ECG

CARDIAC ELECTROPHYSIOLOGY : UNDERSTANDING IONIC FLUXES

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OUTLINE

Introduction

- ☐ **Pacemaker cells** – SA node (others AV node and Purkinje fibers but at a slower rate) : through Slow Action Potential
- ☐ **Non-Pacemaker cells** – contractile unit (atrial and ventricular myocytes) : through Fast Action Potential

The Genesis of Action Potential from SA Node and its Conduction to the Ventricles

SA Node and its Action Potential

Spread of Impulse to Adjacent Atrial Myocytes Through Transitional Zone

AV Nodal delay (0.09 second)

Rapid Transmission Through the Ventricular Purkinje System
(At velocity of 1.5-4 meters /second)

Ventricular Transmission

Phase Wise Classification of Ventricular Action Potential

- Depolarization INa (Phase 0)
- Repolarization Ito Ica Ikr Iks (Phase 1, 2 and 3 respectively)
- Restoration to the resting state by Na^+-K^+ ATPase Pump and IKi (Phase 4)

Cardiac Action Potential occurring at Different Level (In brief)

The Mechanism of Excitation-Contraction Coupling of the Cardiac Muscle

Take Home Message

References

CARDIAC ELECTROPHYSIOLOGY : Understanding Ionic Fluxes

A Narrative Review

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The heart , a poet of its own kind , writes its verses as P-QRS-T on ECG , where the science of cardiac electrophysiology deciphers its rhythm to sustain the life.

- ☐ **The fundamental unit of this rhythm-play smiles through what is known as 'Action Potential'.**
- ☐ **The Cardiac action potential initiates brief changes in voltage across cardiac cell membrane – it is brought about by the fluxes of ions through ion channels.**

All these electrocardiac events are well organised sailing the boat of cardiac life smoothly, without which the life would not be possible.

1. Introduction

The Cardiac Action Potential is a series of brief changes in voltage across the cardiac cell membrane, brought about by fluxes of ions through ion channels. Accordingly , there are two sets of action potentials for the purpose :

A. Pacemaker Potential (Slow Action Potential) : As seen with SA Node
There is an automatic slow depolarization of the pacemaker cells , which is capable of reaching to its threshold level - so as to generate slow upstroke. This occurs due to the influx of **Ca^{++}** ions inside.

B. Non-Pacemaker Potential (Fast Action Potential) : This potential seen in contractile cells (atria and ventricles) that are backed up by rapid depolarization due to the opening of fast **Na^{+}**channels.

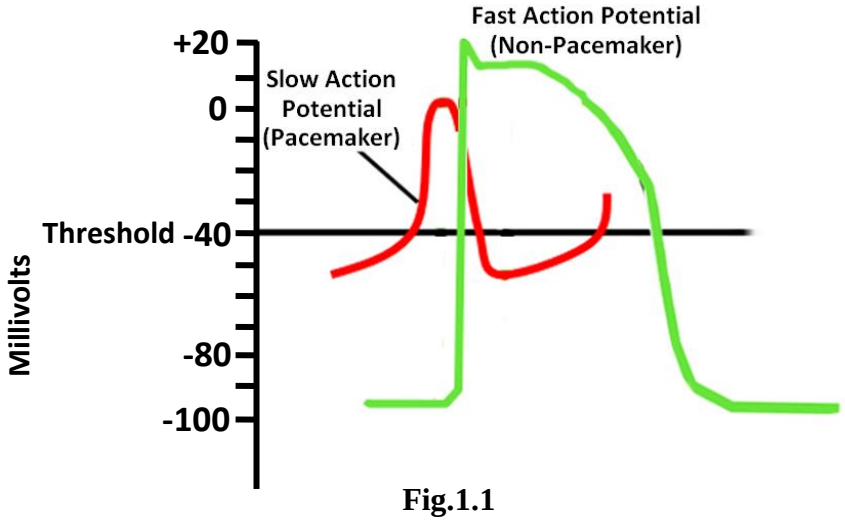


Fig.1.1

2. The genesis of Action Potential from SA node and its conduction to the ventricles

There is well organised cardiac system that causes the automatic generation of action potential from the SA node, which is located in the wall of the right atrium, laterally to the entrance of the superior vena cava, in a region called the sinus venarum (hence termed as sinoatrial node)

Further steps: All cardiac cells are electrically linked to each other through gap junctions, allowing the action potential to pass from one cell to the next.

- The initial action potential generated from the SA node passes to the atria evoking its action potential resulting in its contraction.
- Through the conducting pathway (AV node – HIS-Purkinje system) the impulse passes onwards to the ventricles.
- The ventricular myocytes evoke its action potential causing its contraction.

3. SA Node and its Action Potential

The SA node exhibits **automaticity** – these tissues don't need an external trigger to undergo depolarization. This can be explained by the fact that **the initial potential of this nodal tissues is less negative compared to the RMP of the contractile units of a myocytes**. Thus, this allows Na^+ channels to be automatically activated in a slowly rising semi-curve manner.

Its electrophysiology is summarised as below:

- The spontaneous depolarization of the pacemaker potential during **phase 4** imparts the SA node its auto-rhythmicty. The presence of the so called pacemaker current generated by HCN (Hyperpolarization – activated cyclic Nucleotide gated) channels which are abundant over SA Node and are responsible for the flow of cation – Na^+ + K^+ (mainly Na^+) into the cell. Due to the unusual property of being activated by low negative membrane potential , the movement of ions through these channels is known as **funny current** (If).
- The upstroke of action potential **phase 0** is created by a slowly increase in Ca^{++} conductance through L-type Calcium channels instead of by fast Na^+ currents.
- **Phase 1 and 2 are absent** in the SA node action potential (here there is no question of myocontraction).
- **Phase 3** of repolarization is caused by increase in K^+ conductance, causing an outward flow of K^+ ions. Once the cell is completely repolarized at about -60 mV , the cycle gets spontaneously repeated.

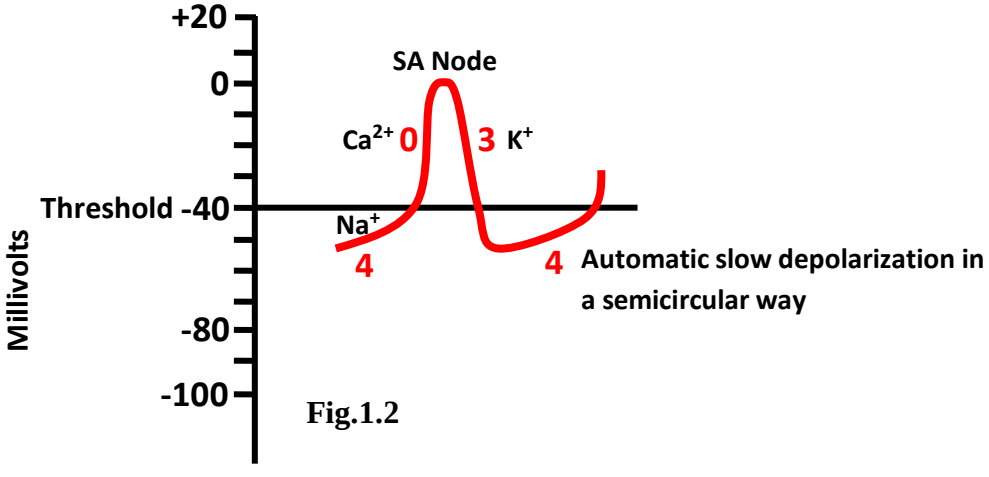


Fig.1.2

4. Spread of impulse to adjacent atrial myocytes to transitional Zone

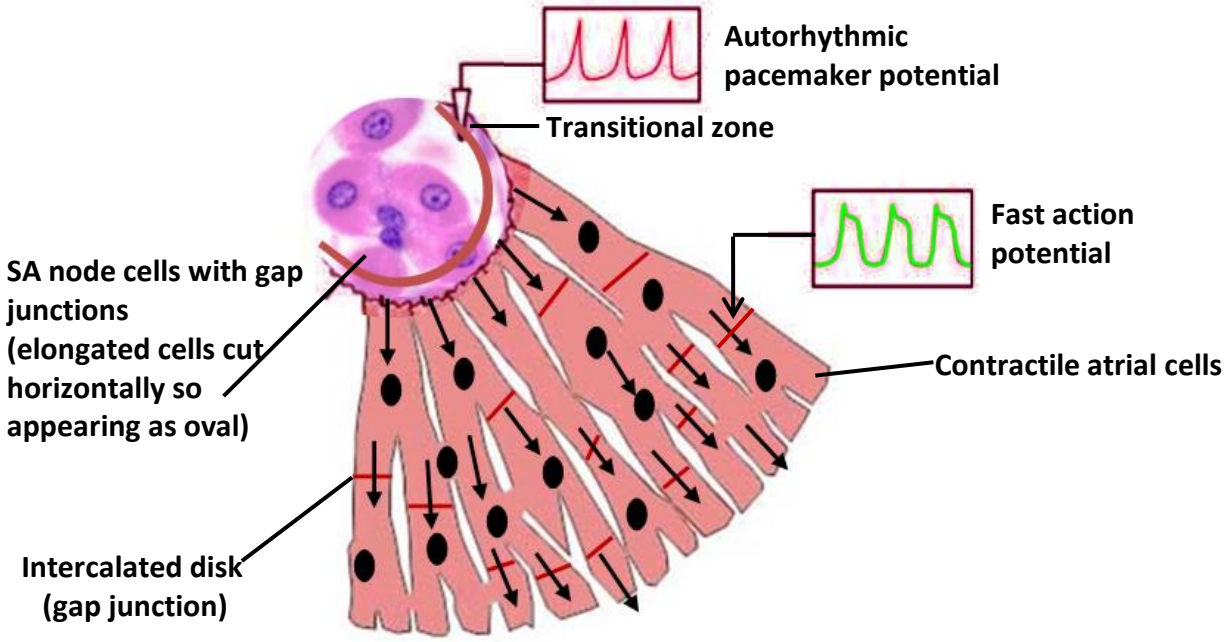


Fig.1.3

The cellular architecture of the SA node:
The main cellular cluster is consisting of elongated cells densely packed within, having its contact with each other , which are also making its connection with the nearby atrial myocardium through the interconnecting collar of **'transitional' cells** (as illustrated in the above sketch). Numerous autonomic ganglia and nerves are found enclosed inside. The SA node is mainly under the influence of vagus nerve and increase in vagal tone slows the heart rate; a decrease in vagal tone accelerates the heart rate. The pacemaker cells are sensitive to stretch by pressure volume, as well
The cytoarchitecture of this transitional zone makes contact with atrial myocytes and this is essential for smooth propagation of SA node action potential through its geometrical arrangements , with sub-bifurcation channels to maintain the dynamic flow of the impulse onwards to the atria.

5. AV Nodal delay

AV node is situated over the posterior wall of the right atrium, just behind tricuspid valve. There is a momentary delay of the impulse in the AV nodal system, **due to the diminished number of gap junctions between successive cells and thus, there is a comparative resistance to the ongoing conduction**. There is a delay of almost 0.09 second in the AV node.

Gap Junctions : These are constituted with the connexin proteins that form gaps through which the fluxes of ions may pass across the cardiac cell membrane. Since potassium is highest intracellularly , these ions may pass through these gaps. The increased potassium in the nearby cells causes the membrane potential to be increased slightly towards negativity , and thus there is an activation of fast sodium channels of contractile cellular units.

6. Rapid transmission through the ventricular Purkinje system

Purkinje fibers are very large fibers, even longer than the ventricular muscle fibers. There is a speedy conduction of the action potential at velocity of 1.5 to 4 m/s. This rapid propagation transmits the electrical potential almost instantaneously to the entire ventricular muscular system. This rapid transmission is offered to the system by a very high level of permeability of the intercalated disc gaps.

7. Ventricular transmission

The standard model used to demonstrate cardiac action potential is that of the ventricular myocytes.

The contractile unit of ventricular myocytes lies in between endocardium and epicardium. The current of **depolarization** is spread through endocardial cells with an inner rich network of Purkinje fibers adjoining with myocytes forming **Purkinje-myoctes unit**. This allows the propagation of impulses from endocardium to epicardium and from apex to the base (due to the spiral arrangements of the ventricular muscle the impulse from the Purkinje fibers takes the spiral conduction from apex to the base). **This is to mention here that the depolarization makes the entire myocardium somewhat isoelectric but with reverse polarity on either side so that a harmonized myocardial contraction may set in without its trembling**. The **repolarization** journey starts towards the epicardium firstly by a transient opening of a specialized channel known as calcium-insensitive **transient outward** current (Ito) . This Ito current opens L-type current ('L' stands for long lasting referring to the length of activation) and this further opening of Ca^{2+} channel is responsible for the exchange in between Ca^{2+} and K^{+} to bring 'excitation-contraction coupling' operation resulting in harmonized myocardial contraction. Once the myocardial contraction gets completed , there is a further sequential opening of different K^{+} channels in succession and ultimately restoration of the myocytes to the previous polarized state by Na-K ATPase pump and inward rectifier channels (IKi).

The concept of ionic channels is summarized as below :

:

- **Fast Na^{+} Channel** brings positive charge inside the cell and depolarizes the cardiac membrane , the threshold potential for this purpose is at -70 mV.
- **Ito channel** (transient outward current) The opening and closing of the channel rapidly allows a transient flow of potassium ions out of the cell , making the membrane potential slightly more negative .
- **Ica^{2+} Channel** Ito channels open the Ica^{2+} channels to facilitate the exchange in between calcium ions and potassium ions.
- The main potassium channels involved during repolarization are the rapid rectifiers **(IKr)** , slow rectifiers **(IKs)** and the inward rectifiers **(IKi)**.
  IKr and IKs channels are activated from the beginning of repolarization – IKs act upto the phase 3 of repolarization and IKi remain active upto the last phase of repolarization to push the remaining potassium ions inside the cardiac cells.

This is to be mentioned here that depolarization current is only concerned with the reversal of the polarized state resulting in negatively charged surface outside the cardiac membrane and positively charged inside. This is possible by the inward current facilitated through Na^+ conductance pushing the sodium ions inside the membrane. That's why , the endocardial cells are rich in INa showing 'dome pattern'. **This whole happens due to the transmission through the syncytial ventricular mass and only INa channels are opened during depolarization**.

The repolarization is a journey proceeding towards normal polarity. That's why , **it is accordingly equipped with genetically determined ion channels – Ito , Ica, Ikr , Iks , Iki which are opened in succession during repolarization travelling through the syncytial ventricular mass.** These epicardial cells exhibits spike-and-dome pattern brought about by the Ito ion channels to initiate the subsequent phases of repolarization.

In Nutshell, 'Cardiac Action Potential' results with the sequential opening and closing of genetically determined ion channels (INa, Ito , Ica, Ikr, Iks ,Iki, etc)
The 'Endocardial cells' and 'Epicardial cells' do not show the ionic mirror image. The following differences in between two are observed:

- 'Endocardial cells' without notch pattern (dome pattern), having little or no expression of Ito channels. This is to be mentioned here that 'Endocardial cells' is concerned mainly with the depolarization of the ventricles.
- The 'Epicardial cells' exhibits spike-and-dome pattern brought about by the pool of Ito ion channels to initiate the subsequent phases of repolarization.
- In the experiment in canine myocytes no sustained component of L-type Ca^{2+} channel was observed in ENDO cells, while with EPI cells a somewhat deeper and longer notch was associated with a larger population of Ca^{2+} channels. The notch is practically absent in ENDO cells, i.e. the major difference between the EPI and ENDO cells is that **EPI cells do have a remarkable functional pool of Ca^{2+} channel to be activated while ENDO cells do not**.
  (**Reference** :Endocardial versus epicardial differences in L-type calcium current in canine ventricular myocytes studied by action potential voltage clamp by Tamas Banyasz et al, https://pubmed.ncbi.nlm.nih.gov/12667947/

The events discussed upto this stage may be summarized with the following formulas, as illustrated below phasewise :

- **Depolarization INa (Phase 0)**
- **Repolarization Ito Ica Ikr Iks (Phase 1, 2 and 3 respectively)**
- **Restoration to the resting state by Na^+-K^+ ATPase Pump and IKi (Phase 4)**

8. Phase wise classification of Ventricular Action Potential

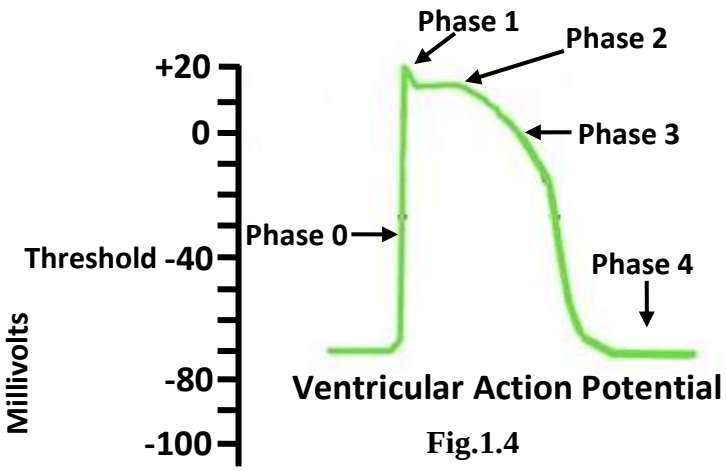
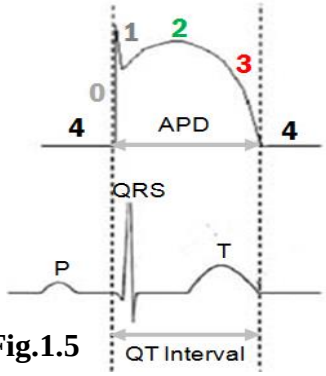


Fig.1.4

The Events of Cardiac Action Potential And Genesis of ECG Changes :

A relation of the 'Action Potential ' to the ECG is illustrated below by the following sketch: (The standard model used to demonstrate the cardiac action potential is that of the ventricular myocytes)



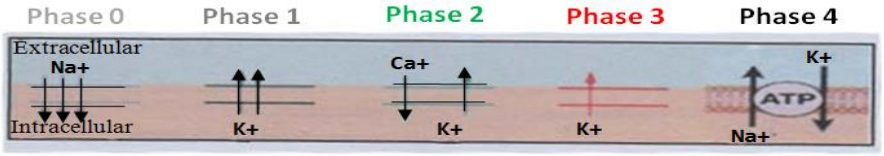
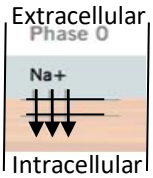
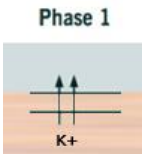


Fig.1.5

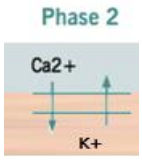
The inside of the cardiac membrane is more negative than the outside. The main ions responsible for this state are $3Na^+$ outside the cells and $2K^+$ inside the cells



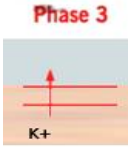
- During Phase 0 , the Rapid Inward cellular current facilitated through Na^+ conductance brings positive charge inside the cell - this depolarizes the cardiac membrane of the ventricles inscribing QRS complex



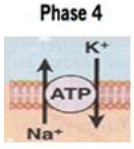
- During phase 1, there is some outward movement of K^+ for a transient period making the membrane potential slightly more negative. This is referred as a 'notch' over the action potential. The same is being reflected on ECG as a notch known as j (junctional) point at the end of the QRS complex.



- The plateau in phase 2 is due to the balance between inward movement of Ca^{2+} and outward movement of K^+. This phase actually corresponds to the ventricular contraction and is being reflected on ECG as an isoelectric ST segment.



- Replolarization occurs during phase 3 due to the further outward movement of K^+ ions with the closing of Ca^{++} channels and this phase is reflected on ECG in the form of T wave.



- The phase 3 ends in phase 4 where the resting membrane potential is brought to the original state mainly by the Na^+ - K^+ - ATPase pump , other being Na^+/Ca^{2+} exchanger current and inwardly rectifying K^+ current. This resting phase on ECG is further reflected by TP segment - an isoelectric line.

9. Cardiac action potential occurring at different levels (in brief) are illustrated below in a sequential manner

SA node is having a considerable higher frequency of depolarization (60-100/min) and overrides the pacemaker activity of AV node. AV node serves as an electrical relay station delaying the electrical current sent by the sinoatrial node before the signal is allowed to pass down to the ventricles. This delay allows atria enough time to empty its blood contents into the ventricles before ventricular contraction takes place.

SA Node Potential

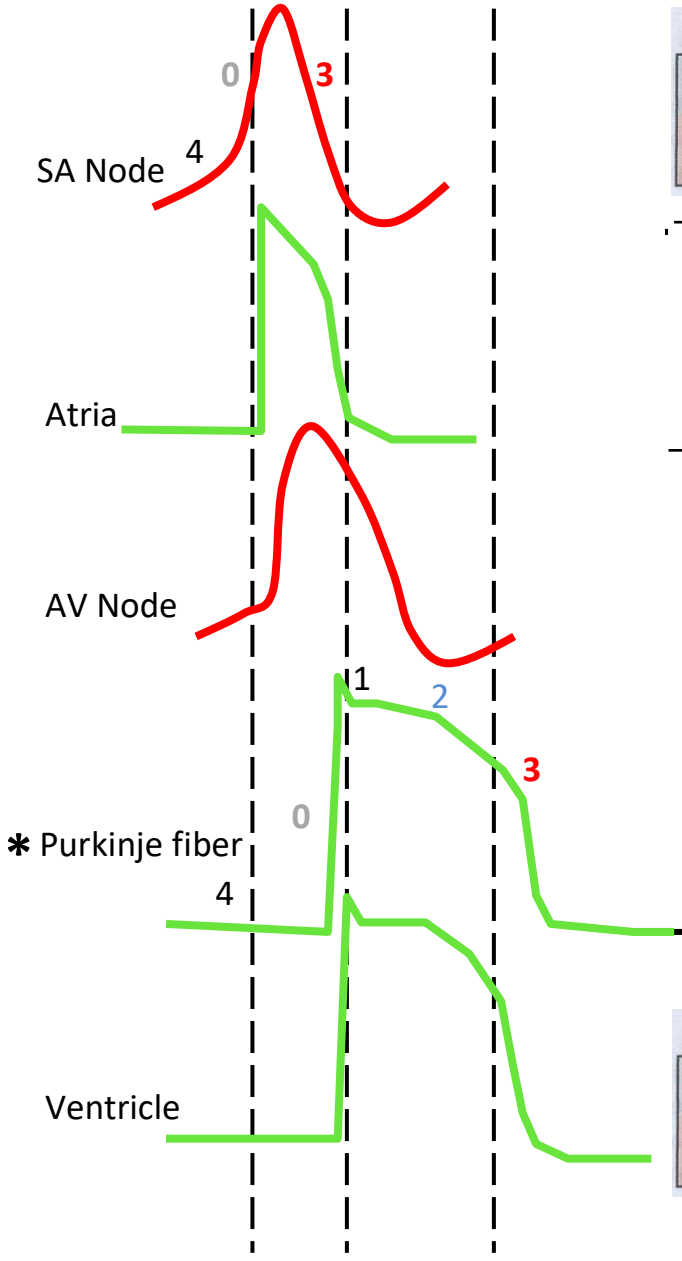
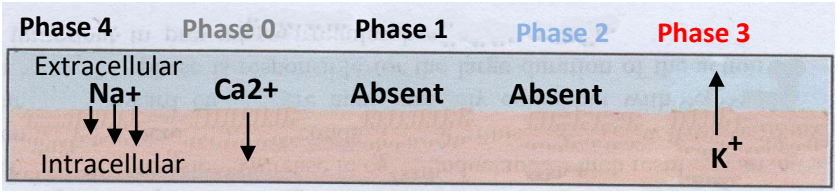


Fig.1.6

SA Node Action Potential



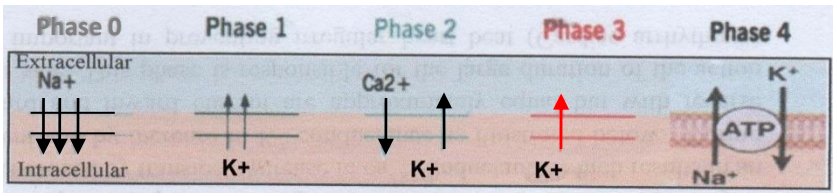
Atrial Action Potential – typically exhibits a triangular morphology

A more narrow phase 2 (plateau phase) due to a smaller calcium influx (Less muscular atria)

Relay through AV Node with further propagation.

Action potential in the AV node , like the SA node is governed primarily by changes with inward Ca^{2+} and outward K^{+} currents , and does not involve fast Na^{+} current. AV nodal tissue unlike SA nodal cells have dormant pacemaker activity but with a slower rate (40-60 per minute) due to diminished number of gap junctions between successive cells , with a somewhat resistant to the conduction.

Ventricular Action Potential



✱ Purkinje fibers are having the longest duration of action potential compared to the rest. This helps in preventing the backward impulse propagation from ventricles to upward direction , thus eliminating the chance of reentry mechanism.

10. The mechanism of Excitation Contraction Coupling of the cardiac muscle

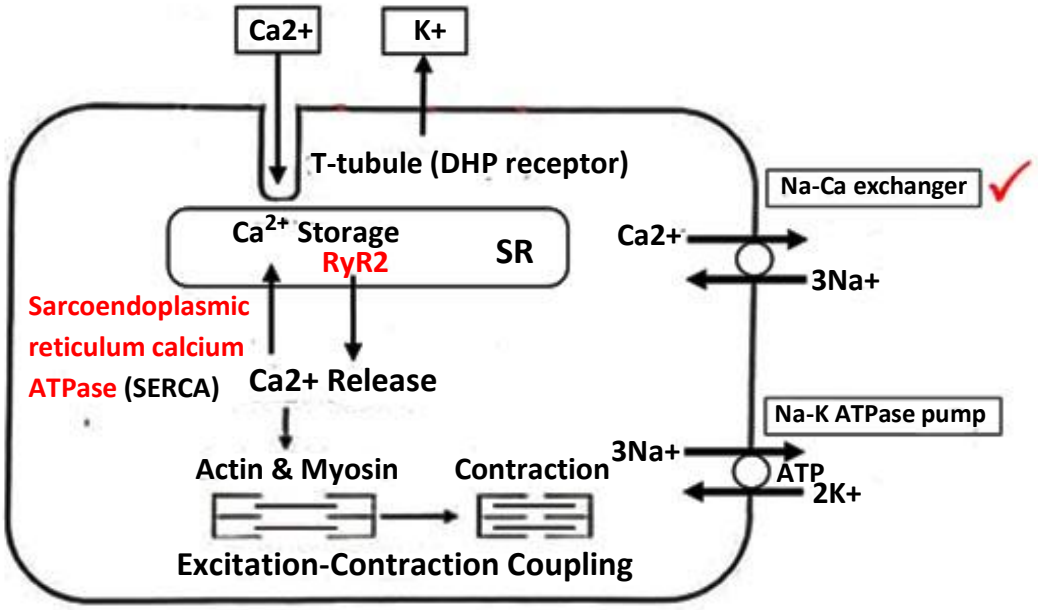


Fig.1.7

Steps in 'Excitation Contraction Coupling' are as follows:

- Action potential causes the impulse to travel along the Sarcolemma down to the transverse tubule (T-tubule) system through the depolarized cell membrane.
- Voltage sensitive DHP (Dihydropyridine) receptors open the gate to allow more calcium entry inside the cells during the Phase 2 of the action potential.
- During this plateau phase of the action potential Ca^{++} ions enter the inward of the cells through L- type calcium channel.
- This entry of Ca^{++} triggers more Ca^{++} release from sarcoplasmic reticulum through special channel – (ryanodine receptors) – RyR2
- With this further release of Ca^{++} ions there is increase in intracellular concentration of Ca^{2+}.
- Actin and myosin filaments are bound together , which allows sliding of these filaments over each other with the help of Ca^{2+} resulting in the contraction of myocardial cell (**Excitation-contraction coupling**)
- Ultimately the cardiac relaxation occurs when Ca^{++} is recycled back to the interior of sarcoplasmic reticulum by 'sarcoplasmic reticulum calcium ATPase' (SERCA). The extra calcium ions might also be pushed outside the cardiac myocytes through Na^{+}-Ca^{2+} exchanger mechanism whenever such ionic operation is needed.

11. Take Home Message

The cardiac action potential can be called as the '**Integrative Biochemical Laboratory of the Heart'**. Without its proper concept it would be rather impossible to understand the basic physiology of the heart and simultaneously it would also be impossible to have the concept of ECG reading. Since we have discussed a lot on cardiac action potential , this becomes necessary to organize this entire concept in mind as a study tool .

- Atrial tachycardia (AT) is a form of supraventricular tachycardia (SVT) originating from a **single** ectopic focus within the atria but outside of the sinus node – since it is having a single point of firing outside the natural pacemaker, it is also known as Focal atrial tachycardia (FAT).

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  There is an automatic slow depolarization of the pacemaker cells , which is capable of reaching to its threshold level - so as to generate slow upstroke. This occurs due to the influx of **Ca^{++}** ions inside.

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- Depolarization INa (Phase 0)
  Repolarization Ito Ica Ikr Iks (Phase 1, 2 and 3 respectively)
  Restoration to the resting state by Na^{+}-K^{+} ATPase Pump and IKi (Phase 4)

- Excitation-Contraction Coupling

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