Introduction

Circulation

1- **Systemic (general) circulation**
   - carries *oxygenated* blood to *all parts of the body*
   - From Lt. ventricle → aorta
   - systemic arteries → arterioles
   - capillaries (for exchange with ISF)
   - venules → veins → SVC & IVC → Rt. atrium

2- **Pulmonary circulation**
   - carries *deoxygenated* blood to the *lungs*
   - From Rt. ventricle → pulmonary artery
   - arterioles → pulmonary capillaries (gas exchange with alveoli)
   - 4 pulmonary veins → Lt. atrium

The heart has 2 main pumps

1- **Left ventricle** *(pressure pump)*
   - pumps blood (at *high pr.* 100–140mmHg)
   - into the greater (systemic) circulation.

2- **Right ventricle** *(volume pump)*
   - pumps blood (at *lower pr.* 20–30mmHg)
   - into the pulmonary circulation

The cardiac valves

1- **Atrioventricular (A–V) valves**
   - *Mitral valve* (2 cusps) prevents backflow of blood from **Lt.** ventricle to **Lt.** atrium
   - *Tricuspid valve* (3 cusps) prevents backflow of blood from **Rt.** ventricle to **Rt.** atrium

2- **Semilunar valves**
   - *Aortic valve* prevents backflow of blood from aorta to **Lt.** ventricle
   - *Pulmonary valve* prevents backflow of blood from pulmonary **a.** to **Rt.** ventricle

Papillary muscles are ventricular muscles flaps attached to the cusps (leaflets) of A–V valves by the *cordae tendineae* ⇒ pull the cusps of the valves toward the ventricles (prevent prolapse of leaflets in atria) during ventricular contraction
Electrical Activity of the Heart

Excitability: ability of cardiac ms. to respond to adequate stimulus by generating a propagating A.P.

1- R.M.P. of cardiac muscle is (~90 mV):

The mechanism of generation of resting potential in cardiac myocyte:
1- K⁺ efflux (along conc. gradient) mainly through K⁺ leak channels & to a lesser extent through inward rectifying K⁺ channels (Kᵊ). Eq. potential for K⁺ is ~94 mV.
2- Na⁺ & Ca²⁺ influx (along conc. gradient) is low ⇒ little role in RMP. Eq. potential for Na⁺ is +61 mV.
3- Na⁺ – K⁺ ATPase (electrogenic pump)

Maintenance of ionic concentrations in cardiac myocytes:
- Disturbances in ionic concentrations & gradients during RMP & AP ⇒ affect RMP
- Ionic pumps & exchangers in sarcolemma ⇒ maintain ionic concentrations:
  1- Na⁺–K⁺ ATPase ⇒ pumps 3 Na⁺ out of the myocytes & 2 K⁺ to inside
  2- Ca²⁺-ATPase ⇒ pumps Ca²⁺ out of the myocytes.
  3- Na⁺ – Ca²⁺ exchanger ⇒ exchange 3 Na⁺ for 1 Ca²⁺.
  This exchanger can operate in both directions depending on the membrane potential & conc. gradient for the ions.

For example: inhibition of Na⁺–K⁺ ATPase ⇒ ↑↑ intracellular Na⁺ conc.
  Na⁺ – Ca²⁺ exchanger ⇒ Na⁺ out & Ca²⁺ inside the myocytes.

2- Action potential of cardiac myocyte:

Rapid depolarization from RMP (~90 mV) to threshold potential; the firing level (~65 mV) & conducted by cell-to-cell conduction

Phase 4 (RMP) continues till the cardiac myocytes becomes depolarized (normally by electric current from adjacent active myocyte).

Phase 0 rapid upstroke from ~90 to +20 mV. “fast response action potential”
Due to ↑↑ in conductance of fast Na⁺ channels (open for very short period & then inactivated)
At the same time, K⁺ conductance falls due to inactivation of inward rectifying K⁺ channels.

Phase 1 rapid small repolarization
Due to inactivation of fast Na⁺ channels & opening of transient outward K⁺ channels Iₖₒ & Cl⁻ channels.

Phase 2 the plateau (membrane potential is sustained around 0 mV).
The duration of plateau phase in ventricular myocyte is about 200 msec.
During plateau phase, membrane potential is maintained constant by a balance between:
- Ca²⁺ inward +ve current through long lasting Ca²⁺ channels (I₉). I₉ open at membrane potential ~40 mV & remain open for long time then become spontaneously inactivated (after certain period of time).
- K⁺ outward +ve current carried through slow delayed rectifier K⁺ channels (Iₖₛ). Iₖₛ channels activation occurs when the membrane is depolarized but due to their slow nature they play a role during phase 2 (plateau) & phase 3.

Phase 3 rapid repolarization phase.
Long lasting Ca²⁺ channels close while slow delayed rectifier K⁺ channels remain open ⇒ Outward K⁺ ⇒ repolarization(-80 to -85mV) & slow delayed rectifier K⁺ channels gradually close, while the inward rectifying K⁺ channels gradually open ⇒ complete repolarization to RMP of -90 mV. (8 remain open through the next phase 4)
Relationship between Action potential and contraction in cardiac myocyte:

- **Contraction** (systole) begins just after the start of depolarization & lasts about 1.5 times as A.P.
- **Systole** reaches its maximum at the end of the plateau
- **Diastole** begins with rapid phase of repolarization

**Repolarization ends** by the end of first half of diastole

Excitability changes during action potential:

1. **The effective (absolute) refractory period**
   - It coincides with phases 0, 1, 2, and part of phase 3
   - The cell is refractory to initiation of new action potentials (i.e., unexcitable).
   - **Cause:** during phases 0, 1 & 2 of AP, the inactivation gates of fast Na⁺ channels are still closed.

2. **The relative refractory period**
   - It coincides with phase 3 of action potential.
   - Supra-threshold stimuli are required to elicit actions potentials.

3. **The supernormal period:** vulnerable period
   - It coincides with the late part of phase 3.
   - During this period the myocyte can respond to a weaker stimulus.
   - Many cardiac arrhythmias can be initiated during this period (vulnerable period)

The refractory period in cardiac ms. is much longer than that in skeletal ms. due to the presence of plateau in cardiac myocytes action potential.

The long refractory period occupies the whole period of contraction & early part of relaxation
⇒ prevents sustained, tetanic contractions of heart (not suitable for the pumping of heart)

Initiation of Cardiac Electrical Activity

**Automaticity & Rhythmicity of the Heart:**

- **Automaticity** is the ability of heart to initiate its own contraction independent of external stimuli.
- **Rhythmicity** means that regularity of heart beat.
- Both are due to the spontaneous & regular pacemaker potentials.
- **Pacemaker cells are present in SA node, AV node & Purkinje fibers.**
- Cells of the SA node are the normal pacemaker of the human heart (control heart rate).
  - Discharge at a rate about 105/min (higher & can suppress other pacemaker tissues).
- Failure of the SA node cells ⇒ the AV node will take over (their rate is about 60/min.)
  - Faster than Purkinje cells (rate about 40/min.)
- The rate of action potential generation by the SA node cells (i.e. the heart rate) can vary (60 – 200/min) under various normal conditions.
- **Pacemaker cells** (specialized cells in cardiac conduction system)
  ⇒ spontaneously generate action potentials “pacemaker potential”.

**Pacemaker potential**

Unstable RMP -60 mV

- Spontaneous gradual depolarization (pre-potential)
- Slow upstroke (slow response action potential)

**Pacemaker currents**

- 60 to -50mV ⇒ funny (inward Na⁺) current
- 50 to -40mV ⇒ inward TCa++ current
- 40 to +10mV ⇒ inward LCa++ current
- 10 to -60mV ⇒ outward K⁺ current
Factors that affect the rate of discharge of SA node: \( (A \ B \ C \ D \ E) \)

1- **Autonomic nerves activity:**

- **Sympathetic activity** \( \uparrow \uparrow \) the rate of SA node discharge
  - \( \uparrow \uparrow \) the heart rate (tachycardia) (\(+\)ve chronotropy)
  - **Mechanism:** sympathetic nerve terminals \( \Rightarrow \) release Norepinephrine at SA node
    - \( \Rightarrow \) binds to \( \beta_1 \)-adrenoreceptors \( \Rightarrow \uparrow \) c-AMP \( \Rightarrow \)
    - a. \( \uparrow \uparrow \) funny current \( \Rightarrow \uparrow \) the slope of phase 4 (reaching the threshold in a shorter time)
    - b. \( \downarrow \downarrow \) threshold of opening & \( \uparrow \uparrow \) conductance of L-type Ca\(^{++} \) channels.

- **Parasympathetic (vagal) activity** \( \downarrow \downarrow \) the rate of SA node discharge
  - \( \downarrow \downarrow \) the heart rate (bradycardia) (\(-\)ve chronotropy).
  - **Mechanism:** vagal nerve terminals \( \Rightarrow \) release ACh at SA node \( \Rightarrow \) binds to muscarinic receptors
    - \( \Rightarrow \downarrow \) c-AMP \( \Rightarrow \) effects opposite to those of sympathetic stimulation
    - ACh \( \Rightarrow \uparrow \uparrow \) K\(^{+} \) conductance \( \Rightarrow \) hyperpolarization of SA node cells.

2- **Body temperature:**

- \( \uparrow \uparrow \) body temperature (fever) \( \Rightarrow \uparrow \uparrow \) the rate of discharge of SA node (tachycardia).
- \( \uparrow \uparrow \) body temperature 1°C \( \Rightarrow \uparrow \) heart rate 10 beats/min.

3- **Catecholamines level in blood:**

- Epinephrine & norepinephrine (similar to sympathetic stimulation) \( \Rightarrow \uparrow \uparrow \) SA node firing rate

4- **Drugs (Ca\(^{++} \) channel blocker)** \( \Rightarrow \) inactivation of L-type Ca\(^{++} \) channels \( \Rightarrow \) bradycardia

5- **Extracellular K\(^{+} \) level:**

- **Hypokalemia** \( \Rightarrow \) tachycardia (\( \uparrow \uparrow \) the slope of phase 4).
  - Hypokalemia \( \Rightarrow \downarrow \downarrow \) K\(^{+} \) conductance (through inhibition of K\(^{+} \)-sensitive K\(^{+} \) channels).

- **Hyperkalemia** \( \Rightarrow \) bradycardia (mechanism opposite to that of hypokalemia).
## Conduction of action potentials within the heart

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Site</th>
<th>Conduction rate (m/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA node (the normal pacemaker)</td>
<td>In right atrial wall at the junction of SVC</td>
<td>0.05</td>
</tr>
<tr>
<td>Atrial pathway</td>
<td>Both atria</td>
<td>0.5</td>
</tr>
<tr>
<td>Internodal tracts</td>
<td>Between SAN &amp; AVN</td>
<td>1</td>
</tr>
<tr>
<td>AV node (the only conducting pathway between the atria &amp; ventricles)</td>
<td>In the right posterior part of the inter-atrial septum &amp; continuous with bundle of His</td>
<td>0.05</td>
</tr>
<tr>
<td>Bundle of His</td>
<td>At the top of the interventricular septum, gives off left bundle branch (LBB) &amp; continue as right bundle branch (RBB) &amp; come in contact with Purkinje system</td>
<td>2</td>
</tr>
<tr>
<td>Purkinje system</td>
<td>Its fibers spread to all parts of the ventricular myocardium</td>
<td>4</td>
</tr>
<tr>
<td>Ventricular muscle</td>
<td>Both ventricles</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**The velocity of conduction of impulses in cardiac cells is determined by**

1. **The intercellular resistance:**
   - intercellular gap junctions are few in AV node ⇒ slow conduction
   - But numerous in Purkinje system ⇒ faster conduction

2. **The speed of upstroke of the action potential:**
   - The ventricular action potential has a high speed of upstroke
   - The SAN & AVN action potential has slower speed of upstroke

### Initiation & propagation of cardiac excitation wave

The cardiac pace-maker (the SA node) initiates impulses that pass through the atrial pathway ⇒ both atria & through internodal tracts ⇒ AV node ⇒ bundle of Hisss ⇒ Purkinje system ⇒ ventricular muscle fibers

- **Atrial depolarization is completed in 0.1 sec.**
- **AV nodal delay (0.1 sec)** as the conduction in the AV node is slow (0.05 m/sec)
  - **Cause:** few gap junctions & slow upstroke AP in AV node.
  - **Significance:**
    1. to allow sufficient time for atria to contract & empty their blood into the ventricles before ventricular systole begins.
    2. to prevent very rapid impulses from atria from reaching ventricles

- **Conduction in Purkinje fibers is very rapid (4m / sec)**
  - **Significance:** to cover both ventricles almost at the same time to contract as one unit ⇒ powerful pumping

- **Sympathetic stimulation ⇒ ↑↑ velocity (rate) of conduction.**
  - **mechanism:** ↑↑ ionic conductance ⇒ faster upstroke of action potentials.

- **Parasympathetic stimulation ⇒ ↓↓ velocity of conduction**
  - **mechanism:** ↓↓ ionic conductance ⇒ slower upstroke of action potentials.

- **Digitalis:** ↓↓ conduction velocity (by stimulating parasympathetic activity)