CVS MODULE
PHYSIOLOGY (LECTURE 1)
Physiology of Cardiac Muscle

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Introduction:

The **cardiovascular system** is a **closed system** of tubes (i.e. vessels) inside which blood circulates continuously by the **pumping action** of the **heart** in **one direction** only by the action of **valves** present in the **heart** and **veins**.

It is composed of **:**

1. The Heart: as a **pumping organ** of the system.

2. Blood Vessels: as **containers**, through which the circulation occurs.

Physiological Properties of the Cardiac Muscle

Cardiac muscle is a **striated muscle** like the skeletal muscle, but it is **different** from the skeletal muscle in being **involuntary** and **syncytial**.

Syncytium means that **cardiac muscle cells are able to excite and contract together** as one unit **due to** the presence of **gap junctions** between adjacent cardiac cells.

Both atria contract together as one unit (**upper syncytium**) and **both ventricles** contract together as one unit (i.e. **lower syncytium**), which are **completely separated** from each other by the **fibrous A-V ring**. So, the excitation waves **cannot be directly transmitted** from one syncytium to the other.

***Myocardium* of the heart** is composed of **two** types of cardiac muscles:

A. Contractile Muscle Cells : (form about 98-99% of the cardiac muscle). Their action potential is called **fast AP**.

B. Non-contractile Muscle Cells: (form about 1-2 % of the cardiac muscles and are the cells that form **excitatory-conductive system** of the heart). Their AP is called **slow or pacemaker AP.**

Cardiac muscle has four properties, due to which the heart is able to fulfill its function as a pumping organ.

They include:

1. **Rhythmicity (Chronotropism).**
2. **Excitability (Bathmotropism).**
3. **Conductivity (Dromotropism).**
4. **Contractility (Inotropism).**

1. Automaticity and Rhythmicity (Auto-rhythmicity)

Automaticity: It is the ability of the heart to initiate its own contraction independent of external stimuli.

Rhythmicity: It means the heart can beat regularly (regular generation of action potential).

Spontaneous rhythmicity and **automaticity** of the cardiac muscle is **due to** the existence of a specialized **excitatory-conductive system**, which is composed of modified **self- exciting**, **non-contractile** cardiac muscle cells called **pacemaker cells**.

Auto-rhythmicity is **myogenic** in origin (i.e. starts from the **muscle** itself **independent** from autonomic nerve supply that **only controls** the heart rate (either ↑ or ↓) **but don't initiate the beat.**

Pacemaker(s) of the heart:

Pacemaker **means** the part of the heart that has the **highest rhythmicity** and the whole other parts of the heart **follow** its rhythm. **They include;**

1. Sinoatrial (auricular) (SA) Node (1ry Pacemaker):

It has the **highest** rhythm **(90-110/min)**.
So, it is called the **normal** or **1ry pacemaker** of the heart.
Its rhythm is called **sinus rhythm**.

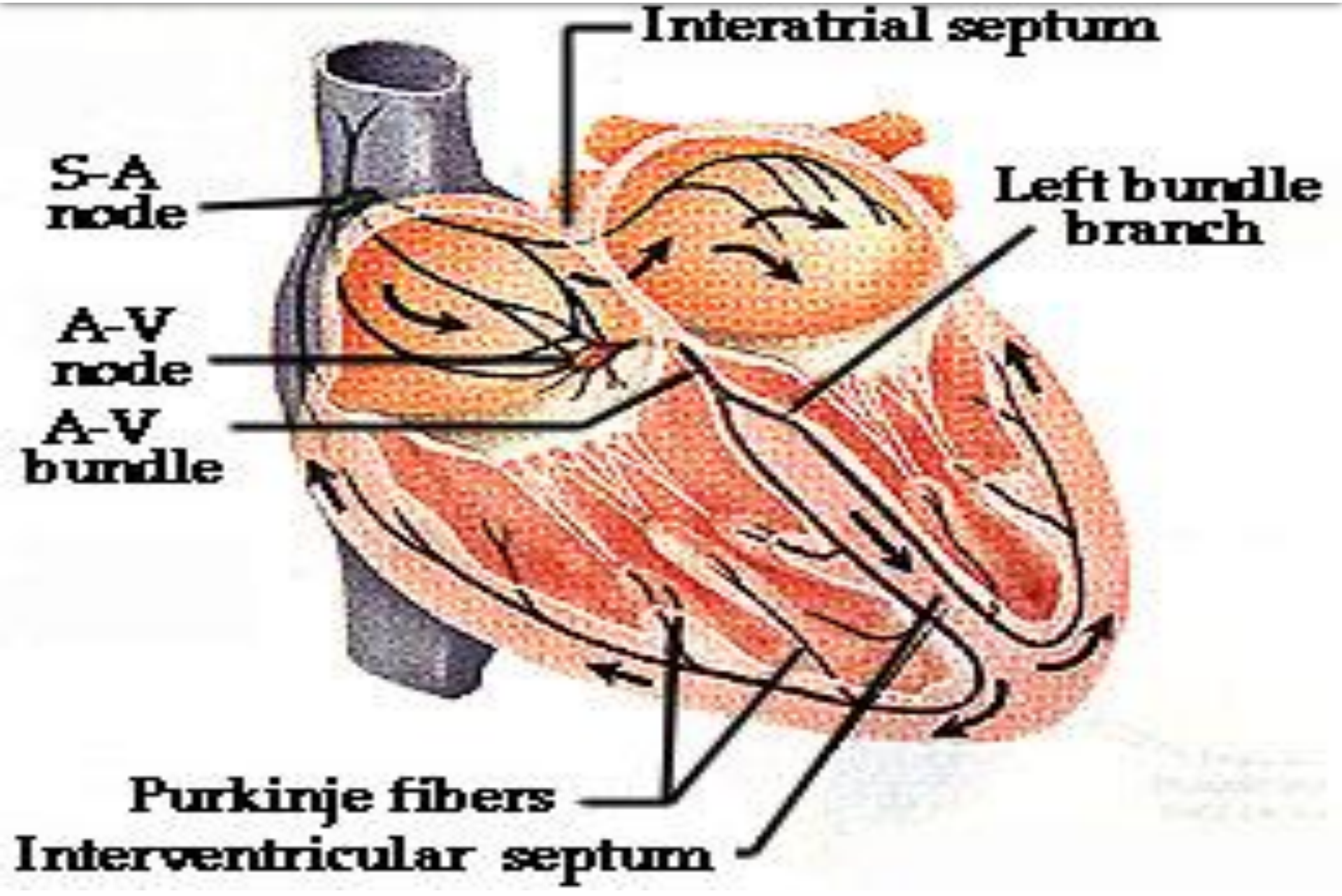
2. Atrioventricular (AV) Node (2ry Pacemaker):

It rate is **45-60 /min.**
It acts **only** if **SA node is damaged or blocked.**
Its rhythm is called **nodal rhythm**.

3. Purkinje fibres (3ry Pacemaker):

It rate is **25-40 /min.**
It takes over **only** if the conduction in **AV node is completely blocked**.
Its rhythm is called **idioventricular rhythm**.

PACEMAKERS


Interatrial septum
S-A node
Left bundle branch
A-V node
A-V bundle
Purkinje fibers
Interventricular septum

Mechanism of Autorhythmicity (Prepotential & Pacemaker AP)

Pacemaker cells can spontaneously and regularly initiate action potential and so they are responsible for automaticity and rhythmicity of the heart.

Pacemaker action potential is composed of:

Phase 4, (Prepotential):

Resting membrane potential is about -60 mV **(unstable)**. At this potential there is activation of a special type of Na^+ channels known as **Na^+ funny channels** → funny current (inward Na^+ **I_f**). As the membrane potential reaches about -**50 mV**, another type of channels called transient or **T-type Ca^{++} channels opens** → Ca^{++} enters down its electrochemical gradient → depolarizes the cell to **-40 mV**.

Phase 0:

As the membrane is depolarized to the firing level **(about -40 mV)** another type of Ca^{++} channels opens. These are known **long-lasting or L-type Ca^{++} channels** → entrance of Ca^{++}. Because the movement of Ca^{++} through these channels into the cell is not rapid, the rate of depolarization (slope of phase 0) is much slower than found in other types of cardiac cells. Therefore AP of pacemaker cells is called **slow response action potential.**

Phase 3, repolarization:

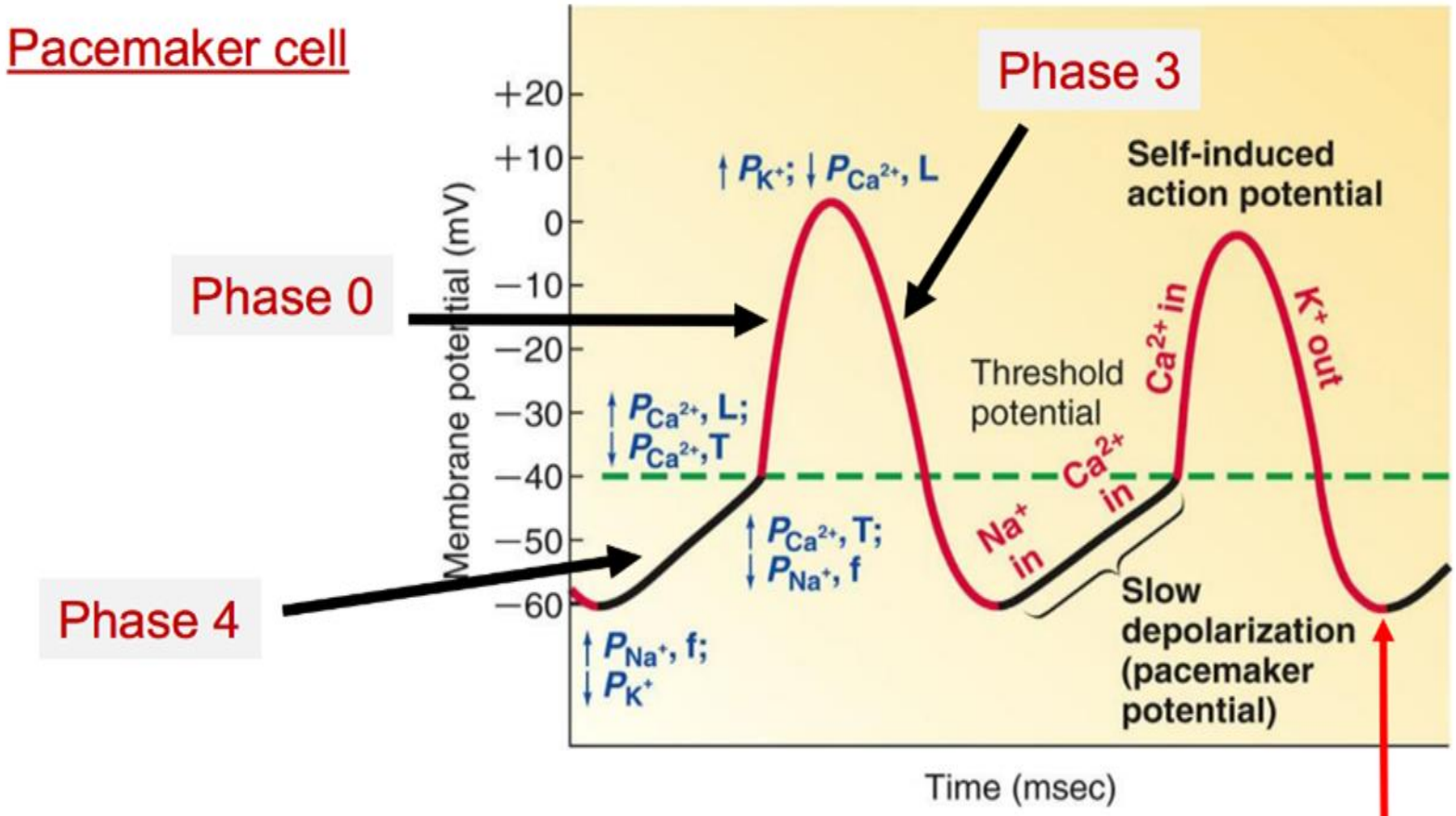
It occurs due **to opening of K^+ channels** → outward directed K^+ current along concentration and electric gradients. At the same time, L-type Ca^{++} channels become inactivated and close → stop entrance of Ca^{++}.

Repolarization continues until the membrane potential reaches **-60 mV**. At this potential the **outward K^+ current becomes gradually inactivated**, while the inward Na^+ current becomes activated again due **to opening of funny current channels** and a new phase 4 is initiated and the whole cycle is spontaneously repeated.

N.B.:

Phase 1 and 2 (which are present in fast AP) are absent.

Pacemaker prepotential



Arrows indicate ion current

KEY

f = Funny channels
T = Transient-type channels
L = Long-lasting channels

Maximal diastolic potential: maximal level of repolarization achievable

N.B.

Although the rhythmicity of the SAN is ~ **110 /min**, the resting heart rate is **only 75 beat/min**, **why**?

ANSWER:

This is due the **continuous inhibitory discharge** from the vagus nerve on S A node **decreasing** its inherited rhythm from **110 to 75 beat/min**. This called **VAGAL TONE.**

The vagus nerve **supplies** the whole cardiac muscle **except** the **ventricles** (i.e. called **VAGAL ESCAPE PHENOMENON).** This phenomenon **protects** the ventricles from **abnormally high** vagal stimulation (which can cause **cardiac arrest**).

Factors affecting the rhythmicity (chronotropism) may be also classified into:

A. Nervous Factors:

1. Vagal stimulation via **acetylcholine (Ach) → (-ve) chronotropic effect.**

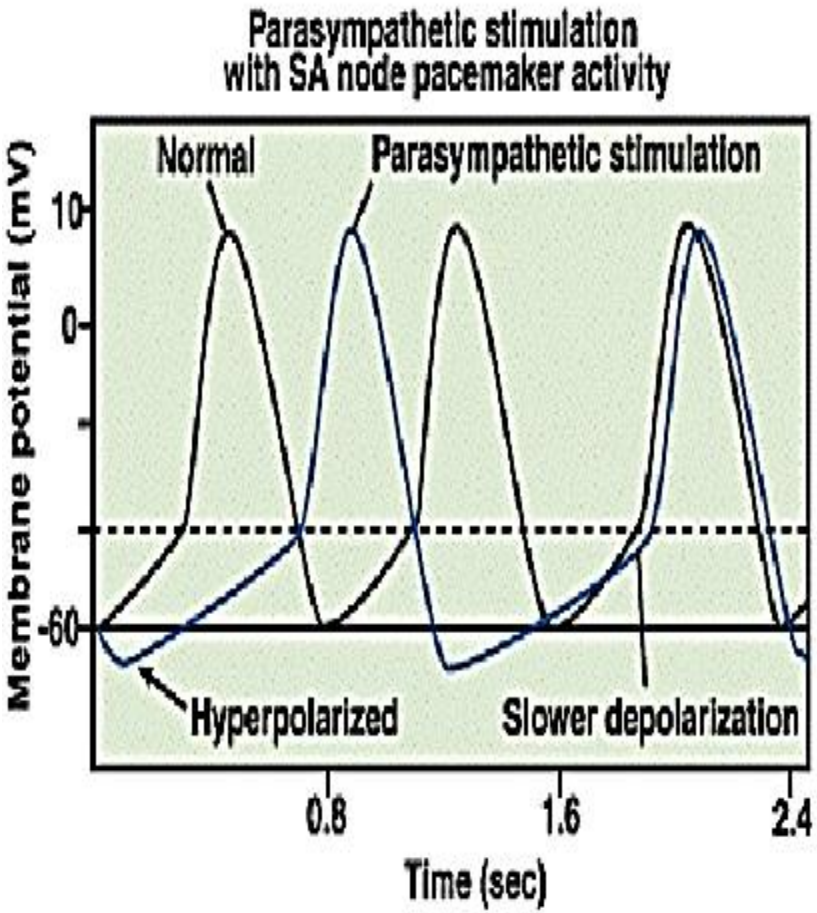
Mechanism:

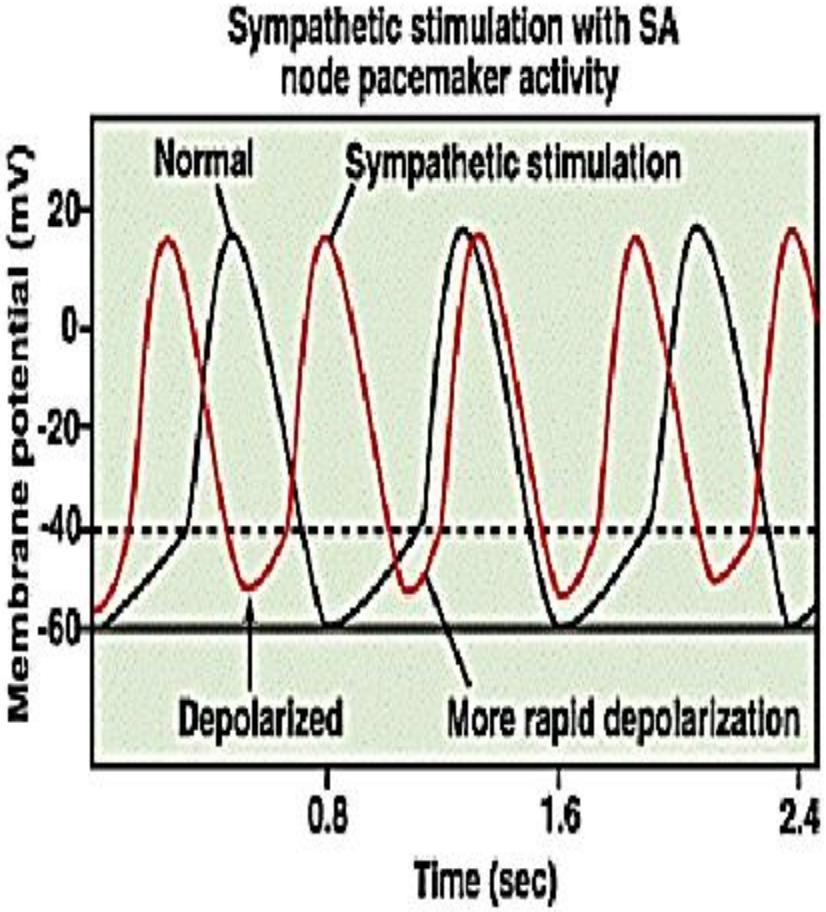
Ach **stimulates M_2** cholinergic receptors → decreased level of cyclic-AMP → **inhibits I_f → ↓ slope of prepotentials → ↓** rhythmicity. In addition Ach **also stimulates a special type of K^+ channels** (known as K_{Ach}) → **K+ efflux.** This K efflux opposes the funny current and decreases the slope of the phase.

2. Sympathetic stimulation via **nor-adrenaline (NA) → (+ve) chronotropic effect.**

Mechanism:

NA **stimulates B_1** adrenergic receptors → increased formation of cyclic-AMP→ **increase inward Na^+ current (I_f) & ↑ Ca^{+2} influx → ↑ slope of prepotentials → ↑** rhythmicity**.**


Parasympathetic stimulation
with SA node pacemaker activity
Normal
Parasympathetic stimulation
Membrane potential (mV)
10
0
-60
Hyperpolarized
Slower depolarization
0.8
1.6
2.4
Time (sec)


Sympathetic stimulation with SA
node pacemaker activity
Normal
Sympathetic stimulation
Membrane potential (mV)
20
0
-20
-40
-60
Depolarized
More rapid depolarization
0.8
1.6
2.4
Time (sec)

B. Chemical Factors:

1. Catecholamines (Adrenaline and NA)→ ↑ rhythmicity.
2. Acetyl choline (Ach) → ↓ rhythmicity.
3. Thyroxine: ↑ rhythmicity
4. Effect of ions (K^+ & Ca^{++}):

K+ :

Hypokalemia causes **tachycardia** due to **increase** the slope of phase 4.

Hyperkalemia causes bradycardia by decreasing the slope of phase 4.

Ca^{++} :

Ca^{++} channel blocking drugs: some types of these drugs causes bradycardia by inactivation of L-type Ca^{+2} channels.

Ca^{++} → helps systole → Excess Ca^{++} → Cardiac arrest in Systole (i.e. calcium rigors).

N.B. Calcium should be injected **very slowly** because **rapid i.v. injection** of calcium **leads** to **death from calcium rigors.**

5. Metabolites & Blood gases:

Severe O_2 lack (↓O_2), ↑ H+ or ↑ Co_2 → ↓ rhythmicity.

6. Effect of Drugs:

- **Sympathomimetic drugs → ↑** rhythmicity.
- **Parasympathomimetic (i.e. cholinergic drugs)** → **↓** rhythmicity.
- **Digitalis:** Although it increases myocardial contractility, it **inhibits** SA node activity and **decreases** HR (i.e. **vagal like effect**)

7. Effect of toxins:

Certain toxins (**(e.g. Diphtheria toxins) →** ↓ rhythmicity.

C. Physical Factors:

Moderate warming → ↑ rhythmicity due to increased rate of discharge of SA node.

Moderate cooling → ↓ rhythmicity due to decreased rate of discharge of SA node.

Excess or severe warming (≥ 45 ^{O}C) → Stop rhythmicity (**due to tissue damage**).

Excess or severe cooling (≤ 15 ^{O}C) → Stop rhythmicity (**due to arrest of metabolism**).

D. Mechanical factors:

Distension of right atrium → ↑ rhythmicity(due to stretch= Bainbridge effect)

2. Excitability

Excitability means the ability of the cardiac muscle to **respond** to an **adequate stimulus**.

The cardiac muscle is **self-excited** by signals **generated** in specific **pacemaker cells** and **conducted** via an **excitatory conductive system** to **generate** an action potential **called (i.e. Cardiac muscle or FAST response Action Potential).**

The **RMP** of the cardiac muscle is ~ **(-80 to -90 mv**).
When the cardiac muscle is **stimulated** → an **Action Potential** is generated which is **responsible** for **initiating** cardiac muscle **contraction**.

Phases of cardiac muscle (i.e. FAST response) Action Potential

Phase 0 (i.e. Depolarization phase):

Caused by **rapid depolarization** (i.e. from -90 to +20 mv) and it is **due to** rapid **sodium influx** (via voltage-gated fast Na^+ channels).

Phase 1 (i.e. rapid initial partial repolarization):

A small rapid repolarization, **due to** inactivation (i.e. **closure)** of voltage-gated Na^+ channels **along with** limited **K^+ efflux** due to opening of K^+ channels.

Phase 2 (i.e. Plateau):

In which **repolarization slows down, and membrane potential is nearly sustained about zero mV.** It is caused by a **BALANCE** between:

Ca^{++} inflow (i.e. depolarizing Ca^{++}) due to **opening** of long lasting Ca^{++} channels **(L-type Ca^{++} Channels)**.

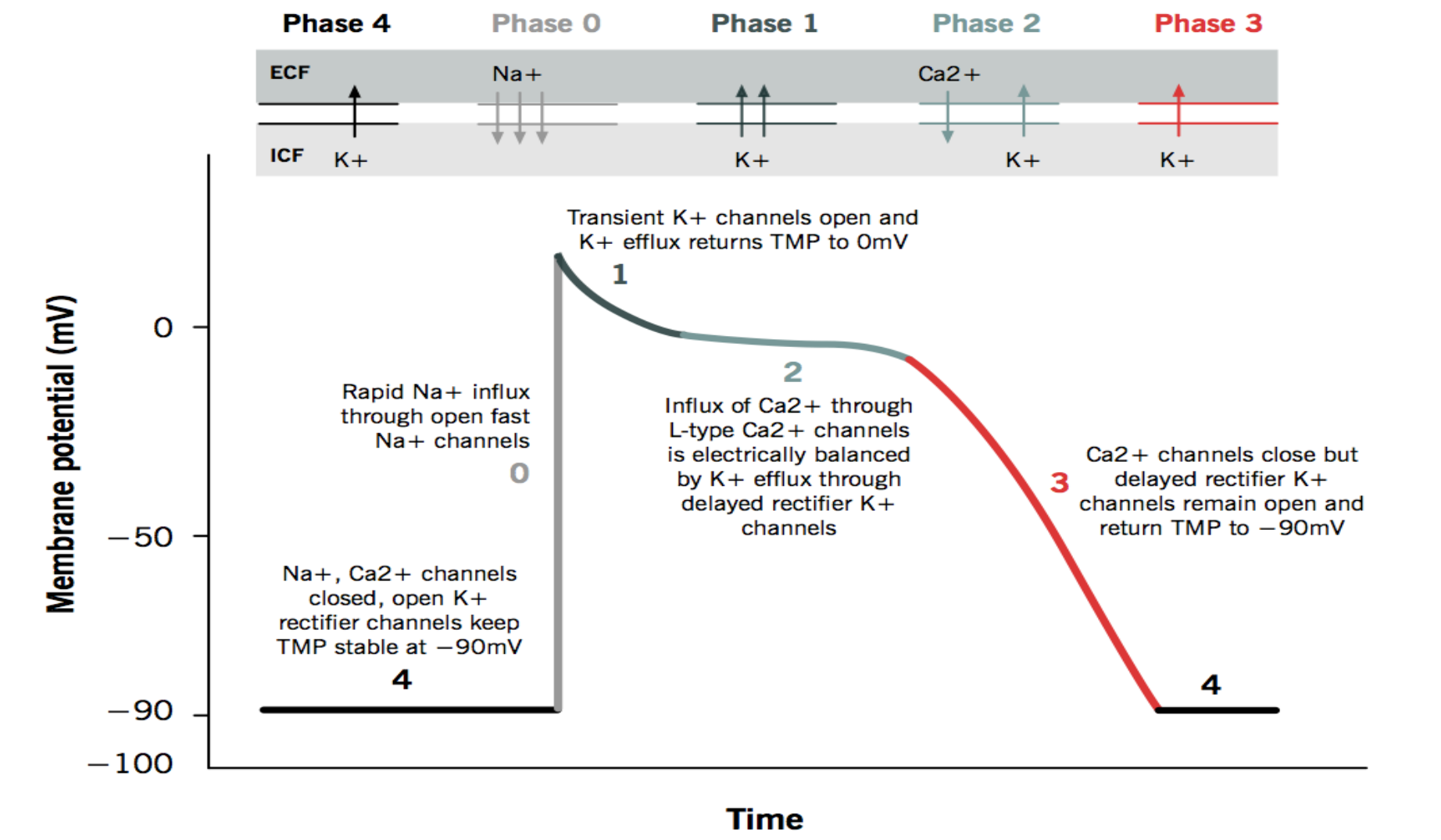
K^{+} outflow through K^{+} channels.

Phase 3 (i.e. Rapid repolarization):

Due to inactivation (i.e. **closure)** of **L-type Ca^{++}** channels while **K^{+} channels** become maximally activated→ **repolarization.**

Phase 4 (complete repolarization and Returning to RMP): This is achieved by increased K^{+} efflux

Cardiac muscle (i.e. FAST response) AP.



Pacemaker potential (slow response)Versus Action potential of the ventricular muscle (Fast response)

Cardiac muscle AP (i.e. Fast Response)	Pacemaker AP (i.e. Slow Response)
• The RMP is ~ -90 mv. • Constant (i.e. stable).	• The RMP is - 55 to - 60 mv. • Unstable (i.e. self-excitation or prepotential).
• The upstroke (i.e. ascending limb) is rapid. • It is due to rapid Na+ influx and reaches up • to ~ +20 mV.	• The upstroke is slow. • It is due to slow Ca^{2+} influx and reaches up • to ~ +10 mv.
• There is a prominent plateau (AP is longer 300-400 ms).	• There is NO plateau (AP is shorter 200-250 ms).
• Repolarization is triphasic.	• Repolarization is one phase only

Excitability Changes during Cardiac Activity:

I. Absolute Refractory Period (ARP);

The excitability is **completely lost** (= **zero**).

It extends from the **start of phase 0** → till the **middle of Phase 3** of the AP (i.e. phases 0, 1, 2 till the middle of phase 3).

It occupies the **whole systole and early part of diastole = long ARP.**

Significance of Long ARP;

1. Prevents the heart from being **tetanized.**
2. Prevents cardiac **fatigue**.

II. Relative Refractory Period (RRP);

The excitability starts to be **restored gradually** but still **less than normal**.

It extends from the **middle of Phase 3** till the membrane potential repolarizes to **about -75mV.**

It occupies the **remaining part of diastole.**

III. Super normal Phase of Excitability:

The excitability is **higher than normal**.

It occurs during **the late part of phase 3.**

It occupies the **end of diastole**.

Early in this phase, there is the **vulnerable period of the heart** (i.e. a **dangerous** period in which the **excitation wave** may lead to **cardiac arrhythmia** as ventricular fibrillation).

Factors that affect excitability

1. Nervous factors:

Sympathetic stimulation increases the excitability.

Parasympathetic stimulation decreases the excitability.

2. Physical factors:

An increase in body temperature increases cardiac excitability and vice versa.

3. Chemical factors:

Hormones: catecholamines and thyroxine increase the myocardial excitability and may activate ectopic foci.

Hypoxia and ischemia: decrease the myocardial excitability

Drugs: xanthines (e.g. caffeine and theophylline) increase the myocardial excitability, while cholinergic drugs decrease it.

Inorganic ions:

Calcium: hypercalcemia decreases the myocardial excitability.

Potassium: hyperkalemia decreases the myocardial excitability and may cause cardiac arrest in diastole while hypokalemia increases it and may activate ectopic foci.

Excitation-Contraction Relationship

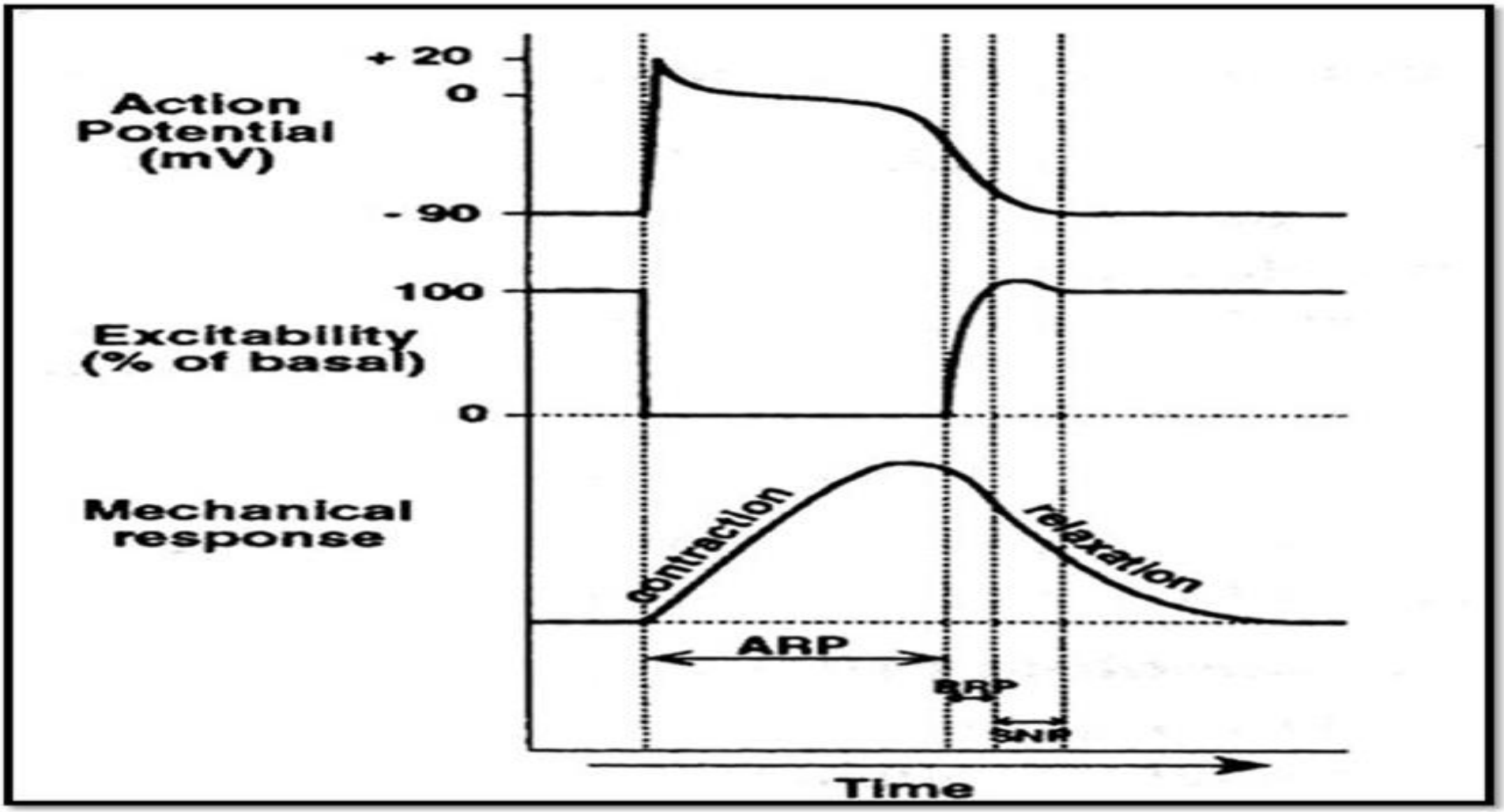
1. The mechanical response (i.e. contraction) of the cardiac muscle **starts** just **after** the beginning of depolarization **(i.e. ~ 0.02 sec.)** and takes **longer time** than the AP **(~ 1.5 time)** as long as the duration of AP.

2. The **systole** reaches its **maximum** at the **end of the plateau** (i.e. **phase 2**).

3. The **diastole starts** with the rapid phase of repolarization (**phase 3**), which is completed at about the **mid-diastole**.

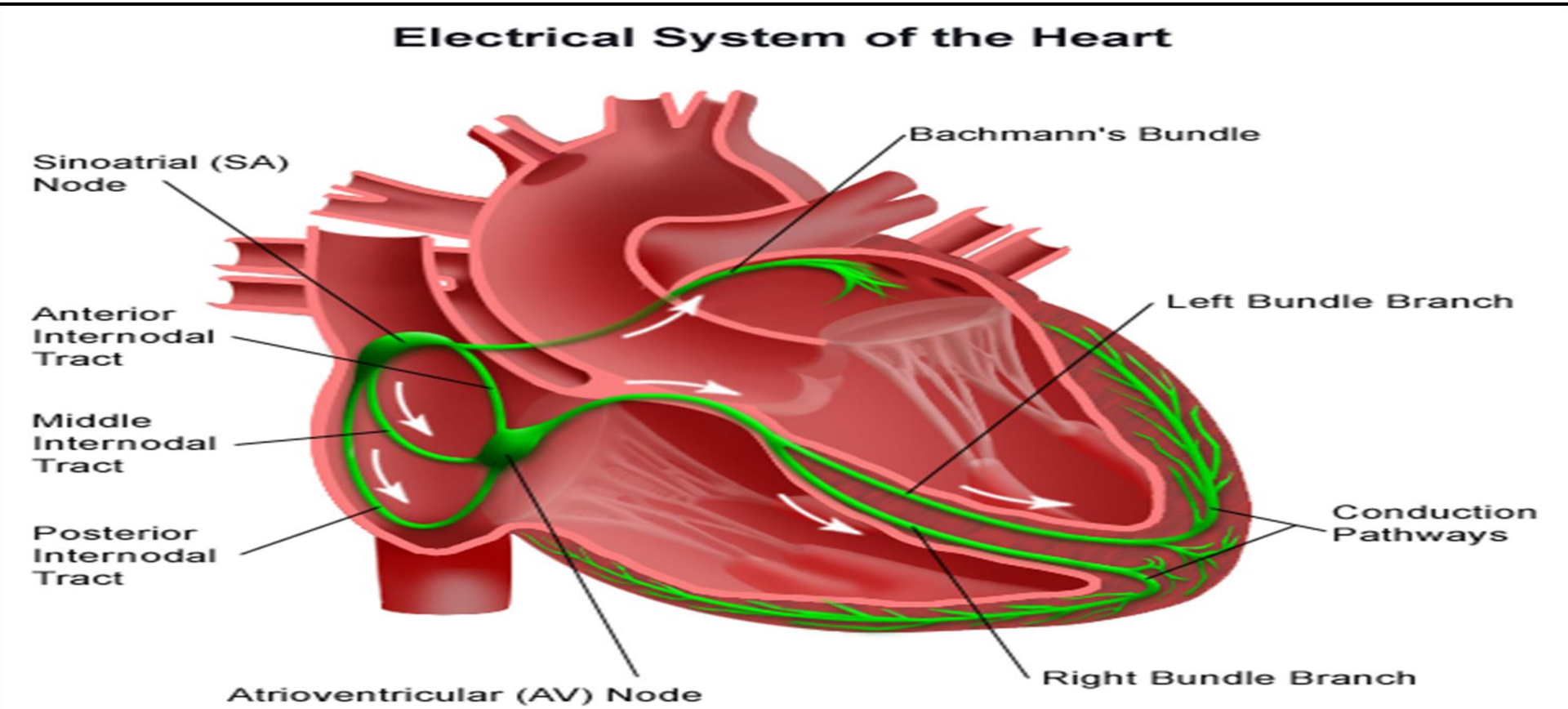
4. The **second half of diastole** coincides with **Phase 4** (i.e. RMP is reached).

Relation between electric response, mechanical response, and excitability changes in the heart



3. Conductivity

It **means** the ability of the cardiac muscle to **transmit** the excitation wave (action potentials) **from** one part of the heart to another **through** the **excitatory conductive system** of the heart.



Parts of Excitatory Conductive System of the Heart

1. Sinoatrial (SA) node (NORMAL pacemaker):

Here the initial impulses start → then conducted to the atria **through** the anterior inter-atrial pathway (to the left atrium) → to the atrial muscle mass **through** the gap junction,

and to → the Atrioventricular node (AV node) **through** anterior, middle, and posterior inter-nodal pathways.

The average velocity of conduction in the atria → one meter/s.

2. Atrioventricular (AV) node (SLOWEST conduction):

The electrical impulses **CANNOT** be conducted **directly** from the atria to the ventricles, because of the **fibrous skeleton**, which is an **electrical isolator**, located between the atria and ventricles.

So the **only** conductive way between atria and ventricles is the **AV node**.

But there is a DELAY in the conduction occurs in the AV node due to:

- The smaller size of the nodal fiber.
- Fewer gap junctions.

The average velocity of conduction in the AV node → 0.02 - 0.05 m/s.

Characters of AV nodal conduction:

1. AV nodal delay:

Significance:

a. **Allows** atria to empty blood into ventricles during the cardiac cycle **before** the beginning of ventricular contraction.

b. **Protects** the ventricles from the **pathological high atrial rhythm** (to prevent ventricular fibrillation).

N.B.

The **maximum rate of transmission** of impulses through **AV node is ~ 230 impulse/min.**

2. The **conduction from AV node** is a **one-way conduction only**.

3. Bundle of His:

A continuous with the AV node that **passes** to the ventricles **through** the inter-ventricular septum.

It is **subdivided** into: **Right** and **left** bundle.

4.Purkinje`s fibers (FASTEST conduction):

It is formed of fibers that spread to all parts of ventricular myocardium

Large fibers with velocity of conduction → **4 m/s.**

It **allows** spread of excitation wave to the whole ventricles simultaneously and thus contraction of the both ventricles as **one unit**)

The high conduction velocity of these fibers is due to:

The abundant gap junctions.

Their nature as very large fibers.

Factors affecting Conductivity (i.e. Dromotropism):

I. Positive (+ve) dromotropic factors:

1. Sympathetic stimulation: it accelerates conduction and decreases AV delay.
2. Hormones: e.g. Catecholamines & Thyroxine.
3. Mild warming.
4. alkalosis
5. Drugs: e.g. Sympathomimetic.

II. Negative (-ve) dromotropic factors:

1. Parasympathetic stimulation (vagal): it decreases conduction and ↑AV delay and may cause heart block.

2. Decreased body temperature.

3. Most of electrolyte disturbances → ↓ conductivity (especially K^+)

5. acidosis

4. Severe ischemia.

5. Drugs: **e.g.** cholinergic drugs, Digitalis.

4. Contractility

It **means** the ability of the cardiac muscle to **convert** electrical energy of action potential **into** mechanical work (i.e. **contraction**).


THANK
YOU