11 Mechanisms of Cardiac Arrhythmias

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Chapter Outline

Normal cardiac function relies on the flow of electric impulses through the heart in an exquisitely coordinated fashion. Abnormalities of the electric rhythm are known as arrhythmias (also termed dysrhythmias) and are among the most common clinical problems encountered. The presentations of arrhythmias range from common 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 heart 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 atrioventricular (AV) node and designated ventricular when they originate from the His–Purkinje system or ventricles. This chapter extends the description of basic cardiac electrophysiology presented in Chapter 1 and explains the mechanisms by which arrhythmias develop, followed by a general approach to their management. Chapter 12 describes specific rhythm disorders, including how to recognize and treat them.

Disorders of heart rhythm result from alterations of **impulse formation, impulse conduction**, or both. The chapter first addresses how abnormalities of impulse formation and conduction occur and under what circumstances they cause arrhythmias. Figure 11-1 provides an organizational schema for this presentation.

While studying the concepts in this chapter, it is important to recall that cardiac tissue is composed of cells that are electrically coupled and operate as a syncytium. As myocytes depolarize and ionic currents result in individual action potentials,

the electrical activity rapidly propagates from one cell to the next with minimal resistance, spreading through a large mass of tissue. As a result, the leading edge of a depolarization may be located several centimeters ahead of its trailing edge, and this property plays an important role in the genesis of certain arrhythmias, as will be described.

NORMAL IMPULSE FORMATION

As described in Chapter 1, electric impulse formation in the heart arises from the intrinsic automaticity of specialized cardiac cells. **Automaticity** refers to a cell's ability to spontaneously depolarize to a threshold voltage to generate an action potential. 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 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 automaticity.

Ionic Basis of Automaticity

Cells with natural automaticity do not have a static resting voltage. Rather, they inherently display gradual depolarization during phase 4 of the action potential (Fig. 11-2). If this spontaneous diastolic depolarization reaches the threshold condition, an action potential upstroke is generated. An important ionic current largely responsible for phase 4 spontaneous depolarization is known as the **pacemaker current (I_f)**. The channels that carry this current are activated by hyperpolarization (increasingly negative voltages) and mainly conduct sodium ions. I_f channels begin to open when the membrane voltage becomes more negative than approximately −50 mV and are different entities than the fast sodium channels responsible for rapid phase 0 depolarization in ventricular and atrial myocytes. The inward flow of Na^+ through these slow channels, driven by its concentration gradient and the negative intracellular potential, depolarizes the membrane toward threshold.

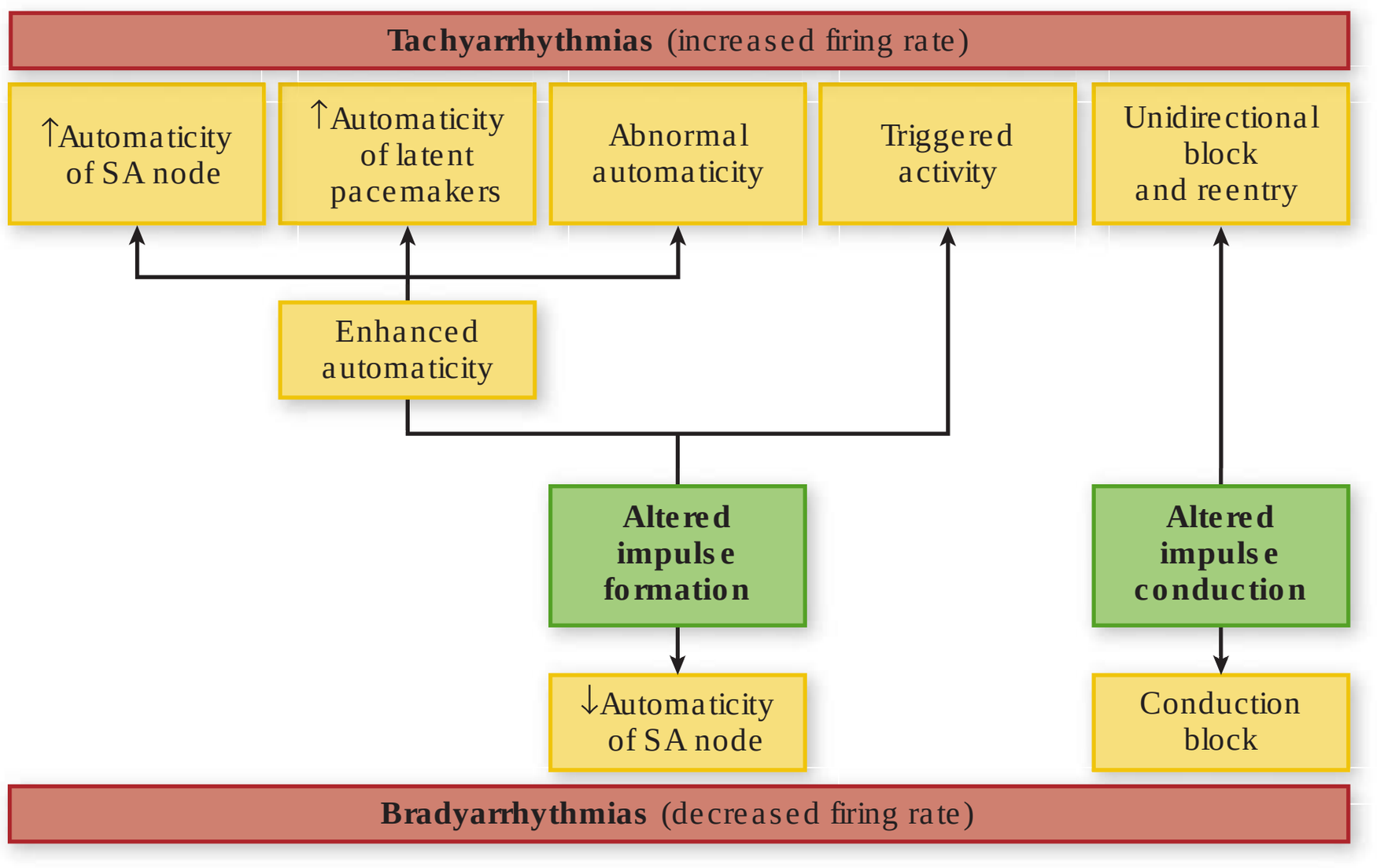

FIGURE 11-1. Arrhythmias result from alterations in impulse formation and/or impulse conduction. Tachyarrhythmias result from enhanced automaticity, unidirectional block with reentry, or triggered activity. Bradyarrhythmias result from decreased automaticity or conduction block. SA, sinoatrial.

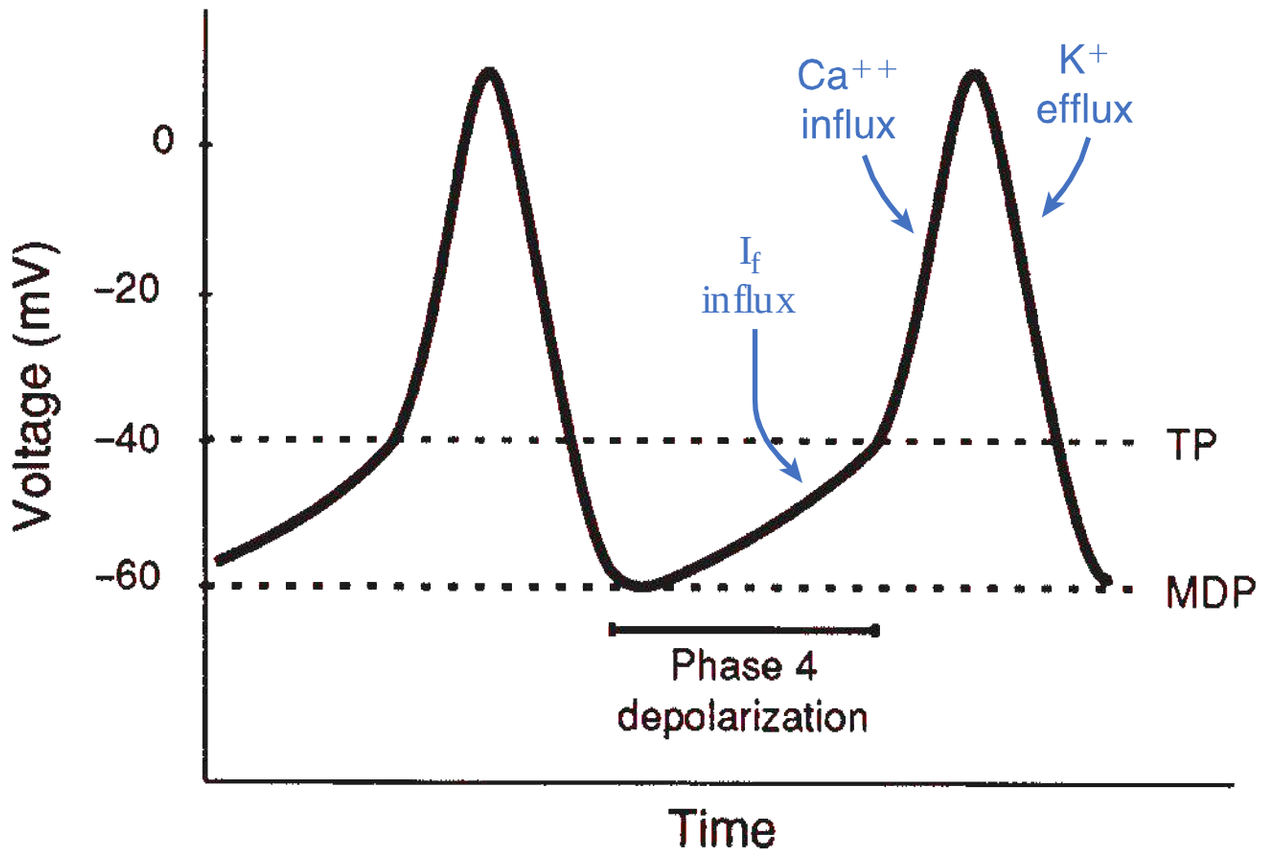

FIGURE 11-2. The action potential (AP) of a pacemaker cell (e.g., the sinus node). The slow phase 4 depolarization is largely caused by the I_f (pacemaker) inward current, which drives the cell to threshold (approximately −40 mV). The upstroke of the AP is caused by the slow inward current of Ca^{++} ions. Reduction of the Ca^{++} current (due to inactivation of calcium channels) and progressive K^+ efflux through voltage-gated potassium channels are responsible for repolarization. MDP, maximum negative diastolic potential; TP, threshold potential.

In the pacemaker cells of the SA node, three other ionic currents also contribute to phase 4 gradual depolarization: (1) a slowly increasing inward calcium current, carried mostly by L-type Ca^{++} channels that become activated at voltages reached near the end of phase 4; (2) a progressively declining outward potassium current; and (3) an additional inward sodium current mediated by activation of the electrogenic sodium–calcium exchanger by calcium release from the sarcoplasmic reticulum.

When the membrane potential of a pacemaker cell reaches the threshold condition, 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). 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 decreases as the resting (diastolic) membrane potential becomes less negative. Because sinus and AV nodal cells have less negative maximum diastolic membrane voltages (−50 to −60 mV) than do Purkinje cells (−90 mV), the large majority of fast sodium channels is inactivated in these pacemaker cells. Thus, the action potential upstroke relies to a great extent on a smaller calcium current (through the relatively slower opening of L-type Ca^{++} channels) and has a less rapid rate of rise than do cells of the Purkinje system or ventricular myocardium. The repolarization phase of pacemaker cells results from both the inactivation of the open calcium channels and the opening of voltage-gated potassium channels that permit efflux of potassium from the cells (see Fig. 11-2).

Native and Latent Pacemakers

The distinct 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 the threshold condition: (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 the 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 size of I_f depends on the number and opening kinetics of the individual pacemaker channels through which this current flows.

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

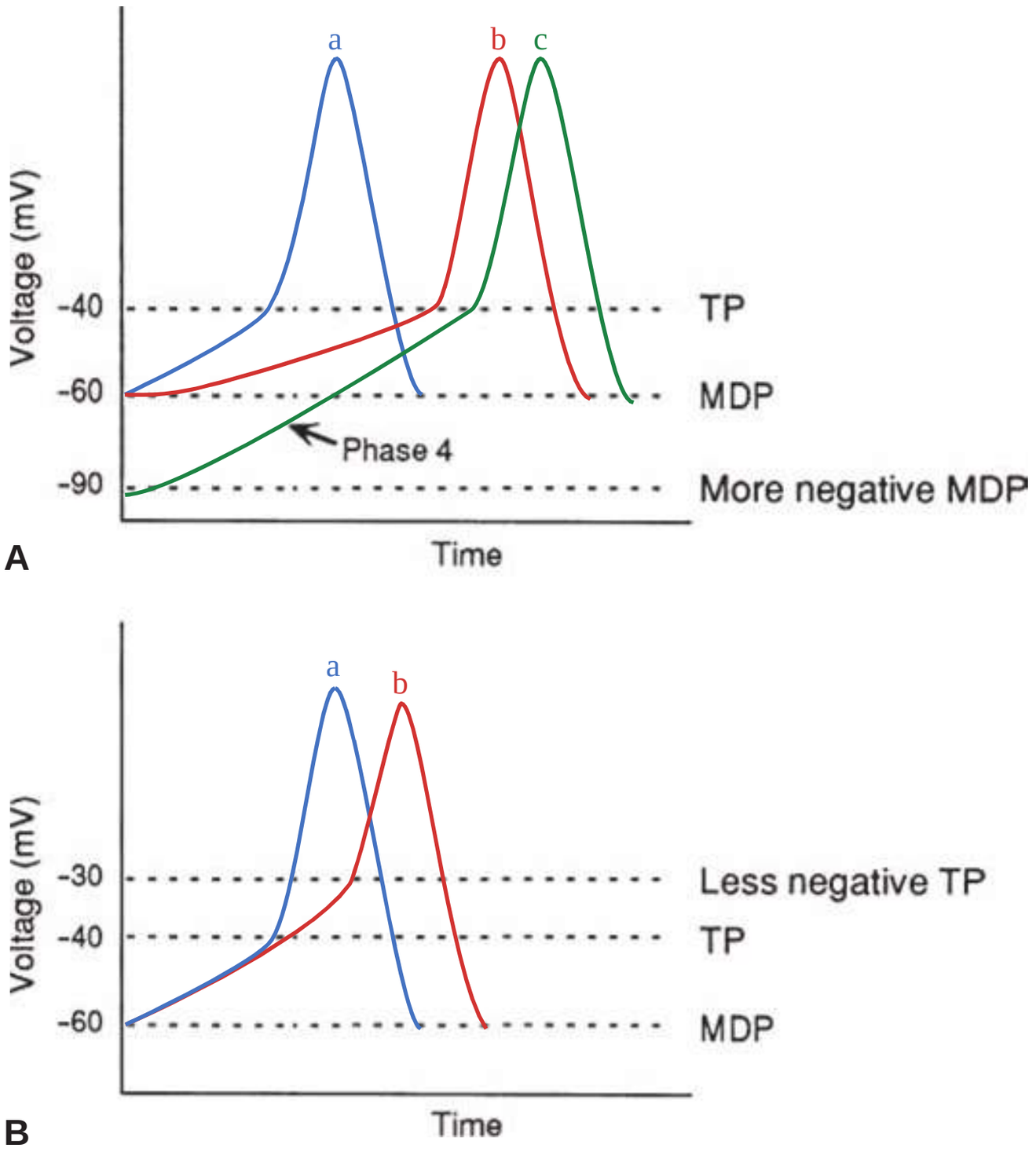

FIGURE 11-3. Determinants of cell f ring rates. A. Alterations in the pacemaker current (I_f) and in the magnitude of the maximum diastolic potential (MDP) alter the cell f ring rate. (a) The normal action potential (AP) of a pacemaker cell. (b) Reduced I_f renders the slope of phase 4 less steep; thus, 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 f ring 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 f ring rate decreases.

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 pacemaker 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 but 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 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, Na^+K^+-ATPase 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 moves the membrane voltage away from threshold, pacemaker cells firing at their own intrinsic rate have an I_f current sufficiently large to overcome this hyperpolarizing inf uence (see Fig. 11-4).

The hyperpolarizing current increases when a cell is caused to fire more frequently than its intrinsic pacemaker rate. The more often 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^+ content, Na^+K^+-ATPase 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.

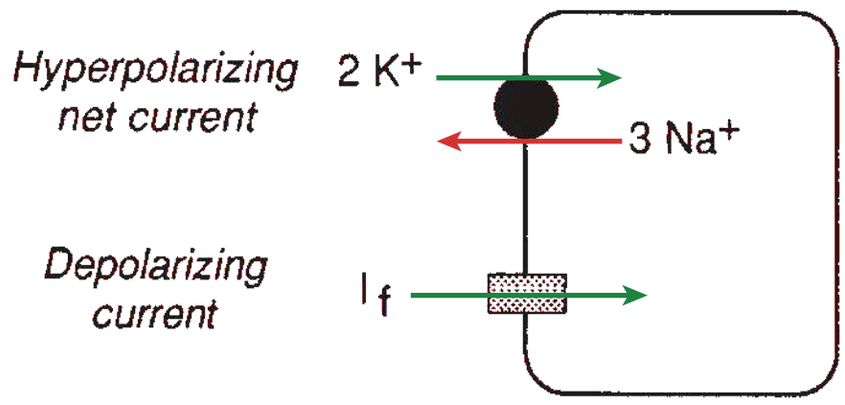

FIGURE 11-4. Competition between the depolarizing pacemaker current (I_f) and Na^+K^+-ATPase, which produces a hyperpolarizing current. Na^+K^+-ATPase transports three Na^+ ions outside the cell in exchange for two K^+ ions transported inward. The hyperpolarizing current acts to suppress automaticity by antagonizing I_f and contributes to overdrive suppression in cells that are stimulated more rapidly than their intrinsic f ring 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 in the ventricle and Purkinje system repolarize to a resting potential of approximately −90 mV, whereas pacemaker cells in the sinus and AV nodes 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 a compromise of electric potentials owing to electrotonic current f ow between the cells, causing relative hyperpolarization of the pacemaker cell and relative depolarization of the nonpacemaker cell (Fig. 11-5). Hyperpolarization

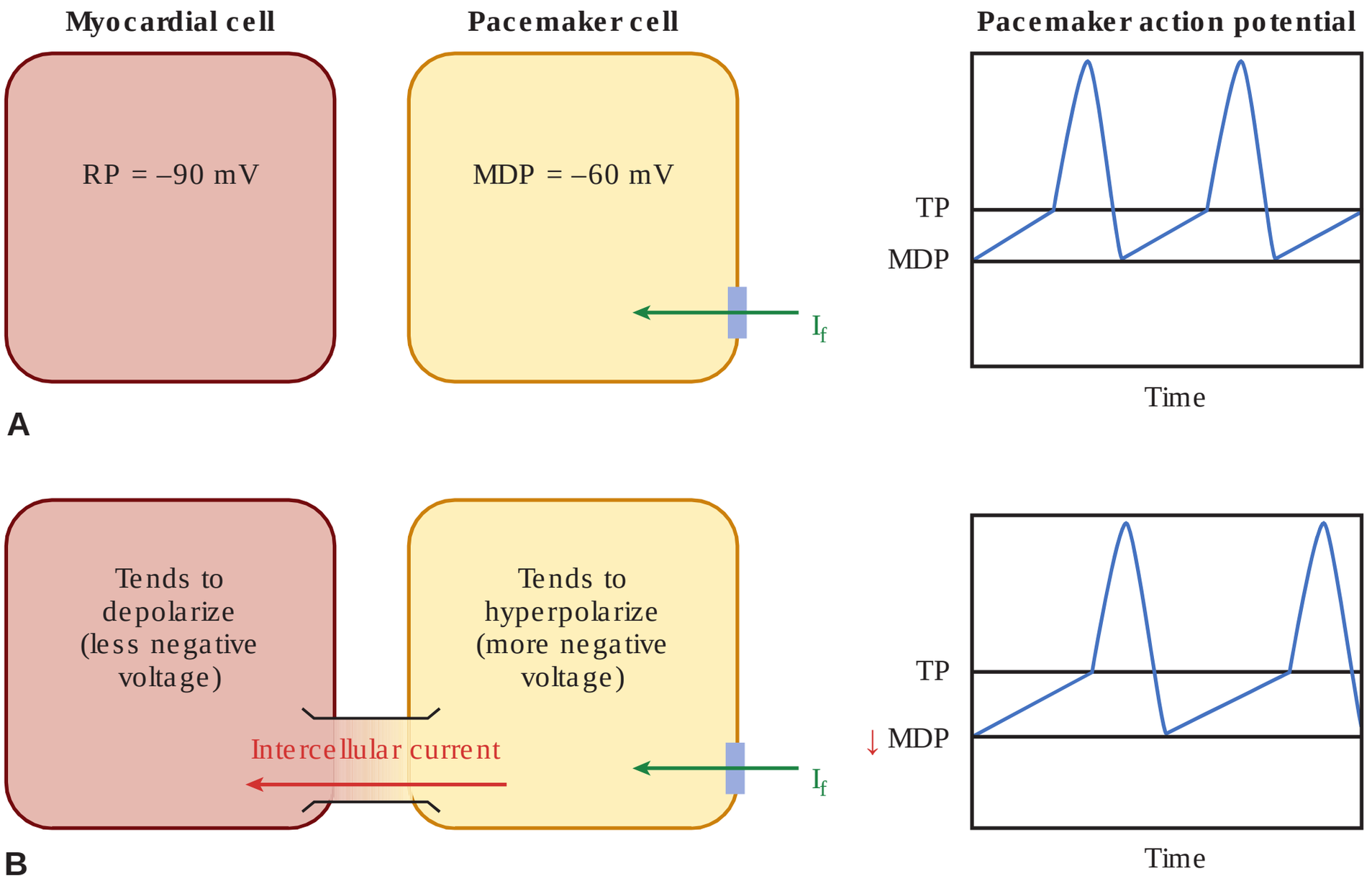

FIGURE 11-5. Electrotonic interaction between pacemaker (e.g., AV nodal) and nonpacemaker (myocardial) cells. A. Pacemaker cells that are not coupled to myocardial cells have a maximum diastolic potential (MDP) of approximately −60 mV, whereas myocardial cells have a resting potential (RP) of approximately −90 mV. **B.** When pacemaker cells and myocytes are neighbors, they may be connected electrically by gap junctions at their intercalated discs (e.g., at the AV node). In this situation, electric 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 hyperpolarizing current renders the MDP more negative, causing it to take longer for spontaneous depolarization to reach the threshold value, thereby suppressing automaticity. If a disease state impairs coupling between cells, the influence of surrounding myocytes on the pacemaker cell is reduced, allowing I_f to depolarize to threshold more readily and enhancing automaticity. TP, threshold potential.

moves the diastolic potential further from threshold and thus slows the heart rate (as shown in Fig. 11-3A). 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 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.

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 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 open probability of the pacemaker channels (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 capable of opening (recall that calcium carries the current of phase 0 depolarization in pacemaker cells). Therefore, phase 4 depolarization reaches the threshold potential earlier. Sympathetic activity thus increases sinus node automaticity both by increasing the rate of pacemaker depolarization via I_f and by causing the action potential threshold to become more negative. Examples of this normal physiologic effect occur during physical exercise or emotional stress, when sympathetic stimulation appropriately increases the heart rate.

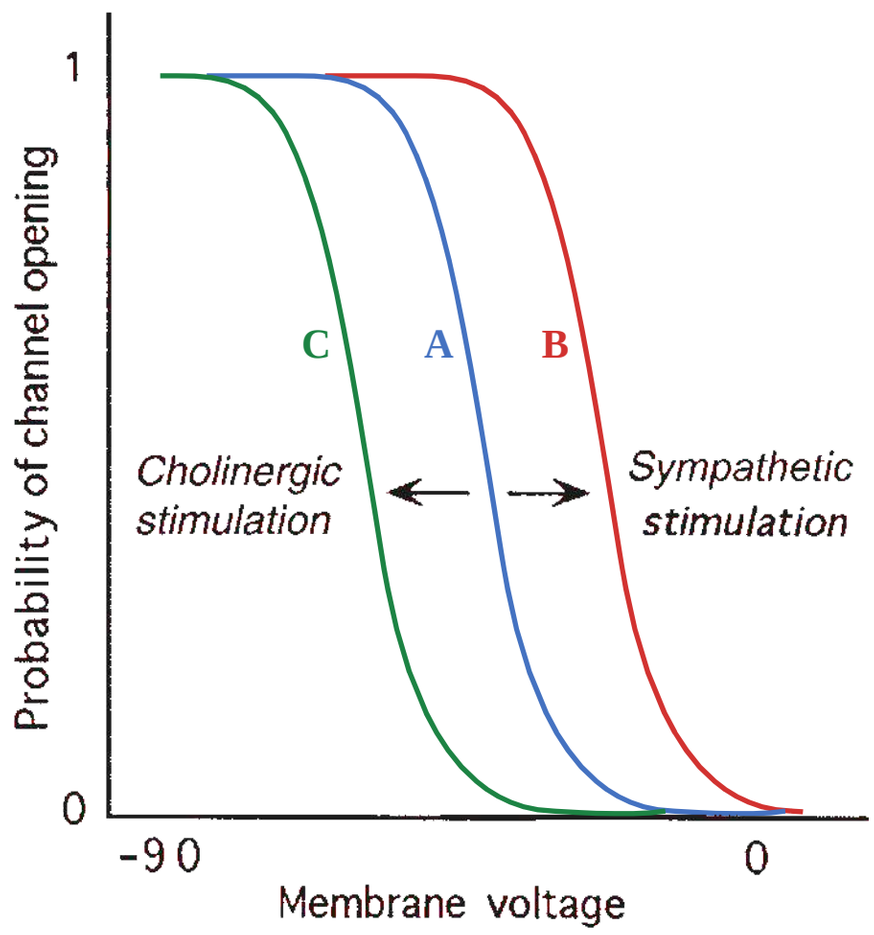

FIGURE 11-6. Effect of sympathetic and parasympathetic (cholinergic) stimulation on pacemaker current channels. The channels through which the pacemaker current (I_f) flows are voltage gated, opening at more negative membrane potentials. At any given voltage, there exists a probability between 0 and 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 cholinergic stimulation (or treatment with a β-blocker, which antagonizes sympathetic stimulation) has the opposite effect, decreasing the probability of a channel being open and therefore inhibiting depolarization.

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 activation of the sympathetic nervous system has a major role in increasing the heart rate during times of stress, the parasympathetic nervous system is the major controller 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, such that the action potential threshold increases to a less negative potential. Furthermore, cholinergic stimulation increases the probability of acetylcholine-sensitive K^+ channels being open at rest. Positively charged K^+ ions exit through these "inward rectifier" channels, which differ from the K^+ channels that are active in phase 3 repolarization (see Chapter 1), producing an outward current that drives the diastolic potential 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 these effects of the autonomic nervous system will also affect the firing rate of the SA node. For example, β-receptor blocking drugs ("β-blockers") 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 much less frequently than normal, the site of impulse formation may shift 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 pathologically 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 varied 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, moderate parasympathetic stimulation slows the sinus rate and allows the pacemaker to shift to the AV node. However, very strong parasympathetic stimulation suppresses excitability at both the SA node and 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**, such an 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 cardiac tissue becomes injured, its cellular 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 spontaneous depolarization probably results from a very slowly inactivating calcium current, a decrease in the outward potassium current that normally acts to repolarize the cell, and less effect of the inward rectifier K^+ current that normally holds cells at a more negative potential range.

Triggered Activity

Under certain conditions, an action potential can "trigger" abnormal depolarizations that result in extra heart beats or tachyarrhythmias. 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.

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

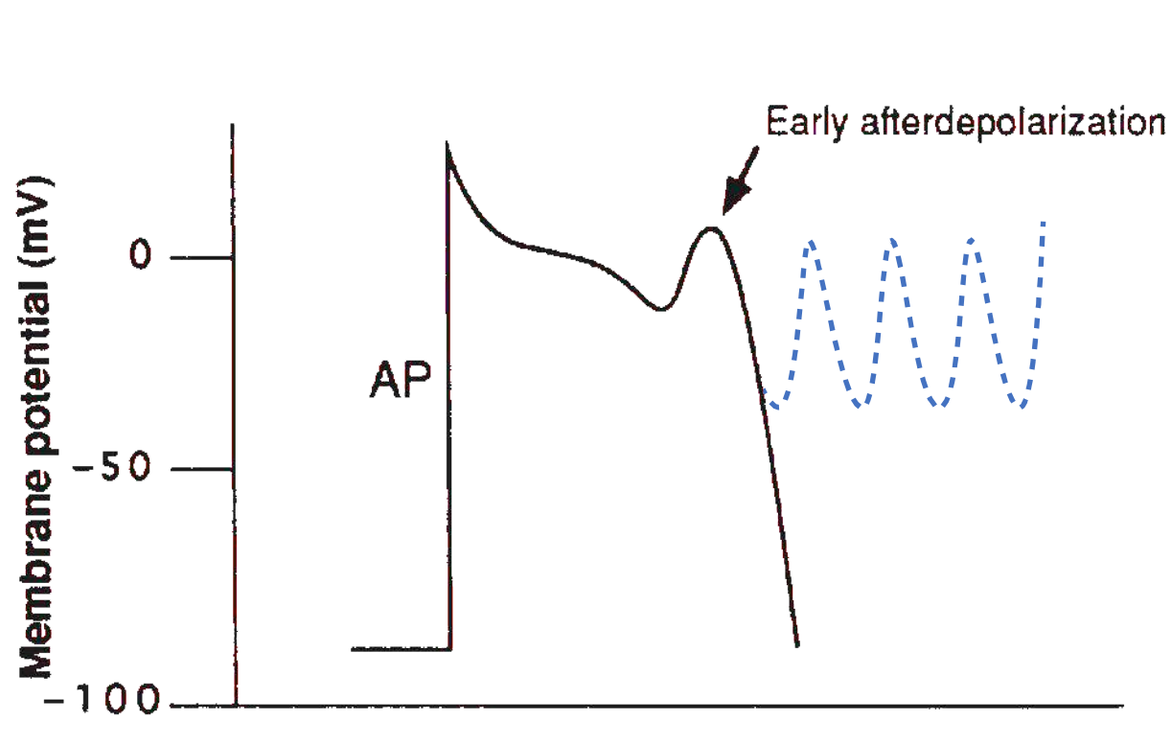

FIGURE 11-7. Triggered activity. An early afterdepolarization (arrow) occurs before the action potential (AP) has fully repolarized. Repetitive afterdepolarizations (dashed curve) may produce a rapid sequence of triggered action potentials and hence a tachyarrhythmia.

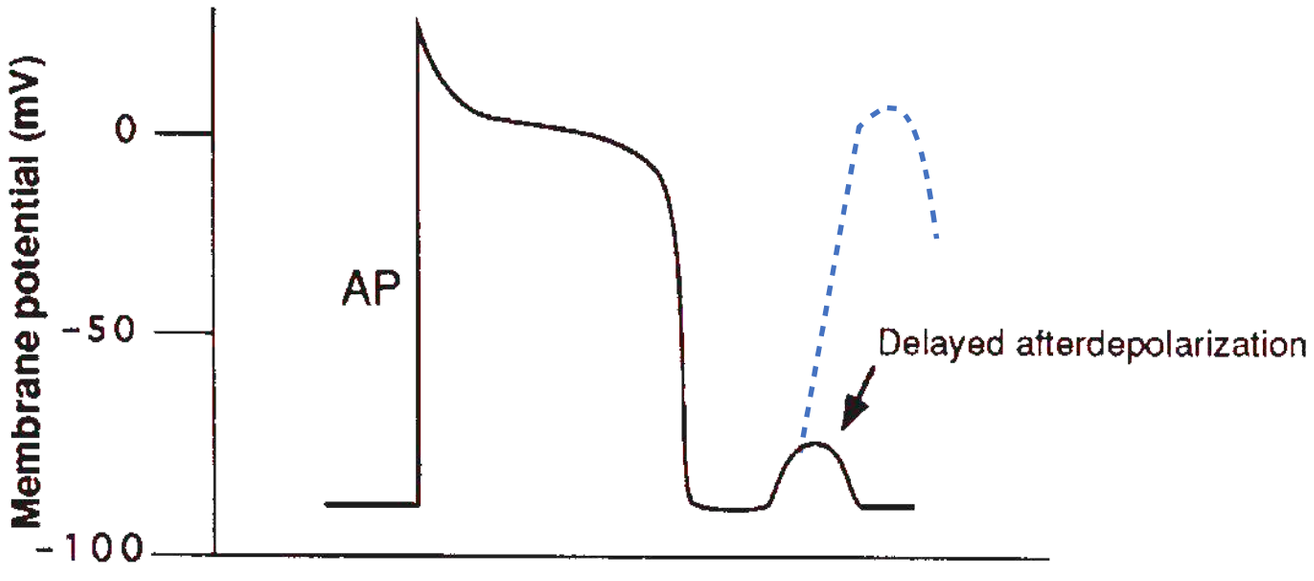

FIGURE 11-8. Triggered activity. A delayed afterdepolarization (arrow) arises after the cell has fully repolarized. If the delayed afterdepolarization reaches the threshold voltage, a propagated action potential (AP) is triggered (dashed curve).

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 still in an inactivated state, the upstroke of the triggered beat relies mostly on an inward Ca^{++} current. If, however, the afterdepolarization occurs during phase 3 (when the membrane voltage is more negative), there is partial recovery of the inactivated Na^+ channels, which then contribute more to the current underlying the triggered beat.

An early afterdepolarization-triggered action potential can be self-perpetuating and lead to a series of depolarizations and therefore a tachyarrhythmia (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 can be self-perpetuating and lead to tachyarrhythmias. Some idiopathic ventricular tachycardias that occur in otherwise structurally normal hearts are likely due to this mechanism, as are atrial and ventricular tachycardias associated with digitalis toxicity (see 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 a short time later, when the tissue is no longer refractory, may be conducted appropriately. For example, antiarrhythmic

drugs that prolong the action potential duration (described in Chapter 17) tend to produce functional conduction blocks. Conversely, when conduction block is caused by a barrier imposed by fibrosis or scarring that replaces myocytes, the block is said to be f xed.

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 altered impulse conduction leads to tachyarrhythmias is termed **reentry**. During such a rhythm, an electric impulse circulates repeatedly around a reentry path, recurrently depolarizing a region of cardiac tissue.

During normal cardiac conduction, each electric 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.

The figure depicts electric activity as it f ows through a branch point anywhere within the conduction pathways. Panel A shows propagation of a normal action potential. At point x, the impulse branches into two 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 portions of the wave fronts that pass through them may collide in the distal conduction tissue and extinguish each other, as shown by the red line.

Panel B shows what happens if conduction is blocked in one limb of the pathways. 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 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 is 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 α 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.

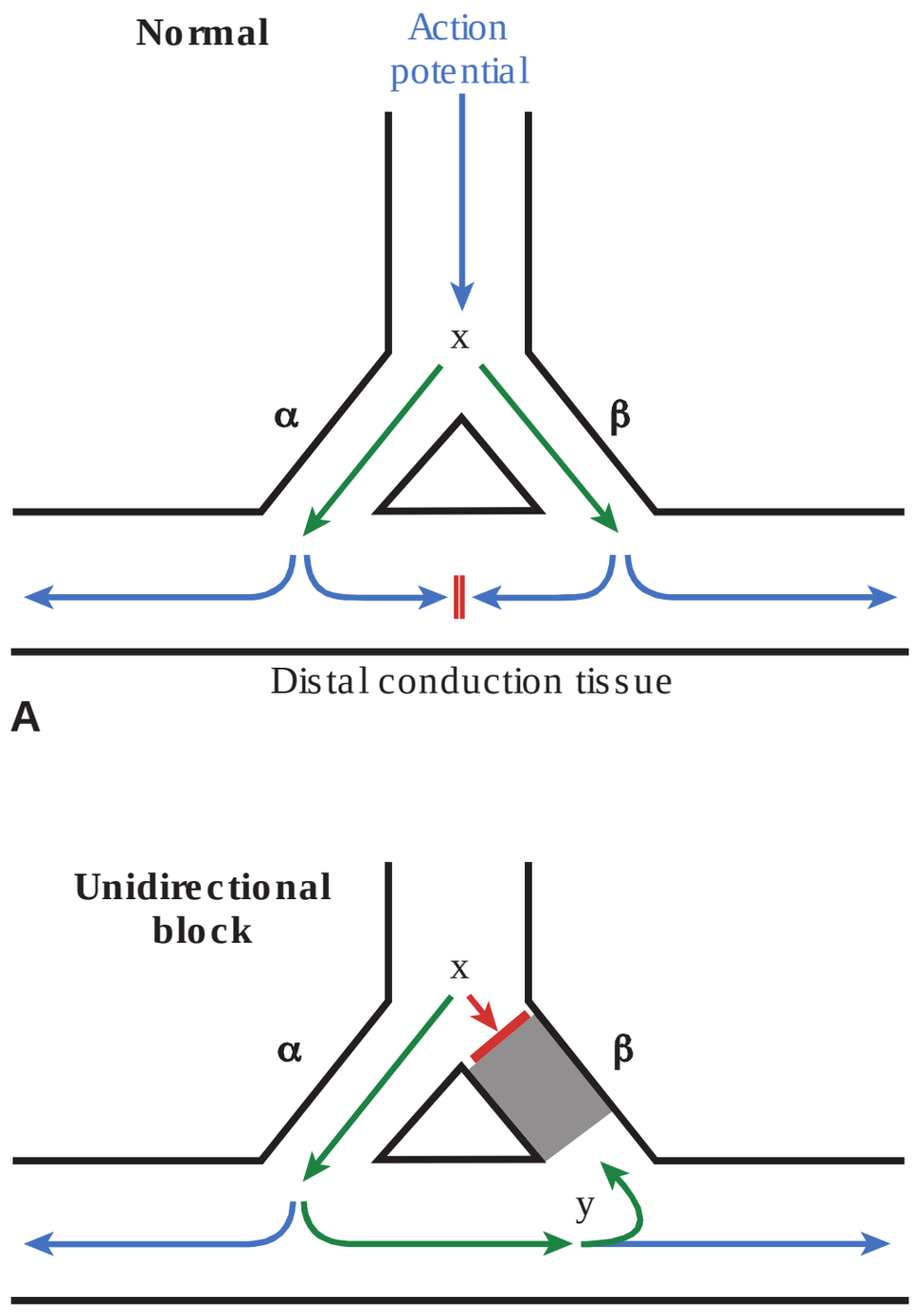

FIGURE 11-9. Mechanism of reentry. A. Normal conduction. When an action potential (AP) reaches a branch in the conduction pathway (point x), the impulse travels down both fibers (α and β) to excite distal conduction tissue. **B.** Unidirectional block. Forward passage of the impulse is blocked in the 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.

Then, the invading impulse is able 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, at an abnormally high rate, 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 in ventricular muscle is approximately 50 cm/s and the average effective refractory period is about 0.2 seconds, 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 shorter 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); that is, in the case of ventricular tachycardia, each QRS has the same appearance as the preceding and subsequent QRS complexes. This is because the reentry path is the same from beat to beat, producing a stable, regular tachycardia. This is the most common mechanism of ventricular tachycardia associated with areas of ventricular scar, as may result from a prior myocardial infarction.

Other types of reentry do not require a stable, fixed path. For example, one form can occur in electrically heterogeneous myocardium, in which waves of reentrant excitation spiral through the tissue, continually changing direction. These so-called “spiral waves” can be initiated when a wave front of depolarization encounters a broad region of functional block, which could be refractory from a preceding wave front, be poorly excitable tissue due to myocardial ischemia, or be under the influence of certain antiarrhythmic medications. Forward propagation of the wave front is asymmetrically blocked by this region, as the remainder of the front proceeds around the block. As the region repolarizes and becomes excitable again, parts of the wave front then spread retrogradely through it and continue in a spiral path following in the wake of the depolarization that had just passed. Unlike an anatomically fixed reentrant tract, the center of the spiral wave can move through the myocardium and even split into two or more reentry waves. In the ventricles, the resulting tachycardia has a continually changing QRS appearance, producing polymorphic ventricular tachycardia. If such activation is rapid and very disorganized, no distinct QRS complexes will be discernable and the rhythm is ventricular fibrillation (as described in Chapter 12).

Accessory Pathways and the Wolff–Parkinson–White Syndrome

The mechanism of reentry is dramatically illustrated by the **Wolff–Parkinson–White (WPW) syndrome**. In the normal heart, an 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 1,500 people has the WPW syndrome and is born with an additional connection between an 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

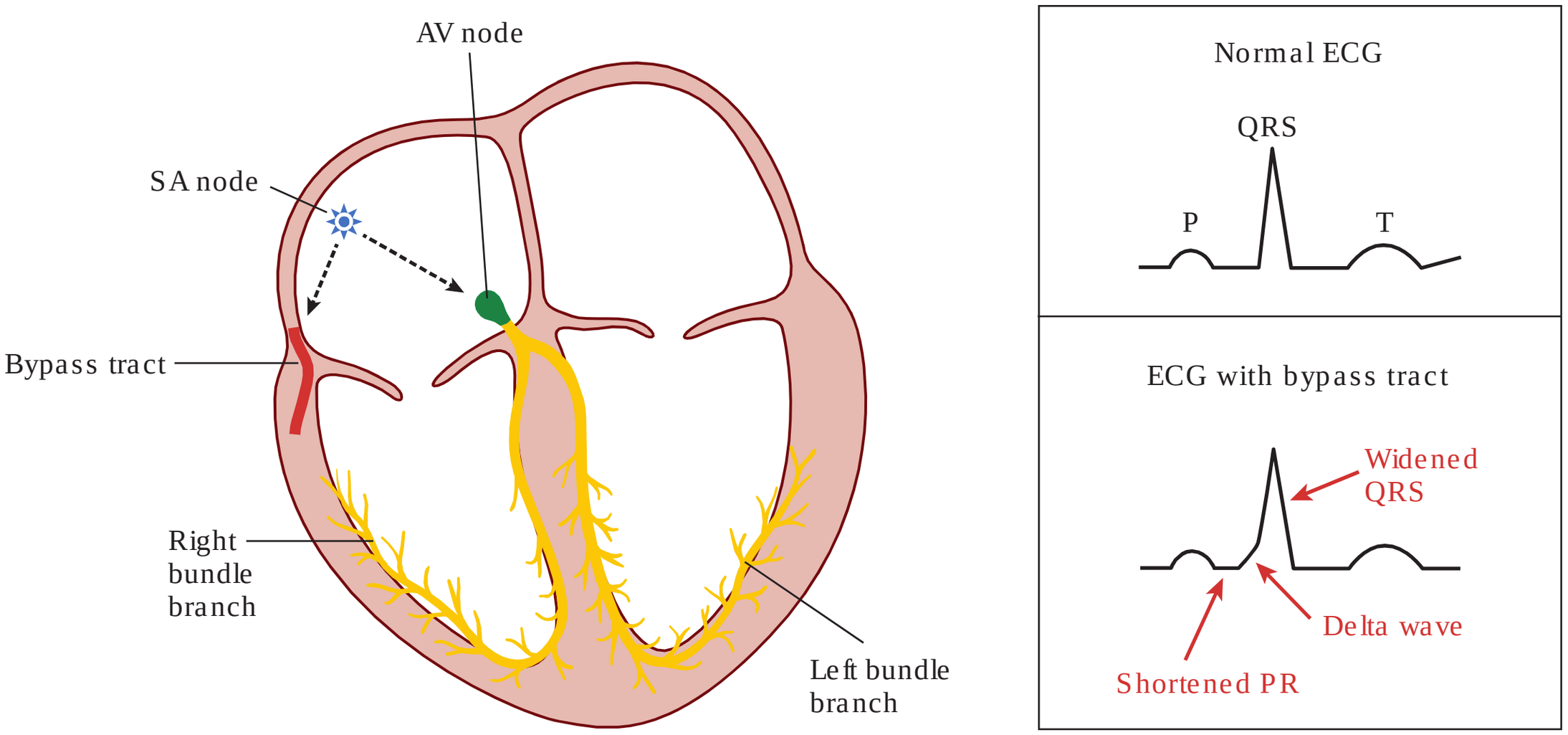

FIGURE 11-10. Accessory pathway (also termed a bypass tract). Example of an atrioventricular bypass tract (bundle of Kent), shown schematically, which can conduct impulses from the atrium directly to the ventricles, bypassing the AV node. The ECG demonstrates a shortened PR interval and a "delta wave" caused by early excitation of the ventricles via the accessory pathway. ECG, electrocardiogram; SA, sinoatrial.

of microscopic fibers (known as a bundle of Kent) that span the AV groove somewhere along the mitral or tricuspid annuli, as shown in Figure 11-10.

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 seconds, 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 electric impulse traveling via the accessory tract and that conducted through the normal Purkinje system. 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 results in this 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 block in the accessory pathway but conduct through 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, 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 WPW 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.

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
AV node		AV junctional tachycardia
Ectopic focus	Acquires phase 4 depolarization	Ectopic atrial tachycardia and some forms of VT
• 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, "idiopathic" VT
Altered impulse conduction		
• Reentry	Unidirectional block plus slowed conduction	
Anatomical		Atrial flutter, AV nodal reentrant tachycardia, VT related to ventricular scar tissue
Functional		Atrial fibrillation, polymorphic VT, ventricular fibrillation

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

PHYSIOLOGIC BASIS OF ANTIARRHYTHMIC THERAPY

Appropriate treatment of a rhythm disorder depends on its severity and its 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 electric "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, or 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 cardioverter–defibrillator (ICD) to automatically terminate malignant 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 specif c treatment. For those that do, pharmacologic therapy can increase the heart rate acutely, but the effect is transient. Electronic pacemakers are used when more sustained therapy is needed.

Pharmacologic Therapy

Pharmacologic therapy of bradyarrhythmias modif es 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 managing certain slow heart rhythms emergently, it is not practical to continue them over the long term to treat persistent bradyarrhythmias.

Electronic Pacemakers

Electronic pacemakers apply repeated electric 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 electric 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 suff cient 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). Electric 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 associated with the catheter.

Permanent pacemakers are more sophisticated than the temporary variety. Various conf gurations can sense and capture the electric 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 to 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 (cardiac resynchronization therapy—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 electronic devices and transvenous catheter–based techniques to intentionally damage (ablate) arrhythmia-causing tissue 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, and the choice of which to use 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. Inhibit 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 these 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 important to recognize that although these drugs suppress arrhythmias, they also 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 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 advanced atherosclerosis involving the carotid arteries.

Electric 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 electric 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 due 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 electric 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 T wave, when a shock could induce reentry (leading to ventricular fibrillation) because regions of myocardium are in different phases of depolarization and recovery.

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 electric discharge, so it is delivered using the "asynchronous" mode of the device.

Implantable Cardioverter–Defibrillators

ICDs automatically terminate dangerous ventricular arrhythmias using internal cardioversion/defibrillation or by way of a special type of artificial 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, the ICD delivers an appropriate intervention, such as an electric shock. Internal cardioversion or defibrillation requires substantially less energy than does external defibrillation but is still painful if the patient is conscious.

The majority of monomorphic ventricular tachycardias can be terminated by an ICD with a rapid burst of electric impulses, termed antitachycardia pacing (ATP), rather than a shock. 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 the ATP technique is that, unlike internal cardioversion, it is painless. However, ATP is not effective for terminating ventricular fibrillation, a situation in which the device is programmed to deliver an electric shock instead.

Catheter Ablation

If an arrhythmia originates from a distinct anatomical reentry circuit or an automatic focus, 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. Such procedures have revolutionized the management of patients with many types of tachycardias, because they often offer a permanent therapeutic solution that spares patients from prolonged antiarrhythmic drug therapy. Additionally, for patients with ICDs and recurrent ventricular tachycardias causing defibrillator shocks, ablation is often effective in reducing the frequency of episodes.

SUMMARY

- Arrhythmias result from disorders of impulse formation, impulse conduction, or both.
- Bradyarrhythmias (abnormally slow heart rhythms) develop because of decreased impulse formation (e.g., sinus bradycardia) or decreased impulse conduction (e.g., AV nodal conduction blocks).
- Tachyarrhythmias (abnormally fast rhythms) result from increased automaticity (of the SA node, latent pacemakers, or abnormal myocardial sites), triggered activity, or reentry.
- 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.
- Bradyarrhythmias are usually treated acutely with drugs that accelerate the rate of sinus node discharge and enhance AV nodal conduction (atropine, isoproterenol) or with temporary electronic pacemakers.
- Permanent electronic pacemakers are implanted when more sustained therapy for bradyarrhythmias is needed.
- 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 utilized.
- 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.
- For patients with ICDs and recurrent ventricular tachycardias causing defibrillator shocks, ablation techniques are often effective in reducing the frequency of episodes.

Chapter 12 describes the diagnosis and management of the most common arrhythmias. Chapter 17 describes commonly used antiarrhythmic drugs.

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