CASE 9

A 68-year-old woman presents to the emergency center with shortness of breath, light-headedness, and chest pain described as being like “an elephant sitting on her chest.” She is diagnosed with a myocardial infarction. She is given oxygen and an aspirin to chew and is not felt to be a candidate for thrombolytic therapy. Her heart rate is 40 beats per minute (bps). Although there are P waves, they seem to be dissociated from the QRS complexes on the electrocardiograph (ECG). The patient is diagnosed with complete heart block, probably as a result of her myocardial infarction. The patient is taken to the intensive care unit for stabilization, and plans are made for pacemaker insertion.

◆ Where are the normal pacemaker and the backup pacemakers of the heart located?

◆ Why does this patient have a bradycardia?

◆ What parts of the heart have the fastest and slowest conduction velocities?
ANSWERS TO CASE 9: ELECTRICAL ACTIVITY OF THE HEART

Summary: A 68-year-old woman with new-onset myocardial infarction presents with complete heart block that is symptomatic.

◆ **Location of pacemakers:** Normal, sinoatrial (SA) node; other pacemakers (in order of recruitment), atrioventricular (AV) node, bundle of His-Purkinje system.

◆ **Cause of bradycardia:** If the AV node is injured by the infarction, both its ability to conduct and its ability to serve as a backup pacemaker may be lost, allowing a slow intrinsic pacemaker in the bundle of His or the Purkinje system to generate the ventricular heartbeat.

◆ **Extreme conduction velocities:** Fastest in the Purkinje system and slowest at the AV node.

**CLINICAL CORRELATION**

Cardiac arrhythmias and heart block are common findings after a myocardial infarction. Depending on the location of the cardiac tissue injury, varying heart rate abnormalities can be seen. If the injury occurs in the AV node area, excitation from the SA node is not conducted to the ventricles, and healthy cardiac cells with the next fastest intrinsic rhythm take over. With complete heart block, the new pacemaker may be from cells in the bundle of His or the Purkinje system. There are varying degrees of heart block. First-degree heart block is defined as a prolongation of the PR interval in the ECG. This can result from slowed conduction through either the AV node or the His-Purkinje fibers. Second-degree heart block occurs when a fraction of the atrial impulses fail to conduct to the ventricles. In third-degree, or complete, heart block none of the atrial impulses reach the ventricle. This patient probably experienced right coronary artery occlusion that led to AV nodal disruption. Her bradycardia is symptomatic, leading to feelings of light-headedness. A pacemaker, first temporary (transvenous) and then permanent, is indicated.

**APPROACH TO CARDIAC CONDUCTION SYSTEM**

**Objectives**

1. Know the normal conduction through the heart.
2. Understand the mechanisms of cardiac action potentials.
3. Understand the mechanisms of pacemaking.
4. Describe regulation by the autonomic nervous system.
DISCUSSION

Excitation of the heart begins with action potential initiation in the cardiac tissue with the fastest intrinsic pacemakers, the SA node. Action potentials then are conducted through gap junctions in intercalated discs from fiber to fiber, proceeding sequentially through the atria, AV node, bundle of His, Purkinje fibers, and contractile cells of the ventricles. The small AV node is the sole conductive path to the ventricles, and its thin fibers and slowly rising action potentials greatly slow conduction, providing time for the ventricles to fill during atrial contraction. The bundle of His and Purkinje fibers, by virtue of their wide diameters and rapidly rising action potentials, conduct extremely rapidly, bringing excitation to all ventricular muscle cells simultaneously and ensuring that they contract in unison.

Cardiac action potentials are generated by the flow of currents through specific ion channels. Working muscle cells of the atria and ventricles, as well as the rapidly conducting fibers of the bundle of His and the Purkinje system, have fast action potentials that depend on Na⁺ influx through depolarization-activated channels. The positive feedback between the opening of Na⁺ channels and the consequent depolarization causes the fast, regenerative upstroke (phase 0) of the action potential (see Figure 9-1). Early, partial repolarization (phase 1) occurs because of slightly delayed, depolarization-induced closing (inactivation) of the Na⁺ channels and because of the activation of a minor K⁺ current. A prolonged plateau (phase 2) follows, which is produced by Ca²⁺ influx through depolarization-activated, L-type Ca²⁺ channels and is aided by the depolarization-induced closing of inward rectifier K⁺ channels. Ca²⁺ influx during phase 2 is important for excitation–contraction coupling, mediating Ca²⁺-induced Ca²⁺ release from the sarcoplasmic reticulum. Complete repolarization (phase 3) occurs because (1) the L-type Ca²⁺ channels spontaneously close (inactivate), (2) very slow, depolarization-activated K⁺ channels open, and (3) the inward rectifier K⁺ channels that had been closed by depolarization begin to open in response to the repolarization. During rest (phase 4), the hyperpolarized potential is maintained by K⁺ current flowing out of the cell through both the leakage channels that are insensitive to voltage and the open inward rectifier K⁺ channels.

Cells in the SA and AV nodes have “slow” action potentials because they lack fast, depolarization-activated Na⁺ channels. Phase 0 is produced by a regenerative (positive feedback) interaction between depolarization and the opening of depolarization-activated, L-type Ca²⁺ channels. Phase 1 is absent, and the plateau and complete repolarization phases involve conductance changes similar to those in phases 2 and 3 in other cardiac cells. Most important for generating the heart beat, SA nodal cells have no true resting potential; instead a slowly depolarizing pacemaker potential begins immediately after complete repolarization from the action potential and continues until action potential threshold is again reached. The pacemaker potential has three
major components. One is the slow closing of depolarization-activated K\(^+\) channels that had been opened by the preceding action potential and served to repolarize the nodal cell’s membrane. The second component is the opening of a hyperpolarization-activated channel permeable to Na\(^+\) and K\(^+\). This current is traditionally called the “funny current” (I\(_h\)) because, before its role in pacemaking was appreciated, it seemed odd that a depolarizing current would be activated by hyperpolarization. As the pacemaker potential depolarizes the SA cell membrane, a level is reached where L-type Ca\(^{2+}\) channels begin to open. This third
component of the pacemaker potential accelerates the depolarization, causing increasing numbers of Ca\textsuperscript{2+} channels to open, soon resulting in a regenerative, \textbf{Ca\textsuperscript{2+}-mediated action potential}. Depolarization during the action potential closes the I\textsubscript{f} channels, which then reopen after repolarization occurs, restarting the cycle. This spontaneously repeating cycle is responsible for generating the heart beat, and can occur even in completely isolated SA nodal cells. (See Figure 9-2 for action potentials for various parts of the heart.)

The AV node has two important functions. First, its extremely slow conduction properties (because of narrow fiber diameter, lack of fast Na\textsuperscript{+} channels, and low density of gap junctions) delay ventricular contraction until

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure9-2.png}
\caption{Action potentials for various parts of the heart.}
\end{figure}
after atrial contraction can fill the ventricles. Second, action potential conduction in the AV node is blocked easily because of the long refractory periods and other features of the action potential. This protects the ventricles from excessive frequencies of contraction, which can prevent effective filling, during atrial tachycardia or atrial fibrillation. Atrial tachycardia may be produced by elevated firing rates in the SA node (eg, from sympathetic stimulation) or by ectopic pacemakers, for example, generated by circulating impulses in reentry loops in the atrium and sometimes either the AV node or abnormal accessory pathways between the atria and ventricles. Reentry or other problems during chronic heart disease (as well as electrocution and certain drugs) also can lead to fibrillation, in which the atria or ventricles undergo continuous, completely uncoordinated excitation and contraction that precludes effective pumping. Ventricular fibrillation is lethal unless a strong shock (electric defibrillation) is used to force the entire myocardium simultaneously into a refractory state that allows the heart to relax and the SA node to regain control of the heartbeat.

The autonomic nervous system modulates electrophysiologic and contractile properties of the heart. Norepinephrine (NE) released by sympathetic postganglionic terminals acts through β receptors coupled to adenylyl cyclase to increase \( I_p \), increase \( I_{Ca} \), and increase depolarization-activated \( I_K \). These effects increase heart rate by accelerating the pacemaker potential and shortening the action potential. Narrowing of the action potential, as well as NE-induced enhancement of the activity of the Ca\(^{2+}\) pump in the sarcoplasmic reticulum (which speeds relaxation), allows more beats to be accommodated per unit time. The increase in \( I_{Ca} \) also increases the amplitude of the action potential in the AV node, which makes conduction block in this node less likely. Finally, the increase in \( I_{Ca} \) in working cardiac cells increases Ca\(^{2+}\) influx and thus enhances contractility.

Parasympathetic input to the heart opposes the sympathetic actions. Acetylcholine (ACh) inhibits adenylyl cyclase and increases the hydrolysis of cyclic adenosine monophosphate (cAMP), directly antagonizing all the effects of NE mediated by the cAMP-protein kinase A (PKA) pathway. In addition, ACh opens inward rectifier K\(^+\) channels, thus hyperpolarizing nodal cells. Together these effects decrease heart rate and increase the chances of AV block. In the atria, parasympathetic stimulation decreases contractility by reducing background PKA activity, thus reducing \( I_{Ca} \) and Ca\(^{2+}\) influx. Few parasympathetic fibers innervate the ventricles.
COMPREHENSION QUESTIONS

[9.1] A 32-year-old woman is seen in the emergency center with supraventricular tachycardia. She is hypotensive. The cardiologist explains to the patient that the rapid heart rate does not allow for sufficient ventricular filling, thus reducing cardiac output. Which of the following best explains how ventricular filling is enabled during atrial contraction?

A. By the elevated contractility of ventricular muscle
B. As a functional consequence of narrow fiber diameter, slow depolarization, and low density of gap junctions in AV nodal cells
C. By the high density of depolarization-activated Na⁺ channels in AV nodal cells
D. By the low basal activity of sarcoplasmic reticulum Ca²⁺ pumps in ventricular muscle
E. By the prolonged time it takes for action potentials to be conducted from the bundle of His to ventricular muscle

[9.2] A 59-year-old man is admitted to the intensive care unit for a myocardial infarction. He is given a β-adrenergic antagonist and instructed to avoid emotional turmoil to decrease sympathetic stimulation of the heart. From a cellular perspective, sympathetic stimulation of the heart does which of the following?

A. Decreases adenylyl cyclase activity in ventricular muscle
B. Decreases Ca²⁺ pump activity in the sarcoplasmic reticulum of atrial muscle
C. Decreases I_{Ca} in the AV node
D. Increases depolarization-activated I_{K} in the SA node
E. Increases hyperpolarization-activated I_{K} (inward rectifier) in the SA node

[9.3] A 28-year-old athlete is noted to have a baseline heart rate of 55 bpm, which his trainer attributes to excellent parasympathetic (vagal) tone. This parasympathetic effect, among other things, increases the ACh released in the SA and AV nodes. ACh released into the AV node increases which of the following in AV fibers?

A. Action potential amplitude
B. Conduction velocity
C. K⁺ equilibrium potential
D. Probability of conduction failure (AV block)
E. Rate of depolarization of the pacemaker potential
Answers

[9.1] **B.** Ventricular filling during atrial contraction depends on a sufficient delay in the propagation of action potentials from the atria to the ventricles. This delay is accomplished by requiring that all atrial-to-ventricular electrical communication be funneled through the AV node and by giving the AV nodal cells narrow diameters and slowly activating Ca\(^{2+}\) channels (rather than rapidly activating Na\(^+\) channels), as well as a low density of gap junctions between AV cells; all these factors slow action potential conduction through the node. The bundle of His (answer E), in contrast, has the opposite features because it is specialized for rapid conduction. Elevated contractility of ventricular muscle (answer A) would not affect ventricular filling directly. The other properties listed (answers C and D) would impede rather than enhance ventricular filling.

[9.2] **D.** By increasing the depolarization-activated I\(_k\) in the SA node, sympathetic stimulation decreases the duration of each action potential in the node; this allows more impulses to be generated per unit time, permitting higher heart rates to be produced. Most of the other effects listed (answers A, B, and C) are opposite to what sympathetic stimulation produces. The hyperpolarization-activated inward rectifier current found in working muscle cells, which is insensitive to ACh, is less important in SA nodal cells and is not increased by sympathetic stimulation.

[9.3] **D.** ACh released by postganglionic fibers innervating the AV node hyperpolarizes the AV fibers, thus increasing the probability of blocking impulse conduction through the node. This also will decrease rather than increase action potential amplitude, conduction velocity, and the rate of rise of the pacemaker potential (answers A, B, and E). The K\(^+\) equilibrium potential is not changed by vagal stimulation.
**PHYSIOLOGY PEARLS**

- Normal excitation of the heart proceeds from the SA node, through atrial muscle fibers, through the AV node (slowly, permitting the ventricles to fill), and rapidly through the bundle of His and Purkinje fibers, ending in the synchronous activation of all the working fibers of the ventricles.

- Working and conductile fibers in the atria and ventricles exhibit fast action potentials that depend on a high density of Na⁺ channels that are activated rapidly by depolarization.

- During the long plateau of the action potential (phase 2), significant amounts of Ca²⁺ enter cardiac muscle cells through depolarization-activated Ca²⁺ channels, and this Ca²⁺ influx triggers contraction via Ca²⁺-induced Ca²⁺ release from the sarcoplasmic reticulum.

- Nodal cells lack fast, depolarization-activated Na⁺ channels and depend on slower depolarization-activated Ca²⁺ channels to produce the action potential.

- The heartbeat is initiated in the SA node by a spontaneously depolarizing pacemaker potential that is initiated by the hyperpolarization-activated, “funny” current, I₇ (carried by Na⁺ and K⁺ ions). Slow waning of the depolarization-activated Iₓ and eventual activation of Iₓ also contribute to the pacemaker potential.

- The AV node is particularly vulnerable to conduction block because the same factors that decrease conduction velocity (narrow fiber diameter, low-amplitude action potentials) increase the probability that the action potential threshold will not be reached during propagation into nodal fibers. This protects the ventricles from excessive contraction frequencies during atrial tachycardia or atrial fibrillation.

- The probability of conduction block in the AV node is decreased by sympathetic stimulation, which increases action potential amplitude. Parasympathetic stimulation increases AV block by hyperpolarizing nodal cells and reducing action potential amplitude.

**REFERENCES**


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