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## Normal and Arrhythmogenic Ionic Channel Mechanism

### Synopsis

#### Generation of Action Potential

Steady-state transmembrane ionic gradients in living cardiac muscle cells at rest generate a potential difference or voltage across the membrane called resting potential.

#### Resting Potential

The resting potential in ventricular muscle cells is  $-90$  mV, inside negative with respect to outside, and is dependent on membrane permeability and ion concentrations (activities) in the cytoplasm inside and in the extracellular fluid outside. Active transport (ionic pumps) and countertransport systems (ion exchangers) contribute to the maintenance of the resting potential.

#### Transient Ionic Currents

The action potential of excitable cardiac cells is generated by a transient flow of ionic currents through ion-specific channels that contain molecular structures called gates. Ionic current flow in some channels is easier inward or outward (rectifier channels). The magnitude of the transient flow of each ion is dependent on the potential and concentration gradients and the conductance of the channel. Voltage-gated ionic channels are activated and inactivated in a characteristic time course along the excitation/repolarization cycle, with the gates opening and closing at specific voltage thresholds.

#### Phase 0 and Phase 1

Normal ventricular excitation starts at the terminal branches of the Purkinje fibers as a propagated response in the electrically coupled syncytium when depolarized by electrotonic interaction to the threshold of the  $I_{Na}$ -channel activation potential of approximately  $-55$  mV. This inward excitatory current is largely responsible for ventricular depolarization (phase 0). It is followed by an overshoot to a positive polarization of 20 mV or more (phase 1) where subepicardial and intramural M cells have a notch. Phase 1 notch is generated by the early transient outward current  $I_{to}$ . From its two components,  $I_{to1}$  is carried through a voltage-gated potassium channel, and  $I_{to2}$  is considered to be a calcium-activated chloride current.  $I_{to}$  currents activate fast during early depolarization and then inactivate.

#### Phase 2 and Phase 3

Phase 1 is a transition point to a quasi-stationary state (phase 2), commonly called plateau although more appropriately denoted as the slow phase of ventricular repolarization. In human ventricular cells, the voltage-gated  $Ca^{2+}$  current  $I_{Ca-L}$  is activated during phase 0 at threshold  $\approx -20$  mV.  $I_{Ca-L}$  is a long-lasting current that is important for membrane voltage balance during phase 2, for release of calcium from the intracellular stores and excitation-contraction coupling, and at the end of phase 2, for initiation of the fast phase of repolarization (phase 3) by the  $Ca^{2+}$ -dependent inactivation and spontaneous closure of this

channel. A number of other ionic channels play an important role in ventricular repolarization by regulating potassium flux, including delayed rectifier  $I_K$  currents  $I_{Kr}$  and  $I_{Ks}$ .

### Temporal Sequence of Repolarization

The temporal sequence of the normal ventricular repolarization is spatially remarkably uniform. This suggests that intrinsically longer action potential durations of the intramural M-type cells are largely moderated by electrotonic coupling to the surrounding myocardial syncytium or that potential gradients generated by diffuse clusters of M cells are largely cancelled spatially. Physiological, pathophysiological and pharmacological agents that prolong QT interval with only minor changes in T waveform act primarily by producing a homogeneous uniform delay of the onset combined with an unaltered slope of phase 3 and unaltered normal spatial/temporal dispersion of action potential duration. Delayed onset of phase 3 occurs with  $I_{Na}$ -blocking agents that reduce the slope of phase 0, with  $I_{to}$  agonists that broaden the notch, and with all agents that cause prolongation of phase 2. Altered T waveform, T amplitude increase or decrease, biphasic T or changed T wave polarity indicate increased or decreased dispersion of the onset or the end of phase 3 (or both) or altered phase 3 slope.

### Cardioactive Agents and Ionic Channels

A variety of ionic channel mechanisms are involved in antiarrhythmic and other effects of cardioactive pharmacological agents. The main differences in drug actions are in their agonistic or antagonistic effect on different receptors, pumps and ionic channels, the affinity and strength of their action, as well as their rate- and voltage-dependence and the kinetics in relation to onset and release of the channel block at various phases of the action potential.

### Abbreviations and Acronyms

APD – action potential duration  
ATP – adenosine triphosphate

AV – atrioventricular  
DAD – delayed afterdepolarizations  
DRT – dispersion of repolarization time  
EAD – early afterdepolarizations  
EMIAT – European Myocardial Infarct Amiodarone Trial  
FDA – Food and Drug Administration  
HVA – high-voltage activated  
LQTS – long QT syndrome  
LVA – low-voltage activated  
PKA – phosphate kinase  
SA – sino-atrial

## 3.1 Cardiac Action Potential

### 3.1.1 Resting Membrane Potential in Cardiac Cells

Cardiac muscle cells, like other living cells, have a potential gradient across the cell membrane. In excitable cardiac muscle cells at the resting phase, the transmembrane voltage, commonly called the resting potential, is dependent on the permeabilities of ionic channels to the flow of each ion and ion concentrations (activities) in the cytoplasm inside and outside in the extracellular fluid. Active transport (ionic pumps) and countertransport systems (ion exchangers) contribute to the maintenance of the resting potential. In ventricular muscle cells, the resting potential is  $-90$  mV, inside negative with respect to the outside. Among the ATP-dependent ionic pumps in the sarcolemma are the Na/K pump and the calcium pump. The Na/K pump generates a small steady outward current throughout the excitation/repolarization cycle (three  $Na^+$  out, two  $K^+$  in). This ionic pump is blocked by digitalis.  $I_{Na/Ca}$  current is generated by the Na/Ca countertransport system. The Na/Ca exchanger is the main mechanism for  $Ca^{2+}$  efflux through the sarcolemma, inwards or outwards depending on the membrane potential and gradients of  $Na^+$  and  $Ca^{2+}$ .

Intracellular and extracellular ion concentration differences (Table 3.1) produce large concentration gradients. Sodium is kept outside by the  $Na^+$  pump. Potassium permeability and influx is high and practically all potassium is intracellular. Extracellular potassium with a concentration of 4 mM makes up only 2% of total body potassium.

**TABLE 3.1** Normal intracellular and extracellular ion concentrations (mmol/l) in resting ventricular muscle cells. Potassium permeability is high and its chemical potential gradient is equal and opposite to the transmembrane potential gradient.

	Intracellular	Extracellular
Potassium	140	3.5–5
Calcium	0.0001	2
Sodium	10	140
Chloride	30	140

Potassium maintains electroneutrality so that the transmembrane potassium  $K^+$  chemical concentration gradient potential (inside positive) is equal and opposite to the transmembrane potential gradient (inside negative). Thus, the transmembrane resting potential gradient (denoted as resting potential) is normally equal to the  $K^+$  equilibrium potential. The intracellular calcium concentration is only 0.0001 mM. In spite of this, very minor variations in the availability of free intracellular calcium from intracellular stores have a major modifying effect on ionic currents.

3.1.2 Action Potential Transients

Transient ionic currents through ionic channels in the membrane generate the action potentials of cardiac ventricular and atrial myocytes, of cardiac pacemaker cells, and of the specialized His–Purkinje conduction system of the ventricles. The ion-specific channels contain molecular structures called gates. The opening and closing of the gates is regulated by the transmembrane voltage in the voltage-gated channels. When the gates are open, specific ions flow in these channels so that the concentration gradients across the membranes change. In addition to the voltage-gated channels, there are so-called rectifying channels that conduct channel current to a variable degree easier inwardly or outwardly across the membrane. The activity of the numerous ionic channels is carefully orchestrated in normal physiological conditions. Each channel is activated and inactivated, opening and closing at different times, changing concentration gradients and charge separation across the membrane, and thus generating the normal action potential.

Electrophysiological investigations including the long QT syndrome (LQTS) have advanced our

understanding of the physiological and pathophysiological mechanisms involved in normal and derailed ionic channel functions, including the mechanism of action of cardioactive drugs.<sup>1</sup> A 1991 treatise of the Task Force of the Working Group on Arrhythmias of the European Society of Cardiology contains a review of the ionic channel mechanisms in relation to drug actions on arrhythmogenic mechanisms.<sup>2</sup> A recent monograph on cardiac repolarization contains notes on the molecular biology of ionic channels and on the electrophysiology and pharmacology of ventricular repolarization, with an extensive list of references in various chapters.<sup>3</sup>

The following notes pertain primarily to ionic channel mechanisms of the ventricular fibers. The characteristics of the action potentials of the sinoatrial (SA) node pacemaker cells, the atrioventricular (AV) node, the specialized ventricular conduction system and the Purkinje fibers are different, and some of their specific features will be pointed out separately.

Functional characteristics of the ionic channels change in the course of growth and maturation. There are species differences in the distribution and characteristics of the ionic channels. This brief description will be largely limited to major ionic channels found in mammalian hearts. The list of references is very short, and the reader is advised to consult extensive sources in electrophysiological literature, including references 1–3 cited above.

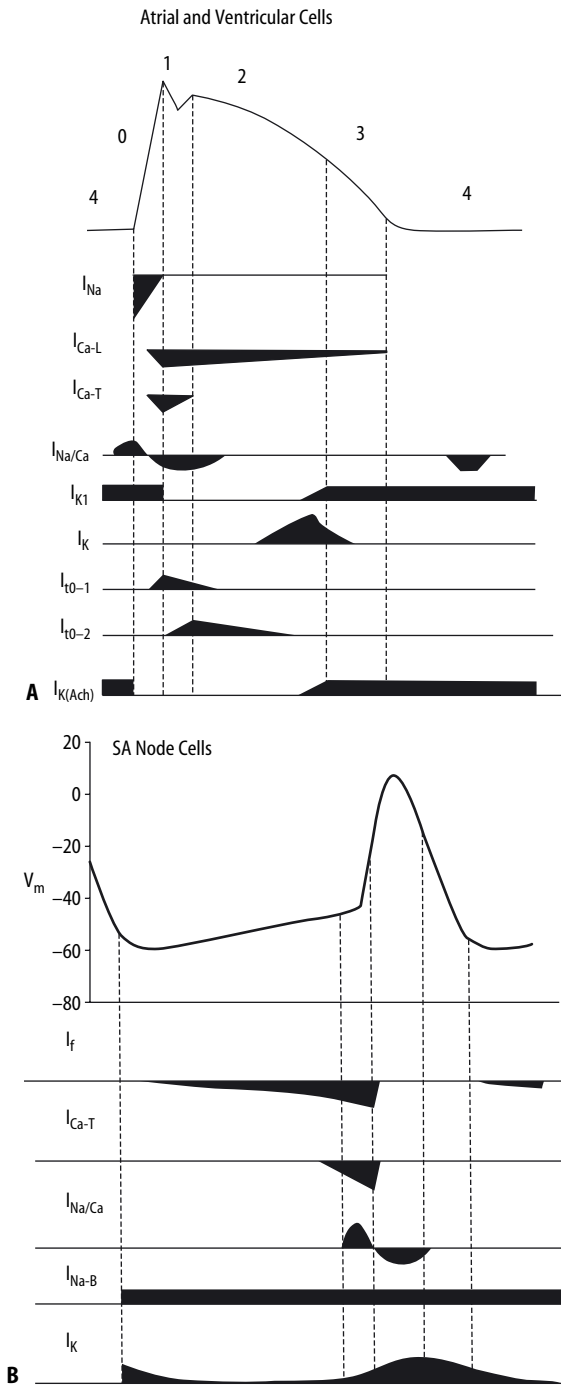
3.2 Ionic Channel Mechanisms that Regulate Action Potentials

The time course of activation and inactivation of ionic currents associated mainly with the generation of normal ventricular and atrial action potentials is illustrated in Figure 3.1.

3.2.1 Ionic Channel Currents and Ventricular Action Potential

3.2.1.1 Inward Excitatory Sodium Current

Inward current flow through voltage-gated sodium channels generates phase 0 of the ventricular



**FIGURE 3.1** Main normal ionic currents involved in generation of normal ventricular and atrial action potentials (*top*) and the SA node action potential transients (*below*). (Source: Task Force of the Working Group on Arrhythmias of the European Society of Cardiology.<sup>2</sup> Circulation 1991;84:1831–51. Copyright © 1991 American Heart Association. Reproduced with permission from Lippincott, Williams & Wilkins.)

action potential. Normal ventricular excitation starts at the terminal branches of the Purkinje fibers as a propagated response in the electrically coupled syncytium when depolarized by electrotonic interaction to the threshold of the  $I_{Na}$ -channel activation potential of approximately  $-55$  mV. Once activated, the current through the sodium channels is intense.  $I_{Na}$  channels have a fast time course of activation and inactivation. In spite of their early closure, some of the sodium channels remain potentially available during a time window for a transition back to the open state. Such a reversible inactivation at a certain level of membrane potential may generate a so-called window current and become one of the determinants of action potential duration (APD) by contributing to the maintenance of relatively steady-state equilibrium during phase 2.

### 3.2.1.2 Early Outward $I_{to}$ Currents

Following the action potential overshoot to a positive polarization of  $+20$  mV or more (phase 1), there is a quasi-stationary state (phase 2) commonly called plateau, although more appropriately denoted as the slow phase of ventricular repolarization. Subepicardial and intramural M cells have a notch at the transition point from phase 1 to phase 2. The notch is generated by the early transient outward current  $I_{to}$ . From its two components,  $I_{to1}$  is an outward current that is under modulating influence of neurotransmitters. It is carried through a voltage-gated potassium channel.  $I_{to2}$  is considered to be a calcium-activated chloride current.  $I_{to1}$  channels have a fast time course of activation and inactivation during early depolarization, and they are also called  $I_{to,f}$  with subscript “f” denoting fast.  $I_{to1}$  channels recover fast from their inactivated state, meaning that they can be activated again after a short pause.  $I_{to2}$  channels also activate and inactivate fast, although slower than  $I_{to1}$  channels, and the time course of the recovery from the inactivated state is slower. These channels are also called  $I_{to,s}$  with subscript “s” denoting slow.

### 3.2.1.3 Inward Calcium Current

Electrophysiological terminology used to describe voltage-gated channels, the calcium channel in particular, is often confusing. At times, the term-

nology is based on physiological–pharmacological time-dependent properties (subscript T referring to transient, short-duration and L to longer lasting), and at times, the terminology is based on activation voltage thresholds (with LVA referring to low-voltage activated, meaning that activation threshold voltage is high negative, and HVA referring to high-voltage activated, meaning that activation occurs at lower, less negative voltage). Calcium channels other than  $I_{Ca-L}$  and  $I_{Ca-T}$  are variously denoted by subscripts N (neither type L nor type T), P (Purkinje), or R (remaining types).

$I_{Ca-T}$  channels are apparently not present or are scarce in mammalian ventricular myocytes. The transient T-type calcium current is carried through a different voltage-gated channel. It may be associated with abnormal automaticity in atria. The  $I_{Ca-L}$  current influx increases from the onset of phase 1 and reaches its peak at the time of the notch of phase 1, then declines slowly during phase 2.

$I_{Ca}$  channels are activated when depolarization has reached a higher level and the activation is delayed with respect to the depolarizing  $I_{Na}$  current. Thus,  $I_{Ca}$  current does not make a notable contribution to phase 0. The activated phase is long lasting.  $I_{Ca}$  triggers intracellular  $Ca^{2+}$  release, important for excitation–contraction coupling. The quasi-stationary equilibrium during phase 2 plateau is dependent to an important extent on the balance of  $Ca^{2+}$  influx and  $K^+$  efflux. With fast inactivation of  $I_{Ca-L}$  channels, the outward  $K^+$  current dominates the transmembrane ionic balance because of the high driving force for the efflux of  $K^+$ , and the fast phase of repolarization begins. Thus,  $I_{Ca-L}$  plays an important role in the generation of phase 3 and as a determinant of APD.  $I_{Ca-L}$  is strongly influenced by neurotransmitters and calcium channel blocker action. In AV and SA node cells, it produces depolarization.

### 3.2.1.4 Outward Voltage-gated Potassium Currents

There are a number of voltage-gated outward currents carried by diverse  $I_K$  channels.  $I_{K1}$ , called “inward rectifier”, is carried through channels that have a high conductance when the membrane

is polarized to a high negative value during phase 4. It plays an important role in establishing the resting potential of cardiac myocytes. The high conductance is sharply reduced at the onset of depolarization when the transmembrane potential increases above  $-40$  mV. In spite of low conductance, during the plateau it maintains the membrane potential in atrial and ventricular cells and also in AV nodal and His–Purkinje cells. The mechanism of this  $I_{K1}$  action is its contribution to outward  $K^+$  current because the driving force for  $K^+$  ions is markedly increased when the membranes are depolarized.  $I_{K1}$  channels are absent in the SA node, thus permitting pacemaker rate modulation by small pacemaker currents during phase 4.

$I_{Ks}$  is a slowly activating delayed rectifier current that is mainly responsible for the fast phase of repolarization when the inward calcium channels are inactivated.  $I_{Ks}$  channels, some of them modulated by neurotransmitters, are turned off slowly after repolarization. These channels contribute to phase 4 depolarization in SA node cells.

$I_{Kr}$  is a rapidly activating delayed potassium current.  $I_{Kr}$  block increases the dispersion of repolarization, at least in part by preferential prolongation of APD of the M cells. Kr block prolongs QT interval and produces a tall, broad-based T wave with or without a notch in the descending limb when the extracellular potassium ( $[K^+]_o$ ) is normal.<sup>4</sup>

$I_{K(ATP)}$  is a metabolically regulated potassium channel blocked by ATP and activated by ischemia, possibly producing APD shortening in myocardial ischemia. While most channel-active agents act by blocking ionic currents, the agents activating  $I_{K(ATP)}$  increase outward potassium current. Experimentally administered antiarrhythmic drugs act either by increasing or decreasing  $I_{K(ATP)}$  and thus either shorten or prolong repolarization.

Among other ionic channel currents are  $I_{Cl}$  and  $I_{NS}$ . The  $Cl^-$  current flow is usually small but is increased by adrenergic receptor activation, thus potentially contributing to repolarization if the  $[Cl^-]_i$  concentration deviates from its normal equilibrium value.

$I_{NS}$  is a current through a non-selective channel, and it is gated by  $Ca^{2+}$  and carried by  $Na^+$ . It may be activated in some abnormal conditions during



the early phase of depolarization and also by  $\text{Ca}^{2+}$  release from the sarcoplasmic reticulum in  $\text{Ca}^{2+}$  overload. In these conditions, it may contribute to generation of delayed afterdepolarizations (DAD).

### 3.3 Ionic Currents that Regulate the Sino-Atrial Node

The ionic currents that regulate the SA node are functionally different from those regulating other cardiac structures, as shown in Table 3.2.

- The  $I_{\text{Na}}$  channel does not exist or its density is sparse in the SA node (like in the AV node), and it has no role in pacemaker action.
- $I_{\text{Na-B}}$  is an inward sodium current carried through a voltage-independent channel in SA node cells. It generates phase 4 of the action potential in pacemaker cells (together with  $I_f$ ).
- $I_{\text{Ca-L}}$  current (with  $I_{\text{Ca-T}}$ ) generates the upstroke of the action potential in the SA node (and the AV node) cells. The upstroke is slower than that generated by  $I_{\text{Na}}$  channels in phase 0 in ventricular cells.
- $I_{\text{Ca-T}}$  is activated already at the end period of phase 4. It may participate in generating abnormal atrial automaticity.
- $I_K$  produces SA node repolarization. It also produces a current that opposes inward sodium current at the early part of phase 4. After  $I_K$

**TABLE 3.2** Major differences in the functional roles of the ionic channels in SA nodal and ventricular muscle cells.

	SA node cells	Ventricular cells
$I_{\text{Ca-L}}$	Generates with $I_{\text{Ca-T}}$ phase 0	Minor role only in generating phase 0
$I_{\text{Ca-T}}$	Activated at end of phase 4. May induce abnormal atrial automaticity	Absent or density low in human ventricular cells
$I_{\text{Na}}$	Does not exist, or density sparse	Main channel generating phase 0 upstroke
$I_{\text{Na-B}}$	Inward sodium channel. Generates with $I_f$ pacemaker potential	Not present
$I_f$	Activated at high depolarized state. Under strong influence of neurohormones. Regulates firing rate of the SA node	Not present

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decay,  $I_{\text{Na-B}}$  generates phase 4 pacemaker potential of the SA node cells.

- $I_{\text{K-ACh}}$  can produce hyperpolarization in SA (and AV) node cells.
- $I_f$  is an inward  $\text{Na}^+$  current through a channel that is activated at high polarized state (also present in AV node and His–Purkinje cells). It produces with  $I_{\text{Na-B}}$  phase 4 of the pacemaker potential. This channel is under a strong modulating influence of neurotransmitters.

Among other ionic channel currents in the SA node are the  $I_{\text{pump}}$  (Na/K pump and the calcium pump) current and  $I_{\text{Na/Ca}}$  current generated by the Na/Ca countertransport system.

### 3.4 Electrolytes and Action Potentials

The effect of some electrolyte concentrations deviating from their normal values can cause notable changes in action potential waveforms, as shown in Table 3.3 and also in body surface ECGs, summarized in Table 3.4. At body surface ECG level, manifestations of changes in potassium concentrations are most readily visible, whereas calcium level variations are apparent in more severe cases only. Sodium or magnesium concentration effects on ECG are not notable in practical clinical electrocardiography. Only potassium effects summarized in Table 3.4 will be discussed here because they are most often associated with visible ECG manifestations.

#### 3.4.1 Hyperkalemia

Hyperkalemia may occur clinically with the use of potassium sparing diuretics or ACE inhibitors, in kidney failure, acidosis and hyperkalemia with excessive administration of potassium supplements. With an increase in extracellular potassium, the resting potential becomes less negative and the action potential amplitude decreases.  $(\text{dV}/\text{dt})_{\text{max}}$  decrease in phase 0 decreases the conduction velocity in atrial and ventricular muscle cells. P wave and QRS broaden. Atrial cells are particularly sensitive. P wave amplitude decreases and at higher concentrations atrial cells become unexcitable. However, the SA node is little influenced, and AV conduction may modestly increase

**TABLE 3.3** Action potential waveform changes with serum potassium and calcium concentration.

	Hyperkalemia	Hypokalemia	Hypercalcemia	Hypocalcemia
Phase 0 (dV/dt) <sub>max</sub>	Decreases	Decreases	Decreases	Increases
Phase 2	Shortens	Prolongs	Shortens	Prolongs
Phase 3	Shortens	Prolongs	Shortens	Prolongs
Phase 4	Decreases	Increases	No change	No change
membrane potential	(becomes less negative)			

(mild hyperkalemia) or decrease (moderate hyperkalemia). With shortening of phase 2 and phase 3, the QT interval shortens. Peaked, high amplitude T wave is the most sensitive ECG indicator of mild hyperkalemia. However, this ECG amplitude change in moderate hyperkalemia is relatively modest, approximately 20%.

A mild hyperkalemia may suppress ectopic latent focal pacemaker activity and it has a transient antiarrhythmic effect. Potassium chloride infusion has extremely potent electrophysiological effects. Slow infusion of potassium produces sinus bradycardia, ending up with sinus arrest, impaired AV conduction, idioventricular rhythm and asystole. Rapid infusion of potassium induces ectopic ventricular rhythms associated with depressed conduction and ends up with fatal ventricular fibrillation.

### 3.4.2 Hypokalemia

Like in hyperkalemia, (dV/dt)<sub>max</sub> and conduction velocity decrease in hypokalemia in atrial and

ventricular muscle cells. P wave and QRS broaden with decreased conduction. The mechanism of P amplitude increase is not entirely clear. QT prolongs with prolongation of phase 2 and phase 3. The emergence of the prominent U wave, T-U fusion and decreasing T wave amplitude (at least the first half) suggests a profound increase of dispersion of ventricular repolarization by a differential effect on endocardial, epicardial, and M cell populations. Compared to the relatively low prevalence of typical ECG changes in hyperkalemia, the prevalence of ECG changes in moderate hypokalemia is high, 78% according to Surawicz et al.<sup>5</sup>

## 3.5 Neurohormones and other Receptor Stimulating Agents

The heart responds to demands for increased cardiac output during stress by increasing the heart rate and contractility. This occurs as a response to adrenergic neurohormones released at postsynaptic nerve terminals. A complex of proteins within the cardiac sarcolemmal membrane, including adrenergic receptors and an effector enzyme, adenylyl cyclase, initiate a series of biochemical processes. Among these processes as the end result of positive inotropic and chronotropic response is the synthesis of an intracellular second messenger cAMP and phosphorylation of protein kinase (PKA).

The receptors, categorized as  $\alpha$ - and  $\beta$ -adrenergic, muscarinic, and purinergic types, modify the functions of various ionic channels and pumps through receptor-effector coupling systems. Activation of one type of receptor can also influence other receptor types. For instance, beta 1-adrenoreceptors and M2 muscarinic receptors have antagonistic features in their actions.

**TABLE 3.4** Changes in ECG waveforms observed in elevated or decreased serum concentration of potassium.

	Hyperkalemia	Hypokalemia
P wave	Low amplitude, broad; vanishes at higher concentrations	Amplitude usually, increases wave broadens; may resemble P pulmonale
QRS	Broadens; at higher concentration QRS-T complex resembles a sine wave	Amplitude increases, wave broadens in severe hypokalemia
ST	Shortened with QRS prolongation, elevated or depressed; vanishes at higher concentrations	Depressed
T	Peaked, high T first ECG sign (although sensitivity low)	Decreased amplitude
U wave	Diminished	Prominent

The autonomic nervous system, acting on the receptors, modulates cardiac rhythm and may contribute to the effects of antiarrhythmic or proarrhythmic agents. Modified receptor functions can influence impulse formation and initiation and propagation of action potentials.

### 3.5.1 Beta-adrenergic Receptor Stimulation

Beta-adrenergic receptor stimulation acts on various potassium channels (only  $I_{K1}$  is apparently not affected), on  $I_{Ca-L}$ ,  $I_{Cl}$ ,  $I_f$  (also sodium channels under some conditions), and it can enhance Na/K pump activity. Beta-adrenergic stimulation or agonist action can thus be expected to have a variety of manifestations under different conditions. Shift of the  $I_f$  activation curve towards a more positive potential produces a chronotropic effect in the SA node and enhances latent pacemaker activity at ectopic atrial and ventricular sites. Increased L-type  $Ca^{2+}$  current enhances contractility (increased intracellular  $Ca^{2+}$ ) and it could also induce triggered activity due to early as well as late afterdepolarizations.

The effect of  $\beta$ -adrenergic receptor stimulation on potassium channels can be expected to shorten the refractory period. Spatial heterogeneity in the distribution of  $I_{to}$  channels (present in subepicardial and M cell regions only) could conceivably induce increased dispersion of the end of the refractory period. In the AV node, combined  $Ca^{2+}$  and  $K^+$  effect may shorten AV node refractoriness and speed up AV conduction. In a healthy heart the conglomerate of the above actions will produce shortening of the QT interval, sinus- and at times ectopic supraventricular tachycardias.

Of the several subtypes of  $\alpha$ -adrenergic receptor-effector coupling systems, subtypes of  $\alpha_1$ -receptor are linked to effector systems that modulate impulse initiation and APD. Their stimulation effect on the Na/K pump may suppress the tendency to ectopic pacemaker-type activity in the atria. The potential role of  $\beta$ -adrenergic receptors in arrhythmogenic mechanisms in humans is unclear.

### 3.5.2 Muscarinic Cholinergic Receptor Stimulation

The  $M_2$  muscarinic receptor is the main cardiac muscarinic receptor. It is particularly important

in the atria where its density is five times higher than in the ventricles. Whereas the ventricles are dominantly under  $\beta$ -adrenergic control, the atria are strongly under vagal control. Vagal stimulation, muscarinic activation, and muscarinic agonist action (digoxin) have antagonistic adrenergic effects. Muscarinic effect is blocked by atropine. In the atria, muscarinic activation effects include a decrease in  $I_f$  and suppression of the SA node through increased conductance of the muscarinic  $K^+$  channel, thus slowing down the heart rate. An increase in  $I_{K(ACh)}$  hyperpolarizes atrial myocytes and shortens atrial APD. A decrease of the SA node impulse rate increases atrial APD in linear proportion, and the direct vagal effect has a simultaneous opposite effect by shortening atrial APD.

At the level of the AV node, the antiadrenergic effect of muscarinic activation on  $Ca^{2+}$  and  $K^+$  currents contributes to decreased conduction. Muscarinic activation can be expected to be effective in supraventricular arrhythmias and arrhythmias involving the AV node. In humans, an antiarrhythmic effect at the ventricular level has not been documented.

### 3.5.3 $A_1$ -purinergic Receptor Stimulation

The cardiac purinergic (adenosine) receptor-effector coupling system is called  $A_1$ . It apparently has the same effector coupling pathway as the muscarinic receptor. Adenosine is effective in terminating tachycardias where the AV node is in the re-entrant pathway. Adenosine  $A_1$ -receptor agonists increase the resilience of ventricular myocardium to ischemic injury even several hours after experimental coronary occlusion and reperfusion.

## 3.6 Antiarrhythmic Drugs

The major classes of antiarrhythmic agents are categorized within the framework of the most commonly used classification system described by Vaughan Williams, summarized in Table 3.5.<sup>6</sup> The system does not necessarily identify the critical "vulnerable parameter" like the so-called Sicilian Gambit classification.<sup>2</sup> The vulnerable parameter is associated with the mode of arrhythmic suppression action of the agents. The



**TABLE 3.5** Major classes of antiarrhythmic drugs according to the scheme of Vaughan Williams. The categories are largely defined on the basis of QT-prolonging effect.

Class	Mechanism of action	Examples
I. Na <sup>+</sup> channel blockers		
IA Prolong QT	Widening of the notch, APD prolongation in epicardial cells; prolonged APD due to combined action with associated K <sup>+</sup> channel block	Procainamide Disopyramide
IB Shorten QT	Quinidine A selective blocker; at higher concentrations shortens epicardial APD due to abolishment of the dome, with only a slight shortening of endocardial APD. No K <sup>+</sup> channel block	Lidocaine Mexiletine Tocainide Phenytoin
IC Little or no effect on QT	Decreased (dV/dt) <sub>max</sub> , conduction velocity in atrial and ventricular muscle cells	Encainide Flecainide Propafenone
II. Beta-adrenergic blockers	Block catecholamine effects on Ca <sup>2+</sup> and K <sup>+</sup> channels; prolong APD and slow AV node conduction.	Propranolol Esmolol Timolol
III. K <sup>+</sup> channel blockers	ADP prolongation, particularly in M cells; effect decreasing progressively with increased rate (reverse use dependence). APD prolongation is less notable in endocardial and epicardial cells. This difference is pronounced for I <sub>Kr</sub> blockers. I <sub>Ks</sub> blockers increase APD on all three types of ventricular cells	Ibutilide Bretylium Sotalol
IV. Calcium <sup>2+</sup> channel blockers	Suppression of SA node and AV conduction (except nifedipine). Some bind to L-type channels (suppression of contractility), except mibefradil (T-type binding)	Verapamil Diltiazem Nifedipine

classification scheme of Vaughan Williams is largely based on the QT-prolonging effect of the drug. The major problem here is that QT prolongation does not necessarily indicate increased dispersion of repolarization and QT shortening does not necessarily indicate decreased dispersion of repolarization. An additional complication with any simple drug classification scheme is that commonly used antiarrhythmic drugs act on multiple ionic channels.

It is important to understand that dispersion of repolarization at cardiac level is a different entity from QT dispersion measured from the QT interval differences in different from body surface ECG leads. Dispersion of repolarization at cardiac level is an important physiological and pathophysiological phenomenon. QT dispersion is based on an unsubstantiated and unproven hypothesis, as will be discussed at the end of Chapter 11.

The following is a brief summary of conceptually reasonably rational expressions of the relationships between the quantities in question. Abnormal dispersion (increased or decreased) of ventricular repolarization can be local (for instance between Purkinje fibers and subendocardial cells or between M cells and subendocardial or subepicardial cells), regional (transmural in a wall section), or global (between myocardial regions).

Normal repolarization, both its onset and end, is always dispersed regionally and globally, otherwise there will be no T wave. Most critical abnormal dispersions are likely to be local or regional.

- Denoting the local or regional end of repolarization by RT (repolarization time, measured for instance from the onset of excitation), dispersion of repolarization can be expressed as dispersion of repolarization time (DRT).
- Change in APD decreases DRT in a given region only if the temporal gradient of APD decreases. This occurs, for instance, if the agent decreases APD of the cells that repolarize later more than that of the cells that repolarize earlier, or if the agent increases APD of the cells that repolarize earlier more than that of the cells that repolarize later in that region. In the latter condition, DRT may initially decrease and then increase again (as shown in Figure 11.2 in Chapter 11).
- Changes in the regional repolarization time or DRT will influence QT measurements in body surface ECG only under special circumstances. In most instances, DRT change will have no notable effect on QT, although it can always be expected to influence ST-T waveform to variable degrees.

- Prolonged repolarization as a response to the action of an agent can be detected from QT measurement in body surface ECG only if APD prolongation involves the cells in the region that repolarized last before the action of the agent, or if APD prolongation in some other region is pronounced enough so that this region now repolarizes last.
- Shortened repolarization can be detected from QT measurement only if APD shortening involves the region that repolarized last before the action of the agent.
- A uniform spatial global increase or decrease of APD increases and decreases QT without a change in DRT.
- There are two alternative conditions that are necessary for detection of local prolonged or shortened DRT from body surface ECG: (1), the presence of nondipolar components in T wave originating from the region that is repolarizing last that are above the threshold of Tend detection criteria; or (2), the presence of nondipolar components in T wave originating from some other local region that are sufficiently strong to modify the effect of the stronger dipolar components and thus to influence the end of T wave detection. The presence of nondipolar components of sufficient magnitude in the T wave for detection of the changes in local or regional DRT has not been demonstrated.
- Thus, detection of increased or decreased DRT is possible only in exceptional circumstances, and the establishment of the association between DRT and various subintervals of QT in time domain is problematic.
- T wave waveform in amplitude domain and its spatial characteristics can be expected to change whenever DRT increases or decreases. These T wave changes also occur whenever action potential phase 3 slope changes differentially in various myocardial regions.

The relationships of the cardiac source events above are reiterated in Chapter 11.

### 3.6.1 Differences in Regional Response Characteristics of Ventricular Cells

Sodium channel blockers such as tetrodotoxin, propranolol and flecainide, slow down ventricular

conduction. They have a differential effect on sub-endocardial and subepicardial action potentials in canine ventricular myocardium.<sup>7</sup> In concentrations that reduce  $(dV/dt)_{\max}$  by approximately 40%, epicardial and M cell APD is prolonged, mainly because of the widening of the notch and the consequent delay of the onset of repolarization. In contrast, endocardial APD may even shorten. With a more pronounced sodium channel blocker action, phase 2 onset will shift to a lower, more negative potential. As a result,  $I_{Ca}$  is diminished and the outward ion currents may dominate, resulting in a pronounced decrease of epicardial APD and possibly an all-or-none repolarization at the end of phase 1. Endocardial APD may shorten only slightly. This may enhance the heterogeneity of ventricular repolarization.

Epicardial and endocardial action potentials differ in their response to parasympathetic and sympathetic agonists. Although vagal stimulation and acetylcholine are known to prolong the ventricular effective refractory period, acetylcholine has no notable effect on endocardial APD. In vivo acetylcholine effect has been thought to be strictly through antagonism of  $\beta$ -adrenergic tone. However, acetylcholine has a direct effect on subepicardial action potentials.<sup>8</sup> At low concentrations acetylcholine accentuates the notch of phase 1 and delays the peak of the dome, prolonging APD. At higher concentrations there is a marked abbreviation of the action potential. The direct acetylcholine effect is thought to be associated with the inhibition of  $I_{Ca}$  and/or activation of  $I_{K-ACh}$  (since acetylcholine does not influence  $I_{to}$ ).

The APD of subepicardial cells shortens more with catecholamine than that of endocardial cells. Catecholamines enhance  $I_{Ca}$  and reduce the notch at the onset of the plateau. All major currents contributing to phase 1 and phase 3 ( $I_{to}$ ,  $I_{Ca}$ ,  $I_K$ ,  $Ca^{2+}$ - and cAMP-activated  $I_{Cl}$ ) are influenced by  $\beta$ -adrenergic agonists.

The M cell action potentials differ in many aspects from both the endocardial and epicardial cells. The APD rate sensitivity of the M cells is higher than that of the endocardial and epicardial cells, and APD prolongation in response to class III agents is pronounced whereas there is a less notable response in endocardial and epicardial cells.<sup>9</sup> This difference is pronounced for  $I_{Kr}$  blockers. M cells may induce early afterdepolarizations

(EAD) with class III-type agents and DAD as a response to digitalis, catecholamines, and high calcium ion concentrations. The APD of the M cells increases markedly in response to  $I_{Ks}$  blockers and  $I_{Kr}$  channel blockers.

There are significant species differences in the presence, density, distribution, and functional properties of ionic channels.<sup>9,10</sup> Various disease conditions may cause profound alterations in electrophysiological functional properties of cardiac cells.<sup>11</sup>

### 3.7 Multifaceted Drug Effects on Ionic Channels

The Food and Drug Administration's (FDA) focus has been heavily on QT-prolonging effect as a surrogate endpoint in evaluating possible toxic effects of drugs in phases 1 and 2 of drug trials. As noted earlier, detection of localized dispersion of myocardial repolarization is possible from QT measurements only in special circumstances. Myocardial dispersion may have little effect on measured QT. The antiarrhythmic effect of class III and class IA agents is assumed to be associated with AP and QT prolongation. Excessive QT prolongation may become proarrhythmic. Class IC drugs block  $Na^+$  channels and decrease  $(dV/dt)_{max}$  with no or little QT-prolonging effect. The sodium channel affinity of most antiarrhythmic drugs is relatively low in the repolarized state of the excitation/repolarization cycle. The affinity of class I drugs increases during the activated state of the channel, i.e. the block is phasic or use-dependent. The "use" occurs mainly when the channel is activated to the open state and increases with stimulus rate (heart rate). Some voltage dependence of sodium channel blocking drugs may be important, especially in the ischemic myocardium, where drugs such as lidocaine have a more pronounced effect on conduction in depolarized or partially depolarized cells.

Selective  $I_{to}$ -blocking agents (4-aminopyridine (4-AP) at low concentrations) abolish arrhythmic effects of ischemia and drugs and neurohormones (sodium channel blockers and acetylcholine) that increase dispersion of repolarization. Also quinidine inhibits  $I_{to}$ . Because of the early short-

duration nature of  $I_{to}$  currents, there seems to be some controversy on its influence on APD, for instance about the reported APD prolongation with downregulation of  $I_{to}$  channel density in heart failure.<sup>11</sup>  $I_{to}$  broadens the notch and decreases phase 2 plateau level and influences all active currents later in phase 2. Therefore,  $I_{to}$  inhibition or reduction of the current can be expected, at least in physiological conditions with normal intracellular ion levels. This will reduce APD in subepicardial and M cells, thus reducing the dispersion of the end of ventricular repolarization.

Chromanol 293B, one of the most specific  $I_{Ks}$  blockers, has an APD-prolonging action similar in all three types of ventricular cells. QT can be expected to prolong without a notable increase in DRT.

Most channel blockers have properties of several drug categories, and prediction of their effect on DRT is complicated. For instance, quinidine (class 1A) and amiodarone (class III) have functional properties of all four drug classes, and they also have additional actions. Quinidine, at lower doses, induces M cell APD prolongation with  $I_{Kr}$  block; at higher dose and a  $I_{Ks}$  block in addition to  $I_{Kr}$  block, M cell APD shortens while endocardial and epicardial APD prolongs. Thus, at lower doses of the drug, DRT can be expected to increase, and a decrease can be expected at higher concentrations, even at toxic doses.

The chronic amiodarone administration effect, although strongest on the  $K^+$  channel,<sup>2</sup> is also multifaceted:  $\beta$ -blocking and blocking of sodium, potassium, and calcium channels. The combined action results in prolonged repolarization without notable increase in DRT. Amiodarone and quinidine, like some other commonly used drugs that have multiple modes of action (procainamide, disopyramide, sotalol), are effective in therapy of a broad range of arrhythmias. Amiodarone in oral form is used to convert atrial fibrillation and flutter into sinus rhythm and to suppress recurrence after conversion. Successful conversion has been achieved in approximately 50–80%.

With class III drugs, prolongation of repolarization is most pronounced at low stimulus (heart) rates, decreasing progressively with increased stimulation rate (reverse use dependence, the effect opposite to that of class 1A drugs). This has raised concern about the loss of efficacy of class

III antiarrhythmic drugs with increased heart rate.

Increased Na/K pump activity may hyperpolarize ventricular cell membranes especially if they are partially depolarized in ischemic states. This may influence the antiarrhythmic effect of drugs.

3.8 Antiarrhythmic Drug Classification

The so-called “Sicilian Gambit” antiarrhythmic drug classification scheme proposed by the European Society of Cardiology Task Force<sup>2</sup> specified the most likely “vulnerable parameter” for characterization of various mechanisms of drug action. The vulnerable parameter was defined as a property the alteration of which will be sufficient to terminate the arrhythmia or to prevent its initiation. Usually alteration of one such vulnerable parameter is most susceptible to a desired change with a minimum of undesirable cardiac effects.

The actual drug classification scheme of the European Task Force is reproduced in Table 3.6 with some modifications. Selected summary comments of various arrhythmogenic mechanisms and the terminology used by electrophysiologists are necessary to facilitate appreciation of the logic of this classification scheme.

3.8.1 Enhanced Normal Automaticity

This category includes the so-called inappropriate sinus tachycardia, atrial tachycardias, and some idioventricular rhythms. Inappropriate sinus tachycardia is a tachycardia of sinus origin persisting both during physical exercise and at rest. Enhanced normal automaticity is generally harmless and only rarely, if severe, may require therapeutic action. The antiarrhythmic effect on the vulnerable parameter is singly or combined a decreased phase 4 depolarization rate, increased maximum resting potential, hyperpolarization level, or the level of the firing threshold. The desirable therapeutic effect can be achieved by

**TABLE 3.6** Categorization of arrhythmogenic mechanisms, desired antiarrhythmic effect on the most likely vulnerable parameter and ionic currents most likely to achieve the desired antiarrhythmic effect.

Mechanism of arrhythmia	Antiarrhythmic effect on vulnerable parameter	Ionic currents most likely to achieve desired effect
Enhanced normal automaticity	Decrease rate of phase 4 depolarization	Block $I_{fr}$ , $I_{Ca-T}$ Activate $I_{K(ACh)}$
Abnormal automaticity	Increase (hyperpolarize) max diastolic potential or decrease rate of phase 4 depolarization in latent focus	Activate $I_{Kf}$ ; $I_{K(ACh)}$ Block $I_{Ca-L}$ ; $I_{Na}$
Triggered activity induced by EAD	Shorten APD	Activate $I_K$ Block $I_{Ca-L}$ ; $I_{Na}$
Triggered activity induced by DAD	Reduce calcium overload or suppress DAD	Block $I_{Ca-L}$ Block $I_{Ca-L}$ ; $I_{Na}$
Na channel-dependent re-entry with primary impaired conduction (long excitatory gap)	Decrease excitability and conduction	Block $I_{Na}$
Na channel-dependent re-entry with conduction encroaching on refractoriness (short excitatory gap)	Prolong effective refractory period	Block $I_K$
Ca channel-dependent re-entry	Decrease excitability and conduction	Block $I_{Ca-L}$
Reflection	Decrease excitability	Block $I_{Ca-L}$ ; $I_{Na}$
Parasystole	Decrease rate of phase 4 depolarization in automatic (Purkinje) focus	Block $I_f$ (if max neg diastolic potential hyperpolarized)

*EAD* early afterdepolarizations, *DAD* delayed afterdepolarizations, *APD* action potential duration.  
Source: Task Force of the Working Group on Arrhythmias of the European Society of Cardiology.<sup>2</sup> Circulation 1991;84:1831–51. Copyright © 1991 American Heart Association. Reproduced with permission from Lippincott, Williams & Wilkins.

$\beta$ -adrenergic blocking agents or sodium channel blockers.

### 3.8.2 Abnormal Automaticity

Abnormal automaticity may arise in damaged, partially depolarized atrial, Purkinje, or other ventricular fibers that start exhibiting enhanced latent pacemaking activity. In damaged Purkinje fibers, phase 4 slope is determined by  $I_f$ , except when maximum diastolic potential is reduced to below  $-55$  mV and the decay of  $K^+$  currents determines the slope of phase 4. Muscarinic receptor M2 agonists, activation of  $I_K$  or  $I_{K-ACh}$  may have a remedial effect on the vulnerable parameter in this situation, and  $I_{Ca-L}$  or  $I_{Na}$  block on phase 4 repolarization.

### 3.8.3 Triggered Activity

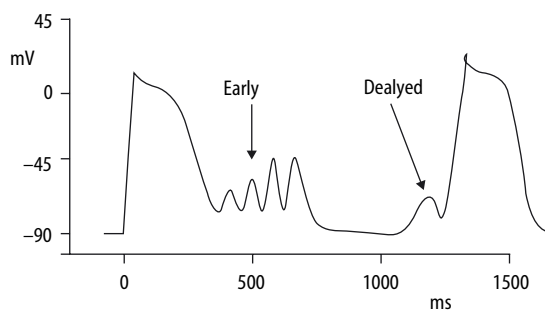
Triggered activity refers to depolarization events associated with afterdepolarizations. They are oscillatory variations in membrane potential that occur when preceding repolarization is not completed, called early afterdepolarizations (EAD), or that occur later on during phase 4, called delayed afterdepolarizations (DAD).

#### 3.8.3.1 Early Afterdepolarizations

The schematic in Figure 3.2 illustrates some possible patterns of EAD and DAD. Several ionic mechanisms may be associated with the mechanism of EAD. It is thought that EAD may be the triggering mechanism in Torsades de Pointes. Facilitating factors for EAD (likely vulnerable parameters) include slow heart (stimulus) rate or a pause, decreased extracellular  $K^+$  concentration, and the actions of drugs that prolong APD ( $I_K$ ,  $I_{K1}$  block). Consequently, the desirable therapeutic approach is to consider withdrawal of drugs that prolong APD and/or the use of  $\beta$ -agonists or vagolytic agents to increase heart rate. Triggering inward currents may be suppressed by calcium or sodium channel blocking agents,  $\beta$ - or  $\alpha$ -adrenergic receptor blocking drugs.

#### 3.8.3.2 Delayed Afterdepolarizations

Delayed afterdepolarizations are associated with intracellular calcium overload. Inward, depolar-



**FIGURE 3.2** Schematic of afterdepolarizations. Early afterdepolarizations occur primarily at slow heart rates and prolonged action potential duration, and may result in repetitive oscillations and under certain circumstances in abnormal automaticity-like activity or possibly Torsades de Pointes. Delayed afterdepolarizations may arise from oscillatory repetitive release of calcium from sarcoplasmic reticulum in calcium overload and they may trigger ventricular ectopic complexes and tachycardias.

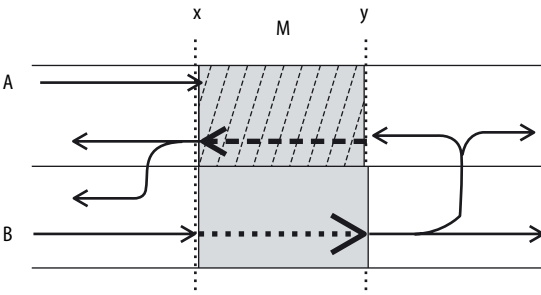
izing currents are caused by repetitive release of calcium from intracellular stores. Arrhythmic events most likely to be initiated by DAD are ectopic ventricular complexes (not necessarily premature), tachycardias associated with digitalis overdose, and some tachycardias related to catecholamine effect. Reduction of calcium overload (the vulnerable parameter), for instance by calcium channel blocking agents, may abolish clinically significant tachycardias in this category. Delayed afterdepolarizations may also be suppressed by agents that block the nonselective inward sodium channel current ( $I_{Ns}$ ).

### 3.8.4 Re-entry

A model of re-entry was originally introduced by Schmitt and Erlanger, who as early as 1928 produced experimental evidence for the condition (Figure 3.3).<sup>12</sup>

Two models of re-entry are described in Figure 3.4. The model on the left was proposed by Schmitt and Erlanger to explain the mechanism of ventricular ectopic complexes with fixed coupling. In the model, the normal excitation arrives from the AV node in D and enters two branches of the Purkinje fibers, which connect to the ventricular muscle fibers below. One branch conducts normally but the other branch has a unidirectional block between A and B. By the time ventricular excitation arrives at B, the fiber has regained its





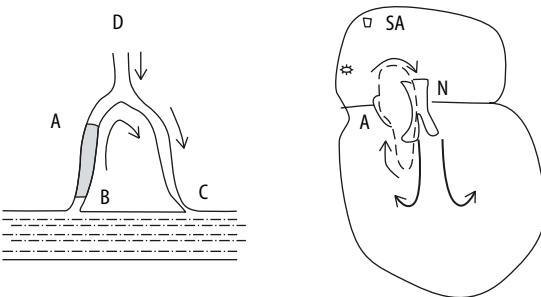
**FIGURE 3.3** Schematic of re-entry from a 1928 model by Schmitt and Erlanger. A segment between x and y subjected to KCl poisoning and pressure injury produced a unidirectional block in fiber A and strongly slowed conduction through fiber B. Excitation exits fiber B after a delay, excites fiber A in both directions and re-enters back to fibers A and B.

excitability and excitation propagates retroactively from B to A and then from the bifurcation to C, eliciting the ectopic complex.

The model on the right in Figure 3.5 illustrates the mechanism of an accessory pathway eliciting reciprocating tachycardia by re-entry involving the AV node.

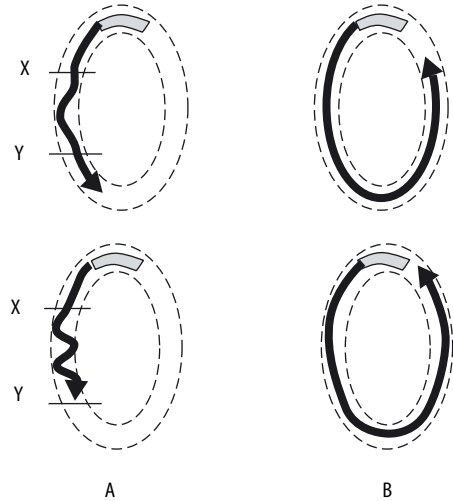
### 3.8.5 Circus Movement and Excitable Gap

A circus movement with re-entry can occur in a circuit of cardiac tissue. In re-entrant arrhythmias, the path of circus movement has to be longer than the wavelength of the excitatory wave in the circuit that is determined by the effective refractory period and conduction velocity. The circuit path can also have a nonconducting boundary,



**FIGURE 3.4** Schematic of a model for the mechanism of ventricular ectopic complexes with fixed coupling (*left*) and the mechanism of an accessory pathway eliciting reciprocating tachycardia by re-entry involving the AV node (*right*).

### 3. Normal and Arrhythmogenic Ionic Channel Mechanism



**FIGURE 3.5** Schematic of the re-entry and circus movement. Black arrows indicate the portion of the circuit that is absolutely refractory, and the gray area at its tail is in the relative refractory phase. The region inside the smaller dotted ellipse is a nonconducting anatomical or functional barrier that prevents short circuiting of the propagating wavefront in the loop. At *top left in A*, there is a long excitatory gap between the head of the circulating wavefront and its tail, and there is an impaired conduction in the segment between lines X and Y. Further depression of conduction by drug action (*bottom left in A*) may block the circulating wavefront. At *top right in B*, the excitatory gap is short. Prolongation of the refractory period of the circulating wavefront may block re-entry at the heavy line in **B** (*bottom right*).

anatomical or functional, on both sides because otherwise there will be a short circuit. An excitatory gap is considered to be present in the circuit if an external stimulus can enter the circuit and elicit an excitatory response. A premature stimulus or overdrive pacing (at a rate higher than the intrinsic arrhythmic rate) may terminate a re-entrant arrhythmia.

If the excitatory gap is long like that shown on the left in Figure 3.5, drugs that depress conduction further in the segment of the circuit susceptible to a block may induce a block and terminate the circuit movement. If the excitatory gap is short like that shown on the right in Figure 3.5, prolonging the refractory period of the traveling wavefront in the circuit may terminate re-entry when the head approaches the tail of the circuit. Prolongation of the refractory period can be achieved by reducing the excitatory current.

### 3.8.6 Atrial Fibrillation

In atrial fibrillation, multiple excitatory wavefronts are present simultaneously. Their pathways are frequently blocked or altered by fibers that are in absolute or relative refractory phase. Drugs that prolong the effective refractory period may reduce the number of wavefronts below a critical point and they may achieve the desired therapeutic effect. Defibrillation shock may terminate fibrillation, at least temporarily. Atrial fibrillation and flutter will be discussed in Chapter 5.

### 3.8.7 Parasystole

Ventricular or atrial parasystole is an ectopic complex arising from a focus where entrance block prevents its excitation from normal regularly timed wavefront until escape complexes occur. Their occurrence is at constant time intervals (or at multiples of the shortest interval). The coupling interval from the regular complexes is variable. The condition is rare and harmless except possibly in ischemic myocardium. Desirable therapeutic action may be achieved, if considered necessary, by a decrease in the rate of phase 4 depolarization by  $I_f$  block if maximum membrane negative diastolic repolarization level is high.

## 3.9 Antiarrhythmic Therapy with Channel Blockers

The medical community became acutely aware of the possibility of unexpected detrimental effects of cardioactive drugs when the results of the Cardiac Arrhythmia Suppression Trial (CAST) were published in 1989.<sup>13</sup> The class 1C ventricular ectopic suppressing drugs flecainide and encainide were associated with a substantial excess (2.5-fold) mortality. Roden, in 1994, classified encainide and flecainide as agents that increase mortality and moricide associated with a short-term increased mortality and possibly with long-term mortality.<sup>14</sup> Other drugs identified as possibly associated with increased mortality were disopyramide and mexiletine. Only  $\beta$ -adrenergic blockers were identified to be associated with

reduced mortality, amioradone in the category that may reduce mortality, and most other drugs as having inadequate data to conclude a significant mortality-reducing effect.

A large number of new drugs have been introduced since 1994, including the class 3 drug amiodarone. More recent developments include class 3 drugs that prolong QT by selectively blocking the delayed rectifier  $K^+$  channel or its fast component  $I_{Kr}$  (dofetilide). They may also have reverse rate dependence, possibly through increased  $I_{Ks}$  at rapid rates. Some other newer drugs (ibutilide) are effective in reverting atrial fibrillation into sinus rhythm by prolonging APD through activation of the slow inward  $Na^+$  current. There are inadequate data available from controlled clinical trials to demonstrate the safety of these newer drugs. In principle, class 3 drugs with enhanced effectiveness at high rates should be effective in preventing arrhythmias and reducing mortality.

The European Myocardial Infarct Amiodarone Trial (EMIAT) reported a 35% reduction ( $p = 0.05$ ) of the risk of arrhythmic deaths in the amiodarone group compared to the placebo group, although there was no significant difference in all-cause and cardiac mortality, the primary endpoints of the trial.<sup>15</sup> The trial enrolled 1,486 myocardial infarction patients with left ventricular ejection fraction  $<40\%$ . The authors concluded that although amiodarone is not indicated for systematic use in post-myocardial infarction patients with impaired left ventricular function, it reduces arrhythmic deaths with no proarrhythmic effect and has only a few minor side effects.

The Amiodarone Trials Meta-Analysis investigators evaluated the effect of prophylactic administration of amiodarone on mortality in patients with acute myocardial infarction or congestive heart failure or both.<sup>16</sup> The total number of patients included from 13 eligible studies was 6,500. To reduce bias in the analysis, the investigators used data from individual patients from each study rather than pooled summary statistics. Of the two statistical models used, the random effects model had an odds ratio 0.85 (0.71–1.02) and the fixed effects model an odds ratio 0.87 (0.78–0.99). The random effects model assumes that each study may have a different outcome, and the fixed effects model that all studies have the same basic effect of the drug on the outcome. The fixed effects

model demonstrated no effect on noncardiac deaths but a substantial, 29%, decrease in arrhythmic/sudden death (odds ratio 0.71 (0.59–0.85)). Adverse noncardiac effects were more common with amiodarone, including pulmonary toxicity, thyroid and liver dysfunction, and peripheral neuropathy.

Beta-adrenergic blocking agents block catecholamine effects on  $\text{Ca}^{2+}$  and  $\text{K}^{+}$  channels, prolong the refractory period, and slow the conduction of action potentials in the AV node cells. These agents will have an antiarrhythmic effect mainly on those arrhythmias where the AV node is involved and that are influenced by the functional state of the AV node. (In atrial fibrillation,  $\beta$ -adrenergic blocking agents slow ventricular response. In Wolf-Parkinson-White tachycardia, they slow the AV node pathway.)

## References

1. Roden DM, Lazzara R, Rosen M et al. Multiple mechanisms in the long-QT syndrome. Current knowledge, gaps, and future directions. *Circulation* 1996;94:1996–2012.
2. Task Force of the Working Group on Arrhythmias of the European Society of Cardiology. The Sicilian Gambit. A new approach to the classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms. *Circulation* 1991;84:1831–51.
3. Gussak I, Antzelevitch C (eds). *Cardiac Repolarization. Bridging Basic and Clinical Science*. Totowa, New Jersey: Humana Press, 2003.
4. Yan GX, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long-QT syndrome. *Circulation* 1998;98:1928–36.
5. Surawicz B, Braun HA, Crum WB et al. Quantitative analysis of electrocardiographic patterns in hypokasemia. *Circulation* 1957;16:750–63.
6. Vaughan Williams EM. Classification of antiarrhythmic drugs. In: Sandoe E, Flensted-Jensen E, Olesen K (eds). *Cardiac Arrhythmias*. Södertälje, Sweden: Astra, 1981, pp 449–72.
7. Krishnan SC, Antzelevitch C. Sodium channel blockade produces opposite electrophysiologic effects in canine ventricular epicardium and endocardium. *Circ Res* 1991;69:277–91.
8. Litovsky SH, Antzelevitch C. Differences in the electrophysiological response of canine ventricular subendocardium and subepicardium to acetylcholine and isoproterenol. A direct effect of acetylcholine in ventricular myocardium. *Circ Res* 1990;67:615–27.
9. Antzelevitch C, Zygmunt AC, Dumaine R. Electrophysiology and pharmacology of ventricular repolarization. In: Gussak I, Antzelevitch C (eds). *Cardiac Repolarization. Bridging Basic and Clinical Science*. Totowa, New Jersey: Humana Press, 2003, pp 63–89.
10. Nerbonne JM, Kass RS. Physiology and molecular biology of ion channels contributing to ventricular repolarization. In: Gussak I, Antzelevitch C (eds). *Cardiac Repolarization. Bridging Basic and Clinical Science*. Totowa, New Jersey: Humana Press, 2003, pp 25–62.
11. Armondas AA, Tomaselli GF. Electrical and structural remodeling of the ventricular myocardium in disease. In: Gussak I, Antzelevitch C (eds). *Cardiac Repolarization. Bridging Basic and Clinical Science*. Totowa, New Jersey: Humana Press, 2003, pp 127–52.
12. Schmitt FO, Erlanger J. Directional differences in the conduction of the impulse through heart muscle and their possible relation to extrasystolic and fibrillatory contractions. *Am J Physiol* 1928;87:326–47.
13. The Cardiac Arrhythmia Suppression Trial investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989;32:406–12.
14. Roden DM. Risks and benefits of antiarrhythmic therapy. *N Engl J Med* 1994;331:785–91.
15. Julian DG, Camm AJ, Frangin G et al. Randomized trial of effect of amiodarone on mortality in patients with left ventricular dysfunction after recent myocardial infarction: EMIAT. European Myocardial Infarct Amiodarone Trial investigators. *Lancet* 1997;349:667–74.
16. The Amiodarone Trials Meta-Analysis investigators. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomized trials. *Lancet* 1997;350:1417–24.

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