Review on Sub Cellular (ionic species) Study of Natural Pacemakers and Impulse Propagation through Cardiac Muscles

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Abstract

The rhythmic contraction of our heart is controlled by electrical impulses that travels throughout the cardiac muscle. The signal is generated by the sinus node, which can be thought of as the natural pacemaker of our heart. This impulse spreads from its initiation in the SA node throughout the atria through specialized internodal pathways, to the atrial myocardial contractile cells and the atrioventricular node.This term paper reviews the anatomy of SA node, Action potential and the impulse propagation through cardiac muscles.

Introduction

Every heartbeat is initiated and coordinated by the cardiac conduction system, which consists of the sinus node (generating pacemaker potentials), the atrioventricular node and His-Purkinje system.The SA node in human, goat and other mammalian species is a group of cells located in the wall of the right atrium of the heart which have the ability to spontaneously produce the electrical impulses to make our hearts beat.The sinus node consists of a small cluster of highly specialized cells located in the upper part of the right atrium. The function of the sinus node is primarily electrical, whereas the function of the atrial and ventricular muscle is primarily contractile.

Anatomy of SA node

In all species, the SA node is located in the right atrium at the junction of the crista terminalis (a thick band of atrial muscle at the border of the atrial appendage) with venous tissue — the superior and inferior vena cava, and the intercaval region between the two great veins. The size of the SA node varies in different species.In the human, published photographs show the SA node beneath the epicardial surface of the crista terminalis. In other species, at least part of the SA node lies in the intercaval region. In the cat, the SA node from the intercaval region can rise up the epicardial face of the crista terminalis before terminating. In the dog, the SA node in the intercaval region appears to abut against the crista terminalis. In the rabbit, SA node tissue from the intercaval region rises up the endocardial face of the crista terminalis and terminates at the

right branch of the sinoatrial ring bundle. Similarly, in the monkey SA node tissue rises up the endocardial face of the crista terminalis. In most species (rabbit, rat, guinea-pig, cat, dog, pig, monkey), perhaps even human, but apparently not cow, the SA node may extend from the superior to the inferior vena cava.

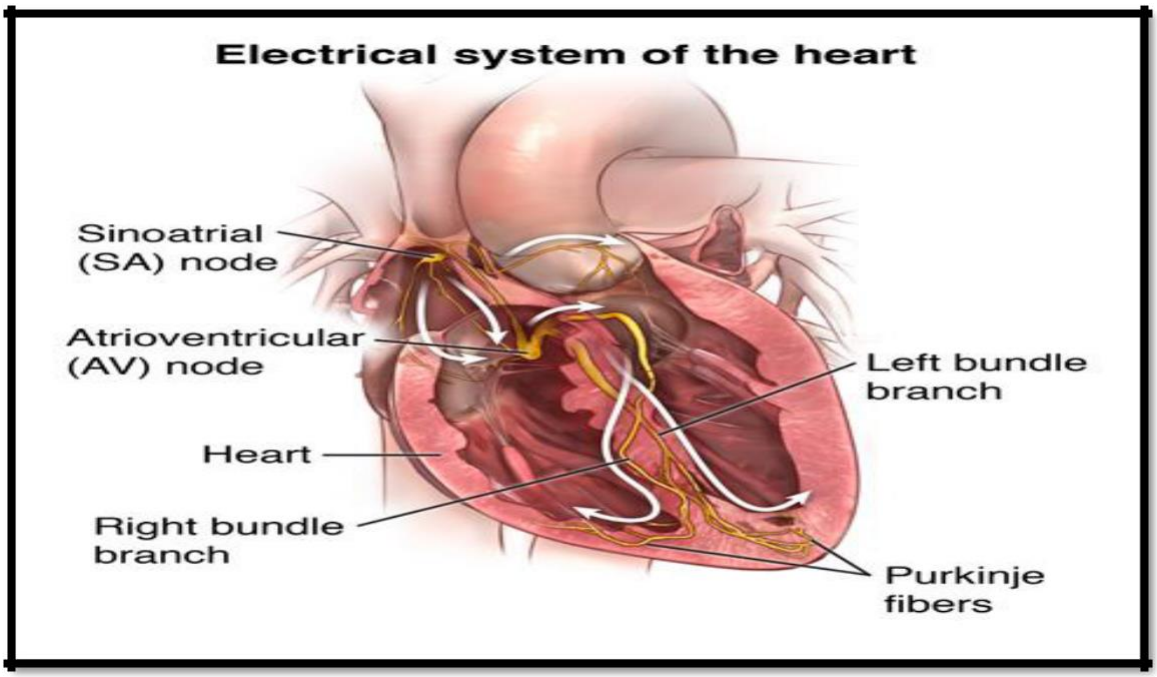


Figure 1

Ion channels

- Two main forces drive ions across cell membranes:
    - ***Chemical potential:*** an ion will move down its *concentration gradient.*
    - ***Electrical potential:*** an ion will move away from ions/molecules of like charge.
- The **transmembrane potential (TMP)** is the electrical potential difference (voltage) between the inside and the outside of a cell. When there is a *net* movement of +ve ions *into* a cell, the TMP becomes more +ve, and when there is a *net* movement of +ve ions *out* of a cell, TMP becomes more –ve.
- Ion channels help maintain ionic concentration gradients and charge differentials between the inside and outside of the cardiomyocytes.

Properties of cardiac ion channels

- **Selectivity***:* they are only permeable to a single type of ion based on their physical configuration.

- **Voltage-sensitive gating**: a specific TMP range is required for a particular channel to be in open configuration; at all TMPs outside this range, the channel will be closed and impermeable to ions. Therefore, specific channels open and close as the TMP changes during cell depolarization and repolarization, allowing the passage of different ions at different times.

- **Time-dependence**: *some* ion channels (importantly, fast Na^+ channels) are configured to close a fraction of a second after opening; they cannot be opened again until the TMP is back to resting levels, thereby preventing further excessive influx.

Action potentials

Action potential: electrical stimulation created by a sequence of ion fluxes through specialized channels in the membrane (sarcolemma) of cardiomyocytes that leads to cardiac contraction.

Action potential in cardiomyocytes

The action potential in typical cardiomyocytes is composed of 5 phases (0-4), beginning and ending with phase 4.

Phase 4: The resting phase

- The resting potential in a cardiomyocyte is −90 mV due to a constant outward leak of K+ through inward rectifier channels.

- Na+ and Ca2+ channels are closed at resting TMP.

Phase 0: Depolarization

- An action potential triggered in a neighbouring cardiomyocyte or pacemaker cell causes the TMP to rise above −90 mV.

- Fast Na+ channels start to open one by one and Na+ leaks into the cell, further raising the TMP.

- TMP approaches −70mV, the threshold potential in cardiomyocytes, i.e. the point at which enough fast Na+ channels have opened to generate a self-sustaining inward Na+ current.

- The large Na+ current rapidly depolarizes the TMP to 0 mV and slightly above 0 mV for a transient period of time called the overshoot; fast Na+ channels close (recall that fast Na+ channels are time-dependent).

- L-type (—long-opening‖) Ca2+ channels open when the TMP is greater than −40 mV and cause a small but steady influx of Ca2+ down its concentration gradient.

Phase 1: Early repolarization

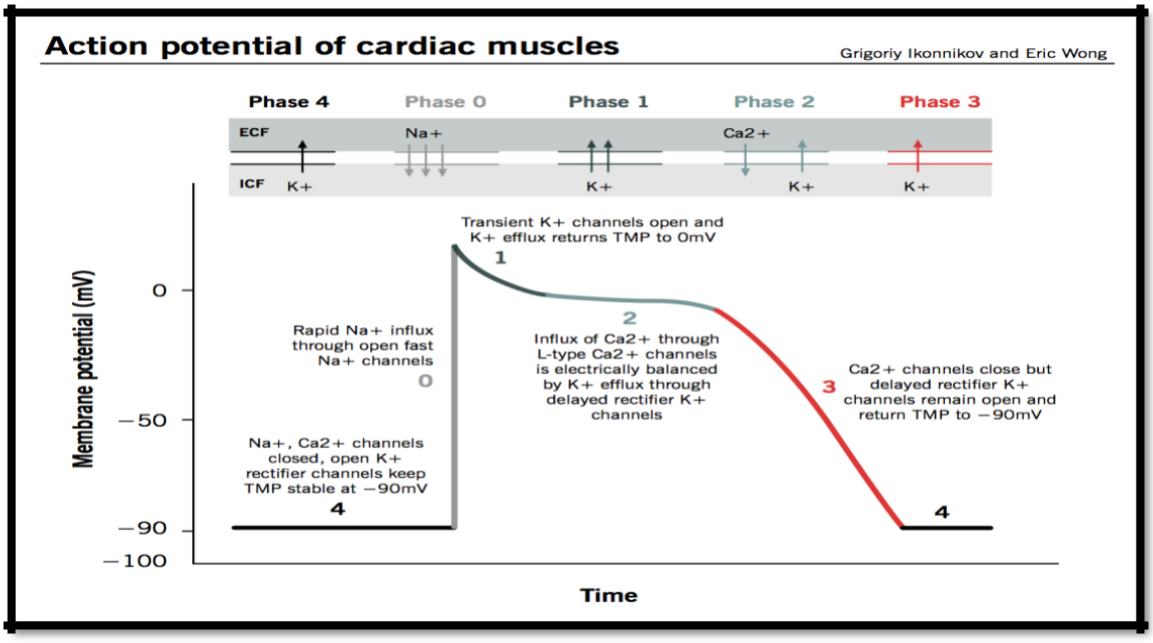
- TMP is now slightly positive.
- Some K+ channels open briefly and an outward flow of K+ returns the TMP to approximately 0 mV.

Phase 2: The plateau phase

- L-type Ca2+ channels are still open and there is a small, constant inward current of Ca2+. This becomes significant in the excitation-contraction coupling process described below.
- K+ leaks out down its concentration gradient through delayed rectifier K+ channels.
- These two countercurrents are electrically balanced, and the TMP is maintained at a plateau just below 0 mV throughout phase 2.

Phase 3: Repolarization

- Ca2+ channels are gradually inactivated.
- Persistent outflow of K+, now exceeding Ca2+ inflow, brings TMP back towards resting potential of −90 mV to prepare the cell for a new cycle of depolarization.
- Normal transmembrane ionic concentration gradients are restored by returning Na+ and Ca2+ ions to the extracellular environment, and K+ ions to the cell interior. The pumps involved include the sarcolemmal Na+-Ca2+ exchanger, Ca2+-ATPase and Na+-K+-ATPase.



Impulse propagation through cardiac muscles

Sinoatrial (SA) Node

The sinus node generates an electrical stimulus regularly, 60 to 100 times per minute under normal conditions. The atria are then activated. The electrical stimulus travels down through the conduction pathways and causes the heart's ventricles to contract and pump out blood. The 2 upper chambers of the heart (atria) are stimulated first and contract for a short period of time before the 2 lower chambers of the heart (ventricles).

This impulse spreads from its initiation in the SA node throughout the atria through specialized internodal pathways, to the atrial myocardial contractile cells and the atrioventricular node. The internodal pathways consist of three bands (anterior, middle, and posterior) that lead directly from the SA node to the next node in the conduction system, the atrioventricular node. The impulse takes approximately 50 ms (milliseconds) to travel between these two nodes. The relative importance of this pathway has been debated since the impulse would reach the atrioventricular node simply following the cell-by-cell pathway through the contractile cells of the myocardium in the atria. In addition, there is a specialized pathway called Bachmann's bundle or the interatrial band that conducts the impulse directly from the right atrium to the left atrium. Regardless of the pathway, as the impulse reaches the atrioventricular septum, the connective tissue of the cardiac skeleton prevents the impulse from spreading into the myocardial cells in the ventricles except at the atrioventricular node. Figure 2 illustrates the initiation of the impulse in the SA node that then spreads the impulse throughout the atria to the atrioventricular node.

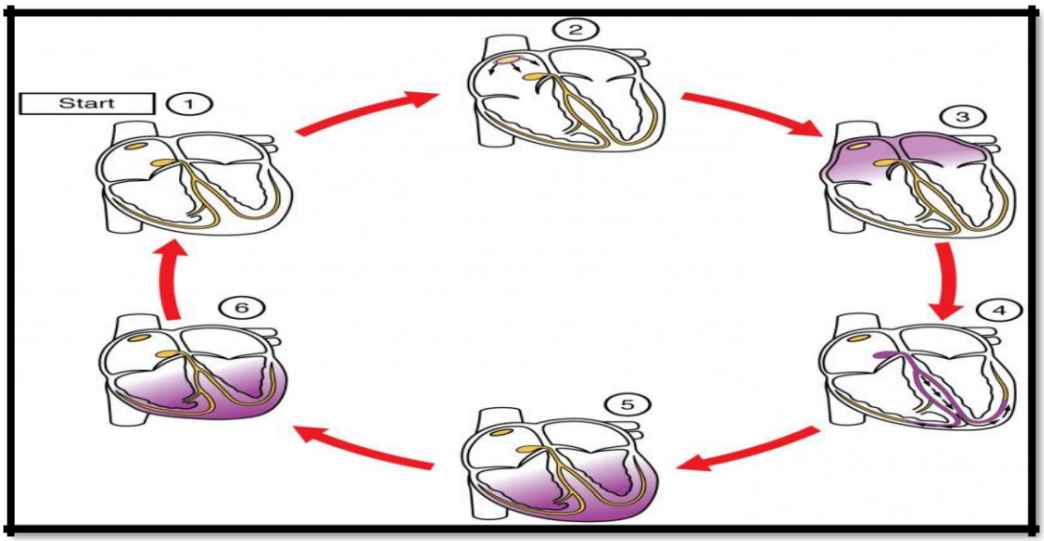


Figure 2 (1) The sinoatrial (SA) node and the remainder of the conduction system are at rest. (2) The SA node initiates the action potential, which sweeps across the atria. (3) After reaching the atrioventricular node, there is a delay of approximately 100 ms that allows the atria to complete pumping blood before the impulse is transmitted to the atrioventricular bundle. (4) Following the delay, the impulse travels through the atrioventricular bundle and bundle branches to the Purkinje fibers, and also reaches the right papillary muscle via the moderator band. (5) The impulse spreads to the contractile fibers of the ventricle. (6) Ventricular contraction begins.

The electrical event, the wave of depolarization, is the trigger for muscular contraction. The wave of depolarization begins in the right atrium, and the impulse spreads across the superior portions of both atria and then down through the contractile cells. The contractile cells then begin contraction from the superior to the inferior portions of the atria, efficiently pumping blood into the ventricles.

Atrioventricular (AV) Node

The atrioventricular (AV) node is a second clump of specialized myocardial conductive cells, located in the inferior portion of the right atrium within the atrioventricular septum. The septum prevents the impulse from spreading directly to the ventricles without passing through the AV node. There is a critical pause before the AV node depolarizes and transmits the impulse to the atrioventricular bundle (see image above, step 3). This delay in transmission is partially attributable to the small diameter of the cells of the node, which slow the impulse. Also, conduction between nodal cells is less efficient than between conducting cells. These factors mean that it takes the impulse approximately 100 ms to pass through the node. This pause is critical to heart function, as it allows the atrial cardiomyocytes to complete their contraction that pumps blood into the ventricles before the impulse is transmitted to the cells of the ventricle itself. With extreme stimulation by the SA node, the AV node can transmit impulses maximally at 220 per minute. This establishes the typical maximum heart rate in a healthy young individual.
Damaged hearts or those stimulated by drugs can contract at higher rates, but at these rates, the heart can no longer effectively pump blood.

Atrioventricular Bundle (Bundle of His), Bundle Branches, and Purkinje Fibers

Arising from the AV node, the atrioventricular bundle, or bundle of His, proceeds through the interventricular septum before dividing into two atrioventricular bundle branches, commonly called the left and right bundle branches. The left bundle branch has two fascicles. The left bundle branch supplies the left ventricle, and the right bundle branch the right ventricle. Since the left ventricle is much larger than the right, the left bundle branch is also considerably larger than the right. Portions of the right bundle branch are found in the moderator band and supply the right papillary muscles. Because of this connection, each papillary muscle receives the impulse at approximately the same time, so they begin to contract simultaneously just prior to the remainder of the myocardial contractile cells of the ventricles. This is believed to allow tension to develop on the chordae tendineae prior to right ventricular contraction. There is no corresponding moderator band on the left. Both bundle branches descend and reach the apex of the heart where they connect with the Purkinje fibers (see image above, step 4). This passage takes approximately 25 ms.

The Purkinje fibers are additional myocardial conductive fibers that spread the impulse to the myocardial contractile cells in the ventricles. They extend throughout the myocardium from the apex of the heart toward the atrioventricular septum and the base of the heart. The Purkinje fibers have a fast inherent conduction rate, and the electrical impulse reaches all of the ventricular muscle cells in about 75 ms (see image above, step 5). Since the electrical stimulus begins at the apex, the contraction also begins at the apex and travels toward the base of the heart, similar to squeezing a tube of toothpaste from the bottom. This allows the blood to be pumped out of the ventricles and into the aorta and pulmonary trunk. The total time elapsed from the initiation of the impulse in the SA node until depolarization of the ventricles is approximately 225 ms.

Membrane Potentials and Ion Movement in Cardiac Conductive Cells

Action potentials are considerably different between cardiac conductive cells and cardiac contractive cells. While Na^+ and K^+ play essential roles, Ca^{2+} is also critical for both types of cells. Unlike skeletal muscles and neurons, cardiac conductive cells do not have a stable resting potential. Conductive cells contain a series of sodium ion channels that allow a normal and slow influx of sodium ions that causes the membrane potential to rise slowly from an initial value of −60 mV up to about –40 mV. The resulting movement of sodium ions creates spontaneous depolarization (or prepotential depolarization). At this point, calcium ion channels open and Ca^{2+} enters the cell, further depolarizing it at a more rapid rate until it reaches a value of approximately +5 mV. At this point, the calcium ion channels close and K^+ channels open, allowing outflux of K^+ and resulting in repolarization. When the membrane potential reaches approximately −60 mV, the K^+ channels close and Na^+ channels open, and the prepotential phase begins again. This phenomenon explains the autorhythmicity properties of cardiac muscle (Figure 3).

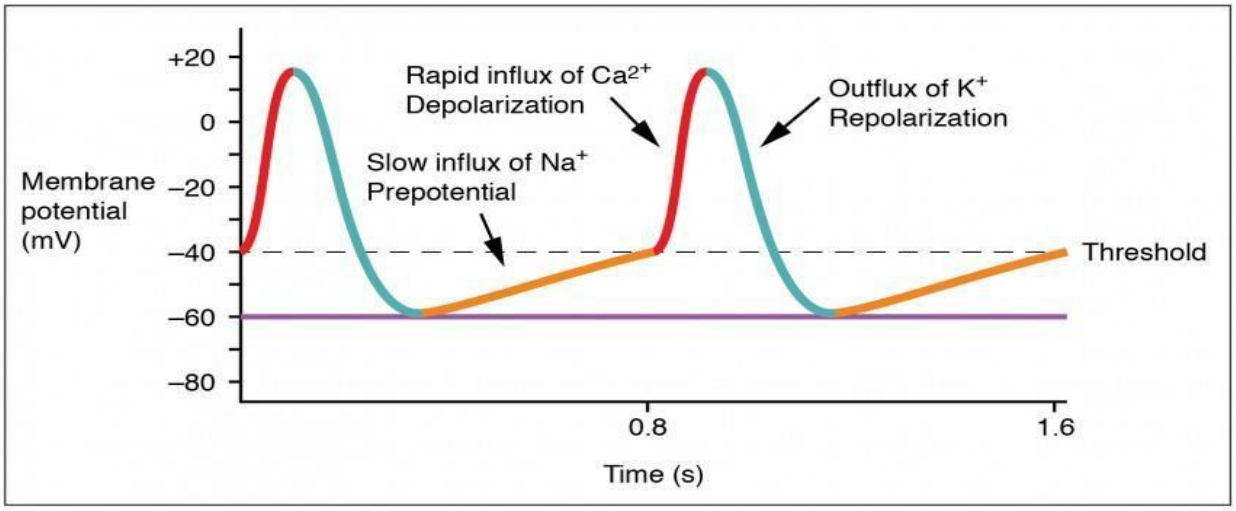


Figure 3 The prepotential is due to a slow influx of sodium ions until the threshold is reached followed by a rapid depolarization and repolarization. The prepotential accounts for the membrane reaching threshold and initiates the spontaneous depolarization and contraction of the cell. Note the lack of a resting potential.

Membrane Potentials and Ion Movement in Cardiac Contractile Cells

There is a distinctly different electrical pattern involving the contractile cells. In this case, there is a rapid depolarization, followed by a plateau phase and then repolarization. This phenomenon accounts for the long refractory periods required for the cardiac muscle cells to pump blood effectively before they are capable of firing for a second time. These cardiac myocytes normally do not initiate their own electrical potential, although they are capable of doing so, but rather wait for an impulse to reach them.

Contractile cells demonstrate a much more stable resting phase than conductive cells at approximately −80 mV for cells in the atria and −90 mV for cells in the ventricles. Despite this initial difference, the other components of their action potentials are virtually identical. In both cases, when stimulated by an action potential, voltage-gated channels rapidly open, beginning the positive-feedback mechanism of depolarization. This rapid influx of positively charged ions raises the membrane potential to approximately +30 mV, at which point the sodium channels close. The rapid depolarization period typically lasts 3–5 ms. Depolarization is followed by the plateau phase, in which membrane potential declines relatively slowly. This is due in large part to the opening of the slow Ca2+ channels, allowing Ca2+ to enter the cell while few K+ channels are open, allowing K+ to exit the cell. The relatively long plateau phase lasts approximately 175 ms. Once the membrane potential reaches approximately zero, the Ca2+ channels close and K+ channels open, allowing K+ to exit the cell. The repolarization lasts approximately 75 ms. At this point, membrane potential drops until it reaches resting levels once more and the cycle repeats. The entire event lasts between 250 and 300 ms.

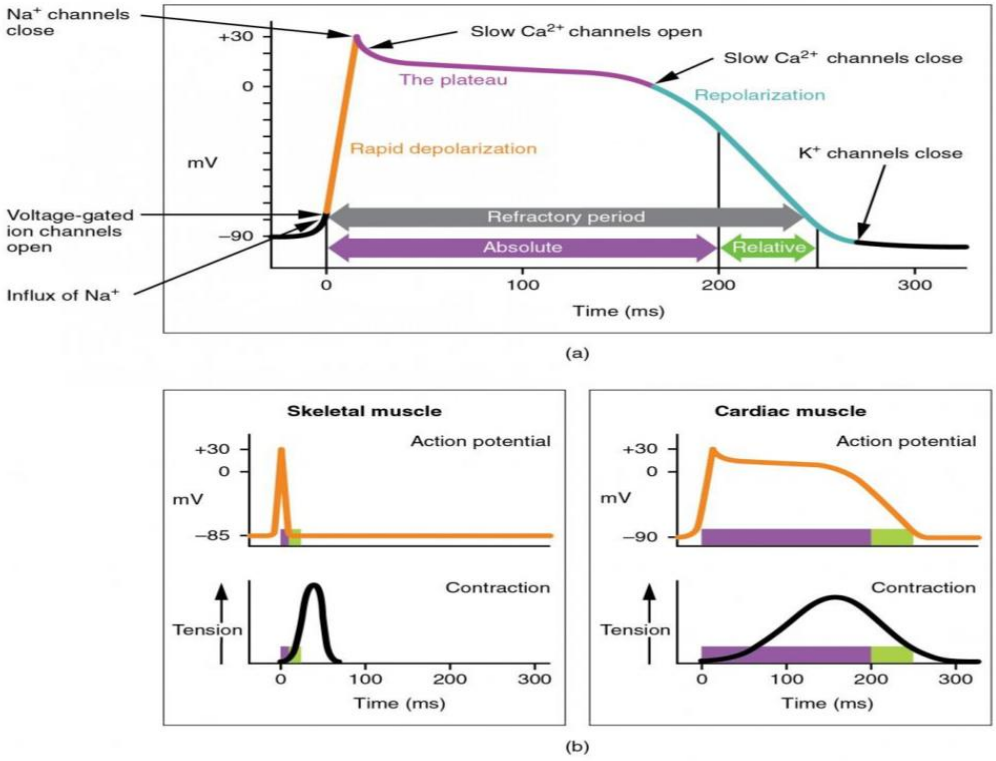


Figure 4 (a) Note the long plateau phase due to the influx of calcium ions. The extended refractory period allows the cell to fully contract before another electrical event can occur. (b) The action potential for heart muscle is compared to that of skeletal muscle.

The absolute refractory period for cardiac contractile muscle lasts approximately 200 ms, and the relative refractory period lasts approximately 50 ms, for a total of 250 ms. This extended period is critical, since the heart muscle must contract to pump blood effectively and the contraction must follow the electrical events. Without extended refractory periods, premature contractions would occur in the heart and would not be compatible with life.

Calcium Ions

Calcium ions play two critical roles in the physiology of cardiac muscle. Their influx through slow calcium channels accounts for the prolonged plateau phase and absolute refractory period that enable cardiac muscle to function properly. Calcium ions also combine with the regulatory protein troponin in the troponin-tropomyosin complex; this complex removes the inhibition that prevents the heads of the myosin molecules from forming cross bridges with the active sites on actin that provide the power stroke of contraction. This mechanism is virtually identical to that of skeletal muscle. Approximately 20 percent of the calcium required for contraction is supplied by the influx of Ca2+ during the plateau phase. The remaining Ca2+ for contraction is released from storage in the sarcoplasmic reticulum.

Comparative Rates of Conduction System Firing

The pattern of prepotential or spontaneous depolarization, followed by rapid depolarization and repolarization just described, are seen in the SA node and a few other conductive cells in the heart. Since the SA node is the pacemaker, it reaches threshold faster than any other component of the conduction system. It will initiate the impulses spreading to the other conducting cells. The SA node, without nervous or endocrine control, would initiate a heart impulse approximately 80–100 times per minute. Although each component of the conduction system is capable of generating its own impulse, the rate progressively slows as you proceed from the SA node to the Purkinje fibers. Without the SA node, the AV node would generate a heart rate of 40–60 beats per minute. If the AV node were blocked, the atrioventricular bundle would fire at a rate of approximately 30–40 impulses per minute. The bundle branches would have an inherent rate of 20–30 impulses per minute, and the Purkinje fibers would fire at 15–20 impulses per minute. While a few exceptionally trained aerobic athletes demonstrate resting heart rates in the range of 30–40 beats per minute (the lowest recorded figure is 28 beats per minute for Miguel Indurain, a cyclist), for most individuals, rates lower than 50 beats per minute would indicate a condition called bradycardia. Depending upon the specific individual, as rates fall much below this level, the heart would be unable to maintain adequate flow of blood to vital tissues, initially resulting in decreasing loss of function across the systems, unconsciousness, and ultimately death.

Problems related to pacemaker dysfuction

Many pacemaker disorders do not cause symptoms. If there are symptoms, they may include:

- A consistently slow heart rate
- Fainting, if the heart rate becomes very slow or if the heart is slow in returning to a normal rhythm after a period of rapid beating
- Periods of slow heartbeats (bradycardia) that alternate with periods of fast (tachycardia), irregular heartbeats (arrhythmia), such as are found sometimes in atrial fibrillation and atrial flutter. (This is a type of sick sinus syndrome sometimes called the bradycardia-tachycardia syndrome.)
- Weakness and tiredness

Conclusion

The sequence of events for pacemaker action potential:

1. Spontaneous flow of ions mainly through slow Na+ channels slowly depolarizes TMP above −60 mV. This is called the funny current (also known as pacemaker current); it is active at TMPs of less than −55 mV.
2. At TMP −55 mV, T-type Ca2+ channels open and continue slow depolarization.
3. TMP −40 mV is the threshold potential for pacemaker cells. L-type Ca2+ channels open and depolarize cell to 0 mV, then overshoot to +40 mV.
4. Delayed rectifier K+ channels counteract the L-type Ca2+ channels for a brief plateau phase and then return the TMP back to −60 mV as Ca2+ channels close.

It can be concluded that the pacemaker generates a signal that causes the upper heart chambers (atria) to contract and then the impulse is spread across atrioventricular node, the atrioventricular bundle and bundle branches to the Purkinje fibers, and also reaches the right papillary muscle via the moderator band. The impulse spreads to the contractile fibers of the ventricle, causing them to contract, or pump. SA node reaches threshold faster than any other component of the conduction system. It will initiate the impulses spreading to the other conducting cells.

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