrane**, then **smooth muscle cells**, and then the supporting tissue, usually the **pericytes**, and then the **connective tissue**, and these comprise the **blood vessels**.
- It is the single most important structure of the body.
- It is not just a barrier between the blood and the extravascular space but is a hormonal organ which releases the hormones.
    - The most potent vasoconstrictor, **endothelin**, and the most potent relaxant (dilator), **nitric oxide**, is also produced by endothelium.
    - **Platelet-activating factors** and **anticoagulants** also come from the endothelium



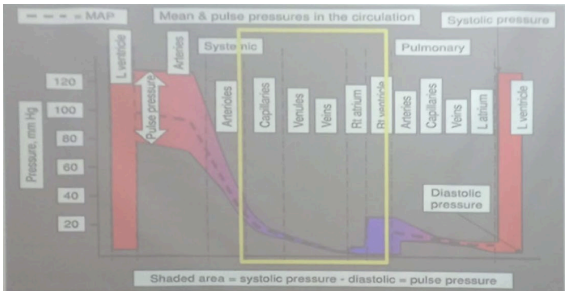
ARTERIES VS. VEINS

Thickness of Tunica Media

- The **vein** has a thinner tunica media, which allows it to become distensible and allows it to become compressible because it does not offer much resistance.
  - Therefore, it is not only a conduit, but it also is a reservoir.
  - The vein is capable of accommodating huge amounts of blood, that is why in the anatomy specimen, the vein is invariably larger than the artery.
- The **artery** has a very thick tunica media, and this allows less distensibility and it allows a blood artery to keep its shape.
  - Therefore, it is not only a conduit. It is a propagator of pulse waves and the source of systemic vascular resistance.
  - It is responsible for the blood to keep going forward.

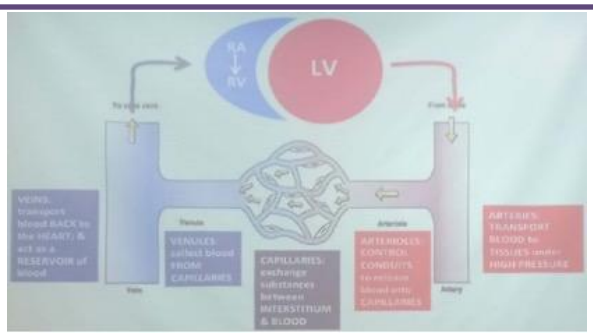
Compliance

- Directly related to volume change and inversely related to pressure change.
- Compliance is the ability of the blood vessel to accommodate volume.
  - The **greater the change in volume** for a given pressure change, the **greater the compliance**.



- The **veins** receive blood from the capillaries (capillary→ venule→ vein), and because it receives from the capillaries and the capillaries are millions, then that means there is a larger volume of blood going into the veins and therefore there is a greater volume change from the little capillaries to the vein.
- The **arteries** come from the heart, and the amount of blood coming from the heart is ejected at such a great force that the body is able to get all of the vessels filled and all of the tissue perfused with just that one pump, so therefore the artery has a great pressure change but the volume is not significantly changed.
  - The arteries are **not distensible** (the higher pressure), it is only one vessel from the heart.
  - The veins have a larger volume and no pressure to deal with because the capillary does not have pressure.

Circulation



- The blood that exits the heart comes from the **left** side. It is driven by the driving force of the heart as it contracts, so it requires the thicker-walled artery to transport blood under a pressure that is big and strong enough to reach all the way from the head to the foot.
- **Arteries:** Transport blood to tissues under high pressure
  - The **arteries** get progressively smaller until they reach the smallest unit, which is the **arterioles**.
- **Arterioles:** Control conduits to release blood into capillaries
  - The arteriole is the main constricting force that regulates the flow into the capillary.
- **Capillaries:** Exchange substances between interstitium and blood
  - The **capillaries** are where the actual exchange of material occurs. It is only in the capillary where there is exchange from the interstitial fluid into the blood vessel.
  - In the conduits in the arteries, there is no exchange and they just serve as conduit and for pressure forward, but the exchange occurs in the capillary.
- **Venules:** Collect blood from capillaries
  - The capillaries carrying their waste product go down into **venules**
- **Veins:** Transport blood back to the heart and act as reservoir of blood
  - The venules coalesce to become larger veins and finally return to the right side of the heart.
- There is no exchange in the artery and vein, only in the capillary. This means that when the blood moves out of the heart, it does so at a speed that is able for all the tissues to get their fair share.

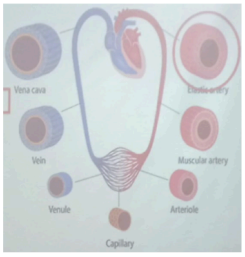
CROSS-SECTIONAL AREAS AND VELOCITIES OF BLOOD FLOW

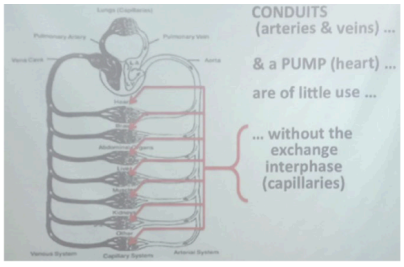
Vessel	Cross-Sectional Area (cm^2)
Aorta	2.5
Small arteries	20
Arterioles	40
Capillaries	2500
Venules	250
Small veins	80
Venae cavae	8

- The velocity of flow is inversely proportional to the cross-section of the passage.
- The **aorta** is the biggest vessel (has an average cross-section area of 2.5 cm^2), but the relationship is flow velocity is inversely proportional to cross-section, but it is fastest in aorta.
- Putting all the **capillaries** together, the cross-sectional is 2,500 cm^2.
- Therefore, since the relationship is:

$$\textbf{Flow velocity} = \frac{Q\ (Total\ flow)}{Cross-sectional\ area}$$

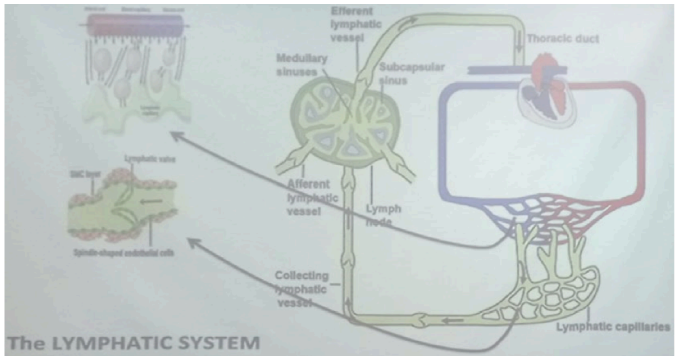
- It means that the flow velocity is inversely proportional to the cross-sectional area, then therefore it is slowest in the capillary because the cross-sectional area of the capillary is huge even if the aorta is the biggest.
- This is necessary because the most important thing is the exchange of life-giving oxygen and nutrients with carbon dioxide and other waste products of metabolism.





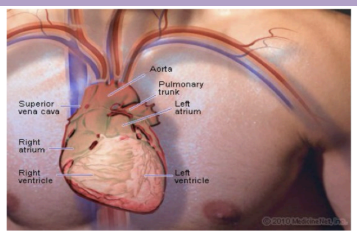
THE LYMPHATIC SYSTEM

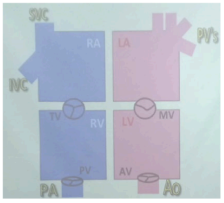
- Blind-ended channels that help to absorb proteins from the interstitial space for transport to the veins
- The lymphatics serve as an accessory drainage for the interstitium, and then once they get all the excess that is in the interstitium, they just bring it back to the vein



NORMAL HEMODYNAMICS

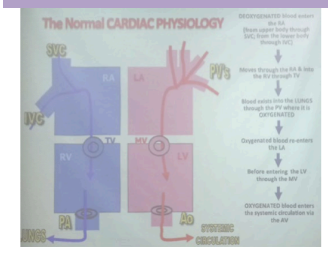
THE NORMAL CARDIAC STRUCTURES

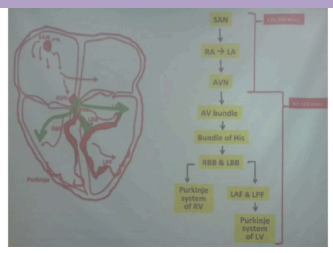




- In the landmarks of the chest, contrary to popular belief when putting the heart in the context of the chest, the heart is not the left side but is in the center and the apex points to the left, but it is in the center.
  - From the front, 2 large veins can be identified, from the upper body, the **superior vena cava** and **inferior vena cava**.
  - 2 large arteries can be identified, the main **pulmonary artery** and the **aorta**.
  - The **heart** itself, the **coronary arteries** (left and right coronary artery), and finally the whole thing is enclosed in the **pericardial sac**.
- The heart begins to twist around the **15 to 20th week of gestation** so that instead of a single tube, it becomes a complex tube.
- The normal cardiac structure consists of 4 chambers, 2 in the upper which are the **atria** (**right and left atrium**) separated by **interatrial septum**.
- There are also 2 in the lower part which are the **ventricles (right and left ventricle)** separated by **interventricular septum.**
  - The entrance to the right ventricle is guarded by the **tricuspid valve** and the entrance to the **left ventricle** is guarded by the mitral valve.
  - The exit from the right ventricle is through the **pulmonic valve** into the **pulmonary artery** to the **pulmonary circulation**, and from the left through the **aortic valve** into the **aorta**, that is to the **systemic circulation**.
  - Entering into the heart are the **superior vena cava** and **inferior vena cava** on the right side carrying **deoxygenated blood** and the **pulmonic veins** on the left side which carry **oxygenated blood**.

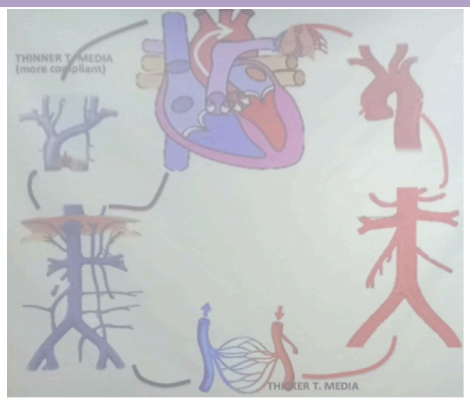
NORMAL CARDIAC PHYSIOLOGY





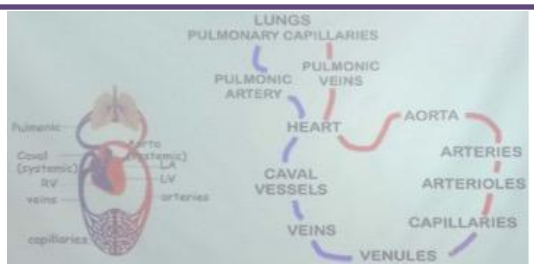
- The deoxygenated blood enters the right atrium from the upper body (**superior vena cava**) and from the lower body (**inferior vena cava**)→ into the **right atrium** and then through the **tricuspid valve** into the **right ventricle**→ blood then exits into the lungs through the **pulmonic artery**.
- In the lungs, the blood is oxygenated. The oxygenated blood returns to the **left atrium**→ through the **mitral valve** into the **left ventricle**→ and then out through the **aortic valve** into the **systemic circulation**.
- These 2 occurs in parallel (not in sequence), which means they are all continuing at the same time so that as the blood enters the right atrium, blood is also entering the left atrium, and as the blood is exiting the right ventricle, blood is also exiting the aorta.
- This kind of system can only be made possible because of the pause and that is why there is the normal conducting system.
  - From the **SA node**, located in the sulcus terminalis between the orifice of the superior vena cava and coronary sinus, when the impulse moves in, it activates the right atrium and the left atrium before going to the **AV node**, and that will cost approximately 120-200 milliseconds, which is enough to get all the blood to get in.
  - Then there is a pause, and the blood enters into the ventricles and then it will take another 40-100 milliseconds from the **AV bundle** all the way to the **Purkinje system** so that the heart will contract and exit all the blood.
- When the electrical phenomenon begins, it is not the contraction (the electrical phenomenon precedes the contraction).
  - It starts in the **SA node**, activates the atria (**right and left atrium**) and causes the **P wave**, then the atria contract.
  - After the depolarization comes the contraction.
  - Activation of the bundle branches, and then the Purkinje, and then the ventricular depolarization and then the ventricles contract.
  - Contraction of the atria→ blood enters
  - Contraction of the ventricle→ blood exits

EXERCISE



- The entry from the body is through the **superior** and **inferior vena cava**, and the heart also has its own venous system through the **coronary sinus**.
- It then goes to the **right atrium** then **right ventricle**, then comes out through the **pulmonary artery** (the only artery in the adult that carries deoxygenated blood).
- It then carries the blood to the lungs where it is oxygenated.
- It enters back into the **left atrium** through the pulmonic veins and then **left ventricle** and then exits through the **aorta**.
- The aorta has 2 parts, the **upper aorta** (ascending, transverse, descending) that is supplying the upper body and the **abdominal aorta** supplying the lower body. These are just conduits (corridors).
- It then goes to the **capillary system**, then it goes to the **venules**, from the lower body (**inferior vena cava**) or upper body (**superior vena cava**), and then back into the **right atrium**.
- The thicker tunica media in the aorta allows the blood to be propagated all the way down and then the thinner media in the veins allows the blood to be accommodated all the way back.

What do blood vessels do?



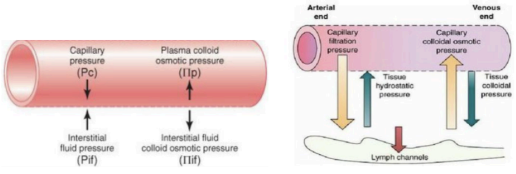
- Hemodynamics ensures that the oxygenated blood cell travels from the heart going to the destination and then back again.
- From the heart to the **aorta** to the **arteries** and then to the **arterioles**, which are the smallest, and create **systemic vascular resistance**. Then it goes to the **capillaries** for exchange, then to the **venules** to the **veins**, and then to the **caval vessels** (inferior and superior vena cava) to the **heart** to the **pulmonic artery** to the **lungs** to the **capillaries** to the **pulmonic veins**.
- The volume of blood that exits from the heart and into the systemic circulation is essentially the same volume that goes into the pulmonic.
    - Despite the pulmonic being a very small circulation, it is still able and necessary to get all the blood into the pulmonic circulation equal to the systemic and this is because blood has to be oxygenated.
    - Therefore, the circulatory system is regulated by many things not just the demand because the demand of the lungs is small since the lungs are nothing but air spaces and it does not need lot of blood and yet the whole blood enters into the pulmonary system because the lungs are necessary to oxygenate, and therefore they need to have that circulation there.

How does the circulatory system manage to do what it does?

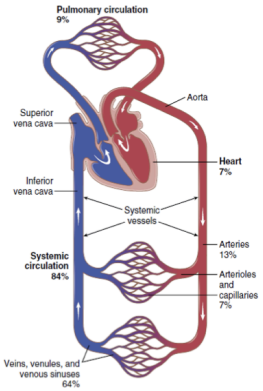
- **The intra- and extravascular fluid volumes**
    - We are about **60-70% water**, the majority of that is **intracellular (6065%)** and only 1/3 is in the **extracellular space (35-40%)**.
    - The extracellular space is also divided into the **interstitial space (65-70%)** and the **intravascular space (30-35%)**.
    - The blood is a very small minority, only about **10-14%** of the total body water and the majority of the water is found inside the cell.

How are the intravascular and interstitial fluid kept separated?

- **Starling's forces** is represented by the force that keeps the blood within the blood vessel and the force that pushes the blood outside of the blood vessel (plasma, because the solid part of blood cannot be pushed out).



- 2 forces of Starling are the **colloidal osmotic pressure (COP)** and the **hydrostatic pressure**.
    - The **colloidal osmotic pressure** which is primarily determined by protein (specifically albumin) is a force that keeps the blood within the blood vessel.
    - The **hydrostatic force** is dependent on blood pressure and is what pushes the blood away (negated by the colloidal osmotic pressure).
- In the **conduits** (**arteries and veins**), when the blood vessel moves through the interstitial space, the interstitial space is equal to the hydrostatic pressure of the blood vessel, and the colloidal osmotic pressure is also equal.
    - Since they are equal, the forces do not move against each other and they are able to stay within their own chamber and that is what makes a conduit (no exchange happens, the pressure within and the pressure without are the same)
- In the **capillaries**, the arterial end still has a significant amount of pressure which causes the capillary pressure to rise. The hydrostatic pressure is now greater than the interstitial fluid tissue hydrostatic pressure, and as a result the movement will be from the capillary into the interstitial space.
    - The artery carries oxygenated blood, so it comes out carrying oxygen, nutrients, hormones, neurotransmitters, at the arterial end. The exchange takes place in the tissue and the waste products of the tissue are drawn back into the capillary.
    - At the venous end, the capillary oncotic pressure is now higher than the colloidal osmotic pressure of the tissue. Since the force that keeps blood in is higher in the venous end, it pulls in the waste products (CO2 and other waste products).

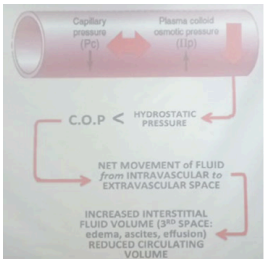


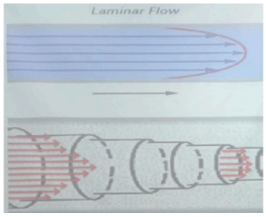
- In the intravascular space, at any one time, the majority is in the **systemic circulation (84%)** and only a little bit left in the **heart and lungs (16%)**.
- In the systemic circulation, a large proportion is in the **vein (64%)**, **13% in the arteries**, **7% in the systemic arterioles and capillaries**, and only **7% in the heart**.
    - 64% of the circulating blood is in the vein because of their property of being very distensible, and that is also why the veins are called **capacitance vessels because** they are a reservoir for blood in case any extras are needed.
    - There is only 7% in the capillaries, that means that the exchange takes place there at any one time, the 7% immediately moves out so that is why at any one time there is only a small amount of blood within the capillary in order that all of that blood will be exchanged in the proper time within the certain cardiac cycle.
    - After the capillaries, all of the blood that goes back to the heart is a huge volume coming into the vein, and compliance is directly related to the volume change and that is why the veins are compliant and much bigger.

APPLICATION

- A man has **liver cirrhosis** (advanced liver disease).
    - Since the liver is for synthesis of all proteins and the main component of colloidal osmotic pressure is albumin, therefore if the liver is malfunctioning and diseased, the synthetic function is affected and the colloidal osmotic pressure will fall because it is dependent on albumin.
    - Nothing happens to the hydrostatic pressure but the colloidal osmotic pressure is less than the hydrostatic pressure so therefore there will be net movement of fluid from intravascular to extravascular space because the intravascular space cannot hold on since it does not have

enough protein, but the hydrostatic pressure is still there and is quite strong and therefore is going to push it out.
  - Clinically, the patient will have an increased interstitial space and that is the current space that means the patient will have edema, ascites, and effusion. As a result, the circulating volume is contracted because it is at the expense of intravascular space. The interstitial space is going to increase so the circulating volume is going to become less.





PHYSICS OF FLUID MOVEMENT IN A CYLINDER

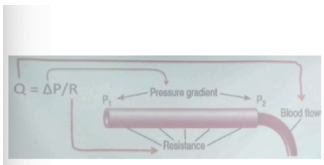
- At any one minute, the volume of blood in any part of the circulation is the same. It means that in any one minute, when the blood exits from the heart, it flows immediately all around and it is only possible because of the inverse relationship between cross-sectional area and velocity of fluids in the cylinder.
- The formula is:

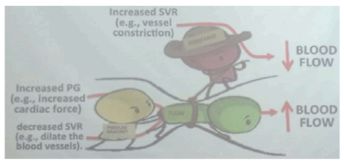
$$\textbf{\textit{Velocity}}\ (V) = \frac{Flow\ (F)}{Cross-sectional\ Area\ (A)}$$

- The cross-sectional area of the capillaries is the largest, therefore it is going to become the area where the flow is lowest, and this is necessary because that is where exchange takes place.
- In the aorta, since it is just a conduit and it needs to take the pressure from the heart so therefore the velocity there is way fast and that is necessary because there is no exchange that is necessary, it just needs to get to its destination as quickly as possible.

Laminar Flow

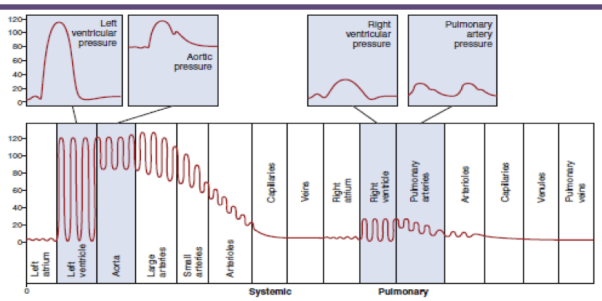
- It is not only the diameter of the vessel that determines forward flow.
  - The behavior of fluids in a cylinder is subject to laminar flow.
- When making a fluid move in a cylinder, the flow in the periphery is going to be much slower because of the effect of friction and because the friction causes a drag, the flow is going to be fastest in the center.
- In a large blood vessel like the aorta, then there is a really fast velocity because it is in the center and the periphery is going to be quite far from the center.
  - But as the artery gets smaller and smaller, there is going to be much contact between the periphery and the blood so there is not much laminar flow in the smallest of blood vessels because the friction is very near to the center and therefore the flow will become slower and does not allow fast flow.





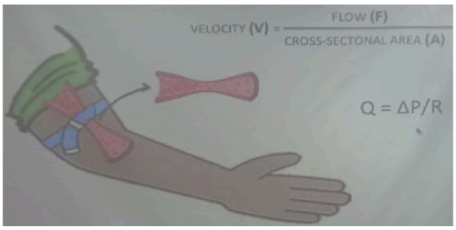
- Laminar flow is the most efficient method of getting from one point to the other, but in the smallest vessels (capillary, arteriole), it is not needed, it is needed to stay a while in order to get exchange.

Pressure Gradient lets the CVS keep the blood moving



- The only way that the blood will flow in a system like this is that there is a **pressure gradient**, that means there must be a pressure change from the aorta and then to the smaller artery to the lesser and lesser so that flow is directly related to the change in pressure. That means if there is a greater change in pressure from the aorta to the blood vessel, then it is going to flow much faster.
- That can be shown in the **AV fistula** of a hemodialysis patient in which there is an artery that is flowing very fast (average velocity: 60 to 120 cm/sec) which will go to a vein which is flowing very slowly (average velocity: 10 cm/sec). If there is a fistula (abnormal communication between artery and vein), then the flow is going to increase (explode) because the gradient is now great and that is why dialysis patients have big blood vessels in their arm.
  - The greater the pressure gradient, there must be a greater flow but then the flow is also inversely related to resistance, that means the greater the resistance (or the smaller the blood vessel), then there will also be initially an increased flow but when the blood vessel is also constricted peripherally, then there will be a decreased blood flow.
  - Therefore, if the resistance is initial (only at that area), the flow will increase, but if the resistance is uniform (distal), then it is going to have a slower blood flow. This is the reason why the pressure gradient will be able to keep the blood moving forward so the pulmonary circulation will have as much blood as a systemic circulation.
- In the pulmonic circulation, there is not much need for a greater velocity because the distance from right ventricle all the way to the left atrium is short so therefore there is not much difference there and the pressure is relatively low, but that low pressure still results in a greater flow (equal to the higher pressure in the systemic circulation).

APPLICATION



- During a medical procedure, a tourniquet was applied to the arm.
- Decrease in **cross-sectional area** slows down the velocity.
  - Since according to the formula, the smaller cross-sectional area, the higher the velocity so therefore when applying a tourniquet, there will be a faster flow, but is inversely proportional to the flow.
- But **flow volume** may not be significantly reduced because the **pressure gradient increases** even if there is **increased resistance**.
  - The flow will be faster but the volume will be less.
- **ANALOGY**: When only one leaflet of the door is open and then everybody goes out, you will get there faster but few will be able

to get out, but if the door is opened all the way, you will be able to get there much slower but there will be more people getting out at the same time.

- The flow is also inversely related to the resistance (tourniquet) but it is directly related to the pressure gradient.
  - Therefore, when there is a constriction, the gradient will be reduced so the pressure change will be reduced because there will be the same pressure. Therefore, the cross-sectional area decrease will slow down the velocity
  - The velocity is inversely proportional to the cross-section. When placing a tourniquet, the narrow cross-section means the velocity decreases, but the flow will not be significantly reduced because the pressure gradient will be able to compensate.

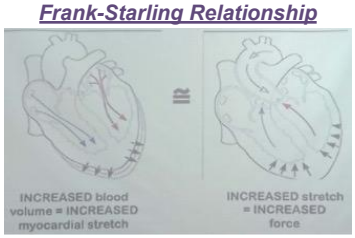
CARDIAC PUMP

- A major determinant of hemodynamics. It ensures that adequate volume will be transmitted to the systemic circulation as well as the pulmonic circulation

Definition of Terms:

- **Stroke volume**: volume of blood that exits the ventricle during each pump.
  - The cardiac pump produces the stroke volume.
  - May be less if dehydrated and may be more if well hydrated.
  - It is compensated by the cardiac output
- **Cardiac output**: stroke volume times number of heart beats per minute (***CO*** = SV x HR)
  - When you are dehydrated, the heart rate will increase.
  - If the stroke volume is reduced by dehydration, but the heart rate increases in compensation, at the end of 1 minute, the cardiac output is unchanged. That is why **heart rate** is an important determinant of the cardiac output.
- **Mean arterial pressure**: force exerted to ensure circulation and tissue perfusion (hydrostatic pressure). It is directly related to the cardiac output and also to systemic vascular resistance (**MAP**=CO x SVR)
  - The greater the cardiac output, the greater the hydrostatic pressure, and it is also directly related to the pressure within the constriction (systemic vascular resistance).
- Stroke volume is affected by **preload**, **afterload**, and **cardiac contractility** (determines the volume of the heart exiting)
- **Preload**: refers to (the volume of blood causing) ventricular stretch at the end of diastole (EDD)
  - It is the volume causing ventricular stretch at the end of the diastole.
  - It is how much blood remains in the heart after the heart has fully relaxed (end-diastolic), so that means it refers to **venous flow** (because that is the amount of blood that enters the heart in the right ventricle from the inferior and superior vena cava and on the left ventricle from the pulmonic veins).
  - Venous flow is the determinant of preload.

Frank-Starling Relationship

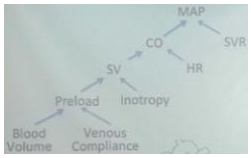


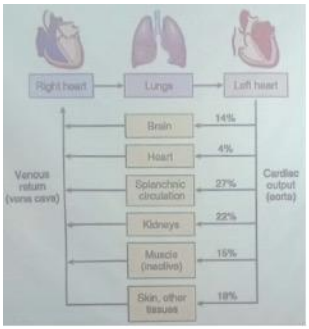
- When stretching the muscle in the heart, the amount of stretch is directly proportional to the amount of contraction. That means the more you stretch, the more force it will be.
- If the heart is filled very much, it will respond to the bigger force.
- The heart fills during **diastole**, and the **heart rate** is the vital sign that is important for the maintenance of diastole. If the heart rate is slow, it allows more time for the heart to fill. If the heart rate is fast, there is less time for the heart to fill.
- Therefore, when the heart rate is slow, the heart fills very much, and then when it contracts, it can be felt.
- In **premature ventricular depolarization**, when there is a regular rhythm and then a premature beat, and then after there is a pause during which the heart fills, and then it contracts and is felt, that is why the people who have PVCs, PVDs, or PADs feel the palpitation because it is the force that was felt.
- The **Starling's law** of the heart means that the greater the stretch, the greater the force of contraction, but this is only up to a limit because eventually if stretched beyond its limit, it will eventually lose its function (like a piece of rubber).
- The **Frank-Starling's law** of the heart is that if in a normal structure heart without excessive volume changes, the greater the stretch the greater, the return contraction.

- **Afterload**: refers to the resistance the ventricle needs to overcome to eject blood with every beat (SVR)
  - When the blood is exiting from the heart, the pressure that it generates together must be enough to overcome the constriction of the main component of systemic vascular resistance (SVR), which is the **arterioles** (the smallest unit of the artery)
  - It is able to do that because the arteriole controls how much blood goes into the capillary, so in times of need (e.g., running), then the arterioles will allow more blood to enter, and then during the time of sleep, the arterioles will not allow more blood to enter. The capillary filling is not continuous, it comes and goes.
  - When there is an afterload, this is the systemic vascular resistance, the resistance to forward flow. If the blood pressure is not enough to overcome the systemic vascular resistance, the blood will go nowhere and that is why it is important in the vital signs to get blood pressure
  - Afterload is the second workload of the heart and it refers to the amount of force/work the heart has to do in order to overcome systemic vascular resistance.
- **Contractility**: refers to the heart's ability to squeeze blood out with every beat (inotropic)

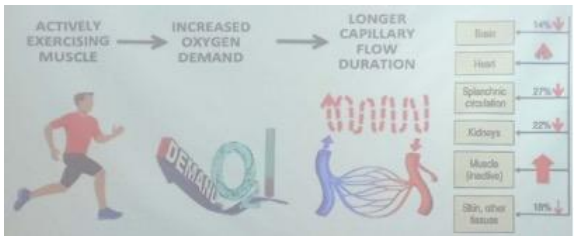
CARDIAC OUTPUT

- The blood filling the ventricles at the end-diastole is determined by circulating **blood volume** and **venous compliance**. It is totally dependent on venous return, and this creates the **preload**.
  - The preload determines stroke volume, which is the amount of blood that exits the heart with every stroke, and it is dependent on how strong the heart contracts.
  - If the heart is not a good contractor, stroke volume reduces
  - If the heart is strong, then the stroke volume is adequate.
  - *Stroke volume x Heart Rate* = ***Cardiac Output***
- The **cardiac output** determines **mean arterial pressure**, that means that it is directly related to blood pressure.
  - The greater the volume, the greater the blood pressure but it is also subject to systemic vascular resistance.
  - *Effect of resistance to forward flow + Cardiac Output =* ***Blood Pressure***
  - Blood pressure is not just the cardiac output. It is also dependent on **systemic vascular resistance.**





- **Cardiac output** is the sum of all the local tissue flow
  - *Cardiac Output = Total Tissue Blood Flow*
  - The circulatory system works to maintain optimum environment for metabolic tissue and it does so by regulating the rate of blood, so blood flow is commensurate to the needs of tissue.
  - The greater the metabolic rate, then also the more blood there is, but there are exceptions:
    - The lung is very small and does not do much, it just exchanges air and yet the volume of blood going to the lungs is large because it needs to oxygenate.
  - In the same way, the volume of blood going to the kidneys is inordinately high and that is because although the kidneys do not themselves use a lot of blood, what they are is excretory so a large volume of blood needs to get to the kidney in order that the body gets rid of its waste products, and that is how blood volume is regulated.

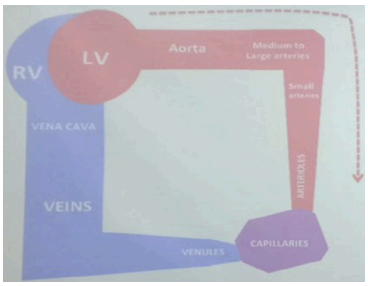


BLOOD FLOW

- **Blood flow** is controlled according to the needs of the metabolizing tissue
  - During the inactive state, the muscles only get about 15% of the blood flow.
  - If one starts exercising, that means the muscles are going to have increased oxygen demand, and due to the increased oxygen demand, a longer time in the capillary is needed to get increased oxygen.
  - The longer capillary flow duration means that the oxygen will get there, but you can only get longer capillary flow if there is more blood going there, and therefore during the time of exercise of the muscle, there is a massive increase in the muscle blood flow and some increase in the heart blood flow (heart is a muscle) and decrease in the blood flow to the other areas.
  - The body is a very primitive organ and it does not know the difference between physical and emotional/mental stress.
    - If there is a fire and you get stressed because you need to get out of the way of danger, then the body will respond by increasing blood flow to the muscles, heart, and reducing blood flow to the other parts of the body, that is why you can lift a whole piano when there is a fire, but after the fire, you are not able to.
    - If you are upset, that upset is also emotional stress and since the body does not know the difference, it responds in the same way. The blood pressure and heart rate goes up and blood is siphoned away from organs the body thinks it does not need. The body responds by fight or flight so all the blood goes to the muscles and are ready to fight or to run away. All the other organs have a lesser blood flow and that is why you get pale because the blood is siphoned in the skin, and that is also why when you are upset, you feel like going to the bathroom all the time because the splanchnic circulation is considered not important in the fight or flight response so the blood withdraws from the GI tract.

APPLICATION

- There is a fire and you need to remove a 32-inch tv down to the garage. You are sweating and you have not had breakfast yet. Which organs will require more blood and which will be able to be put on hibernation?
  - Muscle, heart, and to some extent the skin. Since you are sweating, the skin should have more blood in order to cool you off. There is a decreased demand from the GI tract, brain, since you have not had any food yet.
  - Blood kept in the "reservoir" (veins) released back into active circulation via venous contraction→ vein collapse→ increased circulating volume
  - As a result, the blood kept in the reservoir (veins) are going to be squeezed out because of the increased demand needed, and since you have not had any food yet and are dehydrated, what happens is that the veins will collapse and they will send the blood to the circulation to augment the blood flow to where it is needed and there will be an increase in the blood flow in the artery, systemic arterioles, capillaries, and heart.



- The pump pushes the circulating blood through the arteries, and they are called the **afferent vessels**, towards the tissue and that is going to the interface which is the capillaries.

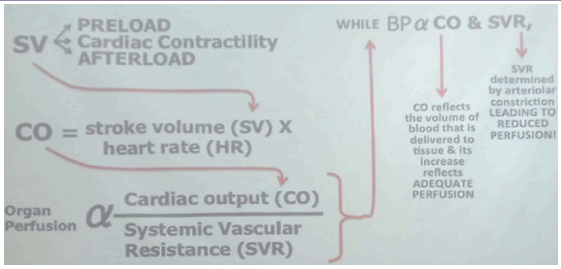
Why do we need an aorta?

- The aorta is not just the biggest blood vessel in the body. It is the conduit through which the blood is ejected from the left ventricle into the systemic circulation.
- It is an organ which is capable of storing pressure
- **Systole:** Aorta expands and absorbs the pressure wave from the contraction of the ventricle (stores energy from pressure wave)
- **Diastole:** Aorta releases the pressure wave via elastic recoil in order that the blood will go forward.
- In the tunica intima of the aorta, there is an **internal** and **external elastic membrane** in order that the elastic recoil of the aorta is very large and this is responsible for the **continuous capillary filling** throughout the diastole.
- **Windkessel Effect:** When the heart pumps, the aorta will dilate and then when the heart relaxes, the aorta continues and is never stopping because it is able to save that pressure.
  - Among all the blood vessels in the body, only the aorta is a Windkessel. It is like a capacitor because it is a form of air, when the capacitor hits, the air will push the fluid forward.
  - The exchange of nutrients occurs in the capillary level.

HOMEOSTASIS | BALANCE

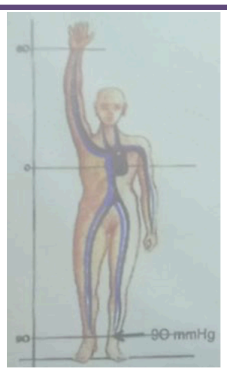
- There is a balance between oxygen requirement and oxygen delivery and the cardiopulmonary system ensures that there is an adequate oxygen delivery to commensurate with the oxygen requirement.

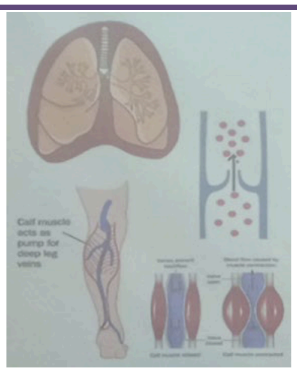
Is a "normal" BP a reflection of adequate perfusion?



- Stroke volume is dependent upon **preload**, **contractility**, and **afterload**, and *Cardiac Output = Heart Rate.*
- The **organ perfusion** is dependent directly on **cardiac output (CO)**, but is inversely proportional to **systemic vascular resistance (SVR)**.
    - **Cardiac output (CO)** reflects the volume of blood that is delivered to tissue and its increase reflects **adequate perfusion**.
    - **Systemic vascular resistance (SVR)** is determined by arteriolar constriction leading to **reduced perfusion**.
    - The more cardiac output, the more perfusion because of the hydrostatic pressure.
    - If there is an increased systemic vascular resistance, there is a resistance to forward flow and therefore, the more the systemic resistance, the less the organ perfusion.
    - The **blood pressure** is directly related to **cardiac output**, but it is also directly related to **systemic vascular resistance** so that therefore, if the blood pressure is maintained because all the blood vessels are constricted, then the perfusion of the organs is compromised, and the **cardiac output** is needed since it is the most important determinant of tissue perfusion.
        - Just because the blood pressure is normal, it does not mean that it is adequately perusing all of the tissues of the body.
- Therefore, organ perfusion, blood pressure, and good circulation are not the same.

How does blood return to the heart?





- The blood in the **artery** is driven by the driving force of the contraction of the heart.
- The **veins** have a pressure of about 0.
    - When lying flat, the pressure is around **0 mmHg** in the feet all the way to the heart. The terminal of all the veins of the body is the right atrium and the pressure there is 0.
    - When standing, the effect of gravity raises the pressure to about **90 mmHg,** and the blood has to fight that pressure to get back to the heart, and it is 0 in there.
- There are 3 mechanisms as to how does it get back
    - The proper inhalation is **full expansion of the chest**, and this creates a vacuum because the chest is a closed cavity and then the lungs, when the lungs expand, there is no way for the chest to get out of the way, therefore creating negative pressure intrathoracic, and that creates a **vacuum effect** and the vacuum effect causes the blood to be sucked upward.
        - Many people have varicose veins because the veins need the proper expansion of the lung to be able to be sucked up and we do not get much effect due to sedentary lifestyle.
    - The **integrity of the valves**. The valves of the vein are different from the other kinds of valves in the heart. They are not active valves so they do not open and close and they are a parachute.
    - When inhaling, the parachute opens and then blood goes through. When exhaling, the parachute closes and the blood is prevented from backing up.
    - Unfortunately, laminar flow allows the blood to flow fast, but in addition to the friction of the blood vessel wall, there are valves which have a tendency to pull the area and create little clots.
    - When there is no movement of the legs, the blood flow becomes static and the blood tends to pull the area and causes a little clot (not enough to cause DVT) that will organize and then pull up the valves since it is stuck to the wall.
    - Prolonged immobilization increases the risk for varicose veins and venous insufficiency.
- The **calf pump**. The most important aspect of the return flow because when the gastrocnemius muscle is constricted, it is able to push 20% of the lower body blood volume back into the heart.
    - When wearing high heels, you are constantly dorsiflexed, and that means that there is no flexion at the back and therefore the blood is going to cool.

NEURO-ENDOCRINE CONTROLS

Oxygen Delivery

- It is dependent primarily on **cardiac output (CO)**.
- It is hindered by **systemic vascular resistance (SVR)**.
- **BP:** *Blood Pressure = CO x SVR*
- **CO:** *Cardiac Output= Heart Rate x Stroke Volume*
- The **cardiac output** is directly affected by an increased **heart rate**, an increased **stroke volume**, but it is not going to be affected by **blood pressure**.

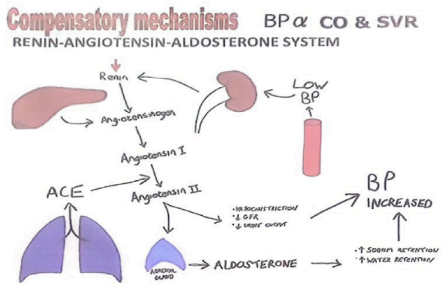
Compensatory Mechanism

- ↓**BP:** ↑ HR, SV, and SVR in order to maintain CO
- ↓**CO:** ↑ HR and SVR
    - The main organ responsive to decreased flow is the **kidney** because it is the main organ for controlling blood pressure.
    - When there is a decreased flow in the kidney, the glomerulus receives less blood, and it stimulates the glomerular tuft, and the glomerular tuft is stimulated to produce **renin**, and renin stimulates the liver to produce **angiotensinogen**.
    - In the blood, the angiotensinogen is converted to **angiotensin I**, which is still inactive and needs to be converted to **angiotensin II,** which is the second most potent vasoconstrictor of the body.
        - The most potent vasoconstrictor in the body is **endothelin**, which is produced by the endothelium.
        - Angiotensin I is converted to angiotensin II by the action of **ACE (angiotensin-converting enzyme), which is produced by the lungs.**

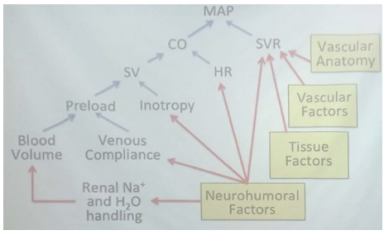
- Angiotensin II also causes adrenergic stimulation, which causes **increased heart rate**, and because it is a vasoconstrictor, it causes **increased systemic vascular resistance**.
  - It also stimulates the adrenal gland to produce the mineralocorticoid (**aldosterone**) that produces sodium, therefore water, which **increases preload.**
- When there is decreased perfusion, the **sympathetic nervous system** causes the release of **catecholamines.**

Cardiovascular Adrenergic Receptors

- The adrenergic receptors are the parts of the different working tissues, especially muscle and skin, that receive the adrenergic stimulant.
- **α1**: **Post-synaptic neurons of the vascular smooth muscle, and their effect is vasoconstriction.**
  - (+) inotropic, (-) chronotropic effects on the myocardium
- **α2**: **Pre-synaptic modulation of large vessel vascular tone**
  - Counter-regulatory to α1
  - It **inhibits norepinephrine**, the most important neurotransmitter
  - Reduces adrenergic activity
  - In CNS, it causes peripheral **vasodilation**.
  - Alpha-adrenergic drugs generally cause vasoconstriction. If there is someone who is resuscitated because of vasoconstriction, it reduces flow to the brain. Since α2 is present in adrenaline, it has a protective effect on the coronary and cerebral, making **adrenaline (epinephrine)** the most important resuscitation drug.
  - Post-synaptic receptors can mediate **arteriolar** and **venous vasoconstriction** (stimulated later on).
- **β1: Increases heart rate** and **myocardial contractility**
- **β2: Vasodilation** and relaxation of bronchial, uterine, GI smooth muscle
  - It relaxes the smooth muscles of the bronchi, that is why β2 agonists are good for asthma, they relax the uterus that is why they are also used in premature contractions.
  - **Drives K+ intracellularly** so that they may cause **hypokalemia** and contribute to development of arrhythmias
- **Dopaminergic**: **Pre-synaptic and post-synaptic receptors** found in the renal, cerebral, and mesenteric vascular beds
  - When stimulated, they cause **vasodilatation**.



- Therefore, the neurohormonal factors affect the renal by causing sodium and water retention, and thus **increasing blood volume and increasing preload.**
  - They also **increase venous compliance** because they will also have an effect on the constricting ability of the artery and the vein. They will also affect inotropy because they are inotropic agents.
  - They will **increase heart rate** by the release of adrenergic stimulation and **increase systemic vascular resistance.**
  - Other factors that affect SVR are the anatomy (vasoconstriction due to tourniquet application), vascular factors (endothelin, nitric oxide, endothelium), and other tissue factors.
- All of the things that happen are interrelated and they will all have an effect somewhere else.

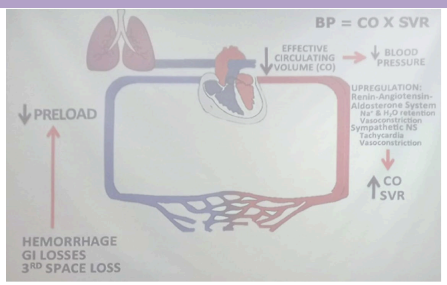


INTRODUCTION TO ABNORMAL HEMODYNAMICS

SUMMARY OF NORMAL HEMODYNAMICS

- The **intravascular fluid volume (30-35%)** is the smallest part of the components of the fluids of the body, and the **interstitial space (65-70%)** is more than twice in size.
- The forces that keep the blood within the circulatory system are kept in balance. The **colloidal osmotic pressure** keeps the fluid within the blood vessel while **hydrostatic pressure** pushes the fluid out of the blood vessel.
  - The colloidal osmotic pressure equals the colloidal osmotic pressure in the interstitial fluid and in the conduit blood vessels.
  - The interstitial hydrostatic pressure equals vessel hydrostatic pressure in the conduit vessels. Therefore, there is no net movement.
- In the capillaries, at the arterial end, the **capillary hydrostatic pressure** is greater than **tissue hydrostatic pressure** pushing the plasma and everything out into the tissue.
  - At the venous end, the **colloidal osmotic pressure** is greater than the one in the tissue causing the blood to move back in carrying all its waste products for excretion.
- The **efficiency of the cardiac pump** is that it is automatic because it is continuously depolarizing and repolarizing in the cardiac action potential. The efficiency of the cardiac pump is subject to the demands of workload: Preload, Afterload, and Inotropy
  - The **preload** is the amount of venous return and it is approximately the end-diastolic diameter (how much the heart dilates).
  - The **afterload** is the resistance to forward flow that has to be overcome by the **cardiac contraction** and finally the **inotropy**.
  - They are affected by neurohormonal factors primarily, but other factors affect systemic vascular resistance including **vascular anatomy, vascular factors, and tissue factors**.

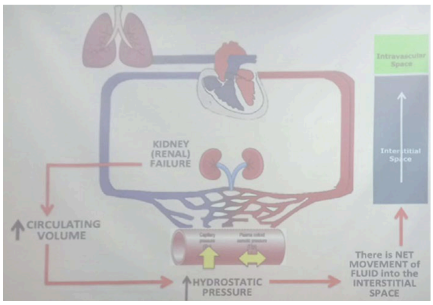
APPLICATION



- You have diarrhea or blood loss. What are the consequences of hemorrhage, diarrhea, or 3rd space loss? Which part of the circulation is affected?
  - If there are losses, the **circulatory volume** is affected. If there is a reduction in circulatory volume, the **preload** will be affected because it is the distention of the ventricle with the return, and is dependent on venous return.
  - The preload will decrease, as a result, there is a reduction in the amount of blood excreted (**decreased stroke volume**), which **decreases blood pressure** and will activate the neurohormonal system and causes upregulation of the RAAS, sympathetic nervous system,

contraction of the venous system in order to compensate for the loss. As a result, there is an **increase in cardiac output and systemic vascular resistance.**

- If you have hemorrhage, GI losses (diarrhea), or edema, you will not just be going to collapse and die. Your body will try to compensate by these mechanisms.



- A patient has renal failure. What does the kidney do?
  - The primary role of the kidney is water and electrolyte balance and is an excretory organ. When the kidney fails, there is an imbalance. If the kidney is unable to produce its function, which is water and electrolyte balance, it will retain water because it cannot leave anymore, therefore there is an **increased circulating volume.**
- It will increase cardiac output and i**ncrease hydrostatic pressure**, and the volume of the blood is increased, but it does not mean that the protein will increase. There will be a dilution of the protein, therefore **colloidal osmotic pressure may decrease** and there will be an increased hydrostatic pressure. There will be a net movement of fluid from the intravascular space into the interstitial space, causing an **increase in interstitial or 3rd space,** and it will be clinically manifested as edema.

SUMMARY

- Hemodynamics refers to the **process** by which **blood** makes its way through conduits (**blood vessels**) as driven by a pump (**heart**).
- Hemodynamics allows the provision of the **optimal environment** for tissue metabolism according to the needs of that tissue.
- This continuous process of **circulation** is made possible by the action of the **pump** and the physics of the movement of fluids within a cylinder; and modified by the **neuroendocrine system** in accordance with the needs of metabolizing tissue.

HISTORY

- 1842
  - Italian scientist Carlo Matteucci realizes that electricity is associated with the heart beat
- 1876
  - French physiologist Etienne-Jules Marey analyzed the electric pattern of a frog's heart
- 1895
  - Dutch physician and physiologist Willem Einthoven was credited for the invention of EKG and later received the Nobel Prize in Physiology and Medicine in 1924
- 1906
  - Using the string electrometer EKG, Willem Einthoven diagnosed some heart problems

WHAT IS AN ECG?

- A recording of the electrical potentials generated by electrical currents from the heart into the adjacent tissues, which are detected by electrodes placed on the surface of the body.
- ECGs help in the diagnosis of cardiac and noncardiac disorders:
  - Arrhythmias and Conduction Blocks
  - Myocardial ischemia and infarction
  - Chamber hypertrophy
  - Pericarditis
  - Pericardial effusion/tamponade
  - Electrolyte disturbances
  - Drug toxicity

ACTION POTENTIAL, ELECTRICAL STIMULATION, AND CARDIAC CONTRACTION

- **Action Potential:** Depolarization and Repolarization phases of the cardiac myocyte membrane
  - It will cause electrical stimulation, which will then be the ultimate cause of cardiac contraction.
  - What is recorded in the ECG is the depolarization and repolarization sequence (it is not contraction but action potential).

The ECG in relation to the Cardiac Cycle

Big Picture First

- The ECG records **electrical activity** of the heart.
- The cardiac cycle describes **mechanical activity** (contraction and relaxation).

→ Electrical events trigger mechanical events.

- So on the timeline: **ECG change → short delay → muscle contracts or relaxes**
- Think of electricity as the **spark**, and contraction as the **engine movement**.

One Complete Cardiac Cycle – Imagine one heartbeat as a loop:
The atria fill with blood → atria contract → ventricles fill → ventricles contract → blood is ejected → ventricles relax → filling starts again.
Now we layer the ECG on top of that story.

P WAVE → ATRIAL DEPOLARIZATION → ATRIAL CONTRACTION

What the P wave is

- The P wave represents **depolarization of atrial muscle fibers**.
- Depolarization = sodium entering atrial cells → membrane potential becomes less negative → cells become electrically active.

What happens mechanically after

- A short moment after the P wave begins, the atria **contract**.
- This contraction is called **atrial systole**.
- Atrial systole pushes the last bit of blood into the ventricles — about **15–20% of ventricular filling** (called the *atrial kick*).

Simple chain
P wave
→ atrial depolarization
→ atrial contraction
→ final ventricular filling

NOTE: If P waves disappear (e.g., atrial fibrillation), ventricular filling decreases → ↓ cardiac output, especially in elderly or stiff ventricles.

PR Interval → AV Nodal Delay

- The PR interval is measured from the **start of the P wave** to the **start of the QRS complex**
- It represents:
- Time for the impulse to travel SA node → atria → AV node → His-Purkinje system
- Why the delay exists – The AV node conducts **slowly**. This delay allows:
  - ✔ Atria to finish contracting
  - ✔ Ventricles to finish filling
    → Before ventricles contract.
- Clinical meaning
  - Normal PR interval: 0.12–0.20 seconds
  - Prolonged PR = first-degree AV block.

QRS Complex → Ventricular Depolarization → Ventricular Contraction

What the QRS complex is

- Represents **rapid depolarization of both ventricles**.
- Large amplitude because ventricular muscle mass is large.
- Atrial repolarization happens here too, but it's hidden inside QRS.

What happens mechanically after

- Shortly after QRS begins:
- Ventricles start to **contract** → ventricular systole begins.
- This creates a rapid rise in ventricular pressure.

Two phases follow:

1. **Isovolumetric contraction –** Valves closed, pressure rising

2. **Ejection phase –** Semilunar valves open, blood exits heart

QRS
→ ventricular depolarization
→ ventricular contraction
→ blood ejection

NOTE: Wide QRS = abnormal ventricular conduction (bundle branch block, ventricular rhythm).

ST Segment → Ventricles Fully Depolarized → Plateau Phase

- The ST segment is the flat line after QRS.

- It represents the time when ventricular muscle cells are:

Uniformly depolarized
This corresponds to the **plateau phase (phase 2)** of ventricular action potentials.

Mechanical meaning
Ventricles are **actively contracting and ejecting blood** during ST segment.

NOTE:
- ST segment ≈ **middle of ventricular systole**
- CLINICAL NOTE: ST elevation or depression = myocardial ischemia or injury.

T Wave → Ventricular Repolarization → Ventricular Relaxation

What T wave is
- Represents **repolarization of ventricular muscle**.
- Potassium exits cells → membrane potential becomes negative again.

What happens mechanically after
- Ventricular muscle **relaxes** → ventricular diastole begins.
- Pressure in ventricles falls.
- Once ventricular pressure drops below atrial pressure:
- AV valves open → ventricular filling starts.

Simple chain
T wave
→ ventricular repolarization
→ ventricular relaxation
→ filling phase

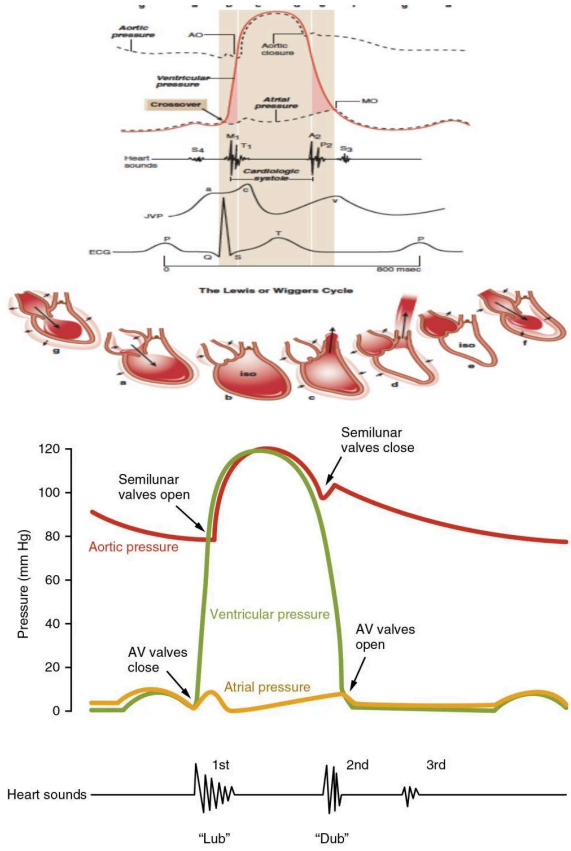
ECG Component	Electrical Event	Mechanical Event
P wave	Atrial depolarization	Atrial contraction
PR interval	AV nodal delay	Ventricles filling
QRS	Ventricular depolarization	Ventricular contraction
ST segment	Ventricles fully depolarized	Blood ejection
T wave	Ventricular repolarization	Ventricular relaxation

Key Principle (Very Testable): Electrical events always precede mechanical events. ***Never the other way around.***

If a question asks:
"What ECG wave occurs during atrial systole?"
Answer: **P wave (slightly before contraction)**

Relationship to Heart Sounds
- **S1 (lub)** occurs just after QRS
  → AV valves close at start of ventricular systole
- **S2 (dub)** occurs near end of T wave
  → Semilunar valves close at start of ventricular diastole

NOTE:
❌ Saying P wave = atrial contraction
✔ Correct: P wave = atrial depolarization
❌ Saying QRS = ventricular systole
✔ Correct: QRS = ventricular depolarization; systole follows
❌ Thinking T wave = diastole
✔ Correct: T wave = repolarization that leads into diastole



Major ECG Waveforms

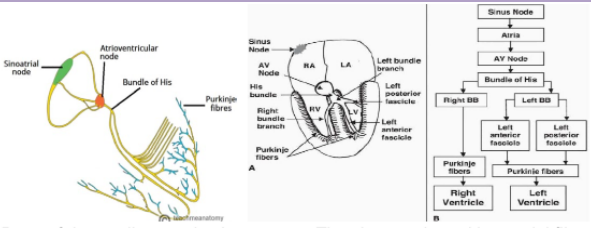
- P and QRS complex occur before major cardiac contractions
- P wave occur during atrial contraction
- QRS complex occur before ventricular contraction
- ST and T wave occur during the diastolic (filling) phases

The Cardiac Conduction System

- Generates electrical impulses to initiate rhythmical contraction of the heart muscle.
- Conducts these impulses rapidly through the heart.
- The heart as an organ is composed of cardiac myocytes (atrial and ventricular myocytes).
- There are specialized myocytes in the heart that function as the electrically conductive tissue of the heart.
- The heart beats itself independent of central nervous system from a few weeks gestation up to the entire life.
- The cause of this battery is the cardiac conduction system.

PARTS OF THE CARDIAC CONDUCTION SYSTEM

The sinus node and interatrial fibers will all converge into the AV node.



- In a normal heart, there should be no other electrical communication between the atria and the ventricles except through the AV node.

- ➔ If there are abnormal pathways communicating the atria to the ventricle, it is called a bypass tract. If it is a functional bypass tract, it will show abnormalities in the ECG.
- ➔ Any block anywhere in the conduction system will have characteristic ECG changes. Major blocks of the right and left bundle are called complete right bundle branch block (CRBBB) and complete left bundle branch block (CLBBB) respectively.
- ➔ From the AV node, it penetrates the interventricular septum as the penetrating bundle or bundle of His.
- ➔ It then divides into 2 major bundle branches, the right and the left branches, and then it will terminate just below the endocardium as the Purkinje fibers or Purkinje system.
- ➔ The left bundle branch before terminating as Purkinje fibers, it will divide into the left anterior and posterior fascicles.

SINOATRIAL NODE (SA NODE)

- The heart's natural pacemaker
- It discharges the fastest rate, at 60–100 beats per minute at rest.

AV NODE

- Receives impulse from SA Node
- Delivers impulse to the His-Purkinje System
- It discharges at 40–60 BPM if SA Node fails to deliver an impulse

BUNDLE OF HIS

- Begins conduction to the ventricles
- At AV junctional tissue
- It discharges at 40–60 beats/minute

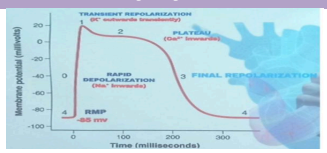
THE PURKINJE NETWORK

- Bundle Branches/Purkinje Fibers
- Moves the impulse through the ventricles for contraction
- Provides "escape rhythm"
- It discharges at 20–40 beats/minute
- In a cardiac arrest patient, for every second that the heart cannot be revived, there is successive ischemia of the cardiac conduction system. The AV nodes, bundle of His and Purkinje fibers will take over (ventricular escape rhythm), which is at a very slow rate.
  - The stroke volume is very dependent on the heart rate.
  - A heart rate that is dependent on ventricular escape rhythm at 20–40 bpm rarely produces a blood pressure that is enough to generate a perfusing blood pressure.

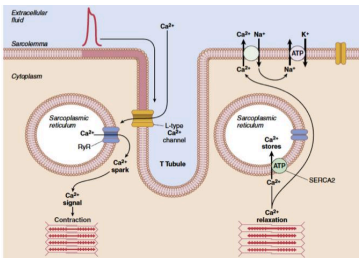
THE CARDIAC ACTION POTENTIALS

If electrodes are placed in the cardiac myocyte membranes, it will generate action potentials, especially if stimulated electrically.

The Ventricular Myocyte Action Potential



- It starts in phase 4, which is the **resting membrane potential** (**-85 mV**), which means -85 mV inside the membrane.
- In phase 0, it will shoot up and is called **rapid depolarization**.
  - ❖ It is caused by Na^+ moving inwards (the inside of the membrane from a very negative value, it will become positive, about 20 mV).
  - ❖ If it reaches that level, it will return back to negative transiently.
- In phase 1, it will return back to negative transiently and is called **transient repolarization**.
  - ❖ It is caused by K^+ going out of the cell, loosing positivity inside the
  - ❖ cell, but is only transient.
- In phase 2, the transient repolarization is offset by a **plateau** phase.
  - ❖ This is characteristic of a myocyte and is not seen anywhere else in the body (not in the skeletal, smooth muscle, or sinus node)
  - ❖ It is caused by slow Ca^{2+} movement towards the inside, that is why positivity is maintained for a few milliseconds.
  - ❖ The transport channel responsible for this is the **L-type calcium channels** which are characteristic of the ventricular myocytes.
- In phase 3 (**final repolarization**), it goes back to a more negative value at resting -85 mV
  - ❖ It is caused by K^+ going out of the cell.
- Anything that brings the potential back to the negative is usually K^+ going outwards.
- The usual ions causing membrane potentials to become more positive are Na^+ and Ca^{2+}.



Mechanism of excitation-contraction coupling and relaxation in cardiac muscle

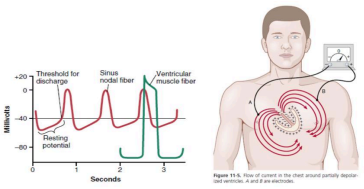
- In this depolarized membrane, this is ready to contract and then it will be propagated all throughout the myocardium before contraction would occur.

The Pacemaker Action Potential

- The **resting membrane potential** (phase 4) is much less negative at around -55 to -60 mV (-85 mV in cardiac myocytes)
  - ❖ The RMP does not rest and it slowly drifts upward (unlike in ventricular myocytes that it becomes isoelectric)
  - ❖ It is due to the **"funny" channels**. It is called as such because it is naturally leaky to Na^+ and Ca^{2+} and does not absolutely close.
    - ➢ It constantly leaks Na^+ out of the cell membrane such that constantly, the inside of the cell is gaining positivity, that is why the RMP drifts slowly towards the positive.
- When it reaches -40 mV, it is the threshold and there is nowhere to go but **rapid depolarization** (phase 0).
  - The rapid depolarization of the sinus node action potential is mainly secondary to Ca^{2+} going in because at this level, the "funny" sodium channels will close.
- There is no **transient repolarization** (phase 0) and **plateau** (phase 1) in the sinus node (unlike in cardiac myocytes).

- It goes to **final repolarization** (phase 3) right away.
  - ❖ It is due to K_+ going out of the cell (loosing positivity inside the cell)
- It then reaches baseline around -55 mV and then it slowly drifts again to -40 mV because of the "funny" sodium channels.
- It is the **pacemaker** because naturally it does not rest in the RMP but it slowly drifts upward, and then threshold, and then it fires.

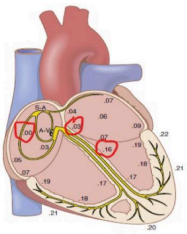
○ **Differences between Sinus-Nodal and Ventricular Muscle Action Potentials**



Flow of Electrical Currents in the Chest Around the Heart

- Current flows from negative to positive primarily in the direction from the base of the heart toward the **apex** during almost the entire cycle of depolarization.
- The waveform of depolarization starts at the base of the heart and then towards the apex.
- The average current flow occurs with negativity towards the base of the heart and with positivity toward the apex.

TRANSMISSION OF CARDIAC IMPULSE THROUGH THE HEART



The numbers indicate the time interval from the sinus node to the rest of the heart (the arrival of the electrical potential)

○ SA to AV = **0.03 second**
- Starting from 0.00. The **sinus node** is located in the junction of the SVC and the RA. Then electrical potential will travel to both **atria** and then it arrives in the **AV node** after 0.03 second.
- In normal hearts, it should be accurate to the millisecond. Any abnormality in the length of time will be visible in the ECG.

○ Within AV Node = **0.09 second**
- There is the **natural atrioventricular nodal delay**.
- When the impulse arrives, it has a 0.09 second delay which is normal because it is for proper atrioventricular synchrony. The atria are not passing chambers and they also contract. When the atria contracts, the ventricles has to relax so that there is proper flow of blood. When the ventricles contract, the atria has to relax.

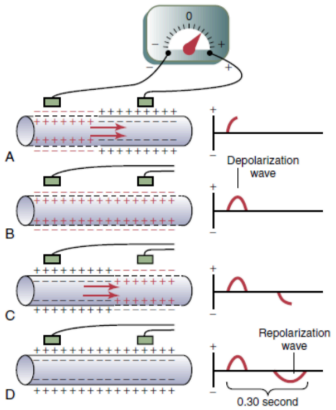
○ AV Node to Penetrating bundle (Bundle of His) = **0.04 second**
- There is an additional 0.04 seconds delay in the bundle of His

○ SA to Penetrating bundle = **0.16 second**

FUNDAMENTAL CARDIAC ELECTROPHYSIOLOGY PRINCIPLES

- **Transmembrane ionic currents** are generated by ion fluxes across the cellular membrane and between adjacent cells.
- These currents are synchronized by cardiac activation and recovery sequences to generate a **cardiac electrical field** in and around the heart that varies with time during the cardiac cycle.
- This electrical field passes through numerous other structures, including the lungs, blood, and skeletal muscle, that perturb the cardiac electrical field.
- The currents reaching the skin are then detected by electrodes placed in specific locations on the extremities and torso that are configured to produce leads, representing the difference in potentials sensed by pairs of electrodes or electrode combinations.
- The outputs of these leads are amplified, filtered, and displayed, using a variety of devices, to produce an ECG recording

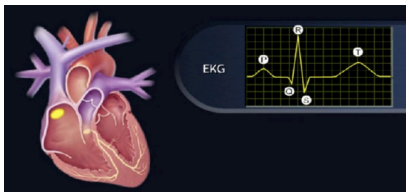
○ **Depolarization vs. Repolarization Waves**



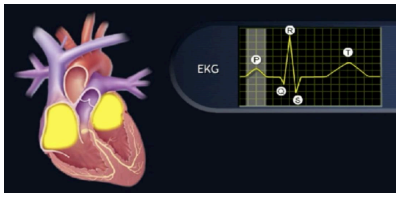
- Electrical impulse that travels toward the positive electrode produces an upright ("positive") deflection.
- Depolarization is the inside of the cell is going positive.
  - In an ECG lead, a lead has a positive input and a negative input.
  - If the depolarization wavefront is going to the positive input of that lead, it will record a positive deflection in the ECG (an upward wave).
  - The reverse is true with repolarization.

THE NORMAL ECG WAVEFORMS

Impulse Generation in the Sinus Node

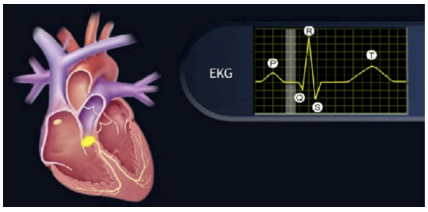


Atrial Depolarization



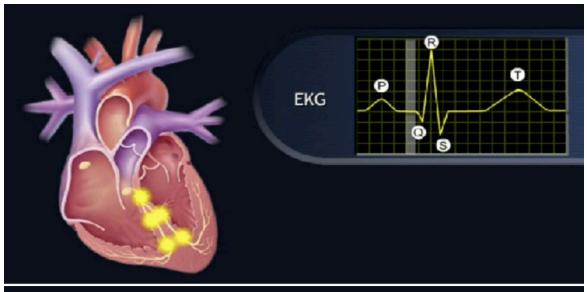
- P wave represents atrial depolarization, the left and right.
  - Mainly the left because ECG mainly records the left because everything in the right is overshadowed by the left (there is more electricity and muscles in the left)

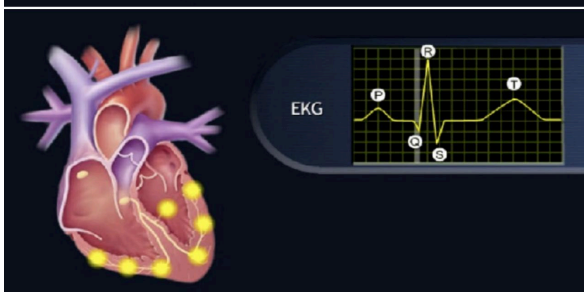
Atrioventricular (AV) Delay



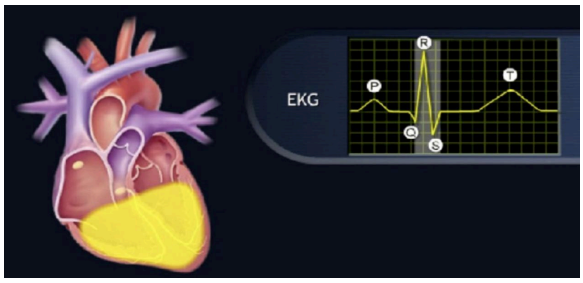
- PR interval is the interval between the P and the QRS. This is the normal AV delay.
    - The AV node is discharging at 0.30 millisecond (for example) from the normal 0.09 second (or 0.16 if including the penetrating bundle), there is more delay than usual in the AV node, the PR interval will prolong because the PR interval represents the AV node.

Conduction through the Bundle Branches and Ventricular Septum



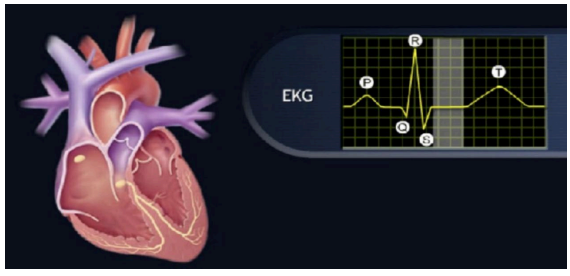


Ventricular Depolarization



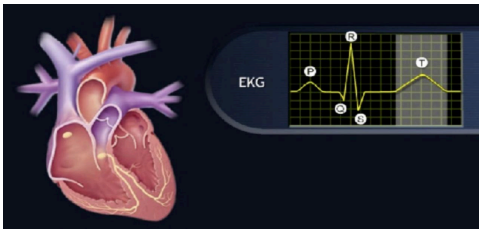
- QRS complex represents ventricular depolarization.
    - The early part of the QRS is the septal but the entire QRS is the depolarization of the ventricles.

Plateau Phase



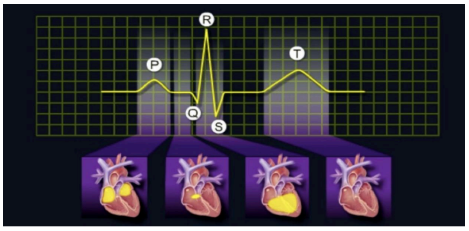
    - ST segment is the plateau (phase 2)

Final Rapid (Phase 3) Repolarization



- T wave is the rapid repolarization (phase 3)

The Major ECG Waveforms



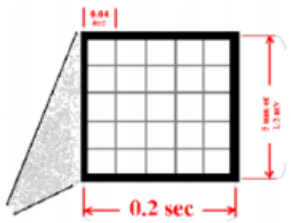
- ECG waveforms are P, QRS, and T.
- Some ECG will produce a U but is specific for a certain disorder.

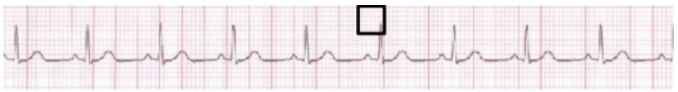
Summary:

- P wave- atrial depolarization
- PR interval- AV node
- QRS complex- ventricular depolarization
- ST segment- plateau
- T wave- repolarization

THE STANDARD ELECTROCARDIOGRAPHIC RECORDING (ECG PAPER)

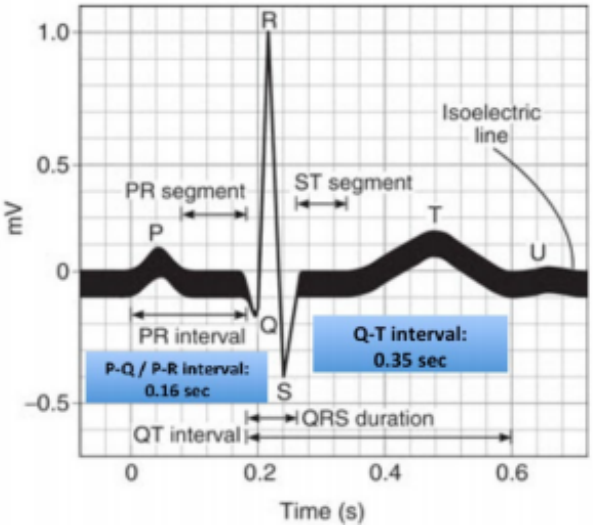
- In the ECG, there are **dark** lines and **light** lines.
- **Voltage and Time Calibration of the ECG**
    - **Horizontally** (time)
        - One small box is **0.04 second**
        - One large box is **0.20 second**
    - **Vertically** (Amplitude)
        - One small box is **0.1 mV**
        - One large box is **0.5 mV**



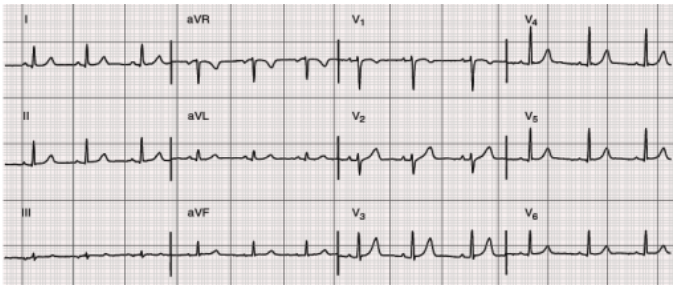


THE NORMAL ECG WAVEFORMS AND INTERVALS

- Normal P-R interval is **0.16 second**, but the range is up to 0.2 seconds, beyond 0.2 (>0.18) is already abnormal.
- Normal Q-T interval is **0.35 second** (represents the entire sequence of ventricular depolarization, plateau, and repolarization)



The Normal ECG



ECG Intervals

Intervals	Normal Durations (second, s) Average	Range	Events in the Heart during Interval
PR interval*	0.18[b]	0.12–0.20	Atrioventricular conduction
QRS duration	0.08	to 0.10	Ventricular depolarization
QT interval	0.40[c]	to 0.43	Ventricular action potential
ST interval (QT minus QRS)	0.32	...	Plateau portion of the ventricular action potential

THESTANDARD ELECTROCARDIOGRAPHIC LEADS

- Measure the difference in electrical potential between two points.
- Two Types
  - **Bipolar Leads**: Two different points in the body (positive and negative input)
    - There are 3 Bipolar Leads
  - **Unipolar Leads**: One point in the body (the positive input) and a virtual reference point with zero electrical potential located in the center of the heart.
    - The negative end is determined by the machine, called the negative (in augmented leads) or Wilson Central Terminal (in precordial leads)
    - 3 Unipolar Augmented Leads
    - 6 Precordial leads
- The Standard ECG recording is taken from 12 standard leads:
  - **3 Bipolar Limb Lead**s

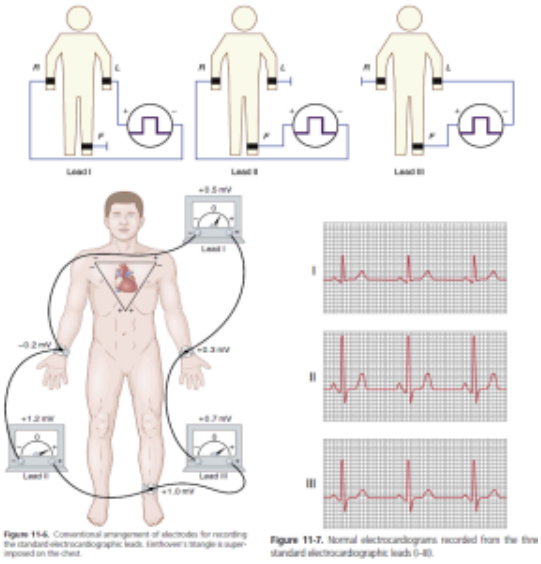


Figure 11-6. Conventional arrangement of electrodes for recording the standard electrocardiographic leads. Einthoven's triangle is superimposed on the chest.

Figure 11-7. Normal electrocardiograms recorded from the three standard electrocardiographic leads (I-III).

- Lead I- (-) right arm; (+) left arm (right to left arm)
- Lead II- (-) right arm; (+) left foot (right arm to left foot)
- Lead III- (-) left arm; (+) left foot (left arm to left foot)
- The **vector** is the direction of depolarization of each lead.
- All of the limb leads are **positive deflections** (above the baseline) because the normal depolarization vector in the normal heart goes from left to right and from up to down. The vectors in the bipolar leads run in parallel.

3 AUGMENTED UNIPOLAR LIMB LEADS:

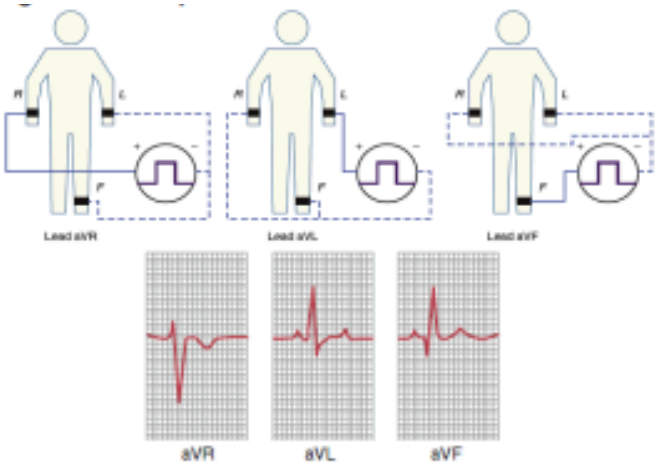
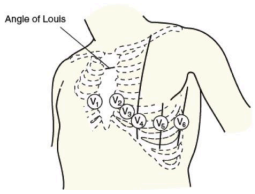


Figure 11-10. Normal electrocardiograms recorded from the three augmented unipolar limb leads.

- The negative input is determined by the machine (extremities that are not used) so only the positive inputs will be placed.
- Nothing will be placed on the right leg (only ground electrode)
  - **Lead aVR**- (+) right arm; (-) combination of the left arm and left leg
  - **Lead aVL**- (+) left arm; (-) combination of the right arm and left leg
  - **Lead aVF**- (+) left foot; (-) combination of the left arm and right arm.
- Lead aVR has the **negative deflections** because the vector in the aVR goes into the right arm and since the normal depolarization rate wavefronts in the normal heart has not wavefronts going to the right arm (exactly opposite the normal depolarization wavefronts in a normal heart)

- Unless if the heart is in the right chest (dextrocardia or wrongly placed leads), the aVR should register negative waveforms.
- 6 **Precordial (Chest)** Leads



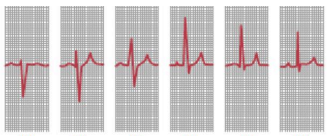
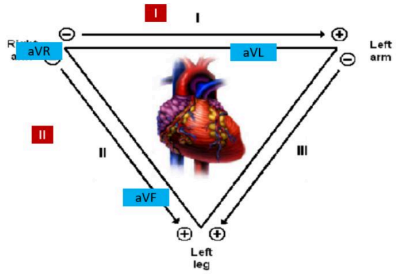
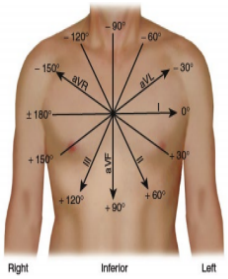


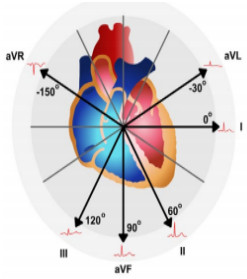
Figure 11-9. Normal electrocardiograms recorded from the six standard chest leads.

- **The Einthoven's Triangle**



  - An imaginary triangle drawn around the area of the heart with the 2 arms and the leg forming the apices of the triangles.
  - It illustrates that the 2 arms and the left leg form apices of a triangle surrounding the heart.
  - Represent the points at which the two arms connect electrically with the fluids around the heart and the lower apex is the point at which the leg connects with the fluids.
- Limb Leads Axes (The Hexaxial System)

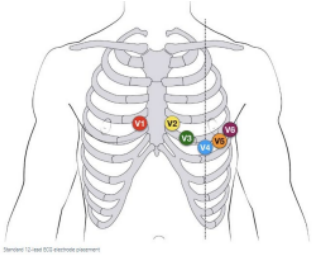


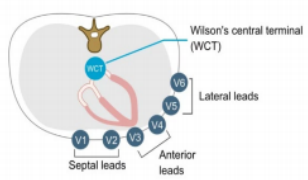


  - A pair of electrodes (positive and negative) connected to the body on opposite sides of the heart, and the direction from negative to positive is the axis or vectors.
  - Composed of the 3 bipolar leads and 3 augmented unipolar leads.

Lead I	going to 0°	**aVL**	going to -30°
Lead II	going to +60°	**aVF**	going to +90°
Lead III	going to +120°	**aVR**	going to -150°

- Precordial **(Chest)** leads

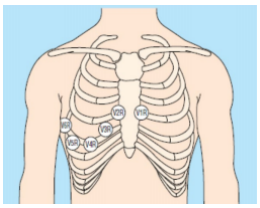


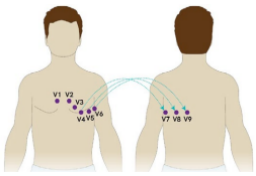


- **V1**- 4th right ICS parasternal (close to the sternum)
- **V2**- 4th left ICS parasternal (opposite to V1)o
- **V4**- 5th left ICS midclavicular line
- **V3**- between V4 and V2 (approximately)o
- **V5**- 5th left ICS anterior axillary line
- **V6**- 5th left ICS midaxillary line

V1 and V2 represents right ventricle; V3-V6 represents left ventricle

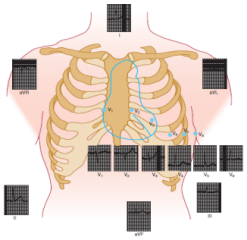
- **Right-sided and Posterior Chest Leads (Non-standard)**





  - The chest leads can be extended to the right when dealing with right ventricular infarction which is represented in the standard ECG.
  - The chest leads can also be extended to the back.

- **12-Lead ECG Recordings**



THE CONTIGUOUS LEAD GROUPINGS

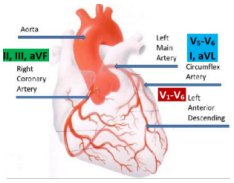
Leads are grouped together according to the general area of the heart (the Left Ventricle) that they represent.

- **Limb Leads** generally view the heart in a Supero-Inferior and MedioLateral dimension
- **Precordial Leads (Chest Leads)** generally view the heart (Left Ventricle) in the Antero-Posterior dimension

- **Arrangement of Leads on the ECG**

I Lateral	aVR None	V_1 Septal	V_4 Anterior
II Inferior	aVL Lateral	V_2 Septal	V_5 Lateral
III Inferior	aVF Inferior	V_3 Anterior	V_6 Lateral

- **Anatomic Groups Based on Contiguous Lead Groupings**
  - **Septum**- When examining a suspected pathology involving the ventricular septum, look at the V1 and V2.
  - **Anterior Wall (Anteroseptal)**- Look at V3 and V4 (V1 to V4 in some sources)
  - **Lateral Wall**- Look at V5, V6, Lead I (going to the left arm), aVL
  - **Inferior Wall**- Look at Lead II, Lead III, aVF (leads going down)
- **The Coronary Artery Distribution based on the Contiguous Lead Groupings**



THE CARDIAC ACTION POTENTIALS

Coronary Artery Territories and ECG Leads

- Left Anterior Descending (LAD) – supplying most of the anterior surface of the heart; V1–V6
- Circumflex Artery (LCX) – supplies the lateral portion of the heart; V5–V6, Lead I, aVL
- Right Coronary Artery (RCA) – supplies the inferior portion of the heart; Lead II, Lead III, aVF

SUMMARY:

- Anterior wall → LAD → V1–V4
- Lateral wall → LCX → I, aVL, V5–V6
- Inferior wall → RCA → II, III, aVF

Example:

- A patient has myocardial infarction in the ECG involving the anterior wall. The culprit vessel is the LAD.
- Since the pathology of MI is acute thrombosis in the coronary vessel, so a thrombus in the left anterior descending is suspected.
- The patient's artery will be opened and to save time, look at the ECG, the thrombus is probably in V1–V4, then canulate the LAD first.

VECTORIAL ANALYSIS AND DETERMINATION OF THE MEAN ELECTRICAL AXIS

THE QRS AXIS AND VECTOR

- The QRS axis represents the overall direction of the ventricles' electrical activity.
- Instantaneous mean vector is the summated vector of the generated potential.
- Abnormalities hint at:
  - Ventricular enlargement (RVH, LVH)
  - Conduction blocks (right bundle, left bundle)
  - Anatomic malposition of the heart

DIRECTION OF VECTOR

→ Denoted in terms of degrees

- Is the average direction of the QRS vector during the spread of depolarization wave through the ventricles.
- It is usually at +59° in a normal heart
- During most of the depolarization wave, the apex of the heart remains positive with respect to the base.
- The wave of depolarization is going towards the apex from base (negative to positive).

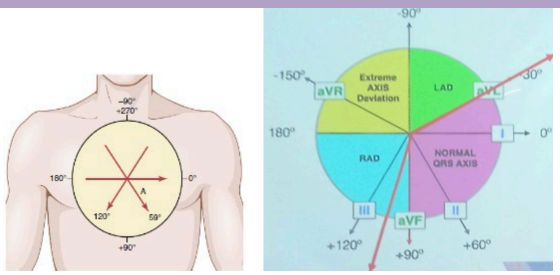
THE QRS AXIS

- Normal QRS Axis: range between -30° to +110° (mean of +59°)
- Left Axis Deviation (LAD): -30° to -90°
- Right Axis Deviation (RAD): +110° to +180°

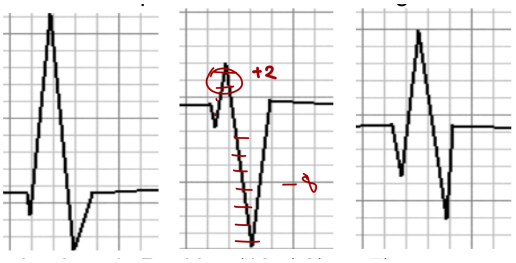
THE LIMB LEADS AND THE CARDIAC VECTOR OR AXIS

The mean QRS vector can be approximated by measuring the net differences between the positive and negative peaks of the QRS.

DETERMINING THE QRS AXIS



1. 1st: Determine the net QRS potential in 2 limb leads (Leads I and III or I and aVF)
2. 2nd: From the net QRS potential determined, you are now ready to plot

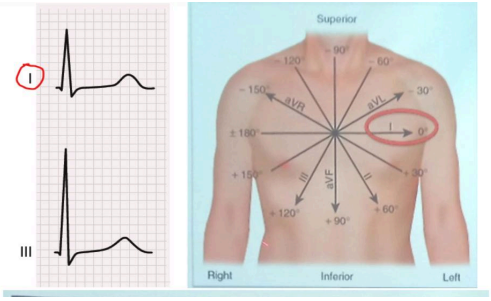


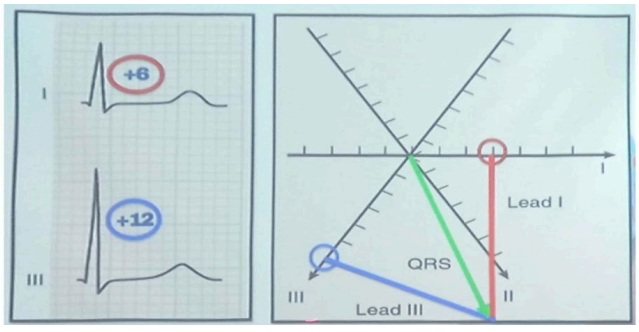
3. Determine the net QRS potential of the following QRS complexes:
   - 1st pic: Predominantly Positive (10+(-3) = +7)
   - 2nd pic: Predominantly Negative (2+(-8) = -6)
   - 3rd pic: Equiphasic (5+(-5) = 0)

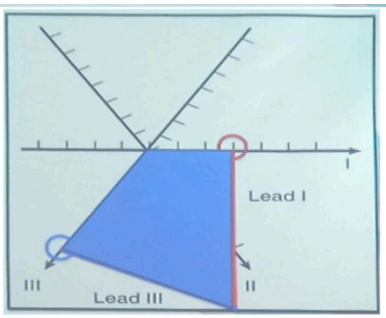
PLOTTING THE ELECTRICAL AXIS

Determine the net QRS potential of the following QRS complexes:

- The mean force during activation is represented by the area under the QRS waveforms, after plotting the vectors of 2 limb leads.
  - Look at the potential in the QRS in Leads I and III, plot and interpolate, and where they meet is the mean QRS potential.







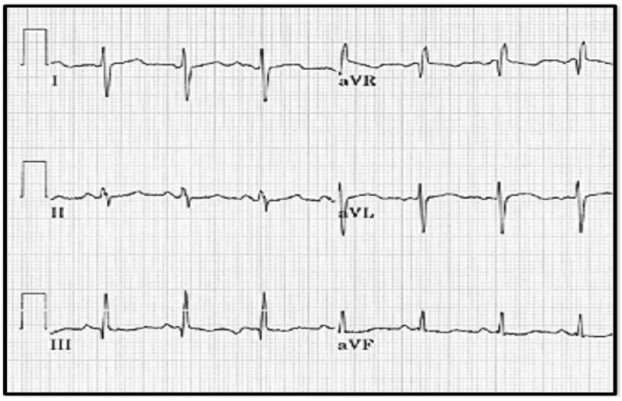
DETERMINING THE ELECTRICAL AXIS (SHORTCUT METHOD)

1. Examine the QRS complexes in leads I and aVF or III
2. Determine/Estimate the net potential of the QRS complexes (if they are predominantly positive or negative).
3. The combination should place the axis into one of the 4 quadrants below:

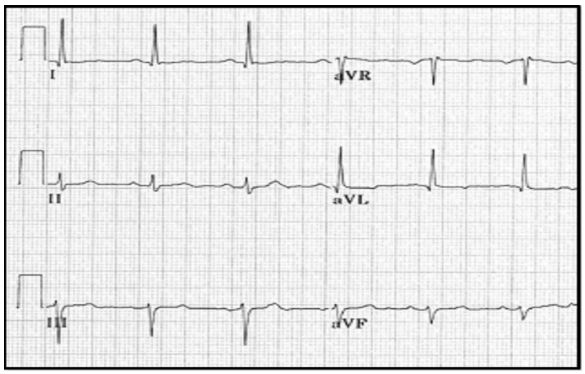
Lead I \ Lead aVF	Positive	Negative
Positive	Normal Axis	LAD
Negative	RAD	Indeterminate Axis

SHORTCUT (FOR ROUNDS PURPOSES)

- Left thumb is Lead I and right thumb is Lead III or aVF
- If positive QRS in that lead, point the thumb upward
- If negative QRS in that lead, point the thumb down
- If both thumbs are upward (both positive), it is a normal QRS axis
- If one is negative, whichever is the thumb that is remaining upwards, that is the direction of the axis.



Negative in I; Positive in aVF→ **Right Axis Deviation (RAD)**



Positive in I; Negative in aVF→ **Left Axis Deviation (LAD)**

I. PHYSIOLOGIC AXIS DEVIATIONS

- Due to changes in the position of the heart in the chest; does not indicate pathology.

A. Shift to the Left

- Occurs when the diaphragm moves upward, causing the heart to shift slightly leftward.
  - End of deep expiration: The diaphragm rises, uplifting the heart and shifting the axis to the left.
  - Supine position.
  - Obesity: Increased abdominal fat pushes the diaphragm upward.

B. Shift to the Right

- Occurs when the diaphragm moves downward, causing the heart to shift rightward.
  - End of deep inspiration: Lungs are fully expanded; the diaphragm contracts downward.
  - Standing position: Especially in patients who cannot lie flat and remain close to a 90° position.
  - Tall, lanky body habitus: The heart becomes elongated in a supero-inferior direction.

II. PATHOLOGIC AXIS DEVIATIONS

- Due to abnormal cardiac or ventricular conditions.

A. Change in the Position of the Heart

- **Dextrocardia:** The heart is located in the right side of the chest.

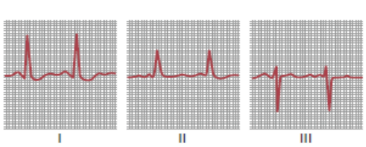
B. Ventricular Hypertrophy

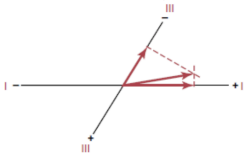
- Axis deviation occurs toward the hypertrophied ventricle because it has more myocardial mass and generates a stronger electrical potential.
  - **Left Ventricular Hypertrophy (LVH)**
  - **Right Ventricular Hypertrophy (RVH)**

C. Bundle Branch Blocks

- **Left Bundle Branch Block (LBBB)**
- **Right Bundle Branch Block (RBBB)**

III. LEFT AXIS DEVIATION RESULTING FROM LEFT VENTRICULAR HYPERTROPHY (LVH) COMMON CAUSES





Systemic hypertension

- In hypertension, there is a very elevated aortic pressure so the

ventricles will contract against higher pressure so it has to hypertrophy to overcome that pressure otherwise blood will not flow (The principle of blood flow is to create a significant pressure gradient. Without a pressure gradient, blood will not flow).
- The ventricle has to create a higher pressure to overcome the pressure in the aorta.

Aortic stenosis

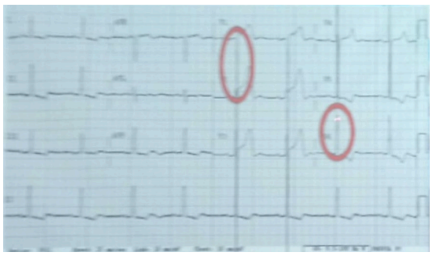
- There is obstruction in the aortic valve so there is a very small aortic opening, so the LV has to contract in a much forceful manner to overcome the obstruction

Other Causes

- **Aortic regurgitation**
- **Congenital heart diseases that causes LVH**
- **Left bundle branch blocks (LBBB)**

QRS Complexes in Left Ventricular Hypertrophy (LVH)

- Different criteria exist for the ECG diagnosis of LVH.
  - The **Sokolow-Lyon Criteria:**
    - R wave in V_5 or V_{56} + S wave in V_1 or V_2 >35mm



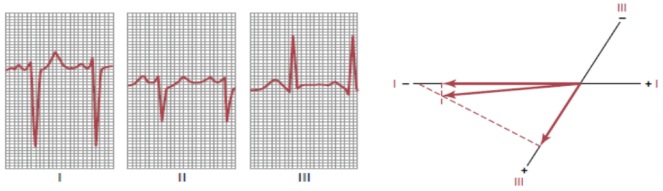
R in V_5 or V_6 and S in V_1 or V_2 when summed up is greater than 35

Common Diagnostic Criteria for Left Ventricular Hypertrophy (LVH)

MEASUREMENT	CRITERIA
Sokolow-Lyon voltages	$SV_1 + RV_5$ >3.5 mV
	RaVL >1.1 mV
Romhilt-Estes point score system*	Any limb lead R wave or S wave >2.0 mV (3 points)
	or SV_1 or SV_2 ≥3.0 mV (3 points)
	or RV_5 to RV_6 ≥3.0 mV (3 points)
	ST-T wave abnormality, no digitalis therapy (3 points)
	ST-T wave abnormality, digitalis therapy (1 point)
	Left atrial abnormality (3 points)
	Left axis deviation ≥–30 degrees (2 points)
	QRS duration ≥90 msec (1 point)
	Intrinsicoid deflection in V_5 or V_6 ≥50 msec (1 point)
Cornell voltage criteria	SV_3 + RaVL >2.8 mV (for men)
	SV_3 + RaVL >2.0 mV (for women)
Cornell regression equation	Risk of LVH = $1 / (1 + e^{-exp})$†
Cornell voltage duration measurement	QRS duration × Cornell voltage >2436 mm-sec‡
	QRS duration × sum of voltages in all leads >1742 mm-sec

LVH, Left ventricular hypertrophy; *PTF,* P terminal force; *PTFV_1,* P terminal force in lead V_1.

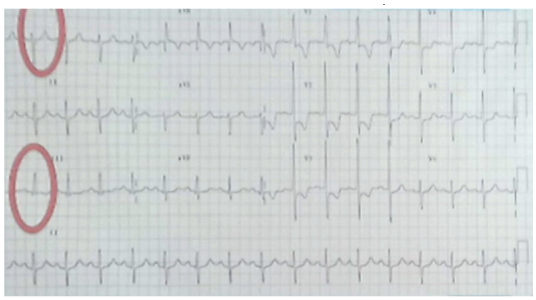
III. RIGHT AXIS DEVIATION RESULTING FROM RIGHT VENTRICULAR HYPERTROPHY (RVH) COMMON CAUSES



- **Pulmonary stenosis**
- **Conditions that result in RV volume or pressure overload:** COPD.
- **Congenital heart diseases that cause RVH:** Tetralogy of Fallot, Ventricular septal defects.
- **Right bundle branch defects (RBBB)**
  - Same principle, there is increased pressure in the right heart so that right heart should hypertrophy.

QRS Complexes in Right Ventricular Hypertrophy (RVH)

- **Criteria**: R axis deviation + R wave in V1 > 7 mm



Tall R in V_1 > 0.6 mV
Increased R/S in V_1 > 1
Deep S in V_5 > 1.0 mV
Deep S in V_6 > 0.3 mV
Tall R in aVR > 0.4 mV
Small S in V_1 < 0.2 mV
Small R in V_{5-6} < 0.3 mV
Reduced R/S ratio in V_5 < 0.75
Reduced R/S ratio in V_6 < 0.4
Reduced R/S in V_5 to R/S in V_1 < .04
$(R_I + S_{III}) - (S_I + R_{III})$ < 1.5 mV
Max R_{V1-2} + Max $S_{I, aVL} - S_{V1}$ > 0.6 mV
$RV_1 + S_{V5-6}$ > 1.05 mV
R peak V_1 > 0.035 msec
QR in V_1 present

IV. CONDITIONS THAT CAUSE ABNORMAL VOLTAGES OF THE QRS COMPLEX

- **Increased voltage:**
  - LVH
  - RVH
- **Decreased voltage:**
  - Cardiac myopathies (primary muscle disorders of the heart)
  - Abnormal conditions surrounding the heart:
    - Pericardial effusion (too much fluid in the pericardial sac)
    - Pleural effusion (too much fluid in the lungs)
    - Pulmonary emphysema (too much air in the lungs
    - What is recorded are electrical potentials from the heart projected to the skin. If there is bigger interference from the heart to the skin (too much fluid from the heart to the skin or too much air), the complexes might record very small.

IV. CONDITIONS THAT CAUSE BIZARRE QRS COMPLEX MORPHOLOGIES

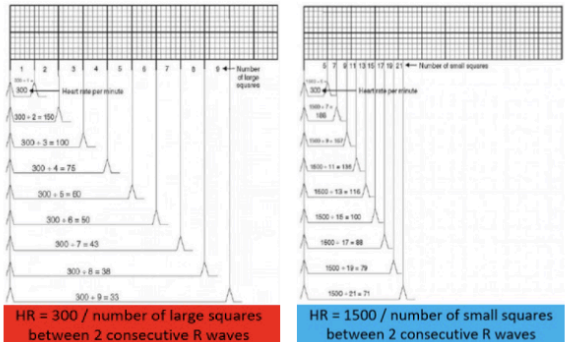
- **Cardiac hypertrophy or dilation** prolong the QRS complex.
- **Destruction of cardiac muscle** in various areas throughout the ventricular system, with replacement of this muscle by scar tissue.
- **Multiple blocks** in the Purkinje system.

ELECTROCARDIOGRAPHIC DETERMINATION OF HEART RATE

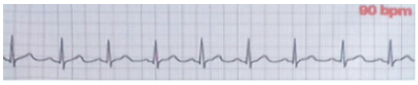
DETERMINING THE HEART RATE

- **Heart Rate** is the reciprocal of the time interval between two successive heartbeats.
  - If the interval between two beats as determined from the time calibration lines is **1 second**, the heart rate is **60 beats per minute**.
  - The normal interval between two successive QRS complexes in the adult person is about **0.83 second**.
    - HR of **60/0.83 times per minute**, or **72 beats per minute**.

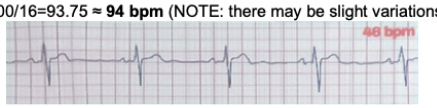
CALCULATING THE HEART RATE



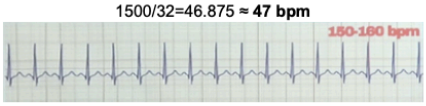
- If looking at the ECG, look at succeeding R waves. 1 R to the next R is one cardiac cycle. Count the number of squares between those 2.
- When using the big squares (dark lines), use 300 (300 divided by the number of big squares in between the R to the next R).
- When using the small squares, use 1,500 divided by the number of small squares from 1 R to the next R.



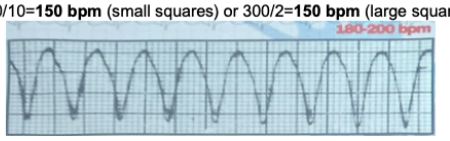
1500/16=93.75 ≈ **94 bpm** (NOTE: there may be slight variations)



1500/32=46.875 ≈ **47 bpm**



500/10=**150 bpm** (small squares) or 300/2=**150 bpm** (large squares)

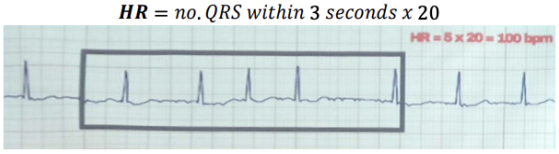


1500/8=187.5 bpm ≈ **188 bpm**

For Irregular Rhythms

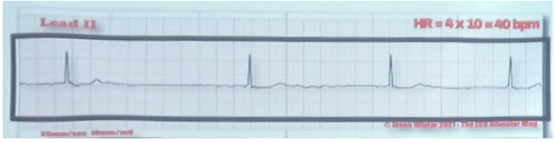
- Calculating HR using a **3-second rhythm strip:** Heart rate is calculated by counting the number of QRS complexes within the 3- second strip and multiplied by 20.
  - A 3-second rhythm strip has **15** big squares. Count the number of R included in that 3-second strip and multiply by 20.

$$HR = no.\,QRS\ within\ 3\ seconds\ x\ 20$$



- Calculating HR using a **6-second rhythm strip:**
  - A 6-second rhythm has **30** big squares. In a very slow irregular rhythm, use a longer strip.

$$HR = the\ no.\,QRS\ complexes\ x\ 10$$



- Calculating HR using a **12-second rhythm strip:**
  - A 12-second rhythm strip has **60** big squares.

$$HR = the\ no.\,QRS\ complexes\ x\ 5$$

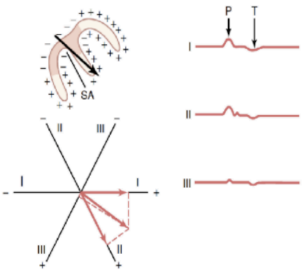
- **Shortcut Method**

No. of Big Boxes	Rate
1	300
2	150
3	100
4	75
5	60
6	50

ANALYSIS OF THE NORMAL ELECTROCARDIOGRAPHIC WAVEFORMS AND INTERVALS

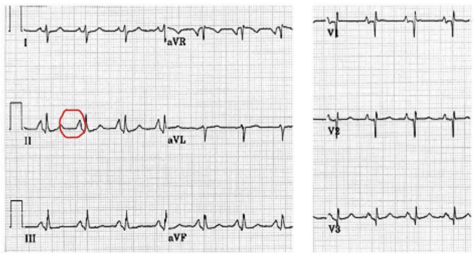
A. P WAVE (ATRIAL DEPOLARIZATION)

- The normal P wave is directed towards the left arm a bit inferiorly and is parallel with leads I, II, and III.
- Always **positive** in lead I and II
- Always **negative** in lead aVR
- **<3** small squares in duration
- **<2.5** small squares in amplitude
- Commonly biphasic in lead V_1
- Best seen in **lead II**



Right Atrial Enlargement

- Tall (**>2.5 mm**), pointed P waves: **P Pulmonale**



Left Atrial Enlargement

- Notched/bifid (M-shaped), Biphasic P waves in limb leads: **P Mitrale**

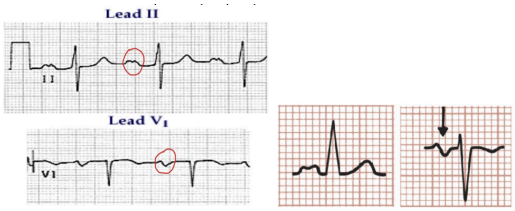


TABLE 14.3 Common Diagnostic Criteria for Left and Right Atrial Abnormalities

LEFT ATRIAL ABNORMALITY	RIGHT ATRIAL ABNORMALITY*
Prolonged P wave duration to >120 msec in lead II	Peaked P waves with amplitudes in lead II to >0.25 mV
Prominent notching of P wave, usually most obvious in lead II, with interval between notches of >40 msec	Prominent initial positivity in lead V_1 or V_2 >0.15 mV
Ratio between duration of P wave in lead II and duration of PR segment >1.6	Increased area under initial positive portion of P wave in lead V_1 to >0.06 mm-sec
Increased duration and depth of terminal-negative portion of P wave in lead V_1 (P terminal force) so that the area subtended by it is >0.04 mm-sec	Rightward shift of mean P wave axis to >+75 degrees
Leftward shift of mean P wave axis to between −30 and −45 degrees	

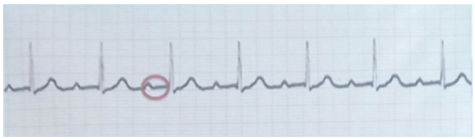
*In addition to criteria based on P wave morphologies, right atrial abnormality is suggested by QRS changes as described in the text.
Reference: Hancock EW, Deal BJ, Mirvis DM, et al. Recommendations for the standardization and interpretation of the electrocardiogram. Part V. ECG changes associated with cardiac chamber hypertrophy. *J Am Coll Cardiol*. 2009;53:992–1002.

B. PR INTERVAL (ATRIOVENTRICULAR/AV DELAY)

Prolonged PR Interval

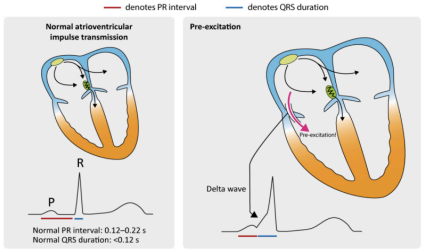
- **1st-degree AV block:** More than 200 milliseconds (>5 small squares)
  - PR interval is from the start of the P wave to the start of the

QRS.
- Common and does not have to be treated; usually secondary to beta-blocker use (down titrate the dose), usually asymptomatic.



o Shortened PR Interval

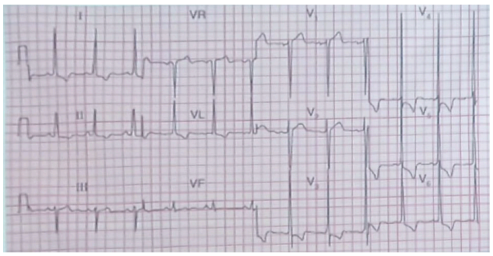
- **Preexcitation Pattern/Wolff-Parkinson-White Pattern:** Triad of Short PR-interval, presence of Delta wave, Prolonged QRS duration
  - Normally, the atria and ventricle should not have any other communication electrically except through the AV node. If there is a bypass track, it may shorten the PR interval (there is an accessory pathway).
  - A bypass track will not exhibit the normal delay exhibited by the AV node and the impulse will travel faster, making the PR shorter.
  - If the impulse will come across the impulse coming from the normal AV node, both will clash, the first part of the QRS will slur (delta wave), making the QRS be prolonged.
  - This pattern is called **WPW pattern** or **pre-excitation pattern** if you only read the ECG pattern and do not know the patient. It is called a syndrome if you know the symptoms of the patient.



C. QRS COMPLEX (VENTRICULAR DEPOLARIZATION)

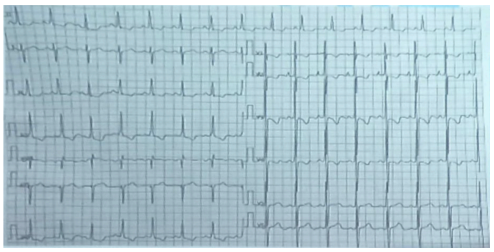
Left Ventricular Hypertrophy (LVH)

- The **Sokolow-Lyon Criteria:**
  - R wave in V_5 or V_{56} +S wave in V_1 or V_2 > 35 mm



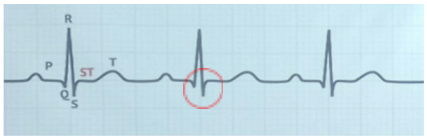
Right Ventricular Hypertrophy (RVH)

- **Criteria:** R axis deviation + R wave in V_1 > 7 mm

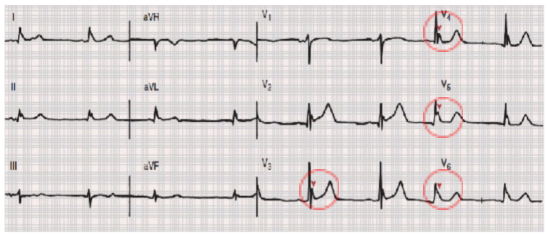


D. ST SEGMENT (PLATEAU PHASE)

- ST Segment is flat (isoelectric).
- Deviation: Elevation or depression of ST-segment by **> 1 mm**.
- **"J" (Junction) point** is the point between QRS and ST-segment.

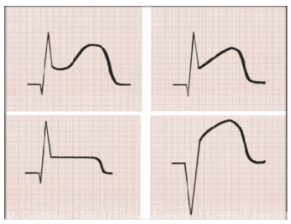


- J point elevation in systemic hypothermia: **Osborn Wave** (not MI)



Variable Shapes of ST-segment Elevations in Acute Myocardial Infarction (AMI)

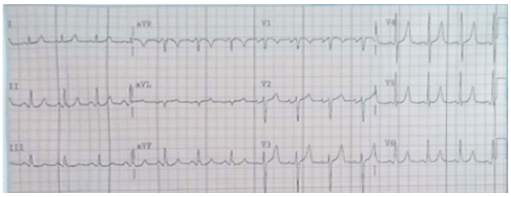
- If there is a deviation of the ST-segment, always think of AMI unless proven otherwise.
- The higher the ST segment, the bigger the myocardial involvement



E. T WAVE (VENTRICULAR REPOLARIZATION)

Abnormalities in the T Wave

- The T wave becomes abnormal when the normal sequence of repolarization does not occur.
- Several factors can change the sequence of repolarization:
  - **Slow conduction** of the depolarization wave.
  - **Shortened depolarization** in portions of the ventricular muscle.
- As a general rule, T wave amplitude corresponds with the amplitude of the preceding R wnave, though the tallest T waves are seen in leads V_3 and V_4.
  - **General Rule**: If the P wave and QRS is positive, the T wave should also be positive.
- Tall T waves may be seen in **acute myocardial ischemia** and are a feature of **hyperkalemia** (electrolyte abnormalities or dialysis patients who missed their dialysis are sensitive to potassium levels).



F. QT INTERVAL (VENTRICULAR DEPOLARIZATION & REPOLARIZATION)

- Extends from the onset of the QRS complex to the end of the T wave.
- Total duration of Depolarization and Repolarization.
- QT interval is **rate-dependent**: Decreases when heart rate increases.
- **Bazzett formula**: Corrects the measured QT interval to the effects of heart rate:

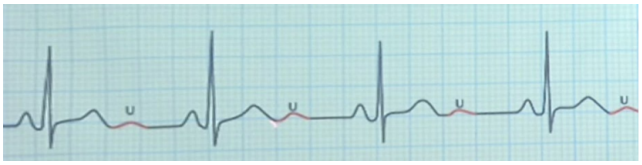
$$QTc = QT/\sqrt{RR}$$

- If the heart rate is abnormal (bradycardic or tachycardic), it is

usually affected and the Bazzett formula will correct for the variation in the heart rate.
- Only compute for the Bazzett formula if the heart rate is grossly abnormal.

G. U WAVE

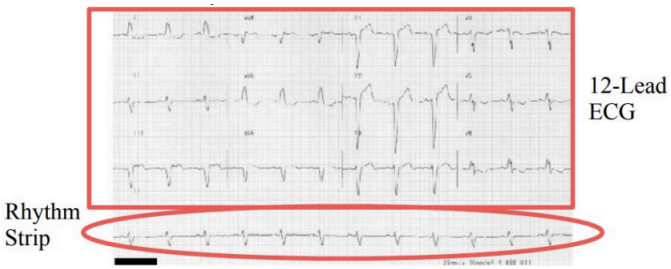
- U wave is related to afterdepolarizations which follow repolarization.
- U waves are small, round, symmetrical and positive in lead II, with amplitude < 2 mm.
- U wave direction is the same as the preceding T wave; more prominent at slow heart rates. Seen in **hypokalemia**.



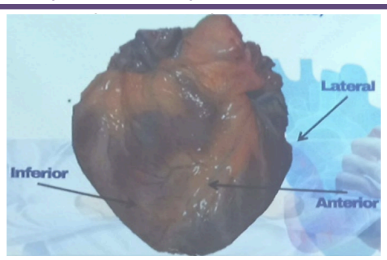
ELECTROCARDIOGRAPHIC DIAGNOSIS OF MYOCARDIAL INFARCTION (MI)

DIAGNOSING MYOCARDIAL INFECTION

- To diagnose myocardial infarction, you need to look beyond a rhythm strip and obtain a standard **12-Lead ECG**.
  - In MI, it is not enough to know there is an MI. You should also have an idea as to where the thrombus is.
  - In a normal ECG, after the 12-Lead is recorded, usually the machine will record a long strip (usually lead I or lead II, 10 second strip).
  - If the problem is more on arrhythmias or conduction abnormalities, the rhythm strip is used, but in MI, the 12-Lead is used because it will show a 3D representation of the heart.

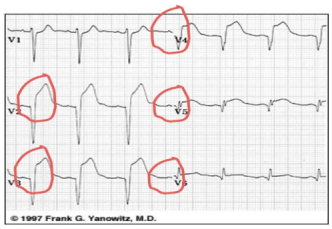


Views of the Heart (Left Ventricle)



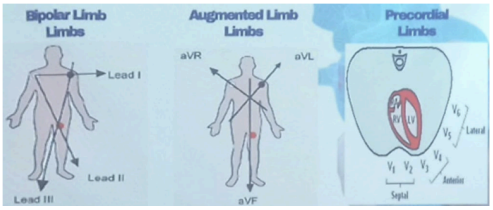
ST-Segment Elevation

- One way to diagnose an acute MI is to look for elevation of the ST segment.
- New ST elevation at the J point in 2 contiguous leads with the following cut points:
  - Any **0.1 mV deviation** in all leads (except V_2 and V_3) should be considered elevation unless proven otherwise, but it should be contiguous lead (the group of leads that would make sense).
    - V_1 and aVF does not represent the coronary distribution.
  - In leads V_2-V_3, the following cut points apply:
    - > 0.2 mV in men 40 years old and above
    - > 0.25 mV in men less than 40 years old
    - > 0.15 mV in women



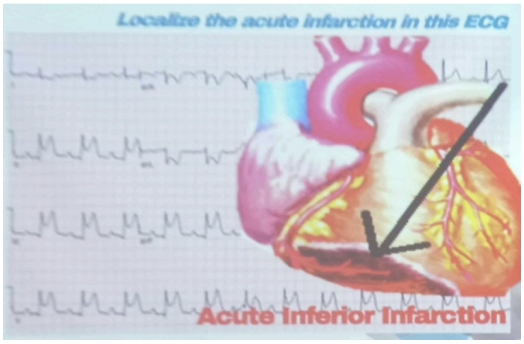
MYOCARDIAL INFARCTION LOCALIZATION

- Remember that the 12-Leads of the ECG look at different areas of the heart (LV and RV):
  - The **limb** and **augmented leads** "see" electrical activity moving to the left or laterally (I, aVL), and to the right (aVR) and inferiorly (II, III and aVF).
  - The **precordial leads** "see" electrical activity in the posterior to anterior direction.

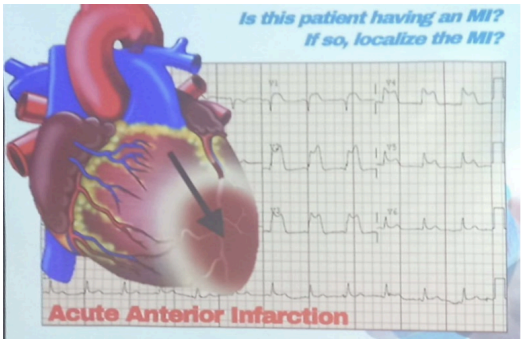


- **Anterior Myocardial Infarction**
  - The anterior portion of the heart is best viewed using leads V_1-V_4.
- **Lateral Myocardial Infarction**
  - The lateral portion of the ventricle is best viewed in Leads I, aVL, V_5-V_6.
- **Inferior Myocardial Infarction**
  - The inferior portion of the heart is best viewed in Leads II, III, aVF.

Localize the Myocardial Infarction:

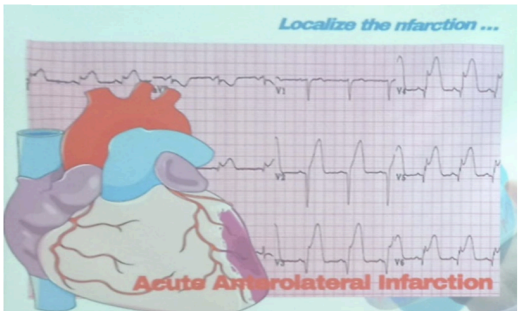


- There is an elevation in the **inferior leads** (leads II, III, and aVF) = MI is in the **inferior**. The **right coronary artery** is the culprit vessel.



- There is an elevation in the **anterior leads** (V_1, V_2, V_3, V_4, and V_5) = MI is in the **anterior**, so there is an acute anterior infarction in the left anterior descending. The more contiguous leads involved,

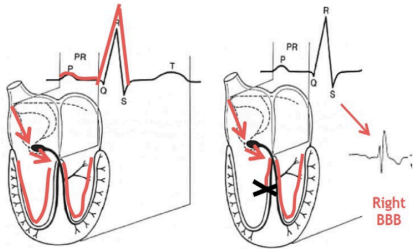
the more proximal the thrombus because the distribution is bigger.



- There is an elevation in all the **anterior** and **lateral leads** (V_1, V_2, V_3, V_4, V_5, aVF). The more **proximal** the thrombus is, the more **acute** is the treatment.

ELECTROCARDIOGRAPHIC DIAGNOSIS OF BUNDLE BRANCH BLOCKS (BBB) – NORMAL IMPULSE CONDUCTION

- **Sinoatrial (SA) node** to **Atrioventricular (AV) node** will record the P wave and PR interval.
- QRS will be the penetrating bundle to the **Purkinje system**.
- Conduction in the Bundle Branches and Purkinje fibers are seen as the QRS complex on the ECG.
  - Therefore, a conduction block of the Bundle Branches would be reflected as a change in the QRS complex.
  - If there are blocks the bundle branches in the right, it will produce **RBBB** and in the left, it will produce **LBBB**.

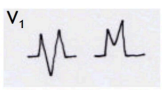


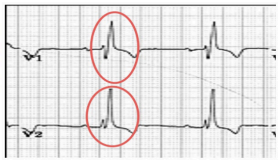
ECG CHANGES

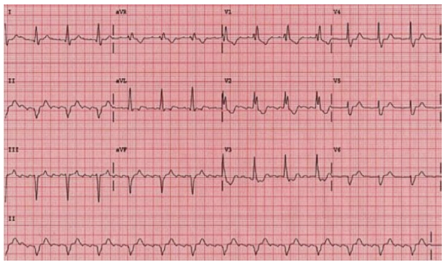
- **QRS complex widens** (> 0.12 sec if the block is complete).
- **QRS morphology changes** (varies depending on ECG lead, and if it is a right vs. left bundle branch block).

Complete Right Bundle Branch Block (CRBBB)

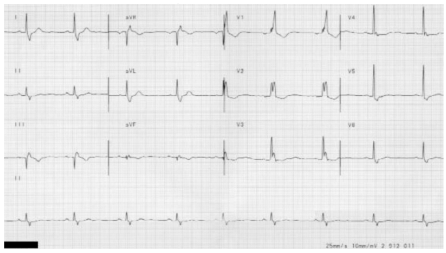
- ECG Changes: The QRS complex widens with a unique, virtually diagnostic shape in those leads overlying the RV.





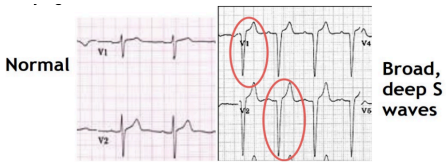


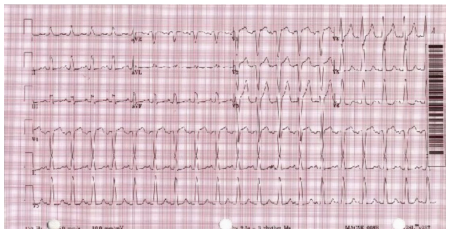
CRBBB: There is RSR in V_1 and V_2. CRBBB is common in females in their 20s. Does not cause any hemodynamic abnormalities.



Complete Left Bundle Branch Block (CLBBB)

- ECG Changes: The QRS complex widens with a **deep QS** in the leads overlying the LV.

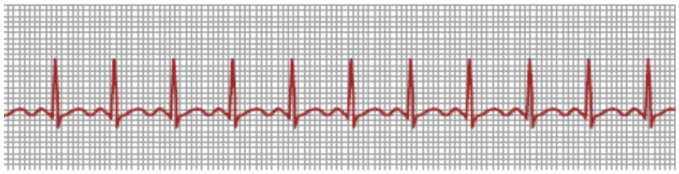




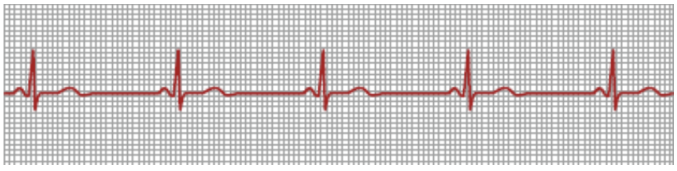
CLBBB: There is deep QS in V_1 and V_2. An acute CLBBB may be a manifestation of acute MI.

ELECTROCARDIOGRAPHIC DIAGNOSIS OF MISCELLANEOUS DISORDERS

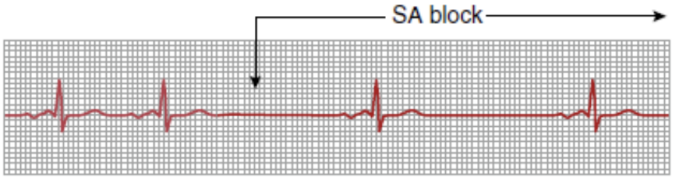
- **Sinus Tachycardia** – Everything is normal except the heart rate is more than 100 bpm.



- **Sinus Bradycardia** – Everything is normal except the heart rate is less than 60 bpm.

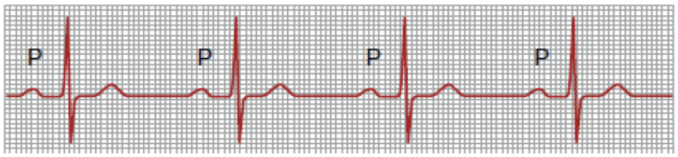


- **Sinoatrial (SA) Block** – For any reason, the sinus node stopped; significant pause will be **3 seconds**.

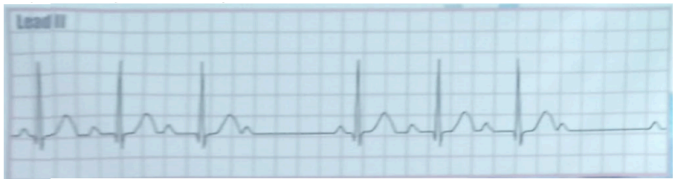


- **1st Degree AV Block** – Prolongation of the PR to more than 5

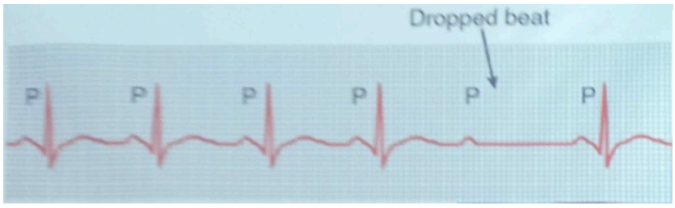
small squares.



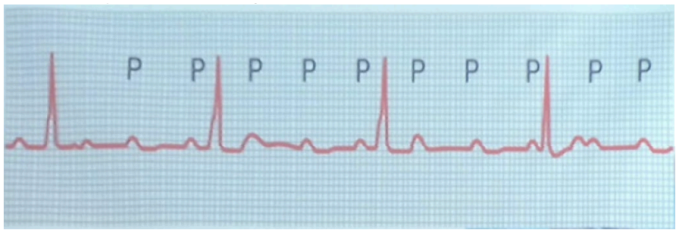
- **Mobitz Type 1 – 2nd Degree AV Block (Wenckebach)**
  - Look for P waves not followed by QRS. The AV node totally disregards the impulse from the sinus node.
  - In the long strip, a **group beating** will be seen, which is a clue for 2nd degree blocks. There are P waves not conducted, it is only up to the atria and after the AV node, it is disregarded.
  - If the PR interval is prolonging before the drop beat, it is type 1 (short, longer, longest, drop).



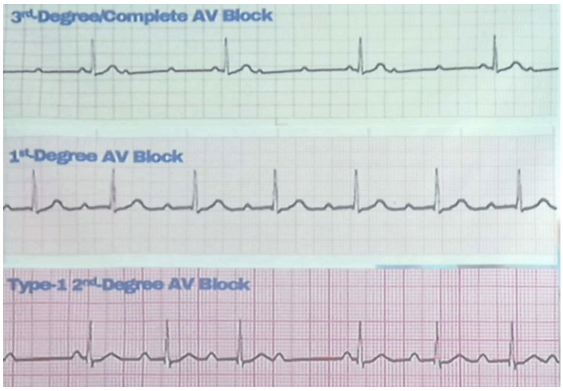
- **Mobitz Type 2 – 2nd Degree AV Block**
  - There is no prolongation of the PR, so the PR appears fixed, and the drop suddenly appears without warning.
  - **More morbid** compared to type 1.
  - A pacemaker is inserted, especially if the cause is reversible (no beta blocker therapy or electrolyte abnormality determined).



- **3rd Degree (Complete) AV Block**
  - Atria and ventricles are completely dissociated (atria and ventricles are conducting by itself and not related).
  - P to the next P and R to the next R appear regular but are not related (completely dissociated).

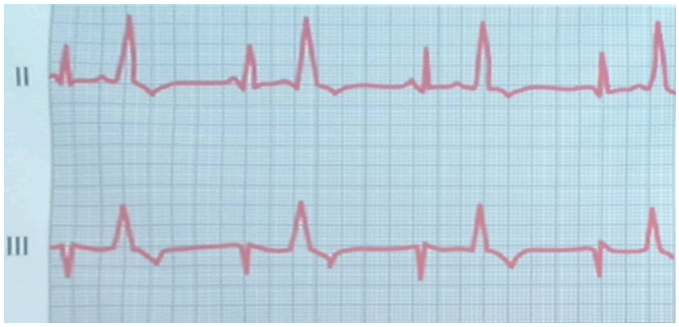


DIFFERENTIATING 1ST, 2ND, AND 3RD DEGREE BLOCKS

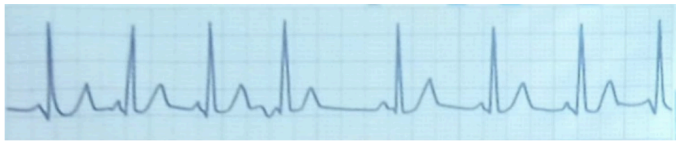


MISCELLANEOUS DISORDERS (CONTD.)

- **Premature Ventricular Contractions (PVC)** – There is an extra QRS after a normal cycle that is bizarre-looking and is not followed by a P wave.

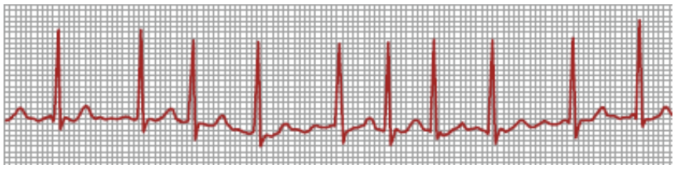


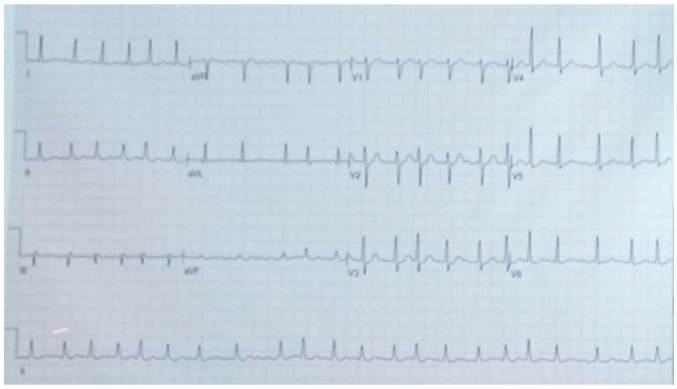
- **Premature Arterial Contractions (PAC)** – Normal looking QRS but preceded by an abnormal P wave (e.g, inverted P and early occurring QRS).



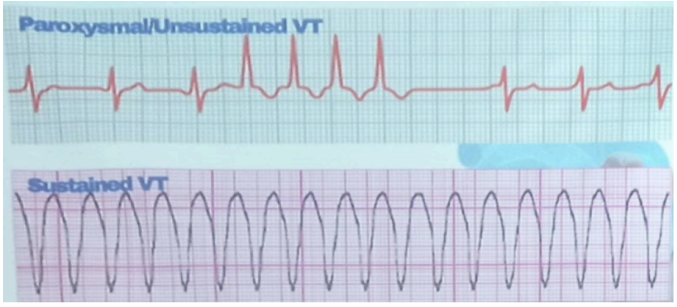
Coming from the atrium lower than the AV node, since P wave is inverted so the vector may be going up.

- **Atrial Fibrillation**
  - Irregularly irregular QRS and a P wave cannot be determined.
  - **T waves** are seen (no P waves) and have no pattern.
  - When the patient's pulses are palpated, they are usually irregular. Very common in the elderly and is a very significant cause of stroke.
  - These patients are maintained on **anticoagulant therapy** because a clot may form in the LA of a fibrillating atria and if it is thrown out to the carotids, it may produce a stroke.

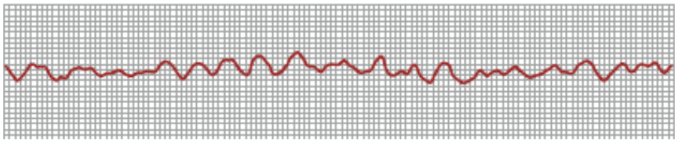


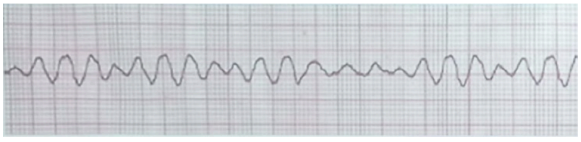


- **Ventricular Tachycardia (V Tach)**
  - Very wide QRS; no one can survive.
  - If PVC occurs at least 3 times, it is already VT; if it will still convert, it is a **non-sustained VT**.

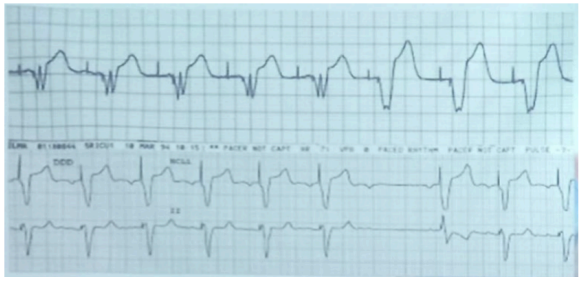


- **Ventricular Fibrillation**
  - No patterns, only wavy lines.
  - If seen and there is a defibrillator at hand, electroshock right away (or CPR). Only sustained ventricular tachycardia and ventricular fibrillation require electroshock. Do not give electroshock to other rhythms otherwise, you are promoting more death.

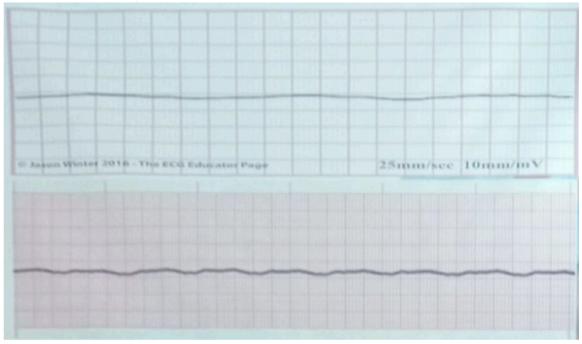




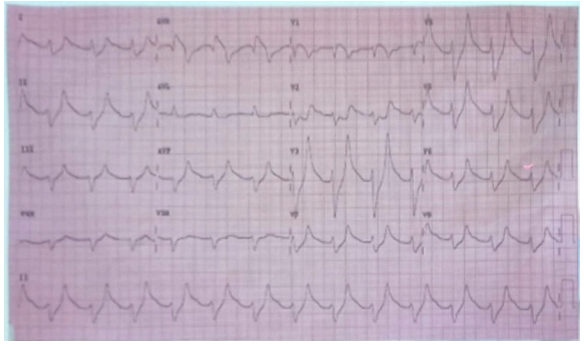
- **Pacemaker Rhythm**
  - Seen in patients with pacers inserted.
  - The blips are not artifacts but are the firing of the pacer.
  - Some pacers may have 2 leads (inserted into the RA and RV).



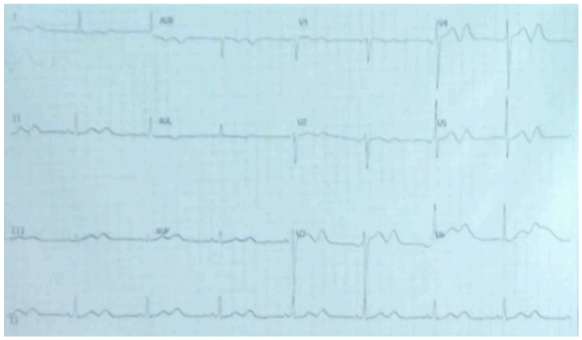
- **Asystole** – “Please see that your leads are attached”.



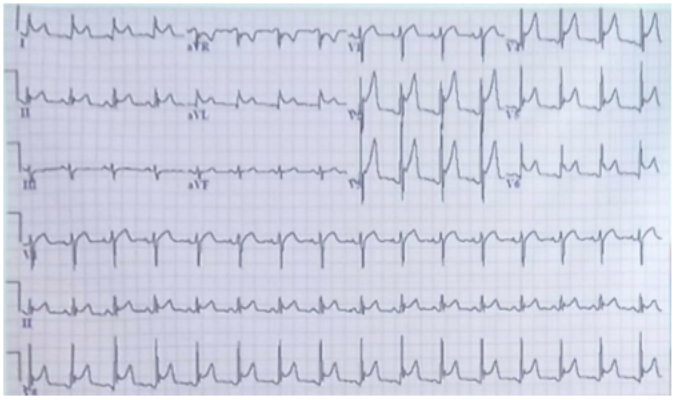
- **Hyperkalemia** – Tall or Peaked T waves; seen in lethal injection (**Potassium chloride**).



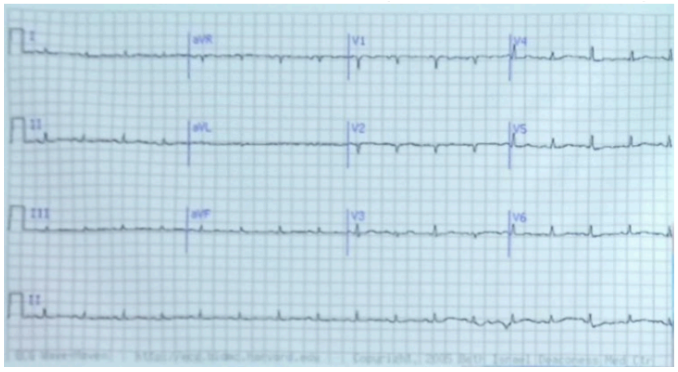
- **Hypokalemia** – Depressed or flat ST-T waves, U waves seen.

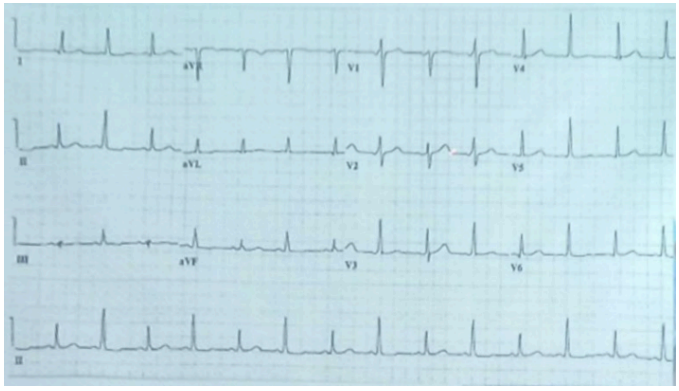


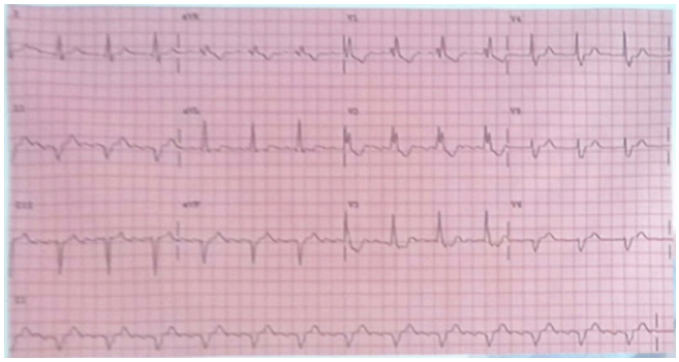
- **Acute Pericarditis**
  - Diffuse S-T elevation (ST elevation on all the leads), P-R depression.
  - Ask the patient for the characteristics of the pain.
    - Pain in MI (angina pectoris) is usually more on numbness and heaviness in the chest, often radiating to the arm or jaw.
    - **Pericardial pain** is usually pinprick and the patient can localize it and find temporary relief by leaning forward or lying on the side.
    - Also, review the patient's profile.



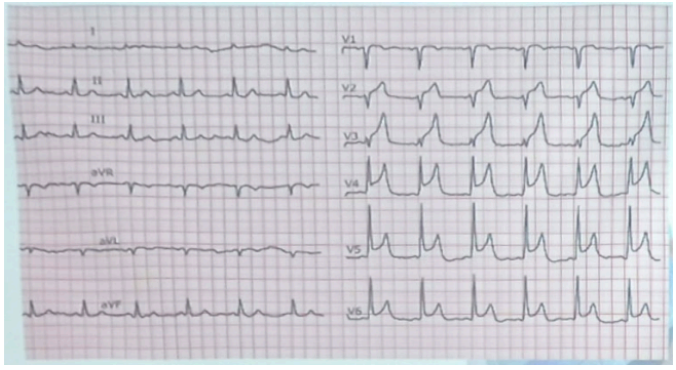
- **Cardiac Tamponade**
  - Low-amplitude complexes, presence of electrical alternans.
    - Because there is excessive interference between the skin and the heart, the QRS complexes will appear very small.
    - Electrical alternans is alternating positive and negative.
  - Too much fluid surrounds the heart in the pericardial sac such that the RA inflow of blood is impeded (low cardiac output).



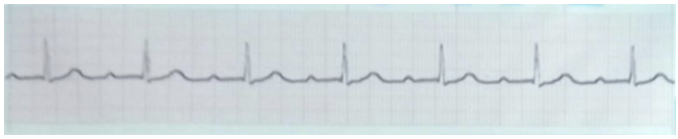




SINUS RHYTHYM WITH CRBBB

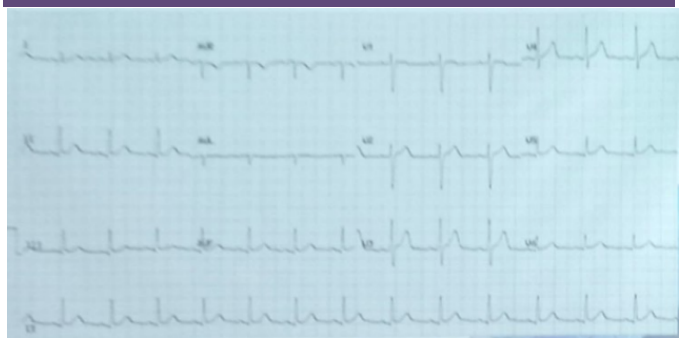


SINUS RHYTHM WITH ACUTE ANTEROLATERAL MI

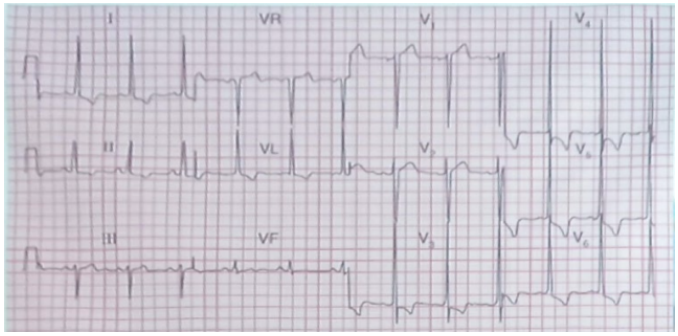


SINUS RHYTHM WITH 1ST DEGREE AV BLOCK

ECG REVIEW



NORMAL SINUS RHYTHM



SINUS RHYTHM WITH LVH BY VOLTAGE CRITERIA

DYNAMICS OF MICROCIRCULATION AND LYMPHATICS

FUNCTIONS OF THE MICROCIRCULATION

Functions of the microcirculation

- Transport of nutrients to the tissues
- Removal of cell excreta.
    - The peripheral circulation of the entire body has about 10 billion capillaries, with a total surface area estimated to be **500 to 700 square meters**.

STRUCTURE OF THE MICROCIRCULATION AND CAPILLARY SYSTEM

- The microcirculation of each organ is organized to serve that organ's specific needs. In general, each nutrient artery entering an organ branches 6-8 times before the arteries become small enough to be called **arterioles**, which generally have internal diameters of only 10 to 15 micrometers. Then, the arterioles branch 2-5 times, reaching diameters of 5 to 9 micrometers at their ends, where they supply blood to the capillaries

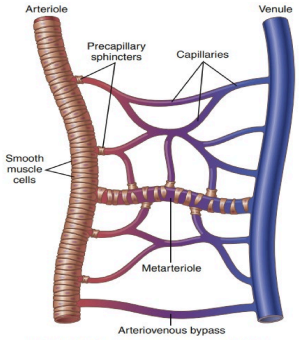


Figure 16-1. Components of the microcirculation.

Arterioles

- Highly muscular, coated with smooth muscle cells, and their diameters can change by many times.
    - **Metarterioles (terminal arterioles)**: do not have a continuous muscular coat, but smooth muscle fibers encircle the vessel at intermittent points.
    - **Precapillary sphincter:** At the point where each true capillary originates from a metarteriole, a smooth muscle fiber usually encircles the capillary (smooth muscles are intermittent and not continuous).

Venules

- Larger than the arterioles, have a much weaker muscular coat, and the pressure in the venules is much less than that in the arterioles, but the venules can still contract considerably, despite the weak muscle

Structure of the Capillary Wall

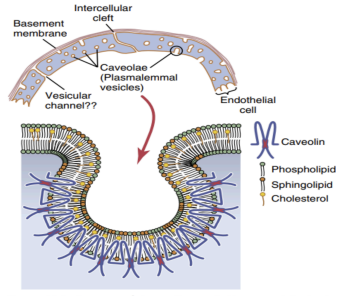


Figure 16-2. Structure of the capillary wall. Note especially the *intercellular cleft* at the junction between adjacent endothelial cells. It is believed that most water-soluble substances diffuse through the capillary membrane along the clefts. Small membrane invaginations, called *caveolae*, are believed to play a role in transporting macromolecules across the cell membrane. Caveolae contain caveolins, which are proteins that interact with cholesterol and polymerize to form the caveolae.

- 0.5 micrometer thick
- Internal diameter: 4 to 9 micrometers
- Composed of a unicellular layer of endothelial cells and is surrounded by a thin basement membrane on the outside of the capillary.
- 2 small passageways connecting the interior with the exterior.
    - **Intracellular cleft:** passageways of nutrients and molecules; the thin-slitted, curving channel between adjacent endothelial cells
    - **Short ridges of protein attachments** that hold the endothelial cells together but, between these ridges, fluid can flow freely throughout the cleft.
    - Diffusion of water, water-soluble ions, and small solutes between the interior and exterior of the capillaries.
- **Caveolae:** believed to play a role in endocytosis and transcytosis of macromolecules across the interior of endothelial cells
    - Many minute plasmalemmal vesicles present in the endothelial cells associated with molecules of cholesterol and sphingolipids.
    - These imbibe small packets of plasma or extracellular fluid that contain plasma proteins, and some of these vesicles may coalesce to form vesicular channels.

Special Types of Pores in Capillaries of Certain Organs

- **Brain:** Tight junctions that only extremely small molecules such as water, oxygen, and carbon dioxide can diffuse
- **Liver:** Almost all dissolved substances of the plasma, including the plasma proteins, can pass from the blood into the liver tissues (since one of the functions of liver is to filter toxic wastes)
- **Gastrointestinal tract:** Midway in size between those of the muscles and those of the liver.
- **Glomerular capillaries of the kidney**- fenestrae penetrate all the way through the middle of the endothelial cells

FLOW OF BLOOD IN THE CAPILLARIES (VASOMOTION)

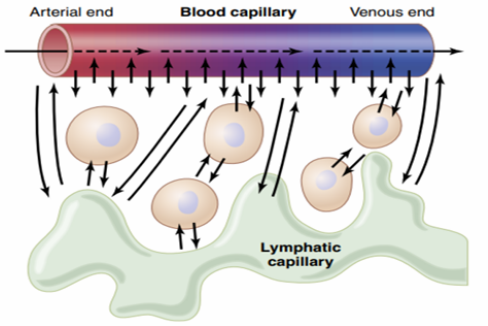


Figure 16-3. Diffusion of fluid molecules and dissolved substances between the capillary and interstitial fluid spaces.

- Blood flows intermittently through the capillaries
    - There is intermittent contraction of the metarterioles and precapillary sphincters.
- The most important factor affecting the degree of opening and closing of the metarterioles and precapillary sphincters is the **concentration of oxygen in the tissues.**
    - When the body senses that a certain part of the body lacks oxygen, there is more vasomotion and the duration of contraction is longer to provide the needed nutrients (oxygen) on that certain area.

EXCHANGE OF WATER AND NUTRIENTS IN THE BLOOD AND INTERSITIAL FLUID

- Diffusion through the Capillary Membrane is the most important means of transferring substances between plasma and interstitial fluid.
- The proteins are the only dissolved constituents in the plasma and interstitial fluids that do not readily pass through the capillary membrane.
  - Proteins are large molecules, that is why proteins should not be seen in the urine. But if there are problems in filtration, proteins will be seen in the urine.
- Lipid-soluble substances diffuse directly through the cell membranes of the capillary endothelium.
  - Exchange of oxygen and carbon dioxide occurs in the alveoli.
- Water-soluble, non-lipid-soluble substances diffuse through intercellular pores in the capillary membrane.

Effect of Molecular Size on Passage Through the Pores

- Width of intercellular cleft pores: 6-7 nm
- The higher the molecular weight, the lesser permeability.

Relative Permeability of Skeletal Muscle Capillary Pores to Different-Sized Molecules

Substance	Molecular Weight	Permeability
Water	18	1.00
NaCl	58.5	0.96
Urea	60	0.8
Glucose	180	0.6
Sucrose	342	0.4
Inulin	5000	0.2
Myoglobin	17,600	0.03
Hemoglobin	68,000	0.01
Albumin	69,000	0.001

Diffusion Through the Capillary Membrane Is Proportional to the Concentration Difference Between the Two Sides of Membrane

- The greater the difference, the greater the net movement of the substance in one direction through the membrane.
- The rates of diffusion through the capillary membranes of most nutritionally important substances are so great that even the slightest difference causes more than adequate transport between the plasma and interstitial fluid.

THE INTERSITITUM AND THE INTERSTITIAL FLUID

- **Interstitium**: spaces between the cells
- **Interstitial Fluid**: fluid in the spaces between the cells
- Structure of the interstitium contains **2 major types of solid structures**:
  - **Collagen fiber bundles**- are extremely strong and provide most of the tensional strength of the tissues
  - **Proteoglycan filaments**- are extremely thin, coiled or twisted molecules composed of about **98% hyaluronic acid and 2% protein.**

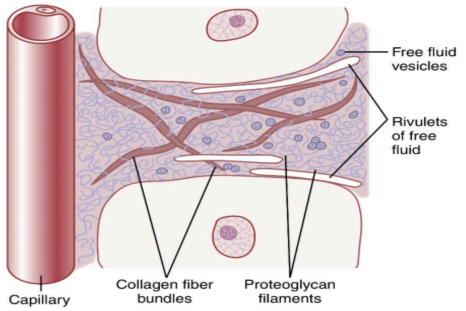


Figure 16-4. Structure of the interstitium. Proteoglycan filaments are everywhere in the spaces between the collagen fiber bundles. Free fluid vesicles and small amounts of free fluid in the form of rivulets occasionally also occur.

Gel in the Interstitium

- The fluid in the interstitium is derived by filtration and diffusion from the capillaries.
- It contains almost the same constituents as plasma except for much lower concentrations of proteins
- The interstitial fluid is entrapped mainly in the minute spaces among the proteoglycan filaments.
- This combination of proteoglycan filaments and fluid entrapped within them have the characteristics of a gel; it is therefore called **tissue gel.**
- Fluid mainly diffuses through the gel by **kinetic thermal motion,** rather than by large numbers of molecules moving together.
  - Diffusion through the gel occurs about **95% to 99%** as rapidly as it does through free fluid.

Free Fluid in the Interstitium

- The amount of free fluid present in most normal tissues is slight, usually **less than 1%**
- When there is **edema**, the small pockets and rivulets expand tremendously until one half or more of the edema fluid becomes free- flowing fluid, independent of the proteoglycan filaments.

FLUID FILTRATION ACROSS CAPILLARIES

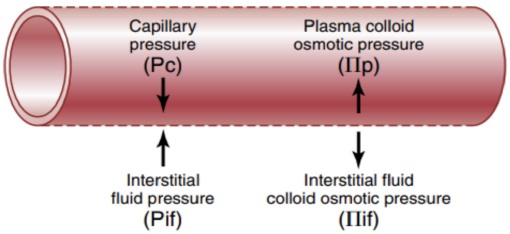


Figure 16-5. Fluid pressure and colloid osmotic pressure forces operate at the capillary membrane and tend to move fluid outward or inward through the membrane pores.

$$NFP = Pc - Pif - \prod p + \prod if$$

4 primary forces that determine whether fluid will move out of the blood
into the interstitial fluid or in the opposite direction (Starling forces):

- **Capillary hydrostatic pressure (Pc)** tends to force fluid outward through the capillary membrane
- **Interstitial fluid hydrostatic pressure (Pif)** tends to force fluid inward through the capillary membrane when Pif is positive but outward when Pif is negative
- **Capillary plasma colloid osmotic pressure (Πp)** tends to cause osmosis of fluid inward through the capillary membrane
- **Interstitial fluid colloid osmotic pressure (Πif)** tends to cause osmosis of fluid outward through the capillary membrane

Interstitial Fluid Pressures in Tightly Encased Tissues

- Some tissues of the body are surrounded by tight encasements, such as the cranial vault around the brain, the strong fibrous capsule around the kidney, the fibrous sheaths around the muscles, and the sclera around the eye.
- In most of these tissues, the interstitial fluid pressures are **positive**.

Interstitial Fluid Pressure in Loose Subcutaneous Tissue

- The interstitial fluid pressure in loose subcutaneous tissue is, in normal conditions, slightly less subatmospheric, averaging about **−3 mm Hg.**
- Intrapleural space (in the lungs): **-8 mm Hg**

- Joint synovial spaces (in the elbows and knees): **-4 to -6 mm Hg**
- Epidural space (in the CNS): **-4 to -6 mm Hg**

Plasma Colloid Osmotic Pressure

	g/dl	Πp (mm Hg)
Albumin	4.5	21.8
Globulins	2.5	6.0
Fibrinogen	0.3	0.2
Total	7.3	28.0

- The proteins of the plasma and interstitial fluids that are responsible for the osmotic pressures on the two sides of the capillary membrane.
- Normal human plasma pressure: approx. **28 mmHg**
- **80%** of the total osmotic pressure is from albumin
- **20%** from globulins

Interstitial Fluid Colloid Osmotic Pressure

- Small amounts of plasma proteins leak into the interstitial spaces through the pores and by transcytosis in small vesicles.
- The total quantity of protein in the entire **12L** of interstitial fluid of the body is slightly greater than the total quantity of protein in the plasma.
- The interstitial volume is four times to the plasma, the average protein concentration of the interstitial fluid is usually **40%** of that in plasma.
- The average interstitial fluid colloid osmotic pressure for this concentration of protein is approx. **8 mmHg.**

Fluid Volume Exchange through the Capillary Membrane

- The average capillary pressure at the arterial ends of the capillaries is **15 to 25 mmHg greater** than at the venous ends.
- Fluid filters out of the capillaries at their arterial ends but at their venous ends, fluid is reabsorbed back into the capillaries.
- **Analysis of the Forces Causing Filtration at the Arterial End of the Capillary**. The approximate average forces operative at the arterial end of the capillary that cause movement through the capillary membrane are shown as follows:

	mm Hg
Forces Tending to Move Fluid Outward	
Capillary hydrostatic pressure (arterial end of capillary)	30
Negative interstitial fluid hydrostatic pressure	3
Interstitial fluid colloid osmotic pressure	8
TOTAL OUTWARD FORCE	41
Forces Tending to Move Fluid Inward	
Plasma colloid osmotic pressure	28
TOTAL INWARD FORCE	28
Summation of Forces	
Outward	41
Inward	28
NET OUTWARD FORCE (AT ARTERIAL END)	13

- **Analysis of Reabsorption at the Venous End of the Capillary.** The low blood pressure at the venous end of the capillary changes the balance of forces in favor of absorption as follows:

	mm Hg
Forces Tending to Move Fluid Inward	
Plasma colloid osmotic pressure	28
TOTAL INWARD FORCE	28
Forces Tending to Move Fluid Outward	
Capillary hydrostatic pressure (venous end of capillary)	10
Negative interstitial fluid hydrostatic pressure	3
Interstitial fluid colloid osmotic pressure	8
TOTAL OUTWARD FORCE	21
Summation of Forces	
Inward	28
Outward	21
NET INWARD FORCE	7

Starling Equilibrium for Capillary Exchange

- The amount of fluid filtering outward from the arterial ends of capillaries are almost exactly equals the fluid that is eventually returned to the circulation.
- The slight disequilibrium that occurs accounts for the fluid that is eventually returned to the circulation by way of the lymphatics.
- The slight excess of filtration is called the net filtration which is normally **2 mL/min.**

Effect of Abnormal Imbalance of Forces at the Capillary Membrane

- If the mean capillary pressure rises significantly above the average value of 17 mmHg, the net force tending to cause filtration of fluid into the tissue spaces rises.
- There will be an imbalance and would result to fluid accumulation in interstitial spaces, resulting to edema.
- If the capillary pressure falls very low, net reabsorption ensues instead of net filtration, and the blood volume will increase at the expense of the interstitial fluid volume.

LYMPHATIC SYSTEM

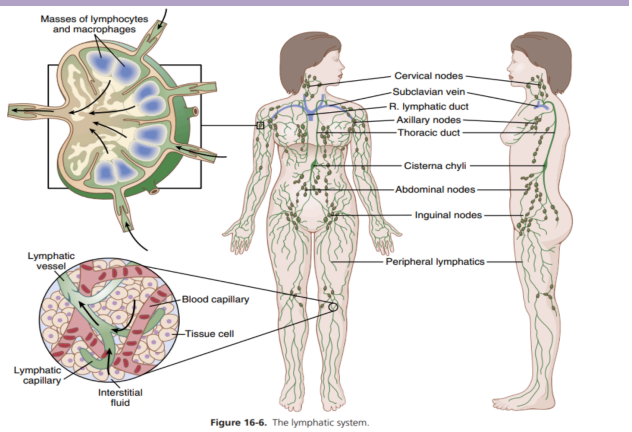


Figure 16-6. The lymphatic system.

- Represents an accessory route through which fluid can flow from the interstitial spaces into the blood.
- The lymphatics can carry proteins and large particulate matter away from the tissue spaces, neither of which can be removed by absorption directly into the blood capillaries.

Lymph Channels of the Body

- **Almost all tissues of the body:** drain excess fluid directly from the interstitial spaces.
- **Thoracic duct:** All lymph vessels from the lower part of the body, left side of the head, left arm, and parts of the chest
- **Right lymphatic duct:** Right side of the head and neck, right arm, and parts of the right thorax.

Terminal Lymphatic Capillaries and Their Permeability

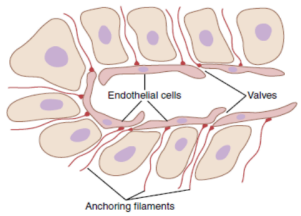


Figure 16-7. Special structure of the lymphatic capillaries that permits passage of substances of high molecular weight into the lymph.

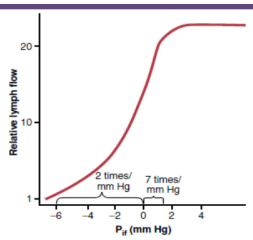


Figure 16-8. Relationship between interstitial fluid pressure and lymph flow in the leg of a dog. Note that lymph flow reaches a maximum when the interstitial pressure (P_{if}) rises slightly above atmospheric pressure (0 mm Hg). *(Courtesy Dr. Harry Gibson and Dr. Aubrey Taylor.)*

- Fluid from the arterial ends of blood capillaries flows among the cells and reabsorbed back into the venous ends of the blood capillaries.
- One tenth of the fluid enters into the lymphatic capillaries and returns to the blood through the lymphatic system.
- **Total lymph: 2-3L per day**
- The fluid return from the lymphatics is extremely important because substances of high molecular weight, such as proteins, cannot be absorbed from the tissues in any other way.
- There are **anchoring filaments** at the junctions of each endothelial cell. There is overlapping, thus forming a minute valve that opens to the interior of the lymphatic capillary.
- Interstitial fluid, along with its suspended particles, can push the valve open and flow directly into the lymphatic capillary.

Formation of Lymph

- Lymph is derived from interstitial fluid that flows into the lymphatics.
- Lymph formed in the **liver** has **6 g/dL protein**.
- Lymph formed in the **intestines** has **3 to 4 g/dL protein**.
- After a **fatty meal**, thoracic duct lymph sometimes contains as much as **1% to 2% fat** (lymphatics is a major route for absorption of fats).
- Large particles, such as bacteria, can push their way between the endothelial cells and enter the lymph almost entirely destroyed.

Rate of Lymph Flow

- About **100 mL/hr** of lymph flows through the **thoracic duct** of a resting
- human
- Approximately another **20 mL** flows into the circulation **each hour**
- Total estimated lymph flow of about **120 mL/hr or 2 to 3 L/day.**

Effect of Interstitial Fluid Pressure on Lymph Flow

- Note that normal lymph flow is very little at interstitial fluid pressures
- more negative than the normal value of **-6 mm Hg.**
- Then, as the pressure rises to **0 mm Hg** (atmospheric pressure), flow increases more than 20-fold. Therefore, any factor that increases interstitial fluid pressure also increases lymph flow if the lymph vessels are functioning normally
- The **lower** the pressure, the **lower** the lymph flow. The higher the pressure, the higher the lymph flow, but there is a limit (plateau).

Factors that increases lymph flow

- Elevated capillary hydrostatic pressure
- Decreased plasma colloid osmotic pressure
- Increased interstitial fluid colloid osmotic pressure
- Increased permeability of the capillaries

Lymphatic Pump Increases Lymph Flow

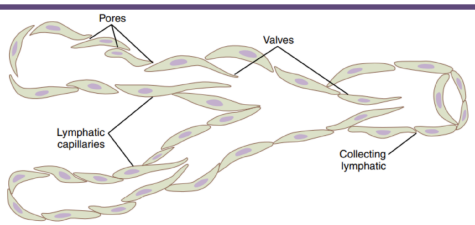


Figure 16-9. Structure of lymphatic capillaries and a collecting lymphatic, with the lymphatic valves also shown.

- When the vessel becomes stretched with fluid, the smooth muscle in the wall of the vessel contracts.
- Each segment of the lymph vessels between successive valves functions as a separate automatic pump.
- The lymphatic pump can generate pressure as high as **50 to 100 mm Hg.**

Pumping Caused by External Intermittent Compression of the Lymphatics

- In addition to the pumping caused by intrinsic intermittent contraction of the lymph vessel walls, any external factor that intermittently compresses the lymph vessel can also cause pumping. **The factors are the following:**
  - Contraction of surrounding skeletal muscles
  - Movement of the parts of the body
  - Pulsations of arteries adjacent to the lymphatics
  - Compression of the tissues by objects outside the body
- The lymphatic pump is very active during exercise, often increasing lymph flow **10- to 30-fold**. Conversely, during periods of rest, lymph flow is sluggish (almost zero).

Lymphatic Capillary Pump

- The terminal lymphatic capillary is also capable of pumping lymph.
- The lymphatic capillary endothelial cells also contain a few contractile actomyosin filaments.
- The lymphatic system also plays a role in controlling the following:
  - Concentration of proteins in the interstitial fluids
  - Volume of interstitial fluid
  - Interstitial fluid pressure

Basic Biomedical Sciences 1

Case/Lecture 1: HEMOGLOBIN SYNTHESIS

BY: *Joselito R. Tumulak Jr., MS (cand.) - Professor of Biochemistry*

BLOCK 04 | MODULE 01

OUTLINE:

1. **Review about the structure of hemoglobin**
2. **The function of hemoglobin**
3. **How do we synthesize hemoglobin**

OVERVIEW

The first breath of a baby inside the uterus

- Breathing is highly reliant on the **oxygen** in the **placenta**

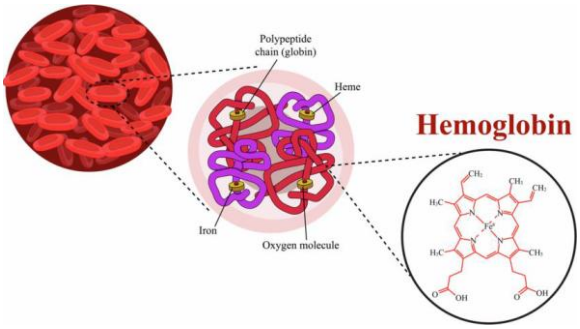
When the baby is born and has its first breath

- There is a change in the biochemical makeup, and that includes the hemoglobin
  - *Transitions from **fetal hemoglobin** to **adult hemoglobin***

Where do we see hemoglobin?

- It can be seen in the Erythrocytes or Red Blood Cells

HEMOGLOBIN



HEMOGLOBIN

- A biomolecule.
- It is a protein, with a **three-dimensional** structure
- Specifically, it is a **CONJUGATED PROTEIN**
  - Made up of **amino acids** to form a long chain and **heme** (non-protein or non-amino acid)

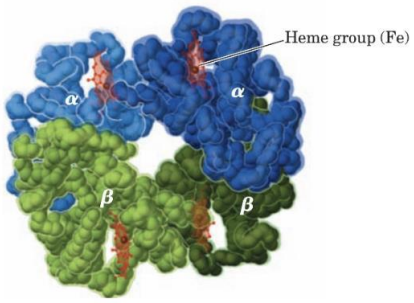
CONJUGATED PROTEIN:

- A protein that contains a non-amino acid moiety.

- It is also a **MULTIMERIC PROTEIN.**
  - Contains different chains of amino acids (represented by colors)
  - Forms together to form a large molecule
  - Each chains contain one **heme** (the prosthetic group)
  - **4 amino acid chains = 4 heme**

WHY IS HEME IMPORTANT?

- This carries oxygen
- In the middle of the heme, there is an iron (iron metal)
- Hemoglobin requires iron
- Iron can have a charge of 2 or 3
- For hemoglobin, it has a charge of 2



TYPES AND STRUCTURE OF HEMOGLOBIN

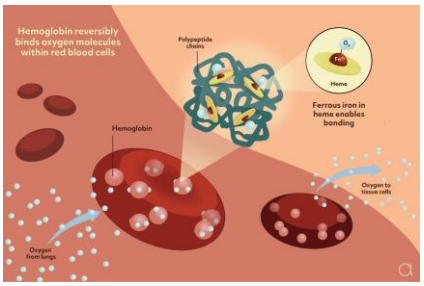
- **HEMOGLOBIN** is a protein composed of four polypeptide chains, and each of these chains contains a heme group. Every heme group can bind one oxygen molecule, which means that a single hemoglobin molecule can carry a total of four oxygen molecules at a time. The polypeptide chains are called globin chains, and this is where the name hemoglobin comes from - "**heme**" refers to the iron-containing component, and "**globin**" refers to the protein portion.

Major forms of hemoglobin in adults:

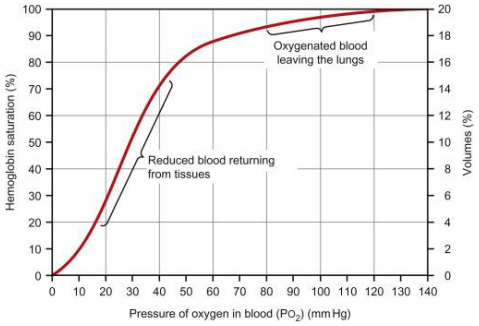
- HbA ($\alpha_2\beta_2$) – 95–97%
- HbA_2 ($\alpha_2\delta_2$) – 2–3%
- HbF ($\alpha_2\gamma_2$) – <1%

- The most common form of hemoglobin found in adults is known as **HbA**, and it consists of: **two alpha chains and two beta chains** ($\alpha_2\beta_2$).
- When globin chains are labeled with the same Greek letter, it indicates that these chains are similar in their amino acid sequence and primary structure. However, HbA is not the only form of hemoglobin present in the body. Adults also have small amounts of **HbA_2**, in which the beta chains are replaced by delta chains, giving it a composition of **$\alpha_2\delta_2$**. The difference between beta and delta chain is the sequence of amino acids.
- Meanwhile, **fetal hemoglobin**, called **HbF**, predominates during fetal life and consists of two alpha chains and two gamma chains (**$\alpha_2\gamma_2$**). Even though these forms differ in their globin chains, all types of hemoglobin contain heme groups where oxygen binding takes place.

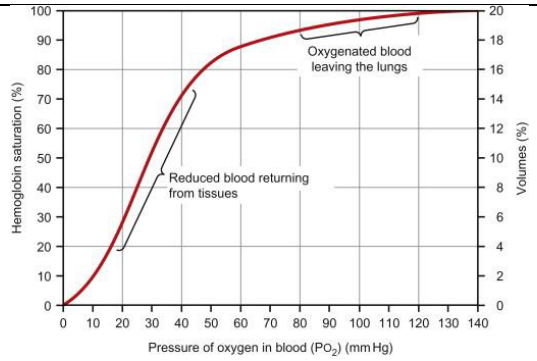
ALLOSTERIC BEHAVIOR & POSITIVE COOPERATIVITY



- Because Hemoglobin is multimeric, it has an **ALLOSTERIC PROPERTY**.
    - It has 4 Globin chains connected together; when you do something in one chain, it affects the other chains.
- This structural behavior explains the characteristic S-shaped oxygen dissociation curve.



- Hemoglobin also demonstrates **POSITIVE COOPERATIVITY**
    - Initially, O2 does not bind well to heme. Because heme is hidden with the Globin chains. Therefore, oxygen binding to heme is NOT spontaneous.
    - When one O2 successfully binds to one heme, it allows the entire molecule structure to change and allows other O2 molecules to then easily bind to the rest of the heme.
    - Low oxygen levels correspond to low hemoglobin saturation, but as oxygen concentration increases, binding becomes more rapid due to **positive cooperativity** (where one oxygen will successfully bind to hemoglobin)**.** In the lungs, the abundance of oxygen promotes strong oxygen binding, while in the tissues, where oxygen levels are lower, hemoglobin releases oxygen more readily. The overall structure of hemoglobin, therefore, perfectly complements its function, demonstrating how biochemical form directly supports physiological purpose.



"OXYGEN BINDING CURVE"

X-axis = Oxygen pressure
(how much O2 is available in the environment)

Y-axis = Hgb Saturation in percent
(how much O2 is found within the Hgb molecule)

NOTE: *With less O2 in the environment, there is less O2 binding for hemoglobin. With higher O2, there will be more O2 binding for the hemoglobin molecule.*

Hemoglobin delivers oxygen from the lungs to the tissues of our body.

Oxygen concentration in the LUNGS = HIGH
With high concentration of O2, Hgb is able to bind to it strongly.

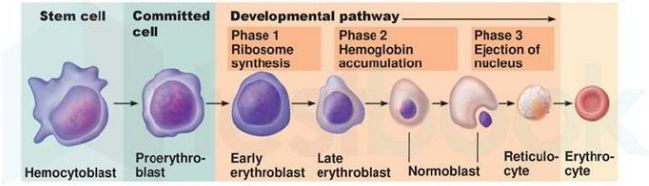
Oxygen concentration in the TISSUES = LOW / LESS
With lower concentrations of O2, Hgb is able to release it.

This is all possible due to the allosteric property of Hemoglobin (aka Structure-Function relationship).

HEMOGLOBIN SYNTHESIS

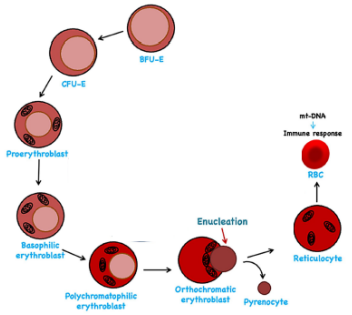
Cellular and Subcellular Site of Hemoglobin Synthesis

- Hemoglobin synthesis occurs in **erythroid precursors** (bone marrow).

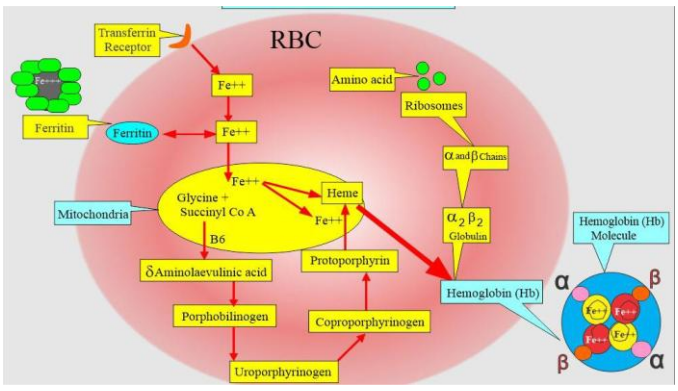


- **ERYTHROID PRECURSORS** – immature, developing RBCs in the bone marrow.
    - Mature RBCs are found in the peripheral / circulating blood, with the ability to carry O2.
    - Mature RBCs cannot synthesize Hemoglobin.

- Heme synthesis occurs in **mitochondrion** and **cytosol**
- Globin synthesis occurs in **ribosome**.

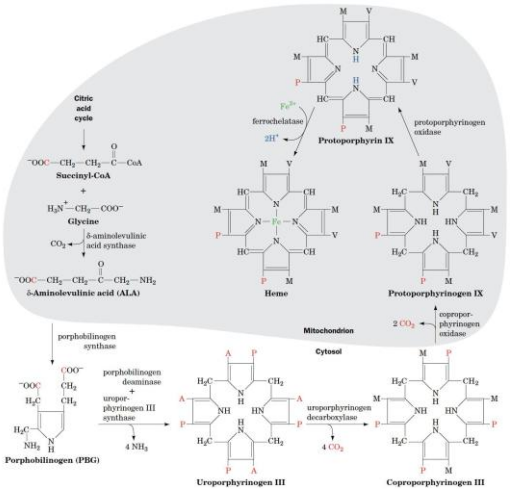


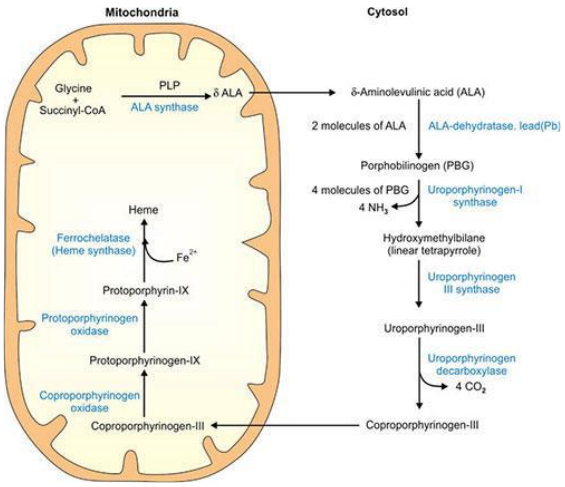
- This explains why mature RBCs cannot produce Hgb:
    - **Absence of mitochondria.**
    - **Absence of ribosomes and nucleus (anuclear).**
        - Globin being a protein is produced in the ribosomes, and for proteins to be synthesized instructions must be taken from the nucleus of the cell.



- **HEMOGLOBIN SYNTHESIS REQUIREMENTS:**
  - **Iron** – with a charge of +2
  - **Enzymes** – for the production of the metabolites in the Hgb synthesis pathway.
    - Defects or deficiency in certain enzymes involved will lead to metabolite accumulation and eventual pathologies and disorders.
  - **NOTE**: For Globin synthesis (coming from ribosomes and instructions from the nucleus), errors such as MUTATIONS can lead to defects in the overall synthesis of hemoglobin.

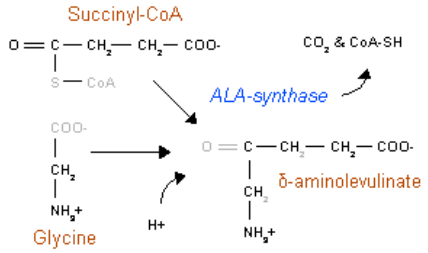
HEME SYNTHESIS





- Heme Synthesis have 8 enzymes involved, and the organelles involved are mitochondrion and cytosol.

PATHWAY FOR THE SYNTHESIS OF HEME



- It starts with an **ALA SYNTHASE**.
  - It condenses **glycine** and **succinyl CoA** forming **DELTA AMINOLEVULINIC ACID (ALA) [$C_5H_9NO_3$].**
    - Functional group is the **carboxylic acid**
    - **Delta Aminolevulinic acid (ALA)** - The amino group is located in the last carbon, fourth (delta) carbon from your carboxylic acid
    - Other carbons:
      - Alpha (1st) carbon
      - Beta (2nd) carbon
      - Gamma (3rd) carbon
  - The reaction is called **CONDENSATION**.
  - Glycine contains 2 carbons [$C_2H_5NO_2$] and Succinyl CoA contains 4 carbons (6 carbons in total); they combine ("condense") together.
    - **Glycine** is an amino acid.
    - **Succinyl CoA** is derived from the Krebs cycle (Citric acid cycle).
  - However, one carbon is lost as **carbon dioxide** so the remaining product is **5 carbons only**.
  - **THIS IS THE RATE DETERMINING STEP OF HEME SYNTHESIS**
    - It is the **slowest step** among the 8 enzymes; thus, it will determine the entire rate of the reaction.
  - It requires a **cofactor** which is a **PYRIDOXAL PHOSPHATE,** derived from vitamin B6 (Pyridoxine).
    - A deficiency in Vit. B6 will ultimately affect the overall synthesis of Heme, and the deficiency of Hemoglobin

- **Cofactor**: Pyridoxal phosphate (Vit B_6)
- **Regulation**:
  - ↓ by Heme (feedback),
  - ↑ by erythropoietin (EPO) & iron

  - **REGULATION**
    - Regulated by **Heme** (negative feedback), slowdown the production when there is sufficient amount.
    - **Erythropoietin** (**EPO**) and **Iron**, activating the enzyme
      - **EPO** – signals the production of more RBCs (more RBCs = more heme)
      - **IRON** – required in heme and Hgb synthesis

FIRST STEP OF HEME SYNTHESIS

- **Reactants**
  - Succinyl-CoA (from Krebs Cycle)
  - Glycine
- **These combine to form δ-Aminolevulinic Acid (ALA).**
- **Why this step matters:**
  - This is the rate-limiting step of the whole pathway.
  - It determines whether heme synthesis continues or stops.
- **Location:**
  - Occurs in the **mitochondrion**.

CONVERSION OF ALA → PORPHOBILINOGEN (PBG)

- 2 ALA molecules combine.
- 2 water molecules are removed.
- **Product:** Porphobilinogen, which has a cyclic ring structure.
- **Importance:**
  - Porphobilinogen is the building block of porphyrin.
  - The heme ring in hemoglobin comes from this structure.

REMEMBER:

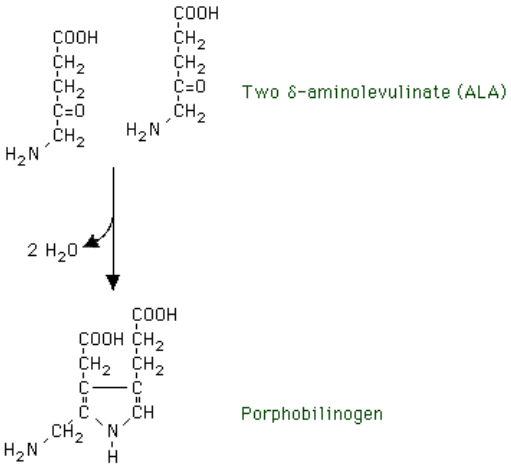
Initially, the structure is linear. However, when it reacts already to form porphobilinogen, it becomes cyclic. And this is **inhibited by lead.**

Quantities to remember:

- 4 PBG → 1 heme skeleton
- 8 ALA → 1 heme molecule

Lead toxicity:

- **Lead inhibits ALA dehydratase**, preventing formation of porphobilinogen → disrupts heme synthesis.
  - Inhibitor: Lead (Pb)



STRUCTURE OF PORPHOBILINOGEN

- Porphobilinogen has two side chains ("tails"):
  - **Propionyl** (3 carbons)
  - **Acetyl** (2 carbons)
    - These can be differentiated by counting carbon atoms.
- **To summarize:** Succinyl-CoA and Glycine are combined to create ALA, and 2 ALAs are combined together to form porphobilinogen. The reaction to produce ALA occurs in the mitochondrion, but that ALA needs to come out of the mitochondrion because the production of porphobilinogen occurs in the cytosol.
  - Succinyl-CoA + Glycine → ALA (mitochondria)
  - ALA exits the mitochondrion
  - 2 ALA → Porphobilinogen (cytosol)

FORMATION OF UROPORPHYRINOGEN

- 4 porphobilinogens combine to form uroporphyrinogen.
  - Porphobilinogen is just one ring, but once it forms the uroporphyrinogen, the four rings combine to form the skeleton of heme.
- This molecule is the first actual backbone (skeleton) of heme.
- The four individual rings from PBG join to create a tetrapyrrole backbone.

NOTE:

If asked: "**What is the first backbone formed in heme synthesis?**"

Answer: Uroporphyrinogen

- This step is a milestone because this is where we see how we utilize four porphobilinogen to form one single molecule of uroporphyrinogen which will serve as a backbone of heme. This backbone will then undergo a series of transformation/chemical reactions until we reach the heme.
- **Location:** Produced in the cytosol.
  - The **production of this backbone occurs in the cytosol.**

UROPORPHYRINOGEN → COPROPORPHYRINOGEN

- Uroporphyrinogen still contains the original acetyl (A) and propionyl (B) side chains contributed by each porphobilinogen.
- These are modified in later steps when it becomes coproporphyrinogen.
- Uroporphyrinogen decarboxylase removes carboxylic acid from Uroporphyrinogen, producing carbon dioxide.
- The backbone of the developing Heme structure contains acetyl, with a carboxyl group, that is what is removed in this step. Meaning that all of the acetyl (A) in the backbone is turned into methyl (M).
- This reaction produces a total of 4 CO2 molecules (**DECARBOXYLATION REACTION**).

COPROPORPHYRINOGEN III

- The next milestone in Heme synthesis involves the reintroduction of the molecule into the mitochondrion.

PROTOPORPHYNOGEN

- This step undergoes several **transformations**
  - Protoporhynogen is the result of the enzyme Coproporphyrinogen oxidase, producing 2 CO2 molecules instead of 4.
  - This change from 4 to 2 CO2 molecules is due to the removal of 2 Propionyl converting them to vinyl.

PROTOPORPHYRIN

- The enzyme protoporphyrinogen oxidase removes 2 Hydrogen ions, an oxidation reaction.

HEME

- The introduction of iron to Protoporphyrin creates Heme
- The enzyme Ferrochelatase introduces the iron while simultaneously removing the last 2 Hydrogen ions from the backbone of the Heme structure

HEME STRUCTURE

- 4 porphobilinogen (PBG); which forms a core with an Iron in the center.
- Iron is where the Oxygen (O2) will bind to.
- Formation of heme is partly cytosolic and partly mitochondrial; occurring in Erythroid precursors.

LIVER

- Also capable of Heme Synthesis
- But the heme produced in the Liver is NOT involved in the Hemoglobin synthesis in the blood

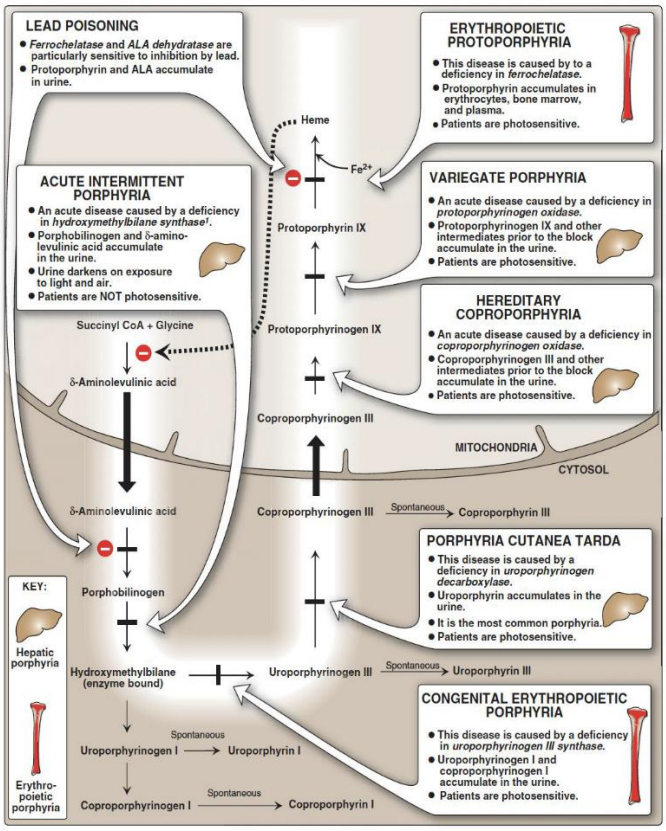
- Note that Heme can also be found in cytochromes (involved in the electron transport chain), and other important metabolic pathways

BONE MARROW

- Site of Heme synthesis specific for Hemoglobin

DEFECTS IN HEME SYNTHESIS: PORPHYRIA

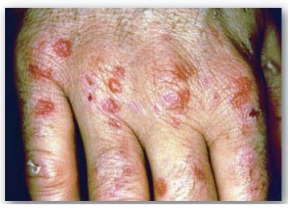
- Involving mainly 8 enzymes
- 8 disorders are as follows:



- Defects in Heme Synthesis are called "**PORPHYRIAS**"
  - Note that Heme is made up of Porphyrin rings; when one of the enzymes for Heme synthesis is deficient or destroyed, the linear pathway is disrupted and therefore cannot continue - leading to the accumulation of these Porphyrin metabolites

- The enzyme affected will determine the type of porphyrin that accumulates, that ultimately determines the type of Porphyria.
- Porphyria may be **HEPATIC** (occuring in the **liver**) or **ERYTHROPOIETIC** (occuring in the **bone marrow**).

- **PORPHYRIA CUTANEA TARDA** is the most common type of Porphyria in humans, which is due to the accumulation of **Uroporphyrinogen**

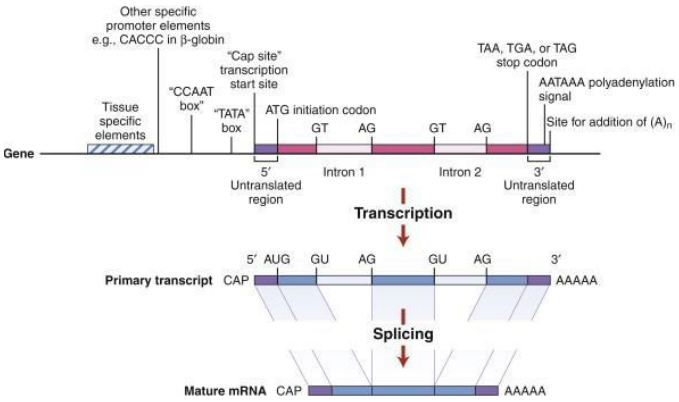



  - Note that Uroporphyrinogen is the product of the combination of Porphobilinogen; considered as a "milestone" as it becomes the backbone of Heme in the formation of Heme.
  - Uroporphyrinogen is ideally converted to Coproporphyrinogen; but in the absence of the converting enzyme, it accumulates leading to **Porphyria Cutanea Tarda**.
  - Characteristics include having photosensitive skin, and port wine red colored urine.

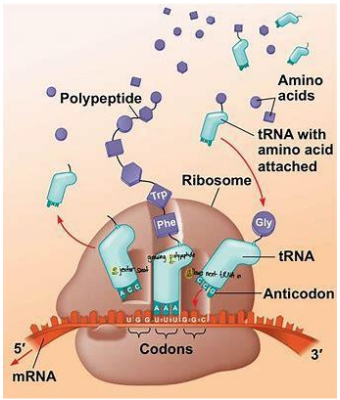
REVIEW:
- **HEME PRECURSORS**: Glycine and Succinyl CoA (together with Fe / Iron)
- **SYNTHESIS LOCATION**: Cytosolic and Mitochondrial
- **DEFECTS**: "Porphyrias".

GLOBIN SYNTHESIS

- **GLOBIN** is the protein portion of Hemoglobin



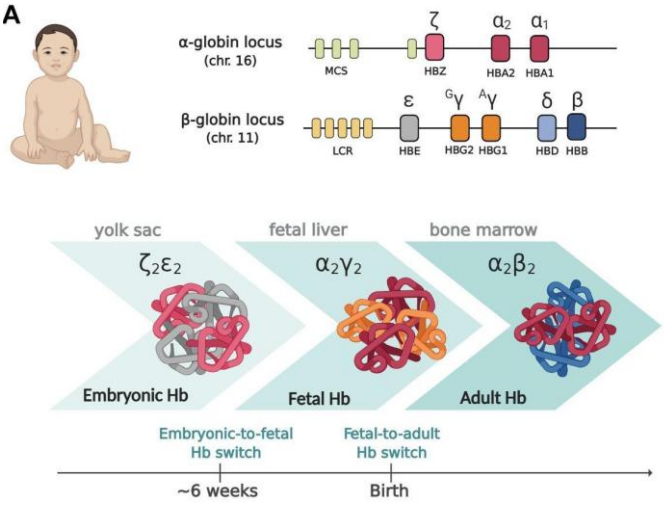
- **REVIEW ON PROTEIN SYNTHESIS:**
  - **(1) TRANSCRIPTION**
    - Copies DNA to form messenger RNA (mRNA).
    - Involves several processes (e.g. Introns, Exons, Splicing, Post-transcriptional modifications, TATA Box, etc.)
  - **(2) TRANSLATION**
    - mRNA undergoes translation within the cell's ribosomes
    - mRNA is read per codon, where each codon represents an amino acid.



DNA, GENES, AND TRANSLATION OF GLOBINS

- DNA is located in the **nucleus** and contains numerous segments called **genes**, each with a specific function.
- During **translation**, the ribosome produces only a **linear polypeptide chain** (e.g., alpha or beta globin).

- After translation, the polypeptides undergo **chaperoning**, where helper proteins assist in proper folding and assembly to form functional globin chains.
- These globin chains later combine with heme to make **mature hemoglobin**.



CHROMOSOMAL LOCATION OF GLOBIN GENES

α-Globin Gene Cluster (Chromosome 16)
— Contains HBA1 and HBA2
— Highly expressed from fetal life through adulthood

β-Globin Gene Cluster (Chromosome 11)
— Includes ε, Gγ, Aγ, δ, and β genes
— Undergoes developmental switching (ε → γ → β)

- Humans have **23 pairs of chromosomes**, and specific globin genes are located on:
  - **Chromosome 16 – Alpha-Globin Cluster**
    - Contains:
      - **α1 and α2 genes** → produce **alpha chains**
      - **ζ (zeta) gene** → embryonic globin, not present in adult hemoglobin
  - **Chromosome 11 – Beta-Globin Cluster**
    - Contains:
      - **ε (epsilon)** – embryonic
      - **γ (gamma)** – fetal
      - **δ (delta)** – minor adult globin (HbA_2)
      - **β (beta)** – major adult globin
    - Because the beta cluster contains **more genes** and undergoes multiple transitions, it is **more prone to errors** (e.g., beta-thalassemia).

TWO MAJOR TYPES OF ADULT GLOBINS

- **Alpha globins**
- Encoded by the α1 and α2 genes
  - **Highly expressed from fetal life to adulthood**
  - Alpha chains are present throughout all developmental stages
- **Beta globins**
  - Undergo **hemoglobin switching** during development
  - Embryo → Fetus → Adult transitions involve multiple β-cluster genes
  - Adults need **β chains** for mature hemoglobin (HbA)

COMBINING HEME AND GLOBIN

- Once globin chains are synthesized and folded, they combine with **heme** to form **functional hemoglobin**.
- Defects can occur in either:
  - **Heme production → PORPHYRIA**
  - **Globin production → THALASSEMIA**

HEMOGLOBIN

HEMOGLOBIN SWITCHING THROUGHOUT DEVELOPMENT

A. Embryonic Stage

- Produces **embryonic hemoglobin**
- Composition:
  - **$\zeta_2\varepsilon_2$ (zeta$_2$ epsilon$_2$)**
- Still maintains the standard structure of:
  - **4 globin chains + 4 hemes → carries 4 O_2 molecules**

B. Fetal Stage

- Transition from embryonic to **fetal hemoglobin (HbF)**
- Composition:
  - **$\alpha_2\gamma_2$ (alpha$_2$ gamma$_2$)**
- Alpha begins to be expressed fully; beta is not yet active.

C. Adult Stage

- Switch from fetal to **adult hemoglobin (HbA)**
- Composition:
  - **$\alpha_2\beta_2$ (alpha$_2$ beta$_2$)**
- This is the final form needed for optimal post-natal oxygen delivery.

TRANSITION FROM FETAL TO ADULT HEMOGLOBIN

- At birth, when the baby takes its **first breath**, a major developmental shift occurs:
  - **HbF ($\alpha_2\gamma_2$) → HbA ($\alpha_2\beta_2$)**
- Adult hemoglobin (HbA) is essential because it:
  - Efficiently **binds oxygen in the lungs**
  - Effectively **releases oxygen to the tissues**
- This transition ensures proper oxygen delivery after the newborn is no longer dependent on placental oxygen.

LOCUS CONTROL REGION (LCR)

Locus Control Region (LCR)
— LCR physically contacts the active globin gene via chromatin looping.
— At different developmental stages, the loop shifts to different globin genes, specifically, ε (embryonic) → γ (fetal) → β (adult), which promotes stage-specific transcription.

- The **beta-globin gene cluster** contains a regulatory segment called the **LCR – Locus Control Region**.
- DNA is not fixed linearly; it can **fold and loop**.
- During different developmental stages, the LCR physically loops to activate specific globin genes:

- **Embryo** → LCR loops to **ε (epsilon)** gene → produces ε-globin
- **Fetus** → LCR loops to **γ (gamma)** gene → produces γ-globin (HbF)
- **Adult** → LCR loops to **β (beta)** gene → produces β-globin (HbA)

- This dynamic looping underlies **hemoglobin switching**.

DO ADULTS STILL HAVE FETAL GLOBIN?

- Yes, but only in **very small amounts**.
- Majority becomes **adult hemoglobin**, needed for proper lung-based oxygenation.

FUNCTIONAL DIFFERENCES: FETAL VS. ADULT HEMOGLOBIN

Fetal Hemoglobin (HbF: $\alpha_2\gamma_2$)

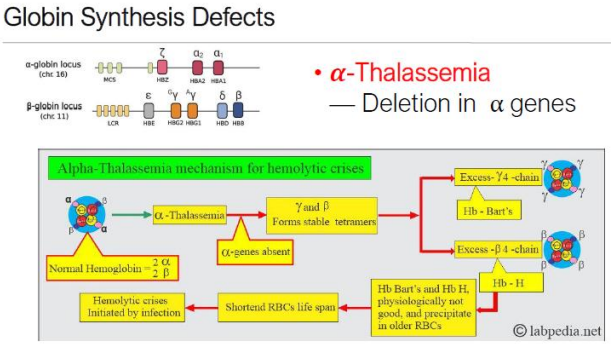
- **Higher oxygen affinity**
- Necessary because:
  - The fetus receives oxygen **indirectly through the placenta**
  - Must pull oxygen away from maternal blood → requires tighter binding

Adult Hemoglobin (HbA: $\alpha_2\beta_2$)

- **Lower oxygen affinity** compared to HbF
- Has **positive cooperativity**:
  - Essential for efficient **oxygen loading in the lungs**
  - And **oxygen unloading to tissues** after birth
- After birth, once the umbilical cord is cut, oxygen comes from the **lungs**, so hemoglobin must optimize release—not tight binding.

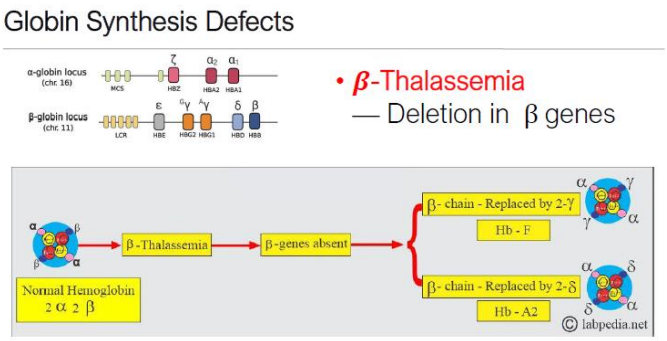
DISORDERS OF GLOBIN SYNTHESIS: THALASSEMIAS

ALPHA THALASSEMIA

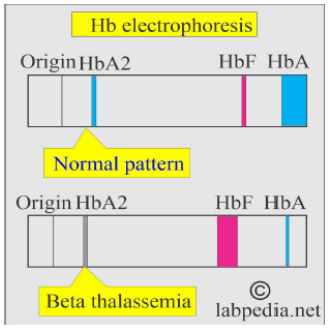


- Cause: Defect or deletion of α-globin genes (on chromosome 16).
- Consequence:
  - Reduced alpha-chain production → Excess beta chains
  - This forms abnormal β_4 tetramers (HbH).
  - Since normal hemoglobin should be $\alpha_2\beta_2$, lack of alpha chains leads to:
    - Hemolytic crises
    - Low hemoglobin
    - Severe anemia
  - Diagnosis: Hemoglobin electrophoresis
    - Shows decreased HbA
    - Increased abnormal hemoglobin types

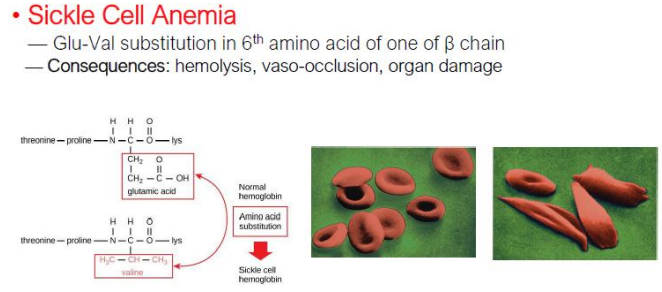
BETA THALASSEMIA



- Cause: Deletion or mutation of β-globin gene (chromosome 11).
- Consequence:
  - Reduced or absent β-chain synthesis
  - Body compensates by producing more γ-globin (fetal) → increased HbF
  - Thus, instead of forming adult HbA, patients produce:
    - Excess fetal hemoglobin (HbF: $\alpha_2\gamma_2$)
  - Electrophoresis Findings:
    - Decreased HbA
    - Elevated HbF and sometimes HbA_2



SICKLE CELL ANEMIA (STRUCTURAL HEMOGLOBINOPATHY)



- Unlike thalassemia (deletion or reduced production), sickle cell is caused by:
  - A single amino acid substitution in the β-globin chain.
- Normal amino acid at position 6:
  - Glutamic acid
- Mutated form:
  - Valine
- This "Glu → Val substitution" is enough to produce:
  - Abnormal hemoglobin HbS
  - Polymerization under low O_2 → sickling of RBCs
- This mutation is a point substitution, not a deletion.
- Unluckily, you will encounter a patient that will have an abnormal hemoglobin because that abnormal hemoglobin will

have a valine instead of a glutamic acid in a six amino acid residue.

- What's going to happen?
  - It will produce a **sickle cell hemoglobin.**
- Why is the substitution very fatal?
  - There are different kinds of amino acid:
    - **Polar**
      - Polar acidic
      - Polar basic
      - Polar neutral
    - **Non-polar**
  - **Glutamic acid:** Polar acidic
  - **Valine:** Non-polar
- Glu-Val substitution in 6th amino acid of one of beta chain (from slides)
  - From **polar** *(glutamic acid - normal)* to **non-polar** *(valine - abnormal)*, it's a major change that could change the structure of the entire protein because they have differences in polarity.
  - And what's going to happen?
    - The red blood cell will have the shape of a sickle.
  - Hence, sickle cell anemia due to the characteristic or form of the red blood cell which will be shaped like a sickle.
- Effects:
  - **Hemolysis**
  - **It cannot carry oxygen.**
    - Abnormally carries less oxygen because the hemoglobin molecule is abnormal.
  - **Blockage in the capillaries (vaso-occlusion) and organ damage**
    - *Remember:* Normal red blood cells are disc shaped which allows for it to flow through capillaries.
    - However, if you have sickle cell red blood cells, it would result in blockage in the capillaries.
    - Blockage = necrosis
      - Because there will no longer be enough oxygen flowing through there.
      - It will kill the organ. And so when the organ is killed, you're also killed.
      - Hence, it is a very fatal disease.
- Treatment:
  - No treatment for it yet.
  - **Gene therapy (tried):** used to correct the defect in the Glu-Val substitution.
    - However, there is no therapeutically approved gene therapy that could correct this.
  - **CRISPR technology (mentioned by sir):** is a gene-editing technology that allows scientists to precisely modify DNA in living organisms by using a system adapted from bacteria.
    - It uses a guide RNA molecule to direct a Cas protein, often Cas9, to a specific DNA sequence to cut, remove, or insert new genetic material.
    - This is used to try to correct sickle cell anemia (no updates on its progress yet).
- Lifespan of patients with sickle cell anemia:
  - Can **live** only up until *childhood.*
  - They **cannot live** until *adulthood*.
  - This is because the condition can cause necrosis.
  - Increased iron intake is needed.
    - Patients can experience iron overload because of continuous blood transfusion which could be fatal.
    - So, the management of the symptoms itself can also cause death.

SUMMARY OF HEMOGLOBIN SYNTHESIS

- Synthesize heme, then globin, and then synthesize hemoglobin.
- Analysis:
  - If you don't have heme, what's going to happen?
    - You will have a lot of globin.
  - What's going to happen to globin if you don't have hemoglobin?
    - Proteins will precipitate.
    - Excess protein always precipitates.
  - What's going to happen once this precipitates?
    - It will eventually kill the erythrocytes.
  - If you do not have globin and always create heme, it will also result in prophyria.
- Also remember: Heme synthesis requires **iron**.
  - Iron is:
    - Stored in the protein, **ferritin (storage form of iron)**.
    - Transported into the blood through **transferrin**.
  - Heme synthesis is affected if there is a defect in either/both ferritin and transferrin.
  - If heme synthesis is affected, it will also affect hemoglobin synthesis.
  - First cell affected if hemoglobin is effected:
    - **Red blood cell** – since it stores hemoglobin.
  - Less hemoglobin = less oxygen in the blood **(hypoxia).**
  - Hypoxia can result in eventual death or other complications.

REGULATORS OF HEMOGLOBIN SYNTHESIS

Regulation of Hemoglobin Synthesis

1. Systemic regulators:
   a. Erythropoietin (EPO): stimulates erythroid progenitor proliferation/differentiation and increases globin/heme synthesis.
   b. Iron homeostasis: dietary iron absorption (duodenal enterocytes), transferrin delivery, ferritin storage
2. Metabolic cofactors:
   a. Vitamin B_6 (pyridoxal phosphate) for ALA Synthase;
   b. Succinyl-CoA supply from TCA cycle and NAD^+ for oxidation steps

SYSTEMIC REGULATORS

- **Erythropoietin (EPO)** stimulates hemoglobin synthesis.
  - It is because EPO produces more **erythroid precursors.**
    - More erythroid precursors = more hemoglobin
- **Iron homeostasis** also affects hemoglobin synthesis.
  - Iron is absorbed in the duodenum.
  - If you have a damaged duodenum, iron will be malabsorbed.
  - **Malabsorption of iron** = cannot create hemoglobin.

METABOLIC COFACTORS

- **Vitamin B6 (pyridoxal phosphate)** is required for the first enzyme (ALA synthase) in heme synthesis.
  - Vit. B6 deficiency affects hemoglobin synthesis.
- **Succinyl-CoA** is a supply from the TCA cycle.
  - Any defects in the Krebs cycle affects hemoglobin synthesis.
  - Hence, Krebs cycle is a central pathway.

SUMMARY OF TOPICS:

- **Hemoglobin** = heme + globin
- **Heme:** produced in the mitochondria and cytosol.
  - **ALA synthase:** first enzyme, key enzyme, rate-limiting determining step because it tells you whether to create heme or not (regulator and inhibitor).
- **Globin:** produced in the ribosome.
  - Beta globin undergoes developmental switching – from Epsilon to Gamma to Beta ($\epsilon \rightarrow \gamma \rightarrow \beta$) – controlled by the LCR (Locus Control Region).
- **Regulation:** heme, iron, EPO, Vitamin B6
- Disorders:
  - **Porphyria**: affects *heme* synthesis
  - **Lead poisoning:** affects 2nd and last enzyme (heme synthesis)
  - **Thalassemias and sickle cell:** affects *globin* synthesis.

QUICK CHECK:

Rate-limiting enzyme in heme synthesis?
- **ALA synthase**

Enzyme/s in heme synthesis affected by Pb poisoning?
- *2nd enzyme:* **ALA-dehydratase**
- *Last enzyme:* **Ferrochelatase**

Order of developmental switching in beta-globulin gene?
- **Epsilon to Gamma to Beta ($\epsilon \rightarrow \gamma \rightarrow \beta$)**

If Hb electrophoresis shows increased HBA2 – diagnosis?
- **Alpha (α)-thalassemia**

Glu → Val mutation in β-globulin leads to?
- **Sickle cell anemia**

Basic Biomedical Sciences 1

Lecture 2: Hemostasis

Dr. Mark Booc

HEMOSTASIS

HEMO

- **Hemo** = blood

STASIS

- **stasis** = stoppage of flow of bodily fluids

HEMOSTASIS

- **Hemostasis** = stopping blood from exiting the bloodstream
  - Process by which blood clots are formed at the site of injury
- If hemostasis is deranged, broadly classified in two groups of disorders:
  1. Hemorrhagic disorders: characterized by excessive bleeding. Hemostatic mechanisms are blunted or insufficient to prevent blood loss.
     - i.e. Hemophilia or factor deficiencies in blood clotting where there are insufficient mechanisms
  2. Thrombotic disorders: Blood clots form within intact blood vessels or within the chambers of the heart.
     - I.e. pulmonary embolism and myocardial infarction
- Sometimes division between bleeding and thrombotic disorders are not so clear cut
  - I.e. generalized activation of clotting sometimes **paradoxically** produces bleeding due to consumption of coagulation factors (Disseminated Intravascular Coagulation)

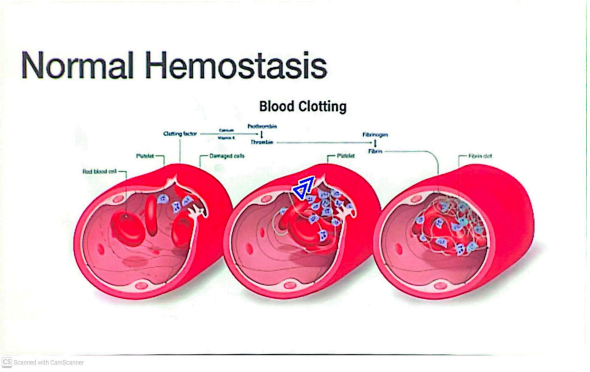


Figure 1: Normal Hemostasis

- The blood vessel got damaged and is exposed to the surrounding tissues. The platelet (blue structures) together with clotting factors, cofactors, vitamin K that would mark the coagulation cascade, ultimately resulting in fibrinogen becoming fibrin. These will form primary clots or platelet plug and once you have fibrin you now have fibrin clot

NORMAL HEMOSTASIS

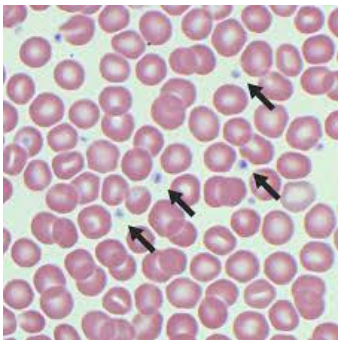
- A process involving platelets, clotting factors, and endothelium that occurs at the site of vascular injury and culminates in formation of blood clot which serves to prevent or limit extent of bleeding.

SEQUENTIAL EVENTS LEADING TO HEMOSTASIS

- **Vasoconstriction**: Occurs immediately and serves to reduce blood flow to the injured area.
  - First response and temporary
  - Due to smooth muscles in the tunica media of the blood vessel to contract. Nerves and factors that regulate or control vasoconstriction and vasodilation.
  - Serves to slow down the blood to prevent blood loss.
  - Temporary; if there is no platelet plug formation, it will go back and blood will be lost

PRIMARY HEMOSTASIS

- **formation of platelet plug**: Disruption of endothelium exposes subendothelium von Willebrand Factor and collagen which promote platelet adherence and activation meaning that they will change their morphology and their granules. Instead of the normal disc shaped platelet you get a “sea urchin” shaped platelet because of its spiny processes and its purpose is to increase surface area so that it can release granules.
- There are two types of granules: Alpha granules and Dense granules



- Peripheral blood smear of what platelets look like under a microscope and their basophilic fragments

VON WILLEBRAND FACTOR (vWF)

- **von Willebrand Factor**
  - Glycoprotein that helps platelet stick to injured vessel walls to form a primary platelet plug
  - Also carries **factor VIII** for coagulation
  - Produced by endothelial cells and megakaryocytes
    - stored in **WEBEL-PALADE BODIES** in the endothelium
    - Alpha granules of platelets
  - Binds to receptor **GP Ib (Glycoprotein Ib)** on platelets so in that way they can stick to each other.

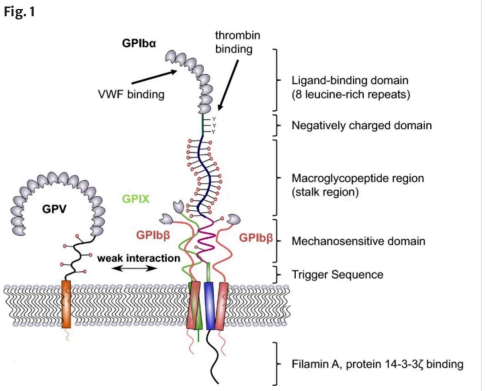


Figure 2: Glycoprotein Ib

- Found in platelets and endothelium and serves as a glue; it will adhere the platelets together (primary hemostasis)

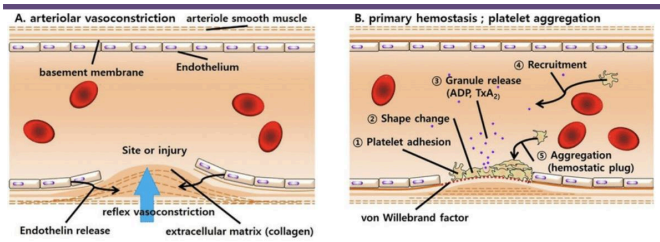


Figure 3: Vasoconstriction ; Primary Hemostasis ; Platelet Aggregation

Here's the diagram, the first step on the left shows that the blood vessel is injured and the immediate reaction is vasoconstriction slowing the blood flow. Because the endothelium is disrupted, it exposes the underlying tissues to collagen and tissue factors. When the von Willebrand factor (vWF) will be released and exposed, it will bind to receptor GP Ib (1) and that way the platelets can now attach to the vWF then it will undergo platelet activation which is basically a change in morphology and releasing of granules which is called **platelet aggregation** (2) and (3)**.** It will release substances such as ADP and thromboxanes A2 which will promote more platelet recruitment and aggregation (positive feedback mechanism). Once all the platelets are joined together, that is the formation of **platelet plug formation.**

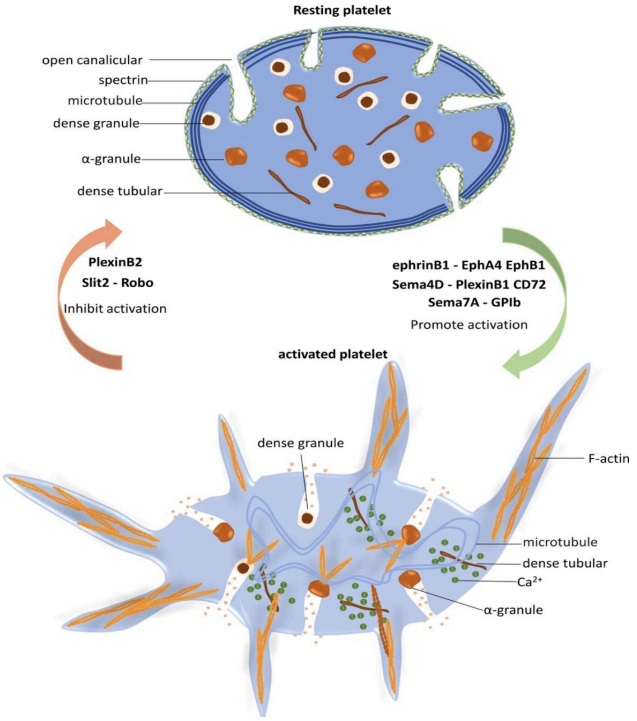


Figure 4: Neuronal activation

When platelets become activated, they exposed phospholipid surfaces that bind to calcium where coagulation cascade nucleate.

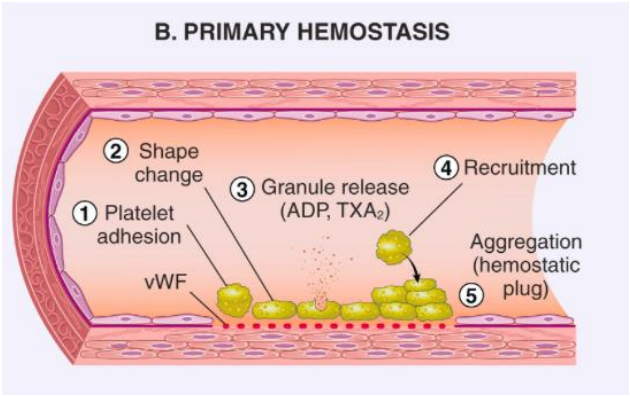


Figure 5: Platelet Plug Formation

The illustration shows the formation of platelet plug; adhesion, activation, recruitment and formation of your plug which is temporary wherein it needs to be stabilized through the production of fibrin. Fibrin is like a meshwork acting as a thick chain of rope that surrounds the platelet plug.

SECONDARY HEMOSTASIS

- deposition of fibrin: Injury exposes tissue factor at sites of injury It binds and activates factor VII setting in motion the coagulation cascade that culminates in **thrombin** generation. Thrombin cleaves through fibrinogen into insoluble fibrin creating a **fibrin mesh work**. This process consolidates the initial platelet plug

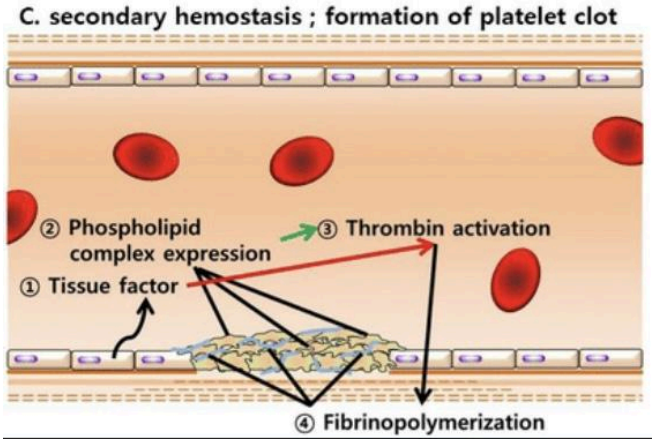


Figure 6: Secondary Hemostasis

The illustration shows secondary hemostasis. The dark-blue lines signify the fibrin. Tissue factor is exposed initiating the coagulation cascade. Phospholipids are produced from the platelets which are the nucleation sites for coagulation factors. Thrombin is activated which will result to fibrin becoming polymerized or insoluble (fibrinopolymerization)

- Secondary plug has **fibrin**
- Initial plugs are just **platelets**

CLOT STABILIZATION AND RESORPTION

- polymerized fibrin and platelet aggregates undergo contraction to form a solid permanent plug. The counter regulatory mechanisms (tissue plasminogen activator, made by endothelial cells) are activated that limit clotting to the site of injury and eventually lead to clot resorption and tissue repair.

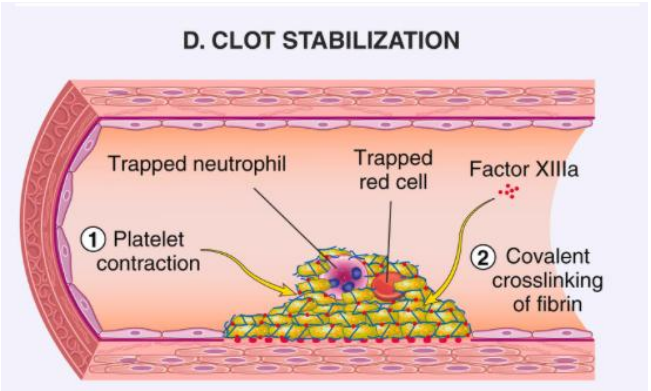


Figure 7: Clot Stabilization

ENDOTHELIAL CELLS

- Central regulators of hemostasis. It depends on the state of endothelium on how to prevent excessive blood clotting.
  - If it is intact: blocks the collagen and tissue factors; platelets cannot reach the tissue factor vWF because they are already stored inside the cell and they are physically blocked by the cell.
  - If it is damaged: blood clot formation is favored

- Balance between antithrombotic and prothrombotic activities determine if thrombus forms and grows or dissolution occurs
- Normal endothelial express anticoagulant factors
- After injury or activation, endothelial cells undergo for coagulation
- Aside from trauma, endothelial activation can be done by microbial pathogens, hemodynamic factors and pro-inflammatory mediators.

3 MAJOR COMPONENTS

PLATELETS

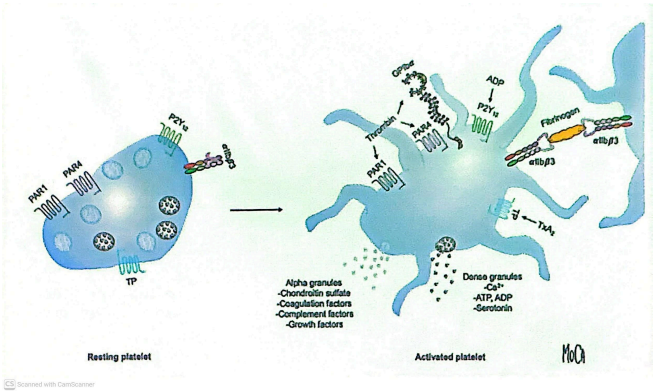


Figure 8: Platelets

- Platelets originate from megakaryocytes from the bone marrow; they are fragments of megakaryocytes.
  - Megakaryocytes give rise to platelets: pinch off the cytoplasm
- Anucleated; dense ovoid structures in peripheral blood smear
- When they come in contact with underlying epithelium, they undergo platelet activation; they change their morphology(sea urchin; spiny processes) and release granules
- Sea urchin morphology - increase surface area in order to release granules
- Platelets play a critical role in forming the primary plug and binds coagulation factors
- Granules of Platelets

TYPES OF GRANULES

- **Types of granules**
  - Alpha Granules
  - Dense Granules

Alpha Granules

- **Alpha Granules:**
  - Molecules For adhesions: P selectin
  - Proteins for coagulation: fibrinogen, coagulations factors (V, XI, vWF)
  - Factors for wound healing: fibronectin, platelet factor 4, PDGF, TGD-Beta

Dense Granules

- **Dense Granules**
  - ADP, ATP, Ionized calcium, serotonin, epinephrine

"Then you have your dense granules which has ATP and other substances"

CELL MEMBRANE OF PLATELETS

- **Cell Membrane of Platelets** - contain several glycoprotein receptors important for hemostasis
  - Gp Ib (vWF)
  - Gp VI and Gp Ia/IIa complex (collagen)
  - GpIIb/ IIIa complex (fibrinogen)

"Then, on the membrane of the platelets there are various receptors. We talked about one of them, the Gp1b for vWF but here's also a receptor for collagen and fibrinogen"

- **What happens when platelets encounter sites of vessel injury**

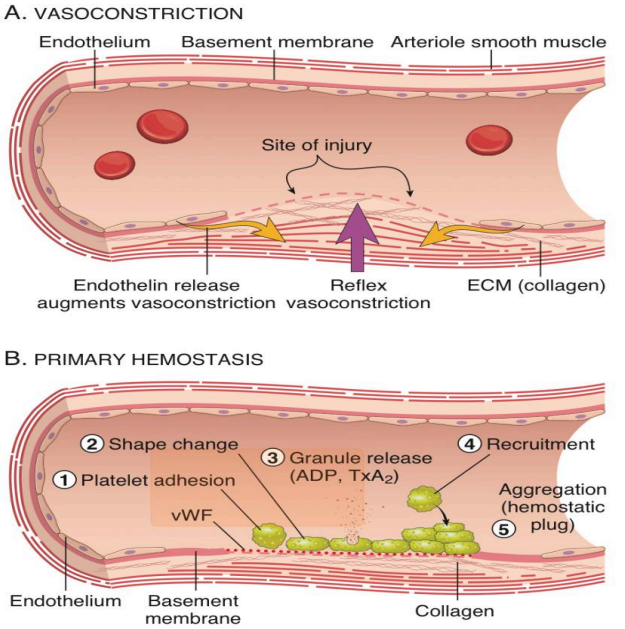


Figure 9: Vasoconstriction ; Primary Hemostasis

  - Vasoconstriction
  - Damaged vessel exposes subendothelial connective tissue (vWF and collagen)
  - Platelets come to contact which causes a sequence of reactions to form a platelet plug

"So what happens to the platelets when they encounter sites of injury. The first step is always vasoconstriction but before vasoconstriction, well, first is injury then vasoconstriction, so the damaged blood vessels will expose the vWF, platelets come in contact and become activated."

SEQUENCE OF PLATELET PLUG FORMATION

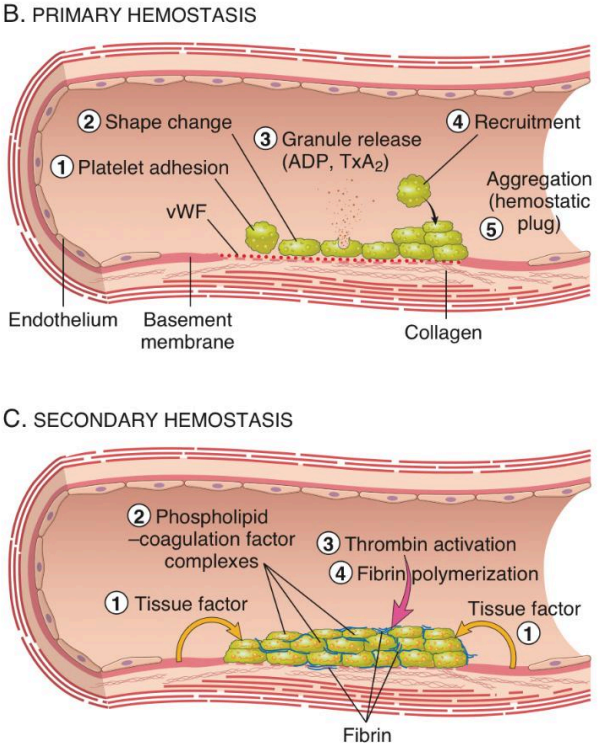


Figure 10: Primary Hemostasis ; Secondary Hemostasis

  - Platelet adhesion
  - Platelet change shape
  - Secretion of granules
  - Platelet aggregation

"So here's the special steps: adhesion, shape change, secretion of granules, and aggregation. Collectively, this is platelet activation."

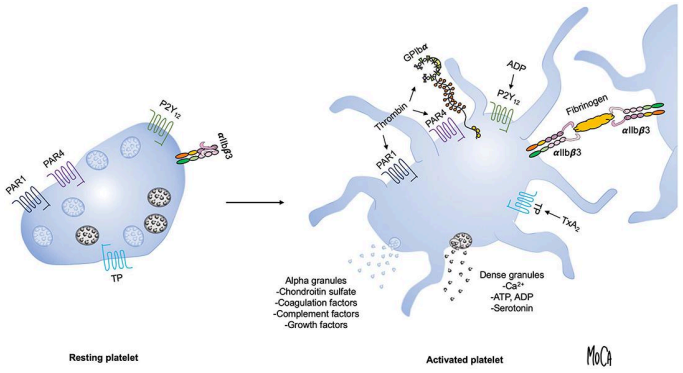


Figure 11: fibrinogen attached to αIIbβ3

"So you see in the diagram that I showed you earlier and I'm showing it to you again. Here is the fibrinogen attached to its αIIbβ3. Note this, you have ATP here will also act as positive feedback and will act on this receptor, the P2Y12 receptor. Thromboxane is important, it's also produced by the platelet by cyclooxygenase. If you are familiar with aspirin, aspirin inhibits cyclooxygenase. Therefore, inhibiting thromboxane formation. Therefore, inhibiting platelet aggregation. That's how it is known as a blood thinner because of inhibition of cyclooxygenase. Then, thrombin itself also will activate platelets by its PAR1 receptor and PAR4 receptor."

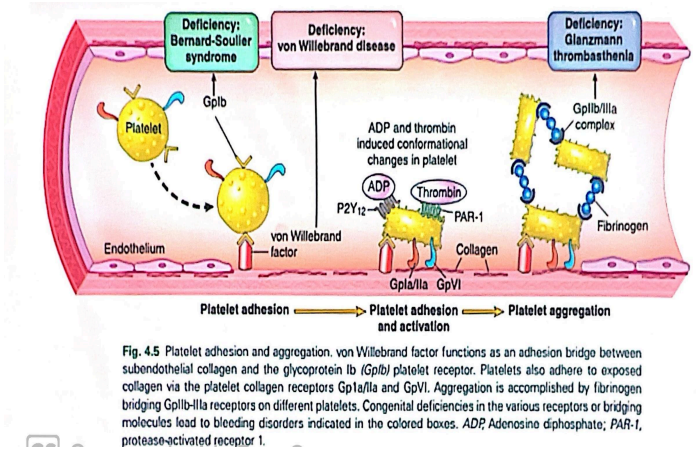


Fig. 4.5 Platelet adhesion and aggregation. von Willebrand factor functions as an adhesion bridge between subendothelial collagen and the glycoprotein Ib *(GpIb)* platelet receptor. Platelets also adhere to exposed collagen via the platelet collagen receptors Gp1a/IIa and GpVI. Aggregation is accomplished by fibrinogen bridging GpIIb-IIIa receptors on different platelets. Congenital deficiencies in the various receptors or bridging molecules lead to bleeding disorders indicated in the colored boxes. *ADP*, Adenosine diphosphate; *PAR-1*, protease-activated receptor 1.

Figure 12: Platelet adhesion ; activation ; aggregation

"You can see those vWF, that's the red little head sticking up, see how it is attached to the receptor, the GpIb. Then it will undergo conformational change/activation. It will release ADP and will self-activate and initiate the coagulation cascade which will reduce thrombin which will also activate more platelets and ultimately result in fibrinogen adhering several platelets together."

When a factor number has a letter "a" after it, it means it is in its activated form

- EXAMPLES.
  - Factor II: Prothrombin (inactive),
  - Factor IIa: Thrombin (active)

The extrinsic and intrinsic pathways will merge to initiate the common pathway. The most important factor in this pathway is **thrombin**.

THE COAGULATION CASCADE

It is a series of amplifying **enzymatic reactions** that lead to **deposition** of an insoluble **fibrin** clot.

- Mediators (factors) are mostly plasma proteins that circulate in inactive form
- Exception is tissue factor (factor III) which is found in cells (i.e. fibroblasts and pericytes) and is released only after tissue injury when exposed to blood.
- Coagulation factors are passed from one step to another
- Each step involves an **enzyme** (activated coagulation factors), **substrate** (inactivated proenzyme of a coagulation factor), and **cofactor**

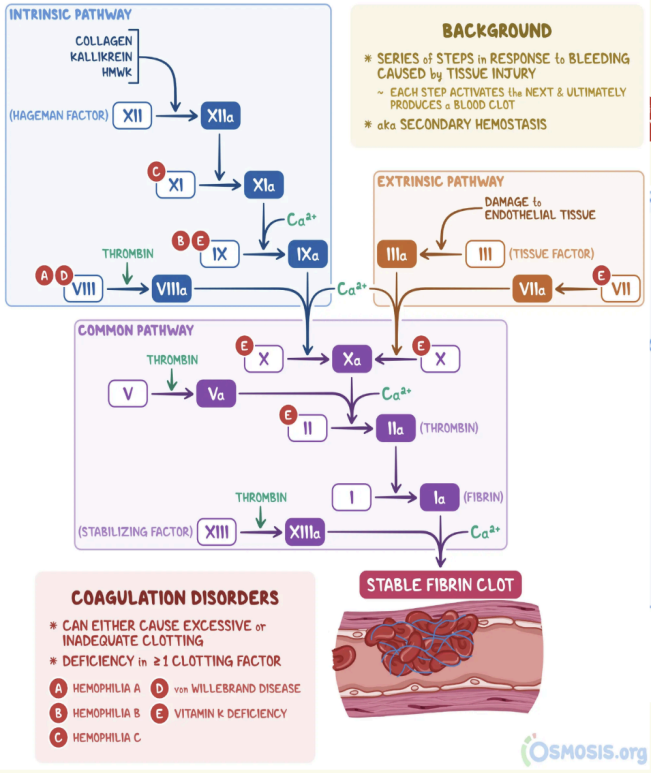


Figure 13: Coagulation Cascade

- Most of these factors are just circulating into the blood themselves, except for tissue factor, which is usually within the tissues.
- Ultimately, the **end result** of the coagulation cascade is to produce the **fibrin**, which will form the secondary clot and stabilize the clot.
- These factors are assembled within the surface of the platelets. The platelets have **phospholipids which** will also bind to **calcium.**
- If the **process** requires calcium, it will bind to a substance which is dependent on **vitamin K.**
  - If you have vitamin K **deficiency,** there is excessive bleeding because portions of the coagulation cascade cannot be completed. That's why vitamin K is given to the **newborns.**
- Factors assembly on phospholipids surface provided by activated platelets and depends on calcium (factor IV) which binds to gamma carboxylated glutamic acid present on **factor II, VII, IX, and X** (vitamin K-dependent)
  - Reactions that produce gamma carboxylated glutamic acid use **vitamin K** as a cofactor.

COAGULATION FACTORS

Name	Synonym
Factor I	Fibrinogen
Factor II	Prothrombin
Factor III	Tissue factor
Factor IV	Calcium
Factor V	Proaccelerin, labile factor

Factor VI	Old name of Factor Va
Factor VII	Proconvertin, stable factor
Factor VIII	Antihemophilic factor A
Factor IX	Antihemophilic factor B
Factor X	Stuart-Prower factor
Factor XI	Plasma thromboplastin anther
Factor XII	Hageman factor
Factor XIII	Fibrin-stabilizing factor

- Laboratory tests used to assess the pathways are divided into two:
  - **Extrinsic Pathway :** assessed by the **prothrombin time (PT)**.
  - **Intrinsic pathway**: assessed by **partial thromboplastin time (PTT)**
- Both of them will measure the **common pathway.**
- If we suspect a **deficiency** in one of the factors, we start off with these lab tests.
  - If **one** of them is **abnormal** and the other one is normal, you can probably assume that there's a deficiency in **either** the extrinsic or intrinsic
  - If **both** of them are **abnormal**, the deficiency is expected in the common pathway.
  - But nowadays, there are assays to measure each individual factor but they are a little bit expensive.

THROMBIN (FACTOR IIA)

- **The most important factor**
  - Effects of Thrombin
    - Conversion of fibrinogen to fibrin
    - Also acts as cofactors for activation of Factors V, VIII
    - Activates Factor XIII which cross links fibrin
  - Platelet Activation
    - Via activating PAR-1
  - Pro inflammatory Effects
    - Repair and angiogenesis
  - Anticoagulant
    - On intact epithelium it acts as anticoagulant

FACTORS THAT LIMIT COAGULATION

- **Dilution**
  - Blood flowing past injury washes out activated coagulation factors which are removed by liver
- Requirement for negatively charged phospholipids done by the platelets
- Factors expressed by notated endothelium adjacent to injury
- **Fibrinolytic Cascade**
  - Limits size of clot and later its dissolution
  - Enzyme **plasmin** which breaks fibrin and interferes with polymerization
- Coagulation cascades meet the phospholipids on the platelets.
- So when the platelets are activated, they will form the phospholipids on the surface, that's where the cascade will occur.
- The factors expressed by the normal endothelium exhibit **anticoagulatory effects**

FIBRINOLYTIC CASCADE

- **Fibrinolytic cascade**
  - **Fibrinolysis**: fibrin breakdown, it prevents the blood clot from forming
  - Broken down by **plasmin**
  - It interferes with the build up fibrin and interferes with polymerization

ENDOTHELIUM

- Endothelium is balanced between anticoagulant and pro coagulant activities, it will either promote or inhibit
  - **Damaged:** promote coagulation
  - **Intact:** inhibit coagulation
- Normal endothelium cells
  - Express factors that inhibit procoagulant activities of platelets and coagulation cells
  - Augment fibrinolysis
- Injured endothelium or endothelium exposed to pro inflammatory factors
  - Loose antithrombotic properties

ANTITHROMBOTIC PROPERTIES OF ENDOTHELIUM

- Platelet inhibitory effects
- Serves as a barrier that shields platelets from sub endothelial vWF and collagen

Secretion of inhibitory factors

- Prostacyclin: produced by COX 1
- Nitric oxide
- Adenosine diphosphotase: enzyme that breaks down ATP
- Thromodulin: works with endothelium protein C to inhibit thrombin
- Heparin like molecules: inhibits thrombin by activating anti-thrombin

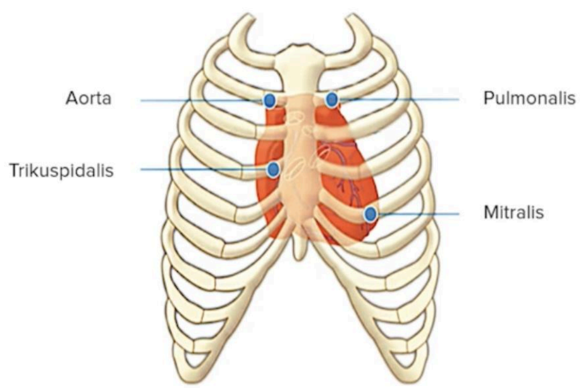
Fibrinolytic factors

- Normal endothelial cells synthesizes t-PA which is importantly in fibrinolytic pathway
- t-PA is the most important activator of plasminogen which forms plasmin

VIDEO 1: CARDIOVASCULAR SYSTEM: ANATOMY OF THE HEART BY LECTURIO

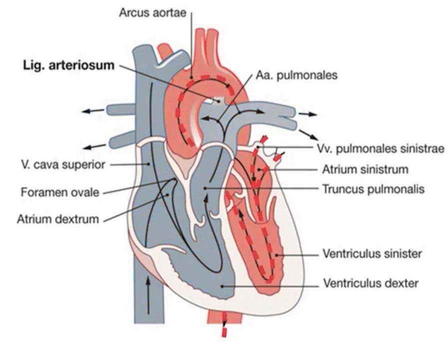
The Anatomy of the Cardiovascular System

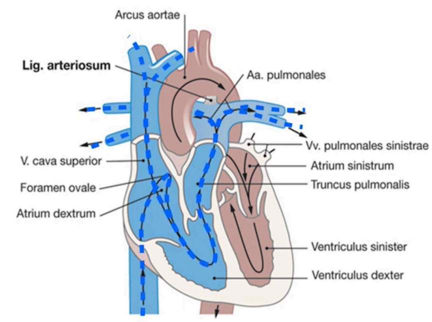
- The heart is not heart shaped!
    - The heart is conical in shape with a rounded point (not a sharp point).
- The heart in embryonic life starts out as a tube that folds on itself and develops into 4 Chambers.
- The heart is a pump.
    - It is a muscle pump that keeps the circulation continuously going in a circle.
- The blood circulates in a never ending circle.
    - What happens is the heart pumps the blood out full of oxygen and nutrients to the cells throughout the body.
    - Then, waste products are given to the blood. The blood returns to the lungs a deep blue and is then reoxygenated (gets oxygen again) and pumped out to the body. There's a continuous circle going on of the circulation.



- Here's a diagram that shows how the heart lies in the chest
- Notice that it is not directly in the center of the chest. In fact, it is slightly to the left. In this view, it looks like it's to the right, but if you were standing behind this person where the heart bulges out it would be to the left. You can see four points are marked on this skeleton with the heart drawn behind it.
- Behind the ribs and the breast bones which we call the sternum, you can see that there are four heart valves and the points that are marked are the places where we listen with our stethoscope when we want to hear that particular valve:
    - Aortic Valve
    - Pulmonic Valve
    - Tricuspid valve
    - Mitral Valve

VIDEO 2: CHAMBERS OF THE HEART BY LECTURIO





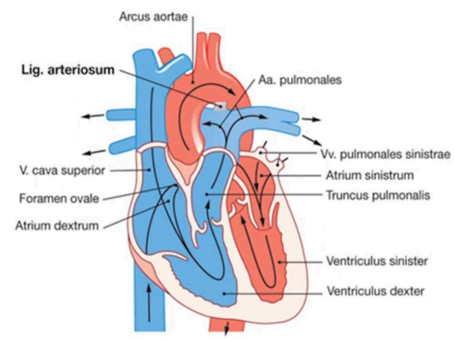


Diagram of the circulation:

- It's made in two colors: blue for the blood that's returning to the right side of the heart.
    - It's exhausted of its oxygen.
    - It's carrying waste products, particularly carbon dioxide.
- Carbon dioxide will be given off in the lungs.
- Oxygen will be introduced to the red blood cells and then they will get to the left side of the heart where they'll be pumped out to the body.

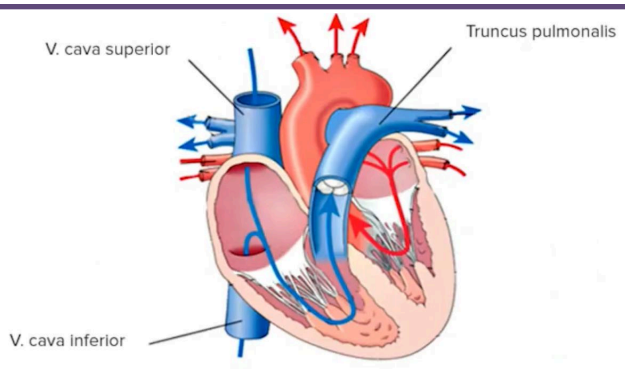
Circulation through the heart:

- There are two large veins here that drain into the right atrium:
    - **Superior vena cava**: drains the blood from the upper body
    - **Inferior vena cava**: drains the blood from the lower body.
- They both empty into the right atrium and then pass through the tricuspid valve into the right ventricle.
- They are pumped out through the pulmonic valve into the lungs.

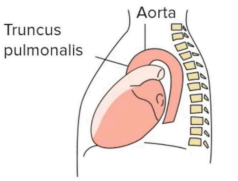
- They return through pulmonary veins to the left atrium and then across the mitral valve into the left ventricle.
- The left ventricle pumps it out through the aortic valve to the aorta and to the whole body.

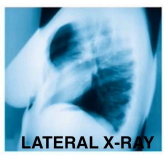
- What you see here is a small catheter working its way through the heart. That's how we measure pressures and the flow the the amount of blood that the heart is pumping during a diagnostic catheterization.
- But again, the blood is not exactly this color blue on the right side of the circulation.
- It's a little bit darker and it's quite bright red on the arterial side.

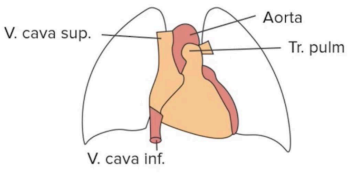
A more anatomically correct diagram



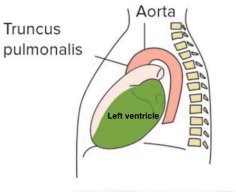
- Notice the superior vena cava, the inferior vena cava, coming into the right atrium draining the deoxygenated or tired blood into the right atrium
- You can see the tricuspid valve as the blood passes into the right ventricle and then it is being pumped out into the pulmonary artery still all in blue
- What's of interest here is that the left ventricle is a lot thicker than the right ventricle. In fact, their shapes are slightly different. It's because they have very different functions. The pressure in the lung is quite low, so that the right ventricle functions like a Bellows like the blacksmith uses to create air for his fire that he's going to be melting and working on horseshoes, for example. It produces large volumes of blood movement at low pressure.
- The left ventricle has to pump blood throughout the body. It has to pump that blood at a much higher pressure.
- And consequently, the walls of the left ventricle are much thicker than the walls of the right ventricle. It's functioning not like a Bellows, but rather like the piston in a car, a high pressure chamber that does a lot of pressure work, as opposed to the right ventricle which does a lot of volume work at much lower pressure.

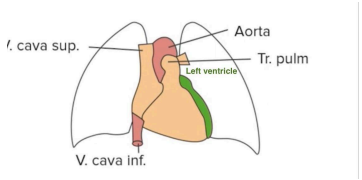




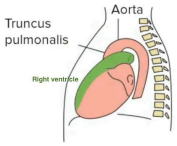


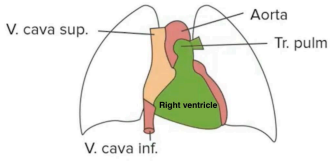
- Now here we see the heart diagrammed in comparison to the chest x-ray
- Notice that the heart is not in the center of the chest but in fact is a little bit more in the left chest than the than the right chest





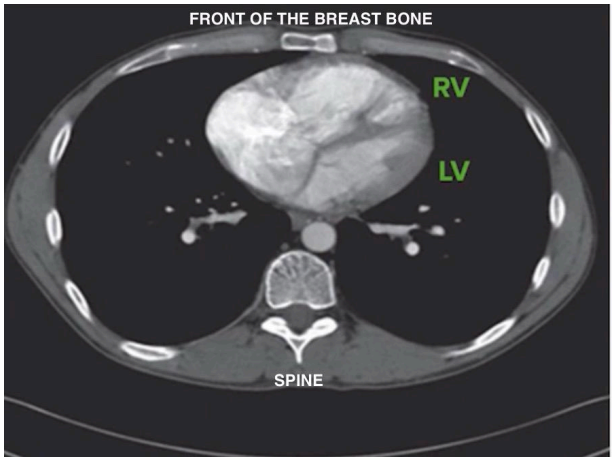
- The bulge down in the left chest is actually the **left ventricular outline.**





- If you want to see the **right ventricle**, you have to look at the lateral View and you see it in front of the left ventricle
- The heart actually has the right ventricle in front of the left ventricle. We'll see that on some further x-rays and magnetic resonance image which will show you that in fact the right ventricle does lie in front, closer to the breast bone than the left ventricle which lies a little bit behind.
- and you can get a hint of that from the the two diagrams here that are reflecting what you see in the chest x-rays

MRI of the chest



- **Top:** front the breast bone
- **Bottom**: spine.
- **Middle**: heart
- **RV**: right ventricle
- **LV**: left ventricle
- Note: The right ventricle is lying in front, that is closer to the chest front wall compared to the left ventricle

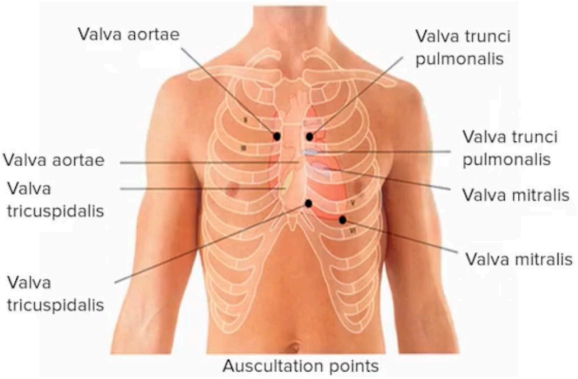
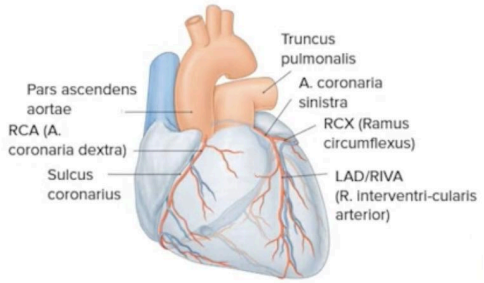


Diagram that shows where the heart is located and where the different points are that you can best hear, with your stethoscope, the sounds made by the four heart valves.

VIDEO 3: ARTERIES AND VEINS BY LECTURIO

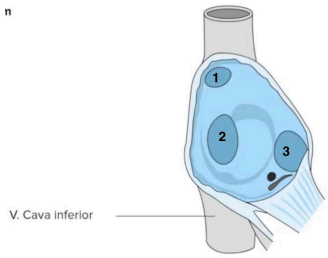
- The arteries carry nourishment and oxygen to the working myocardial cells thereby enabling contraction
- If inadequate blood reaches the myocardial cells, their contractile function deteriorates
- The venous system of the heart drains "depleted" blood from the heart muscle and empties it into the right atrium for eventual passage to the lungs



CORONARY ARTERIES

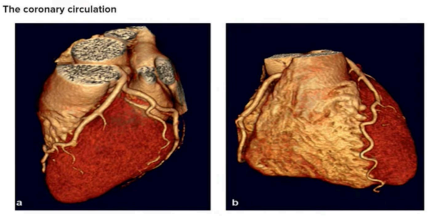
- The coronary arteries are like the fuel line in your car. If you don't have a good open fuel line, and gasoline doesn't get in, or diesel fuel doesn't get in your motor, you know what happens. The motor doesn't function. The same is true about the heart.
- It needs oxygenated blood to nourish it and to enable it to continue to do its mechanical activity
- The heart is a remarkable organ. Remember it beats constantly. It has to continue beating if you want to stay alive
- it's a remarkably strong muscle that is very resistant to injury, except when certain diseases occur. but in fact often tries to do its best job even when injured.
- **Two main coronary arteries:** *left coronary artery* and *right coronary artery*
- In a **triple coronary bypass**, the third coronary artery occurs because the left coronary artery branches early on after its origin. It branches into the ***left anterior descending coronary artery*** and the ***left circumflex coronary artery.*** So, the two main arteries very quickly divide into two main branches. That's how we have the three coronary arteries

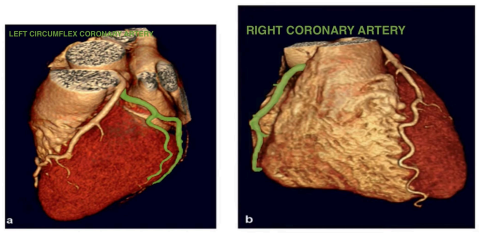
Return of venous blood to the heart

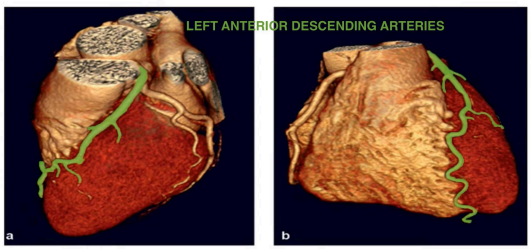


inside of the right atrium:

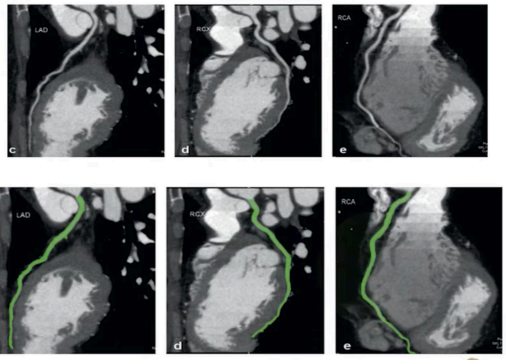
- These three circles represent the venous drainage coming into the heart
- **1:** the entrance of the blood from the superior vena cava. That blood enters the right atrium and drains the the venous blood from the upper part of the body
- **2**: that's the one from the inferior vena cava that's draining blood from the bottom of the body
- **3**: **Coronary sinus.** That's the heart's venous system coming back in because the heart is getting blood. It has to have venous return to the heart, so it also returns to the right atrium.
- The upper part of the body & the lower part of the body and the heart all drain into the right atrium. They pass through the tricuspid valve into the right ventricle. They're pumped to the lung where the blue blood becomes red as it takes on oxygen and gives off carbon dioxide.







- **right coronary artery** - supplies the right ventricle, part of the septum (the wall between the left and right ventricles), and part of the back of the heart
- **left anterior descending coronary artery** - supplies the front of the heart, and part of the septum
- **left circumflex coronary artery** - supplies the lateral wall of the heart, and also part of the back of the heart
- Blockage at any one of these can cause a ***myocardial infarction*** or a ***heart attack***



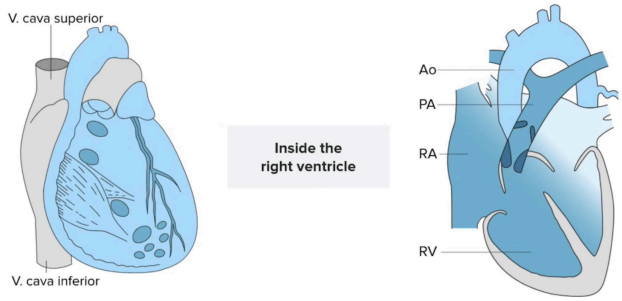
- You can see very clearly the coronary arteries coming off the left, the right, the anterior descending, and the circumflex

PERICARDIUM

- the **pericardium** is the constraint (the protective covering)
- A tough membrane that encloses the heart in a sac-like structure
- It's the “plastic bag” that keeps the heart nicely shaped within the chest.
- It doesn't allow the heart to over-expand and protects the heart as well.
- It's filled with a little bit of fluid so that the heart is able to move smooth within the pericardium.
- When disease happens to the pericardium, and it becomes thickened, and/or weeps fluid into that space = restriction of heart function.

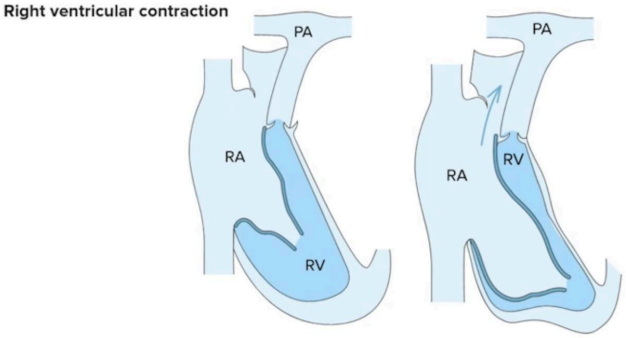
VIDEO 4: COMPONENTS OF THE HEART BY LECTURIO

- The heart has 6 important components:
    - **Muscle**- the heart is a muscle pump
    - **Valves** - You have to have valves to keep the blood flowing in the right direction. If you didn't have valves, all the blood would just slosh back and forth within the heart. You have to have the valves to keep the blood flowing in the right direction.
    - **Electrical Wiring** - what triggers the contraction of the heart is an electrical signal that starts high in the right atrium of the heart with a little automatic Pacemaker, and passes right down through the heart muscle and results in contraction of the heart muscle when the electrical signal gets there.
    - **Arteries** - supply the heart with oxygen and nutrients so it can work. in other words, the fuel line for the heart to put the fuel into the heart cells so they can contract.
    - **Veins** - carry the tired blood, the blood that's lost its oxygen and some of its nutrients and is carrying waste products. it returns to the right atrium along with the superior and inferior vena cava to be circulated again from the right ventricle into the lungs to gain oxygenation and to give up its carbon dioxide.
    - **A protective covering** (the pericardium) - the entire heart is contained in a membrane (a very tough membrane) called the pericardium that protects the heart, for example from infections in the lung, should they occur. It also keeps the heart in a nice shape so that it doesn't expand too much when it's working.
- The heart is a muscle pump that continues to pump blood in a continuous circle through the body and that it is meticulously and beautifully adapted
- The right ventricular muscle wall is rather thin
- The left ventricular muscle wall is quite thick
- The muscle walls of both right and left atria are very thin
- At the microscopic level, the myocardium consists of row upon row of muscle fibers filled with the biological machinery that results in contraction
- The right ventricle is a low pressure pump that functions like a blacksmith's bellows
- The left ventricle is a high pressure pump that functions like the piston in a car engine

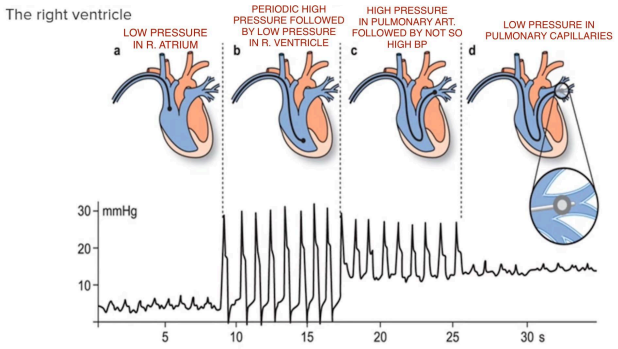


inside these various Chambers:

- here you see a diagram inside the right ventricle
- you can see it shows you the blood is blue –that's the deoxygenated blood
- you can see the right atrium above uh the right ventricle
- and you can see the pulmonary artery and
- the pulmonary valve uh below it
- there are a variety of abnormalities that the heart:
    - found in infants, for example, the pulmonary valve can be stenotic or closed. It has to be fixed at the early in life
    - there can be holes in the heart, for example, a connection between the right and left ventricle where there should be none
- All of these are the areas of the pediatric cardiologists who can make those diagnoses very early in life. And often these days, infants are operated on and have these abnormalities corrected .
- **REMEMBER**: The normal right ventricle will be separated from the left ventricle with a muscle septum that will prevent blood from the right side from getting onto the left side
- when blood from the right side gets onto the left side, the patient actually has a faintly bluish tinge to themselves.



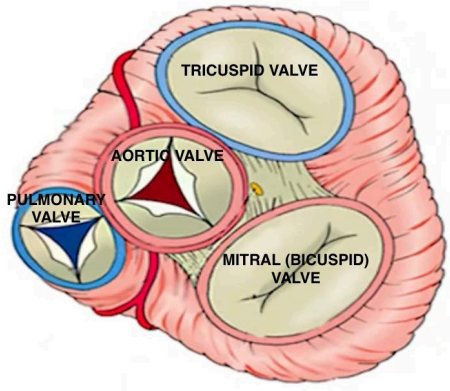
LEFT: contracted right ventricle
RIGHT: the filling right ventricle



- The blood passes through the heart starting at a very low pressure in the right atrium, the tricuspid valve opens, blood flows into the right ventricle, and it squeezes and then you see the pressure going up for the right ventricle
- And then when the pulmonary valve closes, the pressure falls again down to the baseline where the tricuspid valve opens again and blood flows into the right ventricle
- Out in the pulmonary artery when the pulmonary valve closes, the pressure no longer falls anymore and you see a sort of baseline pulmonary artery pressure that's transmitted across to the pulmonary capillaries and eventually to the pulmonary veins and the left atrium

VIDEO 5: VALVES AND ELECTRICAL SYSTEM BY LECTURIO

- There are **4 valves in the heart**
  - two for the right side of the heart
  - two for the left side
- Three of the valves (**tricuspid**, **pulmonic**, and **aortic**) have 3 leaflets.
- The mitral valve has only two leaflets.
- The valves keep the blood flowing in forward fashion through the heart chambers.



the ones in blue are the right-sided ones. the ones in red are the left-sided one

- What we're seeing here is the right and left ventricular systole (aka squeeze). You see that the pulmonary valve and the aortic valve are open and blood is flowing respectively into the pulmonary artery through the pulmonic valve and into the aorta through the aortic valve

Tricuspid Valve

- tricuspid means three cusps
- three components
- there are three parts to the tricuspid valve
- so the blood is now passing through the tricuspid valve into the right ventricle and then there's going to be right ventricular contraction, squeeze, and the blood is going out the pulmonary artery

Pulmonary Artery Valve

- it's open because the right ventricle is squeezing blood through it
- The blood goes to the lungs, gets oxygenated, picks up oxygen, comes back through the pulmonary veins to the left atrium, and then passes through the mitral valve

Mitral (Bicuspid) Valve

- has two cusps
- is between the left atrium and the left ventricle
- it resembles its name for for The Bishop's miter, which is the crown that the bishop wears in the Catholic Church which basically has just two sides to it
- once the blood is in the left ventricle, the left ventricle contracts, and the blood goes out the aortic valve

Aortic Valve

- in the center
- it's also open

The electrical system = The cardiac conduction system

- The electrical system ensures that the heart contracts in an efficient and coordinated manner.
- The sinus node, high in the right atrium, initiates the electrical activity of the heart.
- From the sinus node, a wave of electrical activity passes through all the muscle cells of the heart
- The electrical wave triggers myocardial contraction.

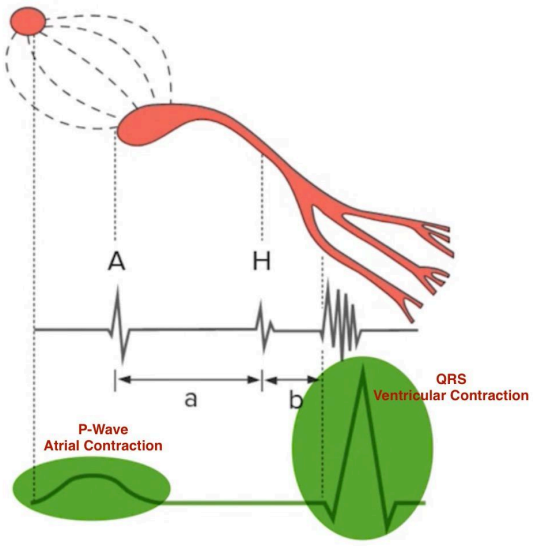
- It's the electrical system which is the trigger for mechanical contraction.
- Without the electrical system, the heart muscle will not contract.
- Each heart cell responds to the electrical activity by contracting. This electrical activity starts at the top of the atrium. There is a pacemaker, an automatic pacemaker, which can be influenced by adrenaline circulating or by nerves from the brain. It can accelerate or it can decelerate depending upon a variety of conditions
- But in any case the impulse starts spontaneously, it passes through a number of little fibers in the atrium into what you see that little bulb (AV node).
- It pauses there for a little bit. Why does it pause? You can't have the atria and the ventricle contracting at the same time. And if the impulse traveled rapidly through, you would have them contracting at the same time, and the blood wouldn't be going anywhere So there's a certain pause while the atria finish their mechanical contraction, and then the electrical activity passes down from that AV node, also called the Bundle of His, down into the branches that are in the ventricle.
- And at that point, the ventricular muscle contracts.

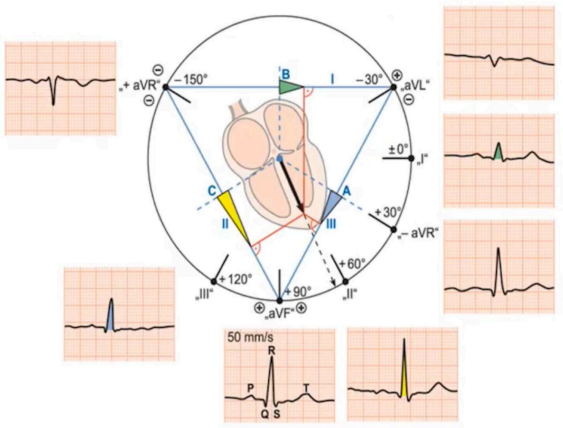
ELECTROCARDIOGRAM

- the first wave is called the **P-Wave** (atrial contraction)
- the big deflection is called the **QRS** (ventricular contraction)

- You can even see the heart sounds in there with atrial contraction and ventricular contraction. You can see the first and second heart sounds
- In fact we record the electrical impulse passing through the heart with something called the electrocardiogram
- The diagram shows *six electrocardiographic leads*.
- They're taken in the frontal plane. They're taken from different angles.
- They are a little electrical biopsy from different angles around the heart and we put all of this information together.
- It helps us to diagnose specific forms of heart disease. It also tells us a lot about how well the wave of depolarization is passing through the heart. Are there abnormalities in the

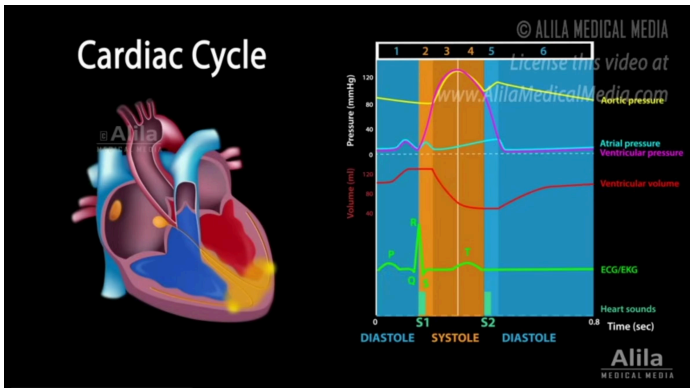
electrical conduction system? Or are there abnormalities in some of the minerals in the blood, for example potassium?

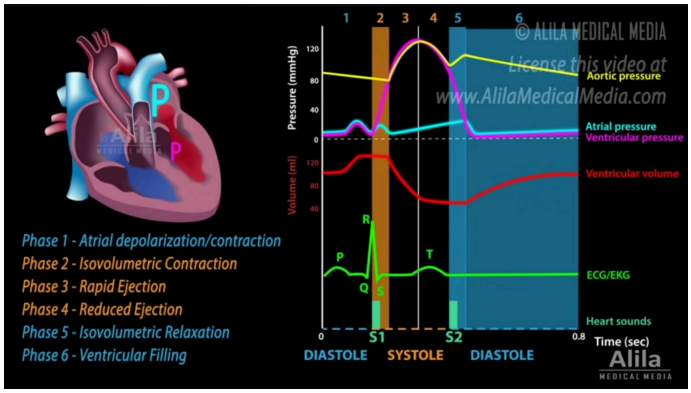




VIDEO 6: THE CARDIAC CYCLE ANIMATION BY ALILA MEDIA

- The **cardiac cycle** refers to the sequence of events that occur and repeat with every heartbeat.
- It can be divided into **2 major phases**: systole and diastole, each of which subdivides into several smaller phases.
- Systole and diastole, when not specified otherwise, refer to ventricular contraction and relaxation, respectively.
- **Basic principles:**
  - Blood flows from higher to lower pressure.
  - Contraction increases the pressure within a chamber, while relaxation lowers the pressure.
  - Valves open/close according to pressure gradients. AV valves open when atrial pressures are higher than ventricular pressures and close when the pressure gradient is reversed. Similarly, semilunar valves open when ventricular pressures are higher than aortic/pulmonary pressures, and close when the reverse is true.
- The cycle is initiated with the firing of the SA node that stimulates the atria to depolarize. This is represented by the P-wave on the ECG. Atrial contraction starts shortly after the P-wave begins, and causes the pressure within the atria to increase, forcing blood into the ventricles. Atrial contraction, however, only accounts for a fraction of ventricular filling, because at this point, the ventricles are already almost full due to passive blood flow down the ventricles through the open AV valves.
- As atrial contraction completes, atrial pressure begins to fall, reversing the pressure gradient across the AV valves, causing them to close. The closing of the AV valves produces the first heart sound, S1, and marks the beginning of systole.
- At this point, ventricular depolarization, represented by the QRS complex, is half way through, and the ventricles start to contract, rapidly building up pressures inside the ventricles.
- For a moment, however, the semilunar valves remain closed, and the ventricles contract within a closed space. This phase is referred to as isovolumetric contraction, because no blood is ejected and ventricular volume is unchanged.
- Ventricular ejection starts when ventricular pressures exceed the pressures within the aorta and pulmonary artery; the aortic and pulmonic valves open and blood is ejected out of the ventricles. This is the rapid ejection phase.
- As ventricular repolarization, reflected by the T-wave, begins, ventricular pressure starts to fall and the force of ejection is reduced.
- When ventricular pressures drop below aortic and pulmonary pressures, the semilunar valves close, marking the end of systole and beginning of diastole.
- Closure of semilunar valves produces the second heart sound, S2. The first part of diastole is, again, isovolumetric, as the ventricles relax with all valves closed.
- Ventricular pressure drops rapidly but their volumes remain unchanged.
- Meanwhile, the atria are being filled with blood and atrial pressures rise slowly. Ventricular filling starts when ventricular pressures drop below atrial pressures, causing the AV valve to open, allowing blood to flow down the ventricles passively.
- The atria contract to finish the filling phase and the cycle repeats itself.





Case 1: "Do I need a CBC?"

Block 4 Module 1

BLOOD

- Blood is a tissue composed of red blood cells (erythrocytes), white blood cells (leukocytes) and platelets suspended in a fluid blood plasma which also contains an immense number of ions, inorganic molecules, and organic molecules including plasma proteins
- Average human possesses: **5 liters** of blood

HEMATOPOIESIS

DEFINITION

- Hematopoiesis is defined as the production, development, differentiation, and maturation of all blood cells

DIFFERENTIATION AS TO SITE OF PRODUCTION BEFORE AND AFTER BIRTH

- The bone marrow is extremely versatile and serves as the body well by supplying life-giving cells with a multiplicity of functions. Various organs serve a role in hemopoiesis, and these organs differ from fetal to adult development.
- The **yolk sac, liver,** and **spleen** are the focal organs in fetal development
  - From 2 weeks until 2 months in the fetal life, most erythropoiesis takes place in the fetal yolk sac (primitive erythroblasts).
  - During the hepatic period (2 through 7 months of fetal life), the **liver** and **spleen** take over the hematopoietic role
    - **Liver** – serves as an erythroid-producing organ primarily but also give rise to fetal hemoglobin (alpha and gamma chains)
    - **Spleen, Thymus, and Lymph Nodes** – also become haematopoietically active during this stage, producing red cells and lymphocytes
  - From 7 months until birth, the bone marrow assumes the primary role in hematopoiesis, a role that continues into adult life.

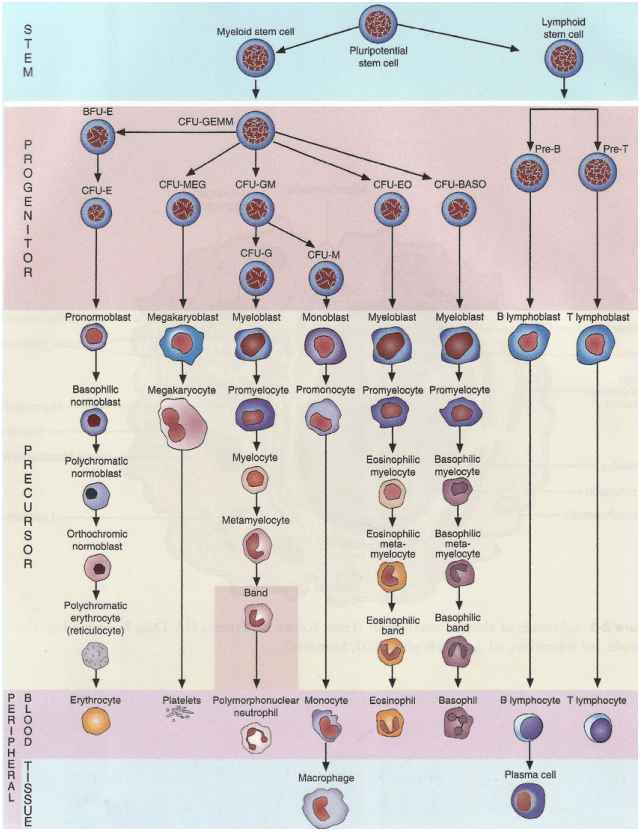
DIFFERENTIATION BETWEEN INTRAMEDULLARY AND EXTRAMEDULLARY HEMATOPOIESIS

- Intramedullary Hematopoiesis - hematopoiesis within the bone marrow
- Extramedullary Hematopoiesis - hematopoiesis outside the bone marrow environment, primarily in the liver and spleen.
- Because these organs play major roles in early fetal hematopoiesis, they retain their hematopoietic memory and capability.
- The liver and spleen can function as organs of hematopoiesis if needed in adult life such as in bone marrow infiltration by leukemic cells.
- If extramedullary hematopoiesis develops, the liver and spleen become enlarged, a condition termed as "hepatomegaly"

FORMED ELEMENTS OF THE BLOOD

DEVELOPMENT

- Formed elements of the blood:
  - Erythrocytes
  - Granulocytes
  - Monocytes
  - Lymphocytes
  - Platelets
- The formed elements of the blood have a common origin in the pluripotent hematopoietic stem cell (found in the red-cell producing bone marrow).
  - This common precursor then gives rise to the lymphoid stem cells which are committed to produce lymphocytes and the trilineage myeloid stem cells which are committed to produce myeloid cells.
- The lymphoid stem cells give rise to precursors of T cells and B cells and possible natural killer (NK) cells.
- From the multipotent myeloid stem cell arise at least three types of "committed stem cells" capable of differentiating along the erythroid/megakaryocytic, eosinophil, and granulocyte – macrophage pathways.
- From the various committed stem cells are derived intermediate stages and ultimately the morphologically recognizable precursors of the differentiated cell lines, that is, proerythroblasts, myeloblast, megalokaryoblasts, monoblasts, and eosinophiloblasts. These turn in give rise to mature progeny.



MECHANISM OF PRODUCTION AND RELEASE

- In the red cell-producing bone marrow are cells called pluripotential hematopoietic stem cells, from which all the cells in the circulating blood are derived.
- Growth and reproduction of the different stem cells are controlled by multiple proteins called growth inducers.
- Four major growth inducers have been described.
  - One of these, **interleukin-3**, promotes growth and reproduction of virtually all the different types of stem cells, whereas the others induce growth of only specific types of committed stem cells.
  - The **growth inducers** promote growth but not differentiation of the cells. This is the function of still another set of proteins called differentiation inducers.
  - Each of these causes one type of stem cell to differentiate one or more steps toward a final type of adult blood cell.
- Formation of the growth inducers and differentiation inducers is itself controlled by factors outside the bone marrow.
  - For instance, in the case of red blood cells, exposure of the body to low oxygen for a long-time results in growth induction, differentiation, and production of greatly increased numbers of erythrocytes.
    - Example: When a person's hemoglobin level is below normal, the oxygen content of the blood drops and the oxygen tension in the kidneys is reduced (hypoxia). This stimulates the kidneys to increase their production of erythropoietin, a low - molecular weight hormone which is dedicated to red cell regeneration. Erythropoietin makes its way through the circulation

and locks onto a receptor on the pronormoblast, the youngest red cell precursor, stimulating the production of 16 mature red cells from every pronormoblast precursor cell.

- The total mass of red blood cells in the circulatory system is regulated within narrow limits. What we know about the control mechanism is diagrammed below:

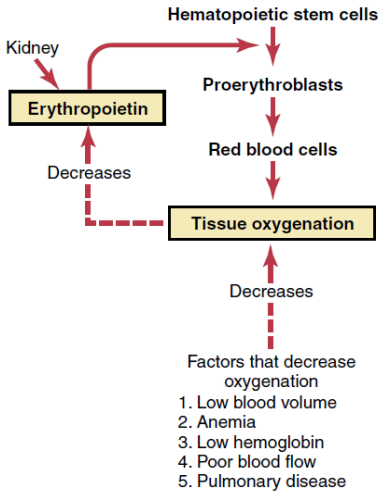


Figure 33-4. Function of the erythropoietin mechanism to increase production of red blood cells when tissue oxygenation decreases.

ERYTHROCYTIC (RED CELL) SERIES

GENERAL DESCRIPTION

- The mature red blood cell is a magnificently designed instrument for hemoglobin delivery. As a hemoglobin - filled sac, the red cell travels more than 300 miles through the peripheral circulation, submitting itself to the swift waters of the circulatory system, squeezing itself through the threadlike splenic sinuses and bathing itself in the plasma microenvironment.
- Average size is 6 - 8 µm.
- Cellular and environmental factors contribute to red cell survival. In order for the red cell to survive for its 120 - day life cycle, these conditions are necessary:
  - The red cells membrane must be deformable
  - Hemoglobin structure and function must be adequate
  - The red cell must maintain osmotic balance and permeability

FUNCTIONS

- The major function of erythrocytes is to transport hemoglobin, which in turn carries oxygen from the lungs to the tissues.
- Erythrocytes also contain a large quantity of carbonic anhydrase, which catalyzes the reversible reaction between carbon dioxide and water, increasing the rate of this reaction several thousand-fold.
  - The rapidity of this reaction makes it possible for the water of the blood to transport enormous quantities of carbon dioxide from the tissues to the lungs in the form of the bicarbonate ion.
- Also, the hemoglobin in the cells is an excellent acid-base buffer, so that the red blood cells are responsible for most of the acid-base buffering power of whole blood.

STAGES OF DEVELOPMENT

Pronormoblast (Rubriblast)

- This is the earliest recognizable erythroid precursor and is the largest of all the erythroid precursors.
- Cell size is variable, nucleus usually occupies more than 80% of the cell and is round to slightly oval with dispersed fine clumps of chromatic and nucleoli.
- Cytoplasm is intensely basophilic.
- This undergoes mitosis and forms two (2) basophilic normoblasts (prorubricyte)

Basophilic Normoblast (Prorubricyte)

- This is slightly smaller than the rubriblast with nucleus usually occupying 75% of the cell.
- The nucleus is round with coarser and more clumped chromatin, parachromatin (the nonstaining area of the nucleus) is slightly visible between the clumps of chromatin, usually nuclei are no longer visible. The cytoplasm is deeply basophilic due to the abundance of RNA.
- After mitosis, evidence of continuing hemoglobin production becomes visible in the cytoplasm of the two daughter cells the polychromatophilic normoblast (rubricyte).

Polychromatophilic Normoblast (Rubricyte)

- Usually smaller than the proubricyte, its round nucleus may be eccentric, nuclear chromatin is very coarse and condensed, and distinct areas of parachomatin are visible.
- The cytoplasm has a varied spectrum of the red- staining of hemoglobin with the of RNA in varying shades. of gray (polychromasia or polychromatophilia)
- This undergoes one or two mitotic divisions. After the last mitosis, the orthochromatophilic normoblast (metarubricyte) stage is reached.

Orthochromaphilic Normoblast (Metarubricyte)

- This is the last nucleated erythrocyte stage and its size is the same as or smaller than a rubricyte.
- Nucleus is pyknotic. The cytoplasm contains more abundant hemoglobin and fewer polyribosomes and remains slightly polychromatophilic (paler blue - gray violet to pink).
- Finally, accompanied by cytoplasmic contractions and undulations, the nucleus and a small rim of cytoplasm are ejected from the orthochromatic normoblast forming the reticulocyte.

Reticulocyte

- This is slightly larger than the erythrocyte and may have irregular cytoplasmic borders.
- The reticulocyte is polychromatophilic as a result of retention of RNA. (pink and blue staining of cytoplasm)

Mature Erythrocyte

- A biconcave disc with a central pale area which gradually fades into a reddish - pink cytoplasm.

LEUKOCYTIC (WHITE CELL) SERIES

GENERAL DESCRIPTION

- The white cell series encompasses those cells that are distinguished by their granules and those that are agranular. In all, there are five maturation stages for neutrophils, four for eosinophils and basophils, and three each for monocytes and lymphocytes. Key features in distinguishing immature and mature stages of any of these cells are: cell size, nucleus - to - cytoplasm (N:C) ratio, chromatin pattern, cytoplasmic quality, and presence of granules.

GRANULOCYTES (NEUTROPHILS, EOSINOPHILS, BASOPHILS)

- In general, as granulocytes mature, the nuclear chromatin becomes more condensed, nucleoli disappear, and abundant basophilic cytoplasm with non-specific granulation progresses to more scant cytoplasm containing granulation specific for the eosinophil, basophil or neutrophil. The nucleus indents and the overall cell size decreases.

Neutrophils

- Stages of maturation of the neutrophilic series from least mature to most mature:
  Myeloblast → promyelocyte (progranulocyte) → myelocyte (granulocyte) → metamyelocyte → band (stab) → segmented neutrophil.
- Morphology:
  - **Myeloblasts**
    - dark blue to blue cytoplasm without visible granules; nucleus is made up of smooth, delicate, uniformly distributed chromatin patter, 2 or more distinct nucleoli, the nucleus occupies most of the cell leaving only a rim of cytoplasm.

- **Promyelocyte**
  - the cytoplasm remains blue; nucleus still with uniform, evenly distributed chromatin pattern; there are large, prominent reddish - purple granules in the cytoplasm, nucleoli may or may not be visible; the nucleus: cytoplasmic ratio decreases
- **Myelocyte**
  - the cytoplasm loses its blue color and shows & pinkish-tan color; specific granules are formed; nucleus is still round, becomes more condensed and the chromatin pattern clumped; nucleoli usually absent.
- **Metamyelocyte**
  - the shape of the nucleus is the chief identification criterion - begins to pattern on one side and begins to constrict or indent (indentation is less than half the width of the nucleus kidney - bean or peanut - shaped); the cytoplasm is uniformly pink with pinkish purple secondary granules evenly distributed.
- **Band (stab)**
  - elongated, curved or sausage - shaped nucleus with no threadlike filament; the cytoplasm stains light pink with numerous specific granules that give it a grainy appearance
- **Segmented neutrophil**
  - the nucleus is segmented into 2 to 5 lobes connected by a threadlike filament, nuclear chromatin is dark purple with densely stained clumps; cytoplasm is like that of a band.

- **General Description**
  - The primary (nonspecific) and secondary (specific) granules of the neutrophils are packaged and released from the Golgi apparatus.
  - **Primary Granules**
    - are membrane bound lysosomes and contain acid phosphatase, peroxidase, esterase, sulfated mucosubstance, β-galactosidase, arylsulfatase, lysozyme and other basic proteins.
  - **Secondary Granules**
    - contain aminopeptidase, collagenase, muramidase, lactoferrin, lysozyme and a number of basic proteins.
- **Functions**
  - Neutrophils are metabolically active. They are capable of both aerobic and anaerobic glycolysis for their source of energy.
  - Their major function is to stop or retard the action of foreign material or infectious agents by means of:
    - moving into the area of inflammation or infection
    - phagocytosis of the foreign material
    - killing and digestion of the offending material

Eosinophils

- **General Description**
  - The eosinophil is primarily a tissue cell. Once it is released into the peripheral blood from the bone marrow, it will be randomly removed from the blood independently of its age. Its half - life in the blood is about 8 hours, there is a diurnal variation in eosinophil counts, with the highest occurring at night. From the blood, it moves into the tissues where it localizes in areas exposed to the external environment, most notably in the skin, nasal membranes, lungs and gastrointestinal tract. For each eosinophil in the peripheral blood, there are 300 - 500 eosinophils in the tissues where their life span is probably several days. Once they migrate to the tissues they are still able to return to the peripheral circulation.
  - The mature eosinophils contain 2 types of granules:
    1. The larger granules are the more numerous, contain a very dense elliptical crystalloid core, which primarily consists of major basic protein (MBP) which is toxic to helminth parasites and may also become toxic to the body's own tissues. Production of these granules stops when the eosinophil becomes mature.
    2. The second type of granule is smaller than the first and may not appear in the cell until after the myelocytic stage.
- The eosinophilic granules contain peroxidase, B - glucorinidase, acid ß - glycerophosphatase, arylsulfatase (in the small granules) phospholipase, acid phosphatase, ribonuclease and cathepsin. The peroxidase is a different form than that found in the neutrophil. Also, the eosinophil granules differ from these in the neutrophil, in that they lack lysozyme, phagocytic, and neutrophil bactericidal cationic proteins.
- **Morphology**
  - The eosinophil usually has a bilobed nucleus with moderately large, refractile cytoplasmic granules that stain deep red or orange.
- **Functions**
  1. Act as phagocytes
  2. Destroy helminths (by generating potent oxidants and releasing cationic proteins from the granules which then damage and degrade the larval wall of the parasitic invaders.)
  3. To dampen hypersensitivity and inflammatory reactions
  - Eosinophils modulate reactions that occur when tissue mast cells and basophils degranulate. Eosinophils express the chemokine receptor CCR3.
  - Among the chemotactic factors that attract eosinophils, eosinophil chemotactic factor of anaphylaxis (ECF - A) is present in basophils and mast cells.
  - Eosinophils also contain substances that inactivate factors released by mast cell and basophils such as histamines, slow - reacting substances of anaphylaxis and platelet - activating factor (PAF).

Basophils

- **General Description**
  - Basophils have a life span similar to eosinophils. Basophils circulate in the blood and are not normally found in tissues, in contrast to mast cells which can spend 9 - 18 months in connective tissue.
  - The granules of mature basophils are metachromatic (red - purple) because of acid mucopolysaccharide (heparin) content. Those granules contain histamine, heparin, peroxidase, eosinophilic chemotactic factor - A, smaller quantities of bradykinin and serotonin.
  - Other cellular constituents are: slow – reacting substance of anaphylaxis and platelet - activating factor.
- **Morphology**
  - Shows large, coarse cytoplasmic granules that stain deep blue) the granules may be seen within the cytoplasm or overlying the irregular nucleus.
- **Functions**
  1. immediate hypersensitivity reactions
  2. some delayed hypersensitivity reactions
  - Basophils as well as mast cells appear to be involved in immediate hypersensitivity reactions such as allergic asthma
  - IgE binds readily to basophil and mast cell membranes. When a specific antigen reacts with the membrane - bound IgE, degranulation occurs with the release of mediators of immediate hypersensitivity (e.g, histamine SRS - A), PAF, heparin and ECF - A). The latter leads to the accumulation of eosinophils, which contain substances that tend to counteract these mediators.
  - Basophils are also involved in some delayed hypersensitivity reactions, "cutaneous basophil hypersensitivity" such as contact allergies, in which they appear to undergo a different type of degranulation response.

AGRANULOCYTES (MONOCYTES, MACROPHAGES, LYMPHOCYTES)

Monocytes and Macrophages

- **General Descriptions**
  - Blood monocytes are distributed in a circulating monocyte pool and marginating monocyte pool, in a ratio of 1:3.5. Once monocytes enter the blood, they leave randomly with a half - time of 8.4 hours.
    - This time period is shortened in splenomegaly or acute infection and may be prolonged in monocytosis. After monocytes leave the blood they spend several months as macrophages.
  - Granules and other constituents: acid hyrolase, arylsulfatase, nonspecific esterase, peroxidase, acid phosphatase.
- **Morphology**
  - In the normal marrow, it is not possible morphologically to distinguish the "monoblast" from the myeloblast.
  - The earliest recognizable cell in the series is the promonocyte, somewhat larger than the myeloblast. The N/C ratio is moderate, and the nucleus may be oval or indented with a fine uniform or slightly streaked chromatin and two to five nucleoli. The cytoplasm is basophilic with a ground - glass appearance and a variable number of five azurophilic granules.
  - The **monocyte** which is present in both blood and marrow, is only slightly smaller; it has a moderate to low N/C ratio and or indented or lobe nucleus with a fine - streaked, only slightly condensed, delicate chromatin pattern. Nucleoli are indistinct or obscured. The cytoplasm is opaque, more gray than blue and contains an abundance of fine azurophilic granules.
  - **Macrophages** are the tissue component of the monocyte system and arise from emigrated blood monocytes. Macrophages are larger than monocytes. They have irregular cell membranes, often with blebs and pseudopods. The N/C ratio is high with an oblong and/or indented nucleus.
- **Functions**
  1. phagocytosis - bacteria, cellular debris, senescent cells
  2. antigen processing
  3. cell - mediated immunity - antibody - dependent cytotoxicity
  4. synthesis of bioactive molecules

MEGAKARYOCYTIC (THROMBOCYTIC) SERIES

GENERAL DESCRIPTION

- **General description**
  - Platelets originate from polypoid megakaryocytes, the largest of all hematopoietic cells which number less than 1% of the total nucleated marrow cells. The fragments of these megakaryocytes are platelets that are released into the bloodstream. The circulating platelets make up about two — third of the platelets that are released from the bone marrow. The other one - third is stored (sequestered) in the spleen.
  - Platelets survive 8 - 12 days in the circulation. Some platelets are utilized in maintaining vascular integrity and in plugging small vascular injuries.
- **Morphology**
  - Megakaryocytes
    - is a giant cell with round multiple nuclei (up to 32) that usually remain connected, and abundant cytoplasm containing numerous small, rather uniformly distributed granules with a reddish - blue hue. The chromatin pattern is linear and coarse with distinct spaces between the strands.
  - Platelets
    - dense blue to purple particles with granules
- **Functions of Platelets**:
  1. maintain the integrity of blood vessels
  2. form hemostatic plugs to stop blood loss from injured vessels and in the process promote coagulation of plasma factors.

COMPLETE BLOOD COUNT

DEFINITION

- The complete blood count (CBC) is one of the most frequently ordered and most time - honored laboratory tests in the hematology laboratory.
- This evaluation consists of several components and offers the clinician a variety of hematological data to interpret and review that directly relate to the health of the bone marrow represented by the numbers and types of cells in the peripheral circulation. It measures the concentration of white blood cells, red blood cells and platelets in the blood and aids in the diagnosis of conditions and diseases

COMPONENTS

- **White Blood Cell Count (WBC)**
  - is the number of white blood cells in a volume of blood.
- **White Blood Cell (WBC) Differential Count**
  - composed of several different types that are differentiated, or distinguished, neutrophils, lymphocytes, monocytes, eosinophils, basophils and Based on their size and shape. The cells in a differential count are neutrophils, lymphocytes, monocytes eosinophils, basophils, and bands
- **Red Cell Count (RBC)**
  - signifies the number of red blood cells in a volume of blood.
- **Hemoglobin (Hb)**
  - this is the amount of hemoglobin in a volume of blood. Hemoglobin is the protein molecule within red blood cells that carries oxygen and gives blood its red color.
- **Hematocrit (Hct)**
  - this is the ratio of the volume of red cells to the volume of whole blood. This is usually measured by spinning down a sample of blood in a test tube which causes the red blood cells to pack at the bottom of the tube.
- **Mean Corpuscular Volume (MCU)**
  - is the average volume of a red blood cell. This is a calculate value derived from the hematocrit and red cell count.
- **Mean Corpuscular Hemoglobin**
  - the average amount of hemoglobin in the average red cell.
- **Mean Corpuscular Hemoglobin Concentration (MCHC)**
  - is the average concentration of hemoglobin in a given volume of red cells.
- **Red Cell Distribution Width (RDW)**
  - is a measurement of the variability of red cell size and shape. Higher numbers indicate greater variation in size.
- **Platelet Count**
  - the number of platelets in a specified volume of blood.

TABLE 31.2
Typical Blood Cell Values in a Normal Population of Young Adults

	Men	Women
White cell count ($\times 10^9$/L blood)	7.8 (4.4–11.3)	
Red cell count ($\times 10^{12}$/L blood)	5.21 (4.52–5.90)	4.60 (4.10–5.10)
Hemoglobin (g/dL blood)	15.7 (14.0–17.5)1	13.8 (12.3–15.3)
Hematocrit (%)	46 (41.5–50.4)	40.2 (35.9–44.6)
Mean cell volume (fL/ red cell)	88.0 (80.0–96.1)	
Mean cell hemoglobin (pg/red cell)	30.4 (27.5–33.2)	
Mean cell hemoglobin concentration (g/dL RBC)	34.4 (33.4–35.5)	
Red cell distribution width (CV, %)	13.1 (11.6–14.6)	
Platelet count ($\times 10^9$/L blood)	311 (172–450)	

The mean and reference intervals (normal range) are given. Because the distribution curves may be nongaussian, the reference interval is the nonparametric central 95% confidence interval. Results are based on 426 normal adult men and 212 normal adult women. Studies were performed on the Coulter model S-Plus IV. From Morris MW, Skrodzki Z, Nelson DA: Zeta sedimentation ratio (ZSR), a replacement for the erythrocyte sedimentation rate (ESR), *Am J Clin Pathol* 164:254–256, 1975.
CV, Cell values; *RBC,* red blood cell.

TABLE 31.3
Normal Leukocyte Count, Differential Count, and Hemoglobin Concentration at Various Ages

Age	LEUKOCYTES* Total Leukocytes	Total Neutrophils	Band Neutrophils	Segmented Neutrophils	Eosinophils	Basophils	Lymphocytes	Monocytes	Hemoglobin (g/dL Blood)
12 months	11.4 (6.0–17.5)	3.5 (1.5–8.5) *31*	0.35 *3.1*	3.2 (1.0–8.5) *28*	0.30 (0.05–0.70) *2.6*	0.05 (0–0.20) *0.4*	7.0 (4.0–10.5) *61*	0.55 (0.05–1.1) *4.8*	12.6 (11.1–14.1)
4 years	9.1 (5.5–15.5)	3.8 (1.5–8.5) *42*	0.27 (0–1.0) *3.0*	3.5 (1.5–7.5) *39*	0.25 (0.02–0.65) *2.8*	0.05 (0–0.2) *0.6*	4.5 (2.0–8.0) *50*	0.45 (0–0.8) *5.0*	12.7 (11.2–14.3)
6 years	8.5 (5.0–14.5)	4.3 (1.5–8.0) *51*	0.25 (0–1.0) *3.0*	4.0 (1.5–7.0) *48*	0.23 (0–0.65) *2.7*	0.05 (0–0.2) *0.6*	3.5 (1.50–7.0) *42*	0.40 (0–0.8) *4.7*	13.0 (11.4–14.5)
10 years	8.1 (4.5–13.5)	4.4 (1.8–8.0) *54*	0.24 (0–1.0) *3.0*	4.2 (1.8–7.0) *51*	0.20 (0–0.60) *2.4*	0.04 (0–0.2) *0.5*	3.1 (1.5–6.5) *38*	0.35 (0–0.8) *4.3*	13.4 (11.8–15.0)
21 years	7.4 (4.5–11.0)	4.4 (1.8–7.7) *59*	0.22 (0–0.7) *3.0*	4.2 (1.8–7.0) *56*	0.20 (0–0.45) *2.7*	0.04 (0–0.2) *0.5*	2.5 (1.0–4.8) *34*	0.30 (0–0.8) *4.0*	15.5 (13.5–17.5) 13.8 (12.0–15.6)

From Altman PL, Dittmer DS, editors: *Blood and other body fluids,* Washington, DC, 1961, Federation of American Societies for Experimental Biology (for leukocyte and differential count); Dalman PR: Developmental changes in red blood cell production and function. In: Rudolph AM, Hoffman JIE, editors: *Pediatrics,* ed 18, Norwalk, CT, 1987, Appleton & Lange, pp 1011–1012 (for hemoglobin concentrations).
*Values are expressed as mean (95% reference) values. For leukocytes and differential count cell types, the units are cells × 10^9/μL; the numbers in italics are mean percentages.

SIGNIFICANCE OF ABNORMAL VALUES

- Hct/ Hgb/ RBC
  - Low – Anemia
  - High – Polycythemia, physiologic variation

White Blood Cell Counts

- White cell counts that are reported on the CBC are directly counted from an automated instrument or by manual method.
- The age of the patient directly influences whether this number within or outside of the reference range. Pediatric reference ranges show more variability than do ranges for adults.

White Blood Cell Differential Count

- The WBC differential is an evaluation of the types of mature white cells in the peripheral circulation. Although only a snapshot of the white cell concentration at a particular moment in time, the differential offers valuable information as to the hematological status of an individual and their response to any circumstances which may alter hematological status. In general terms, the differential is performed on a well - stained, well distributed peripheral smear.
- Because white cells have such a short time span in the peripheral circulation, alterations either in the quantity of or the quality of a particular cell can be quite dramatic. Any increase or decrease in a particular type of cell signals the body's unique response "assaults" of any kind. Infection, inflammation, chronic disease, parasitic infestations, etc., each represents an unexpected occurrence, an opportunity for white cells to mobilize. As white cells respond to infection or other stimuli, changes are seen in the number of and types of a particular cell line.
- If a cell line is increased, the suffix used to designate an increase is "osis" or "philia", such as "eosinophilia" and "leukocytosis." If a cell line is decreased, the suffix used to designate a decrease is "penia" such as "neutropenia." Changes are observed in the CBC as well as in the peripheral blood smear.
- Total WBC (white blood cell) count:
  - Low - leukopenia (infection, conditions with pancytopenia)
  - High - leukocytosis (infection, metabolic toxic states)
- In the bone marrow, there is a 4:1 (ME ratio) - the M:E ratio indicating that four myeloid or white cells are produced for one erythroid cell.
- Daily production of white cells is 1.5 billion. Transit from the bone marrow to the peripheral circulation takes place only after white cells have been held in the maturation storage pool of the bone marrow. Once released into the circulation, most white cells are short - lived before they migrate into tissues. The white cells that are observed in the peripheral circulation are only a snapshot of white cells that are located in three distinct cell compartments" the bone marrow, the circulation, and the tissues.
- White blood cells (WBCs) are referred to as leukocytes. For clarity, the word "leukocytic" applies to the white cells of all stages. White cells are a remarkably versatile group of cells whose primary purpose is to defend against bacteria, viruses, fungi or other foreign substances. To this end, most white cells are granulated and these granules contain enzymes used for digestion and destruction of the invading organisms.
- The granular leukocytes are: neutrophils, eosinophils, basophils
- The agranular leukocytes are: monocytes, lymphocytes
- The term "granulocytic" applies only to granulated white cells. The term "myelocytic" is used in describing a particular white cell condition. The two terms may be used interchangeably but only in reference to the leukemias.
- **Relative vs. Absolute Values**
  - Relative and absolute counts are terms referring to the white cell differential. The "absolute" count refers to the count derived from the total white count multiplied by the percentage of any particular white cell. The "relative" count refers to the percentage of a particular cell counted from the 100 WBC differential. Example of how to calculate and interpret the relative and absolute count:

    WBC: 5.0 × 10^9/L

Differential:		Ref. Range:
Segmental neutrophils:	40%	40% - 70%
Bands	3%	0 - 5%
Lymphocytes	55%	20 - 40%
Monocyte	2%	2 - 8%

    Then: Absolute count of lymphocytes would be
    5000 x 0.55 = 2,500
    (from the total WBC) (lymphocytes)

  - Reference range for absolute lymphocyte count: 1000 - 4,800
  - Therefore: In this patient there is relative lymphocytosis but not an absolute lymphocytosis.
- **The Neutrophils**
  - **Neutrophilia**:
    - Neutrophilic leukocytosis or neutrophilia refers to an absolute concentration of neutrophils above normal for age. Key causes are:
      - Acute inflammatory - collagen vascular, vasculitis
      - Acute infectious - bacterial, some viral, fungal, parasitic
      - Drugs, toxins, metabolic - corticosteroids, growth factors, uremia, ketoacidosis
      - Tissue necrosis - burns, trauma, myocardial infarction, red blood cell
      - hemolysis
      - Physiologic - stress, exercise, smoking, pregnancy
      - Neoplastic - carcinomas, sarcomas, myeloproliferative disorders
    - **Mechanisms**: The primary factors influencing the neutrophil count are:
      1. The rate of inflow of cells from the bone marrow (mitosis/proliferation, maturation/storage and release)
      2. The proportion of neutrophils in marginal (cells adhering to vessel! walls) granulocyte pool (MGP) and the circulating (non-adhering cells) granulocyte pool (CGP) of the blood.
      3. The rate of outflow of neutrophils from the blood (migration from and through vessels into tissue, both randomly and at sites of inflammation, infection, etc.)
  - **Neutropenia**:
    - This is a reduction of the absolute neutrophil count (ANC). The term "agranulocytosis" has been used for severe neutropenia. This can also be associated with depletion of eosinophils and basophils. Causes of neutropenia:
      - Drugs - cancer chemotherapy, chloramphenicol, sulfas/other antibiotics, phenothiazines, benzodiazepine, antithyroids, anticonvulants, quinine, quinidine, indomethacine, procainamide, thiazide
      - Radiation

- Toxins - alcohol, benzene compounds
- Intrinsic defects - Fanconi's Kostmann's, cyclic neutropenia, Chediak - Higashi
- Immune - mediated - collagen vascular disorders, rheumatoid arthritis, AIDS
- Hematologic - megaloblastic anemia, myelodysplasia, marrow failure, marrow replacement
- Infectious - any overwhelming infection
- Others — starvation, hypersplenism

■ **Mechanisms** by which neutropenia occur include:

1. Decreased flow of neutrophils from marrow into blood as a result of either lack of production or ineffective production
2. Increased removal of neutrophils from the blood (survival defect)
3. Altered distribution between CGP and MGP
4. Combinations of the above mechanisms

○ **Eosinophilia**

■ This is typically associated with allergic processes and parasitic infections.

■ Causes of eosinophilia:

- Allergic – urticaria, hay fever, asthma
- Parasitic – trichinosis, filariasis, ascariasis, Schistosomiasis
- Nonparasitic infection - systemic fungal, scarlet fever, chlamydial pneumonia of infancy
- Respiratory - pulmonary eosinophilia syndrome (Loeffler's, tropical pulmonary eosinophilia). Churg - Strauss syndrome
- Neoplastic - chronic myelogenous leukemia, Hodgkin's lymphoma, T cell lymphomas

○ **Basophilia**

■ Causes:

- Myeloproliferative disease
- Allergic - food, drugs, foreign proteins
- Infections - variola, varicella
- Chronic hemolytic anemia - especially post – splenectomy
- Inflammatory - collagen vascular disease, ulcerative colitis

○ **Monocytosis**

■ Causes:

- Infections - tuberculosis, subacute bacterial endocarditis, syphilis, protozoan, rickettsial
- Recovery from neutropenia
- Hematologic – leukemia, myeloproliferative disorders, lymphomas, multiple myeloma
- Inflammatory - collagen vascular diseases, chronic ulcerative colitis, sprue, myositis, polyarteritis, temporal arteritis

○ **Lymphocytosis**

■ Causes:

- Infections - many viral, pertussis, tuberculosis, rickettsial
- Chronic inflammatory - ulcerative colitis, Crohn's
- Immune - mediated - drug sensitivity vasculitis, graft rejection, Grave's disease, Sjogren's syndrome
- Hematologic - acute lymphoblastic leukemia, chronic lymphocytic leukemia, lymphoma
- Stress - acute, transient

○ **Lymphopenia**

■ Causes:

- Destructive – radiation, chemotherapy, steroide
- Debilitative - starvation, aplastic anemia, terminal cancer, collagen vascular disease, renal failure
- Infections – viral hepatitis, influenza, typhoid fever, tuberculosis
- AIDS associated HIV cytopathic effect, nutritional imbalance, drug effect
- Congenital immunodeficiency: Wiskott-Aldrich

Platelets

- The number of platelets in the blood is referred to as the platelet count and is normally between 150,000 to 450,000/ µL/ (one-millionth of a litter).
- Platelet counts less than 150,000 are termed thrombocytopenia.
- Platelet counts greater than 450,000 are called thrombocytosis.

HEMOGLOBIN

GENERAL STRUCTURE AND ROLE IN THE TRANSPORT PROCESS OF GAS

- Synthesis of hemoglobin begins in the proerythroblasts and continues even into the reticulocyte stage because when the reticulocytes leave the bone the blood stream, they continue to form minute marrow and pass into quantities of hemoglobin for another day of so. Figure 32-5 shows the basic chemical steps in the formation of hemoglobin. The most important feature of the hemoglobin molecule is its ability to combine loosely and reversibly with oxygen.
- Its primary function in the body is to combine with oxygen in the lungs and then to release this oxygen ready in the tissue capillaries where the gaseous tension of oxygen is much lower than in the lungs.

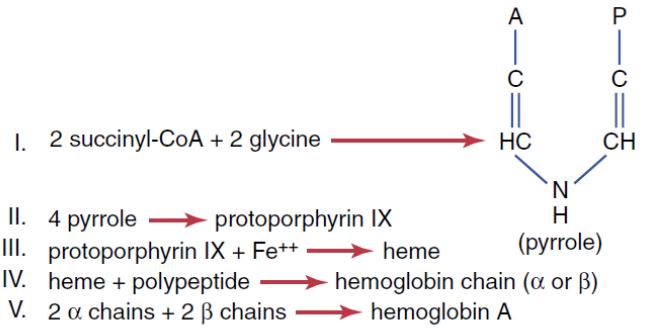


Figure 33-5. Formation of hemoglobin.

PORPHYRIN

- Porphyrins are cyclic compounds formed by the linkage of four pyrole rings through methenyl bridges. A characteristic property of the porphyrins is the formation of complexes with metal ions bound to the nitrogen atom of the pyrrole rings.
  - Examples are the iron porphyrins such as heme of hemoglobin and the magnesium-containing porphyrin chlorophyll, the photosynthetic pigment of plants.
- Proteins that contain heme (hemoproteins) aro widely distributed in nature. The porphyrins found in nature are compounds in which various side chains are substituted for the eight hydrogen atoms numbered in the porphyrin nucleus. As a simple means or showing these substitutions, Fischer proposed a shorthand formula in which the methenyl bridges are omitted and each pyrrole ring is shown as a bracket with the eight substituent positions.
- The arrangement of the acetate and propionate substituents in the uroporphyrin shown in Figure 34-2 is asymmetric. A porphyrin with this type of asymmetric substitution is classified as a type III porphyrin. A porphyrin with a completely symmetric arrangement of the substituents is classified as a type I porphyrin.
- Only types I and III are found in nature, and the type ill series is by far more abundant and more important, because it includes here.
- Heme and its immediate precursor, protoporphyrin IX, are both typo III porphyrins. However, they are sometimes identified as belonging to series IX, because they were designated ninth in a series of isomers postulated by Hans Fischer, the pioneer worker in the field of porphyrin chemistry.

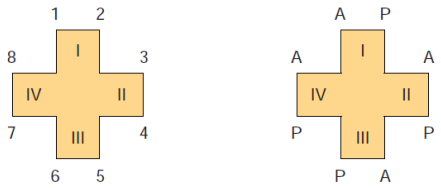


FIGURE 31–2 Uroporphyrin III. (A [acetate] = —CH_2COOH; P [propionate] = —CH_2CH_2COOH.) Note the asymmetry of substituents in ring IV (see text).

BIOSYNTHESIS OF HEME

- Heme is synthesized in living cells by a pathway that has been much studied. The two starting materials are **succinyl-CoA**, derived from the citric acid cycle in mitochondria, and the amino acid glycine. Pyridoxal phosphate is also necessary in this reaction to "activate" **glycine**. The product of the condensation reaction between succinyl-CoA and glycine is α-amino-β-ketoadipic acid, which is rapidly decarboxylated to form α-aminolevulinate (ALA) (Figure 31–5). This reaction sequence is catalyzed by ALA synthase, the rate-controlling enzyme in porphyrin biosynthesis in mammalian liver. Synthesis of ALA occurs in **mitochondria**. In the cytosol, two molecules of ALA are condensed by the enzyme **ALA dehydratase** to form two molecules of water and one of **porphobilinogen** (PBG) (Figure 31–5). ALA dehydratase is a zinccontaining enzyme and is sensitive to inhibition by lead, as can occur in **lead** poisoning.

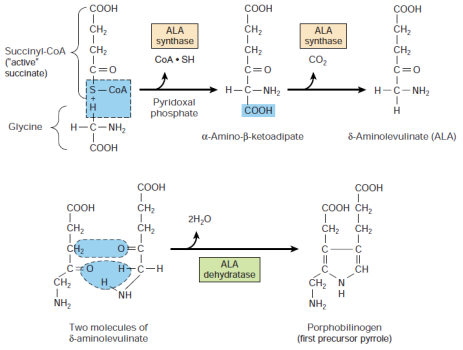


FIGURE 31–5 Biosynthesis of porphobilinogen. ALA synthase occurs in the mitochondria, whereas ALA dehydratase is present in the cytosol.

- The formation of a cyclic tetrapyrrole—ie, a porphyrin— occurs by condensation of four molecules of PBG (Figure 31–6). These four molecules condense in a head-to tail manner to form a linear tetrapyrrole, hydroxymethylbilane (HMB). The reaction is catalyzed by uroporphyrinogen I synthase, also named PBG deaminase or HMB synthase. HMB cyclizes spontaneously to form uroporphyrinogen I (left-hand side of Figure 31–6) or is converted to uroporphyrinogen III by the action of uroporphyrinogen III synthase (right-hand side of Figure 31–6). Under normal conditions, the uroporphyrinogen formed is almost exclusively the III isomer, but in certain of the porphyrias (discussed below), the type I isomers of porphyrinogens are formed in excess.
- Note that both of these uroporphyrinogens have the pyrrole rings connected by methylene bridges (—CH2—), which do not form a conjugated ring system. Thus, these compounds are colorless (as are all porphyrinogens). However, the porphyrinogens are readily auto-oxidized to their respective colored porphyrins. These oxidations are catalyzed by light and by the porphyrins that are formed.
- Uroporphyrinogen III is converted to coproporphyrinogen III by decarboxylation of all of the acetate (A) groups, which changes them to methyl (M) substituents. The reaction is catalyzed by uroporphyrinogen decarboxylase, which is also capable of converting uroporphyrinogen I to coproporphyrinogen I (Figure 31–7). Coproporphyrinogen III then enters the mitochondria, where it is converted to protoporphyrinogen III and then to protoporphyrin III. Several steps are involved in this conversion. The mitochondrial enzyme coproporphyrinogen oxidase catalyzes the decarboxylation and oxidation of two propionic side chains to form protoporphyrinogen. This enzyme is able to act only on type III coproporphyrinogen, which would explain why type I protoporphyrins do not generally occur in nature. The oxidation of protoporphyrinogen to protoporphyrin is catalyzed by another mitochondrial enzyme, protoporphyrinogen oxidase. In mammalian liver, the conversion of coproporphyrinogen to protoporphyrin requires molecular oxygen.

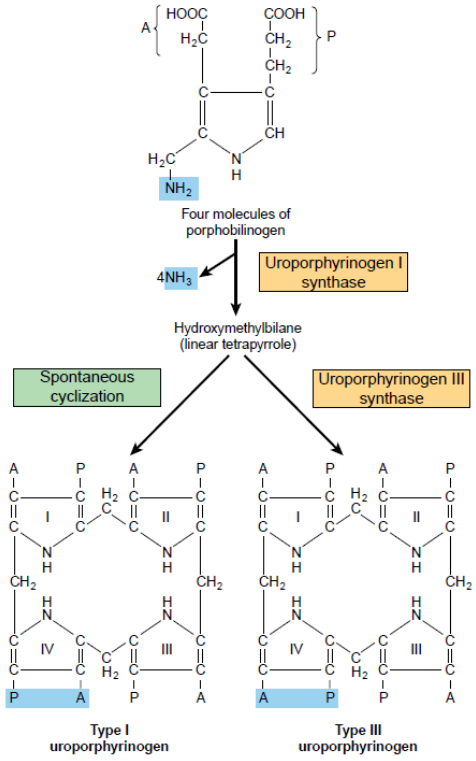


FIGURE 31–6 Conversion of porphobilinogen to uroporphyrinogens. Uroporphyrinogen synthase I is also called porphobilinogen (PBG) deaminase or hydroxymethylbilane (HMB) synthase.

- The final step in heme synthesis involves the incorporation of ferrous iron into protoporphyrin in a reaction catalyzed by ferrochelatase (heme synthase), another mitochondrial enzyme (Figure 31–4).

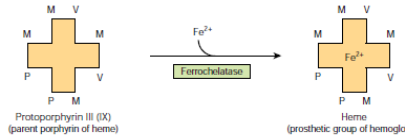


FIGURE 31–4 Addition of iron to protoporphyrin to form heme. (V [vinyl] = —CH═CH_2.)

- A summary of the steps in the biosynthesis of the porphyrin derivatives from PBG is given in Figure 31–8. The last three enzymes in the pathway and ALA synthase are located in the mitochondrion, whereas the other enzymes are cytosolic. Both erythroid and nonerythroid ("housekeeping") forms of ALA synthase are found. Heme biosynthesis occurs in most mammalian cells with the exception of mature erythrocytes, which do not contain mitochondria. However, approximately 85% of heme synthesis occurs in erythroid precursor cells in the bone marrow and the majority of the remainder in hepatocytes.

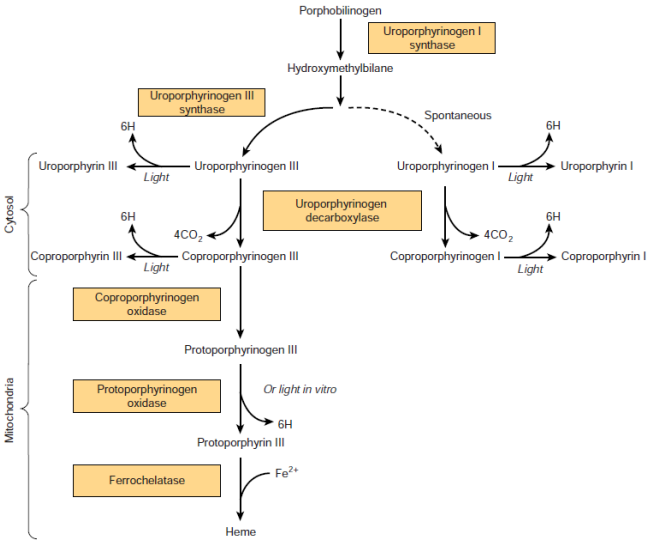


FIGURE 31–8 Steps in the biosynthesis of the porphyrin derivatives from porphobilinogen. Uroporphyrinogen I synthase is also called porphobilinogen deaminase or hydroxymethylbilane synthase.

- The porphyrinogens described above are colorless, containing six extra hydrogen atoms as compared with the corresponding-colored porphyrins. These reduced porphyrins (the porphyrinogens) and not the corresponding porphyrins are the actual intermediates in the biosynthesis of protoporphyrin and of heme.
- The rate-limiting reaction in the synthesis of heme is that catalyzed by ALA synthase, a regulatory enzyme. It appears that heme, probably acting through an aporepressor molecule, acts as a negative regulator of the synthesis of ALA synthase. This repression and depression mechanism is depicted diagrammatically below. It is possible that there is also significant feedback inhibition in which the rate of synthesis of ALA synthase increases greatly in the absence of heme and is diminished in it presence. The turnover rate of ALA synthase is normally rapid in mammalian liver, a common feature of an enzyme catalyzing a rate-limiting reaction.

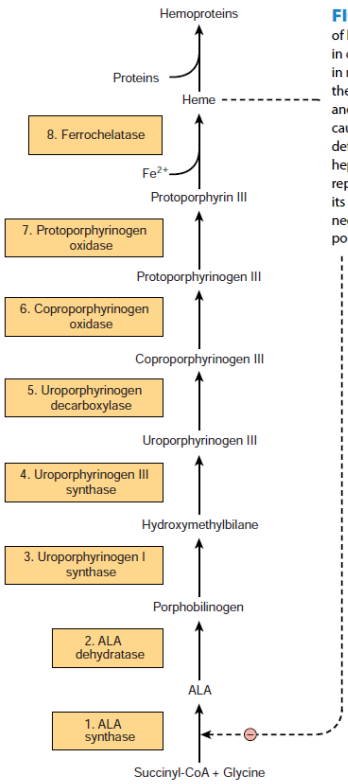


FIGURE 31–9 Intermediates, enzymes, and regulation of heme synthesis. The enzyme numbers are those referred to in column 1 of Table 31–2. Enzymes 1, 6, 7, and 8 are located in mitochondria, the others in the cytosol. Mutations in the gene encoding enzyme 1 causes X-linked sideroblastic anemia. Mutations in the genes encoding enzymes 2–8 cause the porphyrias, though only a few cases due to deficiency of enzyme 2 have been reported. Regulation of hepatic heme synthesis occurs at ALA synthase (ALAS1) by a repression-derepression mechanism mediated by heme and its hypothetical aporepressor. The dotted lines indicate the negative (–) regulation by repression. Enzyme 3 is also called porphobilinogen deaminase or hydroxymethylbilane synthase.

Case 2: “This Oozing Makes Me Woozy”

MECHANISMS INVOLVED IN HEMOSTASIS

VASCULAR CONSTRICTION

- Immediately after a blood vessel has been cut or ruptured, the trauma to the vessel wall itself causes the vessel to contract; this instantaneously reduces the flow of blood from the vessel rupture.
- The contraction results from nervous reflexes, local myogenic spasm, and local humoral factors (e.g. endothelin - a potent endothelium-derived vasoconstrictor) from the traumatized tissues and blood platelets.
- The nervous reflexes are initiated by pain nerve impulses or other impulses that originate from traumatized vessel or from nearby tissues.
- However, most of the vasoconstriction probably results from local direct damage to the vascular wall. For the smaller vessels, the platelets are responsible for much of the vasoconstriction by releasing the vasoconstrictor substance thromboxane A2.
- The more a vessel is traumatized, the greater the degree of spasm; this means that a sharply cut blood vessel usually bleeds much more than does a vessel ruptured by crushing. The local vascular spasm can last for many minutes or even hours, during which time the processes of platelet plugging and blood coagulation can take place.

PLATELET PLUG FORMATION

- If the rent in the blood vessel is very small — and many very small vascular holes do develop throughout the body each day — it is often sealed by a platelet plug, rather than by a blood clot. To understand this, it is important that we first discuss the nature of platelets themselves.
- **Physical and Chemical Characteristics of Platelets**
  - Platelets (also called thrombocytes) are minute round or oval discs 1 to 4 micrometers in diameter.
  - They are formed in the bone marrow from megakaryocytes, which are extremely large cells of the hematopoietic series in the bone marrow; the megakaryocytes fragment into the minute platelets either in the bone marrow or soon after entering the blood, especially as they try to squeeze through the pulmonary capillaries.
  - Platelets have many functional characteristics of whole cells, even though they do not have nuclei and cannot reproduce. In their cytoplasm are active factors such as:
    - (1) actin and myosin molecules, similar to those found in muscle cells, as well as still another contractile protein, thrombosthenin, that can cause the platelets to contract;
    - (2) residuals of both the endoplasmic reticulum and the Golgi apparatus that synthesize various enzymes and especially store large quantities of calcium ions;
    - (3) mitochondria and enzyme systems that are capable of forming adenosine triphosphate and adenosine diphosphate (ADP);
    - (4) enzyme systems that synthesize prostaglandins, which are local hormones that cause many types of vascular and other local tissue reactions;
    - (5) an important protein called fibrin-stabilizing factor;
    - (6) a growth factor that causes vascular endothelial cells, vascular smooth muscle cells, and fibroblasts to multiply and grow, thus causing cellular growth that helps repair damaged vascular walls.
  - The cell membrane of the platelets is also important. On its surface is a coat of glycoproteins that repulses adherence to normal endothelium and yet causes adherence to injured areas of the vessel wall, especially to injured endothelial cells and even more so to any exposed collagen from deep in the vessel wall. In addition, the platelet membrane contains large amounts of phospholipids that play several activating roles at multiple points in the blood-clotting process.
  - Thus, the platelet is an active structure. It has a half-life in the blood of 8 to 12 days, so that over several weeks its functional processes run*out., Then it is eliminated from the circulation mainly by the tissue macrophage system.
- **Mechanism of the Platelet Plug**
  - Platelet repair of vascular openings is based on several important functions of the platelet itself.
  - When platelets come in contact with a damaged vascular surface, such as the collagen fibers in the vascular wall, the platelets themselves immediately change their characteristics drastically. They begin to swell; they assume irregular forms with numerous irradiating pseudopods protruding from their surfaces; their contractile proteins contract forcefully and cause the release of granules that contain multiple active factors; they become sticky so that they adhere to collagen in the tissues and to a protein called von Willebrand factor that spreads throughout the plasma; they secrete large quantities of ADP; and their enzymes form thromboxane A2. The ADP and thromboxane in turn act on nearby platelets to activate them as well, and the stickiness of these additional platelets causes them to adhere to the originally activated platelets. Therefore, at the site of any rent in a blood vessel wall, the damaged vascular wall or extravascular tissues elicit activation of successively increasing numbers of platelets that themselves attract more and more additional platelets, thus forming a platelet plug. This is the process of primary hemostasis. This is at first a loose plug, but it is usually successful in blocking the blood loss if the vascular opening is small. Then, during the subsequent process of blood coagulation, fibrin threads form. These attach tightly to the platelets, thus constructing an unyielding plug. This sequence, secondary hemostasis, takes longer than the initial platelet plug.
  - If the rent in a vessel wall is small, the platelet plug by itself can stop blood loss, but if there is a large hole, a blood clot in addition to the platelet plug is required to stop the bleeding.
  - The platelet-plugging mechanism is extremely important for closing the minute ruptures in very small blood vessels that occur many thousands of times daily. Indeed, multiple small holes through the endothelial cells themselves are often closed by platelets actually fusing with the endothelial cells to form additional endothelial cell membrane. A person who has few platelets develops each day literally thousands of small hemorrhagic areas under the skin and throughout the internal tissues, but this does not occur in the normal person.

FORMATION OF BLOOD CLOT

- The third mechanism for hemostasis is formation of the blood clot. The clot begins to develop in 15 to 20 seconds if the trauma to the vascular wall has been severe and in 1 to 2 minutes if the trauma has been minor. Activator substances from the traumatized vascular wall, from platelets, and from blood proteins adhering to the traumatized vascular wall initiate the clotting process.
- Withing 3 to 6 minutes after rupture of a vessel, if the vessel opening is not too large, the entire opening or broken end of the vessel is filled with clot.
- After 20 minutes to an hour, the clot retracts; this closes the vessel still further. Platelets play an important role in this clot retraction.

COAGULATION FACTORS

- The coagulation factors may be divided into 3 groups based on their properties.
- The thrombin sensitive group consists of fibrinogen and factors V, VIII and XIII.
    - They are consumed during the process of coagulation and are absent in serum and present in plasma.
- The vitamin K dependent group includes prothrombin and factors VII, IX and X.
    - Vitamin K is necessary for their synthesis which takes place in the liver.
- The contact group is composed of factors XI and XII, prekallikrein and HMWK.
    - They are not consumed during coagulation.

FIBRINOGEN

- Fibrinogen is synthesized in the liver
- It is made up of 3 pairs of peptide chains named a, β and δ.
- When acted on by thrombin, the alpha chain yields fibrinopeptide A and the beta chain yields fibrinopeptide B.
- The normal plasma concentration of fibrinogen is approximately 200 to 400 mg/dL.

PROTHROMBIN

- Prothrombin is synthesized in the liver and is almost entirely consumed in the coagulation process so that little remains in the serum.
- It is an alpha-2 globulin and is heat stable.

TISSUE FACTOR (FACTOR III)

- Tissue factor (factor III) is a lipoprotein found in most of the body tissues, with increased concentrations in the lungs and brain.
- It has no enzymatic activity and acts as a cofactor in activating extrinsic coagulation.

CALCIUM (FACTOR IV)

- Calcium (Factor IV), in the ionized state is necessary for coagulation.
- The fact that it is essential for coagulation makes possible the use of anticoagulants, which bind the calcium and, therefore, inhibit coagulation

PROACCELERIN (FACTOR V)

- Factor V (proaccelerin) is synthesized in the liver but does not need for its production.
- It is the most unstable of the vitamin coagulation factors.

PROCONVERTIN (FACTOR VII)

- Factor VII (proconvertin) is synthesized in the liver and requires vitamin K for its production.
- It is a beta globulin and although it is stable at 4°C for 2 or more weeks.
- It is slightly heat labile.

FACTOR VIII

- Factor VIIII circulates in the blood bound to von Willebrand factor.
- This unit is called the factor VIII complex. It was originally thought that factor VIII and vWf were the same molecule. This, however, has been found not to be the case.
- The site of synthesis for factor VIII is not completely understood and it may be produced in multiple sites, including the liver.
- Factor VIII is a single chain glycoprotein.
- It is heat labile and is unstable in citrated plasma.
- During coagulation, it functions as a cofactor to enhance the activation of factor X by IXa with phospholipid and calcium ions.
- Based on its characteristics, factor VIII may be symbolized as follows:
    - (1) factor VIII, factor VIIIC, and factor VIII:C stands for the coagulant property of the factor, that portion of the molecule that is measured by standard factor VIII assays, and it is markedly decreased in classic hemophilia;
    - (2) factor VIII antigen (factor VIII:Ag) represents the antigenic properties of factor VIII measured by immunoassays.
- Von Willebrand factor functions in primary hemostasis, acts as a carrier for the coagulant portion of the factor VIII complex, and constitutes greater than 90% of this complex. It is synthesized in the megakaryocytes and is also present in the alpha granules of platelets.

ANTIHEMOPHILIC B (FACTOR IX)

- Factor IX (antihemophilic B factor) is a single chain glycoprotein synthesized in the live, and requires vitamin K for its production.
- It is decreased in the plasma of patients with Christmas disease.

STUART FACTOR (FACTOR X)

- Factor X (Stuart factor) is a glycoprotein. liver and requires vitamin K for its production.
- It is relatively heat stable and may be stored up to 2 months at 4°C.
- It may be activated by both intrinsic and extrinsic coagulation systems.

PLASMA THROMBOPLASTIN ANTECEDENT (FACTOR XI)

- Factor XI (plasma thromboplastin antecedent) is a beta-2 globulin that is thought to circulate in the plasma in a complex with HMWK.
- It is probably synthesized in the liver and is relatively stable at room temperature.

HAGEMAN FACTOR (FACTOR XII)

- Factor XII (Hageman factor) is a single chain polypeptide.
- The actual site of production is not known.
- It is stable in that it can be stored at 4°C for almost 3 months. It is relatively heat stable.

FIBRIN STABILIZING FACTOR (FACTOR XIII)

- Factor XIII (fibrin stabilizing factor) is heat stable. Although its site of production is not known, it is thought that the liver may play a role.

PREKALLIKREIN (FLETCHER FACTOR)

- Prekallikrein (Fletcher factor) is a single chain y globulin.
- It is produced in the liver but is not dependent on Vitamin k for its production.
- This factor is present in serum.

HIGH MOLECULAR WEIGHT KININOGEN (FITZGERALD FACTOR)

- High molecular weight kininogen (Fitzgerald factor) is a single chain glycoprotein and is present in serum. It is produced in the liver and is not vitamin K-dependent.

BLOOD COAGULATION CASCADE

- More than 50 important substances that affect blood coagulation have been found in the blood and in the tissues - some that promote coagulation, called procoagulants, and others that inhibit coagulation, called anticoagulants. Whether blood will coagulate depends on the balance between these two groups of substances. In the blood stream, the anticoagulants normally predominate, so that the blood does not coagulate while it is circulating in the blood vessels. But when a vessel is ruptured, procoagulants in the area tissue damage become "activated" and override anticoagulants, and then a clot does develop.
- All research workers in the field of blood coagulation agree that clotting takes place in three essential steps:
    - (1) In response to rupture of the vessel or damage to the blood itself, a complex cascade of chemical reactions occurs in the blood involving more than a dozen blood coagulation factors. The net result is formation complex of activated substances collectively called prothrombin activator.
    - (2) The prothrombin activator catalyzes the conversion of prothrombin into thrombin.
    - (3) The thrombin acts as an enzyme to convert fibrinogen into fibrin fibers that enmesh platelets, blood cells, and plasma to form the clot.
- Initiation of Coagulation: Formation of Prothrombin Activator

- Prothrombin activator is generally considered to be formed in two ways, although, in reality, the two ways inter act with each other.
  - (1) by the extrinsic pathway that begins with trauma to the vascular wall and surrounding tissues
  - (2) by the intrinsic pathway that begins in the blood itself

EXTRINSIC PATHWAY

- The extrinsic pathway for initializing the formation of prothrombin activator begins with a traumatized vascular wall or extravascular tissues that come in contact with the blood. This leads to the following steps as shown in the figure below.

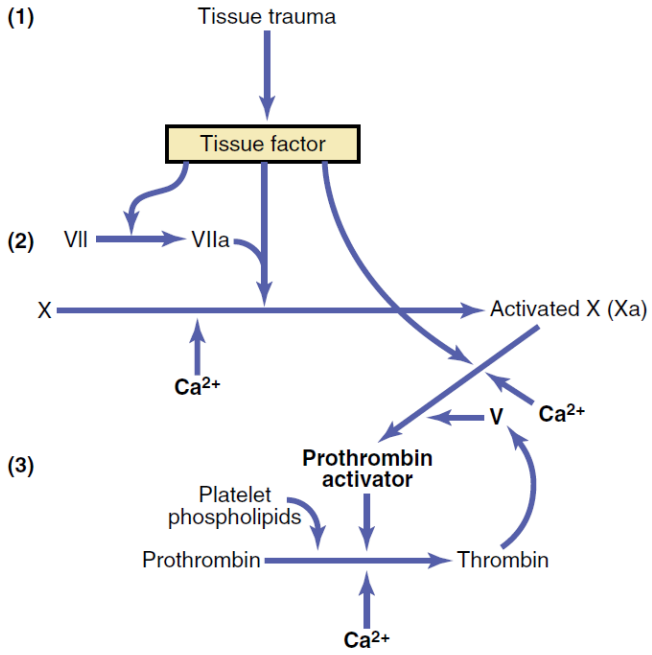


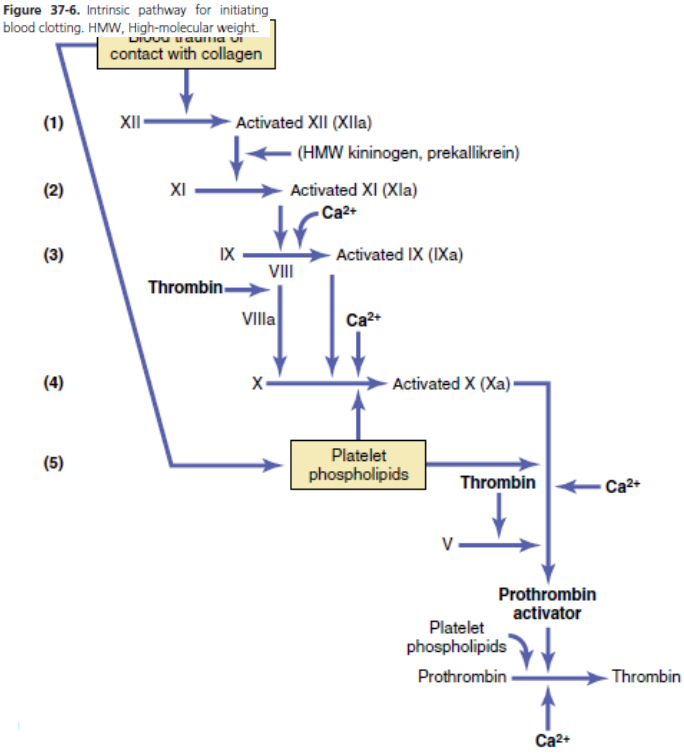
Figure 37-5. Extrinsic pathway for initiating blood clotting.

1. **Release of tissue factor.** Traumatized tissue releases a complex of several factors called tissue factor or tissue thromboplastin. This factor is composed especially of phospholipids from the membranes of the tissue plus a lipoprotein complex that functions mainly as a proteolytic enzyme.
2. **Activation of factor X—role of factor VII and tissue factor.** The lipoprotein complex of tissue factor further complexes with blood coagulation factor VII and, in the presence of calcium ions, acts enzymatically on factor X to form activated factor X (Xa). 3.
3. **Effect of Xa to form prothrombin activator—role of factor V.** The activated factor X combines immediately with tissue phospholipids that are part of tissue factors or with additional phospholipids released from platelets, as well as with factor V, to form the complex called prothrombin activator. Within a few seconds, in the presence of Ca2+, prothrombin is split to form thrombin, and the clotting process proceeds as already explained. At first, the factor V in the prothrombin activator complex is inactive, but once clotting begins and thrombin begins to form, the proteolytic action of thrombin activates factor V. This activation then becomes an additional strong accelerator of prothrombin activation. Thus, in the final prothrombin activator complex, activated factor X is the actual protease that causes splitting of prothrombin to form thrombin. Activated factor V greatly accelerates this protease activity, and platelet phospholipids act as a vehicle that further accelerates the process. Note especially the positive feedback effect of thrombin, acting through factor V, to accelerate the entire process once it begins.

INTRINSIC PATHWAY

- The second mechanism for initiating formation of prothrombin activator, and therefore for initiating clotting, begins with trauma to the blood or exposure of the blood to collagen from a traumatized blood vessel wall. Then the process continues through the series of cascading reactions shown in figure.

Figure 37-6. Intrinsic pathway for initiating blood clotting. HMW, High-molecular weight.



1. **Blood trauma causes (1) activation of factor XII and (2) release of platelet phospholipids.** Trauma to the blood or exposure of the blood to vascular wall collagen alters two important clotting factors in the blood: factor XII and the platelets. When factor XII is disturbed, such as by coming into contact with collagen or with a wettable surface such as glass, it takes on a new molecular configuration that converts it into a proteolytic enzyme called activated factor XII. Simultaneously, the blood trauma also damages the platelets because of adherence to collagen or to a wettable surface (or by damage in other ways); this releases platelet phospholipids that contain the lipoprotein called platelet factor 3, which also plays a role in subsequent clotting reactions.
2. **Activation of factor XI.** The activated factor XII also acts enzymatically on factor XI to activate this factor, which is the second step in the intrinsic path way. This reaction also requires high-molecular-weight kininogen and is accelerated by prekallikrein.
3. **Activation of factor IX by activated factor XI.** The activated factor XI then acts enzymatically on factor IX to activate this factor as well.
4. **Activation of factor X**—role of factor VIII. The activated factor IX, acting in concert with activated factor VIII and the platelet phospholipids and factor III from the traumatized platelets, activates factor X. It is clear that when either factor VIII or platelets are in short supply, this step is deficient. Factor VIII is the factor that is missing in a person who has classic hemophilia, so it is called antihemophilic factor. Platelets are the clotting factor that is lacking in the bleeding disease called thrombocytopenia.
5. **Action of activated factor X to form prothrombin activator—role of factor V.** This step in the intrinsic pathway is the same as the last step in the extrinsic pathway. That is, activated factor X combines with factor V

and platelet or tissue phospholipids to form the complex called prothrombin activator. The prothrombin activator, in turn, initiates the cleavage of prothrombin to form thrombin within seconds, thereby setting into motion the final clotting process, as described earlier.

CONVERSION OF PROTHROMBIN TO THROMBIN

1. Prothrombin activator is formed as a result of rupture of a blood vessel or as a result of damage to special substances in the blood.
2. Prothrombin activator, in the presence of sufficient amounts of ionic calcium (Ca2+), causes conversion of prothrombin to thrombin (Figure 37-3 and 37-4).
3. Thrombin causes polymerization of fibrinogen molecules into fibrin fibers within another 10 to 15 seconds.

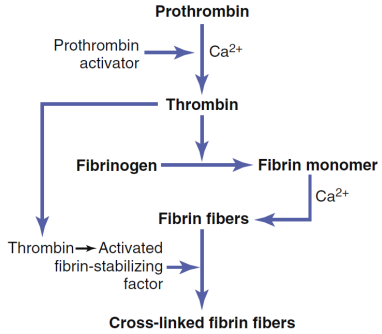


Figure 37-3 Schema for conversion of prothrombin to thrombin and polymerization of fibrinogen to form fibrin fibers.

- Thus, the rate-limiting factor in causing blood coagulation is usually the formation of prothrombin activator and not the subsequent reactions beyond that point because these terminal steps normally occur rapidly to form the clot.
- Platelets also play an important role in the conversion of prothrombin to thrombin because much of the prothrombin first attaches to prothrombin receptors on the platelets that are already bound to the damaged tissue.

ACTION OF THROMBIN ON FIBRINOGEN TO FORM FIBRIN

- Thrombin is a protein enzyme with weak proteolytic capabilities. It acts on fibrinogen to remove four low-molecular-weight peptides from each molecule of fibrinogen, forming one molecule of fibrin monomer that has the automatic capability to polymerize with other fibrin monomer molecules to form fibrin fibers. Therefore, many fibrin monomer molecules polymerize within seconds into long fibrin fibers that constitute the reticulum of the blood clot.
- In the early stages of polymerization, the fibrin monomer molecules are held together by weak non covalent hydrogen bonding, and the newly forming fibers are not cross-linked with one another. Therefore, the resultant clot is weak and can be broken apart with ease. However, another process occurs during the next few minutes that greatly strengthens the fibrin reticulum. This process involves a substance called fibrin stabilizing factor that is present in small amounts in normal plasma globulins but is also released from platelets entrapped in the clot. Before fibrin stabilizing factor can have an effect on the fibrin fibers, it must be activated. The same thrombin that causes fibrin formation also activates the fibrin stabilizing factor. This activated substance then operates as an enzyme to form covalent bonds between more and more of the fibrin monomer molecules, as well as multiple cross-linkages between adjacent fibrin fibers, thus adding tremendously to the three-dimensional strength of the fibrin meshwork.

BLOOD CLOT

- The clot is composed of a meshwork of fibrin fibers running in all directions and entrapping blood cells, platelets, and plasma (see Figure 37-4).
- The fibrin fibers also adhere to damaged surfaces of blood vessels; therefore, the blood clot becomes adherent to any vascular opening and thereby prevents further blood loss.

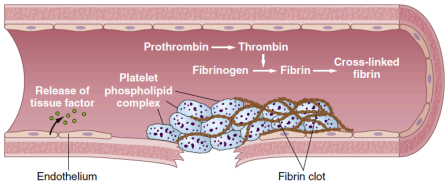


Figure 37-4. Coagulation cascade after vascular injury. Exposure of blood to the vascular wall causes release of tissue factor (also called factor III or thromboplastin) from endothelial cells, phospholipid expression, activation of thrombin, which then acts on fibrinogen to form fibrin, and fibrin polymerization to form a meshwork that stabilizes the platelet plug.

CLOT RETRACTION AND EXPRESSION OF SERUM

- Within a few minutes after a clot is formed, it begins to contract and usually expresses most of the fluid from the clot within 20 to 60 minutes. The fluid expressed is called serum because all its fibrinogen and most of the other clotting factors have been removed; in this way, serum differs from plasma and cannot clot because it lacks these factors.
- Platelets are necessary for clot retraction to occur. Therefore, failure of clot retraction is an indication that the number of platelets in the circulating blood might be low. Electron micrographs of platelets in blood clots show that they become attached to the fibrin fibers in such a way that they actually bond different fibers together. Furthermore, platelets entrapped in the clot continue to release procoagulant substances, one of the most important of which is fibrin stabilizing factor, which causes more and more cross-linking bonds between adjacent fibrin fibers. In addition, the platelets contribute directly to clot contraction by activating platelet thrombosthenin, actin, and myosin molecules, which are all contractile proteins in the platelets; they cause strong contraction of the platelet spicules attached to the fibrin. This action also helps compress the fibrin meshwork into a smaller mass. The contraction is activated and accelerated by thrombin and by calcium ions released from calcium stores in the mitochondria, endoplasmic reticulum, and Golgi apparatus of the platelets.
- As the clot retracts, the edges of the broken blood vessel are pulled together, thus contributing still further to hemostasis.

INTRAVASCULAR ANTICOAGULANTS THAT PREVENT BLOOD CLOTTING IN THE NORMAL VASCULAR SYSTEM

ENDOTHELIAL SURFACE FACTORS

- Probably the most important factors for preventing clotting in the normal vascular system are the following:
  - (1) the smoothness of the endothelial cell surface, which prevents contact activation of the intrinsic clotting system;
  - (2) a layer of glycocalyx on the endothelium (glycocalyx is a mucopolysaccharide adsorbed to the surfaces of the endothelial cells), which repels clotting factors and platelets, thereby preventing activation of clotting; and
  - (3) a protein bound with the endothelial membrane, thrombomodulin, which binds thrombin.
- Not only does the binding of thrombin with thrombomodulin slow the clotting process by removing thrombin, but the thrombomodulin-thrombin complex also activates a plasma protein, protein C, that acts as an anticoagulant by inactivating activated factors V and VIII.
- When the endothelial wall is damaged, its smoothness and glycocalyx-thrombomodulin layer are lost, which activates both factor XII and the platelets, thus setting off the intrinsic pathway of clotting. If factor XII and platelets come into contact with the subendothelial collagen, the activation is even more powerful.
- Intact endothelial cells also produce other substances such a prostacyclin and nitric oxide (NO) that inhibit platelet aggregation and initiation of blood clotting. Prostacyclin, also called prostaglandin I2 (PGI2), is a member of the eicosanoid family of lipids and is a vasodilator, as well as an inhibitor of platelet aggregation. NO is a powerful vasodilator released from healthy vascular endothelial cells throughout the body, and it is an important inhibitor of platelet aggregation. When endothelial cells are damaged, their production of prostacyclin and NO is greatly diminished.

ANTITHROMBIN ACTION OF FIBRIN AND ANTITHROMBIN III

- Among the most important anticoagulants in the blood are those that remove thrombin from the blood. The most powerful of these are the following:
  - (1) the fibrin fibers that are formed during the process of clotting; and
  - (2) an α globulin called antithrombin III or antithrombin-heparin cofactor.
- While a clot is forming, about 85% to 90% of the thrombin formed from the prothrombin becomes adsorbed to the fibrin fibers as they develop. This adsorption helps prevent the spread of thrombin into the remaining blood and, therefore, prevents excessive spread of the clot.
- The thrombin that does not adsorb to the fibrin fibers soon combines with antithrombin III. This further blocks the effect of thrombin on the fibrinogen and then also inactivates thrombin itself during the next 12 to 20 minutes.

HEPARIN

- Heparin is another powerful anticoagulant but, because its concentration in the blood is normally low, it has significant anticoagulant effects only under special physiological conditions. However, heparin is used widely as a pharmacological agent in medical practice in much higher concentrations to prevent intravascular clotting.
- The heparin molecule is a highly negatively charged conjugated polysaccharide. By itself, it has little or no anticoagulant properties, but when it combines with antithrombin III, the effectiveness of antithrombin III for removing thrombin increases by a hundredfold to a thousandfold and thus acts as an anticoagulant. Therefore, in the presence of excess heparin, the removal of free thrombin from the circulating blood by antithrombin III is almost instantaneous.
- The complex of heparin and antithrombin III removes several other activated coagulation factors in addition to thrombin, further enhancing the effectiveness of anticoagulation. The others include activated factors IX through XII.
- Heparin is produced by many different cells of the body, but the largest quantities are formed by the basophilic mast cells located in the pericapillary connective tissue throughout the body. These cells continually secrete small quantities of heparin that diffuse into the circulatory system. The basophil cells of the blood, which are functionally almost identical to the mast cells, release small quantities of heparin into the plasma.
- Mast cells are abundant in tissue surrounding the capillaries of the lungs and, to a lesser extent, capillaries of the liver. It is easy to understand why large quantities of heparin might be needed in these areas because the capillaries of the lungs and liver receive many embolic clots that have formed in slowly flowing venous blood; sufficient production of heparin prevents further growth of the clots.

MECHANISMS AND FACTORS BEHIND FIBRINOLYSIS

- The plasma proteins contain a euglobulin called plasminogen (profibrinolysin) that when activated, becomes a substance called plasmin (fibrinolysin). Plasmin is a proteolytic enzyme that resembles trypsin, the most important proteolytic digestive enzyme of pancreatic secretion. Plasmin digests fibrin fibers and some other protein coagulants, such as fibrinogen, factor V, factor VIII, prothrombin, and factor XII. Therefore, whenever plasmin is formed, it can cause lysis of a clot by destroying many of the clotting factors, thereby sometimes even causing hypocoagulability of the blood.

Activation of Plasminogen to Form Plasmin, Then Clot Lysis

- When a clot is formed, a large amount of plasminogen is trapped in the clot, along with other plasma proteins. This will not become plasmin or cause lysis of the clot until it is activated. The injured tissues and vascular endothelium very slowly release a powerful activator called tissue plasminogen activator (t-PA); a few days later, after the clot has stopped the bleeding, t-PA eventually converts plasminogen to plasmin, which in turn removes the remaining unnecessary blood clot. In fact, many small blood vessels in which blood flow has been blocked by clots are reopened by this mechanism. Thus, an especially important function of the plasmin system is to remove minute clots from millions of tiny peripheral vessels that eventually would become occluded were there no way to clear them.

TESTS TO ASSESS DIFFERENT SYSTEMS INVOLVED IN HEMOSTASIS

TOURNIQUET TEST (CAPILLARY FRAGILITY TEST)

- This test measures the resistance of the capillaries to the increased intraluminal pressure and partial anoxia caused by a carefully controlled tourniquet on the proximal aspect of the upper extremity. It is a crude measure of capillary fragility. Because platelets function to maintain capillary integrity, the degree of thrombocytopenia will correlate with the tourniquet test, as will the bleeding time. In normal patients, none to very few petechiae are formed during the test.
- A positive tourniquet test (presence of numerous petechiae) will be found in thrombocytopenia, decreased fibrinogen and in vascular purpura.

BLEEDING TIME

- This test provides an estimate of the integrity of the primary hemostatic plug and thus measures the interaction between the microvasculature (capillaries) and platelets. Hence it is abnormal in a variety of quantitative and qualitative defects and occasionally in vascular disorders.
- The test requires that an atraumatic subcutaneous incision be made without transecting vessels larger than subcutaneous capillaries. depth and length of the incision requires careful control, as does the removal of blood welling from the incision. It is vital to remove all blood from the incision, otherwise fibrin formation may produce a spuriously low bleeding time.
- The position of the extremity on which the incision is made will interfere with the intracapillary pressure; therefore, most methods now recommend that this be stabilized using an exterior pressure cuff (sphygmomanometer) cuff and constant pressure of 40 mmHg if an upper extremity is used.
- The end point of the test is reached when all bleeding ceases, and this is most conveniently detected for routine purposes using a filter paper to blot away the surplus blood. When the filter paper remains clean, the end point is reached.
- Normal range: Depends on location and orientation of cut and on particular device used, typically 2 to 8 minutes.

CLOTTING TIME

- Whole blood is delivered using a carefully controlled venipuncture and collection process into standardized glass tubes.
- The clotting time of the blood is timed and expressed in minutes.
- It is prolonged in defects of intrinsic and extrinsic coagulation and in the presence of certain pathological anticoagulants and heparin.
- Normal Range (Lee and White method): 4 to 10 minutes

PROTHROMBIN TIME

- Blood removed from the patient is immediately oxalated so that none of the prothrombin can change into thrombin.
- Later, a large excess of calcium ion and tissue factor is suddenly mixed with the oxalated blood.
- The calcium nullifies the effect of the oxalate, and the tissue factor activates the prothrombin to thrombin reaction by means of the extrinsic clotting pathway.
- The time required for coagulation to take place is known as prothrombin time (PT).
- The prothrombin time is a useful screening procedure for the extrinsic coagulation mechanism including the common pathway (dejects deficiencies in factors II, V, VII, and X).
- The PT will also be prolonged when the fibrinogen concentration is less than 80 mg/dL and in cases of dysfibrinogenemia. The test is frequently used to follow the course of oral anticoagulant therapy.
- Normal Range: 10 - 12 seconds

ACTIVATED PARTIAL THROMBOPLASTIN TIME

- The APTT is a most useful procedure for routine screeing of coagulation disorders in the intrinsic system, for detecting the presence of circulating anticoagulants (inhibitors), and for monitoring heparin therapy.
- It measures those factors present in the intrinsic coagulation mechanism except for platelets and factor XIII.
- Normal Range: 25 - 35 seconds

CLOT RETRACTION

- When blood coagulation is complete, the clot normally undergoes retraction (serum is expressed from the clot, and the clot becomes denser).
- In the past, this procedure has been used as a screening test for platelet function. With the advent of more sophisticated tests for platelet function, however, this test is used infrequently. Normal clot retraction requires a normal number of functioning platelets, calcium, ATP, and a normal interaction of platelets with fibrinogen and fibrin.
- Normally, clot retraction begins within 30 seconds after the blood has clotted.
- At the end of 1 hour, there should be appreciable clot retraction with most retraction occurring within the first 4 hours. Clot retraction should be complete within 24 hours.

Case 1 Trigger 1: Shape of My Heart

Block 4 Module 2

EMBRYOLOGY OF THE HEART AND BLOOD VESSELS

- The cardiovascular system is the first major system to function in the embryo.
- The primordial heart and vascular system appears in the middle of the third week
- The CVS is derived mainly from:
  - Splanchnic mesoderm which forms the primordium of the heart
  - Paraxial and lateral mesoderm near the otic placodes from which the internal ears develop
  - Neural crest cells from the region between the otic vesicles and the caudal limits of the third pair of somites
- These sources will produce respectively:
  - The endocardium and the cardiac mesenchymal cells which produce the valvular tissue of the heart
  - The myocardium, including the conducting tissue of the heart, and the specific matrix proteins associated with the developing heart, i.e. the cardiac jelly
  - The aorticopulmonary septum and the media of the great vessels, and, possibly contributes to the conducting tissue of the heart.
- The heart begins to beat at 22 - 23 days
- Blood flow begins during the fourth week and can be visualized by Doppler ultrasonography.
- Three paired veins drain into the tubular heart of a 4-week-old embryo:
  - **Vitelline veins**
    - return poorly oxygenated blood from the yolk sac;
  - **Umbilical veins**
    - carry well-oxygenated blood from the chorionic villi of the embryonic placenta; only the left umbilical vein persists.
  - **Common cardinal veins**
    - return poorly oxygenated blood from the body of the embryo.
- Transformation of the umbilical veins may be summarized as follows:
  - The right umbilical vein and the caudal part of the left umbilical vein between the liver and the sinus venous degenerate.
  - The persistent caudal part of the left umbilical vein becomes the umbilical vein, which carries all the blood from the placenta to the A large venous shunt - the ductus venosus - develops within the liver and connects the umbilical vein with the inferior vena cava (IVC).
  - The ductus venosus forms a bypass through the liver, enabling most of the blood from the placenta to pass directly to the heart without passing through the capillary networks of the liver.

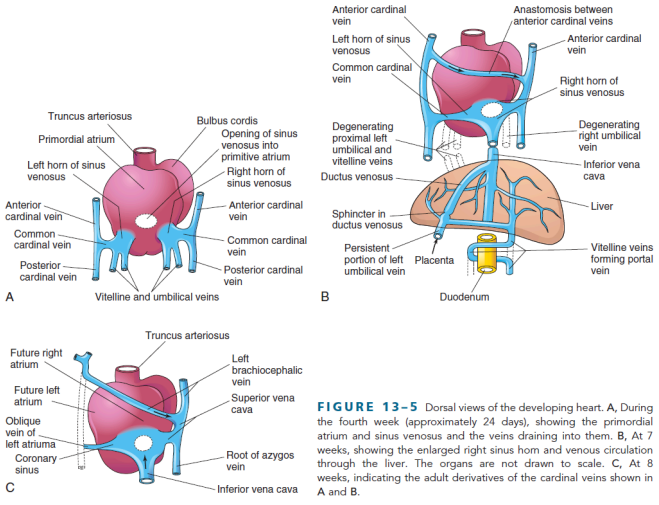


FIGURE 13–5 Dorsal views of the developing heart. A, During the fourth week (approximately 24 days), showing the primordial atrium and sinus venosus and the veins draining into them. B, At 7 weeks, showing the enlarged right sinus horn and venous circulation through the liver. The organs are not drawn to scale. C, At 8 weeks, indicating the adult derivatives of the cardinal veins shown in A and B.

- The cardinal veins constitute the main venous drainage system of the embryo (see Figs. 13-2 and 13-4A). The anterior and posterior cardinal veins, the earliest veins to develop, drain cranial and caudal parts of the embryo, respectively. They join the common cardinal veins, which enter the sinus venosus.

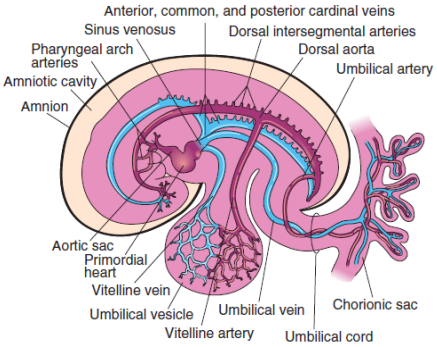


FIGURE 13–2 Drawing of the embryonic cardiovascular system (approximately 26 days), showing vessels on the left side. The umbilical vein carries well-oxygenated blood and nutrients from the chorionic sac to the embryo. The umbilical arteries carry poorly oxygenated blood and waste products from the embryo to the chorionic sac (outermost embryonic membrane).

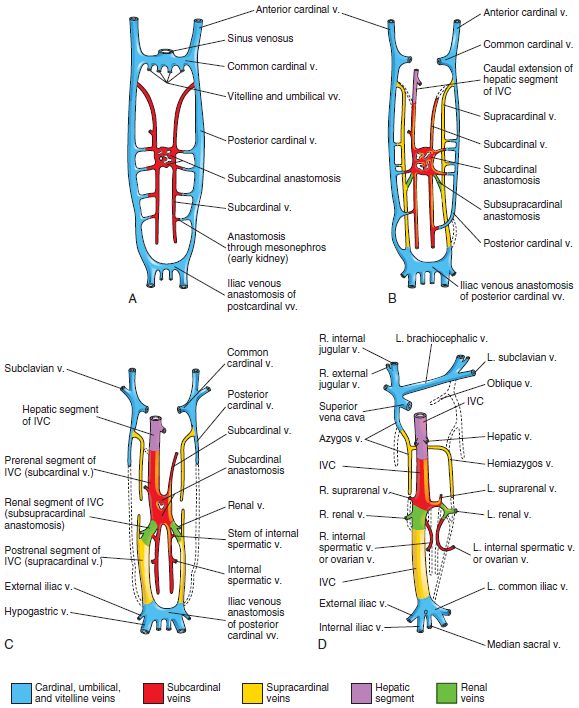


FIGURE 13–4 Illustrations of the primordial veins of bodies (trunks) of embryos (ventral views). Initially, three systems of veins are present: the umbilical veins from the chorion, vitelline veins from the umbilical vesicle, and cardinal veins from the body of the embryos. Next the subcardinal veins appear, and finally the supracardinal veins develop. A, At 6 weeks. B, At 7 weeks. C, At 8 weeks. D, Adult. This drawing illustrates the transformations that produce the adult venous pattern. *IVC*, Inferior vena cava; *L.*, left; *R.*, right; *v.*, vein; *vv.*, veins. *(Modified from Arey LB:* Developmental anatomy, *revised ed 7, Philadelphia, 1974, Saunders.)*

- During the eighth week, the **anterior cardinal veins** are connected by an anastomosis (see Fig. 13-5A and B), which shunts blood from the left to the right anterior cardinal vein. This anastomotic shunt becomes the **left brachiocephalic vein** when the caudal part of the left anterior cardinal vein degenerates (see Figs. 13-4D and 13-5C). **The superior vena cava (SVC)** forms from the right anterior cardinal vein and the right common cardinal vein.
- The **posterior cardinal veins** develop primarily as the vessels of the **mesonephroi** (interim kidneys) and largely disappear with these transitory kidneys. The only adult derivatives of these veins are the root of the azygos vein and common iliac veins (see Fig. 13-4D). The subcardinal and supracardinal veins gradually

develop and replace and supplement the posterior cardinal veins (see Fig. 13-4A to D).

- The **subcardinal veins** appear first (see Fig. 13-4A). They are connected with each other through the **subcardinal anastomosis** and with the posterior cardinal veins through the mesonephric sinusoids. The subcardinal veins form the stem of the left renal vein, the suprarenal veins, the gonadal veins (testicular and ovarian), and a segment of the IVC (see Fig. 13-4D). The subcardinal veins become disrupted in the region of the kidneys (see Fig. 13-4C). Cranial to this region, they are united by an anastomosis that is represented in the adult by the azygos and hemiazygos veins (see Figs. 13-4D and 13-5C). Caudal to the kidneys, the left supracardinal vein degenerates; however, the right supracardinal vein becomes the inferior part of the IVC (see Fig. 13-4D).
- The IVC forms during a series of changes in the primordial veins of the trunk that occur as blood, returning from the caudal part of the embryo, is shifted from the left to the right side of the body. The IVC is composed of four main segments (Fig. 13-4 C):
  - A hepatic segment derived from the hepatic vein (proximal part of right vitelline vein) and hepatic sinusoids
  - A prerenal segment derived from the right subcardinal vein
  - A renal segment derived from the subcardinal–supracardinal anastomosis
  - A postrenal segment derived from the right supracardinal vein
- The superior vena cava (SVC) is derived from the right anterior cardinal vein and the right common cardinal vein.

DERIVATIVES OF THE PHARYNGEAL ARCH ARTERIES

- The pharyngeal arch arteries arise from the aortic sac and terminate in the dorsal aorta. There are six pairs of aortic arches:
  - Derivatives of the first pair
    - Maxillary arteries - supply the ears, teeth, and muscles of the eye and face
    - External carotid arteries
  - Derivatives of the second pair
    - Stapedial arteries - small vessels that run through the ring of the stapes, a small ear bone
  - Derivatives of the third pair
    - Common carotid arteries - supply structures in the head.
    - Internal carotid arteries - supply the ears, orbits, brain and its meninges.
  - Derivatives of the fourth pair
    - Arch of the aorta - formed partly by the fourth aortic arch. The proximal part of the arch develops from the aortic sac and the distal part is derived from the left dorsal aorta (Fig. 13-39 C)
    - Right subclavian artery - its proximal part is derived from the right: fourth pharyngeal arch artery while the distal part is derived from the right dorsal aorta and right seventh intersegmental artery.
  - Derivatives of the fifth pair
    - In 50% of embryos the fifth pair are rudimentary vessels that soon degenerate, leaving no vascular derivatives. In other embryos, these arteries do not develop.
  - Derivatives of the sixth pair
    - The left sixth aortic arch develops as follows:
      - ❖ (1) Proximal part of the left pulmonary artery - derived from the proximal part of the arch.
      - ❖ (2) Ductus arteriosus - a prenatal shunt and derived from the distal part of the arch which passes from the left pulmonary artery to the dorsal aorta.
    - The right sixth aortic arch develop as follows:
      - ❖ Proximal part of the right pulmonary artery - derived from the proximal part of the arch.

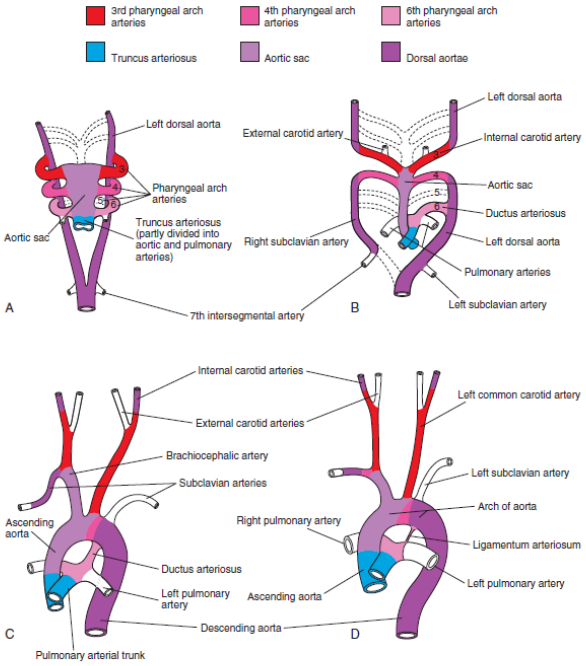
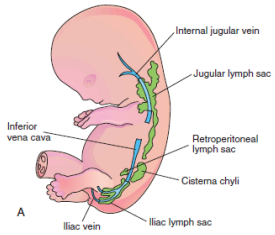


FIGURE 13–39 Schematic drawings illustrating the arterial changes that result during transformation of the truncus arteriosus, aortic sac, pharyngeal arch arteries, and dorsal aortae into the adult arterial pattern. The vessels that are not colored are not derived from these structures. A, Pharyngeal arch arteries at 6 weeks; by this stage, the first two pairs of arteries have largely disappeared. B, Pharyngeal arch arteries at 7 weeks; the parts of the dorsal aortae and pharyngeal arch arteries that normally disappear are indicated with *broken lines*. C, Arterial arrangement at 8 weeks. D, Sketch of the arterial vessels of a 6-month-old infant. Note that the ascending aorta and pulmonary arteries are considerably smaller in C than in D. This represents the relative flow through these vessels at the different stages of development. Observe the large size of the ductus arteriosus in C and that it is essentially a direct continuation of the pulmonary trunk. The ductus arteriosus normally becomes functionally closed within the first few days after birth. Eventually the ductus arteriosus becomes the ligamentum arteriosum, as shown in D.

DERIVATIVES OF LYMPH SACS AND DUCTS

- There are six primary lymph sacs at the end of the embryonic period (Fig. 13-54 A)
  - Two jugular lymph sacs near the junction of the subclavian veins with the anterior cardinal veins (the future internal jugular veins)
  - Two iliac lymph sacs near the junction of the iliac veins with the posterior cardinal veins
  - One retroperitoneal lymph sac in the root of the mesentery on the posterior abdominal wall
  - One cisterna chili located dorsal to the retroperitoneal lymph sac
- Two large channels (right and left thoracic ducts) connect the jugular sacs with the cisterna chyli.



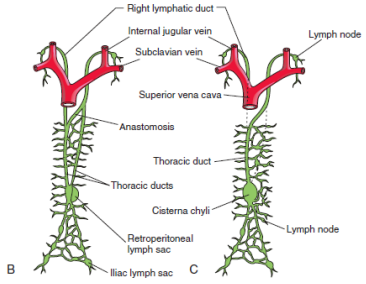


FIGURE 13–54 Development of lymphatic system. A, Left side of a 7.5-week embryo showing the primary lymph sacs. B, Ventral view of the lymphatic system at 9 weeks showing the paired thoracic ducts. C, Later in the fetal period, illustrating formation of the thoracic duct and right lymphatic duct.

- The thoracic duct develops from:
  - The caudal part of the right thoracic duct
  - The anastomosis between the thoracic ducts and the cranial part of the left thoracic duct.
- The right lymphatic duct is derived from the cranial part of the right thoracic duct (Fig. 14-54 C). The thoracic duct and the right

lymphatic duct connect with the venous system at the angle between the internal jugular and subclavian veins.
- The superior part of the embryonic cisterna chili persists, and in the adults, cisterna chyli is about 5 cm long and 6 mm wide.

FUNCTIONS OF THE HEART

- The heart is actually 2 separate pumps
  - Right heart that pumps blood through the lungs
  - Left heart that pumps blood through the peripheral organs

LOCATION OF THE HEART

- It is located between the lungs and lies within the pericardium in the middle mediastinum

ANATOMICAL RELATIONSHIPS

- In front:
  - It is separated from the sternum by the remains of the thymus gland above and is covered by the margins of the lungs specially the left.
- Behind:
  - It rests upon the bronchi, the esophagus and the descending aorta.
- Laterally:
  - It is covered by the pleurae and is related to the inner surface of the lungs, the phrenic nerve and pericardiophrenic vessels.
- The base is attached to the central tendon and to the left of the muscular respiratory diaphragm.

PERICARDIUM

- Pericardium is a fibroserous sac that encloses the heart and the roots of the great vessels.
- Functions:
  - To restrict excessive movements of the heart as a whole.
  - To serve as a lubricated container in which the different parts of the heart can contract.
- Location:
  - Lies within the middle mediastinum, posterior to the body of the sternum and the second to the sixth costal cartilages

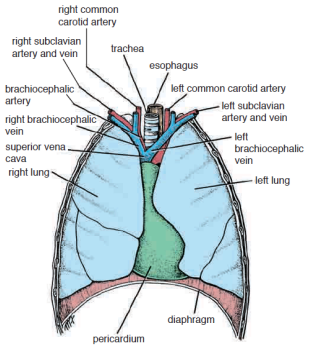


FIGURE 3.30 The pericardium and the lungs exposed from in front.

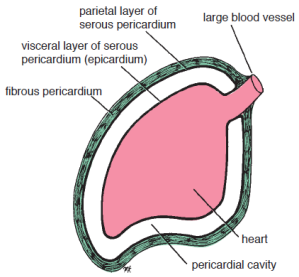


FIGURE 3.31 Different layers of the pericardium.

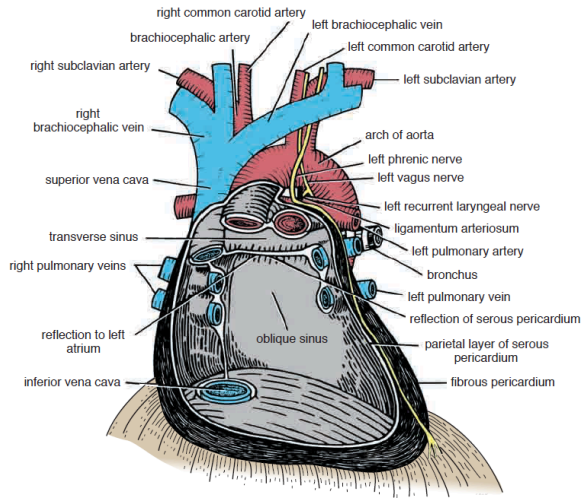


FIGURE 3.32 The great blood vessels and the interior of the pericardium.

COMPONENTS OF THE PERICARDIUM

- **Fibrous Pericardium**
  - The strong fibrous part of the sac.
  - It is firmly attached below the central tendon of the diaphragm.
  - It fuses with the outer coats of the great blood vessels passing through it, namely, the aorta, pulmonary trunk, superior and inferior vena cava, and pulmonary veins.
  - It is attached in front to the sternum by the, sternopericardial ligaments.
- **Serous Pericardium**
  - Has 2 layers:
    - **Parietal Layer**
      - ❖ lines the fibrous pericardium and is reflected around the roots of the great vessels to become continuous with the visceral layer that closely covers the heart.
    - **Visceral Layer**
      - ❖ closely applied to the heart and is often called the epicardium.
- **Pericardial cavity**
  - Slit like space between the parietal and visceral layers containing a small amount of tissue fluid, the pericardial fluid, which acts as a lubricant to facilitate movements of the heart.

PERICARDIAL SINUSES

- **Oblique Sinus**
  - a recess formed by the reflection of the serous pericardium around the large veins found on the posterior surface of the heart.
- **Transverse Sinus**
  - a short passage that lies between the reflection of serous pericardium around the aorta and pulmonary trunk and the reflection around the large veins located on the posterion surface of the heart.

GREAT BLOOD VESSELS AT THE BASE OF THE HEART

ARTERIES

Aorta

- **Ascending Aorta**
  - lies behind the right half of sternum at the level of the sternal angle
  - begins at the base of left ventricle, gives off 2 branches right and left coronary arteries.
- **Aortic Arch**
  - continuation of ascending AORTA
  - lies behind the manubrium sternae
  - Branches:
    - Brachiocephalic artery
      - ❖ Right Subclavian artery
      - ❖ Right common carotid artery
    - Left common carotid artery
      - ❖ Left subclavian artery
  - Descending thoracic aorta
    - lies at T4-T12
    - Branches:
      - ❖ Posterior intercostal arteries
      - ❖ Subcostal arteries
      - ❖ Pericardial arteries
      - ❖ Bronchial arteries
      - ❖ Esophageal arteries
      - ❖ Mediastinal arteries
      - ❖ Phrenic arteries

Pulmonary Trunk

- Conveys blood from the right ventricle to the lungs
- Branches:
  - Right and Left Pulmonary Arteries

LARGE VEINS OF THE THORAX

- Brachiocephalic veins:
  - Right
  - Left: formed by the union of subclavian and internal jugular veins
- Superior vena cava
  - Formed by the union of brachiocephalic veins.
- Azygos veins
- Inferior vena cava
- Pulmonary veins

BORDERS AND SURFACES OF THE HEART

SURFACES

- **Posterior Surface (Base of the Heart)**
  - Formed mainly by the left atrium, into which open the 4 pulmonary veins.
  - It lies opposite the apex.
- **Sternocostal Surface (Anterior)**
  - formed mainly by the right atrium and right ventricle.
- **Diaphragmatic Surface (Inferior)**
  - formed mainly by the right and left ventricles and the inferior surface of the right atrium into which the IVC opens.
- **Apex of the Heart**
  - formed by the left ventricle, is directed downward, forward, and to the left.
  - It lies at the level of the fifth) left intercostals space, 3 ½ inches (9 cm) from the midline.

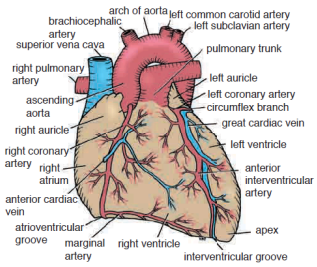


FIGURE 3.34 The anterior surface of the heart and the great blood vessels. Note the course of the coronary arteries and the cardiac veins.

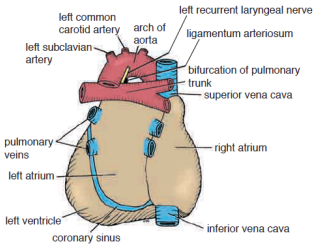


FIGURE 3.35 The posterior surface, or the base, of the heart.

BORDERS

- **Superior Border**
  - Formed by the roots of the great blood vessels, extend from a point on the second left costal cartilage ½ inch (1.3 cm) from the edge of the sternum to a point on the third right costal cartilage ½ inch (1.3 cm) from the edge of the sternum.
- **Left Border**
  - formed by the left ventricle, extends from a point on the second left costal cartilage ½ inch (1.3 cm) from the edge of the sternum to the apex of the heart.
- **Inferior Border**
  - formed by the right ventricle and the apical part of the left ventricle, extends from the sixth-costal cartilage ½ inch (1.3 cm) from the sternum to the apex

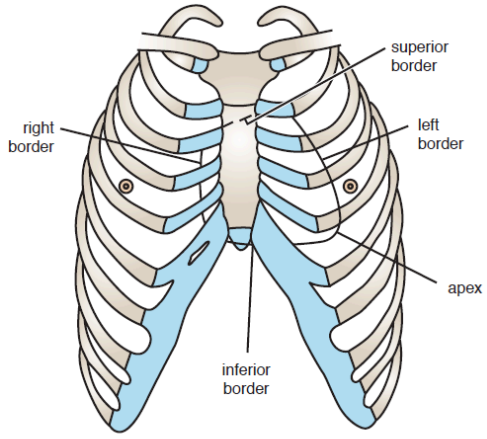


FIGURE 2.26 Surface markings of the heart.

CHAMBERS OF THE HEART

MAIN CHAMBERS

- Right and Left Atrium
- Right and Left Ventricle

ANATOMICAL FEATURES OF THE MAIN CHAMBERS

Right Atrium

- **Auricle**
  - a small outpouching, conical in shape, presents at the internal surface muscular ridges called musculi pectinati which end behind on a smooth vertical ridge - crista terminalis which is indicated externally as sulcus terminalis.
- **Sinus Venosus**
  - principal cavity situated posteriorly
  - **Fossa Ovalis**
    - located on the atrial septum
    - a shallow depression which is the remnant of the foramen ovale
- **Openings in the right atrium:**
  - SVC (Superior Vena Cava)
    - opens in the upper part, no valve
  - IVC (inferior Vena Cava)
    - opens in the lower part, guarded by eustachian valves
  - Coronary sinus
    - opens between IVC and A-V opening, guarded by Thebesian valve.
  - Right atrio-ventricular opening
    - lies anterior to IVC opening, guarded by tricuspid valve
  - Many small orifices of veins

Left Atrium

- Similar to right atrium, smaller in size, thicker wall, longer narrow auricle.
- Openings:
  - 4 pulmonary veins, no valves
  - Left AV opening guarded by mitral valve

Right and Left Ventricles

- Trabeculae carnae
  - muscular bundles in the internal ventricular wall.
- Papillary muscles
  - conical projections whose bases are attached to the ventricular wall.
- Chordae tendinae
  - fibrous chords extending from the apices of the papillary muscles to the cusps of the tricuspid and mitral valves.
- Right Ventricle:
  - Moderator band
    - attached to the ventricular wall at their ends
  - Infundibulum
    - Funnel shaped structure below the pulmonary orifice.
  - Openings:
    - Right Atrio-ventricular opening
      - ❖ guarded by the tricuspid valve consisting of 3 cusps: anterior, septal and posterior or inferior.
    - Pulmonary
      - ❖ guarded by a pulmonary valve consisting of 3 semilunar cusps.
- Left Ventricle:
  - 3x thicker than the right so has more trabeculae carnae
    - aortic vestibule - part below the aortic orifice
    - 2 large papillary muscles
  - Openings:
    - Left atrio-ventricular
      - ❖ guarded by the mitral valve consisting posterior cusps, anterior and posterior
    - Aortic
      - ❖ guarded by aortic semilunar valves similar in structure to pulmonary valve.

SEPTUM

- Structure that divides the heart into 4 chambers
- The **atrioventricular septum** separates the atrium from the ventricles.
- The **atrial septum** separates the right and left atrium.
- The **interventricular septum** separates the right and left ventricles.

ATRIOVENTRICULAR OPENINGS

- **Right Atrium**
  - Superior vena cava (SVC)
    - opens in the upper part no valve
  - Inferior vena cava (IVC)
    - opens in the lower part, guarded by Eustachian valve.
  - Coronary sinus
    - opens between IVC and A-V opening, guarded by Thebesian valve
  - Right atrioventricular opening
    - lies anterior to IVC opening, guarded by tricuspid valve
  - Many small orifices of veins
- **Left Atrium**
  - 4 pulmonary veins, no valves
  - Left AV opening guarded by the mitral valve
- **Right Ventricle**
  - Right atrioventricular opening
    - Guarded by the tricuspid valve consisting of 3 cusps: anterior, septal, and posterior or inferior
  - Pulmonary orifice
    - Guarded by aortic semilunar valves similar in structure to pulmonary valve
- **Left Ventricle**
  - Left atrioventricular opening
    - Guarded by the mitral valve consisting of 2 cusps, anterior and posterior
  - Aortic orifice
    - Guarded by aortic semilunar valves similar in structure to pulmonary valve.

LOCATION OF VALVES

CLINICAL LOCATION

- Clinical Valve Areas
  - Areas where the different heart sounds are best heard
    - **Mitral Area:**
      - ❖ at and around the cardiac apex (over the apex of the left ventricles)
    - **Tricuspid Area:**
      - ❖ at or near the lower left sternal border (over the right ventricle)
    - **Pulmonic Area:**
      - ❖ 2nd and 3rd left interspace close to the sternum (upward along the pulmonary area)
    - **Aortic Area:**
      - ❖ 2nd right interspace (upward along the aorta)

ANATOMICAL LOCATION

- **Tricuspid Valve:**
  - Right half of the sternum opposite the 4th ICS
- **Mitral Valve:**
  - Left half of the sternum opposite 4th left costal cartilage
- **Pulmonary Valve:**
  - Medial end of the 3rd left costal cartilage and adjoining part of sternum
- **Aortic Valve:**
  - Left half of the sternum opposite the 3rd ICS

CORONARY CIRCULATION

RIGHT CORONARY ARTERY

- Arises from the anterior aortic sinus of the ascending aorta
- Runs forward between the pulmonary trunk and right auricle then descends in the right AV groove then it goes to the inferior border of the heart posteriorly to anastomose with the left coronary artery.
- Branches:
  - **Right Conus Artery**
    - supplies the anterior surface of the pulmonary conus (infundibulum of the right ventricle) and the upper part of the anterior wall of the right ventricle
  - **Anterior Ventricular Branches**
    - 2 or 3 in number, supply the anterior surface of the right ventricle
    - Marginal branch
      - ❖ the largest and runs along the lower margin of the costal surface to reach the apex.
  - **Posterior Ventricular Branches**
    - usually 2 in number
    - supply the diaphragmatic surface of the right ventricle,
  - **Posterior Interventricular (Descending) Artery**
    - runs toward the apex in the posterior interventricular groove.
    - It gives off branches to the right and left ventricles, including its inferior wall.
    - It supplies branches to the posterior part of the ventricular septum but not to the apical part.
      - ❖ A large septal branch supplies the AV node.
      - ❖ In 10% of individuals this artery (post interventricular artery) is replaced by a branch from the left coronary artery.
  - **Atrial Branches**
    - supply the anterior and lateral surfaces of the right atrium
    - One branch supplies the posterior surface of both the right and left atria.
      - ❖ The artery of the SA node supplies the node and the left and right atrla; in 35% of individuals, it arises from the left coronary artery.

LEFT CORONARY ARTERY

- Usually larger than the right coronary artery, supplies the major part of the heart, including the greater part of the left atrium, left ventricle and ventricular septum.
- It arises from the left posterior aortic sinus of the ascending aorta and passes forward between the pulmonary trunk and the left auricle, then enters the atrioventricular groove and divides into branches:
  - **Anterior Interventricular (Descending) Branch**
    - runs downward in the anterior interventricular groove to the apex of the heart and enter the posterior interventricular groove and anastomose with the terminal branches of the right coronary artery. It supplies the right and left ventricles with numerous branches that also supply the anterior part of the ventricular septum.
    - **Left diagonal artery**
      - ❖ may arise directly from the trunk of the left coronary artery.
    - **Left Conus Artery**
      - ❖ supplies the pulmonary conus.
  - **Circumflex Artery**
    - the same size as the anterior interventricular artery.
    - Winds around the left margin of the heart in the atrioventricular groove.
      - ❖ **Left Marginal Artery**
        - a large branch that supplies the left margin of the left ventricle down to the apex.
      - ❖ **Anterior Ventricular and Posterior Ventricular Branches**
        - Supply the left ventricle
      - ❖ **Atrial Branches**
        - Supply the left atrium

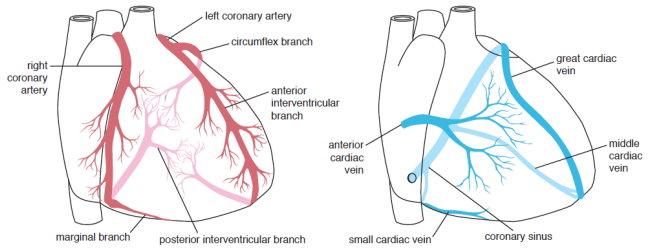


FIGURE 3.41 Coronary arteries and veins.

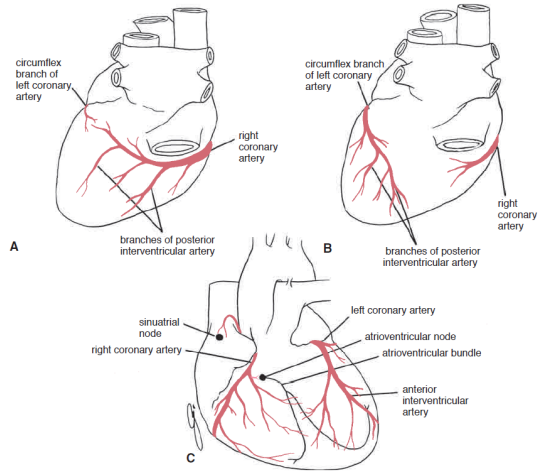


FIGURE 3.42 **A.** Posterior view of the heart showing the origin and distribution of the posterior interventricular artery in the right dominance. **B.** Posterior view of the heart showing the origin and distribution of the posterior interventricular artery in the left dominance. **C.** Anterior view of the heart showing the relationship of the blood supply to the conducting system.

SUMMARY OF OVERALL ARTERIAL SUPPLY TO THE HEART IN MOST INDIVIDUALS

The **right coronary artery** supplies all of the right ventricle (except for the small area to the right of the anterior interventricular groove), the variable part of the diaphragmatic surface of the left ventricle, the posteroinferior third of the ventricular septum, the right atrium and the part of the left atrium, and the sinoatrial node and the atrioventricular node and bundle. The LBB also receives small branches.

The left coronary artery supplies most of the left ventricle, a small area of the right ventricle to the right of the interventricular groove, the anterior two-thirds of the ventricular septum, most of the left atrium, the RBB, and the LBB.

VENOUS DRAINAGE

CORONARY SINUS

- Drains blood to the right atrium from the whole heart (including its septa) except the anterior region of the right ventricle and small, variable parts of both atria and left ventricle.
- It is about 2-3 cm long, lying posterior in the coronary sulcus (atrioventricular groove) between the left atrium and ventricle
- It opens into the right atrium between the opening of the inferior vena cava and the right atrioventricular orifice, and its opening is guarded by an endocardial fold (semilunar valve of the coronary sinus)

Tributaries:

- **Great Cardiac Vein**
  - begins at the cardiac apex, ascends in the anterior interventricular sulcus to the coronary sulcus and follows this to the left and round posterior to the heart to enter the coronary sinus at its origin. It receives tributaries from the left atrium and both ventricles, including the large left marginal vein ascending the left aspect ('obtuse border') of the heart.
- **Small Cardiac Vein**
  - lies posterior in the coronary sulcus between the right atrium and ventricle and opens into the coronary sinus near its atrial end. It receives blood from the back of the right atrium and
- **Middle Cardiac Vein**
  - beginning at the cardiac apex, it runs back in near its atrial interventricular groove to end in the coronary sinus near its atrial end.
- **Posterior Vein of the Left Ventricle**
  - found on the diaphragmatic surface of the left ventricle a little left of the middle cardiac vein
  - it usually opens into the center of the coronary sinus but sometimes into the great cardiac vein
- **Oblique Vein of the Left Atrium**
  - descends obliquely on the back of the left atrium to join the coronary sinus near its end; it is continuous above with the ligament of the left vena cava; the two structures are remnants of the left common cardinal vein.
- All veins except the oblique vein of the left atrium have valves on their orifices.

ANTERIOR CARDIAC VEIN

- Drain an anterior part of the right ventricle and a region around the right cardiac border when the right marginal vein join this group, ending principally in the right atrium.
- There are usually 2 or 3, sometimes even 5, they ascend in subepicardial tissue to cross the right part of the atrioventricular sulcus, passing deep or superficial to the right coronary artery. They end in the right atrium, near the sulcus, separately or in variable combinations.

VENAE CORDIS MINIMAE (THEBESIUS' VEINS)

- Opens into the right atrium and ventricle and, to a lesser extent, the left atrium and sometimes left ventricle.

NERVE SUPPLY OF THE HEART

- **Cardiac plexus** situated below the arch of the aorta.
  - The sympathetic supply arises from the cervical and upper thoracic portions of the sympathetic trunks.
  - The parasympathetic supply comes from the vagus nerve.
- The postganglionic sympathetic fibers terminate on the sinoatrial and atrioventricular nodes, on cardiac muscle fibers, and on the coronary arteries. Activation of these nerves result in
  - Cardiac acceleration
  - Increased force of contraction of cardiac muscle
  - Dilatation of the coronary arteries
- The postganglionic parasympathetic fibers terminate on the sinoatrial and atrioventricular nodes, cardiac muscle fibers, and on the coronary arteries. Activation of these nerves result in:
  - Reduction in the rate and force of contraction of the heart
  - Constriction of the coronary arteries

CARDIAC SKELETON

- The cardiac skeleton is a chondroid tissue that serves as a central support of the heart. It provides attachment for the cardiac muscles. It is made up of the following parts:
  - **Annuli Fibrosi**
    - firm connective tissue made up of elastic fibers found around AV openings and openings of blood vessels that spring from the heart.
  - **Trigona Fibrosa**
    - triangular fibrous tissue in between the right & the left atria.
  - **Septum Membranaceum**
    - found in the superior part of the inter-ventricular septum and connects it to the trigma fibrosa.

LAYERS OF THE WALL OF THE HEART

- Endocardium
  - Innermost layer
  - Endothelium
    - Layer of flattened cells which form a long tubule
  - Sub-endothelial Layer
    - Contains nerves and blood vessels, fibroblasts, collagen, and elastic fibers
  - Subendocardial Layer
    - Main mass of the endocardium
    - Contains Purkinje fibers

- Myocardium
    - Middle and thickest layer made up of cardiac muscle
- Epicardium
    - Outermost layer composed of mesothelium and areolar tissue. Forms the visceral layer of the pericardium

HISTOLOGIC FEATURES

CARDIAC MUSCLE

- Independent of nervous stimulation
- Long and branching with end-to-end attachment (intercalated disc)
- One nucleus at main segment
- Myofibrils in parallel bundles
- Fainter and closer cross striations

PURKINJE FIBERS

- Specialized for conduction impulses
- Bigger but shorter, more sarcoplasm but fewer myofibrils
- Cross striations are fainter
- Nuclei fewer, larger and paler

Case 1 Trigger 2: Rhythm of My Heart

DEFINITION OF TERMS

- **Action Potential**
  - A property of excitable cells (nerve, muscle) consisting of rapid depolarization followed by repolarization of the membrane potential.
  - Action potentials have stereotypical size and shape, are propagating, and are "all-or-none".
- **Depolarization**
  - Makes the membrane potential less negative,
  - Hyperpolarization makes the membrane potential more negative.
- **Inward Current**
  - The flow of positive charge ion into the cell.
  - Inward currents depolarize the membrane potential.
- **Outward Current**
  - The flow of positive charge out of the cell.
  - It hyperpolarizes the membrane potential
- **Threshold Potential**
  - The membrane potential at which occurrence of the action potential is inevitable.
  - Inward currents depolarize the membrane to threshold.
  - Subthreshold inward currents do not bring the membrane to threshold and do not produce an action potential.
- The resting membrane potential is determined by the conductance of K and approaches the K^+ equilibrium potential.
- Inward current brings positive charge into the cell and depolarizes the membrane potential.
- Outward current takes positive charge out of the cell and hyperpolarizes the membrane potential.
- The role of the Na^+-K^+ adenosine triphosphatase (Na-K ATPase) is to maintain ion gradients across the cell membrane.

RESTING MEMBRANE POTENTIAL

- It is the measured potential difference across the cell membrane in millivolts (mV).
- It is the intracellular potential relative to the extracellular potential.
- A resting membrane potential of -70 mV means 70 mV, cell negative.
- It is established by diffusion potentials resulting from concentration differences of permeant ions.
- Each permeant ion attempts to drive the membrane potential towards its equilibrium potential.
- Ions with the highest permeabilities or conductances will make the greatest contributions to the resting membrane potential, and those with the lowest permeabilities will make little or no contribution.
- The Na^+-K^+ pump contributes indirectly to the resting membrane po-rentarty maintaining, across the cell membrane, the Na^+ and po. concentration gradients that then produce diffusion potentials. The direct electrogenic contribution of the pump (because it pumps $3Na^+/2K^+$) is small.

VENTRICLE, ATRIA, AND PURKINJE SYSTEM ACTION POTENTIAL

- Have stable resting membrane potentials of about -90 mV, which approaches the K^+ equilibrium potential (-85 mV).
- Action potentials are of long duration, especially in the ventricle, with duration of 300 msec.

Phase 0

- is the upstroke of the action potential.
- is caused by a transient increase in Na^+ conductance. This increase results in an inward Na^+ current that depolarizes the membrane.
- At the peak of the action potential, the membrane potential approaches the equilibrium potential for Na (+65 mV).

Phase 1

- is a brief period of initial repolarization
- initial repolarization is caused by an outward current, in part because of K^+ ions moving out of the cell (favored by both chemical and electrical gradients) and in part because of a decrease in Na^+ conductance.

Phase 2

- is the plateau of the action potential.
- current and an increase in K^+ conductance.
- During the plateau, outward and inward currents are approximately equal, so the membrane potential is stable at the plateau level

Phase 3

- is repolarization.
- During this phase, Ca^{2+} conductance decrease, but K^+ conductance increases and therefore predominates.
- The high K^+ conductance results in a large outward K^+ current which hyperpolarizes the membrane back toward the K^+ equilibrium potential.

Phase 4

- is the resting membrane potential

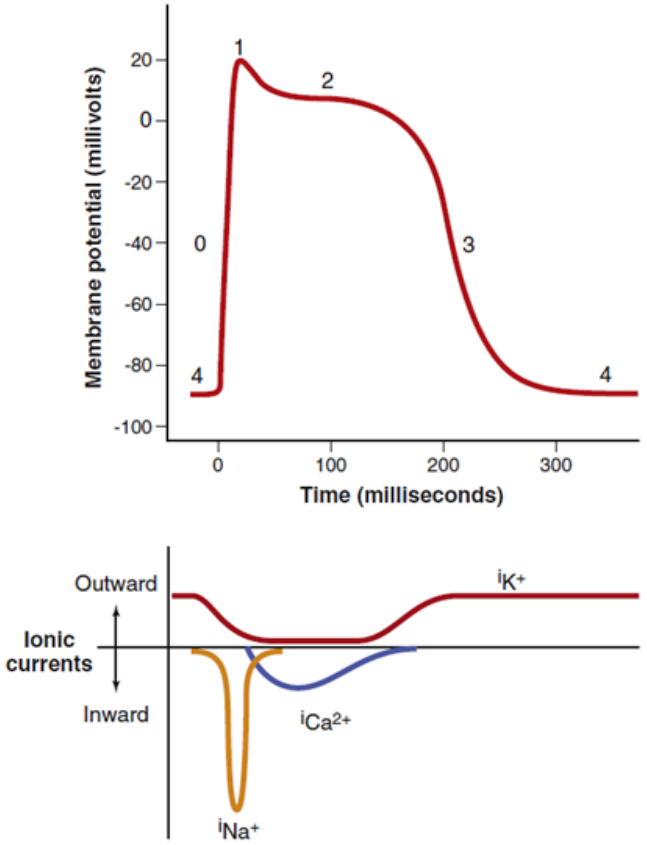


Figure 9-5. Phases of action potential of cardiac ventricular muscle cell and associated ionic currents for sodium ($^iNa^+$), calcium ($^iCa^{2+}$), and potassium ($^iK^+$).

SINOATRIAL (SA) NODE ACTION POTENTIAL

- Is normally the pacemaker of the heart
- Does not have a constant resting potential
- Exhibits phase 4 depolarization or automaticity
- The intrinsic rate of phase 4 depolarization (and heart rate) is the fastest in the SA node. Slower in the AV node & slowest Purkinje system

Phase 0

- is the upstroke of the action potential.
- is caused by a transient increase in Ca^{2+} conductance. This increase results in an inward Ca^{2+} current that drives the membrane potential toward the Ca^{2+} equilibrium potential (+120mV)
- the ionic bases for phase 0 is different from that in the ventricle

Phase 3

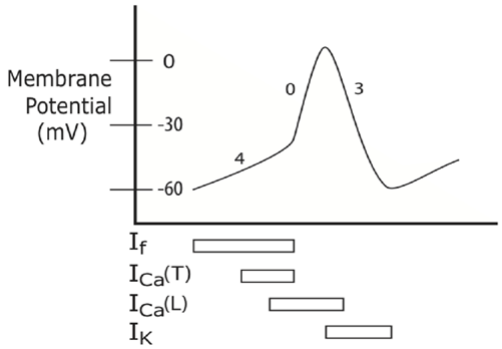
- is repolarization
- is caused by an increase in K^+ conductance. This increase results in an outward K^+ current that causes repolarization of the membrane potential

Phase 4

- is the slow depolarization
- accounts for the pacemaker activity of the SA node (automaticity)
- is caused by an increase in Na^+ conductance, which results in an inward Na^+ current called If
- If is turned on by repolarization of membrane during the preceding action potential

Phase 1 and 2

- are not present in the SA node action potential



FOUR MAJOR TIME-DEPENDENT AND VOLTAGE-GATED MEMBRANE CURRENTS

- **Na+ current (INa)**
  - Responsible for the rapid depolarizing phase of the action potential in atrial and ventricular muscle and in Purkinje fibers
- **Ca2+ current (ICa)**
  - Responsible for the rapid depolarizing phase of the action potential in the SA node and AV node
  - Also triggers contraction in all cardiomyocytes
- **K+ current (Ik)**
  - Responsible for the repolarizing phase of the action potential in all cardiomyocytes
- **Pacemaker current (If)**
  - Responsible, in part for pacemaker activity in Sa nodal cells, AV nodal cells, and Purkinje fibers

REFRACTORY PERIOD

- The interval of time during which a normal cardiac impulse cannot re-excite an already excited are of cardiac muscle

ABSOLUTE REFRACTORY PERIOD (ARP)

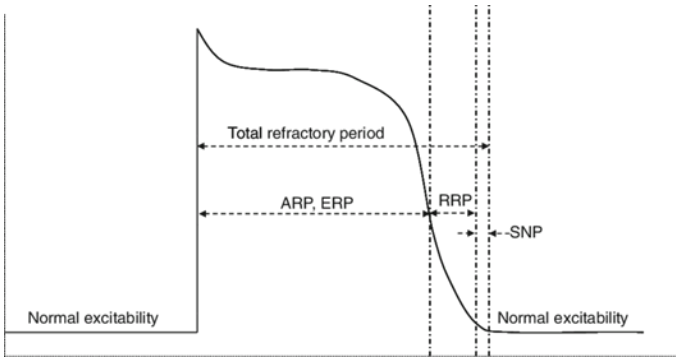
- Lasts from initiation of the spike to a time after the peak when repolarization is almost complete
- Constitute that period during which the membrane cannot be re excited by an outside stimulus, regardless fo the level of external voltage applied

EFFECTIVE REFRACTORY PERIOD (ERP)

- Constitute that period which only a local response can be produced by a larger than normal depolarizing stimulus
- During this period, the membrane can respond, but a propagated action potential that will carry the impulse throughout the cell network cannot be generated

RELATIVE REFRACTORY PERIOD (RRP)

- The muscle is more difficult than normal to excite but nevertheless can be excited by a very strong excitatory signal
- Stronger than normal stimulus can cause excitation
- A second action potential can be evoked during this period but the minimal stimulus necessary for activation is stronger or longer
- Commences/begins at the end or after/near the end of the absolute refractory period and constitute that time interval late in the action potential during which a propagated action potential can be generated but with a depolarizing stimulus that is larger than normal



FAST RESPONSE ACTION POTENTIAL VS SLOW RESPONSE ACTION POTENTIAL

- Fast response action potential - caused almost entirely by sudden opening of large numbers of so-called fast sodium channels that allow tremendous numbers of sodium ions to enter the cardiac muscle fiber. These channels are called "fast" channels because they remain open only for a few 10,000ths of a second and then abruptly close. At the end of this closure. repolarization occurs, and the action potential is over within another 10,000ths of a second.
- Slow response action potential — caused by an entirely different population of slow calcium channels, also called calcium—sodium channels which are slower to open and remain open for several tenths of a second. During this time a large quantity of both calcium and sodium ions flow through these channels to the interior of the cardiac muscle fiber, and this maintains a prolonged period of depolarization, causing the plateau in the action potential.

COMPONENTS OF THE IMPULSE CONDUCTING SYSTEM

SINOATRIAL NODE

- located in the superior posterolateral wall of the right atrium immediately below and slightly lateral to the opening of the SVC.

INTERNODAL PATHWAY

- 3 bundles of atrial fibers that contain Purkinje type fibers and connect the SA node to the AV node.
  1. Anterior internodal pathway (Anterior Internodal Tract of Bachman)
     - leaves the anterior end of the SA node and passes anterior to the superior vena caval opening. It descends on the atrial septum and ends in the AV node.
  2. Middle Internodal Pathway (Middle Internodal Tract of Wenkeback)
     - leaves the posterior end of the SA node and passes posterior to the superior vena caval opening. It descends on the atrial septum of the AV node.
  3. Posterior Internodal Pathway (Posterior Internodal Tract of Thorel)
     - leaves the posterior part of the SA node and descends through the crista terminalis and the valve of the inferior vena cava to the AV node.

ATRIOVENTRICULAR NODE

- located in the posterior wall of the right atrium immediately behind the tricuspid valve and adjacent to the opening of the coronary sinus.

AV BUNDLE (BUNDLE OF HIS)

- the only pathway of cardiac muscle that connects the myocardium of the atria and the myocardium of the ventricle and is the only route along which the cardiac impulse can travel from the atria to the ventricles.
- **Right Bundle Branch**
  - passes down on the right side of the ventricular septum to reach the moderator band, where it crosses the anterior wall of the right ventricle. Here it becomes continuous with the fibers of the Purkinje plexus.

- **Left Bundle Branch**
  - Pierces the septum and passes down on its left side beneath the endocardium.
  - It usually divides into 2 branches (anterior and posterior), which eventually become continuous with the fibers of the Purkinje plexus of the left ventricle

PURKINJE FIBERS

- Spreads to all parts of the ventricular myocardium

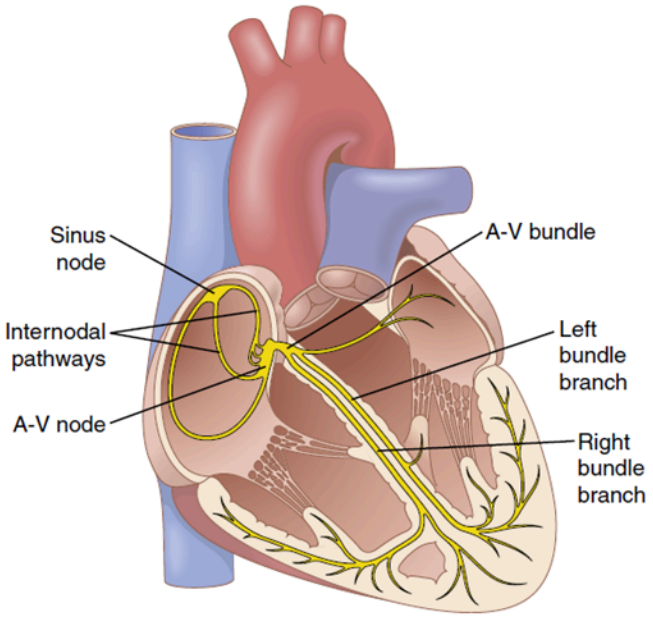


Figure 10-1 Sinus node and the Purkinje system of the heart, showing also the atrioventricular (A-V) node, atrial internodal pathways, and ventricular bundle branches.

SPECIALIZED CONDUCTING TISSUES AND THE ELECTROPHYSIOLOGIC EXPLANATION FOR CONDUCTION OF ACTION POTENTIAL

1. SA Node	• Is a small flattened, ellipsoid strip of specialized muscle about 3 mm wide, 15 mm long, and 1 mm thick • The fibers have almost no contractile filaments • Displays self-excitation to the greatest extent, so it controls the rate of the beat of the entire heart • The inherent leakiness of the sinus nodal fibers to sodium ions causes their self-excitation • The interaction among three time-dependent and voltage-gated membrane currents controls the intrinsic- rhythmicity of the SA node.
2. AV Node	• Has a well-formed compact zone made up of interlocking nodal cells which frequently show cell zones. Superficially and posteriorly are found in the transitional cell zones. • Delay the transmission of cardiac impulse from the atria into the ventricles. This delay allows time for the atria to empty their blood into the ventricles before ventricular contraction begins. • Like the SA node, the intrinsic rhythmicity of the AV. node depends. on. the interaction of three time-dependent and voltage-gated currents: IK, ICa, and If.

3. AV Bundles	• Conduction is extremely slow which is caused by:
	  ○ Partly due to their sizes which are smaller than the sizes of normal atrial muscle fibers.
	  ○ Diminished numbers. of gap junctions between the successive muscle cells in the conducting pathway, so that there is great resistance to conduction of excitatory ons from one cell to the next
	• One-way conduction
	• A special characteristic is the inability, except in abnormal states, of action potentials to travel backward in the bundle from the ventricles to the atria. This prevents re-entry of cardiac impulses by this route from the ventricles to the atria, allowing only forward conduction from the atria to the ventricles.

4. Purkinje Fibers	• Are very large fibers, even.larger than the normal ventricular muscle fibers and they transmit action potentials at a velocity of 1.5 to 4.0 m/sec, a velocity about 6x.that in usual ventricular muscle and 150x that in some of the AV nodal fibers. Allows immediate transmission of the cardiac impulse throughout the entire remainder of the ventricular muscle. • The rapid transmission of action potentials is caused by a very high level of permeability. of the gap junction at the intercalated disc between the successive cardiac cells that make up.the Purkinje fibers • Have very few myofibrils, meaning they barely contract during the course of impulse transmission

PACEMAKER VS LATENT PACEMAKER

- **Pacemaker Tissue**
  - makes up the conduction system that normally spreads impulses throughout the heart.
  - It is characterized by an unstable membrane potential that slowly decreases after each impulse until the firing level is reached and another impulse is generated
- **Latent Pacemaker**
  - can take over when the SA and AV nodes are depressed or conduction from them is blocked.
  - Atrial and ventricular muscle fiber do not have pre potentials, and they discharge spontaneously only when injured or abnormal

AUTOMATICITY & RHYTHMICITY

- **Automaticity**
  - Is the ability of the heart muscle to contract independently of external stimulus or to generate an impulse spontaneously, best seen in nodal tissues. This is due to the "inner stimulus" (concentration of ions in the heart muscles)
  - Ability of the heart to initiate its own beat
- **Cardiac Rhythmicity**
  - The spontaneous depolarization and repolarization event that occurs in a repetitive and stable manner within the cardiac muscle.
  - Regularity of the pacemaker activity of the heart

MECHANISM OF AUTOMATICITY AND RHYTHMICITY EXHIBITED BY PACEMAKER TISSUE

- Some cardiac fibers have the capability of self-excitation, a process that can cause automatic rhythmical discharge and contraction. This is especially true of the fibers of the heart's specialized conducting system. The portion of this system that displays self-excitation to the greatest extent including the fibers of the sinus node.

- The resting membrane potential of the sinus nodal fiber between discharges has a maximum negativity of only -55 to -60 millivolts in comparison with -85 to -90 millivolts for the ventricular muscle fiber.
- The cause of this lesser negativity is that the cell membrane of the sinus fibers are naturally leaky to sodium ions, and the positive charges of the entering sodium ions neutralize much of the intracellular negativity.
- In the cardiac muscles, three types of membrane ion channels play important roles in causing the voltage charges of the action potential. They are:
  - (1) fast sodium channels,
  - (2) slow calcium-sodium channels, and
  - (3) potassium channels
- Opening of the fast sodium channel for a few 10,000ths of a second is responsible for the rapid upstroke spike of the action potential observed in ventricular muscle, because of rapid influx of positive sodium ions into the interior of the fiber.
- Then the plateau of the ventricular action potential is caused primarily by slower opening of the slow calcium-sodium channels which lasts for about 1/10 of a second.
- Finally, increased opening of the potassium channels allows diffusion of large amounts of positive potassium ions outward from the inside of the fiber and returns the membrane potential to its resting level.

SA NODE AS THE PRIMARY PACEMAKER OF THE HEART

- The discharge rate of the sinus node is considerably faster than the natural self-excitatory discharge rate of either the AV node or the Purkinje fibers.
- Each time the sinus node discharges, its impulse is conducted into both the AV node and the Purkinje fibers, discharging their excitable membranes.
- Then these tissues as well as the sinus node recover from the action potential and start over nearly at the same time.
- But the sinus node discharges again much more rapidly than does either of the two and emits a new impulse before either the AV node or the Purkinje fibers can reach their own threshold for self-excitation.
- The new impulse from the sinus node again discharges both the AV node and the Purkinje fibers. Thus, the sinus node controls the heart beat because its rate of rhythmical discharge is greater than that of any other part of the heart.

SECONDARY PACEMAKERS

- Atria = 60/min
- AV Node = 40-60/min
- Purkinje fibers = 15-40/min
- Penetrating portions of AV Bundle
- Ventricles = 20-40/min

FACTORS AFFECTING IMPULSE DISCHARGES OF THE SA NODE

AUTONOMIC NERVOUS SYSTEM

Parasympathetic	Sympathetic

• Stimulation of the right vagus slows the heart by inhibiting the SA node, whereas stimulation of the left vagus mainly slows AV conduction.
• Stimulation of the right stellate ganglion accelerates the heart, whereas stimulation of the left stellate ganglion shortens the AV nodal conduction time and refractoriness.
• **Effects of acetylcholine on the heart:**
  ○ Decrease the rate of rhythm of the SA node.
  ○ Decrease the excitability of the AV junctional fibers between the atrial musculature and the AV node thereby slowing transmission of the cardiac impulse into the ventricles
• **Mechanism vagal effect:**
  ○ Acetylcholine released at the vagal nerve endings greatly increases the permeability of the fiber membrane to K^+, which allows rapid leakage of K out of the conductive fibers. This causes hyperpolarization, which makes this excitable tissue much less excitable.
	• Increases the rate of sinus nodal discharge.
	• Increases the rate of conduction as well as the level of excitability in all portions of the heart.
	• Increases greatly the force of contraction of all the cardiac musculature, both atrial and ventricular.
	• Sympathetic stimulation increases the overall activity of the heart.
	• **Mechanism of sympathetic effect:**
	  ○ Norepinephrine released at the sympathetic nerve endings increases the permeability of the fiber membrane to Na+ and Ca2+ ions.
	  ○ In the sinus node, an increase of Na^+ permeability causes more action potential to occur because threshold potential is reached more quickly, thus heart rate increases.
	  ○ In the AV node, an increased Na^+ permeability, increases conduction velocity. Action potentials are conducted more quickly from atria to ventricles.
	  ○ The increase in permeability to Ca^{2+} ions is at least partly responsible for the increase in contractile strength of the cardiac muscle under the influence of sympathetic stimulation because Ca^{2+} ions play a powerful role in exciting the contractile process of the myofibrils.

CHANGES IN IONIC CONCENTRATION

- The action potential in the SA & AV nodes are largely due to Ca2+ with little contributions by Na+ influx.
- There is no sharp, rapid depolarizing spike before the plateau, as there is in other parts of the conduction system.
- Prepotentials are normally prominent only in SA & AV nodes.

TEMPERATURE

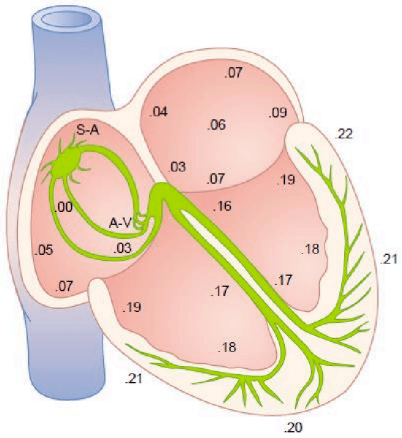
- Discharge frequency of the SA node is increased when the temperature rises, and this may contribute to the tachycardia associated with fever.

DRUG

- Digitalis depresses nodal tissue & exerts an effect like that of vagal stimulation, particularly on the AV node.

NORMAL PATHWAY OF CARDIAC IMPULSE

- Normal rhythmical impulse is generated in SA node → internodal pathways conduct the impulse from the SA node to the AV node → AV node in which the impulse from the atria is delayed before passing into the ventricles → AV bundle which conducts the impulse from atria into the ventricles → left & right bundles of Purkinje fibers which conduct the cardiac impulse to all parts of the ventricles.



CONDUCTION THROUGH THE AV NODE

- The AV node is located in the posterior wall of the right atrium immediately behind the tricuspid valve and adjacent to the opening of the coronary sinus.
- The impulse, after traveling through the internodal pathways, reaches the AV node about 0.03 second after its origin in the sinus node.
- Then there is a delay of about 0.09 second in the AV node itself before the impulse enters the penetrating portion of the AV bundle, where it passes into the ventricles.

TRANSMISSION OF CARDIAC IMPULSE IN THE VENTRICULAR MUSCLE

- Once the impulse reaches the ends of the Purkinje fibers, it is transmitted through the ventricular muscle mass by the ventricular muscle fibers themselves. The velocity of transmission is now only 0.3 -0.5-m/sec., one sixth than in the Purkinje fibers
- The cardiac muscle wraps around the heart in a double spiral with fibrous septa between the spiraling layers; therefore the cardiac impulse does not necessarily travel directly outward the surface of the heart but instead angulates toward the surface along the directions of the spirals.
- Because of this, transmission from the endocardial surface to the epicardial surface of the ventricle requires as much as another 0.03 sec. approximately equal to the time required for transmission through the entire ventricular portion of the Purkinje system

ELECTROCARDIOGRAM

- **Electrocardiogram (ECG)**
  - is a graphic recording of electric potential generated by the heart.
- **Einthoven's triangle**
  - a triangle with the heart at its center, can be approximated by placing electrodes on both arms and on the left leg.

EINTHOVEN'S LAW

- Einthoven's law states that if the electrical potentials of any two of the three bipolar limb leads are known at any given instant, the third one can be determined mathematically from the first two by simply summing the first two but note that the positive and negative signs of the different leads must be observed when making the summation.
- Example:
  - Lead I: (4) 0.5 mV (millivolts)
  - Lead III: (+) 0.7 mV
  - Lead II: (+) 0.5 + (+) 0.7 = (+) 1.2 mV

DIFFERENT LEADS AND THEIR ELECTRODE PLACEMENT

Bipolar Limb Leads	• Lead I - left arm positive (+) terminal and right arm negative (-) terminal • Lead II - left leg positive (+) and right arm negative- (-) • Lead III - left leg positive (+) and left arm negative (-)
Unipolar Limb Leads	• aVR- right arm (RA) electrode (+) • aVL - left arm (LA) electrode (+) • aVF - left leg (LL) electrode (+)
Chest leads (Precordial leads)	• V_1 - 4th intercostal space, right sternal border • V_2 - 4th intercostal space, left sternal border • V_3 - midway between V_2 and V_4 • V_4 - 5th ICS, left midclavicular line • V_5 - left anterior axillary line at the same horizontal level as V_4 • V_6 - 5th ICS, left mid axillary line at the same horizontal level as V_4 and V_5

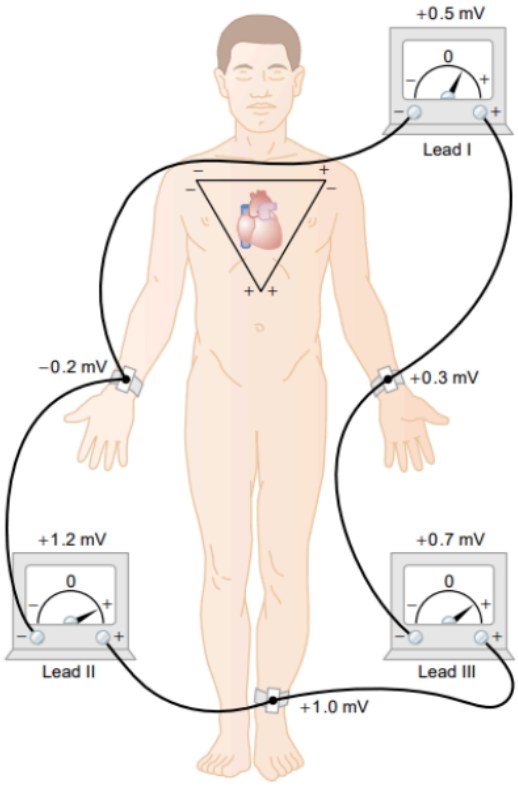


Figure 11–6

Conventional arrangement of electrodes for recording the standard electrocardiographic leads. Einthoven's triangle is superimposed on the chest.

COMPONENTS OF THE NORMAL ECG AND ITS ELECTROPHYSIOLOGIC BASIS

- **P Wave**
  - Represents depolarization of atrial muscle.
  - Does not include atrial repolarization, which is "buried in the QRS complex."
  - Location: precedes the QRS complex
  - Amplitude: 2 - 3 mm High
  - Duration: 0.06 - 0.12 second
  - Configuration: usually rounded and upright
  - Deflection: positive or upright in leads I, II, aVf, and V2 to V6; usually positive but may vary in leads III and aVL; negative or inverted in lead aVR: biphasic or variable in lead V1.
- **PR Interval**
  - Is the interval from the first atrial depolarization to the beginning of the Q wave (initial depolarization of the ventricle)
  - Increases if conduction velocity through the AV node is slowed (as in heart block)
  - When the heart rate increases, the PR interval decreases
  - Location: from the beginning of the P wave to the beginning of the QRS complex
  - Duration: 0.12 - 0.20 second
- **QRS Complex**
  - Represents depolarization of the ventricle.
  - Location: follows the PR interval
  - Amplitude: 5 - 30 mm High, but differs for each lead used
  - Duration: 0.06 - 0.10 second or half of the PR interval
  - Configuration: consists of the Q wave (the first negative deflection, or deflection below the baseline, after the P wave), the R wave (the first positive deflection after the Q wave) and the S wave (the first negative deflection after the R wave). All 3 waves may not always be seen in the ECG.
  - Deflection: positive (with most of the complex above the baseline) in leads I, II, III, aVL, AvF, and V4 to V6, negative in leads aVr and V1 to V2, and biphasic in lead V3.

- **QT Interval**
  - Measures the time needed for ventricular depolarization and repolarization
  - Its length varies according to heart rate
  - Location: extends from the beginning of the Q wave to the end of the T wave
  - Duration: varies according to age, gender, and heart rate; usually lasts from 0.36 - 0.44 second; shouldn't be greater than half the distance between the two consecutive R wave (called the R-R interval) when the rhythm is regular.
- **ST Segment**
  - Represents the end of ventricular conduction or depolarization and the beginning of ventricular recovery or repolarization
  - Location: extends from the end of the S wave to the beginning of the T wave
  - Deflection: usually isoelectric or on the baseline (neither positive nor negative); may vary from -0.5 to 1 mm in some precordial leads
- **T Wave**
  - Represents the relative refractory period of repolarization or ventricular recovery (ventricular repolarization)
  - Location: follows the ST segment
  - Amplitude: 0.5 mm in leads I, II, and III and up to 10 mm in the precordial leads
  - Configuration: typically rounded and smooth
  - Deflection: usually positive or upright in leads I, II, and V2 to V6; inverted in lead aVR; variable in leads III and V1.

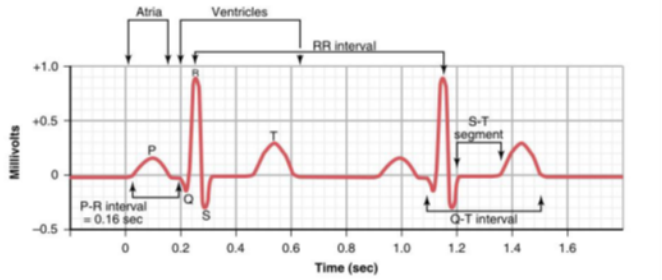


Figure 11-1 Normal electrocardiogram.

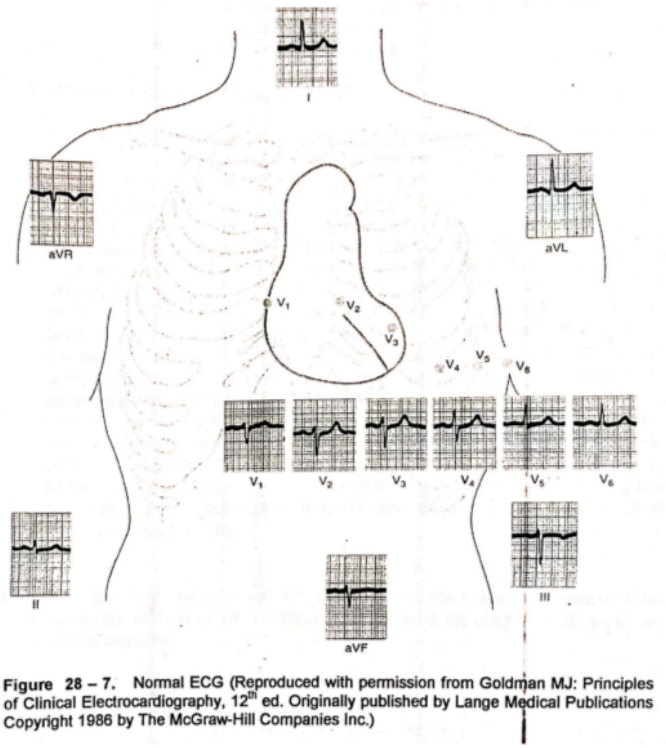


Figure 28 – 7. Normal ECG (Reproduced with permission from Goldman MJ: Principles of Clinical Electrocardiography, 12th ed. Originally published by Lange Medical Publications Copyright 1986 by The McGraw-Hill Companies Inc.)

THE CARDIAC MUSCLE

- The cardiac muscle fibers are made up of many individual cells connected in series with one another, through the intercalated discs.
- The electrical resistance through the intercalated discs is only 1/400.
- The resistance through the outside membrane of the cardiac muscle fiber because the membranes fuse with one another in such a way that they form permeable “communicating” junctions (gap junctions) that allow almost totally free diffusion of ions.
- Therefore, ions move with ease in the intracellular fluid along the longitudinal axis of the cardiac muscle fibers, so that action potentials travel from one cardiac muscle cell to the next, part the intercalated discs with negligible hindrance.
- Thus, cardiac muscle is a syncytium of many heart muscle cells, in which cardiac cells are so interconnected that when one of these cells becomes excited, the action potential spreads to all of them from cell to cell throughout the latticework interconnection.

“ALL OR NONE” RESPONSE OF THE CARDIAC MUSCLE

- Cardiac muscle response is “all or none".
- Once an action potential has been elicited at any point on the membrane of a normal fiber, the depolarization process travels over the entire membrane if conditions are right, or it might not travel at all if conditions are not right.
- This is called the all-or-nothing principle and it applies to all normal excitable tissues. For continued propagation of an impulse to occur; the ratio of action potential to threshold for excitation must at all times be greater than one. This "greater than 1" requirement is called the safety factor for propagation.

Case 2: Flow of the Heart

Block 4 Module 2

CARDIAC CYCLE

- Are the events that occur from the beginning of one heartbeat to the beginning of the next.
- It consists of a period of relaxation called diastole, during which the heart fills with blood, followed by a period of contraction called systole.

PHASES OF THE CARDIAC CYCLE

1. Atrial Systole	• Is preceded by the P wave • Contributes to, but is not essential for ventricular filling. • The increase in atrial pressure (venous pressure) caused by atrial systole is the A wave in venous pulse. • Filling the ventricle by atrial systole causes the fourth heart sound (S4), which is not audible in normal adults.
2. Isovolumetric Ventricular Contraction	• Begins after the onset of the QRS wave • When ventricular pressure becomes greater than atrial pressure, the atrio-ventricular valves (tricuspid and mitral valves) close ○ Their closure corresponds to the first heart sound (S1). • Because the mitral valve close before the tricuspid valve, the first heart sound may be split. • Ventricular pressure rises isovolumetrically as a result of contraction, but no blood leaves the ventricle because the aortic valve is closed.
3. Rapid Ventricular Ejection	• Ventricular pressure reaches its maximum value. • When ventricular pressure becomes greater than aortic. pressure, the aortic valve opens. • There is rapid ejection of blood into the aorta due to the pressure gradient between the ventricle and the aorta. • Ventricular volume decreases dramatically since most of the stroke volume is ejected during this phase. • Atrial filling begins. • The onset of the T wave marks the end of the contraction and the end of rapid ventricular ejection
4. Reduced Ventricular Ejection	• Ejection of blood from the ventricle continues but is slower. • Ventricular pressure begins to fall. • Aortic pressure also falls because run-off of blood from large arteries into smaller arteries is faster than the flow of blood from the ventricle into the aorta. • Atrial filling continues.
5. Isovolumetric Ventricular Relaxation	• Repolarization of the ventricle is complete (the T wave) • The aortic valve closes, followed by closure of the pulmonic valve; • Closure of the semilunar valves (aortic and pulmonic valves) corresponds to the second heart sound (S2). ○ Inspiration causes splitting of S2. • The atrio-ventricular (AV) valves remain closed. • Ventricular pressure falls rapidly since the ventricle is now relaxed, and ventricular volume is constant because all valves are closed. • The "blip" in the aortic pressure tracing occurs following closure of the aortic valve and is called the dicrotic notch, or incisura.
6. Rapid Ventricular Filling	• When ventricular pressure falls below atrial pressure the mitral valve opens and the left ventricle begins to fill. • Aortic pressure continues to fall because blood continues to run off into the smaller arteries. • Rapid flow of blood from the atria into the ventricles cause the third heart sound (S3), which is normal in children but in adults are associated with disease.
7. Reduced Ventricular Filling (Diastasis)	• Ventricular filling continues but at a slower rate. • The time for diastasis depends upon heart rate; ○ Increased heart rate decreases the time for ventricular filling.

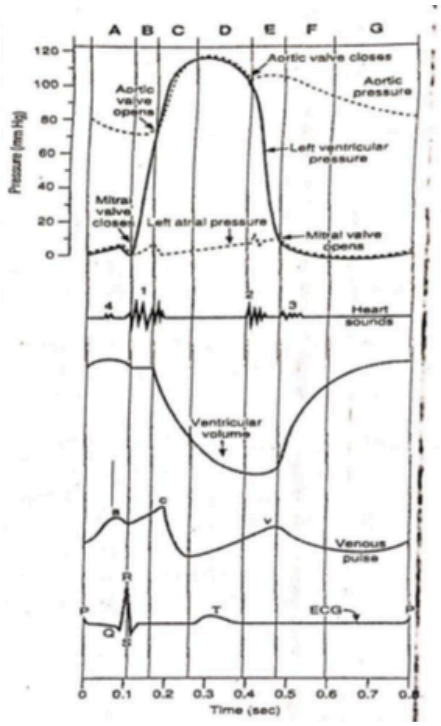


Figure 3 –12. The cardiac cycle. *A* = atrial systole; *B* = isovolumetric ventricular contraction; *C* = rapid ventricular filling; *D* = reduced ventricular ejection; *E* = isovolumetric ventricular relaxation; *F* = rapid ventricular filling; *G* = reduced ventricular filling.

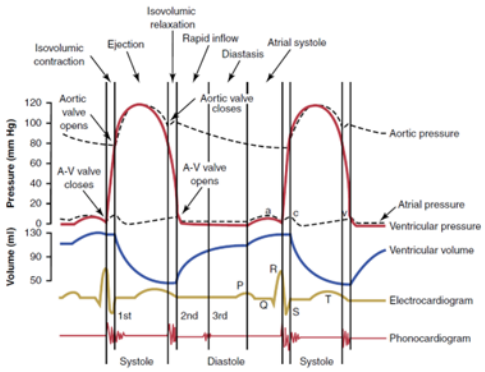


Figure 9-8. Events of the cardiac cycle for left ventricular function, showing changes in left atrial pressure, left ventricular pressure, aortic pressure, ventricular volume, the electrocardiogram, and the phonocardiogram. A-V, Atrioventricular.

MECHANISM OF THE ATRIAL PRESSURE CHANGES AND THE JUGULAR PRESSURE

- Atrial pressure rises during atrial systole and continues to rise during isovolumetric ventricular contraction when the AV valves are pulled down by the contracting ventricular muscle, pressure falls rapidly and then rises as blood flows into the atria until the AV valves open early in diastole.
- The return of the AV valves to their relaxed position also contributes to this pressure by reducing atrial capacity.
- Atrial pressure changes are transmitted to the great veins, producing three characteristic waves in the record of jugular pressure:

1. A wave	• Due to atrial systole. • Some blood regurgitates into the great veins when the atria contract, even though the orifices of the great veins are constricted. • In addition, venous inflow stops, and the resultant rise in venous pressure contributes to the a wave
2. C wave	• Is the transmitted manifestation of the rise in atrial pressure produced by bulging the tricuspid valve into the atria during isovolumetric ventricular contraction.
3. V wave	• Mirrors the rise in atrial pressure before the tricuspid valve opens during diastole.

HEART SOUNDS

1. First heart sound (S1)	• Is a low slightly prolonged "lub", caused by vibration set up by the sudden closure of the mitral and tricuspid valve at the start of ventricular systole. • Normally heard over the entire precordium • S1 is usually louder than S2 at the cardiac apex (left 5th ICS near the midclavicular line) • It is usually fainter than S2 at the base of the heart • It marks the beginning of ventricular systole
2. Second heart sound (S2)	• Is a shorter, high-pitched "dup", caused by vibrations associated with closure of the aortic and pulmonary valves just after the end of ventricular systole. • The aortic valve component (A2) precedes the pulmonic component (P2). • S2 best heard in the medial end of 2nd right ICS while P2 is best heard in the medial end of 2nd left ICS • It is usually louder than S1 at the base of the heart
3. Third heart sound (S3)	• Soft, low-pitched heart about one-third of the way through diastole in many normal young individuals. • It coincides with the period of rapid ventricular filling and is probably due to vibrations set up by the in rush of blood.
4. Fourth heart sound (S4)	• Sometimes heard immediately before (S1) when atrial pressure is high. • It is due to ventricular filling and is rarely heard in normal adults.

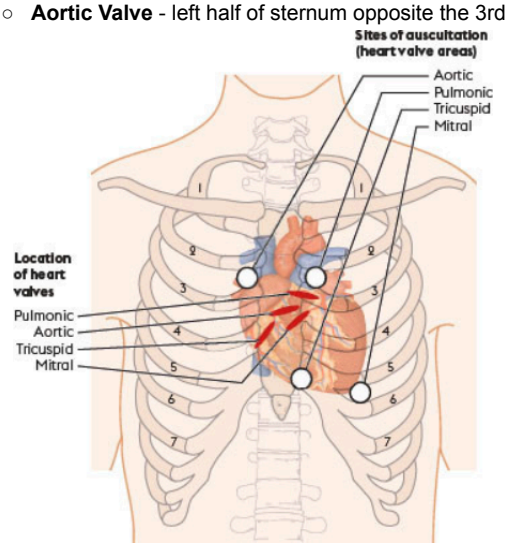
LOCATION OF VALVE AREAS

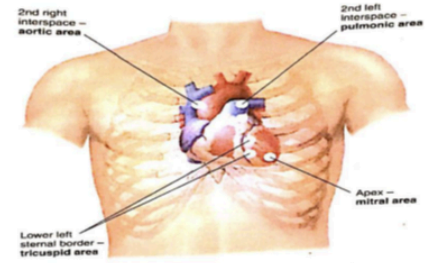
CLINICAL VALVE AREAS

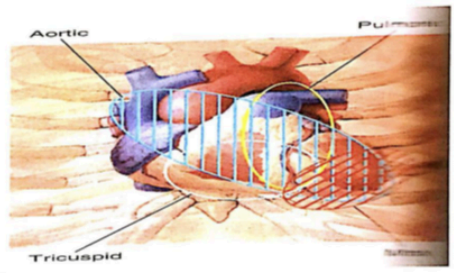
- Clinical valve areas - areas where the different heart sounds are best heard.
  - **Mitral Area** - at and around the cardiac apex (over the apex of the left ventricles)
  - **Tricuspid Area** - at or near the lower left sternal border (over the right ventricle)
  - **Pulmonic Area** - 2nd and 3rd left interspaces close to the sternum (upward along the pulmonary areas
  - **Aortic Area** - 2nd right interspace (upward along the aorta)

CLINICAL VALVE AREAS

- lies behind:
  - **Tricuspid Valve** - right half of sternum opposite the 4th ICS
  - **Mitral Valve** - left half of the sternum opposite 4th Left Costal Cartilage
  - **Pulmonary Valve** - medial end of 3rd Left Costal Cartilage and adjoining part of sternum
  - **Aortic Valve** - left half of sternum opposite the 3rd ICS.







TERMS

- **End-Diastolic Volume**
  - Increase in volume of each ventricle to about 110-120 milliliters as a result of ventricular filling during diastole
- **End-Systolic Volume**
  - The remaining volume in each ventricle at the end of systole about 40-50ml
- **Stroke Volume**
  - The amount of blood pumped out of each ventricle per beat, which is about 70ml. In a resting man of average size in supine position.
- **Preload**
  - The degree of tension on the cardiac muscle when it begins to contract or the degree to which the myocardium is stretched before it contracts.
- **Afterload**
  - AKA "the resistance against which blood is expelled"
  - Load against which the cardiac muscle exerts its contractile force
- **Ejection Fraction**
  - The fraction of the end-diastolic volume that is ejected, with each stroke, which is equal to 60%.
  - It is a valuable index of ventricular function.
- **Cardiac Output**
  - The amount of blood pumped into the aorta each minute by the heart.
- **Cardiac Index**
  - The cardiac output per minute per square meter of body surface area (average 3.26)
- **Cardiac Reserve**
  - The maximum percentage that the cardiac output can increase above the normal level.
- **Cardiac Contractility**
  - The ability of the cardiac muscle to develop force at a given muscle length.
  - Is also called inotropism
  - Can be estimated by the ejection fraction (stroke volume / end- diastolic volume), which is normally 0.55 (55%).
  - The force of contraction of cardiac muscle is dependent upon its preloading and its afterloading.
  - Agents that produce a decrease in contractility have a negative inotropic

NORMAL CARDIAC OUTPUT AND REGULATION MECHANISM

- Cardiac output is the output of the heart per unit time.
- In a resting, supine man, it averages about 5.0L/min. (70ml X 72 beats/min.).
- Variations in cardiac output can be produced by changes in cardiac rate or stroke volume.
  - The cardiac rate is controlled primarily by the cardiac innervation, sympathetic stimulation increasing the rate and parasympathetic stimulation decreasing it.
  - The stroke volume is also determined in part by neural input, sympathetic stimuli making the myocardial muscle fibers contract with greater strength at any given length and parasympathetic stimuli having the opposite effect.
- The cardiac accelerator action of the catecholamines liberated by sympathetic stimulation is referred to as their chronotropic action, whereas their effect on the strength of cardiac contraction is called their inotropic action.

EFFECTS OF VARIOUS CONDITIONS ON CARDIAC OUTPUT

EFFECT	CONDITIONS
No change	• Sleep • Moderate changes in environmental temperature
Increase	• Anxiety and excitement (50-100%) • Eating (30%) • Exercise (700%) • High environmental temperature • Pregnancy • Epinephrine
Decrease	• Sitting or standing from lying position (20-30%) • Rapid arrhythmias • Heart disease

PRESSURE VOLUME RELATIONSHIPS IN BOTH THE LEFT AND RIGHT VENTRICLE

- The movements of the right and left ventricle in ejecting the blood:
  - Ventricular pressure - Volume loops
    - Are constructed by combining systolic and diastolic pressure curves.
    - The diastolic pressure curve is the relationship between the diastolic pressure and diastolic volume in the ventricle.
    - The systolic pressure curve is the corresponding relationship between systolic pressure and systolic volume in the ventricle.
    - A cycle of ventricular contraction, ejection, relaxation, and refilling can be visualized by combining the two curves into a pressure volume loop.

A. 1➞2 (Isovolumetric or Isovolumic, or Isometric Contraction)	• Begin during diastole at point 1. • The ventricle has been filled and its volume is about 140ml (end-diastolic volume). • The pressure is low because the ventricular muscle is relaxed. • Upon excitation, the ventricle contracts and ventricular pressure increases. • Because all valves are closed, no blood can be ejected from the ventricle (isovolumetric).
B. 2➞3 (Ventricular Ejection)	• The aortic valve opens at point 2 when pressure in the ventricle exceeds pressure in the aorta. • Blood is ejected into the aorta, and the ventricular volume falls. • The volume that is ejected is the stroke volume. Thus, stroke volume can be measured graphically by the width of the pressure-volume loop.
C. 3➞4 (Isovolumetric Relaxation)	• At point 3, the ventricle relaxes. • When the ventricular pressure falls to a value less than aortic pressure, the aortic valve closes. • Because all valves are closed again, ventricular volume is constant (isovolumetric).
D. 4➞1 (Ventricular Filling)	• Once ventricular pressure falls below atrial pressure, the mitral valve opens, and filling of the ventricle begins. • During this phase, ventricular volume is increased back to about 140ml (end-diastolic volume).

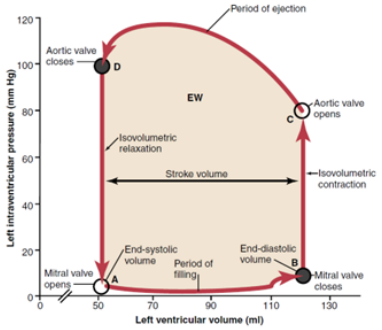


Figure 9-11. The volume-pressure diagram demonstrating changes in intraventricular volume and pressure during a single cardiac cycle (*red line*). The *shaded area* represents the net external work (EW) output by the left ventricle during the cardiac cycle.

FACTOR CONTROLLING CARDIAC OUTPUT

- **Cardiac Rate**
  - Is controlled primarily by cardiac innervation; sympathetic stimulation increases the rate and parasympathetic stimulation decreases it.
  - A heart beating at a very fast rate sometimes does not remain relaxed long enough to allow complete filling of the cardiac chambers before the next contraction. So, increase heart rate decreases cardiac output.
- **Stroke Volume**
  - Is determined in part by neural input, sympathetic stimuli making the myocardial muscle fibers contract with greater strength at any given length and parasympathetic stimuli having the opposite effect.
  - By both increasing the end-diastolic volume and decreasing the end-systolic volume, the stroke volume can be increased to as much as double the normal. So, increase stroke volume = ↑ cardiac output.

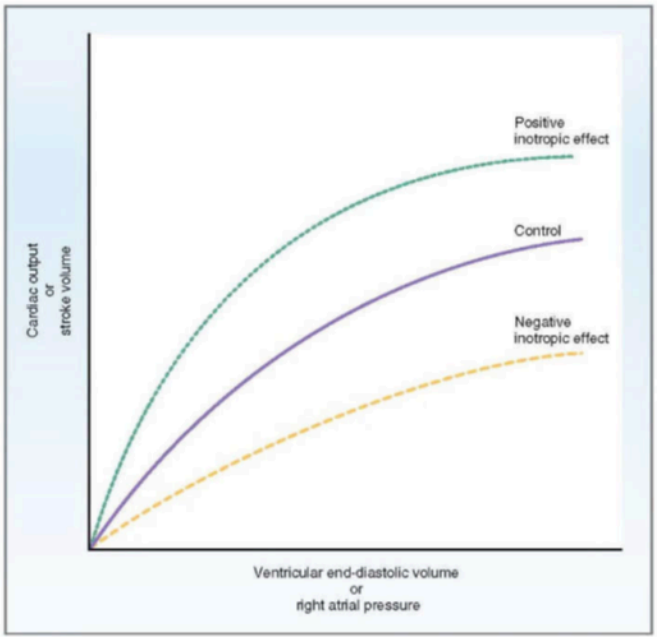
MECHANISMS OF REGULATION OF HEART PUMPING

- The basic means by which the volume pumped by the heart is regulated are:
  - Control of heart rate and strength of heart pumping by the autonomic nervous system.
  - Intrinsic cardiac regulation of pumping in response to changes in volume of blood flowing into the heart (Frank-Starling mechanism)

MECHANISMS IN CARDIAC INTRINSIC REGULATION

FRANK-STARLING LAW

- States that the greater the heart muscle is stretched during filling, the greater the force of contraction and the greater the quantity of blood pump into the aorta.
- Describes the increase in cardiac output (or stroke volume) that occurs in response to an increase in venous pressure or end-diastolic volume
- Based on the length-tension relationship; an increase in end-diastolic volume cause an increase in fiber length, which cause an increase in developed tension.
- Is the mechanism that matches cardiac output to venous return.
- Changes in contractility shift the Frank-Starling curve upward (increased contractility) or downward (decreased contractility)
  - Increase in contractility cause an increase in cardiac output for any level of venous pressure, right atrial pressure, or end-diastolic volume
  - Decrease in contractility cause a decrease in cardiac output for any level of venous pressure, right atrial pressure, or end-diastolic volume.



LENGTH-TENSION RELATIONSHIP

- Describes the effect of ventricular cell length on the strength of contraction
- Is similar to that in skeletal muscle.

1. Preload for ventricular muscle	• Is equivalent to end-diastolic volume or venous filling pressure. • When ventricular filling is increased, the ventricular muscle fibers are stretched
2. Afterload	• Is equivalent to aortic pressure • Is increased by increasing aortic pressure
3. Sarcomere length	• Determine the maximum number of cross-bridges that can form • Determine maximum tension or strength of contraction
4. Velocity of contraction at fixed muscle length	• Is maximal when there is no afterload. • Is decreased by increasing afterload.

RATE-INDUCED REGULATION OF MYOCARDIAL CONTRACTION

- **Rate - Induced Regulation**
  - A sustained change in contraction frequency affects the strength of contraction by altering the rate of influx of Ca++ into the cell per minute
  - A transient change in contraction frequency alters contractile strength because an appreciable delay exists between the time that Ca++ is taken up by the sarcoplasmic reticulum and the time that it becomes available again for release.

FACTORS AFFECTING END-DIASTOLIC VOLUME

- Increase length of ventricular muscle fibers (Increase end-diastolic volume)
  - Stronger atrial contraction
  - Increased total blood volume
  - Increased venous tone
  - Increased pumping action of skeletal muscle
  - Increased negative intrathoracic pressure
- Decrease length of ventricular muscle fiber (Decrease end-diastolic volume)
  - Standing
  - Increased intrapericardial pressure
  - Decreased ventricular compliance i.e., an increase in ventricular stiffness produced by myocardial infarction, infiltrative disease.

FACTORS AFFECTING CARDIAC CONTRACTILITY

- **Increased heart rate**
  - increases contractility because more action potentials per unit time means more Ca++ entry into the myocardia ell, more Ca++ released from the SR, and greater tension produced during contraction
  - Examples of effect of heart rate are:
    - Positive staircase or Bowditch staircase.
      - ❖ Increased heart rate increases the strength of contraction in a stepwise fashion as the intracellular [Ca2+] increases over several beats.
    - Post-extrasystolic potentiation.
      - ❖ The beat following an extrasystolic beat has increased strength of contraction because of the increased intracellular [Ca++].
- **Catecholamines**
  - Exert their inotropic effect via an action on cardiac ß1 – adrenergic receptors and Gs, with resultant activation of adenylyl cyclase and increased intracellular cAMP.
- **Sympathetic & Parasympathetic Nerve Impulses**
  - Sympathetic stimulation via ß receptors increases the strength of contraction by two mechanisms :
    - It increases the entry of Ca++ into the cell during the plateau of each cardiac action potential.

        - It increases the activity of the Ca++ pump of the SR (phospholamban); therefore, more Ca++ will be accumulated and thus will be available for release in subsequent beats.
    - Parasympathetic stimulation (Ach) via muscarinic receptors decrease the strength of contraction in atria by decreasing Ca++ entry into the cell during the plateau of the cardiac action potential (inward Ca^{2+} current).
- **Cardiac Glycosides (Digitalis) and Other Inotropic Agents**
    - Digitalis increase the strength of contraction by inhibiting Na^+ - K^+ ATPase in the cardiac muscle cell.
        - As a result, the intracellular Na^+ rises, diminishing the Na^+ gradient across the cell membrane.
        - Ca^{2+} - Na^+ exchange (a mechanism that extrudes $Ca2^+$ from the cell) depends on the size of this Na^+ gradient and is diminished, causing a rise in the intracellular Ca^{2+}.
    - Xanthines such as caffeine and theophylline inhibit the breakdown of camp. These agents are positively inotropic.
    - Glucagon increases the formation of cAMP, and is positively inotropic.
- Other Pharmacologic Agents
    - Quinidine, procainamide, and barbiturates depress myocardial contractility.

EFFECT OF TEMPERATURE ON CARDIAC FUNCTION

- Increased temperature (fever) greatly increased the heart rate.
- Decreased temperature greatly decreased the heart rate.
- Mechanism:
    - Heat causes increased permeability of the cardiac muscle membrane to the controlling ions, resulting in acceleration of the self-excitation process.
- Contractile strength of the heart is enhanced temporarily by a moderate increase in temperature, but prolonged elevation of the temperature exhausts the metabolic systems of the heart and eventually causes weakness.
- Optimal function of the heart depends greatly on proper control of the body temperature by the temperature control mechanism.

	SYMPATHETIC		PARASYMPATHETIC	
	Effect	**Receptor**	**Effect**	**Receptor**
Heart Rate	↑	β1	↓	Muscarinic
Conduction Velocity (AV Node)	↑	β1	↓	Muscarinic
Contractility	↑	β1	↓ (atria only)	Muscarinic
Vascular Smooth Muscle	Constriction			
Skin, Splanchine	Constriction	α		
Skeletal Muscle	Relaxation	β2		

MECHANISMS IN CARDIAC EXTRINSIC REGULATION

NERVOUS CONTROL OF CARDIAC ACTIVITY

- The control of the heart by the sympathetic and parasympathetic neurons
- Action potentials in these neurons trigger the release of norepinephrine, which binds to ß - adrenergic receptors on the surface of heart muscle cells. This causes the activation of adenylate cyclase, the enzyme that catalyzes formation of cyclic AMP from ATP. The resulting increase in cyclic AMP levels in the muscle cell alters the function of plasma membrane calcium channels, such that the amount of calcium entering cells with each action potential increases. The end result is a general increase in intracellular calcium concentration, which has a two-fold effect:
    - Binding of calcium to troponin increases, which results in more active cross bridges and more contractile force
    - Calcium ion triggers an increase in the calcium permeability of the sarcoplasmic reticulum, which increases the amount of calcium released during an action potential
- Sympathetic stimulation via B receptor:
    - ↑ heart rate
    - ↑ conduction velocity (AV node)
    - ↑ force of heart contraction
    - ↑ cardiac output
- Parasympathetic stimulation via muscarinic receptor:
    - ↓ heart rate
    - ↓ conduction velocity (AV node)
    - ↓ contractility (atria only)
    - ↓ cardiac output

CHEMICAL CONTROL OF CARDIAC ACTIVITY

- **Hormones**
    - Epinephrine, the principal hormone secreted by the adrenal medulla, binds to ß receptors on the heart muscle cells and affects intracellular cAMP levels. It increases myocardial contractility, thereby promoting increases in stroke volume and cardiac output.
    - Thyroid hormones affect the composition of myosin isoenzymes in cardiac muscle. By increasing these isoenzymes with the greatest ATPase activity, thyroid hormones enhance myocardial contractility.
    - Insulin has a prominent, direct, positive inotropic effect on the heart. Its positive inotropic effect is potentiated by ß - adrenergic receptor antagonists.
    - Glucagon has potent positive inotropic and chronotropic effects on the heart. Its effects on the heart closely resemble those of the catecholamines and certain metabolic effects are similar.
        - Both glucagons and catecholamines activate adenylyl cyclase to increase myocardial tissue levels of cyclic AMP. The consequent rise in cAMP increases Ca++ influx through the Ca++ channels in the sarcolemma, and facilitates Ca++ release and receptake by the sarcoplasmic reticulum.
- **Blood Gases**
    - Changes in oxygen tension (PaO_2) of the blood perfusing the brain and the peripheral chemoreceptors affect the heart through nervous mechanisms. These indirect effects of hypoxia are usually prepotent. When a subject is exposed to moderate degrees of hypoxia, heart rate, cardiac output, and myocardial contractility are usually enhanced.
    - The PO2 of the arterial blood perfusing the myocardium also influences myocardial performance directly.
        - The effect of hypoxia is biphasic: mild hypoxia is stimulatory, but more severe hypoxia is depressant because oxidative metabolism is limited.
    - Changes in $PaCO_2$ may also affect the myocardium directly and indirectly.
        - The direct effects on the heart elicited by changes of PCO2: decreasing it to 34 mmHg increases the left ventricular systolic pressure (stimulatory), whereas increasing it to 86 mm has the reverse effect (depressant).
        - The indirect, neurally mediated effects produced by an increased PCO_2 in the systemic arterial blood are similar to those evoked by a decrease in PaO_2. The effect of moderate increase in systemic arterial PCO_2 on the CVS is to increase heart rate, cardiac output, and arterial blood pressure.
        - Neither the arterial PCO_2, nor the blood pH is a primary determinant of myocardial behavior; the associated change in intracellular pH is the critical factor.
            - ❖ The reduced intracellular pH diminishes the amount of Ca++ released from the sarcoplasmic reticulum in response to excitation. The diminished pH also decreases the sensitivity of the myofilaments to Ca++.
            - ❖ Increases in intracellular pH have the opposite effect; that is, they enhance the sensitivity to Ca++.

- **Effect of Ions**
  - **Potassium Ions**
    - Excess K+ in the extracellular fluids causes the following:
      - ❖ Heart becomes dilated and flaccid
      - ❖ Decrease heart rate
      - ❖ Block conduction of the cardiac impulse from the atria to the ventricles thru the A-V bundle.
    - Mechanism:
      - ❖ High K+ concentration in the extracellular fluids decreases the resting membrane potential in the cardiac muscle fiber. As the membrane potential decreases, the intensity of action potential also decreases, which makes contraction of the heart progressively weaker.
  - **Calcium Ions**
    - Excess of calcium ion causes the heart to go toward spastic contraction. This is caused by the direct effect of Ca++ ions in exciting the cardiac contractile process
    - Deficiency of Ca++ ion causes cardiac flaccidity, similar to the effect of high K.

SOURCE OF ENERGY REQUIRED FOR CARDIAC CONTRACTILITY

- Heart muscle, like skeletal muscle, uses chemical energy to provide work for contraction.
- This energy is derived mainly from oxidative metabolism of fatty acids and, to a lesser extent of other nutrients, especially lactate and glucose.

FACTORS THAT INCREASE CARDIAC OXYGEN CONSUMPTION

- The O_2 consumption of the heart is determined primarily by the intramyocardial tension, the contractile state of the myocardium, and the heart rate.
- Is increased by:
  - increased afterload (aortic pressure)
  - increased size of the heart (law of Laplace: tension is proportional to radius)
  - increased contractility
  - increased heart rate
  - can be expressed by the following equation:
  - cardiac output = stroke volume X heart rate
- The work done by the heart is the product of stroke volume and mean arterial pressure in the pulmonary artery (for the right ventricle) or the aorta (for the left ventricle) and can be expressed by the following equation :
- Stroke work = stroke volume x aortic pressure or mean arterial pressure
- Fatty acids are the primary source of energy for stroke work.