

# **Cardiac Arrhythmia Management**

**A Practical Guide  
for Nurses and  
Allied Professionals**

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# Section 1

## **Basics of Cardiac Anatomy and Electrophysiology**





# Cardiac Anatomy, Physiology, Electrophysiology, and Pharmacology

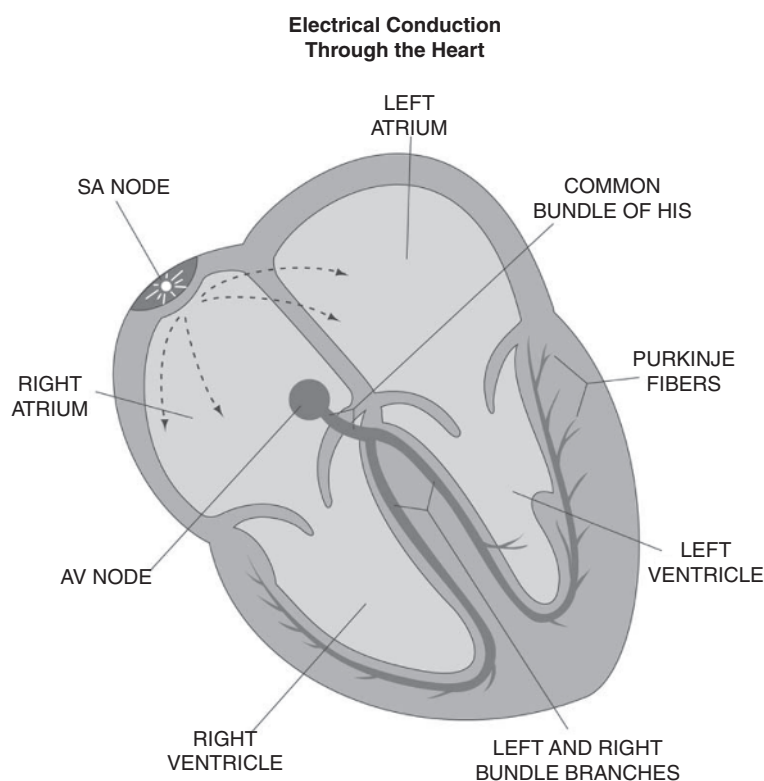
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Electrical stimulation is the key in initiating the sequence of events that result in cardiac contraction, the ultimate measure of cardiac performance. The inherent pacing properties that are required to generate an electrical impulse, the intrinsic conduction pathways that move depolarization from the initial impulse throughout the entire cardiac muscle, and finally, the patterns of depolarization that create an optimal squeeze of the cardiac muscle are the result of the electrical conduction system and mechanical system functioning synchronously. Impulse generation and dispersion to all areas of the heart muscle via cell-to-cell activation and via electrical pathways must be well understood to comprehend the complexity of electrical conduction and the strategies for treating conduction abnormalities. This chapter will provide an overview of cellular physiology, electrical physiology, the anatomy of the conduction system, and the medications that can be used to treat conduction abnormalities. A thorough

understanding of the normal anatomy and physiology of the conduction system will enable the allied professional to understand the rationale for utilizing specific arrhythmia treatment modalities, whether it be medications, ablations, or devices.

## ANATOMY OF THE CARDIAC CONDUCTION SYSTEM

The anatomy of the conduction system is composed of electrical tracts within the myocardium. This electrical network is strategically arranged in the nodes, bundles, bundle branches, and branching networks of fascicles. The cells that form these structures lack contractile capability but can generate spontaneous electrical impulses and alter the speed of electrical conduction throughout the heart. The sinoatrial (SA) node, internodal tracts, atrioventricular (AV) node, bundle of His, right



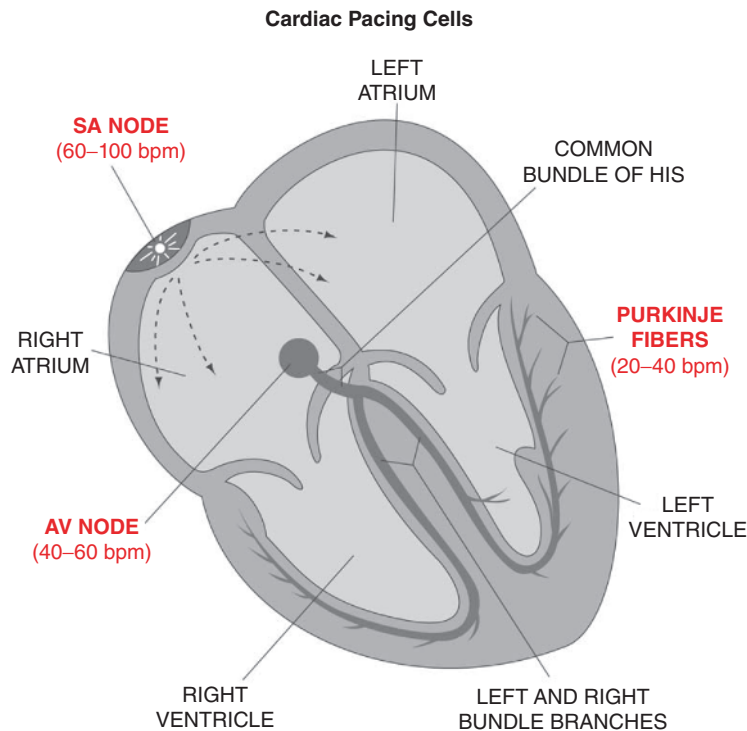
**Figure 1.1.1** Anatomy of the conduction system.

bundle, left bundle, anterior and posterior fascicles, and the Purkinje fibers are all the necessary conduction routes established throughout the cardiac muscle (Fig. 1.1.1). Normal conduction utilizes this electrical conduction system to expedite transmission of the electrical impulse from the top of the heart to the bottom. Abnormal conduction or arrhythmias are the result of an arrhythmogenic site or region that interferes, alters, or bypasses the normal conduction circuit. Therefore, a comprehensive understanding of normal conduction provides a foundation for better understanding the mechanisms present in abnormal conduction or arrhythmias.

Anatomically, the SA node is subepicardially located in the left upper corner of the right atrium, near its junction with the superior vena cava. The SA node is the native pacemaker site

within the heart and is composed of cells capable of impulse formation or “pacing.” Pacing cells within the SA node independently move to a threshold potential, thereby initiating depolarization. The SA node establishes the intrinsic heart rhythm between 60–100 pulses per minute but is influenced by the autonomic nervous system to meet the changing requirements of the body (Fig. 1.1.2). The region of the sinus node has numerous nerve endings and is predominantly regulated by the parasympathetic system or acetylcholine at rest and the sympathetic tone is mediated with the release of norepinephrine to meet increased energy requirements.

The sinus node lies near the central artery whereby it obtains its blood supply from the right coronary artery 55–65% of the time, while in 35–45% the left circumflex provides blood



**Figure 1.1.2** Pacing rates associated with pacing sites within conduction system.

flow (Anderson et al. 1979). The function of the sinus node may be jeopardized if the blood supply is reduced due to coronary artery disease or an increase in fibrous tissue with maturity, resulting in fewer SA cells available for impulse formation within the sinus node (Davies and Pomerance 1972).

Once the impulse is initiated within the SA node, it not only travels cell to cell through the atrium but also utilizes more specialized, expedient pathways known as internodal tracts (Fig. 1.1.1). The Bachmann's bundle moves away from the SA node anteriorly around the superior vena cava and then bifurcates with one branch leading from the right to the left atrium, while the other branch descends along the interatrial septum into the anterior portion of the AV node (fast pathway). The Wenckebach's tract transfers the stimulus from the superior region of the SA node, posterior to the superior

vena cava, and travels through the atrial septum to the AV node, while the third pathway (Thorel's) is responsible for moving the impulse inferiorly and posteriorly along the coronary sinus, arriving into the posterior portion of the AV node (slow pathway).

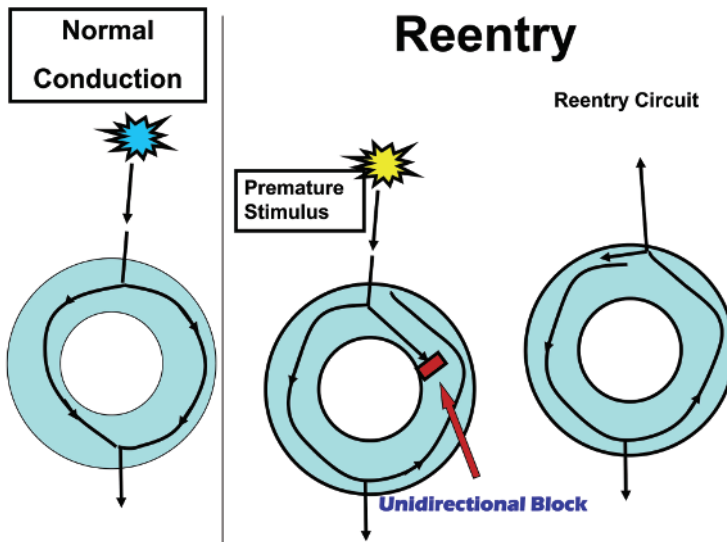
Once atrial depolarization is completed, depolarization moves into the AV node via the internodal tracts previously described or via cell-to-cell conduction. Normally, the structure of the AV node is the only conduction route from the atrium to the ventricle because the chambers are separated by fibrous and fatty tissue that is nonconductive. The primary function of the AV node is to slow electrical conduction adequately to synchronize atrial contribution to ventricular systole. The AV node is also capable of rescue pacing when the SA node fails and will provide a heart rate of 40–60 bpm (Fig. 1.1.2). By contrast, an ectopic

site within the AV node is capable of pacing competitively against the SA node to produce arrhythmias or junctional tachycardias greater than 100bpm.

The fast and slow pathways of the AV node are anatomical as well as functional structures. Slow pathway physiology is not seen in every individual. The fast pathway conducts more quickly but has a longer refractory period or recovery period. By contrast, the slow pathway conducts more slowly but has a shorter refractory or recovery period. Conducted impulses commonly travel along the fast pathway through the AV node, but with increased heart rates or the presence of a premature stimulus, the fast pathway may be unable to transmit the stimulus or be "refractory." Because the slow pathway has a shorter effective recovery time or is able to recover more quickly, it is able to transmit a signal down the slow pathway while the fast pathway is still recovering. The timing of recovery and the ability or inability to transmit a signal can result in a reentrant tachycardia (Fig. 1.1.3). Reentry is the result of a circuit that is initiated by a

signal, often early, being blocked and forced to move in the opposite direction. When the electrical signal conducts back toward the area of block, the structure has had time to recover and is now able to transmit the signal in the opposing direction. Hence, the critical timing sequence of the signal being transmitted creates an independent reentrant circuit.

Once the activation through the AV node occurs, depolarization travels to the common bundle of His (also called His bundle or common bundle). The region where the AV node (node of Tawara) and the His bundle join can be termed the triangle of Koch. Anatomically, the triangle of Koch includes the coronary ostium, the tendon of Todaro, and the tricuspid valve annulus along the septal leaflet. The AV node is approximately 5–6 mm long and 2–3 mm wide, and 0.5–1.0 mm thick, although there is some discrepancy in what is included in the AV node (Hecht et al. 1973; Becker and Anderson 1976). The blood supply of the AV node is the AV nodal artery and is usually dual supplied by the right coronary artery in 90% of the patients and the remaining 10% receive blood from the left circumflex coronary artery. Similar



**Figure 1.1.3** Reentry of the fast and slow pathways.



to the SA node, there is evidence of a generous autonomic innervation of the AV node, and therefore, the autonomic nervous system influences the rate of conduction through the AV node. AV nodal conduction abnormalities arise from altered blood supply, change in autonomic tone, increased fibrous tissue replacing AV nodal tissue, and an alteration in the normal conduction route.

Once depolarization moves through the bundle of His, it branches out to the right and left bundle branches. The right bundle branch remains compact until it reaches the right distal septal surface, where it branches into the interventricular septum and proceeds toward the free wall of the right ventricle. Because the left ventricle is larger in size, the left bundle branch moves conduction down the left septum and then bifurcates into a posterior and anterior descending fascicle. The left fascicles extend to the base of the papillary muscles and the adjacent myocardium, while the right bundle stays along the interventricular septum superficially within the endocardium (see Fig. 1.1.1).

The final destination is the arrival into the complex network of the specialized Purkinje fibers, capable of independently pacing at a rate of 20–40bpm if needed along with rapid conduction (Fig. 1.1.2). Once the impulses arrive at the Purkinje fibers, they proceed slowly from the endocardium to epicardium throughout the left and right ventricles. This assures earlier activation at the apex of the heart, the sequence necessary to achieve the most efficient cardiac pumping, which is the intended outcome of cardiac depolarization.

## CARDIAC ACTION POTENTIAL

The conduction system is composed of two distinctly different cells, pacing cells and nonpacing cells. “Pacing” cells are specialized cells with automaticity, meaning that they can move to a threshold potential independently and propagate or spontaneously initiate an impulse.

The specialized cells with automaticity reside within the SA node, AV node, and the Purkinje fibers. All the rest of the cardiac cells, myocytes, are “nonpacing cells” or conducting cells, which means they can be stimulated by an electrical impulse arriving at the cell and then conduct or transmit the impulse from one cell to another cell once the cell is stimulated. Therefore, cardiac cells are unable to initiate an impulse contrary to pacing cells.

Cells have the property of pacing or conductivity due to the electrical charge or voltage on the inside of the cell compared with the voltage on the outside of the cell. If the electrical charge inside the cell is less than the charge on the outside, the transmembrane potential is “negative.” By contrast, if the electrical charge is greater inside the cell than outside the cell, the transmembrane potential is “positive.” Depolarization occurs when the transmembrane potential is positive, while repolarization restores the cell to its negative state, making it available to accept an electrical stimulus in its negative or resting state. Pacing cells are able to depolarize independently, in contrast to a nonpacing cell, which is dependent on an outside stimulus to initiate depolarization.

The transmembrane potential is altered by ions moving in and out of the cell across the cellular membrane. Ion movement is the result of the selective permeability of ion channels distributed along the cell membrane. The movement of the  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Ca}^{2+}$  ions are the most predominant throughout the cardiac action potential. These ions move in or out of the cell as a result of a change in concentration gradient, electrical gradient, ion pumps, and altered membrane permeabilities (Table 1.1.1). Alterations in permeability to specific ions are most often regulated by voltage-gated channels that will open or close depending on the current measured between the inside and the outside of the cell, but there are additional properties that are responsible for moving ions in and out of the cell (Table 1.1.2). Some of these ion shifts occur passively, while other transport

**Table 1.1.1** Fundamentals of ion transport.

- 
- I. Passive ion movement—no energy requirement
    - A. Concentration gradient
      - Ions shifting from an area of greater concentration to an area of lesser concentration in an effort to equalize the two sides
    - B. Electrical gradient
      - Ions shifting from an area of greater electrical charge to an area of lesser electrical charge in an effort to equalize the two sides
  - II. Active ion pumps or transporters (require energy!)
    - A. Sodium/potassium pump (sodium ATPase)
      - $\text{Na}^+$  and  $\text{K}^+$  transported against their concentration gradients and sodium moves out of the negatively charged interior
      - Three  $\text{Na}^+$  ions OUT of the cell
      - ← Two  $\text{K}^+$  move INTO the cell
    - B. Calcium pump
      - $\text{Ca}^{2+}$  removal from inside cell during repolarization
      - $\text{Ca}^{2+}$  to OUTSIDE of the cell
    - C. Sodium/calcium exchange (NCX)
      - A small ionic gradient current is generated resulting in the transport of three  $\text{Na}^+$  ions in exchange for one  $\text{Ca}^{2+}$  ion; the direction of the ion transfer is dependent on the electrical charge of the cell
      - 1. Repolarization
        - ← Three  $\text{Na}^+$  move INTO the cell
        - One  $\text{Ca}^{2+}$  moves OUT of the cell
      - 2. Depolarization phase
        - Three  $\text{Na}^+$  move OUT of the cell
        - ← One  $\text{Ca}^{2+}$  moves INTO the cell
  - III. Ion channel properties
    - A. Ion permeability
      - The selective permeability that allow ions to move through the open channel at specific times
    - B. Gating—opening/closing of ion channels
      - 1. Voltage gated
        - Ion permeability enhanced or decreased based on the measured voltage of the membrane potential
      - 2. Ligand-dependent gating
        - The opening of the channel is dependent on activation of a protein along the binding site (i.e.,  $I_{\text{KAch}}$  → acetylcholine binds to M-2 receptor → activates G protein-signaling pathway → activates inward rectifying  $\text{K}^+$  channel)
      - 3. Mechanosensitive gating
        - A physical input transfers into an electrical signal, that is, stretch → electrical signal
        - Least studied but responsible for arrhythmias associated with dilatation
-

**Table 1.1.2** Ion-specific channel characteristics.

- 
- I. Sodium channels
    - a. Voltage gated
      - $I_{Na}$ —fast inward current
        - Increased transmembrane potential of  $-90$  to  $-60$  mV
        - Inactivation—rapid response followed by no  $Na^{++}$  entry
    - b. Target for antiarrhythmics—class I
      - Block occurs when  $Na^{++}$  channel is either open or inactivated during the action potential
      - Increased heart rate (increase in number of action potentials) with reduced recovery time results in an accumulation of block that is use-dependent
    - c. Abnormalities causing arrhythmias
      - Inactivation of the sodium channel does not occur, but continues with brief bursts of Na channel openings; this phenomenon is the basis for the subgroup of long QT syndromes (LQT3)
      - Mutations of the sodium channel gene, SCN5A, is associated with LQTS, Brugada syndrome, and primary cardiac conduction disease (Wang et al. 1990)
  - II. Potassium channels
    - a. Voltage gated
      - $I_{to}$ —transient outward current in phase 1
        - Rapid activation that provides a transient outward current
      - $I_{Kur}$ ,  $I_{Kr}$ , and  $I_{Ks}$ —delayed rectifiers—phase 3
        - $I_{Kur}$ —ultrarapid
        - $I_{Kr}$ —rapid
        - $I_{Ks}$ —slow
        - Voltage-gated channels open in response to membrane depolarization, which generate a current to restore resting potential
        - Slowly activating outward current (moves  $K^+$  outside the cell) during repolarization
      - $I_{K1}$ —inward rectifier
        - Moves  $K^+$  into cell in phase 4
    - b. Ligand gated
      - $I_{KAch}$ —activated by muscarinic receptors
        - May cause hyperpolarization and shorten APD
        - Outward current
      - $I_{KAdo}$ —activated by adenosine
        - Outward current
      - $I_{KATP}$ —blocked by ATP
        - Activated when ATP is low (ischemia)
        - Shortens APD when activated
    - c. Voltage and ligand
      - $I_f$ —nodal tissue during phase 4
        - Activated by hyperpolarization (about  $-40$  mV)
    - d. Target for antiarrhythmics—class III
  - III. Calcium channels
    - a. Two types
      - $I_{Ca-L}$ —slow, inward calcium current
        - Low-threshold type with long-lasting openings
        - Contributes to cardiac cell phase 2 (plateau)
      - $I_{Ca-T}$ —transient inward current
        - Found principally in pacemaker cells
        - Opens transiently in phase 4
    - b. Target for antiarrhythmics—class IV
-

mechanisms require energy at the cellular level. The ion “pumps” or ion transfers that require energy will be at risk in the event that the cell does not have an energy source or is oxygen deprived, for example, ischemia provides an opportunity for arrhythmias to occur.

## Phases of the Cardiac Action Potential

The cardiac action potential of the “nonpacing” cell consists of five phases:

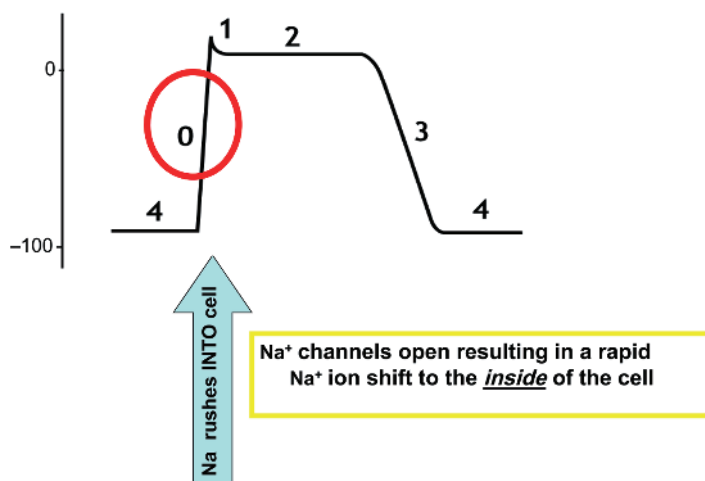
- Phase 0—rapid depolarization
- Phase 1—early rapid repolarization
- Phase 2—plateau phase
- Phase 3—repolarization
- Phase 4—resting phase

The cell moves from one phase to another very quickly with the entire process occurring within milliseconds. Although we describe each specific phase, the transition from one phase to another is dynamic and seamless. The action potential takes a round-trip journey in that the signal is able to arrive at baseline (phase 4) and is able to travel to the destination (depolarization—phase 0). Then, the action

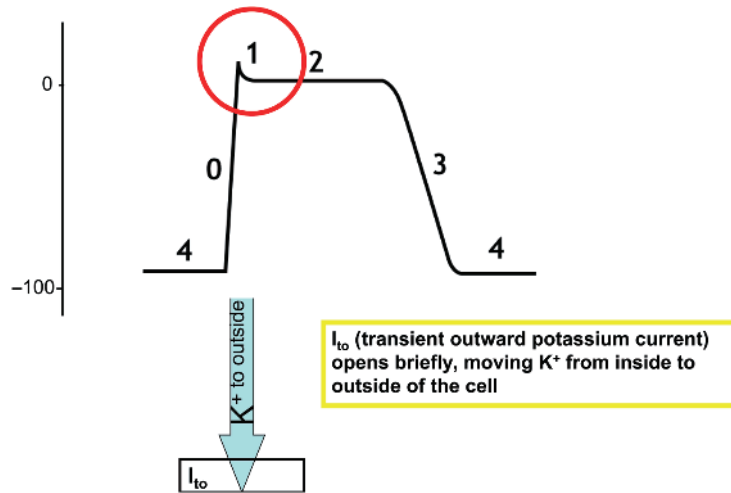
potential is able to return back to home (repolarization—phases 1–4) and prepare to depart from home or baseline (resting—phase 4) once again. What actually occurs at each phase is described below.

## Phase 0—Rapid Depolarization

When an electrical impulse arrives at the cell, the membrane potential shifts from approximately  $-90$  to  $-60$  mV and reaches “threshold” potential. The shift in voltage triggers the “voltage-gated” sodium channels to open and the permeability of the plasma membrane to sodium ions ( $P_{Na^+}$ ) increases, thereby resulting in rapid movement of sodium ions from extracellular to intracellular along their electro-mechanical gradient. Positively charged  $Na^+$  ions shift from the outside of the cell to the inside of the cell, causing the membrane potential to become more positive, now to approximately  $0$  mV (Fig. 1.1.4). The “fast” sodium channels inactivate within a few milliseconds, decreasing permeability of the cellular membrane to  $Na^+$  and preventing any further voltage increase.



**Figure 1.1.4** Phase 0—rapid depolarization. Sodium moving into the cell quickly increases the intracellular charge, creating a positive transmembrane potential.



**Figure 1.1.5** Phase 1—early rapid repolarization. Potassium channel ( $I_{to}$ —transient outward current) opens briefly, moving  $K^+$  outside the cell, resulting in a less positive intracellular charge.

### Phase 1—Early Rapid Repolarization

Transient outward  $K^+$  current,  $I_{to}$ , is turned on briefly by depolarization and drives the potassium out of the cell. This transient outward current rapidly inactivates, so the rapid outward current is brief, resulting in a slightly reduced intracellular charge as the positively charged  $K^+$  ions move outside of the cell (Fig. 1.1.5).

### Phase 2—Plateau Phase

The following ions are in motion in phase 2:

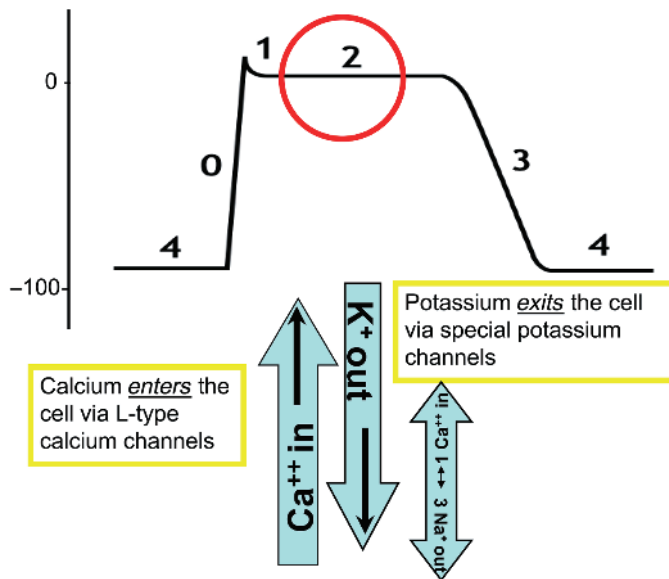
- Calcium moves slowly to the inside of the cell through the  $I_{Ca-L}$  channel (inward calcium channel)
- Potassium moves to the outside of the cell with the voltage and concentration gradient in an effort to equalize the voltage and the concentration of  $K^+$  within the inside and the outside of the cell
- Three sodium ions are moving into the cell in exchange for one calcium ion moving out of the cell

The cumulative, simultaneous movement of these ions results in a stable voltage along the membrane or a “plateau phase” (Fig. 1.1.6).

### Phase 3—Final Repolarization

In final repolarization, potassium diffuses to the outside of the cell with the increased permeability along the cell membrane with potassium channels opening and due to the movement caused by the concentration gradient. These voltage-dependent potassium channels are delayed rectifier currents and are slowly activating outward currents ( $I_{Kur}$ ,  $I_{Kr}$ ,  $I_{Ks}$ ). Concurrently,  $Ca^{2+}$  channels close, so the inward movement of calcium stops, while potassium continues to move outside of the cell and allows the membrane potential to go back to a negative resting membrane potential. Ion movement includes the following:

- Inactivation of the  $I_{Ca-L}$  stops  $Ca^{2+}$  entry into cell
- Delayed rectifier  $K^+$  currents,  $I_{Ks}$  (slow),  $I_{Kr}$  (rapid), and  $I_{Kur}$  (ultrarapid), moving  $K^+$  to the outside of the cell, while inwardly



**Figure 1.1.6** Phase 2—plateau phase. Stable charge created by equivalent ion movement to the inside and to the outside of the cell.

rectifying currents,  $I_{K1}$  and  $I_{K_{ACh}}$  result in the movement of positive charges out of the cell.

- Potassium conductance falls to plateau levels as a result of the inward rectification, membrane conductance changes with voltage ( $K^+$  channels are open at negative potentials but closed at less negative or positive voltages) (Fig. 1.1.7)

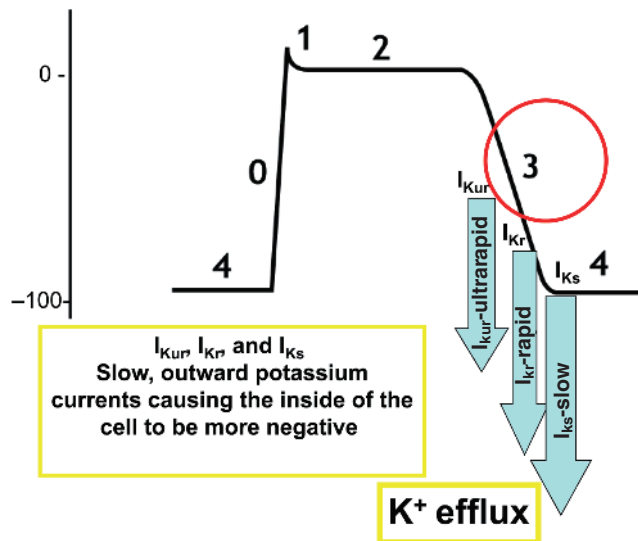
### Phase 4—Resting Membrane Potential

The cardiac action potential relies on the cell to adequately prepare for depolarization in the resting phase. It is during the cardiac cell resting phase that the intracellular potential is  $-50$  to  $-95$  mV relative to the measured voltage outside of the cell, making it negative. During resting phase, there are more potassium ions within the cellular membrane (intracellular), while the majority of sodium and calcium ions are kept on the outside of the cell membrane (extracellular).

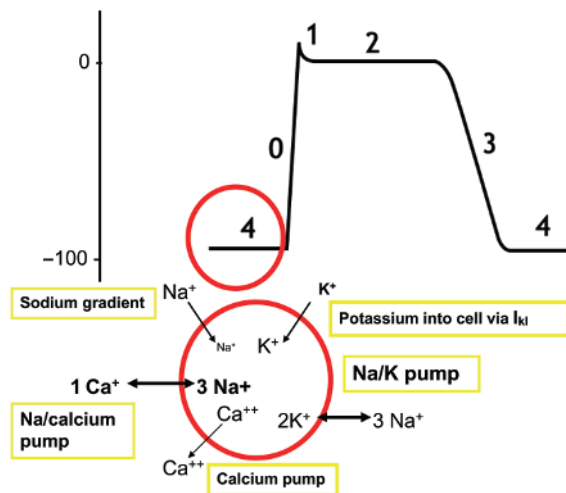
Although phase 4 is referred to as “resting” phase, the negative intracellular voltage is the result of ion movement related to a combination of complex systems that include the opening of selective ion channels, altering membrane permeability, concentration gradients, electrogenic gradients, and active ion pumps (Fig. 1.1.8). This phase includes the sodium-potassium pump, which requires energy, thus it relies on oxygenation to the area to maintain resting phase. Maintaining the resting membrane potential of  $-90$  to  $-100$  mV allows the cell to be ready to accept an outside stimulus or to be depolarized.

### Action Potential of Pacemaker Cells (Slow Response)

The unique quality of the pacing cells is that they have the capability of reaching depolarization independently. Therefore, they can initiate a stimulus as opposed to being able to only



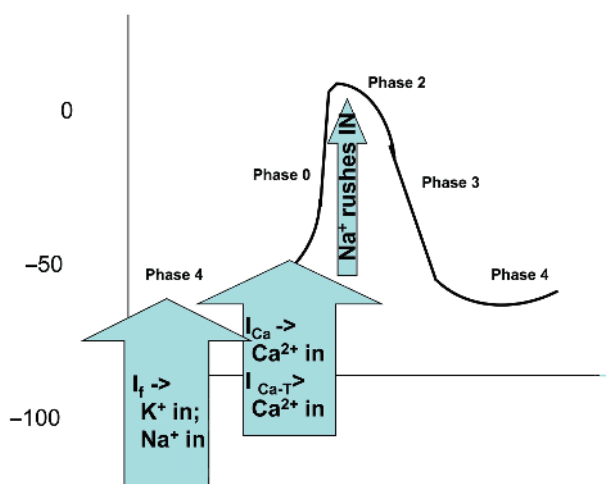
**Figure 1.1.7** Phase 3—final repolarization. Potassium efflux is the essential ion movement.



**Figure 1.1.8** Phase 4—resting phase. 1. Open, inward rectifying  $K^+$  channels,  $I_{K1}$ , moving potassium to the inside of the cell. 2. Three  $Na^+$  ions move to the outside of the cell while two  $K^+$  ions are transferred to the inside of the cell by the active  $Na^+/K^+$  pump. 3. With the negative transmembrane potential, the  $Na^+/Ca^{2+}$  exchanger is exchanging three  $Na^+$  ions to the inside of the cell while moving one  $Ca^{2+}$  ion outside the cell. 4. Plasma membrane calcium (PMCA) pump removes calcium.

conduct or transmit a stimulus. The specialized cells with automaticity reside within the SA node, AV node, and the Purkinje fibers. Their inherent pacing rate of the specialized cells is most rapid in the sinus node while slowest in

the ventricles. This provides rescue pacing if the higher pacing sites fail, for example, the AV node will pace at a rate of 40–60bpm in the absence of the sinus node firing at a rate of 60–100bpm (Fig. 1.1.2). As mentioned



**Figure 1.1.9** Action potential of pacing cell.

previously, the intrinsic pacing rate is greatly influenced by the balance between the sympathetic and parasympathetic autonomic nervous system.

The ability to “pace,” propagate, or initiate a signal is the result of independent ion shifting within the cell through specialized ion channels that are only available within the pacing cell structure. Phase 4 and phase 0 in the pacing cells are the most distinctly different phases when compared with cardiac cells (Fig. 1.1.9). The unique characteristics of the pacing cell are described in detail below.

### Phase 4—Diastolic Depolarization of the Pacing Cell

Automaticity of the pacing cell is the result of ions shifting to achieve a net gain in intracellular positive charges during diastole. This ion movement allows the cell to independently reach a “threshold” potential. There are a number of differences between the action potential of the pacing cell and the cardiac cell that allow this to be achieved. First, the transmembrane potential of the pacing cell does not return to the same negative membrane poten-

tial as the cardiac cell in resting phase. Instead, the voltage of the cell at the onset of phase 4 is  $-40$  to  $-70$ . This is the result of the presence of the  $I_f$  channel, pacemaker or “funny” current, which is a current activated by hyperpolarization and causes  $\text{Na}^+$  and  $\text{K}^+$  to enter the cell, thus allowing the cell to independently move to depolarization. Automaticity is dependent on a combination of the  $I_f$  channel, the deactivation of  $I_{K1}$  current, and the transient inward calcium current,  $I_{Ca-T}$ . The  $I_f$  channel moves  $\text{Na}^+$  and  $\text{K}^+$  into the cell to offset the deactivation of  $I_{K1}$  current, which causes an inward  $\text{K}^+$  current. The  $I_{Ca-T}$  current is limited to pacing cells exclusively and the opening of this calcium current allows calcium to move slowly into the cell, moving the charge inside of the cell to  $-30$  and  $-40$ , resulting in “threshold” potential, and finally, opening of the fast  $\text{Na}^+$  channels for depolarization to occur.

### Phase 0—Depolarization of the Pacing Cell

The significant contrast of the pacemaker cell and the cardiac cell during phase 0 is the absence of a stimulus to alter the transmembrane potential in the pacing cell. The cell itself



moves from a transmembrane potential of  $-60$  to “threshold potential” by a slow, inward current rather than a fast inward Na current, as described above. The discharge rate of the sinus node normally exceeds the discharge rate of the other potentially automatic pacemaker sites, and therefore, maintains the dominant rate. It is also more sensitive to the effects of norepinephrine (sympathetic) and acetylcholine (parasympathetic) so it provides the best physiological heart rate. The lower, alternative pacing sites in the AV node and Purkinje fibers provide an electrical stimulus in the absence of an intact sinus node. The complex intrinsic pacing capability of the heart is essential in providing optimal blood flow and meeting the oxygen demands of the body during times of increased physical activity and/or increased stress.

## DRUGS FOR CARDIAC ARRHYTHMIAS

Cardiac arrhythmias generally result from an abnormality in the rate, rhythm, or conduction of an electrical impulse in the heart (Perry and Illsley 1986). These abnormalities are disturbances in normal impulse initiation (automaticity), impulse conduction, or both. Various antiarrhythmic agents affect intracellular and extracellular concentrations of sodium, potassium, calcium, and magnesium. The balance of all these molecular components have varying effects on the electrophysiology of the heart and are critical to controlling arrhythmias with antiarrhythmic medications. In general, antiarrhythmic medications are available to treat tachyarrhythmias. There are no currently available medications to treat bradyarrhythmias effectively, particularly in oral form.

The classification of antiarrhythmic agents is discussed below, with emphasis on the particular electrophysiological action of each drug classification. Several of the drugs studied had more than one of the four actions, so that it deserves emphasis that the classification is not so much categorization of drugs in accordance

with chemical structures or physical properties, but describes four ways in which abnormal cardiac rhythms can be corrected or prevented (Vaughan Williams 1984). Based on the Vaughan Williams classification, there are four main classes of antiarrhythmic medications (Tables 1.1.3 and 1.1.4). Although much maligned, the Vaughan Williams classification system is still the most commonly used by those in the medical field worldwide. Because the antiarrhythmic drugs usually target a specific ion and either block or enhance its movement in or out of the cell, there are electrocardiogram (ECG) changes that may be evident as a result of that (see Table 1.1.5).

The classes are further simplified and subdivided based on the primary electrophysiological effect of either their ability to convert the rhythm or control the rate (Table 1.1.6). Class I and class III drugs are more effectively utilized to prevent arrhythmias and maintain sinus rhythm. Class IV drugs provide rate control with the primary goal of reducing conduction through the AV node, while class II drugs are used to reduce heart rate and maintain sinus rhythms in those patients who have arrhythmias that are triggered by catecholamines. The discussion below describes each group in more detail.

### **Class I Drugs: Sodium Channel Blockade**

The class I drugs act by modulating or blocking the sodium channels, thereby inhibiting or altering phase 0 depolarization (Fig. 1.1.4). Their dominant electrophysiological property has been related to their ability to reduce the maximal rate of depolarization in cardiac muscle. A reduction in the rate of depolarization by therapeutic concentrations of these drugs has been found to be associated with an increase in the threshold of excitability, a depression in conduction velocity, and a prolongation in the effective refractory period (Singh 1978). Three different subgroups, class IA, IB, and IC, have been identified because

**Table 1.1.3** Drug effects on ECG.

Drug		Effects on ECG		
Amiodarone		Bradycardia, prolongs PR, QRS, and QT		
Acebutol, esmolol, metoprolol, propranolol		Bradycardia, prolongs PR		
Diltiazem, verapamil		No change in QRS		
Adenosine		Prolongs PR, heart block (transient)		
Sotalol		Bradycardia, prolongs PR and QT		
Dofetilide, ibutilide		Prolongs QT		
Flecainide, propafenone		Prolongs PR and QRS		
Digoxin		Prolongs PR, depresses ST segment, flattens T wave		
Lidocaine, mexilitine		No significant change		
Dronedarone		Bradycardia, prolongs QT		

Class	Effect on repolarization/depolarization	Phase of cardiac action potential	Effect on action potential duration	Effect on ECG
IA: sodium channel blockade	Prolongs repolarization	Phase 0	Depression	Prolongs
IB	Shortens depolarization	Phase 0	Weak phase 0 depression	Decrease
IC	No effect	Strong phase 0	Depression	No effect or mildly prolongs
II: beta adrenergic blockade	Enhanced depolarization	Enhanced phase 4		
III: potassium channel blockers	Prolongs repolarization	Phase 3	Prolongs	QT interval is longer at slower heart rates, decreases as heart rate increases
IV: calcium channel blockers	Slows depolarization	Phase 4	Prolongs	Slows the sinus rate and increases PR

their mechanism or duration of action is somewhat different due to variable rates of drug binding to and dissociation from the channel receptor (Snyders et al. 1991).

The major drugs with class IA classification are *quinidine*, *procainamide*, and *disopyramide*. These drugs depress phase 0 (sodium-

dependent) depolarization, thereby slowing conduction. They also have moderate potassium channel blocking activity (which tends to slow the rate of repolarization and prolong action potential duration [APD]), anticholinergic activity, and depress myocardial contractility. At slower heart rates, when use-dependent

**Table 1.1.4** Specifics of each drug classification.

Class I: sodium channel blockers
Class IA, IB, IC
Slow down the depolarization
Class II: beta adrenergic blockers
Slow depolarization by blocking the beta receptors in the parasympathetic nervous system
Class III: potassium ion channel blockers
Prolong phase 3 (action potential duration)
Prolong the effective refractory period and lengthen the QT interval
Class IV: calcium channel blockers
Affect primarily SA and AV nodes
Block the influx of calcium into the cell
Shorten depolarization, prolong repolarization, slow down the conduction down the AV node
Class V: miscellaneous (none of the above)
Adenosine: slows sinus node automaticity and AV conduction
Digoxin: increases phase 4 slope and decreases resting membrane potential, decreases conduction velocity, increases vagal tone

blockade of the sodium current is not significant, potassium channel blockade may become predominant (reverse use dependence), leading to prolongation of the APD and QT interval and increased automaticity.

The class IB drugs include *lidocaine*, *mexiletine*, and *tocainide*. They have less prominent sodium channel blocking activity at rest but effectively block the sodium channel in depolarized tissues. This group tends to bind in the Na<sup>+</sup> channel inactivated state (which follows the fast channel opening in phase 0 depolarization) and dissociate from the sodium channel more rapidly than other class I drugs. As a result, they are more effective with tachyarrhythmias than with slow arrhythmias.

The class IC drugs, *flecainide* and *propafenone*, block both the open and inactivated sodium channels and thus, slow conduction. They dissociate slowly from the sodium channels during diastole, resulting in increased effect at more rapid rate (use dependence). This characteristic is the basis for their antiarrhythmic efficacy,

**Table 1.1.5** Antiarrhythmic drug effects on the ECG.

Antiarrhythmic medication	Conduction effects	PR	QRS	QT	ST	T wave
Amiodarone	Bradycardia	Prolonged	Prolonged	Prolonged		
Acebutolol, esmolol, metoprolol, propanolol	Bradycardia	Prolonged				
Diltiazem, verapamil,			No change			
Adenosine	Transient heart block	Prolonged				
Sotalol	Bradycardia	Prolonged		Prolonged		
Dofetilide, ibutilide				Prolonged		
Flecainide, propafenone		Prolonged	Prolonged			
Digoxin		Prolonged			Depressed	Flattens
Lidocaine, mexiletine	No significant change					

**Table 1.1.6** Common drugs for atrial fibrillation and supraventricular arrhythmias.

Arrhythmia	Drug of choice	Alternative
Atrial flutter/fibrillation		
Acute management	Rate control: verapamil, diltiazem, beta blocker, or digoxin given intravenously	
Chronic treatment	Rhythm conversion: DC cardioversion Rate control: oral verapamil, diltiazem, beta blocker, or digoxin	Catheter ablation to eliminate arrhythmia
Other supraventricular tachycardias	Maintain sinus rhythm: amiodarone, sotalol, flecainide, propafenone, or dofetilide IV verapamil, adenosine, or diltiazem	Quinidine, procainamide, disopyramide, amiodarone (may require drug loading)
Acute management		IV esmolol, another beta blocker, or digoxin for termination
Long-term suppression	Beta blockers, verapamil, diltiazem, flecainide, propafenone, amiodarone, sotalol, or digoxin	Vagotonic maneuvers (such as carotid sinus massage, gagging, or the Valsalva maneuver) that impair AV nodal conduction may be tried first Catheter ablation can cure most patients

DC, direct current; IV, intravenous.

especially against supraventricular arrhythmia. Use dependence may also contribute to the proarrhythmic activity of these drugs, especially in the diseased myocardium, resulting in incessant ventricular tachycardia.

- Flecainide was first introduced in 1985 for treatment of ventricular arrhythmias then subsequently for oral use to prevent supraventricular arrhythmias. The indications for using flecainide to treat ventricular arrhythmias were limited after a controlled trial found that postmyocardial infarction patients with asymptomatic ventricular arrhythmias who took the drug had twice as high a mortality rate as patients who took placebo (Echt et al. 1991). Flecainide decreases the rate of cardiac conduction in all parts of the heart. In animals, at normal resting heart rates, the drug causes only a small increase in the refractory period, but at the rapid rates typical of atrial fibrillation, flecainide mark-

edly increases atrial APD and refractoriness (Wang et al. 1990). The drug is metabolized in the liver and excreted in the urine. Rarely, patients may be deficient in the enzyme system required for metabolism of the drug. Flecainide is effective for prevention of paroxysmal supraventricular tachycardia, moderately effective for suppression of paroxysmal atrial fibrillation, and is generally well tolerated. Because of its proarrhythmic effects, however, use of the drug should be restricted to patients without clinically significant structural heart disease who have disabling symptoms refractory to other drugs.

- Propafenone, much like flecainide, markedly decreases cardiac conduction velocity. And like flecainide, it can also aggravate existing arrhythmias or precipitate new ones, especially in patients with underlying heart disease and sustained ventricular tachycardia. Propafenone has a low degree of beta blocking activity in some patients.

## Class II Drugs: Beta Blockade (Antagonists)

Hyperactivity of the sympathetic nervous system has been recognized for many years as a factor in the genesis of cardiac arrhythmias. The class II drugs, such as *atenolol*, *metoprolol*, *carvedilol*, act by inhibiting sympathetic activity, primarily by causing beta blockade. Their principal electrophysiological effect on heart muscle in clinically relevant concentrations is the depression of phase 4 depolarization (see Fig. 1.1.8), resulting in a reduced heart rate. Only in very high concentrations do these drugs exert effects on other parameters, such as the upstroke velocity of the phase 0 of the action potential (Singh 1978). Beta agonists or catecholamines (i.e., epinephrine and norepinephrine) are endogenous, neurohormonal substances that mediate diverse physiological and metabolic responses in man by interaction with adrenergic receptors (beta receptors) in various tissues. As a result of this, beta agonists potentiate positive chronotropic (increased heart rate) and inotropic (increased contractility) actions. By contrast, beta adrenergic antagonists' main therapeutic effect is to slow the heart rate and decrease myocardial contractility. They reduce sinus rate, especially when sympathetic control of the heart is dominant, as during exercise. They have less effect on heart rate in an individual at rest. They also decrease the rate of spontaneous depolarization of ectopic pacemakers, slow conduction in the atria and AV node, and increase the refractory period of AV node.

## Class III Drugs: Potassium Channel Blockade

Class III drugs, *amiodarone*, *ibutilide*, *dofetilide*, *sotalol*, *azimilide*, and *dronedarone*, block the potassium channels, thereby prolonging repolarization, the APD, and the refractory period (Arnsdorf et al. 2009; see Fig. 1.1.7). These

changes are manifested on the surface ECG by prolongation of the QT interval, providing the substrate for torsade de pointes, a polymorphic ventricular tachycardia. Amiodarone is an exception, with very little proarrhythmic activity. Amiodarone has since been found to be a potent antiarrhythmic drug in the clinic, but although it does prolong the QTc (corrected QT) interval on the ECG in patients, ventricular arrhythmias have not been encountered during prolonged periods of treatment in large numbers of patients (Singh 1978; see Table 1.1.5).

- **Amiodarone**—Among available antiarrhythmics, amiodarone (*Cordarone* and others) is the most effective for prevention of atrial fibrillation and of ventricular tachycardia or fibrillation. The antiarrhythmic actions of amiodarone can be attributed to its property of inhibiting adrenergic stimulation (alpha and beta blocking properties), its effects on sodium, potassium, and calcium channels, its ability to prolong the action potential with consequent lengthening of the effective refractory period in myocardial tissue and decreasing AV nodal conduction and sinus node function. Multiple clinical trials have indicated that amiodarone is the most potent antiarrhythmic agent for the control of refractory ventricular tachyarrhythmias and for the prophylaxis of recurrent supraventricular tachyarrhythmias, including atrial fibrillation or flutter complicating the Wolff–Parkinson–White syndrome. Amiodarone is well tolerated by most patients, but there are several potential side effects that need to be monitored for closely.
- **Dronedarone**—This is one of the newer class III antiarrhythmic drugs and is a “cousin” to amiodarone; it is indicated for the treatment of atrial arrhythmias. The primary differences compared with amiodarone are attributable to the lack of iodine in the molecular structure, along with a reduced half-life due to its less hydrophobic nature. As a result, it may be associated with fewer long-term

complications compared with amiodarone. Its efficacy can be evaluated more quickly, as achieving therapeutic levels is not reliant on a “loading” regimen; rather it is given twice daily, with steady state achieved usually within 3–7 days.

- **Sotalol**—Sotalol is a racemic mixture of D-sotalol and L-sotalol; both isomers have similar class III antiarrhythmic effects, while the L-isomer is responsible for virtually all of the beta blocking activity. Sotalol contains both beta adrenoreceptor blocking (class II) and cardiac APD prolongation (class III) properties. The noncardioselective beta-blocking effect of sotalol (increased sinus cycle length, slowed heart rate, decreased AV nodal conduction, and increased AV nodal refractoriness) occurs at oral doses as low as 25 mg/day. The class III effects (prolongation of the atrial and ventricular monophasic action potentials, and effective refractory prolongation of atrial muscle, ventricular muscle, and AV accessory pathways in both the antegrade and retrograde directions) are seen only at oral doses  $\geq 160$  mg/day. Sotalol should be initiated and doses increased in a hospital with facilities for cardiac rhythm monitoring and assessment, as proarrhythmic events can occur after initiation of therapy and with each upward dosage adjustment.
- **Dofetilide**—Dofetilide has no effect on sodium channels, adrenergic alpha receptors, or adrenergic beta receptors. It increases the monophasic APD and effective refractory period of the myocyte, thereby terminating reentrant tachyarrhythmias and preventing their reinduction (Roukoz et al. 2007). The increase in the QT interval is a function of prolongation of both effective and functional refractory periods in the His-Purkinje system and the ventricles. Changes in cardiac conduction velocity and sinus node function have not been observed in patients with or without structural heart disease. PR and QRS width remain the same

in patients with preexisting heart block and or sick sinus syndrome. Dofetilide is generally well tolerated but like other antiarrhythmic agents in its class, torsades de pointes may be induced as a consequence of therapy. Therefore, it should be initiated and doses titrated while in a hospital with facilities for cardiac rhythm monitoring and assessment.

### **Class IV Drugs: Calcium Channel Blockade (Antagonists)**

As a class, calcium channel antagonists do not increase the effective refractory period of the atria, ventricle, His-Purkinje fibers, or the accessory pathways in the heart. The dominant effect of calcium channel antagonists is slowing of conduction in the AV node with the prolongation of the AV nodal refractory period (Singh et al. 1983). Selective calcium channel antagonists, such as verapamil and diltiazem, have been found to have some antiarrhythmic activity. They preferentially affect slow-response myocardial tissue rather than fast-response tissue. Slow-response tissues (the SA and AV nodes) depend on calcium currents to generate slowly propagating action potentials. By contrast, fast-response myocardial tissues (the atria, specialized infranodal conducting system, the ventricles, and accessory pathways) depend on sodium channel currents. Verapamil is the prototype calcium antagonist and has the most clearly defined antiarrhythmic properties (Singh et al. 1983). Verapamil, as well as diltiazem, terminate paroxysmal supraventricular tachycardia and slow the ventricular response in atrial flutter and fibrillation. They also have prophylactic value in preventing recurrences of paroxysmal supraventricular tachycardia and controlling the ventricular response in atrial flutter and fibrillation during long-term oral therapy. They play a much more limited role in the treatment of ventricular arrhythmias (Singh et al. 1983).

Antiarrhythmic drugs are available as one treatment option for controlling arrhythmias. As you can see, there are a variety of medications available to treat the full spectrum of tachyarrhythmias. Each clinician may prefer one agent over the other, and a particular patient's arrhythmia control and tolerance of medications may vary considerably. Therefore, the use of antiarrhythmics in patient management may not be straightforward and may require increased patient surveillance. Additional methods of treatment, that is, ablation, may be utilized as an adjunct to medication and provides the patient with additional options for controlling arrhythmias.

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