Part 1

Basic principles

CHAPTER 1
Mechanisms of cardiac tachyarrhythmias

Using antiarrhythmic drugs safely is difficult. Indeed, it is nearly impossible without a firm understanding of the basic mechanisms of cardiac tachyarrhythmias and the basic concepts of how antiarrhythmic drugs work. Part 1 of this book covers these basics. Chapter 1 reviews the normal electrical system of the heart and the mechanisms and clinical features of the major cardiac tachyarrhythmias. Chapter 2 examines the principles of how antiarrhythmic drugs affect arrhythmias.

The electrical system of the heart

On a very fundamental level, the heart is an electrical organ. The electrical signals generated by the heart not only cause muscle contraction (by controlling the flux of calcium ions across the cardiac cell membrane) but also organize the sequence of muscle contraction with each heartbeat, thus optimizing the pumping action of the heart. In addition, and especially pertinent to the subject of this book, the pattern and timing of the cardiac electrical signals determine the heart rhythm. Thus, a well-functioning electrical system is vital for adequate cardiac performance.

Anatomy

The heart's electrical impulse originates in the sinoatrial (SA) node, high in the right atrium near the superior vena cava (Figure 1.1). From the SA node, the impulse spreads radially across both atria. When it reaches the atrioventricular (AV) groove, the impulse encounters the fibrous "skeleton" of the heart, which separates the atria from the ventricles. The fibrous skeleton is electrically inert, and therefore stops the electrical impulse. The only way for the impulse

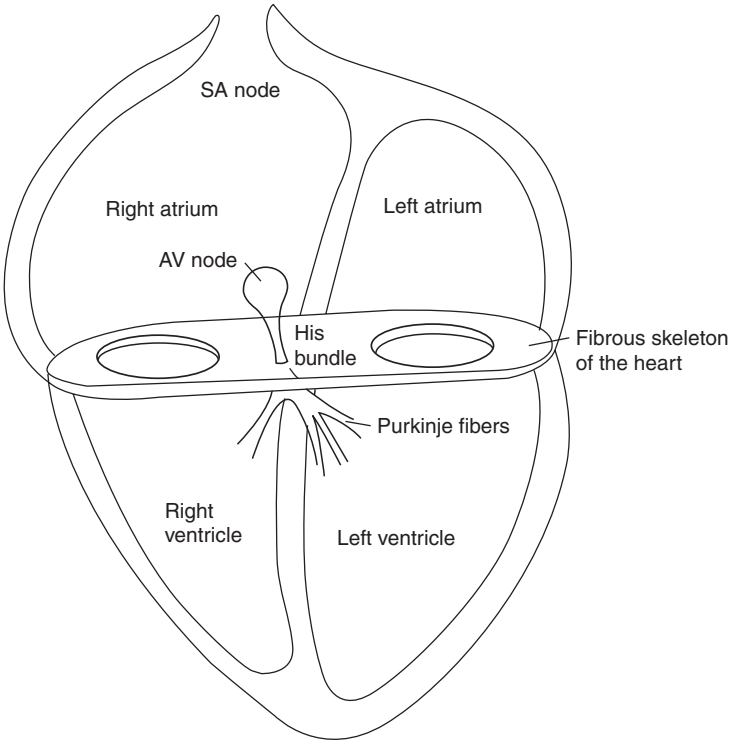


Figure 1.1 Anatomy of the electrical system of the heart.

to cross over to the ventricular side is by means of the specialized AV conducting tissues—the AV node and the His-Purkinje system.

The AV node conducts electricity slowly; when the electrical impulse enters the AV node, its passage is delayed. The delay is reflected in the PR interval on the surface electrocardiogram (ECG). Leaving the AV node, the electrical impulse enters the His bundle, the most proximal part of the rapidly conducting His-Purkinje system. The His bundle penetrates the fibrous skeleton and delivers the impulse to the ventricular side of the AV groove.

Once on the ventricular side, the electrical impulse follows the His-Purkinje system as it divides first into the right and left bundle branches and then into the Purkinje fibers. The Purkinje fibers speed the impulse to the furthermost reaches of the ventricular myocardium. In this way, the electrical impulse is rapidly distributed throughout the ventricles.

The heart's electrical system thus organizes the sequence of myocardial contraction with each heartbeat. As the electrical impulse spreads across the atria, the atria contract. The delay provided by the AV node allows complete emptying of the atria before the electrical impulse reaches the ventricles. Once the impulse leaves the AV node, it is distributed rapidly throughout the ventricular muscle by the Purkinje fibers, thus providing brisk and orderly ventricular contraction.

Cardiac action potential

The electrical impulse of the heart is actually the summation of thousands of tiny electrical currents generated by thousands of individual cardiac cells. The electrical activity of an individual cardiac cell is described by the cardiac action potential (Figure 1.2). The action potential is inherently a bit complex and nonintuitive. Fortunately, for our purposes there are only a few things one needs to know about the action potential, and these are reasonably simple to understand.

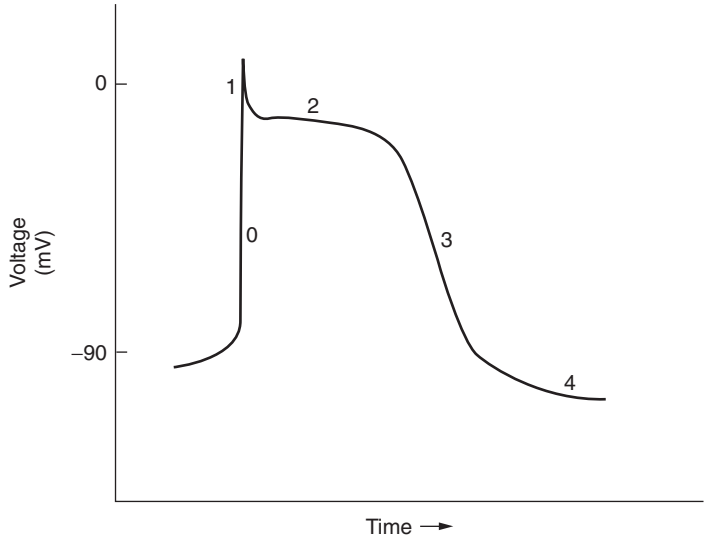


Figure 1.2 Cardiac action potential. Numbers on the curve indicate the five phases of the action potential. Phase 0 corresponds to depolarization. Phases 1–3 correspond to repolarization. Phase 4 corresponds to the resting phase.

The inside of every living cell has a negative electrical charge. The voltage difference across the cell membrane (normally –80 to –90 mV) is called the transmembrane potential and is the result of an accumulation of negatively charged molecules within the cell. The magnitude of the transmembrane potential remains fixed throughout the lives of most living cells.

However, some cells—notably, cardiac cells—are excitable. When excitable cells are stimulated in just the right way, a variety of tiny channels in the cell membrane are induced to open and close in a complex sequence, which allows various electrically charged particles—ions—to pass back and forth across the membrane in an equally complex sequence. The movement of electrical current across the cell membrane occurs in a very stereotypic pattern and leads to a patterned sequence of changes in the transmembrane potential. When the stereotypic changes in voltage are graphed against time, the result is the cardiac action potential.

Although the cardiac action potential is classically divided into five phases (named, somewhat perversely, phases 0 through 4), it is most helpful to consider the action potential in terms of three general phases: depolarization, repolarization, and the resting phase.

Depolarization

The depolarization phase of the action potential, phase 0, occurs when the so-called rapid sodium channels in the cell membrane are stimulated to open, which allows positively charged sodium ions to rush into the cell. The sudden influx of positive ions causes a voltage spike—a rapid, positively directed change in the transmembrane potential. The voltage spike, called *depolarization*, accounts for the heart's electrical impulse; phase 0 is when the "action" of the action potential occurs.

The sodium channels that allow this rapid depolarization are *voltage dependent*; that is, they open when the cell's resting transmembrane potential reaches a certain threshold voltage. The event that raises a cell's transmembrane potential to threshold voltage is most often the depolarization of a nearby cardiac cell. Thus, the depolarization of one cell leads to depolarization of adjacent cells; once a cardiac cell is depolarized, a wave of depolarization (the electrical impulse) tends to spread across the heart, cell by cell.

Further, the speed at which one cell is depolarized (represented by the slope of phase 0) determines how quickly the next cell is stimulated to depolarize, and thus determines the speed at which

the electrical impulse is propagated. If something causes the slope of phase 0 to change, the conduction velocity also changes; the faster the depolarization of the cardiac cells, the faster an electrical impulse moves across the heart.

Repolarization

If you fire a Colt 45, you cannot fire it again until you recock it. Similarly, once a cell is depolarized, it cannot be depolarized again until the ionic fluxes that occur during depolarization are reversed. The process of getting the ions back to where they started is called *repolarization*. Repolarization corresponds to phases 1 through 3, and therefore accounts for almost the entire duration of the action potential. Because the cell is refractory to depolarization until after it is repolarized, the time from the end of phase 0 to late in phase 3 is called the *refractory period* of the cell. The duration of the action potential thus determines the refractory period; if one does something to change the duration of the action potential, one also changes the refractory period.

The repolarization of cardiac cells is complex and incompletely understood. Repolarization begins rapidly (phase 1), but the process is almost immediately interrupted by a plateau phase (phase 2), which is unique to cardiac cells (e.g., there is no plateau phase in nerve cells). Phase 2 is mediated by "slow" calcium channels, which allow positively charged calcium ions to enter the cell slowly and thus to interrupt repolarization and prolong the duration of the action potential.

The most important ionic shift that occurs during repolarization is the outward flow of positively charged potassium ions, which has the effect of returning the action potential toward its baseline, negatively polarized state. At least six different potassium "currents" have been identified; they operate at different times during the action potential and are modulated by different factors (including voltage, calcium ions, muscarinic receptors, acetylcholine, and adenosine triphosphate) under different circumstances.

Dumping sodium and calcium ions into a cardiac cell to depolarize it and then draining potassium ions out of the cell to repolarize it may return the transmembrane voltage to baseline levels, but these actions do not return the cell chemistry to the baseline state. Various poorly characterized mechanisms are called on to rectify remaining chemical imbalances (the most important of which is the sodium–potassium pump). Although depolarization seems

fairly straightforward, any attempt to fully understand repolarization quickly leads one into a maze of seemingly conflicting channels, gates, receptors, and pumps which only a basic electrophysiologist could love.

Fortunately, the essential features of repolarization are relatively simple: (1) repolarization returns the cardiac action potential to the resting transmembrane potential; (2) this process takes time; (3) this time, roughly corresponding to the width of the action potential, is the refractory period of cardiac tissue; (4) depolarization mainly depends on sodium channels, and repolarization mainly depends on potassium channels.

The resting phase

For most cardiac cells, the resting phase (the period of time between two action potentials, corresponding to phase 4) is quiescent; there is no net movement of ions across the cell membrane.

For some cells and in some circumstances, however, the so-called resting phase is not quiescent. Instead, there is leakage of ions back and forth across the cell membrane during phase 4 in such a way as to cause a gradual increase in transmembrane potential (Figure 1.3). When the transmembrane potential reaches the threshold voltage, the appropriate channels are engaged and the cell is depolarized (since, as noted, the channels mediating depolarization are voltage dependent). Depolarization, in turn, stimulates nearby cells to depolarize, and the resultant spontaneously generated electrical impulse is then propagated across the heart. This phase 4 activity, which leads to spontaneous depolarization, is called automaticity.

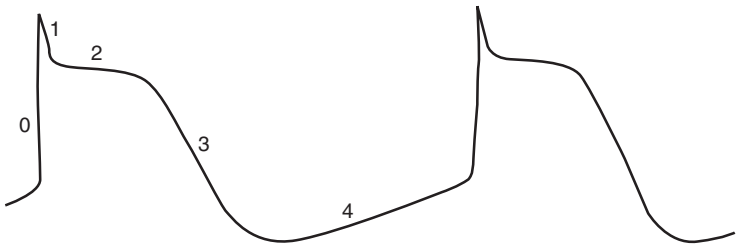


Figure 1.3 Automaticity. In some cardiac cells, leakage of ions across the cell membrane during phase 4 causes a gradual, positively directed change in the transmembrane voltage. When the transmembrane voltage becomes sufficiently positive, the appropriate channels are automatically activated to generate another action potential. Numbers on the curve indicate phases.

Automaticity is the mechanism by which the normal heart rhythm is generated. Cells in the SA node—the pacemaker of the heart—normally have the fastest phase 4 activity. If for any reason the automaticity of the SA node fails, secondary pacemaker cells (often located in the AV junction) usually take over the pacemaker function of the heart, but they do so at a slower rate because their phase 4 activity is slower.

Localized variations

Two localized differences in the heart's electrical system are important in understanding cardiac arrhythmias: differences in the action potential and differences in autonomic innervation.

Localized differences in the action potential

The cardiac action potential does not have the same shape in every cardiac cell. The action potential shown in Figure 1.2, for instance, represents a typical Purkinje fiber action potential. Figure 1.4 shows the differences in shape among representative action potentials from several key locations of the heart. The action potentials that differ most radically from the Purkinje fiber model are found in the SA node and the AV node. Notice the slow depolarization phases (phase 0) in these action potentials. Slow depolarization occurs

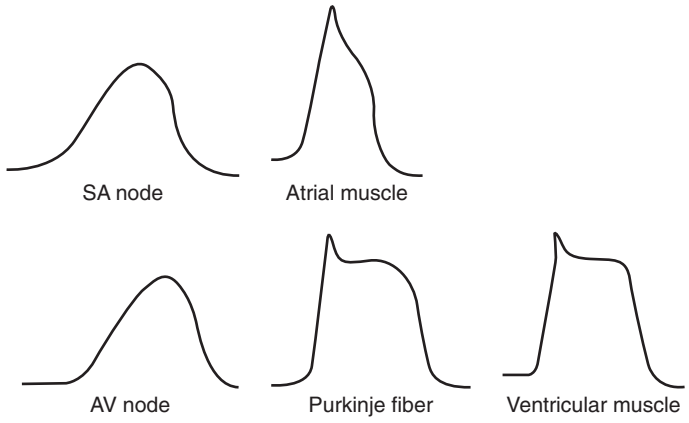


Figure 1.4 Localized differences in cardiac action potential. Action potentials generated in different areas of the heart have different shapes because different electrophysiologic properties (i.e., conduction velocity, refractoriness, and automaticity) are seen in various tissues within the heart.

because the SA nodal and AV nodal tissues lack active, rapid sodium channels and are thought to depend entirely on the slow calcium channel for depolarization. Because the speed of depolarization (the slope of phase 0) determines conduction velocity, the SA and AV nodes conduct electrical impulses slowly.

Localized differences in autonomic innervation

In general, an increase in sympathetic tone causes enhanced automaticity (pacemaker cells fire more rapidly), increased conduction velocity (electrical impulses spread more rapidly), and decreased refractory periods (cells are ready for repeated depolarizations more quickly). Parasympathetic tone has the opposite effect (depressed automaticity, decreased conduction velocity, and increased refractory periods).

Both sympathetic and parasympathetic fibers richly supply the SA and AV nodes. In the remainder of the heart's electrical system, although sympathetic innervation is reasonably abundant, parasympathetic innervation is sparse. Thus, changes in parasympathetic tone have a relatively greater effect on the SA nodal and AV nodal tissues than they do on other tissues of the heart.

Relationship between action potential and surface ECG

The cardiac action potential represents the electrical activity of a single cardiac cell. The surface ECG reflects the electrical activity of the entire heart. Essentially, the ECG represents the summation of all the action potentials of all the cardiac cells. Consequently, the information one gleans from the surface ECG derives from the characteristics of the action potential (Figure 1.5).

In most of the heart, the depolarization phase of a cell is essentially instantaneous (occurring in 1–3 ms), and occurs sequentially from cell to cell. Thus, the instantaneous wave of depolarization can be followed across the heart by studying the ECG. The P wave represents the depolarization front as it traverses the atria; the QRS complex represents the wave of depolarization as it spreads across the ventricles. Because depolarization is relatively instantaneous, the P wave and the QRS complex yield specific directional information. Changes in the spread of the electrical impulse, such as those that occur in bundle branch block or a transmural myocardial infarction, can be readily discerned.

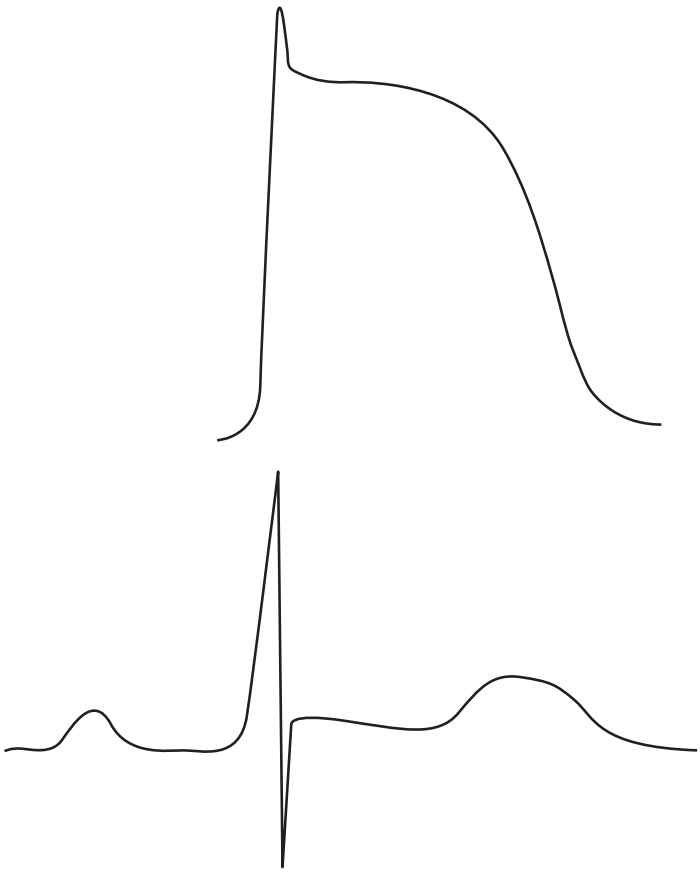


Figure 1.5 Relationship between the ventricular action potential (top) and the surface ECG (bottom). The rapid depolarization phase (phase 0) is reflected by the QRS complex on the ECG. Because phase 0 is almost instantaneous, the QRS complex yields directional information on ventricular depolarization. In contrast, the repolarization portion of the action potential (phases 1–3) has significant duration. Consequently, the portion of the surface ECG that reflects repolarization (the ST segment and the T wave) yields little directional information.

In contrast, the repolarization phase of the action potential is not instantaneous; indeed, repolarization has significant duration, lasting hundreds of times longer than depolarization. Thus, although depolarization occurs from cell to cell sequentially, repolarization of the cells overlaps; all the repolarizations can be thought of as

occurring simultaneously. For this reason, the ST segment and the T wave (the portions of the surface ECG that reflect ventricular repolarization) give very little directional information, and abnormalities in the ST segments and T waves are most often (and quite properly) interpreted as being nonspecific. The QT interval represents the time from the beginning of depolarization (the beginning of the QRS complex) to the end of repolarization (the end of the T wave) of the ventricular myocardium, and thus reflects the average action potential duration of ventricular muscle.

Mechanisms of cardiac tachyarrhythmias

Most rapid cardiac arrhythmias are thought to be due to one of two general mechanisms: abnormal automaticity or reentry. In recent years, however, a third general mechanism—the "channelopathy"—has been recognized as the cause of several relatively unusual varieties of cardiac arrhythmias.

Automaticity

As already noted, automaticity is an important feature of the normal electrical system; the pacemaker function of the heart depends upon it. Under some circumstances, however, abnormal automaticity can occur. When an abnormal acceleration of phase 4 activity occurs at some location within the heart, an automatic tachyarrhythmia is the result. Such an automatic focus can arise in the atria, the AV junction, or the ventricles and can lead to automatic atrial tachycardia, automatic junctional tachycardia, or automatic ventricular tachycardia.

Automatic tachyarrhythmias are not particularly common; they probably account for less than 10% of all tachyarrhythmias. Further, automatic tachyarrhythmias are usually recognizable by their characteristics and the clinical settings in which they occur. Consideration of some of the features of sinus tachycardia, which is the only normal variety of automatic tachycardia, may be helpful in this regard. Sinus tachycardia usually occurs as a result of appropriately increased sympathetic tone (e.g., in response to exercise). When sinus tachycardia develops, the heart rate gradually increases from the basic (resting) sinus rate; when sinus tachycardia subsides, the rate likewise decreases gradually.

Similarly, automatic tachyarrhythmias often display "warm-up" and "warm-down" in rate when the arrhythmia begins and ends.

Also, analogous to sinus tachycardia, automatic tachyarrhythmias often have metabolic causes, such as acute cardiac ischemia, hypoxemia, hypokalemia, hypomagnesemia, acid–base disturbances, high sympathetic tone, or the use of sympathomimetic agents. Therefore, automatic arrhythmias are frequently seen in acutely ill patients, usually in the intensive care unit (ICU) setting.

Common examples of automatic tachyarrhythmias are the multifocal atrial tachycardias (MATs) that accompany acute exacerbations of chronic pulmonary disease, many of the atrial and ventricular tachyarrhythmias seen during the induction of and recovery from general anesthesia (probably a result of surges in sympathetic tone), and the ventricular arrhythmias seen during the first minutes to hours of an acute myocardial infarction. (Enhanced automaticity in this situation is thought to be mediated by ischemia.)

Of all tachyarrhythmias, automatic arrhythmias are closest to resembling an "itch" of the heart. The balm of antiarrhythmic drugs is occasionally helpful, but the primary treatment of these arrhythmias should always be directed toward identifying and treating the underlying metabolic cause. In general, these "ICU arrhythmias" resolve once the patient's acute medical problems have been stabilized.

Reentry

The mechanism of reentry accounts for most clinically significant tachyarrhythmias. Recognition of this fact and of the fact that reentrant arrhythmias are amenable to study in the laboratory led to the widespread proliferation of electrophysiology laboratories in the 1980s.

The mechanism of reentry, although less intuitive than the mechanism of automaticity, can still be reduced to a few simple concepts. Reentry cannot occur unless certain underlying conditions exist (Figure 1.6). First, two roughly parallel conducting pathways must be connected proximally and distally by conducting tissue, thus forming a potential electrical circuit. Second, one pathway must have a longer refractory period than the other pathway. Third, the pathway with the shorter refractory period must conduct electrical impulses more slowly than does the opposite pathway.

If all these seemingly implausible conditions are met, reentry can be initiated by introducing an appropriately timed premature impulse to the circuit (Figure 1.7). The premature impulse must enter the circuit early enough that the pathway with the long refractory period is still refractory from the latest depolarization, but late

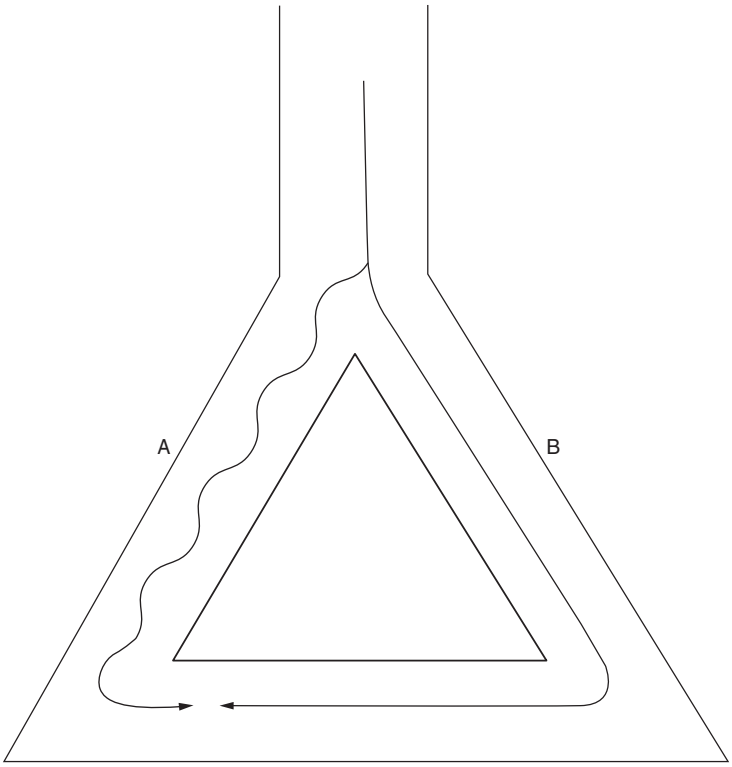


Figure 1.6 Prerequisites for reentry. An anatomic circuit must be present in which two portions of the circuit (pathways A and B) have electrophysiologic properties that differ from one another in a critical way. In this example, pathway A conducts electrical impulses more slowly than pathway B; pathway B has a longer refractory period than pathway A.

enough that the pathway with the shorter refractory period has recovered and is able to conduct the premature impulse. The impulse enters the pathway with the shorter refractory period but is conducted slowly because that pathway has the electrophysiologic property of slow conduction. By the time the impulse reaches the long-refractory-period pathway from below, that pathway has had time to recover and is able to conduct the impulse in the retrograde direction. If the retrograde impulse now reenters the first pathway and is conducted antegradely (as is likely because of the short refractory period of the first pathway), a continuously circulating impulse is established, which rotates around and around the reentrant

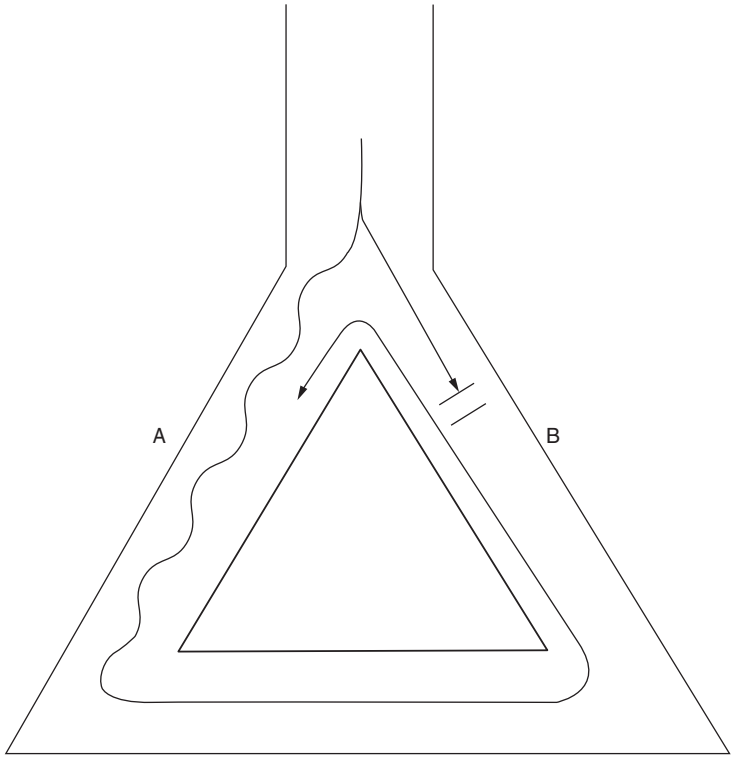


Figure 1.7 Initiation of reentry. If the prerequisites described in Figure 1.6 are present, an appropriately timed, premature electrical impulse can block in pathway A (which has a relatively long refractory period) while conducting down pathway A. Because conduction down pathway A is slow, pathway B has time to recover, allowing the impulse to conduct retrogradely up pathway B. The impulse can then reenter pathway A. A continuously circulating impulse is thus established.

circuit. All that is necessary for the reentrant impulse to usurp the rhythm of the heart is for the impulse to exit from the circuit at some point during each lap and thereby depolarize the remaining myocardium outside the circuit.

Because reentry depends on critical differences in the conduction velocities and refractory periods among the various pathways of the circuit, and because conduction velocities and refractory periods, as we have seen, are determined by the shape of the action potential, the action potentials of the two pathways in any reentrant circuit

must be different from one another. Thus, drugs that change the shape of the action potential might be useful in the treatment of reentrant arrhythmias.

Reentrant circuits, while always abnormal, occur with some frequency in the human heart. Some reentrant circuits are present at birth, notably those causing supraventricular tachycardias (e.g., reentry associated with AV bypass tracts and with dual AV nodal tracts). However, reentrant circuits that cause ventricular tachycardias are almost never congenital, but come into existence as cardiac disease develops during life. In the ventricles, reentrant circuits arise in areas in which normal cardiac tissue becomes interspersed with patches of fibrous (scar) tissue, thus forming potential anatomic circuits. Thus, ventricular reentrant circuits usually occur only when fibrosis develops in the ventricles, such as after a myocardial infarction or with cardiomyopathic diseases.

Theoretically, if all anatomic and electrophysiologic criteria for reentry are present, any impulse that enters the circuit at the appropriate instant in time induces a reentrant tachycardia. The time from the end of the refractory period of the shorter-refractory-period pathway to the end of the refractory period of the pathway with a longer refractory time, during which reentry can be induced, is called the *tachycardia zone*. Treating reentrant arrhythmias often involves trying to narrow or abolish the tachycardia zone with antiarrhythmic drugs (by using a drug that, one hopes, might increase the refractory period of the shorter-refractory-period pathway, or decrease the refractory period of the longer-refractory-period pathway).

Because reentrant arrhythmias can be reproducibly induced (and terminated) by appropriately timed impulses, these arrhythmias are ideal for study in the electrophysiology laboratory. In many instances (very commonly with supraventricular arrhythmias, but only occasionally with ventricular arrhythmias), the pathways involved in the reentrant circuit can be precisely mapped, the effect of various therapies can be assessed, and critical portions of the circuit can even be ablated through the electrode catheter.

The channelopathies

In recent years, some varieties of tachyarrhythmias have been attributed to genetic abnormalities in the channels that mediate ionic fluxes across the cardiac cell membrane. Such "channelopathies"—abnormally functioning channels due to inheritable mutations—can affect any electrically active cell and are not limited to the heart. For

instance, some varieties of migraine, epilepsy, periodic paralysis, and muscle disorders are apparently due to channelopathies.

While several distinctive cardiac arrhythmias are now thought to be caused by channelopathies, the most clinically relevant and the most common channelopathic arrhythmias are those related to triggered activity.

Triggered activity

Triggered activity is caused by abnormal fluxes of positive ions into cardiac cells. These ionic fluxes produce an abnormal "bump" in the action potential during late phase 3 or early phase 4 (Figure 1.8). The bump is called an afterdepolarization. In most if not all cases, afterdepolarizations are thought to be due to inherited abnormalities in the channels that control the movement of calcium ions across the cell membrane. If the afterdepolarizations are of sufficient amplitude, they can trigger the rapid sodium channels (which, as noted, are voltage dependent), and thus cause another action potential to be generated.

Digitalis-toxic arrhythmias, torsades de pointes, and some of the rare ventricular tachycardias that respond to calcium-blocking agents have all been advanced as arrhythmias that are most likely caused by triggered activity.

Clinical features of the major tachyarrhythmias

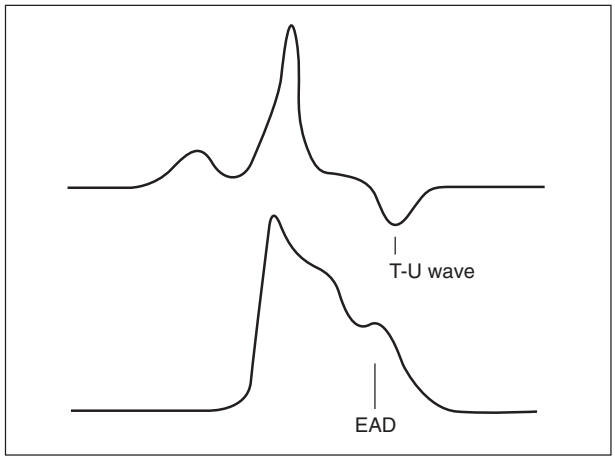
Before considering how antiarrhythmic drugs work, it will be helpful to review the salient clinical features of the major cardiac tachyarrhythmias.

Supraventricular tachyarrhythmias

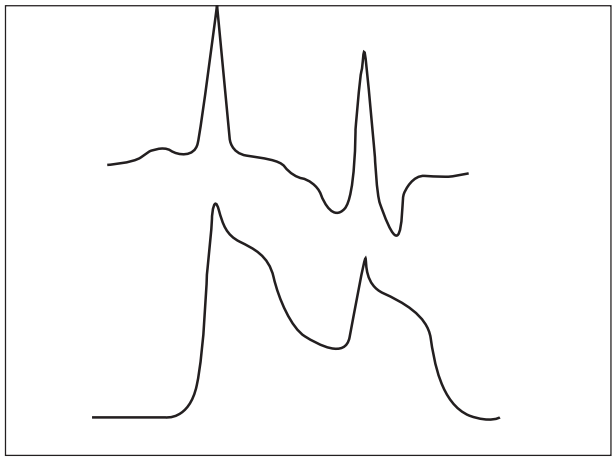
Table 1.1 classifies the supraventricular tachyarrhythmias according to mechanism.

Automatic supraventricular tachyarrhythmias

Automatic supraventricular arrhythmias are seen almost exclusively in acutely ill patients, most of whom have one of the following conditions: myocardial ischemia, acute exacerbations of chronic lung disease, acute alcohol toxicity, or major electrolyte disturbances. Any of these disorders can produce ectopic automatic foci in the atrial myocardium.



(a)



(b)

Figure 1.8 Triggered activity. Both panels show a surface ECG (top) and a simultaneous ventricular action potential (bottom). (a) Phase 3 of the action potential is interrupted by a "bump"—an EAD. The EAD is reflected on the surface ECG by a prolonged and distorted T wave (T-U wave). (b) The EAD is of sufficient amplitude to engage the rapid sodium channel and generate another action potential. The resultant premature complex is seen on surface ECG. Note that just as the premature action potential is coincident with the EAD (since it is generated by the EAD), the premature ventricular complex is also coincident with the T-U wave of the previous complex.

Table 1.1 Classification of supraventricular tachyarrhythmias

Automatic arrhythmias
Some atrial tachycardias associated with acute medical conditions
Some multifocal atrial tachycardias
Reentrant arrhythmias
SA nodal reentrant tachycardia
Intra-atrial reentrant tachycardia
Atrial flutter and atrial fibrillation
AV nodal reentrant tachycardia
Macroreentrant (bypass-mediated) reentrant tachycardia
Triggered arrhythmias (probable mechanism)
Digitalis-toxic atrial tachycardia
Some multifocal atrial tachycardias

SA, sinoatrial; AV, atrioventricular.

Clinically, the heart rate with automatic atrial tachycardias is usually less than 200 beats/min. Like all automatic rhythms, the onset and offset are usually relatively gradual; that is, they often display warm-up, in which the heart rate accelerates over several cardiac cycles. Each QRS complex is preceded by a discrete P wave, whose shape generally differs from the normal sinus P wave, depending on the location of the automatic focus within the atrium. Likewise, the PR interval is often shorter than it is during sinus rhythm, since the ectopic focus may be relatively close to the AV node. Because automatic atrial tachycardias arise in and are localized to the atrial myocardium (and thus the arrhythmia itself is not dependent on the AV node), if AV block is produced, atrial arrhythmia itself is unaffected.

MAT (Figure 1.9) is the most common form of automatic atrial tachycardia. It is characterized by multiple (usually at least three) P-wave morphologies and irregular PR intervals. MAT is thought to be caused by the presence of several automatic foci within the atria, firing at different rates. The arrhythmia is usually associated with exacerbation of chronic lung disease, especially in patients receiving theophylline.

Pharmacologic therapy is usually not very helpful in treating automatic atrial tachycardia, though drugs that affect the AV node can

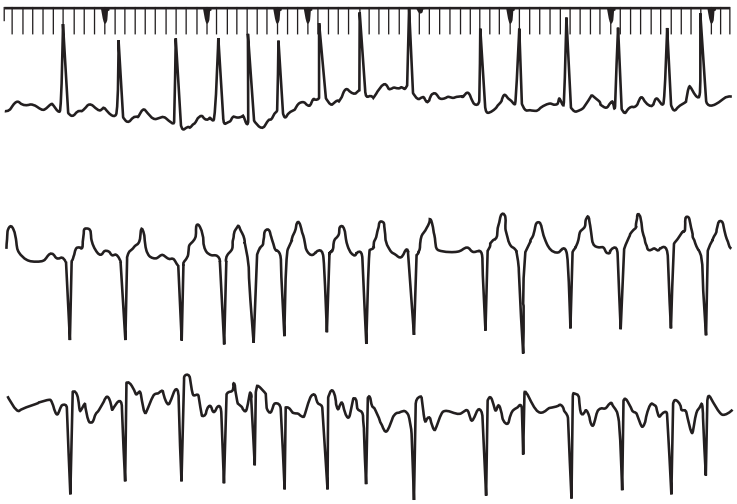


Figure 1.9 MAT is an irregular atrial tachyarrhythmia that superficially resembles atrial fibrillation. However, in MAT (in contrast to atrial fibrillation), each QRS complex is preceded by a discrete P wave. Further, at least three distinct P-wave morphologies are present, which reflects the multifocal origin of atrial activity in this arrhythmia.

sometimes slow the ventricular rate by creating second-degree block. The basic strategy for treating automatic atrial arrhythmias is to aggressively treat the underlying illness.

Reentrant supraventricular tachyarrhythmias

In general, patients have reentrant supraventricular tachyarrhythmias because they are born with abnormal electrical pathways that create potential reentrant circuits. Accordingly (in contrast to patients with automatic supraventricular arrhythmias), these patients most often initially experience symptoms when they are young and healthy. Most supraventricular tachyarrhythmias seen in otherwise healthy patients are caused by the mechanism of reentry.

The five general categories of reentrant supraventricular arrhythmias are listed in Table 1.1. Many clinicians lump these arrhythmias together (except for atrial fibrillation and atrial flutter, which generally are easily distinguishable) as paroxysmal atrial tachycardia (PAT). In most instances, an astute clinician can tell which specific

category of PAT he or she is dealing with (and therefore can institute appropriate therapy) merely by carefully examining a 12-lead ECG of the arrhythmia.

AV nodal reentrant tachycardia

AV nodal reentrant tachycardia is the most common type of PAT, accounting for nearly 60% of regular supraventricular tachyarrhythmias. In AV nodal reentry, the reentrant circuit can be visualized as being enclosed entirely within an AV node that is functionally divided into two separate pathways (Figure 1.10). The dual pathways form the reentrant circuit responsible for the arrhythmia. Because

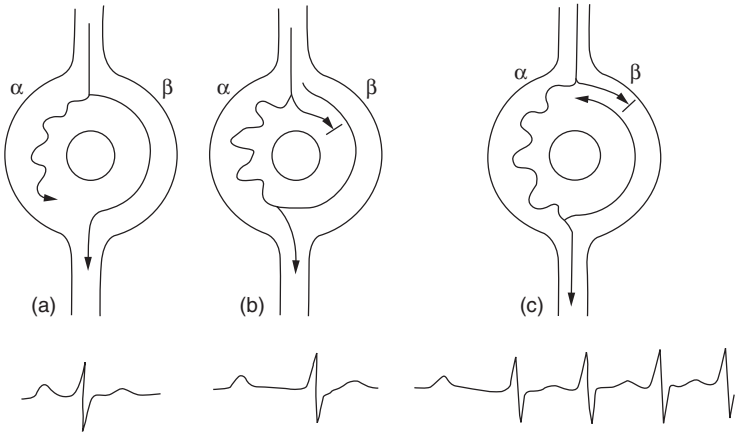


Figure 1.10 AV nodal reentrant tachycardia. (a) In patients with AV nodal reentry, the AV node is functionally divided into two separate pathways (alpha (α) and beta (β) pathways). Similar to the example shown in Figures 1.6 and 1.7, the alpha pathway conducts more slowly than the beta pathway, and the beta pathway has a longer refractory period than the alpha pathway. Since the beta pathway conducts more rapidly than does the alpha pathway, a normal atrial impulse reaches the ventricles via the beta pathway. (b) A premature atrial impulse can find the beta pathway still refractory at a time when the alpha pathway is not refractory. Because conduction down the alpha pathway is slow, the resultant PR interval is prolonged. (c) If conditions are right, a premature impulse can block in the beta pathway and conduct down the alpha pathway (as in (b)), then travel retrograde up the beta pathway and reenter the alpha pathway in the antegrade direction. AV nodal reentrant tachycardia results when such a circuitous impulse is established within the AV node.

the reentrant circuit is within the AV node, the pharmacologic treatment of AV nodal reentry usually involves giving drugs that act upon the AV node.

Bypass-tract-mediated macroreentrant tachycardia

Tachycardia mediated by AV bypass tracts (also called accessory pathways) is the next most common type of reentrant supraventricular tachycardia and accounts for approximately 30% of arrhythmias presenting as PAT. Most patients with such bypass tracts do not have overt Wolff-Parkinson–White syndrome, however. Instead, they have *concealed* bypass tracts, that is, bypass tracts that are incapable of conducting in the antegrade direction (from the atrium to the ventricles), and therefore never display delta waves. Concealed bypass tracts are able to conduct electrical impulses only in the retrograde direction (from the ventricles to the atrium).

The reentrant circuit responsible for these tachycardias is formed by the bypass tract (which almost always constitutes the retrograde pathway), and the normal AV nodal conducting system (the antegrade pathway), connected by the atrial and ventricular myocardium (Figure 1.11). Because the reentrant circuit is large (involving the AV node, the His-Purkinje system, the ventricular myocardium, the bypass tract, and the atrial myocardium), it is termed a *macroreentrant circuit*. Also, because the circuit consists of several types of tissue, it can be attacked on many levels by many different kinds of drugs—drugs that affect the AV node, the bypass tract, the ventricular myocardium, or the atrial myocardium.

Intra-atrial reentry

Intra-atrial reentry accounts for only a small percentage of arrhythmias presenting as PAT. The reentrant circuit in intra-atrial reentry resides entirely within the atrial myocardium and does not involve the AV conducting system (Figure 1.12). Intra-atrial reentry resembles automatic atrial tachycardia because discrete (most often atypical) P waves precede each QRS complex, and AV block can occur without affecting the arrhythmia itself. Intra-atrial reentry differs from automatic tachycardia because of its sudden onset and termination, and, like all reentrant arrhythmias, it can be induced by pacing. Intra-atrial reentry is affected only by drugs that affect the atrial myocardium.

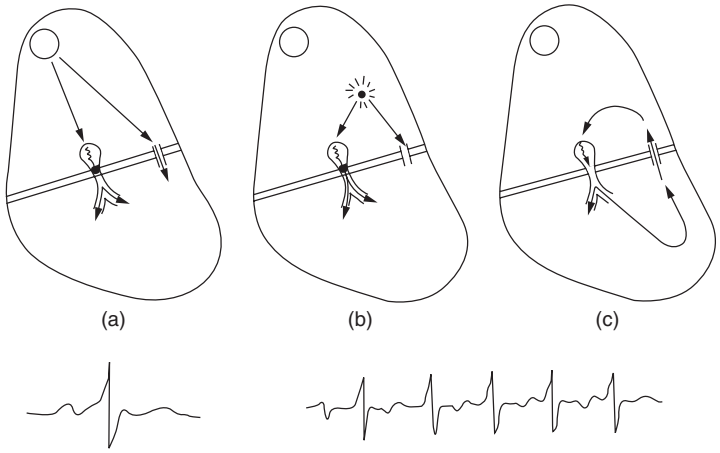


Figure 1.11 Bypass-tract-mediated macroreentrant tachycardia. (a) Because a bypass tract is present, a normal sinus beat is transmitted to the ventricles via two separate pathways. Because the ventricle is partially preexcited (i.e., some ventricular myocardium is depolarized early via the bypass tract), the QRS complex displays a delta wave. A bypass tract usually has a longer refractory period than the normal conducting system, and the normal conducting system includes the slow-conducting AV node and conducts electrical impulses more slowly than the bypass tract. Thus, the substrate for reentry is present. (b) A premature atrial complex occurs during the refractory period of the bypass tract and is therefore conducted solely via the normal conducting system. The resultant QRS complex displays no delta wave. (c) Because conduction via the normal conducting system is relatively slow, the bypass tract may no longer be refractory by the time the impulse reaches the ventricles. Thus, the bypass tract may be able to conduct the impulse retrogradely back to the atrium. If so, a reentrant impulse may be established, which travels antegradely down the normal conducting system and retrogradely up the bypass tract. The result is a large (macro) reentrant circuit.

Atrial flutter and atrial fibrillation

Atrial flutter and atrial fibrillation are special forms of intra-atrial reentrant tachycardias and are generally distinguishable quite readily from other kinds of atrial tachyarrhythmias (commonly labeled PAT) by reviewing a 12-lead ECG.

In atrial flutter, the atrial activity is regular, in excess of 220 beats/min, and usually displays a typical sawtooth pattern (Figure 1.13). Atrial flutter is almost always accompanied by AV block, most often in a 2:1 pattern.

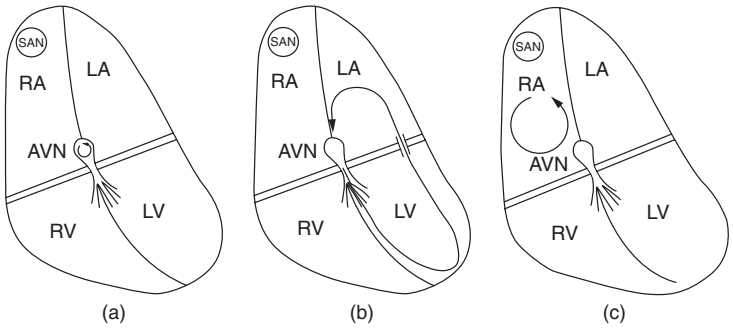


Figure 1.12 The components of the reentrant circuit determine which antiarrhythmic drugs are likely to be effective in treating supraventricular tachycardia. Both AV nodal reentry (a) and macroreentry (b) include the AV node within the reentrant circuit. Therefore, drugs that affect the AV node affect the reentrant circuit itself and may be useful in terminating or preventing the arrhythmia. In contrast, in intra-atrial reentry (c), the reentrant circuit does not include the AV node. Drugs that affect the AV node generally do not affect intra-atrial reentry itself, although they may be effective in slowing the ventricular response during the arrhythmia. Atrial fibrillation, atrial flutter, and automatic atrial tachycardia are similar to intra-atrial reentry in that the AV node is not required for initiating or sustaining these arrhythmias. AVN, atrioventricular node; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; SAN, sinoatrial node.

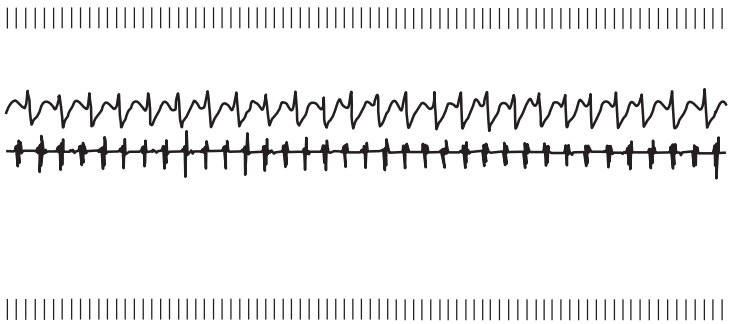


Figure 1.13 Atrial flutter. A surface ECG (top) and an intracardiac electrogram that directly records intra-atrial electrical activity (bottom) are shown. Note the two atrial impulses (seen on the intracardiac electrogram) for every QRS complex; AV block occurs in a typical 2:1 pattern.

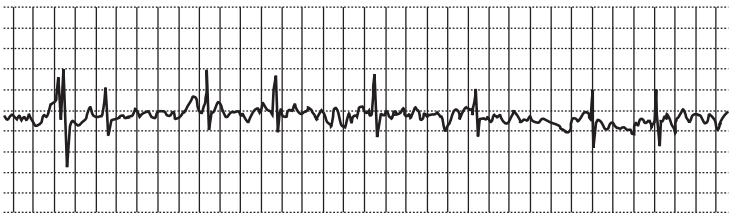


Figure 1.14 Atrial fibrillation. Note the randomly irregular ventricular response and the absence of discrete P waves.

In atrial fibrillation, the atrial activity is continuous and chaotic, and discrete P waves cannot be distinguished (Figure 1.14). The ventricular response is completely irregular, reflecting the chaotic nature of the atrial activity.

Since atrial fibrillation and atrial flutter are intra-atrial arrhythmias, AV block (which occurs in almost every case) does not affect the arrhythmia itself. Drug therapy is usually aimed at converting the arrhythmia by use of drugs that affect the atrial myocardium or at controlling the ventricular response with drugs that affect AV conduction.

SA nodal reentry

SA nodal reentry is a relatively uncommon arrhythmia in which the reentrant circuit is thought to be enclosed entirely within the SA node (i.e., dual SA nodal pathways are thought to exist, similar to those seen in AV nodal reentry). Discrete P waves identical to sinus P waves precede each QRS complex. SA nodal reentry is distinguishable from normal sinus tachycardia (which is automatic in mechanism) by its sudden onset and offset, and by the fact that it is inducible with pacing. It is affected by drugs that affect the SA and AV nodes.

Triggered supraventricular tachyarrhythmias

The only supraventricular tachycardia commonly attributed to triggered activity is that seen with digitalis toxicity. Digitalis toxicity can produce delayed afterdepolarizations (DADs; see Figure 1.16a) that can lead to atrial tachycardias. Clinically, since digitalis toxicity also produces AV block, digitalis-toxic arrhythmias often manifest as atrial tachycardia with block. In fact, the presence of atrial

tachycardia with block should always make one consider the possibility of digitalis toxicity.

Electrocardiographic patterns of supraventricular tachyarrhythmias

Often it is possible to specifically diagnose a patient's supraventricular arrhythmia by examining a 12-lead ECG. Atrial flutter and atrial fibrillation can usually be distinguished by simple inspection. In the supraventricular tachycardias commonly labeled as PAT (i.e., regular, narrow-complex tachycardias), both the relationship of the P waves to the QRS complexes and the morphology of the P waves during the tachycardia can be very helpful. Figure 1.15 shows the essential electrocardiographic characteristics of the four types of PAT.

Ventricular tachyarrhythmias

Table 1.2 classifies the ventricular tachyarrhythmias according to mechanism.

Automatic ventricular tachyarrhythmias

Abnormal automaticity accounts for a relatively small proportion of ventricular tachyarrhythmias. As is the case with automatic atrial arrhythmias, automatic ventricular arrhythmias are usually associated with acute medical conditions, such as myocardial ischemia, acid–base disturbances, electrolyte abnormalities, and high adrenergic tone. Automatic ventricular arrhythmias are most often seen in patients with acute myocardial ischemia or infarction, or some other acute medical illness. Most arrhythmias occurring within the first few hours of an acute myocardial infarction are thought to be automatic. Once the ischemic tissue dies or stabilizes, however, the substrate for automaticity is no longer present.

In general, the treatment of automatic ventricular arrhythmias consists of treating the underlying illness. Antiarrhythmic drugs are occasionally beneficial.

Reentrant ventricular tachyarrhythmias

Most ventricular arrhythmias are reentrant in mechanism. While the conditions producing automatic ventricular arrhythmias are usually temporary in nature (e.g., cardiac ischemia), the substrate necessary for producing reentrant ventricular arrhythmias, once present, tends to be permanent.

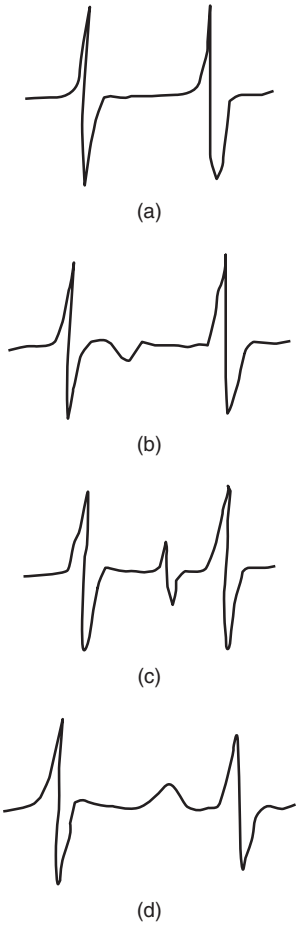


Figure 1.15 Typical P-wave relationships in four kinds of PAT. Surface ECG lead II is depicted. (a) In AV nodal reentrant tachycardia, the P wave is usually buried within the QRS complex and is most often not discernible even with careful study of all 12-lead ECG. (b) In bypass-tract-mediated macroreentrant tachycardia, the inferior ECG leads usually show a negative P wave. (It has a superior axis because the atria are activated in the retrograde direction.) Also, the P wave is usually closer to the preceding QRS complex than to the following QRS complex. (c) In intra-atrial reentry, discrete P waves almost always are seen before each QRS complex. Because the intra-atrial reentrant circuit can be located anywhere within the atria, the P-wave morphology can have any configuration. The PR interval is usually normal or short. (d) In SA nodal reentry, P waves and the PR interval appear normal.

Table 1.2 Classification of ventricular tachyarrhythmias

Automatic arrhythmias
Some ventricular tachycardias associated with acute medical conditions
Acute myocardial infarction or ischemia
Electrolyte and acid–base disturbances or hypoxia
High sympathetic tone
Reentrant arrhythmias
Ventricular tachycardia and fibrillation associated with some chronic heart diseases
Previous myocardial infarction
Dilated cardiomyopathy
Hypertrophic cardiomyopathy
Channelopathies
Triggered arrhythmias (probable mechanism)
Pause-dependent torsades de pointes (EADs) associated with drugs that prolong QT interval
Catechol-dependent torsades de pointes (DADs) associated with digitalis toxicity or idiopathy
Brugada syndrome and SUNDS

EADs, early afterdepolarizations; DADs, delayed afterdepolarizations; SUNDS, sudden unexpected nocturnal death syndrome.

Reentrant circuits within the ventricular myocardium usually arise after scar tissue develops, a condition most commonly seen in patients who have myocardial infarctions or cardiomyopathy. Once the scar tissue gives rise to a reentrant circuit, the circuit persists, and the potential for a ventricular arrhythmia always exists. Thus, the "late" sudden deaths that occur after a myocardial infarction (i.e., from about 12 h to several years after the acute event) are usually a result of reentrant arrhythmias. Reentrant ventricular arrhythmias are seen only rarely in individuals who have normal ventricles.

Most antiarrhythmic drugs affect the ventricular myocardium and, accordingly, most are used to treat ventricular tachyarrhythmias.

Channelopathic ventricular tachyarrhythmias

Channelopathies probably account for several distinctive types of ventricular tachyarrhythmias, at least two of which have now been

well characterized. These are the ventricular arrhythmias due to triggered activity and Brugada syndrome.

Triggered activity in the ventricles

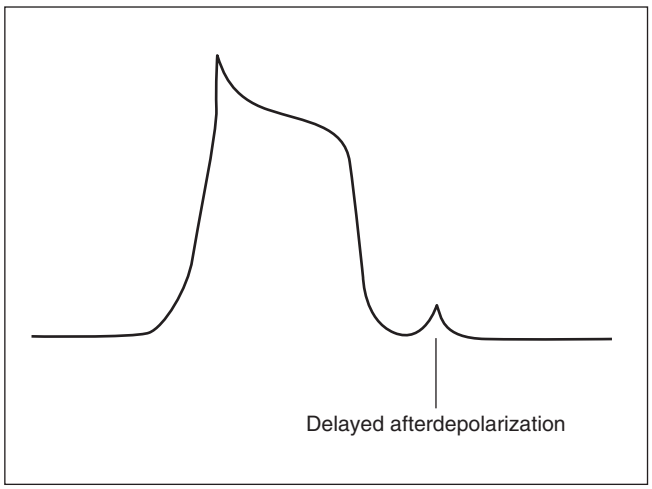
Because ventricular tachyarrhythmias due to triggered activity are reasonably common, and because the management of triggered ventricular arrhythmias is very different from the management of more typical ventricular arrhythmias, it is important to recognize their characteristics. Two fairly distinct clinical syndromes are caused by ventricular triggered activity: catechol-dependent arrhythmias and pause-dependent arrhythmias. In each syndrome, the resultant ventricular arrhythmias are similar. They are the classically polymorphic ventricular tachyarrhythmias generally referred to as *torsades de pointes*.

Catechol-dependent triggered arrhythmias. Catechol-dependent triggered arrhythmias are caused by DADs, which occur during phase 4 of the action potential (Figure 1.16a). DADs are seen in susceptible patients in the setting of digitalis intoxication and cardiac ischemia. They are also seen in certain patients who have a congenital form of QT prolongation associated with what is thought to be an imbalance in the sympathetic innervation of the heart, with predominant input coming from the left stellate ganglia—stimulation of which can reproduce DADs.

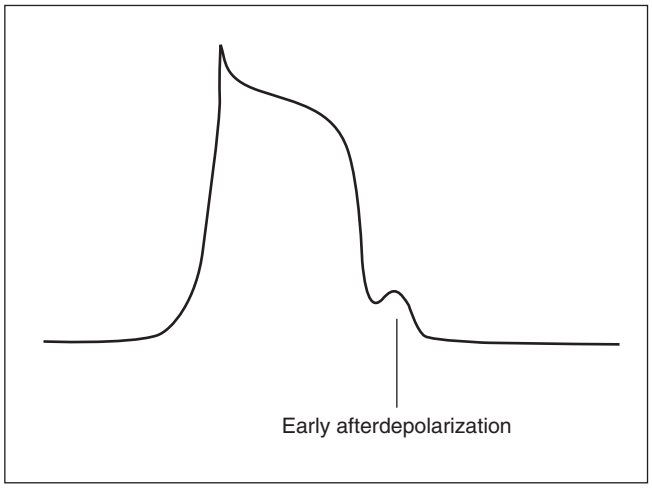
The ventricular arrhythmias caused by DADs typically are polymorphic, and are seen in conditions of high sympathetic tone. Patients with catechol-dependent triggered activity therefore experience arrhythmias (often manifested by syncope or cardiac arrest) in times of severe emotional stress or during exercise. Often they have normal ECGs at rest but will develop QT abnormalities during exercise. The onset of the arrhythmia is not associated with a pause.

Left stellate sympathectomy has eliminated arrhythmias in some of these patients. Medical treatment has generally consisted of beta blockers and calcium-channel blockers (consistent with the fact that DADs are thought to be mediated by abnormalities in the calcium channels). Many of these patients, however, end up receiving implantable defibrillators.

Pause-dependent triggered arrhythmias. Pause-dependent triggered arrhythmias are caused by afterdepolarizations that occur during



(a)



(b)

Figure 1.16 Early and delayed afterdepolarizations. (a) DADs of the type thought to be responsible for catechol-dependent triggered arrhythmias. The DAD occurs during phase 4 of the action potential. (b) EAD of the type thought to be responsible for pause-dependent triggered arrhythmias. The EAD occurs during phase 3 of the action potential.

phase 3 of the action potential; hence, they are called early afterdepolarizations (EADs; see Figure 1.16b). If the EAD reaches the threshold potential of the cardiac cell, another action potential is generated and an arrhythmia occurs. EADs are generally seen only under circumstances that prolong the duration of the action potential, such as electrolyte abnormalities (hypokalemia and hypomagnesemia), and with the use of certain drugs that cause widening of the action potential, predominantly antiarrhythmic drugs (Table 1.3).

Table 1.3 Drugs that can cause torsades de pointes

Class I and Class III antiarrhythmic drugs
Quinidine
Procainamide
Disopyramide
Propafenone
Sotalol
Amiodarone
Bretylium
Ibutilide
Tricyclic and tetracyclic antidepressants
Amitriptyline
Imipramine
Doxepin
Maprotiline
Phenothiazines
Thioridazine
Chlorpromazine
Antibiotics
Erythromycin
Trimethoprim-sulfamethoxazole
Others
Bepridil
Lidoflazine
Probucol
Haloperidol
Chloral hydrate

It appears that some finite subset of the apparently normal population is susceptible to developing EADs. These patients, from available evidence, have one of several channelopathies that become clinically manifest only when their action potential durations are increased by drugs or electrolyte abnormalities.

The ventricular arrhythmias associated with EADs are typically polymorphic, and most often occur repeatedly and in short bursts, although prolonged arrhythmic episodes, leading to syncope or sudden death, can occur. The repolarization abnormalities responsible for these arrhythmias (i.e., the afterdepolarizations) are reflected on the surface ECG, where the T-wave configuration is often distorted and a U wave is present. The U wave is the ECG manifestation of the EAD itself. The T-U abnormalities tend to be dynamic; that is, they wax and wane from beat to beat, mainly depending on beat-to-beat variations in heart rate. The slower the heart rate, the more exaggerated the T-U abnormality; hence, this condition is said to be pause dependent. Once a burst of ventricular tachycardia is generated (triggered by an EAD that is of sufficient amplitude to reach the threshold potential), it tends to be repeated in a pattern of "ventricular tachycardia bigeminy." An example is shown in Figure 1.17. In this figure, each burst of polymorphic ventricular tachycardia causes a compensatory pause, and the pause causes the ensuing normal beat to be associated with pronounced U-wave abnormalities (i.e., a large EAD). The large EAD, in turn, produces another burst of tachycardia. Pause-dependent triggered activity should be strongly suspected whenever this ECG pattern is seen, especially in the setting of overt QT prolongation or in the setting of conditions that predispose to QT prolongation.

The acute treatment of pause-dependent triggered activity consists of attempting to reduce the duration of the action potential, to eliminate the pauses, or both. Drugs that prolong the QT interval should be immediately discontinued and avoided. Electrolyte abnormalities should be corrected quickly. Intravenous magnesium often ameliorates the arrhythmias even when serum magnesium levels are in the normal range. The mainstay of emergent treatment of the arrhythmias, however, is to eliminate the pauses that trigger the arrhythmias—that is, to increase the heart rate. This is most often accomplished by pacing the atrium or the ventricles (usually, at rates of 100–120 beats/min) or, occasionally, by using an isoproterenol infusion.

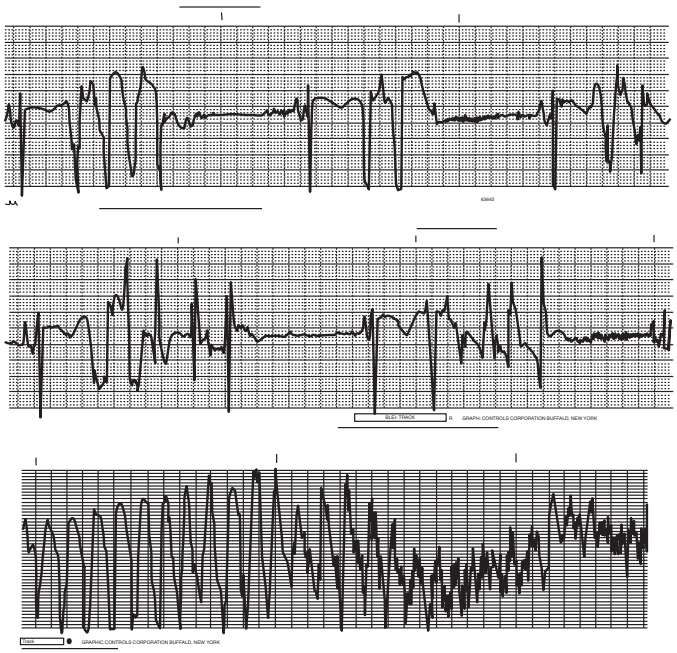


Figure 1.17 Pause-dependent triggered arrhythmias. The figure depicts rhythm strips from a patient who developed torsades de pointes after receiving a Class IA antiarrhythmic agent. The top two strips show the typical pattern—each burst of polymorphic ventricular tachycardia is followed by a compensatory pause; the pause, in turn, causes the ensuing sinus beat to be followed by another burst of ventricular tachycardia. The bottom strip shows the sustained polymorphic ventricular tachycardia that followed after several minutes of ventricular tachycardia bigeminy. Note the broad T-U wave that follows each sinus beat in the top two strips. The T-U wave is thought to reflect the pause-dependent EADs that are probably responsible for the arrhythmia.

Once the underlying cause for the EADs has been reversed, chronic treatment focuses on avoiding conditions that prolong action potential duration.

Brugada syndrome

Brugada syndrome is characterized by ventricular tachyarrhythmias (often causing syncope or cardiac arrest, and often occurring during sleep) in the setting of an underlying characteristic ECG pattern

consisting of unusual, nonishchemic ST-segment elevations in leads V1–V3 and "pseudo" right bundle branch block. Brugada syndrome is usually seen in males and is probably the same disorder as the sudden unexpected nocturnal death syndrome seen in Asian males.

Patients with Brugada syndrome have genetic abnormalities in the rapid sodium channel. Several varieties of sodium channelopathies have been identified, probably accounting for the several clinical varieties seen with Brugada syndrome. For instance, in some patients, the characteristic ECG changes are not seen unless a Class I antiarrhythmic drug (i.e., a drug that operates on the sodium channel) is administered. The implantable defibrillator is the mainstay of therapy for patients with Brugada syndrome.

Table 1.4 Clinical features of uncommon ventricular tachycardias

Idiopathic left ventricular tachycardia
Younger patients, no structural heart disease
Inducible VT with RBBB, superior axis morphology
Responds to beta blockers and calcium-channel blockers
Both reentry and triggered activity have been postulated as mechanisms
Right ventricular outflow tract tachycardia (repetitive monomorphic VT)
Younger patients, no structural heart disease
VT originates in RV outflow tract; has LBBB, inferior axis morphology; often not inducible during EP testing
Responds to beta blockers, calcium blockers, and transcatheter RF ablation
Postulated to be due to automaticity or triggered automaticity
Ventricular tachycardia associated with right ventricular dysplasia
Younger patients with RV dysplasia (portions of RV replaced by fibrous tissue)
LBBB ventricular tachycardia; almost always inducible during EP testing
Treatment similar to treatment of reentrant VT in setting of coronary artery disease
Bundle branch reentry
Patients with dilated cardiomyopathy and intraventricular conduction abnormality
Rapid VT with LBBB morphology; reentrant circuit uses RBB in downward direction and LBB in upward direction
Can be cured by RF ablation of RBB

EP, electrophysiologic; LBB, left bundle branch; LBBB, left bundle branch block; RBB, right bundle branch; RBBB, right bundle branch block; RV, right ventricle; VT, ventricular tachycardia.

Miscellaneous ventricular arrhythmias

Several clinical syndromes have been described involving unusual ventricular arrhythmias that do not fit clearly into any of these categories. Nomenclature for these arrhythmias is unsettled in the literature, reflecting the lack of understanding of their mechanisms. Table 1.4 lists the salient features of relatively uncommon ventricular arrhythmias. It is likely that at least some of these will eventually prove to be due to channelopathies. They are discussed in more detail in Chapter 12.