CHAPTER 11

Mechanisms of Cardiac Arrhythmias

Hillary K. Rolls
William G. Stevenson
Gary R. Strichartz
Leonard S. Lilly

Normal cardiac function relies on the flow of electrical impulses through the heart in an exquisitely coordinated fashion. Abnormalities of the electrical rhythm are known as *arrhythmias* (also termed *dysrhythmias*) and are among the most common clinical problems encountered. The presentations of arrhythmias range from benign palpitations to severe symptoms of low cardiac output and death; therefore, a thorough understanding of these disorders is important to the daily practice of medicine.

Abnormally slow rhythms are termed *bradycardias* (or *bradyarrhythmias*). Fast rhythms are known as *tachycardias* (or *tachyarrhythmias*). Tachycardias are further characterized as *supraventricular* when they involve the atrium or AV node and designated *ventricular* when they originate from the His-Purkinje system or ventricles. This chapter describes the mechanisms by which such arrhythmias develop, followed by a general description of their management. Chapter 12 summarizes specific rhythm disorders and how to recognize and treat them.

Disorders of heart rhythm result from alterations of **impulse formation**, **impulse conduction**, or both. This chapter first addresses how alterations of impulse formation and conduction occur and under what circumstances they cause arrhythmias. Figure 11.1 provides an organizational schema for this discussion.

Fig. 1

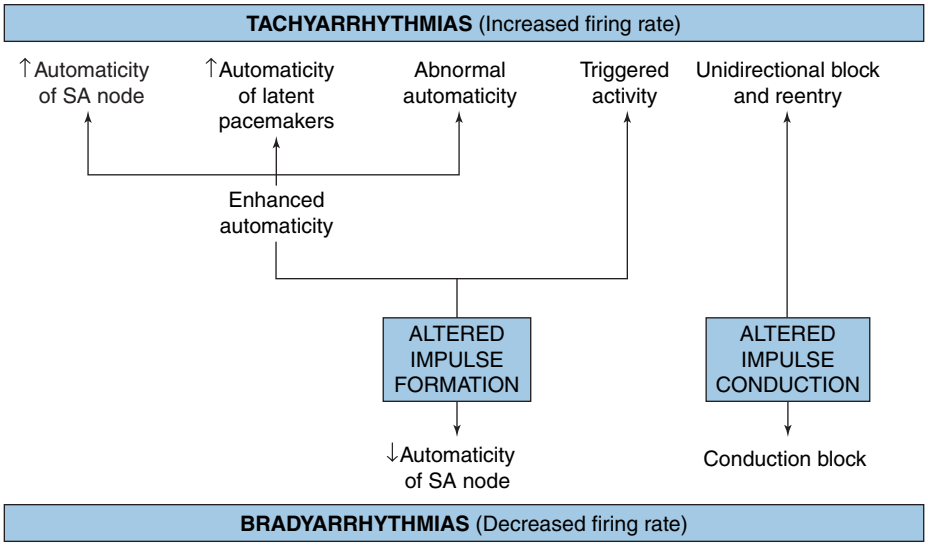

Figure 11.1. Arrhythmias result from alterations in impulse formation and/or impulse conduction. Tachyarrhythmias result from enhanced automaticity, unidirectional block with reentry, or triggered activity. Bradyarrhythmias result from decreased automaticity or conduction block. SA, sinoatrial.

NORMAL IMPULSE FORMATION

As presented in Chapter 1, electrical impulse formation in the heart arises from the intrinsic automaticity of specialized cardiac cells. **Automaticity** refers to a cell's ability to depolarize itself to a threshold voltage in a rhythmic, repeated fashion, such that *spontaneous* action potentials are generated. Although atrial and ventricular myocytes do not have this property under normal conditions, the cells of the specialized conducting system do possess natural automaticity and are therefore termed **pacemaker cells.** The specialized conducting system includes the sinoatrial (SA) node, the atrioventricular (AV) nodal region, and the ventricular conducting system. The latter is composed of the bundle of His, the bundle branches, and the Purkinje fibers. In *pathologic situations,* myocardial cells outside the conducting system may also acquire the property of automaticity.

Ionic Basis of Automaticity

Cells with natural automaticity do not have a static resting potential. Rather, they display a gradual depolarization during phase 4 of the action potential (Fig. 11.2) If this spontaneous diastolic depolarization reaches the threshold voltage, an action potential is generated. An important ionic current largely responsible for phase 4 spontaneous depolarization is known as the **pacemaker current (I_f).** This current is activated by hyperpolarization (increasingly negative voltages) and is carried mainly by sodium ions. The channels that carry I_f open when the membrane voltage becomes more negative than approximately –50 mV and are *different* from the fast sodium channels responsible for rapid phase 0 depolarization in nonpacemaker cells. The inward flow of Na^+ through these slow channels, driven by its concentration gradient and the negative intracellular charge, forces the membrane potential to depolarize toward the threshold voltage.

In the pacemaker cells of the sinoatrial node, alterations in two other ionic currents also contribute to phase 4 depolarization: (1) a slow inward calcium current, the channels of which become activated at voltages reached near the end of phase 4, and (2) a progressive decline of an *outward* potassium current. Activation of the latter current is responsible for cellular repolarization during phase 3 of the action potential, and it pro-

Fig. 2

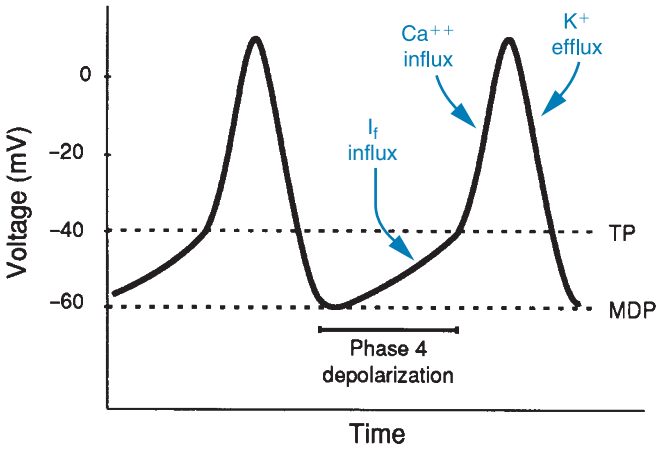

Figure 11.2. The action potential (AP) of a pacemaker cell. Notice the slow phase 4 depolarization, largely caused by the I_f (pacemaker) current through slow Na^+ channels, which drives the cell to threshold potential (approximately –40 mV). The upstroke of the AP is caused by the slow inward current of Ca^+ ions. Inactivation of the calcium channels and K^+ efflux through potassium channels are responsible for repolarization. MDP, maximum negative diastolic potential; TP, threshold potential.

gressively diminishes during phase 4. The combination of the inward I_f, inward, Ca^{++} and reduced outward K^+ currents acts to gradually depolarize the SA nodal cells to the threshold potential.

When the membrane potential of the pacemaker cell reaches the threshold value, the upstroke of the action potential is generated. In contrast to the phase 0 upstroke of cells in the Purkinje system, that of cells in the sinus and AV nodes is much slower (see Fig. 11.2; compare with Fig. 1.14). The reason for the difference is that the membrane potential determines the proportion of fast sodium channels that are in a resting state capable of depolarization, compared with an inactivated state. The number of available (or resting-state) fast sodium channels increases as the resting membrane potential becomes more negative. Because sinus and AV nodal cells have *less negative* maximum diastolic membrane voltages (–50 to –60 mV) than do Purkinje cells (–90 mV), a greater proportion of the fast sodium channels is inactivated in these pacemaker cells. Thus, the action potential upstroke relies to a greater extent on *calcium* ion inflow (through the relatively slower opening Ca^{++} channels) and its slope is less steep in these cells. The repolarization phase of pacemaker cells depends on inactivation of the calcium channels and the opening of voltage-gated potassium channels that permit efflux of potassium from the cells.

Native and Latent Pacemakers

The different populations of automatic cells in the specialized conduction pathway have different intrinsic rates of firing. These rates are determined by three variables that influence how fast the membrane potential reaches threshold: (1) the rate (i.e., the slope) of phase 4 spontaneous depolarization, (2) the maximum negative diastolic potential, and (3) the threshold potential. A more negative maximum diastolic potential, or a less negative threshold potential, slows the rate of impulse initiation because it takes longer to reach that threshold value (Fig. 11.3). Conversely, the greater the I_f, the steeper the slope of phase 4 and the faster the cell depolarizes. The rate of I_f depends on the number and kinetics of the individual pacemaker channels through which this current flows.

Because all the healthy myocardial cells are electrically connected by gap junctions, an action potential generated in one part of the myocardium will ultimately spread to all

Fig. 3

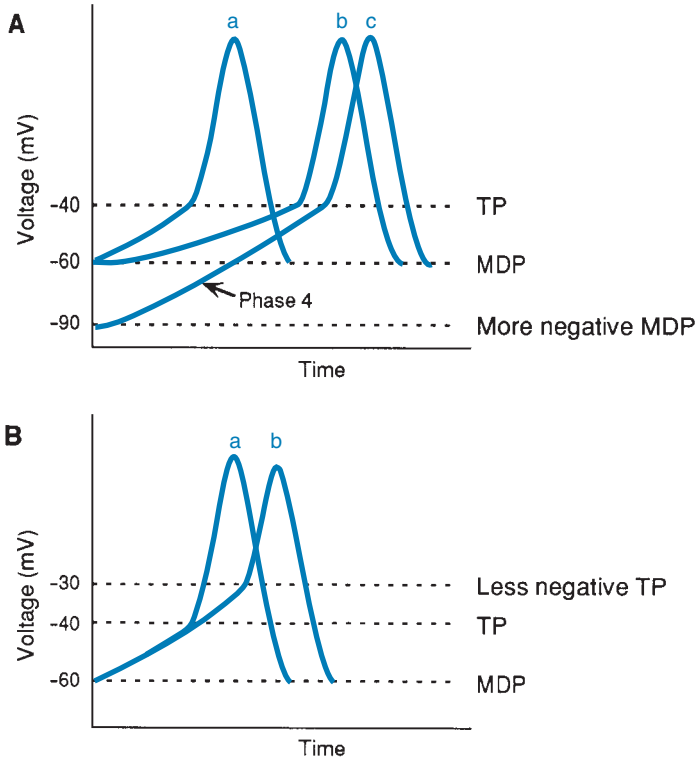

Figure 11.3. Determinants of cell-firing rates. A. Alterations in the pacemaker current (I_f) and in the magnitude of the maximum diastolic potential (MDP) alter the cell-firing rate. (a) The normal action potential (AP) of a pacemaker cell. (b) Reduced I_f renders the slope of phase 4 less steep; thus, the time required to reach threshold potential (TP) is increased. (c) The MDP is more negative; therefore, the time required to reach TP is increased. **B.** Alterations in TP change the firing rate of the cell. Compared with the normal TP (a), the TP in *b* is less negative; thus, the duration of time to achieve threshold is increased, and the firing rate decreases.

other regions. When an impulse arrives at a cell that is not yet close to threshold, current from the depolarized cell will bring the adjacent cell membrane potential to the threshold level so that it will fire (regardless of how close its intrinsic I_f has brought it to threshold). Thus, the pacemaker cells with the fastest rate of depolarization set the heart rate. In the normal heart, the dominant pacemaker is the *sinoatrial node,* which at rest initiates impulses at a rate of 60 to 100 bpm. Because the sinus node rate is faster than that of the other tissues that possess automaticity, its repeated discharges prevent spontaneous firing of other potential pacemaker sites.

The SA node is known as the **native pacemaker** because it normally sets the heart rate. Other cells within the specialized conduction system harbor the potential to act as pacemakers if necessary and are therefore called **latent pacemakers** (or **ectopic pacemakers**). In contrast to the SA node, the AV node and the bundle of His have intrinsic firing rates of 50 to 60 bpm, and cells of the Purkinje system have rates of approximately 30 to 40 bpm. These latent sites may initiate impulses and take over the pacemaking function if the SA node slows or fails to fire, or if conduction abnormalities block the normal wave of depolarization from reaching them.

Overdrive Suppression

Not only does the cell population with the fastest intrinsic rhythm preempt all other

automatic cells from spontaneously firing, it also directly *suppresses* their automaticity. This phenomenon is called overdrive suppression. Cells maintain their transsarcolemmal ion distributions because of the continuously active Na^+K^+-ATPase pump that extrudes three Na^+ ions from the cell in exchange for two K^+ ions transported in (Fig. 11.4). Because its net transport effect is one positive charge in the outward direction, the Na^+K^+-ATPase pump creates a *hyperpolarizing* current (i.e., it tends to make the inside of the cell *more negative*). As the cell potential becomes increasingly negative, additional time is required for spontaneous phase 4 depolarization to reach the threshold voltage (see Fig. 11.3A), and therefore the rate of spontaneous firing is decreased. Although the hyperpolarizing current antagonizes I_f, pacemaker cells firing at their own intrinsic rate have an I_f current sufficiently large to overcome this hyperpolarizing influence (see Fig. 11.4).

Fig. 4

The hyperpolarizing current *increases* when a cell is forced to fire faster than its intrinsic pacemaker rate. The more frequently the cell is depolarized, the greater the quantity of Na^+ ions that enter the cell per unit time. As a result of the increased intracellular Na^+, the Na^+K^+-ATPase pump becomes more active, thereby tending to restore the normal transmembrane Na^+ gradient. This increased pump activity provides a larger hyperpolarizing current, opposing the depolarizing current I_f, and further decreases the rate of spontaneous depolarization. Thus, overdrive suppression decreases a cell's automaticity when that cell is driven to depolarize faster than its intrinsic discharge rate.

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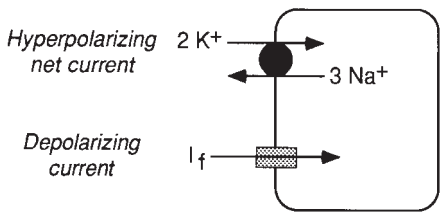

AQ3

Figure 11.4. Competition between the depolarizing pacemaker current (I_f) and the Na^+K^+-ATPase pump, which produces a hyperpolarizing current. The Na^+K^+-ATPase pump transports three positive charges outside the cell for every two it pumps in. The hyperpolarizing current acts to suppress automaticity by antagonizing I_f and contributes to overdrive suppression in cells that are stimulated more rapidly than their intrinsic firing rate.

Electrotonic Interactions

In addition to overdrive suppression, *anatomic connections* between pacemaker and nonpacemaker cells are important in determining how adjacent cells suppress latent pacemaker foci. Myocardial cells that are not part of the specialized conducting system repolarize to a resting potential of –90 mV, whereas pacemaker cells repolarize to a maximum diastolic potential of about –60 mV. When these two cell types are adjacent to one another, they are *electrically coupled* through low resistance gap junctions concentrated in their intercalated discs. This coupling results in an equilibration of electrical potentials owing to electrotonic current flow between the cells, causing relative *hyperpolarization* of the pacemaker cell and relative *depolarization* of the nonpacemaker cell (Fig. 11.5). The hyperpolarizing current in the coupled pacemaker cell competes with I_f and causes the slope of phase 4 diastolic depolarization to be less steep, thereby reducing the cell's automaticity. Electrotonic effects may be particularly important in suppressing automaticity in the AV node (via connections between atrial myocytes and AV nodal cells) and in the distal Purkinje fibers (which are coupled to nonautomatic ventricular myocardial cells). In contrast, cells in the center of the SA node are less tightly coupled to atrial myocytes; thus, their automaticity is less subject to electrotonic interactions.

Fig. 5

Decoupling of normally suppressed cells, such as those in the AV node (e.g., by ischemic damage), may reduce the inhibitory electrotonic influence and *enhance* automaticity, producing ectopic rhythms by the latent pacemaker tissue.

ALTERED IMPULSE FORMATION

Arrhythmias may arise from altered impulse formation at the SA node or from other sites, including the specialized conduction

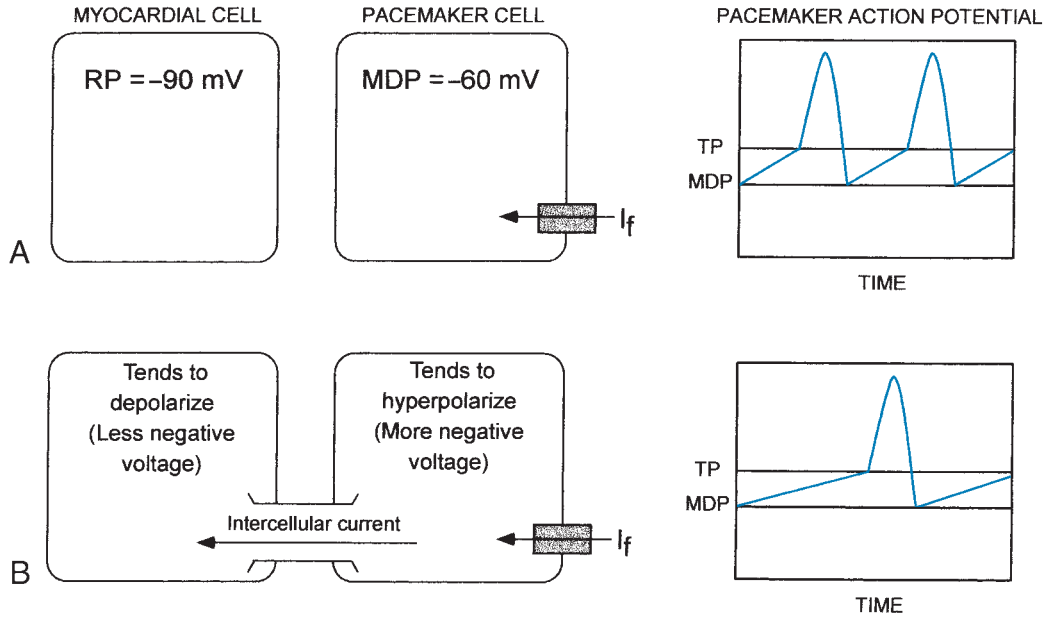

Figure 11.5. Electrotonic interaction between pacemaker (e.g., AV nodal) and nonpacemaker (myocardial) cells. A. When pacemaker cells are not coupled to myocardial cells (as in the SA node), they have a maximum negative potential (MDP) of approximately –60 mV, whereas myocardial cells have a resting potential (RP) of approximately –90 mV. **B.** When pacemaker cells and myocytes are neighbors, they may be connected electrically by gap junctions in their intercalated discs (e.g., in the AV node). In this situation, electrical current flows between the pacemaker cell and the myocardial cell, tending to hyperpolarize the former and depolarize the latter, driving their membrane potentials closer to one another. The more negative potential of atrial cells opposes I_f of the pacemaker cell, such that the slope of phase 4 depolarization is less steep and therefore cellular automaticity is suppressed. If a disease state reduces coupling between cells, the influence of surrounding myocytes on the pacemaker cell is reduced, allowing I_f to depolarize to threshold more readily and accelerating the rate of automaticity. TP, threshold potential.

pathways or regions of cardiac muscle. The main abnormalities of impulse initiation that lead to arrhythmias are (1) **altered automaticity** (of the sinus node or latent pacemakers within the specialized conduction pathway), (2) **abnormal automaticity** in atrial or ventricular myocytes, and (3) **triggered activity.**

Alterations in Sinus Node Automaticity

The rate of impulse initiation by the sinus node, as well as by the latent pacemakers of the specialized conducting system, is regulated primarily by neurohumoral factors.

Increased Sinus Node Automaticity

The most important modulator of normal sinus node automaticity is the autonomic nervous system. Sympathetic stimulation, acting through β_1-adrenergic receptors, increases the probability of the pacemaker channels being open (Fig. 11.6), through which I_f can flow. The increase in I_f leads to a steeper slope of phase 4 depolarization, causing the SA node to reach threshold and fire earlier than normal and the heart rate to increase.

In addition, sympathetic stimulation shifts the action potential threshold to more-negative voltages by increasing the probability that voltage-sensitive Ca^{++} channels are open (recall that calcium carries the current of phase 0 depolarization in pacemaker cells). Therefore, diastolic depolarization reaches the threshold potential earlier. Sympathetic activity thus increases sinus node automaticity both by causing the action potential threshold to become more negative and by increasing the rate of pacemaker depolarization via I_f. Examples of this normal physiologic effect occur during exercise or

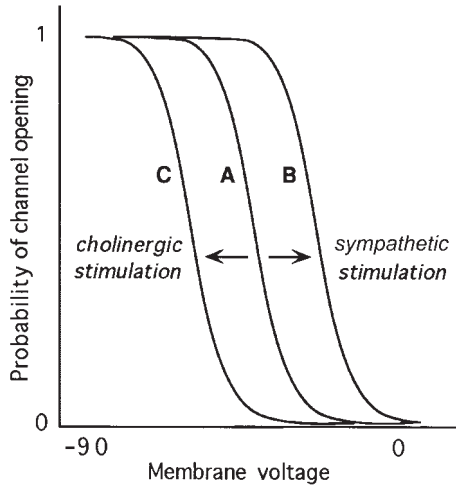

Figure 11.6. The channels through which the pacemaker current (I_f) flows are voltage gated, opening at more negative membrane potentials. At any given voltage, there exists a probability between 0 and 1 that a specific channel will be open. Compared with normal baseline behavior (curve A), sympathetic stimulation (curve B) or treatment with anticholinergic drugs shifts this probability to a higher value for any given level of membrane voltage, thus increasing the number of open channels and the rate at which the cell will fire. Curve C shows that parasympathetic stimulation (or treatment with β-blockers) has the opposite effect, decreasing the probability of a channel being open, and therefore inhibiting depolarization.

emotional stress, when sympathetic stimulation appropriately increases the heart rate.

Decreased Sinus Node Automaticity

Normal decreases in SA node automaticity are mediated by reduced sympathetic stimulation and by increased activity of the parasympathetic nervous system. Whereas the sympathetic nervous system exerts a dominant effect on the heart rate during times of stress, the parasympathetic nervous system is the major mediator of the heart rate at rest.

Cholinergic (i.e., parasympathetic) stimulation via the vagus nerve acts at the SA node to reduce the probability of pacemaker channels being open (see Fig. 11.6). Thus, I_f and the slope of phase 4 depolarization are reduced, and the intrinsic firing rate of the cell is slowed. In addition, the probability of the Ca^{++} channels being open is decreased; thus, the action potential threshold increases to a more positive potential. Furthermore, cholinergic stimulation increases the probability of the acetylcholine-sensitive K^+ channels being open at rest. Positively charged K^+ ions exit through these channels, producing an outward current that drives the diastolic potential to become more negative. The overall effect of reduced I_f, a more negative maximum diastolic potential, and a less negative threshold level is a slowing of the intrinsic firing rate and therefore a reduced heart rate.

It follows that the use of pharmacologic agents that modify the effects of the autonomic nervous system will also affect the firing rate of the SA node. For example, β-blocking drugs antagonize the β-adrenergic sympathetic effect; therefore, they *decrease* the rate of phase 4 depolarization of the SA node and slow the heart rate. Conversely, atropine, an anticholinergic (antimuscarinic) drug, has the opposite effect: by blocking parasympathetic activity, the rate of phase 4 depolarization *increases* and the heart rate accelerates.

Escape Rhythms

If the sinus node becomes suppressed and fires less frequently than normal, the site of impulse formation often shifts to a latent pacemaker within the specialized conduction pathway. An impulse initiated by a latent pacemaker because the SA node rate has slowed is called an **escape beat.** Persistent impairment of the SA node will allow a continued series of escape beats, termed an **escape rhythm.** Escape rhythms are protective in that they prevent the heart rate from becoming too slow when SA node firing is impaired.

As discussed in the previous section, suppression of sinus node activity may occur because of increased parasympathetic tone. Different regions of the heart have different sensitivities to parasympathetic (vagal) stimulation. The SA node and the AV node are most sensitive to such an influence, followed by atrial tissue. The ventricular conducting system is the least sensitive. Therefore, mod-

erate parasympathetic stimulation slows the sinus rate and allows the pacemaker to shift to another atrial site. However, very strong parasympathetic stimulation suppresses excitability at both the SA node and atrial tissue, can cause conduction block at the AV node, and may therefore result in the emergence of a ventricular escape pacemaker.

Enhanced Automaticity of Latent Pacemakers

Another means by which a latent pacemaker can assume control of impulse formation is if it develops an intrinsic rate of depolarization *faster* than that of the sinus node. Termed an **ectopic beat**, the impulse is *premature* relative to the normal rhythm, whereas an escape beat is *late* and terminates a pause caused by a slowed sinus rhythm. A sequence of similar ectopic beats is called an **ectopic rhythm.**

Ectopic beats may arise in several circumstances. For example, high catecholamine concentrations can enhance the automaticity of latent pacemakers, and if the resulting rate of depolarization exceeds that of the sinus node, then an ectopic rhythm will develop. Ectopic beats are also commonly induced by hypoxemia, ischemia, electrolyte disturbances, and certain drug toxicities (such as digitalis, as described in Chapter 17).

Abnormal Automaticity

Cardiac tissue injury may lead to pathologic changes in impulse formation whereby myocardial cells *outside* the specialized conduction system acquire automaticity and spontaneously depolarize. Although such activity may appear similar to impulses originating from latent pacemakers within the specialized conduction pathways, these ectopic beats arise from cells that do not usually possess automaticity. If the rate of depolarization of such cells exceeds that of the sinus node, they transiently take over the pacemaker function and become the source of an abnormal ectopic rhythm.

Because these myocardial cells have few or no activated pacemaker channels, they do not normally carry I_f. How injury allows such cells to spontaneously depolarize has not been fully elucidated. However, when myocytes become injured, their membranes become "leaky." As such, they are unable to maintain the concentration gradients of ions, and the resting potential becomes less negative (i.e., the cell partially depolarizes). When a cell's membrane potential is reduced to a value less negative than –60 mV, gradual phase 4 depolarization can be demonstrated even among nonpacemaker cells. This slow spontaneous depolarization is probably related to a slow calcium current and by closure of a subset of K^+ channels that normally help repolarize the cell.

Triggered Activity

Under certain conditions, an action potential can "trigger" abnormal depolarizations that result in extra heart beats or rapid arrhythmias. This process may occur when the first action potential leads to oscillations of the membrane voltage known as *afterdepolarizations*. Unlike the *spontaneous* activity seen when enhanced automaticity occurs, this type of automaticity is *stimulated* by a preceding action potential. As illustrated in Figures 11.7 and 11.8, there are two types of afterdepolarizations depending on their timing after the inciting action potential: *early* afterdepolarizations occur during the repolarization phase of the inciting beat, whereas *delayed* afterdepolarizations occur shortly after repolarization has been completed. In either case, abnormal action potentials are triggered if the afterdepolarization reaches a threshold voltage. **Fig. 7-8**

Early afterdepolarizations are changes of the membrane potential in the positive direction that interrupt normal repolarization (see Fig 11.7). They can occur either during the plateau of the action potential (phase 2) or during rapid repolarization (phase 3). Early afterdepolarizations are more likely to develop in conditions that prolong the action potential duration (and therefore the electrocardiographic QT interval), as may

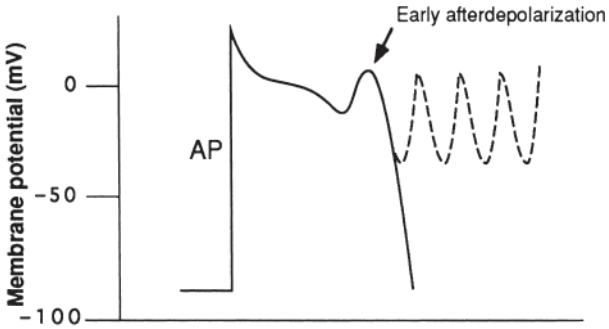

Figure 11.7. Triggered activity. An early afterdepolarization (arrow) occurs before the action potential (AP) has fully repolarized. Repetitive afterdepolarizations (dashed curve) may produce a rapid sequence of triggered action potentials and hence a tachyarrhythmia.

occur during therapy with certain drugs (see Chapter 17) and in the inherited long-QT syndromes (see Chapter 12).

The ionic current responsible for an early afterdepolarization depends on the membrane voltage at which the triggered event occurs. If the early afterdepolarization occurs during phase 2 of the action potential, when most of the Na^+ channels are in an inactivated state, the upstroke of the triggered beat relies on an inward Ca^{++} current. If, however, it occurs during phase 3 (when the membrane voltage is more negative), there is partial recovery of the fast Na^+ channels, which are then available to contribute to the current.

An early afterdepolarization-triggered action potential can be self-perpetuating and lead to a series of depolarizations (see Fig. 11.7). Early afterdepolarizations appear to be the initiating mechanism of the polymorphic ventricular tachycardia known as *torsades de pointes,* which is described in Chapter 12.

Delayed afterdepolarizations may appear shortly after repolarization is complete (see Fig. 11.8). They most commonly develop in states of *high intracellular calcium,* as may be present with digitalis intoxication (see Chapter 17), or during marked catecholamine stimulation. It is thought that intracellular Ca^{++} accumulation causes the activation of chloride currents or of the Na^+-Ca^{++} exchanger that results in brief inward currents that generate the delayed afterdepolarization.

As with early afterdepolarizations, if the amplitude of the delayed afterdepolarization reaches a threshold voltage, an action potential will be generated. Such action potentials

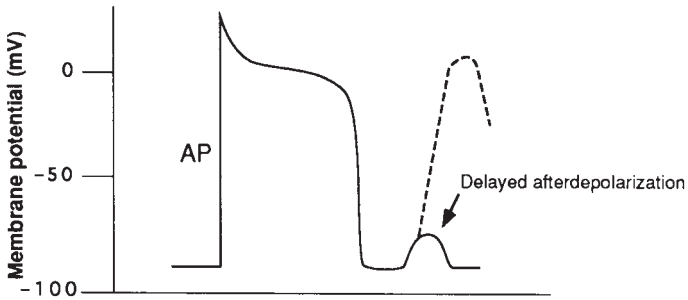

Figure 11.8. Triggered activity. A delayed afterdepolarization (arrow) arises after the cell has fully repolarized. If the delayed afterdepolarization reaches the threshold voltage, a propagated action potential (AP) is triggered (dashed curve).

can be self-perpetuating and lead to tachyarrhythmias. For example, atrial and ventricular tachycardias associated with digitalis toxicity are thought to be the result of delayed afterdepolarizations, as described in Chapter 17.

ALTERED IMPULSE CONDUCTION

Alterations in impulse conduction also lead to arrhythmias. Conduction blocks generally slow the heart rate (bradyarrhythmias); however, under certain circumstances, the process of reentry (described later) can ensue and produce abnormal fast rhythms (tachyarrhythmias).

Conduction Block

A propagating impulse is blocked when it encounters a region of the heart that is electrically unexcitable. Conduction block can be either transient or permanent and may be unidirectional (i.e., conduction proceeds when the involved region is stimulated from one direction, but not when stimulated from the opposite direction) or bidirectional (conduction is blocked in both directions). Various conditions may cause conduction block, including ischemia, fibrosis, inflammation, and certain drugs. When conduction block occurs because a propagating impulse encounters cardiac cells that are still refractory (from a previous depolarization), the block is said to be *functional*. A propagating impulse that arrives later may be able to be conducted. For example, antiarrhythmic drugs that prolong action potential duration tend to produce functional conduction block. When conduction block is caused by a barrier imposed by fibrosis or scarring that replaces myocytes, conduction block is *fixed*.

Conduction block within the specialized conducting system of the AV node or the His-Purkinje system prevents normal propagation of the cardiac impulse from the sinus node to more distal sites. This atrioventricular block (AV block) removes the normal overdrive suppression that keeps latent pacemakers in the His-Purkinje system in check. Thus, conduction block usually results in emergence of escape beats or escape rhythms, as the more distal sites assume the pacemaker function.

AV block is common and a major reason for implantation of a permanent pacemaker, as discussed in Chapter 12.

Unidirectional Block and Reentry

A common mechanism by which a combination of conduction block and altered impulse conduction leads to tachyarrhythmias is termed **reentry.** During a reentrant rhythm, an electrical impulse circulates repeatedly around a reentry path, recurrently depolarizing a region of cardiac tissue.

During normal cardiac conduction, each electrical impulse that originates in the SA node travels in an orderly, sequential fashion through the rest of the heart, ultimately depolarizing all the myocardial fibers. The refractory period of each cell prevents immediate reexcitation from adjacent depolarized cells, so that the impulse stops when all of the heart muscle has been excited. However, conduction blocks that prevent rapid depolarization of parts of the myocardium can create an environment conducive to continued impulse propagation and reentry, as illustrated in Figure 11.9.

Fig. 9

The figure depicts electrical activity as it flows through a branch point anywhere within the conduction pathways. Panel A shows propagation of a normal action potential. At point *x,* the impulse reaches two parallel pathways (α and β) and travels down each into the more distal conduction tissue. In the normal heart, the α and β pathways have similar conduction velocities and refractory periods such that the wave fronts that pass through them collide in the distal conduction tissue and extinguish each other.

Panel B shows what happens if conduction is blocked in one limb of the pathway. In this example, the action potential is obstructed when it encounters the β pathway from above and therefore propagates only down the α tract into the distal tissue. As the impulse continues to spread, it encounters the distal end of the β pathway (at point *y*). If the tissue in the distal β tract is also

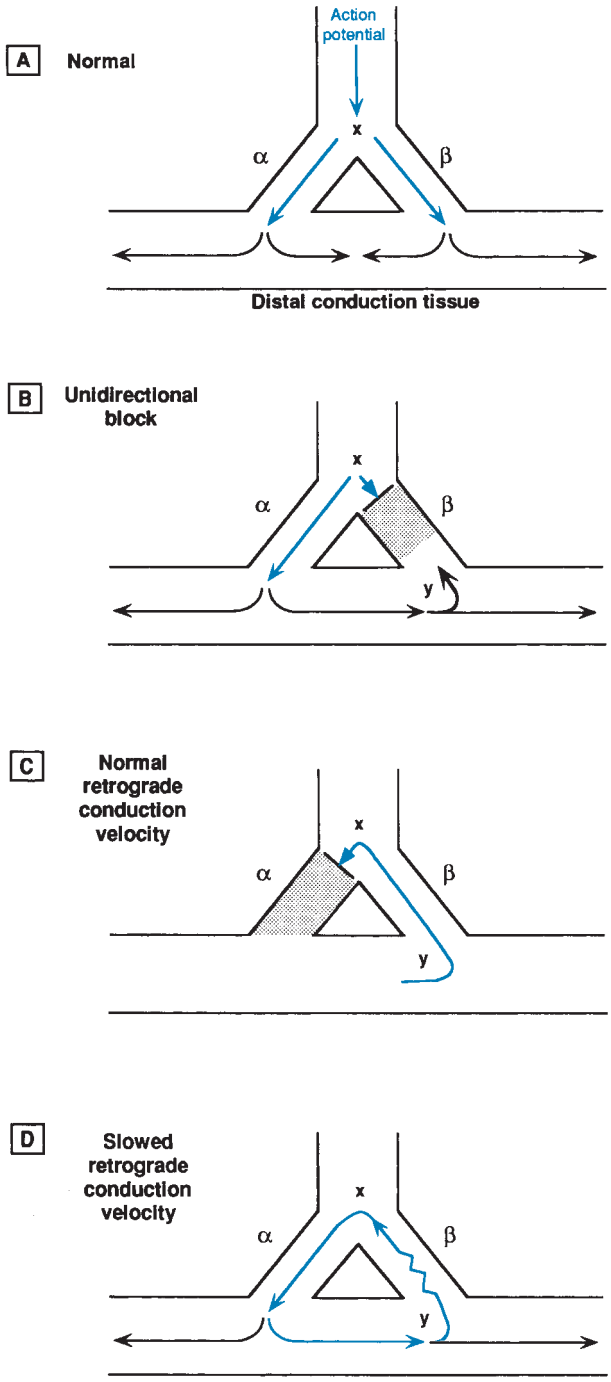

Figure 11.9. Mechanism of reentry. A. Normal conduction. When an action potential (AP) reaches a branch in the conduction pathway (point *x*), the impulse travels down both fibers (α and β) to excite distal conduction tissue. **B.** Unidirectional block. Forward passage of the impulse is blocked in the β pathway but proceeds normally down the α pathway. When the impulse reaches point *y,* if retrograde conduction of the β pathway is intact, the AP can enter β from below and conduct in a retrograde fashion. **C.** When point *x* is reached again, if the α pathway has not had sufficient time to repolarize, then the impulse stops. **D.** However, if conduction through the retrograde pathway is sufficiently slow (jagged line), it reaches point *x* after the α pathway has recovered. In that circumstance, the impulse is able to excite the α pathway again and a reentrant loop is formed.

unable to conduct, the impulse simply continues to propagate into the deeper tissues and reentry does not occur. However, if the impulse at point *y is* able to propagate retrogradely (backward) into pathway β, one of the necessary conditions for reentry has been met.

When an action potential can conduct in a retrograde direction in a conduction pathway, whereas it had been prevented from

doing so in the forward direction, **unidirectional block** is said to be present. Unidirectional block tends to occur in regions where the refractory periods of adjacent cells are heterogeneous, such that some cells recover before others. In addition, unidirectional block may occur in states of cellular dysfunction, and in regions where fibrosis has altered the myocardial structure.

As shown in panel C of Figure 11.9, if the impulse is able to propagate retrogradely up the β pathway, it will again arrive at point *x*. At that time, if the β pathway has not yet repolarized from the previous action potential that had occurred moments earlier, that limb is refractory to repeat stimulation and the returning impulse simply stops there.

However, panel D illustrates what happens if the velocity of retrograde conduction in the diseased β path is not normal but *slower than normal*. In that case, sufficient time may elapse for the α pathway to repolarize before the returning impulse reaches point *x* from the β limb. Then the impulse is free to stimulate the α pathway once again, and the cycle repeats itself. This circular stimulation can continue indefinitely, and each pass of the impulse through the loop excites cells of the distal conduction tissue, which propagates to the rest of the myocardium, resulting in a tachyarrhythmia.

For the mechanism of reentry to occur, the propagating impulse must continuously encounter excitable tissue. Thus, the time it takes for the impulse to travel around the reentrant loop must be greater than the time required for recovery (the refractory period) of the tissue, and this must be true for each point in the circuit. If the conduction time is shorter than the recovery time, the impulse will encounter refractory tissue and stop. Because normal conduction velocity is approximately 50 cm/sec and the average effective refractory period is about 0.2 sec, a reentry path circuit would need to be at least 10 cm long for reentry to occur in a normal ventricle. However, with *slower* conduction velocities, a smaller reentry circuit is possible. Most clinical cases of reentry occur within small regions of tissue because the conduction velocity within the reentrant loop is, in fact, abnormally slow.

In summary, the two critical conditions for reentry are (1) unidirectional block and (2) slowed conduction through the reentry path. These conditions commonly occur in regions where fibrosis has developed, such as infarction scars. In some cases, reentry occurs over an anatomically fixed circuit or path, such as AV reentry using an accessory pathway (as discussed in the following section). Reentry around distinct anatomic pathways usually appears as a *monomorphic* tachycardia on the electrocardiogram (ECG; i.e., in the case of ventricular tachycardia, all the QRS complexes have the same appearance). This is because the reentry path is the same from beat to beat, producing a stable, regular tachycardia.

Other types of reentry do not require a stable, fixed path. For example, reentry can occur in electrophysiologically heterogeneous myocardium, in which waves of reentrant excitation spiral through the tissue, continually changing direction. Ischemic myocardium provides such a setting because the affected tissue is a mosaic of unexcitable and partially excitable zones with reduced conduction velocities. When reentrant ventricular tachycardia develops in an area of ischemia, the reentry circuit incessantly changes and the QRS complexes typically vary from beat to beat, causing a polymorphic ventricular tachycardia pattern on the ECG. As described in Chapter 12, *fibrillation* of the atria or ventricles is likely caused by multiple circulating reentry wave fronts.

Accessory Pathways and the Wolff-Parkinson-White Syndrome

The concept of reentry is dramatically illustrated by the **Wolff-Parkinson-White (WPW) syndrome.** In the normal heart, the impulse generated by the SA node propagates through

atrial tissue to the AV node, where expected slower conduction causes a short delay before continuing on to the ventricles. However, approximately 1 in 1,000 people has the WPW syndrome and is born with an additional connection between the atrium and ventricle. Termed an accessory pathway or bypass tract, this connection allows conduction between the atria and ventricles to bypass the AV node. The most common type of accessory pathway consists of microscopic fibers that span the atrioventricular groove somewhere along the mitral or tricuspid annuli (known as a *bundle of Kent*), as shown in Figure 11.10.

Fig. 10

Because accessory pathway tissue conducts impulses faster than the AV node, stimulation of the ventricles during sinus rhythm begins earlier than normal, and the PR interval of the ECG is therefore *shortened* (usually <0.12 sec, or <3 small boxes). In this situation, the ventricles are said to be "preexcited." However, the accessory pathway connects to ventricular myocardium rather than to the Purkinje system, such that the subsequent spread of the impulse through the ventricles from that site is slower than usual. In addition, because *normal* conduction over the AV node proceeds concurrently, ventricular depolarization represents a combination of the electrical impulse traveling via the accessory tract *and* that conducted through the normal conduction pathway. As a result, the QRS complex in patients with WPW is wider than normal and demonstrates an abnormally slurred initial upstroke, known as a *delta wave* (Fig. 11.10).

During sinus rhythm, simultaneous conduction through the accessory pathway and AV node creates an interesting ECG appearance but causes no symptoms. The presence of the abnormal pathway, however, creates an ideal condition for reentry because the refractory period of the pathway is usually different from that of the AV node. An appropriately timed abnormal impulse (e.g., a premature beat) may encounter blockage in the accessory pathway but conduction over the AV node, or vice versa. If the propagating impulse then finds that the initially blocked pathway has recovered (unidirectional block), it can conduct in a retrograde direction up to the atrium and then down the other pathway back to the ventricles. Thus, a large anatomic loop is established,

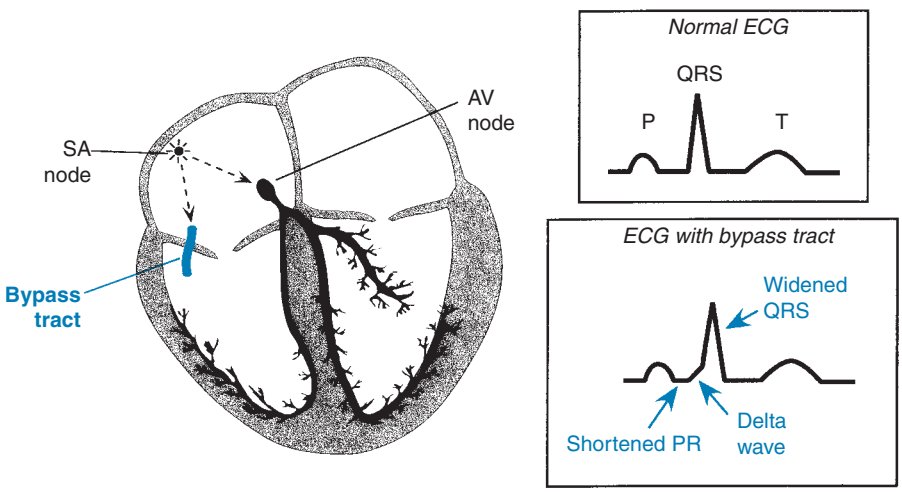

Figure 11.10. Accessory pathway (also termed the bypass tract). Example of an atrioventricular bypass tract (bundle of Kent), shown schematically, which can conduct impulses from the atrium directly to the ventricles, bypassing the AV node. The ECG demonstrates a short PR interval and a "delta wave" caused by early excitation of the ventricles via the accessory pathway. ECG, electrocardiogram; SA, sinoatrial.

LINE SHORT

with the accessory pathway serving as one limb and the normal conduction pathway through the AV node as the other. The clinical characteristics of the Wolff-Parkinson-White syndrome, including the types of reentrant tachycardia associated with it, are described in Chapter 12.

The mechanisms of altered impulse formation and conduction form the basis of all common arrhythmias, both abnormally slow rhythms (bradyarrhythmias) and abnormally fast ones (tachyarrhythmias). Table 11.1 lists the underlying mechanisms and examples of their commonly associated rhythm disturbances.

APPROACHES TO ANTIARRHYTHMIC TREATMENT

The treatment of a rhythm disorder depends on its severity and likely mechanism. When an arrhythmia produces severe hypotension or cardiac arrest, it must be immediately terminated to restore effective cardiac function. Therapy for termination may include electrical cardioversion (an electrical "shock") for tachycardias, cardiac pacing for bradycardias, or administration of medications.

Additional therapy to prevent recurrences is guided by the etiology of the rhythm disturbance. Correctable factors that contribute to abnormal impulse formation and conduction (such as ischemia or electrolyte abnormalities) should be corrected. If there is a risk of recurrent arrhythmia, medications that alter automaticity, conduction and/or refractoriness may be administered. Sometimes, catheter or surgical ablation of conduction pathways is undertaken to physically disrupt the region responsible for the arrhythmia. Other advanced options include implantation of a permanent pacemaker for serious bradyarrhythmias or an internal ICD to automatically terminate ma-

TABLE 11.1. Mechanisms of Arrhythmia Development

Abnormality	*Mechanism*	*Examples*
Bradyarrhythmias		
Altered impulse formation		
• Decreased automaticity	Decreased phase 4 depolarization (e.g., parasympathetic stimulation)	Sinus bradycardia
Altered impulse conduction		
• Conduction blocks	Ischemic, anatomic, or drug-induced impaired conduction	First-, second-, and third-degree AV blocks
Tachyarrhythmias		
Altered impulse formation		
• Enhanced automaticity		
Sinus node	Increased phase 4 depolarization (e.g., sympathetic stimulation)	Sinus tachycardia
Ectopic focus	Acquires phase 4 depolarization	Ectopic atrial tachycardia
• Triggered activity		
Early afterdepolarization	Prolonged action potential duration	Torsades de pointes
Delayed afterdepolarization	Intracellular calcium overload (e.g., digitalis toxicity)	APBs, VPBs, digitalis-induced arrhythmias
Altered impulse conduction		
• Reentry	Unidirectional block plus slowed conduction	
Anatomical		Atrial flutter, AV nodal reentrant tachycardia
Functional		Atrial fibrillation, ventricular fibrillation

AV, atrioventricular; APB, atrial premature beat; VPB, ventricular premature beat.

lignant tachyarrhythmias should they recur. The following sections summarize the common therapeutic modalities, and Chapter 12 describes how they are used to address specific rhythm disorders.

Bradyarrhythmias

Not all slow heart rhythms require specific treatment. For those that do, pharmacologic therapy can increase the heart rate acutely, but their effect is transient. Electronic pacemakers are used when a more sustained action is needed.

Pharmacologic Therapy

Pharmacologic therapy of bradyarrhythmias modifies the autonomic input to the heart in one of two ways:

1. *Anticholinergic drugs* (i.e., antimuscarinic agents such as atropine). Vagal stimulation reduces the rate of sinus node depolarization (which slows the heart rate) and decreases conduction through the AV node, through the release of acetylcholine onto muscarinic receptors. Anticholinergic drugs competitively bind to muscarinic receptors and thereby reduce the vagal effect. This results in an increased heart rate and enhanced AV nodal conduction.
2. β_1*-receptor agonists* (e.g., isoproterenol). Mimicking the effect of endogenous catecholamines, these drugs increase heart rate and speed AV nodal conduction.

Atropine and isoproterenol are administered intravenously. Although these drugs are useful in treating certain slow heart rhythms emergently, it is not practical to continue them over the long term for persistent bradyarrhythmias.

Electronic Pacemakers

Electronic pacemakers apply repeated electrical stimulation to the heart to initiate depolarizations at a desired rate, thereby assuming control of the rhythm. Pacemakers may be installed on a temporary or a permanent basis. Temporary units are used to stabilize patients who are awaiting implantation of a permanent pacemaker or to treat transient bradyarrhythmias, such as those caused by reversible drug toxicities.

There are two types of **temporary pacemakers.** *External* transthoracic pacemakers deliver electrical pulses to the patient's chest through large adhesive electrodes placed on the skin. The advantage of this technique is that it can be applied rapidly. Unfortunately, because the current used must be sufficient to initiate a cardiac depolarization, it stimulates thoracic nerves and skeletal muscle, which can be quite uncomfortable. Therefore, this form of pacing is usually used only on an emergency basis until another means of treating the arrhythmia can be implemented.

The other option for temporary pacing is a *transvenous* unit. In this case, an electrode-tipped catheter is inserted percutaneously into the venous system, passed into the heart, and connected to an external power source (termed a pulse generator). Electrical pulses are applied directly to the heart through the electrode catheter, which is typically placed in the right ventricle or right atrium. This type of pacing is not painful and can be effective for days. There is, however, a risk of infection and/or thrombosis that increases with time.

Permanent pacemakers are more sophisticated than the temporary variety. Various configurations can sense and capture the electrical activity of the atria and/or ventricles. One or more wires (known as leads) with pacing electrodes are passed through an axillary or subclavian vein into the right ventricle or right atrium or through the coronary sinus into a cardiac vein (to stimulate the left ventricle). The pulse generator, similar in size to two silver dollars stacked on top of one another, is connected to the leads and then implanted under the skin, typically in the infraclavicular region. The pacemaker battery typically lasts about 10 years.

Modern permanent pacemakers sense cardiac activity and pace only when needed. They incorporate complex functions to track the patient's normal heart rate and can

stimulate beats automatically in response to activity. They can also record useful data, such as whether fast rates have been sensed (that might indicate a tachyarrhythmia), the amount of pacing that has been required, and other parameters of pacemaker function. An external radio frequency programming device is used to "interrogate" the pacemaker to obtain the recorded information and adjust the pacing functions.

Although the most common indications for permanent pacemakers are bradyarrhythmias, pacemakers that incorporate a left ventricular pacing lead are also used to improve cardiac performance in some patients with heart failure (see Chapter 9).

Tachyarrhythmias

The treatment of tachyarrhythmias is directed at (1) protection of the patient from the consequences of the arrhythmia and (2) the specific mechanism responsible for the abnormal rhythm. Pharmacologic agents and cardioversion/defibrillation are commonly used approaches, but innovative electrical devices and transvenous catheter-based techniques have revolutionized treatment of these disorders.

Pharmacologic Therapy

Pharmacologic management of tachyarrhythmias is directed against the underlying mechanism (abnormal automaticity, reentrant circuits, or triggered activity). Many antiarrhythmic drugs are available, the pharmacology and actions of which are addressed in Chapter 17. The choice of drug relies on the cause of the specific arrhythmia. From consideration of the arrhythmia mechanisms presented in this chapter, the following strategies emerge.

Desired Drug Effects to Eliminate Rhythms Caused by Increased Automaticity

1. Reduce the slope of phase 4 spontaneous depolarization of the automatic cells
2. Make the diastolic potential more negative (hyperpolarize)
3. Make the threshold potential less negative

Desired Antiarrhythmic Effects to Interrupt Reentrant Circuits

1. Decrease conduction in the reentry circuit to the point that conduction fails, thus stopping the reentry impulse
2. Increase the refractory period within the reentrant circuit so that a propagating impulse finds tissue within the loop unexcitable and the impulse stops
3. Suppress premature beats that can initiate reentry

Desired Drug Effects to Eliminate Triggered Activity

1. Shorten the action potential duration (to prevent early afterdepolarizations)
2. Correct conditions of calcium overload (to prevent delayed afterdepolarizations)

Drugs used to achieve the goals modulate the action potential through interactions with ion channels, surface receptors, and transport pumps. Many drugs have multiple effects and may attack arrhythmias through more than one mechanism. The commonly used antiarrhythmic drugs and their actions are described in Chapter 17.

It is extremely important to recognize that in addition to suppressing arrhythmias, these drugs have the potential to *aggravate* or *provoke* certain rhythm disturbances. This undesired consequence is referred to as **proarrhythmia** and is a major limitation of contemporary antiarrhythmic drug therapy. For example, antiarrhythmic agents that act therapeutically to prolong the action potential duration can, as an undesired effect, cause early afterdepolarizations, the mechanism underlying the polymorphic ventricular tachycardia known as torsades de pointes (see Chapter 12). In addition, most agents used to treat tachyarrhythmias have the potential to aggravate bradyarrhythmias, and all antiarrhythmics have potentially toxic noncardiac side effects. These shortcomings have led to an increased reliance on nonpharmacologic treatment options, as described in the following sections.

Vagotonic Maneuvers

Many tachycardias involve transmission of impulses through the AV node, a structure that is sensitive to vagal modulation. Vagal tone can be transiently increased by a number of bedside maneuvers, and performing these may slow conduction, which terminates some reentrant tachyarrhythmias. For example, **carotid sinus massage** is performed by rubbing firmly for a few seconds over the carotid sinus, located at the bifurcation of the internal and external carotid arteries on either side of the neck. This maneuver stimulates the baroreceptor reflex (see Chapter 13), which elicits the desired increase in vagal tone and withdrawal of sympathetic tone. This maneuver should be performed on only one carotid sinus at a time (to prevent interference with brain perfusion) and is best avoided in patients with known atherosclerosis involving the carotid arteries.

Electrical Cardioversion and Defibrillation

Cardioversion and defibrillation involve the application of an electric shock to terminate a tachycardia. A shock with sufficient energy depolarizes the bulk of excitable myocardial tissue, interrupts reentrant circuits, establishes electrical homogeneity, and allows the sinus node (the site of fastest spontaneous discharge) to regain pacemaker control. Tachyarrhythmias that are caused by reentry can usually be terminated by this procedure, whereas arrhythmias owing to abnormal automaticity may simply persist.

External cardioversion is used to terminate supraventricular tachycardias or organized ventricular tachycardias. It is performed by briefly sedating the patient and then placing two large electrode paddles (or adhesive electrodes) against the chest on either side of the heart. The electrical discharge is electronically *synchronized* to occur at the time of a QRS complex (i.e., when ventricular depolarization occurs). This prevents the possibility of discharge during the relative refractory period of the ventricle (see Fig. 1.16), which could induce ventricular fibrillation.

External defibrillation is performed to terminate ventricular fibrillation, employing the same equipment as that used for cardioversion. However, during fibrillation, there is no organized QRS complex on which to synchronize the electrical discharge, so it is delivered using the "asynchronous" mode of the device.

Implantable Cardioverter-Defibrillators

ICDs automatically terminate dangerous ventricular arrhythmias using *internal* cardioversion or defibrillation, or a technique known as antitachycardia pacing. These devices are implanted, in a manner similar to that of permanent pacemakers, in patients at high risk of sudden cardiac death from ventricular arrhythmias. The device continuously monitors cardiac activity, and if the heart rate exceeds a certain programmable threshold for a specified time (e.g., >12 beats), the ICD delivers an appropriate intervention, such as an electrical shock. Internal cardioversion or defibrillation requires substantially less energy than external defibrillation but is still uncomfortable if the patient is conscious.

In addition, many monomorphic ventricular tachycardias can be terminated by an ICD with a rapid burst of electrical impulses, termed *antitachycardia pacing (ATP)*. The goal is to artificially pace the heart at a rate faster than the tachycardia to prematurely depolarize a portion of a reentrant circuit, thereby rendering it refractory to further immediate stimulation. Consequently, when a reentrant impulse returns to the zone that has already been depolarized by the device, it encounters unexcitable tissue, it cannot propagate further, and the circuit is broken. An advantage of ATP is that, unlike internal cardioversion, it is painless. However, ATP is not effective for terminating ventricular fibrillation.

Catheter Ablation

If an arrhythmia originates from distinct anatomical reentry circuits or automatic foci, electrophysiologic mapping techniques can

be used to localize the region of myocardium or conduction tissue responsible for the disturbance. It is then often possible to ablate the site via a catheter that applies radiofrequency current to heat and destroy the tissue. These procedures have revolutionized the management of patients with many types of supraventricular tachycardias, because they often offer a permanent therapeutic solution that spares patients from undergoing chronic antiarrhythmic drug therapy. For patients with recurrent ventricular tachycardias causing defibrillator shocks, ablation is often effective in reducing the frequency of episodes.

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SUMMARY

1. Arrhythmias result from disorders of impulse formation, impulse conduction, or both.
2. Bradyarrhythmias develop because of decreased impulse formation (e.g., sinus bradycardia) or decreased impulse conduction (e.g., AV nodal conduction blocks).
3. Tachyarrhythmias result from increased automaticity (of the SA node, latent pacemakers, or abnormal myocardial sites), triggered activity, or reentry.
4. Bradyarrhythmias are usually treated with drugs that accelerate the rate of sinus node discharge and enhance AV nodal conduction (atropine, isoproterenol) or electronic pacemakers.
5. Pharmacologic therapy for tachyarrhythmias is directed at the mechanism responsible for the rhythm disturbance. For refractory tachyarrhythmias, or in emergency situations, electrical cardioversion or defibrillation is used. Catheter-based ablative techniques are useful for long-term control of certain tachyarrhythmias. ICDs are lifesaving devices implanted in patients at high risk of sudden cardiac death because of ventricular tachyarrhythmias.

Chapter 12 summarizes the diagnosis and management of the most common arrhythmias. Chapter 17 describes currently available antiarrhythmic drugs.

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Chapter 11—Author Queries
1. AU: Correct to add?
2. AU: Correct meaning of VT acronym?
3. AU: Correct to add? See also below.