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

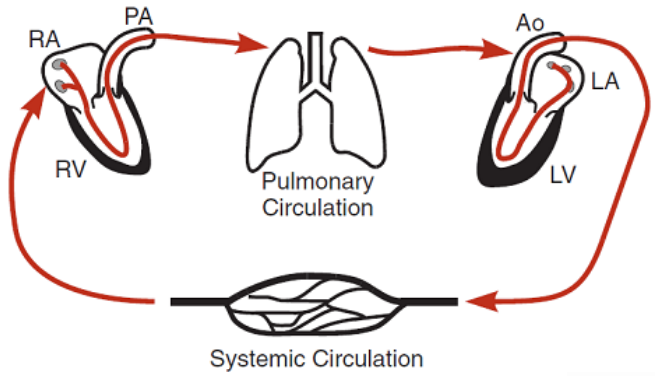
1- Atrioventricular (A-V) valves

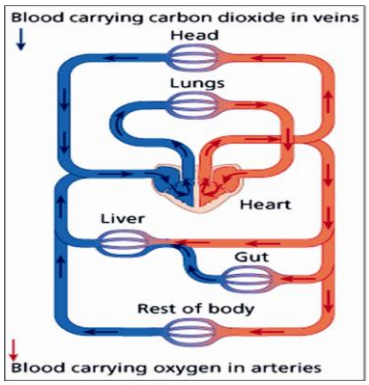
- ***Mitral valve*** (2 cusps) prevents backflow of blood from ***Lt.*** ventricle to Lt. atrium
- ***Tricuspid valve*** (3 cusps) prevents backflow of blood from ***Rt.*** ventricle to Rt. atrium

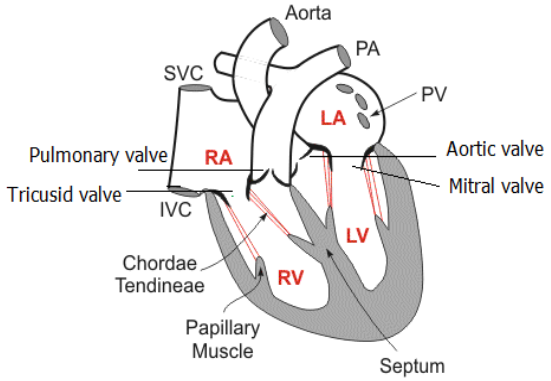
2- Semilunar valves

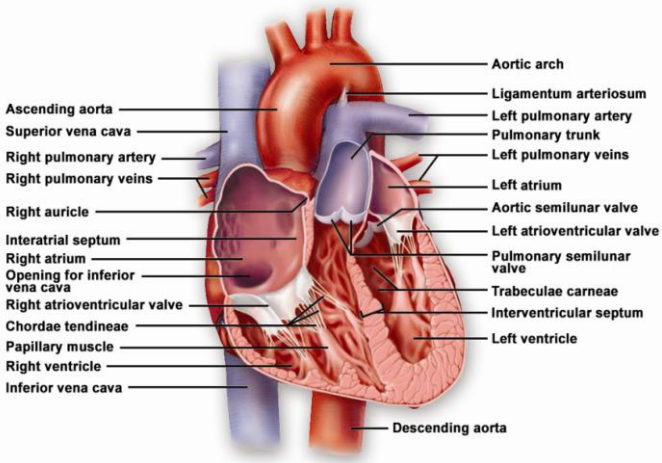
- ***Aortic valve*** prevents backflow of blood from ***aorta*** to Lt. ventricle
- ***Pulmonary valve*** prevents backflow of blood from ***pulmonary*** a. to Rt.ventricle

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.

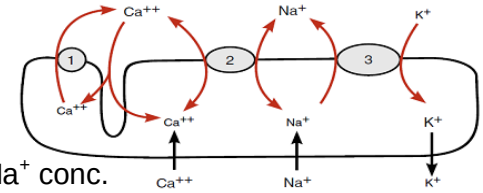
1- R.M.P. of cardiac muscle is (– 90 mV):

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*** (***K_{ir}***). Eq. potential for K^+ is -94 mV.
2- ***Na^+ & Ca^{++} 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- ***Ca^{++}-ATPase*** ⇨ pumps ***Ca^{++} out*** of the myocytes.
  3- ***Na^+ – Ca^{++} exchanger*** ⇨ exchange ***3 Na^+ for 1 Ca^{++}***.
  This exchanger can operate ***in both directions*** depending on the membrane potential & conc. gradient for the ions.



1 = ATP-dependent Ca^{++} pump
2 = Na^+/Ca^{++} exchanger (3:1)
3 = Na^+/K^+-ATPase pump (3:2)

For example: inhibition of Na^+–K^+ ATPase ⇨ ↑↑ intracellular Na^+ conc.
Na^+ – Ca^{++} exchanger ⇨ Na^+ out & Ca^{++} 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).

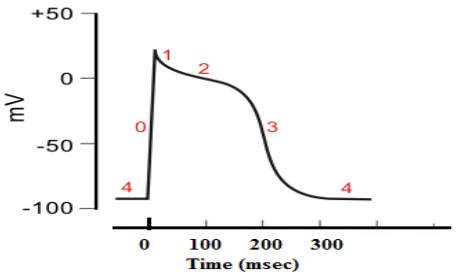
Phase 0 ***rapid upstroke*** from – 90 to +20 mV. ***"fast response action potential"***
Due to ↑↑ in conductance of ***fast Na^+ channels*** (open for very short period & then inactivated)
At the same time, K^+ conductance falls due to inactivation of inward rectifying K^+ channels.

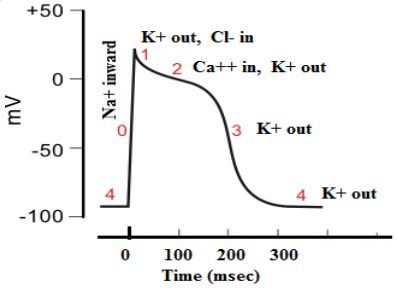
Phase 1 ***rapid small repolarization***
Due to inactivation of fast Na^+ channels
& opening of ***transient outward K^+ channels I_{kto}*** & Cl^- channels.

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***:

- ❒ Ca^{++} inward +ve current through ***long lasting Ca^{++} channels (I_{CaL})***.
  I_{CaL} 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 (I_{Ks})***.
  I_{Ks} 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 Ca^{++} 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. (& remain open through the next phase 4)

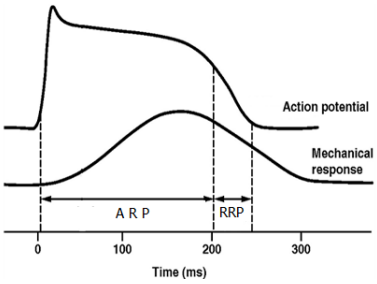




Relationship between Action potential and contraction in cardiac myocyte:

- ***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:

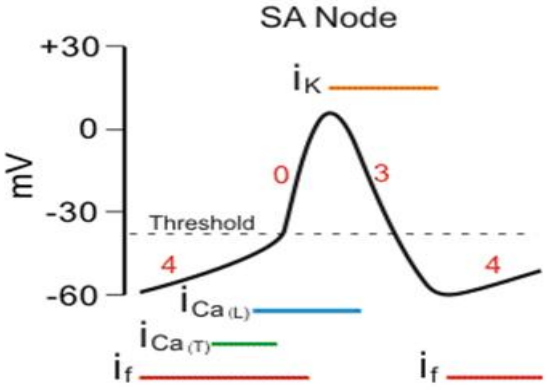
- ❒ **Automaticity** is the ability of heart to initiate its own contraction independent of external stimuli.
- ❒ **Rhythmicity** means that regularity of heart beat.
- ❒ Both are due to the ***spontaneous & regular pacemaker potentials***.
- ❒ ***Pacemaker cells are present in SA node, AV node & Purkinje 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 $T_{Ca^{++}}$ current
– 40 to +10mV ⇨ inward $L_{Ca^{++}}$ current
+10 to –60mV ⇨ outward K^+ current



Pacemaker potential: ***"slow response action potential"*****: 3 phases**

Phase 4: spontaneous gradual depolarization (***pre-potential***):
- ❒ At membrane potential (***-60 mV***): **"funny" current** (I_f): slow, inward (depolarizing) Na^+ current.
- ❒ At membrane potential (***-50 mV***): ***inward directed Ca^{++} currents (I_{CaT})***: Ca^{++} enters the cell through transient or ***T-type Ca^{++} channels*** down its electrochemical gradient.

Phase 0: ***depolarization (upstroke)***
- ❒ At the firing level (***-40 mV***): **long-lasting** (**L-type**) **Ca^{++} channels** open ⇨ more Ca^{++} enter the cell
- ❒ Ca^{++} entry is ***slow***; the rate of ***depolarization*** (slope of phase 0) is much ***slower*** than in other types of cardiac cells. Hence the name "***slow response***" ***action potential.***
- ❒ During phase 0: the "funny" current (I_f) & transient Ca^{++} current (I_{CaT}) gradually stop due to closure of their channels.
- ❒ During phase 0: depolarization causes gradual opening of ***delayed rectifying K^+ channels*****.**

Phase 3: ***repolarization***
- ❒ Due to opening of ***delayed rectifying K^+ channels*** ⇨ outward directed K^+ current (I_k) along conc. & electrical gradients.
- ❒ L-type Ca^{++} channels become inactivated & close ⇨ inward depolarizing Ca^{++} current (I_{CaL}) stops
- ❒ At repolarization -60 mV ⇨ outward K^+ current (I_k) becomes inactivated, while the funny current (I_f) becomes activated again & a new cycle is spontaneously repeated on & on again.

Factors that affect the rate of discharge of SA node: (A B C D E)

1- Autonomic nerves activity:

- ❒ ***Sympathetic activity*** ⇨ ↑↑ the rate of SA node discharge
  ⇨ ↑↑ the heart rate (***tachycardia***) (**+ve chronotropy**)

  Mechanism: sympathetic nerve terminals ⇨ release Norepinephrine at SA node
  ⇨ binds to β1-adrenoreceptors ⇨ ↑↑ c-AMP ⇨
  a. ↑↑ funny current ⇨ ↑↑ the slope of phase 4 (reaching the threshold in a shorter time)
  b. ↓↓ threshold of opening & ↑↑ conductance of L-type Ca^{++} channels.

- ❒ ***Parasympathetic (vagal) activity*** ⇨ ↓↓ the rate of SA node discharge
  ⇨ ↓↓ the heart rate (***bradycardia***) (**–ve chronotropy)**.

  Mechanism: vagal nerve terminals ⇨ release Ach at SA node ⇨ binds to muscarinic receptors
  ⇨ ↓↓c-AMP ⇨ effects opposite to those of sympathetic stimulation
  Ach ⇨ ↑↑ K^+ conductance ⇨ hyperpolarization of SA node cells.

2- Body temperature:

↑↑ body temperature (fever) ⇨ ↑↑ the rate of discharge of SA node (tachycardia).
↑↑ body temperature 1˚C ⇨ ↑↑ heart rate 10 beats/min.

3- Catecholamines level in blood:

Epinephrine & norepinephrine (similar to sympathetic stimulation) ⇨↑↑ SA node firing rate

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

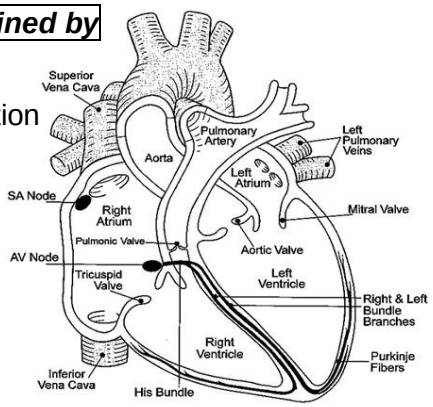
5- Extracellular K^+ level:

- ❒ ***Hypokalemia*** ⇨ ***tachycardia*** (↑↑ the slope of phase 4).
  Hypokalemia ⇨ ↓↓ K^+ conductance (through inhibition of K^+-sensitive K^+ channels).
- ❒ ***Hyperkalemia*** ⇨ ***bradycardia*** (mechanism opposite to that of hypokalemia).

Conduction of action potentials within the heart

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

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 Hiss ⇨ ***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)