Basic Biomedical Sciences I

Case 1 Trigger 2: Rhythm of My Heart

Block 4 Module 2

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

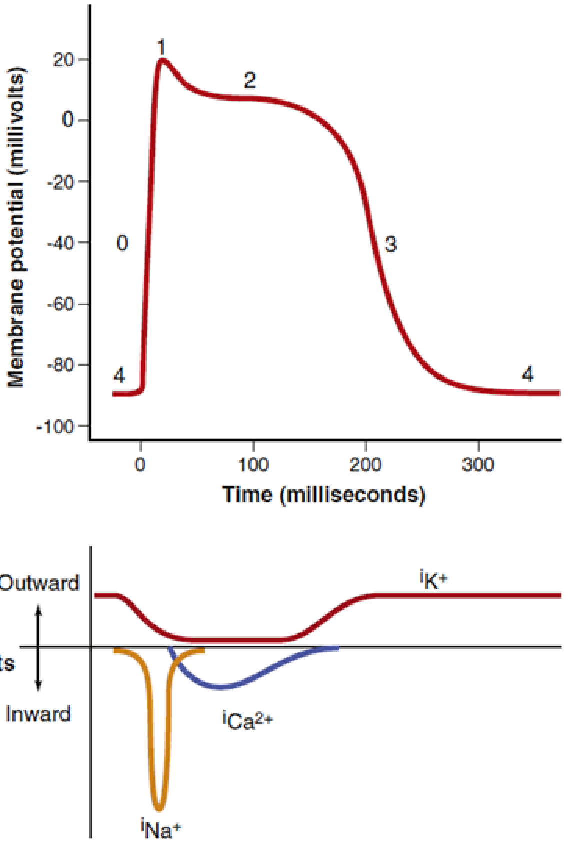


Figure 9-5. Phases of action potential of cardiac ventricular muscle cell and associated ionic currents for sodium ($^iNa^+$), calcium ($^iCa^{2+}$), and potassium ($^iK^+$).

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

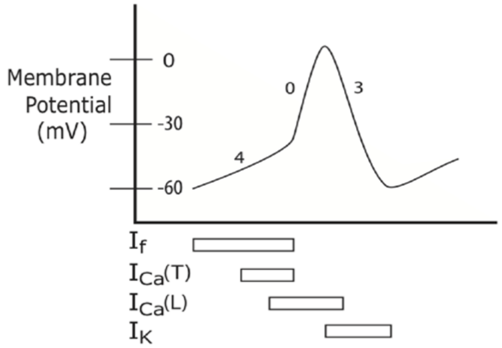
- is repolarization
- is caused by an increase in K^+ conductance. This increase results in an outward K^+ current that causes repolarization of the membrane potential

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)

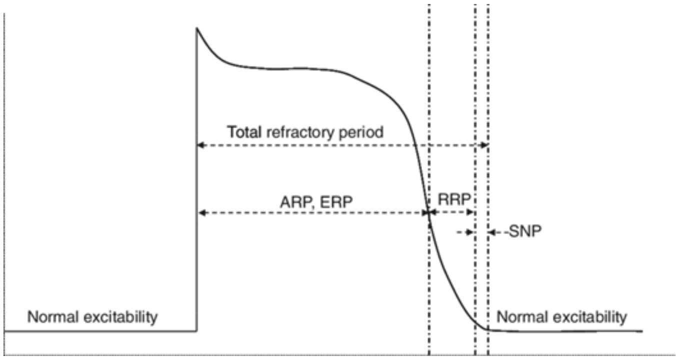
- Lasts from initiation of the spike to a time after the peak when repolarization is almost complete
- Constitute that period during which the membrane cannot be re excited by an outside stimulus, regardless fo the level of external voltage applied

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

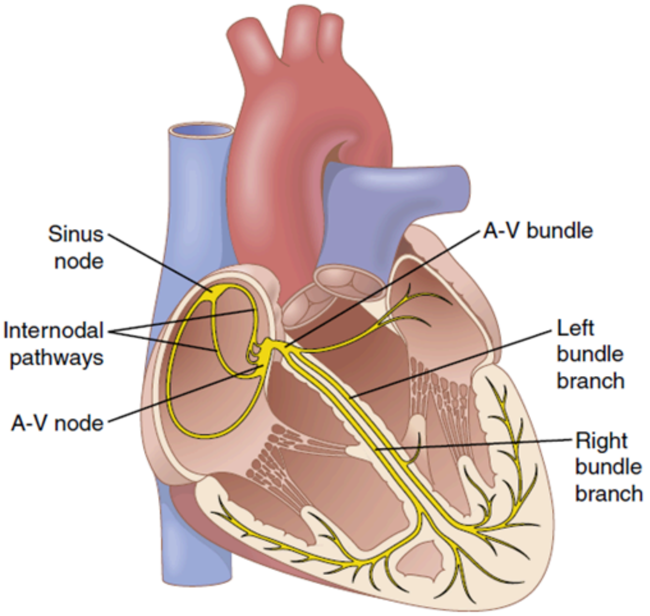


Figure 10-1 Sinus node and the Purkinje system of the heart, showing also the atrioventricular (A-V) node, atrial internodal pathways, and ventricular bundle branches.

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

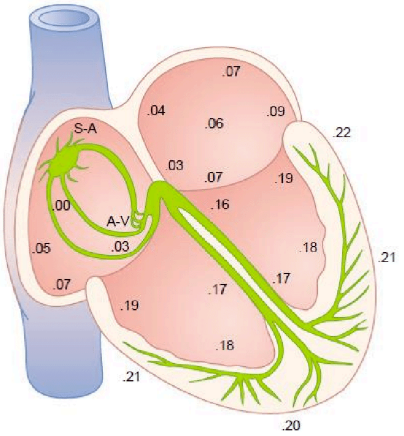
- Discharge frequency of the SA node is increased when the temperature rises, and this may contribute to the tachycardia associated with fever.

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

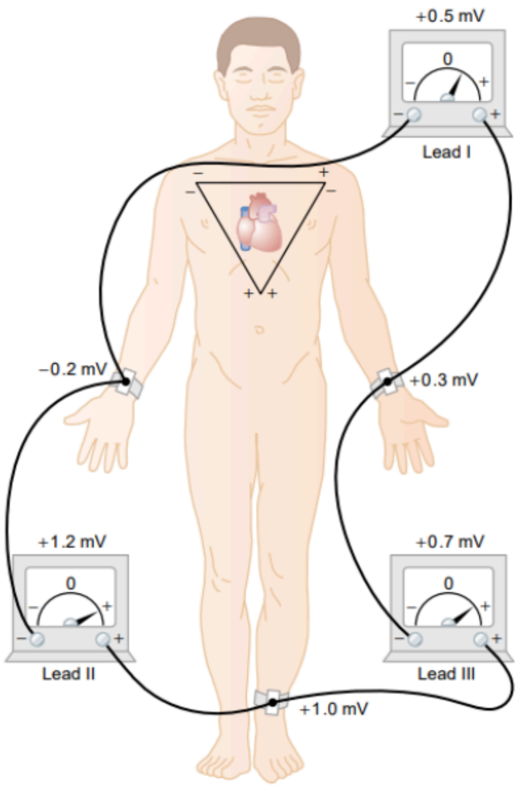


Figure 11–6

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.

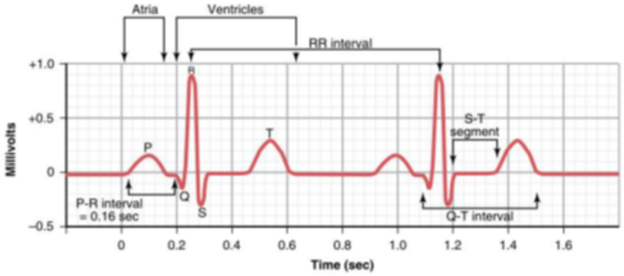


Figure 11-1 Normal electrocardiogram.

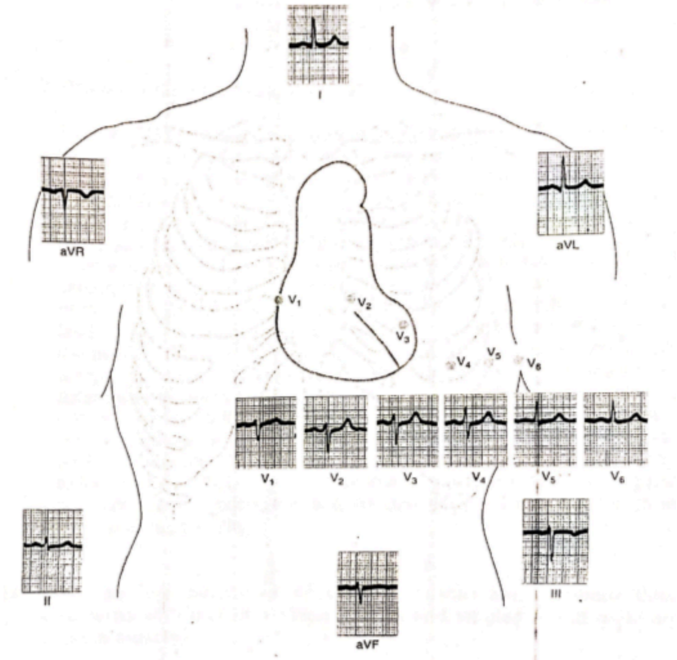


Figure 28 – 7. Normal ECG (Reproduced with permission from Goldman MJ: Principles of Clinical Electrocardiography, 12th ed. Originally published by Lange Medical Publications Copyright 1986 by The McGraw-Hill Companies Inc.)

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.