CHAPTER 19

The Arrhythmias

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KEY CONCEPTS

1. The use of antiarrhythmic drugs in the United States has declined because of major trials that show increased mortality with their use in several clinical situations, the realization of proarrhythmia as a significant side effect and the advancing technology of nondrug therapies such as ablation and the implantable cardioverter-defibrillator (ICD).
2. Antiarrhythmic drugs frequently cause side effects and are complex in their pharmacokinetic characteristics. The therapeutic range of these agents provide only a rough guide to modifying treatment; it is preferable to attempt to define an individual's effective (or target) concentration and match that during long-term therapy.
3. The most commonly prescribed antiarrhythmic drug is now amiodarone. This agent is effective in terminating and preventing a wide variety of symptomatic supraventricular and ventricular tachycardias. However, because this antiarrhythmic drug is plagued by frequent side effects, it requires close monitoring. The most concerning toxicity is pulmonary fibrosis; side-effect profiles of the intravenous (IV) (acute, short-term) and oral (chronic, long-term) forms differ substantially.
4. In patients with atrial fibrillation (AF), therapy is traditionally aimed at controlling ventricular response (digoxin, nondihydropyridine calcium channel blockers [CCBs], β-blockers), preventing thromboembolic complications (warfarin, aspirin), and restoring and maintaining sinus rhythm (antiarrhythmic drugs, direct-current cardioversion [DCC]). Studies show there is no need to aggressively pursue strategies to maintain sinus rhythm (i.e., long-term antiarrhythmic drugs); rate control alone (leaving the patient in AF) is often sufficient in patients who can tolerate it. Nonetheless, it is not uncommon for patients to have remaining troublesome symptoms with the rate-control strategy alone, necessitating oral antiarrhythmic drug therapy.
5. Paroxysmal supraventricular tachycardia (PSVT) is usually a result of reentry in or proximal to the atrioventricular (AV) node or AV reentry incorporating an extranodal pathway; common tachycardias can be terminated acutely with AV nodal-blocking agents such as adenosine, and recurrences can be prevented by ablation with radiofrequency current.
6. Patients with Wolff-Parkinson-White (WPW) Syndrome may have several different tachycardias that are acutely treated by different strategies: orthodromic reentry (adenosine), antidromic reentry (adenosine or procainamide), and AF (procainamide or amiodarone). Atrioventricular nodal-blocking drugs are contraindicated in patients with WPW and AF.
7. Because of the results of the Cardiac Arrhythmia Suppression Trial (CAST) and other trials, antiarrhythmic drugs (with the exception of β-blockers) should not be routinely used in patients with prior myocardial infarction (MI) or left ventricular (LV) dysfunction and minor ventricular rhythm disturbances (e.g., premature ventricular complexes [PVCs]).
8. Patients with hemodynamically significant ventricular tachycardia (VT) or ventricular fibrillation (VF) not associated with an acute MI who are successfully resuscitated (electrical cardioversion, vasopressors, amiodarone) are at high risk for sudden cardiac death (SCD) and should receive an ICD ("secondary prevention").
9. Implantation of an ICD should be considered for the primary prevention of SCD in certain high-risk patient populations. High-risk patients include those with a history of MI and LV dysfunction (regardless of whether they have inducible sustained ventricular arrhythmias), as well as those with New York Heart Association (NYHA) class II or III heart failure (HF) as a result of either ischemic or nonischemic causes.
10. Life-threatening ventricular proarrhythmia generally takes two forms: sinusoidal or incessant monomorphic VT (type Ic antiarrhythmic drugs) and torsade de pointes (TdP) (type Ia or III antiarrhythmic drugs and many other noncardiac drugs).

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The heart has two basic properties, namely an electrical property and a mechanical property. The synchronous interaction between these two properties is complex, precise, and relatively enduring. The study of the electrical properties of the heart has grown at a steady rate, interrupted by periodic salvos of scientific breakthroughs. Einthoven's pioneering work allowed graphic electrical tracings of cardiac rhythm and probably represents the first of these breakthroughs. This discovery (of the surface electrocardiogram [ECG]) has remained the cornerstone of diagnostic tools for cardiac rhythm disturbances. Since then, intracardiac recordings and programmed cardiac stimulation have advanced our understanding of arrhythmias, and microelectrode, voltage-clamping, and patch-clamping techniques have allowed considerable insight into the electrophysiologic actions and mechanisms of antiarrhythmic drugs. Certainly, the new era of molecular biology and mapping of the human genome promises even greater insights into mechanisms (and potential therapies) of arrhythmias. Noteworthy in this regard is the discovery of genetic abnormalities in the ion channels that control electrical repolarization (heritable long QT syndrome) or depolarization (Brugada syndrome).

The clinical use of drug therapy started with the use of digitalis and then quinidine, followed somewhat later by a surge of new agents in the 1980s. A theme of drug discovery during this decade was initially to find orally absorbed lidocaine-congeners (such as mexiletine and tocainide); later, the emphasis was on drugs with extremely potent effects on conduction (i.e., flecainide-like agents). The most recent focus of investigational antiarrhythmic drugs are the potassium channel blockers, with dofetilide being the most recently approved in the United States. Previously, there was some expectation that advances in antiarrhythmic drug discovery would lead to a highly effective and nontoxic agent that would be effective for a majority of patients (i.e., the so-called magic bullet). Instead, significant problems with drug toxicity and proarrhythmia have resulted in a decline in the overall volume of antiarrhythmic drug usage in the United States since 1989. [1] The other phenomenon, which has significantly contributed to the decline in antiarrhythmic drug usage, is the development of extremely effective nondrug therapies. Technical advances have made it possible to permanently interrupt reentry circuits with radiofrequency ablation, which renders long-term antiarrhythmic drug use unnecessary in certain arrhythmias. Furthermore, the impressive survival data associated with the use of ICDs for the primary and secondary prevention of SCD has led most clinicians to choose "device" therapy as the first-line treatment for patients who are at high-risk for life-threatening ventricular arrhythmias. Both of these nondrug therapies have become increasingly popular for the management of arrhythmias so that the potential proarrhythmic effects and organ toxicities associated with antiarrhythmic drugs can be avoided. What does the future hold for the use of antiarrhythmic drugs? Certainly new knowledge and technologic advances have forced investigators and clinicians to rethink the concept of traditional membrane-active drugs. Although some degree of enthusiasm exists for some of the newer or investigational agents, the overall impact of these drugs has yet to be determined.

This chapter reviews the principles involved in both normal and abnormal cardiac conduction and addresses the pathophysiology and treatment of the more commonly encountered arrhythmias. Certainly, many volumes of complete text could be (and have been) devoted to basic and clinical electrophysiology. Consequently, this chapter briefly addresses those principles necessary for clinicians.

ARRHYTHMOGENESIS

NORMAL CONDUCTION

Electrical activity is initiated by the sinoatrial (SA) node and moves through cardiac tissue by a tree-like conduction network. The SA node initiates cardiac rhythm under normal circumstances because this tissue possesses the highest degree of automaticity or rate of spontaneous impulse generation. The degree of automaticity of the SA node is largely influenced by the autonomic nervous system in that both cholinergic and sympathetic innervations control sinus rate. Most tissues within the conduction system also possess varying degrees of inherent automatic properties. However, the rates of spontaneous impulse generation of these tissues are less than that of the SA node. Thus these latent automatic pacemakers are continuously overdriven by impulses arising from the SA node (primary pacemaker) and do not become clinically apparent.

From the SA node, electrical activity moves in a wave front through an atrial specialized conducting system and eventually gains entrance to the ventricle via the atrioventricular (AV) node and a large bundle of conducting tissue referred to as the bundle of His. Aside from this AV nodal–Hisian pathway, a fibrous AV ring that will not permit electrical stimulation separates the atria and ventricles. The conducting tissues bridging the atria and ventricles are referred to as the junctional areas. Again, this area of tissue (junction) is largely influenced by autonomic input, and possesses a relatively high degree of inherent automaticity (about 40 beats/min, less than that of the SA node). From the bundle of His, the cardiac conduction system bifurcates into several (usually three) bundle branches: one right bundle and two left bundles. These bundle branches further arborize into a conduction network referred to as the Purkinje system. The conduction system as a whole innervates the mechanical myocardium and serves to initiate excitation–contraction coupling and the contractile process. After a cell or group of cells within the heart is electrically stimulated, a brief period of time follows in which those cells cannot again be excited. This time period is referred to as the refractory period. As the electrical wavefront moves down the conduction system, the impulse eventually encounters tissue refractory to stimulation (recently excited) and subsequently dies out. The SA node subsequently recovers, fires spontaneously, and begins the process again.

Prior to cellular excitation, an electrical gradient exists between the inside and the outside of the cell membrane. At this time the cell is polarized. In atrial and ventricular conducting tissue, the intracellular space is approximately 80 to 90 mV negative with respect to the extracellular environment. The electrical gradient just prior to excitation is referred to as resting membrane potential (RMP) and is the result of differences in ion concentrations between the inside and the outside of the cell. At RMP, the cell is polarized primarily by the action of active membrane ion pumps, the most notable of these being the sodium-potassium pump. For example, this specific pump (in addition to other systems) attempts to maintain the intracellular sodium concentration at 5 to 15 mEq/L and the extracellular sodium concentration at 135 to 142 mEq/L; the intracellular potassium concentration at 135 to 140 mEq/L and the extracellular potassium concentration at 3 to 5 mEq/L. The RMP can be calculated by using the Nernst equation:

$$\text{RMP} = 61.5 \log \left(\frac{[K^+] \text{ outside}}{[K^+] \text{ inside}} \right)$$

Electrical stimulation (or depolarization) of the cell will result in changes in membrane potential over time or a characteristic action potential curve (Fig. 19–1). The action potential curve results from the transmembrane movement of specific ions and is divided into different phases. Phase 0 or initial, rapid depolarization of atrial and ventricular tissues is caused by an abrupt increase in the permeability of the membrane to sodium influx. This rapid depolarization more than equilibrates (overshoots) the electrical potential, resulting in a brief initial repolarization or phase 1. Phase 1 (initial depolarization) is caused by a transient and active potassium efflux (i.e., the I_{Kto} current). Calcium begins to move into the intracellular space at about –60 mV (during phase 0) causing a slower depolarization. Calcium influx continues throughout phase 2 of the action potential (plateau phase) and is balanced to some degree by potassium efflux. Calcium entrance (only through L channels in myocardial tissue) distinguishes cardiac conducting cells from nerve tissue, and provides the critical ionic link to excitation-contraction coupling and the mechanical properties of the heart as a pump (see Chap. 16). The membrane remains permeable to potassium efflux during phase 3, resulting in cellular repolarization. Phase 4 of the action potential is the gradual depolarization of the cell and is related to a constant sodium leak into the intracellular space balanced by a decreasing (over time) efflux of potassium. The slope of phase 4 depolarization determines, in large part, the automatic properties of the cell. As the cell is slowly depolarized during phase 4, an abrupt increase in sodium permeability occurs, allowing the rapid cellular depolarization of phase 0. The juncture of phase 4 and phase 0 where rapid sodium influx is initiated

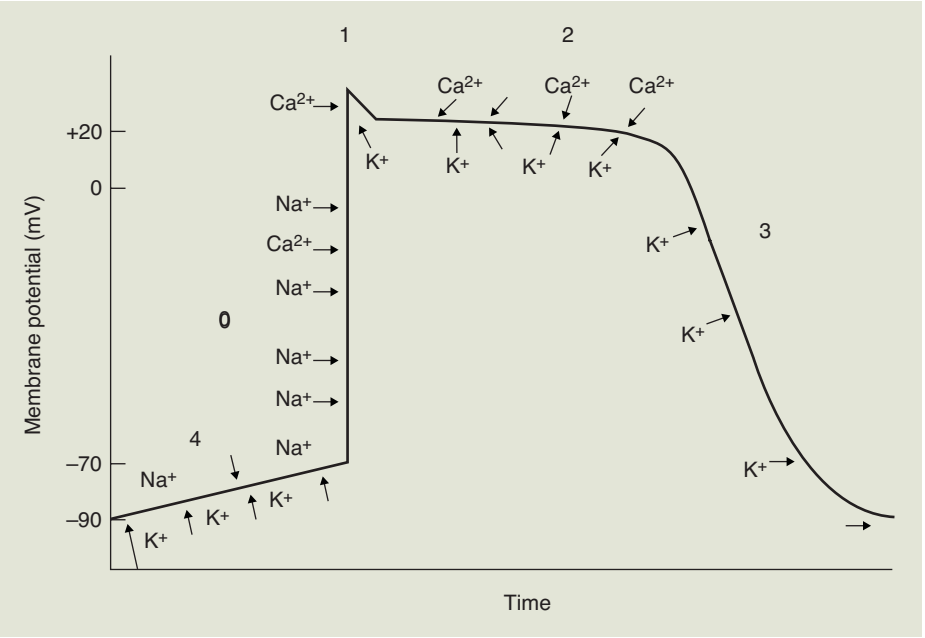

FIGURE 19-1. Purkinje fiber action potential showing specific ion flux responsible for the change in membrane potential. Ions outside of the line (e.g., sodium) move from the extracellular space to the intracellular space and ions on the inside of the line (e.g., potassium) move from the inside of the cell to the outside. Below the line is the corresponding ventricular excitation and recovery from the surface ECG. One can see that excessive sodium channel block from drugs may lead to QRS prolongation and excessive potassium channel block from drugs may lead to QT prolongation.

is referred to the threshold potential of the cell. The level of threshold potential also regulates the degree of cellular automaticity.

Not all cells in the cardiac conduction system rely on sodium influx for initial depolarization. Some tissues depolarize in response to a slower inward ionic current caused by calcium influx. These "calcium-dependent" tissues are found primarily in the SA and AV nodes (both L and T channels) and possess distinct conduction properties in comparison to "sodium-dependent" fibers. Calcium-dependent cells generally have a less-negative RMP (–40 to –60 mV) and a slower conduction velocity. Furthermore, in calcium-dependent tissues, recovery of excitability outlasts full repolarization, whereas in sodium-dependent tissue, recovery is prompt after repolarization. These two types of electrical fibers also differ dramatically in how drugs modify their conduction properties.

Ion conductance across the lipid bilayer of the cell membrane occurs via the formation of membrane pores or "channels" (Fig. 19–2). Selective ion channels probably form in response to specific electrical potential differences between the inside and the outside of the cell (voltage dependence). The membrane itself is composed of both organized and disorganized lipids and phospholipids in a dynamic sol-gel matrix. During ion flux and electrical excitation, changes in this sol-gel equilibrium occur and permit the formation of activated ion channels. Besides channel formation and membrane composition, intrachannel proteins or phospholipids, referred to as gates also regulate the transmembrane movement of ions. These gates are thought to be positioned strategically within the channel to modulate ion flow (Fig. 19–2). Each ion channel conceptually has two types of gates: an activation gate and an inactivation gate. The activation gate opens during depolarization to allow the ion current to enter or exit from the cell, and the inactivation gate later closes to stop ion movement. When the cell is in a rested state, the activation gates are closed and the inactivation gates are open. The activation gates then open to allow ion movement through the channel, and the inactivation gates later close to stop ion conductance. Thus, the cell cycles between three states: resting, activated or open, and inactivated or closed. Activation of SA and AV nodal tissue is dependent on a slow depolarizing current through calcium channels and gates, whereas the activation of atrial and ventricular tissue is dependent on a rapid depolarizing current through sodium channels and gates.

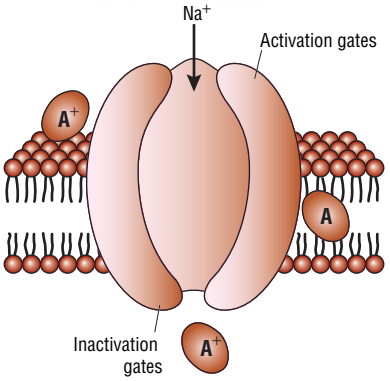

FIGURE 19-2. Lipid bilayer, sodium channel, and possible sites of action of the type I agents (*A*). Type I antiarrhythmic drugs may theoretically inhibit sodium influx at an extracellular, intramembrane, or intracellular receptor site. However, all approved agents appear to block sodium conductance at a single receptor site by gaining entrance to the interior of the channel from an intracellular route. Active ionized drugs block the channel predominantly during the activated or inactivated state and bind and unbind with specific time constants (described as fast on-off, slow on-off, and intermediate).

ABNORMAL CONDUCTION

The mechanisms of tachyarrhythmias have been classically divided into two general categories: those resulting from an abnormality in impulse generation or "automatic" tachycardias and those resulting from an abnormality in impulse conduction or "reentrant" tachycardias.

Automatic tachycardias depend upon spontaneous impulse generation in latent pacemakers and may be a result of several different mechanisms. Experimentally, chemicals, such as digitalis glycosides or catecholamines, and conditions, such as hypoxemia, electrolyte abnormalities (e.g., hypokalemia), and fiber stretch (cardiac dilation), may lead to an increased slope of phase 4 depolarization in cardiac tissues other than the SA node. These factors, which experimentally lead to abnormal automaticity, are also known to be arrhythmogenic in clinical situations. The increased slope of phase 4 causes heightened automaticity of these tissues and competition with the SA node for dominance of cardiac rhythm. If the rate of spontaneous impulse generation of the abnormally automatic tissue exceeds that of the SA node, then an automatic tachycardia may result. Automatic tachycardias have the following characteristics: (a) the onset of the tachycardia is unrelated to an initiating event

such as a premature beat; (b) the initiating beat is usually identical to subsequent beats of the tachycardia; (c) the tachycardia cannot be initiated by programmed cardiac stimulation; (d) the onset of the tachycardia is usually preceded by a gradual acceleration in rate and termination is usually preceded by a gradual deceleration in rate. Clinical tachycardias resulting from the classic forms of enhanced automaticity described above are not as common as once thought. Examples are sinus tachycardia and junctional tachycardia.

Triggered automaticity is also a possible mechanism for abnormal impulse generation. Briefly, triggered automaticity refers to transient membrane depolarizations that occur during repolarization (early after-depolarizations [EADs]) or after repolarization (late after-depolarizations [LADs]) but prior to phase 4 of the action potential. After-depolarizations may be related to abnormal calcium and sodium influx during or just after full cellular repolarization. Experimentally, EADs may be precipitated by hypokalemia, type Ia antiarrhythmic drugs, or slow stimulation rates—any factor that blocks the ion channels (e.g., potassium) responsible for cellular repolarization. Early after-depolarizations provoked by drugs that block potassium conductance and delay repolarization are the underlying cause of TdP. Late after-depolarizations may be precipitated by digitalis or catecholamines and suppressed by CCBs, and have been suggested as the mechanism for multifocal atrial tachycardia, digitalis-induced tachycardias and exercise-provoked VT. Triggered automatic rhythms possess some of the characteristics of automatic tachycardias and some of the characteristics of reentrant tachycardias (described below).

As previously mentioned, the impulse originating from the SA node in an individual with sinus rhythm eventually meets previously excited and thus refractory tissue. Reentry is a concept that involves indefinite propagation of the impulse and continued activation of previously refractory tissue. There are three conduction requirements for the formation of a viable reentrant focus: two pathways for impulse conduction; an area of unidirectional block (prolonged refractoriness) in one of these pathways; and slow conduction in the other pathway (Fig. 19–3). Usually a critically timed premature beat initiates reentry. This premature impulse enters both conduction pathways but encounters refractory tissue in one of the pathways at the area of unidirectional block. The impulse dies out because it is still refractory from the previous (sinus) impulse. Although it fails to propagate in one pathway, the impulse may still proceed in a forward direction (antegrade) through the other pathway because of this pathway's relatively shorter refractory period. The impulse may then proceed through a loop of tissue and "reenter" the area of unidirectional block in a backward direction (retrograde). Because the antegrade pathway has slow conduction characteristics, the area of unidirectional block has time to recover its excitability. The impulse can proceed retrograde through this (previously refractory) tissue and continue around the loop of tissue in a circular fashion. Thus, the key to the formation of a reentrant focus is crucial conduction discrepancies in the electrophysiologic characteristics of the two pathways. The reentrant focus may excite surrounding tissue at a rate greater than that of the SA node and a clinical tachycardia results. The above model is anatomically determined in that there is only one pathway for impulse conduction with a fixed circuit length. Another model of reentry, referred to as a functional reentrant loop or leading circle model, may also occur (Fig. 19–4).[1] In a functional reentrant focus, the length of the circuit may vary depending on the conduction velocity and recovery characteristics of the impulse. The area in the middle of the loop is continually kept refractory by the inwardly moving impulse. The length of the circuit is not fixed, but is the smallest circle possible, such that the leading edge of the wavefront is continuously exciting tissue just as it recovers; that is, the head of the impulse nearly catches its tail. It differs from the anatomic model in that the leading edge of the impulse is not preceded by an excitable gap of tissue, and it does not have an obstacle in the middle or a fixed anatomic circuit. Clinically, many reentrant foci probably have both anatomic and functional characteristics. In the figure 8 model, a zone of unidirectional block is present; allowing for two impulse loops that join and reenter the area of block in a retrograde fashion to form a pretzel-shaped reentrant circuit. This model combines functional characteristics with an excitable gap. All of these theoretical models require a critical balance of refractoriness and conduction velocity within the circuit and as such have helped to explain the effects of drugs on terminating, modifying, and causing cardiac rhythm disturbances.

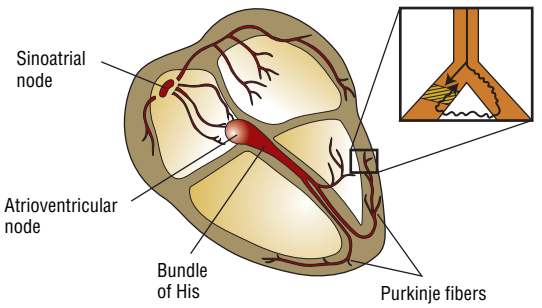

FIGURE 19-3. Conduction system of the heart. The magnified portion shows a bifurcation of a Purkinje fiber traditionally explained as the etiology of reentrant ventricular tachycardia. A premature impulse travels to the fiber, damaged by heart disease or ischemia. It encounters a zone of prolonged refractoriness (area of unidirectional block; *cross-hatched area*) but fails to propagate because it remains refractory to stimulation from the previous impulse. However, the impulse may slowly travel *(squiggly line)* through the other portion of the Purkinje twig and will "reenter" the cross-hatched area if the refractory period is concluded and it is now excitable. Thus, the premature impulse never meets refractory tissue; circus movement ensues. If this site stimulates the surrounding ventricle repetitively, clinical reentrant ventricular tachycardia results.

What causes reentry to become clinically manifest? Reentrant foci may occur at any level of the conduction system: within the branches of the specialized atrial conduction system, the Purkinje network, and even within portions of the SA and AV nodes. The anatomy of the Purkinje system appears to provide a suitable substrate for the formation of microreentrant loops and is often used as a model to facilitate the understanding of reentry concepts (see Fig. 19–4). Of course, because reentry does not usually occur in normal, healthy conduction tissue, various forms of heart disease or conduction abnormalities must usually be present before reentry becomes manifest. In other words, the various forms of heart disease (e.g., ischemic heart disease, LV dysfunction) can result in changes in conduction in the pathways of a suitable reentrant substrate. An often-used example is reentry occurring as a consequence of ischemic or hypoxic damage: with inadequate cellular oxygen, cardiac tissue resorts to anaerobic glycolysis for adenosine triphosphate production. As high-energy phosphate concentration diminishes, the activity of the transmembrane ion pumps declines and RMP rises. This rise in RMP causes inactivation in the voltage-dependent sodium channel and the tissue begins to assume slow conduction characteristics. If changes in conduction parameters occur in a discordant manner due to varying degrees of ischemia or hypoxia, then a reentry circuit may become manifest. Furthermore, an ischemic, dying cell liberates intracellular potassium, which also causes a rise in RMP. In other cases, reentry may occur as a consequence of anatomic or functional variants in the normal conduction system. For instance, patients may possess two (instead of one) conduction pathways near or within the AV node, or have an anomalous extranodal AV pathway that possesses different electrophysiologic characteristics from the normal AV nodal pathway. Reentry in these cases may occur within the AV node or encompass both atrial and ventricular tissue. Reentrant tachycardias have the following characteristics: (a) the onset of the tachycardia is

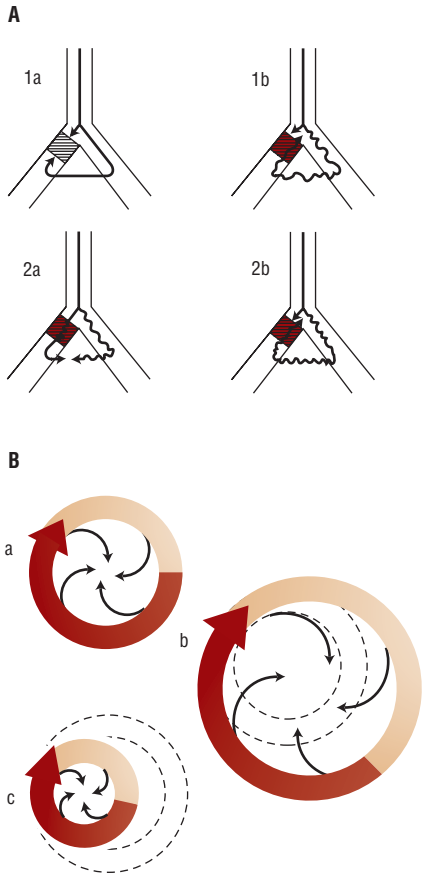

FIGURE 19-4. *A.* Possible mechanism of proarrhythmia in the anatomic model of reentry. *(1a)* Nonviable reentrant loop due to bidirectional block *(shaded area)*. *(1b)* Instance where a drug slows conduction velocity without significantly prolonging the refractory period. The impulse is now able to reenter the area of unidirectional block *(shaded area)* because slowed conduction through the contralateral limb allows recovery of the block. A new reentrant tachycardia may result. *(2a)* Nonviable reentrant loop due to a lack of a unidirectional block. *(2b)* Instance where a drug prolongs the refractory period without significantly slowing conduction velocity. The impulse moving antegrade meets refractory tissue *(shaded area)* allowing for unidirectional block. A new reentrant tachycardia may result. *B.* Mechanism of reentry and proarrhythmia. *(a)* Functionally determined *(leading circle)* reentrant circuit. This model should be contrasted with anatomic reentry; here the circuit is not fixed (it does not necessarily move around an anatomic obstacle) and there is no excitable gap. All tissue inside is held continuously refractory. *(b)* Instance where a drug prolongs the refractory period without significantly slowing conduction velocity. The tachycardia may terminate or slow in rate as shown as a consequence of a greater circuit length. The *dashed lines* represent the original reentrant circuit prior to drug treatment. *(c)* Instance where a drug slows conduction velocity without significantly prolonging the refractory period (i.e., type Ic agents) and accelerates the tachycardia. The tachycardia rate may increase (proarrhythmia) as shown as a consequence of a shorter circuit length. The dashed lines represent the original reentrant circuit prior to drug treatment. *(From McCollam PL, Parker RB, Beckman KJ, et al. Proarrhythmia: A paradoxic response to antiarrhythmic agents. Pharmacotherapy 1989;9:146, with permission.)*

usually related to an initiating event (i.e., premature beat), (b) the initiating beat is usually different in morphology from subsequent beats of the tachycardia, (c) the initiation of the tachycardia is usually possible with programmed cardiac stimulation, and (d) the initiation and termination of the tachycardia is usually abrupt without an acceleration or deceleration phase. There are many examples of reentrant tachycardias including AF, atrial flutter, AV nodal or AV reentrant tachycardia, and recurrent VT.

ANTIARRHYTHMIC DRUGS

In a theoretical sense, drugs may have antiarrhythmic activity by directly altering conduction in several ways. First, a drug may depress the automatic properties of abnormal pacemaker cells. An agent may do this by decreasing the slope of phase 4 depolarization and/or by elevating threshold potential. If the rate of spontaneous impulse generation of the abnormally automatic foci becomes less than that of the SA node, normal cardiac rhythm can be restored. Second, drugs may alter the conduction characteristics of the pathways of a reentrant loop.[1,2] An agent may facilitate conduction (shorten refractoriness) in the area of unidirectional block, allowing antegrade conduction to proceed. On the other hand, an antiarrhythmic may further depress conduction (prolong refractoriness) in either the area of unidirectional block or in the pathway with slowed conduction and a relatively shorter refractory period. If refractoriness is prolonged in the area of unidirectional block, retrograde propagation of the impulse is not permitted, causing a "bidirectional" block. In the anatomic model, if refractoriness is prolonged in the pathway with slow conduction, antegrade conduction of the impulse is not permitted through this route. In either case, drugs that reduce the discordance and cause uniformity in conduction properties of the two pathways may suppress the reentrant substrate. In the functionally determined model, if refractoriness is prolonged without significantly slowing conduction velocity, the tachycardia may terminate or slow in rate as a consequence of a greater circuit length (see Fig. 19–4). There are other theoretical ways to stop reentry: a drug may eliminate the critically timed premature impulse that triggers reentry; a drug may slow conduction velocity to such an extent that conduction is extinguished; or a drug may reverse the underlying form of heart disease that was responsible for the conduction abnormalities that led to the arrhythmia (i.e., "reverse remodeling").

Antiarrhythmic drugs have specific electrophysiologic actions that alter cardiac conduction in patients with or without heart disease. These actions form the basis of grouping antiarrhythmics into specific categories based upon their electrophysiologic actions *in vitro*. Vaughan Williams proposed the most frequently used classification system (Table 19–1).[2] This classification has been criticized because (a) it is incomplete and does not allow for the classification of agents such as digoxin or adenosine; (b) it is not pure and many agents have properties of more than one class of drugs; (c) it does not incorporate drug characteristics such as mechanisms of tachycardia termination/prevention, clinical indications, or side effects; and (d) agents become "labeled" within a class although they may be distinct in many regards.[3] These criticisms formed the basis for an attempt to reclassify antiarrhythmic agents based upon a variety of basic and clinical characteristics (called the Sicilian Gambit[3]). Nonetheless, the Vaughan Williams classification remains the most frequently used despite many proposed modifications and alternative systems.

The type Ia antiarrhythmic drugs—quinidine, procainamide, and disopyramide—slow conduction velocity, prolong refractoriness, and decrease the automatic properties of sodium-dependent (normal and diseased) conduction tissue. Although type Ia agents are primarily considered sodium channel blockers, their electrophysiologic actions can also be attributed to blockade of potassium channels. In reentrant tachycardias, these drugs generally depress conduction and prolong refractoriness, theoretically transforming the area of unidirectional block into a bidirectional block. Clinically, type Ia drugs are broad-spectrum antiarrhythmics that are effective for both supraventricular and ventricular arrhythmias.

The type Ib antiarrhythmic drugs—lidocaine and phenytoin—were historically categorized separately from quinidine-like drugs. This was a result of early work demonstrating that lidocaine had distinctly different electrophysiologic actions. In normal tissue models, lidocaine generally facilitates actions on cardiac conduction by

TABLE 19-1 Classification of Antiarrhythmic Drugs

Type	Drug	Conduction Velocity[a]	Refractory Period	Automaticity	Ion Block
Ia	Quinidine Procainamide Disopyramide	↓	↑	↓	Sodium (intermediate) Potassium
Ib	Lidocaine Mexiletine	0/↓	↓	↓	Sodium (fast on-off)
Ic	Flecainide Propafenone[b] Moricizine[c]	↓↓	0	↓	Sodium (slow on-off) Potassium[d]
II[e]	β-blockers	↓	↑	↓	Calcium (indirect)
III	Amiodarone[f] Dofetilide Sotalol[b] Ibutilide	0	↑↑	0	Potassium
IV[e]	Verapamil Diltiazem	↓	↑	↓	Calcium

AV, atrioventricular; SA, sinoatrial.
[a]Variables for normal tissue models in ventricular tissue.
[b]Also has type II, β-blocking actions.
[c]Classification controversial.
[d]Not clinically manifest.
[e]Variables for SA and AV nodal tissue only.
[f]Also has sodium, calcium, and β-blocking actions; see Table 19–2.

shortening refractoriness and having little effect on conduction velocity. Thus, it was postulated that these agents could improve antegrade conduction, eliminating the area of unidirectional block. Of course, arrhythmias do not usually arise from normal tissue, leading investigators to study the actions of lidocaine and phenytoin in ischemic and hypoxic tissue models. Interestingly, studies have shown these drugs to possess type Ia quinidine-like properties in diseased tissues. Therefore, it is probable that lidocaine acts in clinical tachycardias in a similar fashion to the type Ia drugs (i.e., prolong refractoriness in diseased ischemic tissues leading to bidirectional block in a reentrant circuit). Lidocaine and similar agents have accentuated effects in ischemic tissue caused by the local acidosis and potassium shifts that occur during cellular hypoxia. Changes in pH alter the time that local anesthetics occupy the sodium channel receptor, thereby affecting the agent's electrophysiologic actions. In addition, the intracellular acidosis that ensues as a consequence of ischemia could cause lidocaine to become "trapped" within the cell, allowing increased access to the receptor. The type Ib agents are considerably more effective in ventricular arrhythmias than supraventricular arrhythmias. As a group these drugs are relatively weak sodium channel antagonists (at normal stimulation rates).

The type Ic antiarrhythmic drugs include propafenone, flecainide, and moricizine. These agents are extremely potent sodium blockers, profoundly slowing conduction velocity while leaving refractoriness relatively unaltered. The type Ic drugs theoretically eliminate reentry by slowing conduction to a point where the impulse is extinguished and cannot propagate further. Although the type Ic drugs are effective for both ventricular and supraventricular arrhythmias, their use for ventricular arrhythmias has been limited by the risk of proarrhythmia.

Type I agents are grouped together because of their common action in blocking sodium conductance. The receptor site for these antiarrhythmics is probably inside the sodium channel so that, in effect, the drug plugs the pore. The agent may gain access to the receptor either via the intracellular space through the membrane lipid bilayer or directly through the channel. Several principles are inherent in antiarrhythmic sodium channel receptor theories[4]:

1. Type I antiarrhythmics have predominant affinity for a particular state of the channel (e.g., during activation or inactivation). For example, lidocaine and flecainide block sodium current primarily when the cell is in the inactivated state, whereas quinidine is predominantly an open (or activated)-channel blocker.
2. Type I antiarrhythmics have specific binding and unbinding characteristics to the receptor. For example, lidocaine binds to and dissociates from the channel receptor quickly (termed "fast on-off") but flecainide has very "slow on-off" properties. This explains why flecainide has such potent effects on slowing ventricular conduction whereas lidocaine has little effect on normal tissue (at normal heart rates). In general the type Ic antiarrhythmics are slow on-off, the type Ib antiarrhythmics are fast on-off, and the type Ia antiarrhythmics are intermediate in their binding kinetics.
3. Type I antiarrhythmics possess rate dependence (i.e., sodium channel blockade and slowed conduction are greatest at fast heart rates and least during bradycardia). For slow on-off drugs, sodium channel blockade is evident at normal rates (60 to 100 beats/min) but for fast on-off agents, slowed conduction is only apparent at rapid rates of stimulation.
4. Type I antiarrhythmics (except phenytoin) are weak bases with a pK_a >7.0 and block the sodium channel in their ionized form. Consequently, pH will alter these actions: acidosis accentuates and alkalosis diminishes sodium channel blockade.
5. Type I antiarrhythmics appear to share a single receptor site in the sodium channel. It should be noted, however, that a number of type I antiarrhythmics have other electrophysiologic properties. For instance, quinidine has potent potassium channel blocking activity (manifest predominantly at low concentrations) as does *N*-acetylprocainamide (manifest predominantly at high concentrations), the primary metabolite of procainamide. Additionally propafenone has β-blocking actions.

These principles are important in understanding additive drug combinations (e.g., quinidine and mexiletine), antagonistic combinations (e.g., flecainide and lidocaine), and potential antidotes to excess sodium channel blockade (sodium bicarbonate or propranolol). They also explain a number of clinical observations, such as why lidocaine-like drugs are relatively ineffective for supraventricu-

lar tachycardia. The type Ib antiarrhythmics are fast on-off, inactivated sodium blockers; atrial cells, however, have a very brief inactivated phase relative to ventricular tissue.

The β-blockers are classified as type II antiarrhythmic drugs. For the most part, the clinically relevant acute antiarrhythmic mechanisms of the β-blockers result from their antiadrenergic actions. Because the SA and AV nodes are heavily influenced by adrenergic innervation, β-blockers would be most useful in tachycardias in which these nodal tissues are abnormally automatic or are a portion of a reentrant loop. These agents are also helpful in slowing ventricular response in atrial tachycardias (e.g., AF) by their effects on the AV node. Furthermore, some tachycardias are exercise-related or precipitated by states of high sympathetic tone (perhaps through triggered activity), and β-blockers may be useful in these instances. β-adrenergic stimulation results in increased conduction velocity, shortened refractoriness, and increased automaticity of the nodal tissues; β-blockers will antagonize these effects. Propranolol is often noted to have "local anesthetic" or quinidine-like activity; however, suprapharmacologic concentrations are usually required to elicit this action. In the nodal tissues, β-blockers interfere with calcium entry into the cell by altering catecholamine-dependent channel integrity and gating kinetics. In sodium-dependent atrial and ventricular tissue, β-blockers shorten repolarization somewhat, but otherwise have little direct effect. The antiarrhythmic properties of β-blockers observed with long-term, chronic therapy in patients with heart disease are less well understood. Although it is clear that β-blockers decrease the likelihood of SCD (presumably arrhythmic death) after myocardial infarction (MI), the mechanism for this benefit remains unclear but may relate to the complex interplay of changes in sympathetic tone, damaged myocardium, and ventricular conduction. In patients with HF, drugs such as β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers may prevent arrhythmias such as AF by attenuating the structural remodeling process in the myocardium and subsequently improving ventricular performance over time.[5,6]

The type III antiarrhythmic drugs include those agents that specifically prolong refractoriness in atrial and ventricular tissue. This class includes very different drugs: bretylium, amiodarone, sotalol, ibutilide, and dofetilide; they share the common effect of delaying repolarization by blocking potassium channels. While rarely used, bretylium has complex pharmacology: in addition to blocking potassium channels and delaying repolarization, it first releases then depletes catecholamines. Bretylium increases the VF threshold and seems to have selective antifibrillatory but not antitachycardic effects. In other words, bretylium can be effective in VF, whereas it is often ineffective in VT.

In contrast, amiodarone and sotalol are effective in most supraventricular and ventricular tachycardias. Amiodarone displays electrophysiologic characteristics of all the classes within the Vaughan Williams scheme; it is a sodium channel blocker with relatively fast on-off kinetics, has noncompetitive, nonselective β-blocking actions, blocks potassium channels and also has a small degree of calcium antagonist activity (Table 19–2). At normal heart rates and with chronic use, its predominant effect is to prolong repolarization. Upon IV administration, its onset is relatively quick (unlike the oral form) and β-blockade predominates initially. Theoretically, amiodarone, like type I agents, may interrupt the reentrant substrate by transforming an area of unidirectional block into an area of bidirectional block. However, electrophysiologic studies using programmed cardiac stimulation imply that amiodarone may leave the reentrant loop intact. In addition, the potent β-blocking properties of amiodarone may contribute significantly to both its acute and chronic efficacy. The impressive effectiveness of amiodarone coupled with its low proarrhythmic potential has challenged the notion that selective ion channel blockade by antiarrhythmic agents is preferable. Sotalol is a potent inhibitor of outward potassium movement during repolarization and also possesses nonselective β-blocking actions. Unlike amiodarone and sotalol, ibutilide and dofetilide are only used for the treatment of supraventricular arrhythmias. Both ibutilide (only available IV) and dofetilide (only available orally) can be used for the acute conversion of AF or atrial flutter to sinus rhythm. Dofetilide can also be used to maintain sinus rhythm in patients with AF or atrial flutter of longer than 1 week's duration who have been converted to sinus rhythm. Both of these agents are structurally similar to sotalol and exert their electrophysiologic effects by blocking the rapid component of the delayed potassium rectifier current (I_{Kr}).

There are a number of different potassium channels which function during normal conduction; all approved type III antiarrhythmic drugs inhibit the delayed rectifier current (I_K) responsible for phases 2 and 3 repolarization. Subcurrents make up I_K; an ultrarapid component (I_{Kur}), a rapid component (I_{Kr}), and the slow component (I_{Ks}). *N*-acetylprocainamide, sotalol, ibutilide, and dofetilide selectively block I_{Kr}, whereas amiodarone and azimilide (investigational) block both I_{Kr} and I_{Ks}. New drugs that selectively block I_{Kur} (found predominantly in the atrium but not ventricle) are being investigated for supraventricular arrhythmias. The clinical relevance of selectively blocking components of the delayed rectifier current remains to be determined. Potassium current blockers (particularly those with selective I_{Kr} blocking properties) display "reverse use dependence" (i.e., their effects on repolarization are greatest at low heart rates). Sotalol and drugs like it also appear to be much more effective in preventing VF (in dog models) than the traditional sodium channel blockers. They also decrease defibrillation threshold in contrast to type I agents, which tend to increase this parameter. This could be important in patients with ICDs, as concurrent therapy with type I drugs may require more energy for successful cardioversion or may render the ICD ineffective in terminating the ventricular tachyarrhythmia. The Achilles' heel of all type III agents is an extension of their underlying ionic mechanism (i.e., by blocking potassium channels and delaying repolarization, they may also cause proarrhythmia in the form of TdP by provoking EADs).

TABLE 19-2 Time Course and Electrophysiologic Effects of Amiodarone

				IV		Oral	
Class	**Mechanism**	**EP**	**ECG**	***Min-Hrs***	***Hrs-Days***	***Days-Wks***	***Wks-Mos***
Type I	Na^+ block	↑ HV	↑ QRS	0	+	+	++
Type II	β-block	↑ AH	↑ PR ↓ HR	++	++	++	++
Type III	K^+ block	↑ VERP ↑ AERP	↑ QT	0	+	++	++++
Type IV	Ca^{2+} block[a]	↑ AH	↑ PR	+	+	+	+

[a]Rate-dependent.

AERP, atrial effective refractory period; AH, atria-His interval; ECG, electrocardiographic effects; EP, electrophysiologic actions; HR, heart rate; HV, His-ventricle interval; VERP, ventricular effective refractory period.

The nondihydropyridine CCBs—verapamil and diltiazem—comprise the type IV antiarrhythmic category. At least two types of calcium channels are operative in SA and AV nodal tissues: an L-type channel and a T-type channel. Both L-channel blockers (verapamil and diltiazem) and selective T-channel blockers (mibefradil—previously approved but withdrawn from the market) will slow conduction, prolong refractoriness, and decrease automaticity (e.g., due to EADs or LADs) of the calcium-dependent tissue in the SA and AV nodes. Therefore, these agents are effective in automatic or reentrant tachycardias, which arise from or use the SA or AV nodes. In supraventricular arrhythmias (e.g., AF), these drugs can slow ventricular response by slowing AV nodal conduction. Furthermore, because calcium entry seems to be integral to exercise-related tachycardias and/or tachycardias caused by some forms of triggered automaticity, these agents may be effective in the treatment of these types of arrhythmias. In all likelihood, verapamil and diltiazem work at different receptor sites because of their dissimilar chemical structures and pharmacologic actions. Calcium channel blockers can slightly shorten repolarization in normal sodium-dependent tissue, but otherwise have little effect. The dihydropyridine CCBs (e.g., nifedipine) do not have significant antiarrhythmic activity because a reflex increase in sympathetic tone caused by vasodilation counteracts their direct negative dromotropic action.

All antiarrhythmic agents currently available have an impressive side-effect profile (Table 19–3). A considerable percentage of patients cannot tolerate long-term therapy with these drugs and chances are good that an agent will have to be discontinued because of side effects. 2 In one trial,[7] more than 50% of patients had to discontinue long-term procainamide (mostly because of a lupus-like syndrome) after MI. In another study,[8] disopyramide caused anticholinergic side effects in approximately 70% of patients. Flecainide, propafenone, and disopyramide may precipitate congestive HF in a significant number of patients with underlying LV systolic dysfunction; consequently, these drugs should be avoided in this patient population.[9] The type Ib agents, such as tocainide and mexiletine, cause neurologic and/or gastrointestinal toxicity in a high percentage of patients. Tocainide, specifically, has been reported to cause both pulmonary fibrosis and leukopenia, the significance of which came to light after its approval by the Food and Drug Administration; it has now been withdrawn from the market and is currently unavailable. One of the most frightening adverse effects related to antiarrhythmic drugs is the aggravation of underlying ventricular arrhythmias or the precipitation of new (and life-threatening) ventricular arrhythmias.[10]

Amiodarone has assumed a prominent place in the treatment of both chronic and acute supraventricular and ventricular arrhythmias and is now the most commonly prescribed antiarrhythmic drug.[11] Once considered a drug of last resort, it is now the first drug considered in many symptomatic tachycardias. Yet amiodarone is a peculiar and complex drug, displaying unusual pharmacologic effects, pharmacokinetics, dosing schemes, and multiorgan side effects. Amiodarone has an extremely long elimination half-life and large volume of distribution; consequently, its onset of action with the oral form is delayed (days to weeks) despite a loading regimen and its effects persist long (months) after discontinuation. Amiodarone inhibits P-glycoprotein and most cytochrome P450 (CYP) enzymes, resulting in the potential for numerous drug interactions (e.g., it will cause digoxin levels to approximately double and one must reduce the maintenance dose of warfarin by one-third to one-half). Acute administration of amiodarone is usually well-tolerated by patients, but severe organ toxicities may result with chronic use. Severe bradycardia (sometimes requiring pacing to allow the patient to remain on amiodarone), hyper- and hypothyroidism, photosensitivity, and a blue-gray skin discoloration on exposed areas are common. Fulminant hepatitis (uncommon) and pulmonary fibrosis (5% to 10% of patients) have caused death.[12,13] Although amiodarone can cause corneal microdeposits (which usually do not affect vision) in virtually every patient, it has also been associated with the development of optic neuropathy/neuritis, which can lead to blindness. All of these side effects mandate close and continued monitoring (liver enzymes, thyroid function tests, eye exams, chest radiographs, pulmonary function tests) and have led to a proliferation of "amiodarone clinics" designed just for patients receiving this agent on a chronic basis (Table 19–4). 3[14]

Table 19–5 summarizes the pharmacokinetics of the antiarrhythmic agents and Table 19–6 lists recommended dosages of the oral dosage forms. Table 19–7 lists the dosing recommendations for the corresponding IV forms.

TABLE 19-3 Side Effects of Antiarrhythmic Drugs

Quinidine	Cinchonism, diarrhea, abdominal cramps, nausea, vomiting, hypotension, TdP, aggravation of underlying HF, conduction disturbances or ventricular arrhythmias, fever, hepatitis, thrombocytopenia, hemolytic anemia
Procainamide	Systemic lupus erythematosus, diarrhea, nausea, vomiting, TdP, aggravation of underlying HF, conduction disturbances or ventricular arrhythmias, agranulocytosis
Disopyramide	Anticholinergic symptoms (dry mouth, urinary retention, constipation, blurred vision), nausea, anorexia, TdP, HF, aggravation of underlying conduction disturbances and/or ventricular arrhythmias
Lidocaine	Dizziness, sedation, slurred speech, blurred vision, paresthesia, muscle twitching, confusion, nausea, vomiting, seizures, psychosis, sinus arrest, aggravation of underlying conduction disturbances
Mexiletine	Dizziness, sedation, anxiety, confusion, paresthesia, tremor, ataxia, blurred vision, nausea, vomiting, anorexia, aggravation of underlying conduction disturbances or ventricular arrhythmias
Moricizine	Dizziness, headache, fatigue, insomnia, nausea, diarrhea, blurred vision, aggravation of underlying conduction disturbances or ventricular arrhythmias
Flecainide	Blurred vision, dizziness, dyspnea, headache, tremor, nausea, aggravation of underlying HF, conduction disturbances or ventricular arrhythmias
Propafenone	Dizziness, fatigue, bronchospasm, headache, taste disturbances, nausea, vomiting, bradycardia or AV block, aggravation of underlying HF, conduction disturbances or ventricular arrhythmias
Amiodarone	Tremor, ataxia, paresthesia, insomnia, corneal microdeposits, optic neuropathy/neuritis, nausea, vomiting, anorexia, constipation, TdP (<1%), bradycardia or AV block (IV and oral use), pulmonary fibrosis, liver function test abnormalities, hepatitis, hypothyroidism, hyperthyroidism, photosensitivity, blue-gray skin discoloration, hypotension (IV use), phlebitis (IV use)
Dofetilide	Headache, dizziness, TdP
Ibutilide	Headache, TdP, hypotension
Sotalol	Dizziness, weakness, fatigue, nausea, vomiting, diarrhea, bradycardia, TdP, bronchospasm, aggravation of underlying HF

AV, atrioventricular; HF, heart failure; IV, intravenous; TdP, torsades de pointes.

SUPRAVENTRICULAR ARRHYTHMIAS

The common supraventricular tachycardias that often require drug treatment are (a) AF or atrial flutter, (b) PSVT, and (c) automatic atrial tachycardias. Other common supraventricular arrhythmias that usually do not require drug therapy include premature atrial complexes, wandering atrial pacemaker, sinus arrhythmia, and sinus tachycardia. As an example, premature atrial complexes rarely cause symptoms, never cause hemodynamic compromise, and therefore drug therapy is usually not indicated. Likewise, sinus tachycardia is usually the result of underlying metabolic or hemodynamic disorders (e.g., infection, dehydration, hypotension) and therapy should be directed at the underlying cause, not the tachycardia per se. Of course,

TABLE 19-4 Amiodarone Monitoring

Side Effect	Monitoring Recommendations	Management of Side Effect
Pulmonary fibrosis	Chest radiograph (baseline, then every 12 months) Pulmonary function tests (if symptomatic)	Discontinue amiodarone immediately; initiate corticosteroid therapy
Hypothyroidism	Thyroid function tests (baseline, then every 6 months)	Thyroid hormone supplementation (e.g., levothyroxine)
Hyperthyroidism	Thyroid function tests (baseline, then every 6 months)	Antithyroid drugs
Optic neuritis/neuropathy	Ophthalmologic examination (baseline, then every 12 months)	Discontinue amiodarone immediately
Corneal microdeposits	Slit-lamp examination (routine monitoring not necessary)	No treatment necessary
Increased LFTs	LFTs (baseline, then every 6 months)	Consider lowering the dose or discontinuing amiodarone if LFTs >3× normal
Bradycardia/heart block	ECG (baseline, then every 3–6 months)	Lower the dose, if possible, or discontinue amiodarone if severe
Tremors, ataxia, peripheral neuropathy	History/physical examination (each office visit)	Lower the dose, if possible, or discontinue amiodarone if severe
Photosensitivity/blue-gray skin discoloration	History/physical examination (each office visit)	Advise patients to wear sunblock while outdoors

ECG, electrocardiogram; LFTs, liver function tests.

TABLE 19-5 Pharmacokinetics of Antiarrhythmic Drugss

Drug	Bioavailability (%)	Primary Route of Elimination[a]	Substrate[b]	Inhibitor[b]	$V_{D\ ss}$ (L/kg)	Protein Binding (%)	$t_{1/2}$[c]	Therapeutic Range (mg/L)
Quinidine	70–80	H	CYP3A4 (M) CYP2C9	CYP2D6 (S) CYP3A4 (S) CYP2C9 P-GP	2.0–3.5	80–90	5–9 h	2–6
Procainamide	75–95	H/R	NAT CYP2D6 (M)	–	1.5–3.0	10–20	5–6 h (SAs) 2–3 h (FAs)	4–15
Disopyramide	70–95	H/R	CYP3A4 (M)	–	0.8–2.0	50–80	4–8 h	2–6
Lidocaine	–	H	CYP3A4 (M) CYP2D6 (M) CYP1A2 CYP2C9	CYP1A2 (S) CYP2D6 CYP3A4	1–2	65–75	1–3 h	1.5–5.0
Mexiletine	80–95	H	CYP2D6 (M) CYP1A2 (M)	CYP1A2 (S)	5–12	60–75	12–20 h (PMs) 7–11 h (EMs)	0.8–2.0
Moricizine	34–38	H	CYP3A4 (M)	–	6–11	92–95	2–4 h	–
Flecainide	90-95	H/R	CYP2D6 (M) CYP1A2	CYP2D6	8–10	35–45	14–20 h (PMs) 10–14 h (EMs)	0.2–1.0
Propafenone[d]	11–39	H	CYP2D6 (M) CYP1A2 CYP2D6	CYP1A2 CYP2D6	2.5–4.0	85–95	10–25 h (PMs) 3–7 h (EMs)	–
Amiodarone	22–88	H	CYP3A4 (M) CYP1A2 CYP2C19 CYP2D6	CYP2C9 CYP2D6 CYP3A4 CYP1A2 CYP2C19 P-GP	70–150	95–99	15–100 d	1.0–2.5
Sotalol	90–95	R	–	–	1.2–2.4	30–40	10–20 h	–
Dofetilide	85–95	R/H	CYP3A4	–	2.5–3.5	60–70	6–10 h	–
Ibutilide	–	H	–	–	6–12	40–50	3–6 h	–
Verapamil	20–40	H	CYP3A4 (M) CYP1A2 CYP2C9	CYP3A4 CYP1A2 CYP2C9 CYP2D6 P-GP	1.5–5.0	95–99	4–12 h	–
Diltiazem	35–50	H	CYP3A4 (M) CYP2C9 CYP2D6	CYP3A4 CYP2C9 CYP2D6 P-GP	3–5	70–85	4–10 h	–

[a] H, hepatic; R, renal.
[b] CYP, cytochrome P450 isoenzyme; M, major; NAT, *N*-acetyltransferase; P-GP, P-glycoprotein; S, strong.
[c] EMs, extensive metabolizers; FAs, fast acetylators; PMs, poor metabolizers; SAs, slow acetylators.
[d] Variables for parent compound (not 5-OH-propafenone).

TABLE 19-6 Typical Maintenance Doses of Oral Antiarrhythmic Drugs

Drug	Dose	Dose Adjusted
Quinidine	200–300 mg sulfate salt q 6 h 324–648 gluconate salt q 8–12 h	HEP, age >60 yr
Procainamide	500–1,000 mg q 6 h (Pronestyl SR) 1,000–2,000 mg q 12 h (Procanbid)	HEP, REN[a]
Disopyramide	100–150 mg q 6 h 200–300 mg q 12 h (SR form)	HEP, REN
Mexiletine	200–300 mg q 8 h	HEP
Flecainide	50–150 mg q 8 h	HEP, REN
Propafenone	150–300 mg q 8 h	HEP
Moricizine	200 mg q 8 h	HEP, REN
Sotalol	80–160 mg q 12 h	REN[b]
Dofetilide	500 mcg q 12 h	REN[c]
Amiodarone	400 mg two to three times daily until 10 g total, then 200–400 mg daily[d]	

HEP, hepatic disease; REN, renal dysfunction; SR, sustained release.
[a]Accumulation of parent compound or metabolite (e.g., NAPA) may occur.
[b]Should not be used for atrial fibrillation when creatinine clearance <40 mL/min.
[c]Dose should be based upon creatinine clearance; should not be used when creatinine clearance <20 mL/min.
[d]Usual maintenance dose for atrial fibrillation is 200 mg/day (may further decrease dose to 100 mg/day with long-term use if patient clinically stable in order to decrease risk of toxicity); usual maintenance dose for ventricular arrhythmias is 300–400 mg/day.

there are exceptions to these suggestions. For example, sinus tachycardia may be deleterious in patients after cardiac surgery or MI. In another unusual tachycardia termed *nonparoxysmal sinus tachycardia*, chronically elevated heart rates may cause alterations in LV function. In both of these instances, antiarrhythmic drugs, such as β-blockers, may be indicated. Stated in another way, although many arrhythmias generally do not require therapy, clinical judgment and patient-specific variables play an important role in this decision. Nevertheless, for the purpose of this discussion, only the tachycardias usually requiring antiarrhythmic drug therapy, as listed above, are addressed.

CLINICAL PRESENTATION: SUPRAVENTRICULAR TACHYCARDIA

Atrial Fibrillation/Flutter

General

- These rhythms are usually not directly life-threatening nor do they generally cause hemodynamic collapse or syncope; 1:1 atrial flutter (ventricular response ~300 beats/min) is an exception. Also, patients with underlying forms of heart disease that are heavily reliant on atrial contraction to maintain adequate cardiac output (e.g., mitral stenosis, obstructive cardiomyopathy) display more severe symptoms of AF or atrial flutter.

Symptoms

- Most often, patients complain of rapid heart rate/palpitations and/or worsening symptoms of HF (shortness of breath, fatigue). Medical emergencies are severe HF (i.e., pulmonary edema, hypotension) or AF occurring in the setting of acute MI.

Diagnostic Tests/Signs (ECG; See Text for Details)

- Atrial fibrillation is an irregularly, irregular supraventricular rhythm with no discernible, consistent atrial activity (P waves). Ventricular response is usually 120 to 180 beats/min and the pulse is irregular. Atrial flutter is (usually) a regular supraventricular rhythm with characteristic flutter waves (or sawtooth pattern) reflecting more organized atrial activity. Commonly, the ventricular rate is in factors of 300 beats/min (e.g., 150, 100, or 75 beats/min).

Paroxysmal Supraventricular Tachycardia caused by Reentry

General

- These rhythms can be transient, resulting in little, if any, symptoms.

Symptoms

- Patients frequently complain of intermittent episodes of rapid heart rate/palpitations that abruptly start and stop, usually without provocation (but occasionally as a result of exercise). Severe symptoms include syncope. Often (in particular, those with AV nodal reentry), patients complain of a chest pressure or neck sensation. This is caused by simultaneous AV contraction with the right atrium contracting against a closed tricuspid valve. Life-threatening symptoms (syncope, hemodynamic collapse) are associated with an extremely rapid heart rate (e.g., >200 beats/min) and AF associated with an accessory AV pathway.

Diagnostic Tests/Signs (ECG; See Text for Details)

- Most commonly, PSVT is a rapid, narrow QRS tachycardia (regular in rhythm) that starts and stops abruptly. Atrial activity, although present, is difficult to ascertain on surface ECG because P waves are "buried" on the QRS or T wave.

ATRIAL FIBRILLATION AND ATRIAL FLUTTER

Mechanisms and Background

Atrial fibrillation and atrial flutter are common supraventricular tachycardias. These tachycardias occur more often in men and the

TABLE 19-7 Intravenous Antiarrhythmic Dosing

Drug	Clinical Situation	Dose
Amiodarone	Pulseless VT/VF	300 mg IV/IO push (can give additional 150 mg IV/IO push if persistent VT/VF), followed by infusion of 1 mg/min for 6 h, then 0.5 mg/min
	Stable VT (with a pulse)	150 mg IV over 10 min, followed by infusion of 1 mg/min for 6 h, then 0.5 mg/min
	AF (termination)	5 mg/kg IV over 30 min, followed by infusion of 1 mg/min for 6 h, then 0.5 mg/min
Diltiazem	PSVT; AF (rate control)	0.25 mg/kg IV over 2 min (may repeat with 0.35 mg/kg IV over 2 min), followed by infusion of 5–15 mg/h
Ibutilide	AF (termination)	1 mg IV over 10 min (may repeat if needed)
Lidocaine	Pulseless VT/VF	1–1.5 mg/kg IV/IO push (can give additional 0.5–0.75 mg/kg IV/IO push every 5–10 min if persistent VT/VF [maximum cumulative dose = 3 mg/kg]), followed by infusion of 1–4 mg/min (1–2 mg/min if liver disease or HF)
	Stable VT (with a pulse)	1–1.5 mg/kg IV push (can give additional 0.5–0.75 mg/kg IV push every 5–10 min if persistent VT [maximum cumulative dose = 3 mg/kg]), followed by infusion of 1–4 mg/min (1–2 mg/min if liver disease or HF)
Procainamide	AF (termination); stable VT (with a pulse)	15–18 mg/kg IV over 60 min, followed by infusion of 1–4 mg/min
Verapamil	PSVT; AF (rate control)	2.5–5 mg IV over 2 min (may repeat up to maximum cumulative dose of 20 mg); can follow with infusion of 2.5–10 mg/h

AF, atrial fibrillation; IO, intraosseous; IV, intravenous; PSVT, paroxysmal supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

elderly. In the general population, the overall prevalence of AF is 0.4% to 1% and this increases with age (e.g., approximately an 8% prevalence in patients >80 years old).[15] The prevalence of AF also appears to increase as patients develop more severe HF, increasing from 4% in asymptomatic NYHA functional class I patients to 50% in patients with NYHA functional class IV HF.[15]

Atrial flutter and AF may present as a chronic, established tachycardia, an acute tachycardia, or a self-terminating, paroxysmal form. The following semantics and definitions are sometimes used specifically for AF:[15,16] acute AF (onset within 48 hours); paroxysmal AF (terminates spontaneously in <7 days); recurrent AF (two or more episodes); persistent AF (duration >7 days and does not terminate spontaneously); and permanent AF (does not terminate with attempts at pharmacologic or electrical cardioversion). Atrial fibrillation is characterized as an extremely rapid (atrial rate of 400 to 600 beats/min) and disorganized atrial activation. With this disorganized atrial activity, there is a loss of the contribution of synchronized atrial contraction (atrial kick) to forward cardiac output. Supraventricular impulses penetrate the AV conduction system in variable degrees resulting in an irregular activation of the ventricles and an *irregularly, irregular* pulse. The AV junction will not conduct most of the supraventricular impulses causing ventricular response to be considerably slower (120 to 180 beats/min) than the atrial rate. It is sometimes stated that "AF begets AF"; that is, the arrhythmia tends to perpetuate itself. Long episodes are more difficult to terminate perhaps because of tachycardia-induced changes in atrial function (mechanical and/or electrical "remodeling").

Atrial flutter occurs less frequently than AF, but is similar in its precipitating factors, consequences, and drug therapy approach. This arrhythmia is characterized by rapid (270 to 330 atrial beats/min) but regular atrial activation. The slower and regular electrical activity results in a regular ventricular response that is in approximate factors of 300 beats/min (i.e., 1:1 AV conduction = ventricular rate of 300 beats/min; 2:1 AV conduction = ventricular rate of 150 beats/min; 3:1 AV conduction = ventricular rate of 100 beats/min). Atrial flutter may occur in two distinct forms (type I and type II). Type I flutter is the more common classic form with atrial rates of approximately 300 beats/min and the typical "sawtooth" pattern of atrial activation as shown by the surface ECG. Type II flutter tends to be faster, being somewhat of a hybrid between classic atrial flutter and AF. Although the ventricular response usually has a regular pattern, atrial flutter with varying degrees of AV block or that occur with episodes of AF ("fib-flutter") can cause an irregular ventricular rate.

It is generally accepted that the predominant mechanism of AF and atrial flutter is reentry. Atrial fibrillation appears to result from multiple atrial reentrant loops (or wavelets) while atrial flutter is caused by a single, dominant, reentrant substrate (counterclockwise circus movement in the right atrium around the tricuspid annulus). Atrial fibrillation or flutter usually occurs in association with various forms of structural heart disease that cause atrial distension, including myocardial ischemia or infarction, hypertensive heart disease, valvular disorders such as mitral stenosis or mitral insufficiency, congenital abnormalities such as septal defects, dilated or hypertrophic cardiomyopathy, and obesity. Disorders that cause right atrial stretch and are associated with AF or atrial flutter include acute pulmonary embolus and chronic lung disease resulting in pulmonary hypertension and cor pulmonale. Atrial fibrillation may also occur in association with states of high adrenergic tone such as thyrotoxicosis, surgery, alcohol withdrawal, sepsis, and excessive physical exertion. Atrial fibrillation that develops in the absence of clinical, electrocardiographic, radiographic, and echocardiographic evidence of structural heart disease is defined as lone AF. Other states in which patients are predisposed to episodes of AF are the presence of an anomalous AV pathway (i.e., Kent bundle) and sinus node dysfunction (i.e., tachy-brady or sick sinus syndrome).

Patients with AF or artrial flutter may experience the entire range of symptoms associated with other supraventricular tachycardias, although syncope as a presenting symptom is uncommon. Because atrial kick is lost with the onset of AF, patients with LV systolic or diastolic dysfunction may develop worsening signs and symptoms of HF as they often depend on the contribution of their atrial kick to maintain an adequate cardiac output. Thromboembolic events, resulting from atrial stasis and poorly adherent mural thrombi, are an additional complication of AF. Of course, the most devastating complication in this regard is the occurrence of an embolic stroke. Approximately 15% of all strokes in the United States can be attributed to AF.[17] The average rate of ischemic stroke in patients with AF who are not receiving antithrombotic therapy is approximately 5% per year.[17,18] Stroke can precede the onset of documented AF, probably as a result of undetected paroxysms prior to the onset of established AF. The risk of stroke significantly increases with age, with the annual attributable risk increasing from 1.5% in individuals ages 50 to 59 years to almost 24% in those ages 80 to 89 years of age.[17] Patients with concomitant AF and rheumatic heart disease are at particularly high risk for stroke, with their risk being increased 17-fold compared to patients in sinus rhythm.[17] Other risk factors for stroke identified from recent trials are previous ischemic stroke, transient ischemic attack, or other systemic embolic event; moderate or severe LV systolic dysfunction and/or congestive HF; hypertension; and diabetes.[17] Younger patients (age <65 years) with AF in whom precipitating factors cannot be identified (i.e., lone AF) are considered to be at low risk for stroke.[17] The risk of stroke in patients with only atrial flutter has been traditionally believed to be low, prompting some to recommend only aspirin for prevention of thromboembolism in this particular patient population. However, because patients with atrial flutter may also intermittently have episodes of AF, this patient population also may be at risk for a thromboembolic event. Although the role of antithrombotic therapy in patients with atrial flutter has not been adequately studied in clinical trials, the most recent guidelines suggest that the same risk stratification scheme and antithrombotic recommendations used in patients with AF also be applied to those with atrial flutter.[17]

Management

The traditional approach to the treatment of AF can be organized into several sequential goals: (a) First, evaluate the need for acute treatment (usually the administration of drugs that slow ventricular rate). (b) Next, contemplate methods to restore sinus rhythm taking into consideration the risks (e.g., thromboembolism). (c) Last, consider ways to prevent the long-term complications of AF such as arrhythmia recurrences and thromboembolism. 4 One of the biggest controversies in the management of AF is whether or not the restoration and maintenance of sinus rhythm is a desirable goal for all patients with AF. A review of the management of AF/atrial flutter, including a discussion of this controversy follows, organized according to the goals outlined above. Figure 19–5 shows an algorithm for the management of AF and atrial flutter. In addition, Table 19–8 summarizes the recommendations for pharmacologically controlling ventricular rate and restoring and maintaining sinus rhythm from the most recent AF guidelines developed by the American College of Cardiology (ACC)/American Heart Association (AHA)/European Society of Cardiology (ESC).[15]

Acute Treatment First, consider the patient with new-onset, symptomatic AF or atrial flutter. Although uncommon, patients may present with signs and/or symptoms of hemodynamic instability (e.g., severe hypotension, angina, or pulmonary edema), which qualifies as a medical emergency. In these situations, DCC is indicated as first-line therapy in an attempt to immediately restore sinus rhythm (without regard to the risk of thromboembolism).

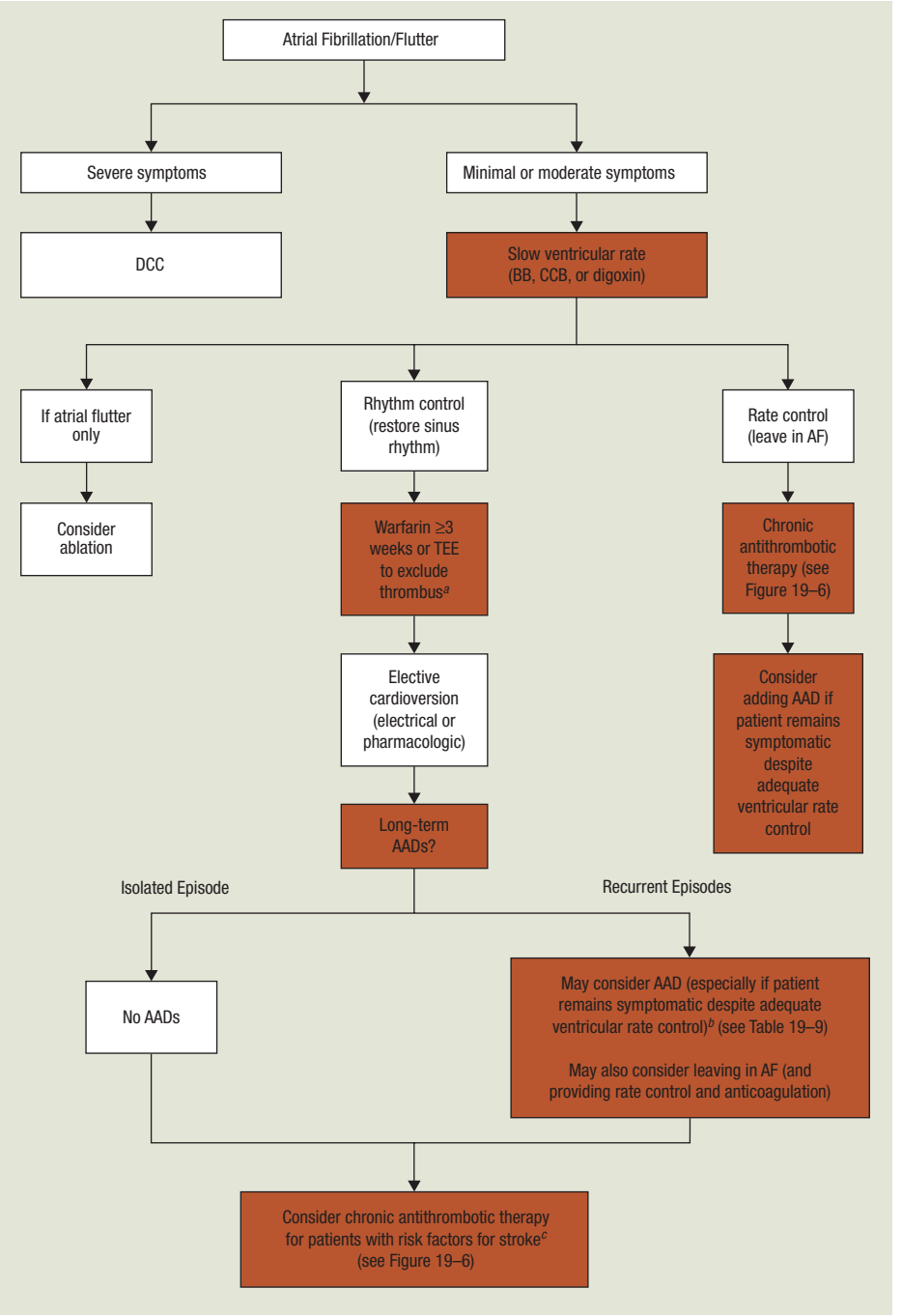

FIGURE 19-5. Algorithm for the treatment of atrial fibrillation and atrial flutter. [a]If AF <48 hours, anticoagulation prior to cardioversion is unnecessary; may consider TEE if patient has risk factors for stroke. [b]Ablation may be considered for patients who fail or do not tolerate ≥1 AAD. [c]Chronic antithrombotic therapy should be considered in all patients with AF and risk factors for stroke regardless of whether or not they remain in sinus rhythm. (AAD, antiarrhythmic drug; AF, atrial fibrillation; BB, β-blocker; CCB, calcium channel blocker [i.e., verapamil or diltiazem]; DCC, direct-current cardioversion; TEE, transesophageal echocardiogram.)

Atrial flutter often requires relatively low energy levels of countershock (i.e., 50 joules), whereas AF often requires higher energy levels (i.e., greater than 200 joules).

If patients are hemodynamically stable, there is no emergent need to restore sinus rhythm. Instead, the focus should be directed toward controlling the patient's ventricular rate. Achieving adequate ventricular rate control should be a treatment goal for all patients with AF. To achieve this goal, drugs that slow conduction and increase refractoriness in the AV node (e.g., β-blockers, nondihydropyridine CCBs, or digoxin) should be used as initial therapy. Although loading dosages of digoxin have been historically recommended as first-line treatment to slow ventricular rate, use of this drug for achieving ventricular rate control, especially in patients with normal LV systolic function (left ventricular ejection fraction [LVEF] >40%) has declined.[11] In this patient population, IV β-blockers (propranolol, metoprolol, esmolol), diltiazem, or verapamil is preferred. A few of the potential reasons for the declining use of digoxin in this patient population are its relatively slow onset and its inability to control the heart rate during exercise. Although an initial decrease in the ventricular rate can sometimes be observed within 1 hour of IV administration, full control (heart rate <80 beats/min at rest and <100 beats/min during exercise) is usually not achieved for 24 to 48 hours. In addition, digoxin tends to be ineffective for controlling ventricular rate under conditions of increased sympathetic tone (i.e., surgery, thyrotoxicosis) because it slows AV nodal conduction primarily through vagotonic mechanisms. In contrast, IV β-blockers and nondihydropyridine CCBs have a relatively quick onset and can effectively control the ventricular rate at rest and during exercise. β-blockers are also effective for controlling ventricular rate under conditions of increased sympathetic tone.

Based on the most recent guidelines for the treatment of AF, the selection of a drug to control ventricular rate in the acute setting should be primarily based on the patient's LV function.[15] In patients with normal LV function (LVEF >40%), IV β-blockers, diltiazem, or verapamil is recommended as first-line therapy to control ventricular rate.[15] All of these agents have proven efficacy in controlling the

TABLE 19-8 Evidence-Based Pharmacologic Treatment Recommendations for Controlling Ventricular Rate, Restoring Sinus Rhythm, and Maintaining Sinus Rhythm in Patients with Atrial Fibrillation

Treatment Recommendations	ACC/AHA/ESC Guideline Recommendation
Ventricular rate control (acute setting)	
In the absence of an accessory pathway, IV β-blockers, or IV nondihydropyridine CCBs are recommended for patients without hypotension or HF.	Class I
In the absence of an accessory pathway, IV digoxin or IV amiodarone is recommended for patients with HF.	Class I
IV amiodarone can be used to control the ventricular rate in patients who are refractory to or have contraindications to IV β-blockers, nondihydropyridine CCBs, or digoxin.	Class IIa
IV procainamide or ibutilide is a reasonable alternative in patients with an accessory pathway when DCC is not necessary.	Class IIa
IV procainamide, ibutilide, or amiodarone may be considered for hemodynamically stable patients with an accessory pathway.	Class IIb
IV nondihydropyridine CCBs are not recommended in patients with decompensated HF.	Class III
Ventricular rate control (chronic setting)	
Oral digoxin is effective for controlling the ventricular rate at rest in patients with HF or LV dysfunction, and in those who are sedentary.	Class I
Combination therapy with oral digoxin and either an oral β-blocker or nondihydropyridine CCB is reasonable to control the ventricular rate both at rest and during exercise.	Class IIa
Oral amiodarone can be used when the ventricular rate cannot be adequately controlled at rest and during exercise with an oral β-blocker, nondihydropyridine CCB, and/or digoxin.	Class IIb
Digoxin should not be used as the only agent for controlling the ventricular rate in patients with paroxysmal AF.	Class III
Restoration of sinus rhythm	
Flecainide, dofetilide, propafenone, or ibutilide is recommended for pharmacologic cardioversion of AF.	Class I
Amiodarone is a reasonable option for pharmacologic cardioversion of AF.	Class IIa
The "pill-in-the-pocket" approach (see text) can be used to terminate persistent AF on an outpatient basis once the treatment has been used safely in the hospital, in patients without sinus or AV node dysfunction, bundle-branch block, QT interval prolongation, Brugada syndrome, or structural heart disease (Note: AV node must be adequately blocked before initiating this therapy.)	Class IIa
Amiodarone can be used on an outpatient basis in patients with paroxysmal or persistent AF when rapid restoration of sinus rhythm is not necessary.	Class IIa
Quinidine or procainamide might be considered for pharmacologic cardioversion of AF, but their efficacy is not well established.	Class IIb
Digoxin and sotalol should not be used for pharmacologic cardioversion of AF (may be harmful).	Class III
Quinidine, procainamide, disopyramide, and dofetilide should not be initiated on an outpatient basis	Class III
Maintenance of sinus rhythm	
Antiarrhythmic therapy can be useful for maintaining sinus rhythm and preventing tachycardia-induced cardiomyopathy.	Class IIa
Outpatient initiation of antiarrhythmic therapy is reasonable in patients without structural heart disease.	Class IIa
Propafenone or flecainide may be initiated on an outpatient basis in patients with paroxysmal AF who have no structural heart disease and are in sinus rhythm at the time therapy is initiated.	Class IIa
Sotalol may be initiated on an outpatient basis in patients without structural heart disease, QT interval prolongation, electrolyte abnormalities, or other risk factors for proarrhythmia.	Class IIa
An antiarrhythmic drug should not be used when patients have risk factors for proarrhythmia with that particular agent.	Class III
Antiarrhythmic therapy is not recommended in patients with sinus or AV node dysfunction unless a pacemaker is present.	Class III

ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; AV, atrioventricular; CCB, calcium channel blocker; DCC, direct-current cardioversion; ESC, European Society of Cardiology; HF, heart failure; IV, intravenous; LV, left ventricular.

Adapted from reference 15.

ventricular rate in patients with AF. Propranolol and metoprolol can be administered as intermittent IV boluses, whereas esmolol (because of its very short half-life of 5 to 10 minutes) must be administered as a series of loading doses followed by a continuous infusion. Likewise, because control of ventricular rate can be transient with a single bolus, verapamil or diltiazem can be given as an initial IV bolus followed by a continuous infusion.[19] These continuous infusions can be adjusted in monitored settings to the desired ventricular response (e.g., acutely <100 beats/min). In situations where AF or atrial flutter is precipitated by states of increased adrenergic tone, IV β-blockers can be highly effective and should be considered first.

In patients with LV dysfunction (LVEF ≤40%), IV diltiazem or verapamil should be avoided because of their potent negative inotropic effects. Intravenous β-blockers should be used with caution in this patient population and should be avoided if patients are in the midst of an episode of decompensated HF. In those patients who are having an exacerbation of HF symptoms, IV administration of either digoxin or amiodarone should be used as first-line therapy to achieve ventricular rate control.[15] Intravenous amiodarone can also be used in patients who are refractory to or have contraindications to β-blockers, nondihydropyridine CCBs, and digoxin.[15] However, clinicians should be aware that the use of amiodarone for controlling ventricular rate may also stimulate the conversion of AF to sinus rhythm, and place the patient at risk for a thromboembolic event, especially if the AF is at least 48 hours or of unknown duration.

Patients may present with a slow ventricular response (in the absence of AV nodal-blocking drugs) and thus, do not require therapy with β-blockers, nondihydropyridine CCBs, or digoxin. This type of presentation should alert the clinician to the possibility of preexisting SA or AV nodal conduction disease such as sick sinus syndrome. In these patients, DCC should not be attempted without a temporary pacemaker in place.

Restoration of Sinus Rhythm? After treatment with AV nodal-blocking agents and a subsequent decrease in the ventricular rate, the patient should be evaluated for the possibility of restoring sinus rhythm if AF persists. Within the context of this evaluation, several factors should be considered. First, many patients spontaneously convert to sinus rhythm without intervention, obviating therapy needed to achieve this goal. For instance, AF occurs frequently as a complication of cardiac surgery and often spontaneously reverts to sinus rhythm without therapy. Second, restoring sinus rhythm is not a necessary or realistic goal in some patients. To date, a total of five clinical trials (Pharmacological Intervention in Atrial Fibrillation [PIAF], Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation [RACE], Atrial Fibrillation Follow-up Investigation of Rhythm Management [AFFIRM], Strategies of Treatment of Atrial Fibrillation [STAF], and How to Treat Chronic Atrial Fibrillation [HOT-CAFE]), have been published that have shed some light on this particular issue.[20–24] Of these, the AFFIRM is the largest study to

compare the effects of a rate-control (controlling ventricular rate; patient remains in AF) and rhythm-control (restoring and maintaining sinus rhythm) strategy in patients with AF.[22] In the AFFIRM trial, patients with AF and at least one risk factor for stroke were randomized to either a rate-control or rhythm-control group. Rate-control treatment involved AV nodal-blocking drugs (digoxin, β-blockers, and/or CCBs) first, then nondrug treatment (AV nodal ablation with pacemaker implantation), if necessary. All patients in this group were anticoagulated with warfarin to achieve an international normalized ratio (INR) of 2.0 to 3.0. In the rhythm-control group, type I or type III antiarrhythmic drugs were used to maintain sinus rhythm. The choice of antiarrhythmic therapy was left up to each patient's physician; however, by the end of the trial, more than 60% of patients had received at least one trial of amiodarone and approximately 40% of patients had received at least one trial of sotalol. In this group, anticoagulation was encouraged but could be discontinued if sinus rhythm had been maintained for at least 4 weeks. After a mean follow-up period of 3.5 years, overall mortality was not statistically different between the two strategies but tended ($P = 0.08$) to be higher in the rhythm-control group. The results of the PIAF, RACE, STAF, and HOT-CAFE trials were consistent with those of the AFFIRM trial.[20,21,23,24] In addition, a recently published meta-analysis of the data from all of these trials demonstrated no significant difference in overall mortality between rate-control and rhythm-control strategies, which persisted even when the results from the AFFIRM trial were excluded from this analysis.[25] Overall, the results of these trials collectively demonstrate that a rate-control strategy is a viable alternative to a rhythm-control strategy in patients with persistent AF.

Clearly, these important findings temper the old approach of aggressively attempting to maintain sinus rhythm. Because a rhythm-control strategy does not confer any advantage over a rate-control strategy in the management of AF, it now remains acceptable to allow patients to remain in AF, while being chronically treated with AV nodal-blocking agents to achieve adequate ventricular rate control (e.g., heart rate <80 beats/min at rest and <100 beats/min during exercise). 4 Overall, the selection of an AV nodal-blocking agent to control ventricular rate in the chronic setting should be primarily based on the patient's LV function.[15] In patients with normal LV function (LVEF >40%), oral β-blockers, diltiazem, or verapamil are preferred over digoxin because of their relatively quick onset and maintained efficacy during exercise. When adequate ventricular rate control cannot be achieved with one of these agents, the addition of digoxin may provide an additive lowering of the heart rate. If adequate ventricular rate control during rest and exercise cannot be achieved with β-blockers, nondihydropyridine CCBs, and/or digoxin, oral amiodarone can be used as alternative therapy to control the heart rate.[15] Verapamil and diltiazem should not be used in patients with LV dysfunction (LVEF ≤40%). Instead, β-blockers (i.e., metoprolol, carvedilol, or bisoprolol) and digoxin are preferred in these patients, as these agents are also concomitantly used to treat chronic HF; if possible, β-blockers should be considered over digoxin in this situation because of their survival benefits in patients with LV systolic dysfunction. If patients are having an episode of decompensated HF, digoxin is preferred as first-line therapy to achieve ventricular rate control. Occasionally, patients may be encountered who are highly refractory to AV nodal-blocking agents (including combination drug therapy) and continue to have a rapid ventricular rate. In this situation, aggressive attempts to lower the heart rate are necessary as chronic tachycardia can result in a progressive decline in LV function causing so-called *tachycardia-induced cardiomyopathy*. Hence, in drug-refractory patients, ablation or modification of the AV node by a transvenous catheter delivering radiofrequency current is indicated.[15,26] This procedure often completely blocks conduction from the atrium to the ventricle, requiring the concurrent implantation of a permanent pacemaker with a ventricular lead. Regardless of the situation, if the decision is made to allow a patient to remain in AF, consideration must be given to selecting the most appropriate antithrombotic therapy for these patients as they continue to be at risk for thromboembolic complications (see below).

Because a rate-control strategy is now considered a reasonable approach for the chronic management of AF, the question that remains to be answered is, "In which patients should restoration of sinus rhythm be considered?" Given the results of the AFFIRM trial, this decision should be left to clinical judgment but one could imagine that several groups of patients should undergo electrical or pharmacologic cardioversion. They include those patients who are judged to have a relatively low chance of recurrence (e.g., first episode of lone AF in young individuals, transient states of high sympathetic tone) and those with troublesome symptoms despite adequate ventricular rate control. In the former patient population, chronic antiarrhythmic therapy is usually not needed since the AF is often self-limiting.

In those patients in whom it is decided to restore sinus rhythm, one must consider that this very act (regardless of whether an electrical or pharmacologic method is chosen) places the patient at risk for a thromboembolic event. The reason for this is that the return of sinus rhythm restores effective contraction in the atria, which may dislodge poorly adherent thrombi. Administering antithrombotic therapy prior to cardioversion not only prevents clot growth and the formation of new thrombi but also allows existing thrombi to become organized and well-adherent to the atrial wall. It is a generally accepted principle that patients become at increased risk of thrombus formation and a subsequent embolic event if the duration of the AF exceeds 48 hours. Therefore, it is vital for clinicians to estimate the duration of the patient's AF, so that appropriate antithrombotic therapy can be administered prior to cardioversion, if needed. According to the most recent guidelines derived from the Seventh American College of Chest Physicians Consensus Conference on Antithrombotic Therapy, patients with AF for longer than 48 hours or an unknown duration should receive warfarin treatment (target INR 2.5; range: 2.0 to 3.0) for at least 3 weeks prior to cardioversion.[17] The common clinical scenario is to discharge the patient from the hospital, monitor them on an ambulatory basis, and readmit for elective cardioversion after this time period. After restoration of sinus rhythm, full atrial contraction does not occur immediately. Rather, it returns gradually to a maximum contractile force over a 3- to 4-week period. Consequently, warfarin should be continued for at least 4 weeks after effective cardioversion and return of sinus rhythm. To shorten the time to cardioversion, these patients may alternatively undergo transesophageal echocardiography (TEE) to provide guidance regarding the need for antithrombotic therapy prior to cardioversion. If no thrombus is noted on TEE, then these patients can be cardioverted without the mandatory 3 weeks of warfarin pretreatment. However, IV unfractionated heparin should still be administered during the TEE and cardioversion procedures to prevent the formation of thrombi during the pericardioversion and postcardioversion periods. After effective cardioversion and return of sinus rhythm, these patients should receive 4 weeks of warfarin therapy, as their atria may still be mechanically stunned during this period. If the TEE performed prior to cardioversion reveals thrombus, patients should then be anticoagulated indefinitely, and cardioversion should not be attempted until there is absence of thrombus on repeat TEE. Overall, the use of TEE in this manner has been compared to the conventional 3 weeks of anticoagulation before cardioversion in patients with AF.[27] In this large, multicenter, randomized trial, the incidence of thromboembolic events was not different between the two strategies, but bleeding episodes were higher in the "3 weeks of warfarin" group. Patients in the TEE strategy group had a higher success rate of achieving sinus rhythm, probably because it's more difficult to terminate AF the longer a patient remains in it (i.e., "AF begets AF").

In patients with AF that is less than 48 hours in duration, anticoagulation prior to cardioversion is unnecessary because there has not been sufficient time to form atrial thrombi.[17] However, it is recommended that these patients should receive either IV unfractionated heparin or a low-molecular-weight heparin (subcutaneously at treatment doses) at presentation prior to cardioversion. If these patients have risk factors for stroke, a TEE could alternatively be performed prior to cardioversion to exclude the presence of thrombus. Patients with AF that is less than 48 hours in duration do not require the 4 weeks of postcardioversion anticoagulation therapy unless they have risk factors for stroke or if the AF recurs.

After prior anticoagulation or TEE, the methods available to restore sinus rhythm can be considered. There are two methods of restoring sinus rhythm in patients with AF or atrial flutter: pharmacologic cardioversion and DCC. Which of these is the method of choice is generally a matter of clinical preference. The disadvantages of pharmacologic cardioversion are the risk of significant side effects (e.g., drug-induced TdP),[28] the inconvenience of drug–drug interactions (e.g., digoxin–amiodarone), and the fact that drugs are generally less effective when compared to DCC. The advantages of DCC are that it is quick and more often successful (80% to 90% success rate). The disadvantages of DCC are the need for prior sedation/anesthesia and a risk (albeit small) of serious complications such as sinus arrest or ventricular arrhythmias. Contrary to past beliefs, DCC carries very little risk in patients who are receiving digoxin and have no evidence of digitalis toxicity.

Nonetheless, despite the relatively high success rate associated with DCC, some clinicians elect to use antiarrhythmic drugs first, then resort to DCC in the event that these agents fail. Pharmacologic cardioversion appears to be most effective when initiated within 7 days after the onset of AF.[15] According to the most recent treatment guidelines for AF, there is relatively strong evidence for efficacy of the type III pure I_K blockers (ibutilide and dofetilide), the type Ic antiarrhythmics (e.g., flecainide and propafenone), and amiodarone (oral or IV).[15] Type Ia antiarrhythmics have limited efficacy in this setting. Sotalol is not effective for cardioversion of paroxysmal or persistent AF. Single, oral loading doses of propafenone (600 mg) and flecainide (300 mg) are effective compared to placebo for conversion of recent-onset AF and provide a simple regimen.[29] A method called the "pill-in-the-pocket" approach was recently endorsed by the treatment guidelines.[15] With this method, outpatient, patient-controlled self-administration of a single, oral loading dose of either flecainide or propafenone can be a relatively safe and effective approach for the termination of recent-onset AF in a selected patient population that does not have sinus or AV node dysfunction, bundle-branch block, QT interval prolongation, Brugada syndrome, or structural heart disease.[30] In addition, this treatment regimen should only be considered in patients who have been successfully cardioverted with these drugs on an inpatient basis. In patients with AF that is longer than 7 days in duration, only dofetilide, amiodarone, and ibutilide have proven efficacy for cardioversion.[15] The types Ia and Ic antiarrhythmics have limited efficacy in this setting.

Overall, when considering pharmacologic cardioversion, the selection of an antiarrhythmic drug should be based on whether the patient has structural heart disease (e.g., LV dysfunction, coronary artery disease, valvular heart disease, LV hypertrophy).[15] In the absence of any type of structural heart disease, the use of a single, oral loading dose of flecainide or propafenone is a reasonable approach for cardioversion; the "pill-in-the-pocket" approach should only be used in select patients (see above). Ibutilide can also be used as an alternative agent in this patient population; however, this agent can only be administered in the hospital because it is only available in IV form. In patients with underlying structural heart disease, these antiarrhythmics should be avoided because of the increased risk of proarrhythmia, and amiodarone or dofetilide should be used instead. Although amiodarone can be administered safely on an outpatient basis because of its low proarrhythmic potential, dofetilide can only be initiated in the hospital. Additionally, it should be remembered that a patient's ventricular rate should be adequately controlled with AV nodal-blocking drugs prior to administering a type Ic (or Ia) antiarrhythmic for cardioversion. The types Ia and Ic agents may paradoxically increase ventricular response. Traditionally, this observation has been attributed to the vagolytic action of these drugs despite the fact that only disopyramide displays significant anticholinergic side effects. Therefore, a more likely alternative explanation exists: all of these agents slow atrial conduction, decreasing the number of impulses reaching the AV node; as a result, the AV node paradoxically allows more impulses to gain entrance to the ventricular conduction system (increasing ventricular rate).

Long-Term Complications There are two forms of therapy that the clinician must consider in each patient: long-term antithrombotic therapy to prevent stroke, and long-term antiarrhythmic drugs to prevent recurrences of AF. Consider the issue of antithrombotic therapy first. In the past, patients with AF were not routinely anticoagulated (unless there was a history of stroke or concurrent mitral valve disease) because it was believed that the risk of warfarin exceeded its potential (though unknown) benefit. In the past several years, a large number of randomized, placebo-controlled trials designed to evaluate this issue have been published. All possess relatively similar findings and many were terminated prematurely because of a significant effect in the treatment group (warfarin). In all, these studies culminated in the following recommendations from the Seventh American College of Chest Physicians Consensus Conference on Antithrombotic Therapy for patients with paroxysmal, persistent, or permanent AF[17]: warfarin (target INR: 2.5; range: 2.0 to 3.0) should be prescribed to all patients who are at high risk for stroke (rheumatic mitral valve disease; previous ischemic stroke, transient ischemic attack, or other systemic embolic event; age >75 years; moderate or severe LV systolic dysfunction and/or congestive HF; hypertension; or prosthetic heart valve); those at intermediate risk (age 65 to 75 years with none of the above high-risk factors) should receive either warfarin (target INR: 2.5; range: 2.0 to 3.0) or aspirin 325 mg/day; and those at low risk (age <65 years with none of the above high-risk factors) should receive aspirin 325 mg/day. In the intermediate-risk group, the decision of whether to use warfarin or aspirin should be based on such factors as the patient's risk for bleeding, patient preference, potential drug interactions with warfarin, and the availability of an appropriate monitoring system for warfarin therapy. Although it was previously an acceptable practice to continue antithrombotic therapy for only 4 weeks after successful cardioversion (with the belief that a patient's risk for thromboembolism had abated since they were in sinus rhythm), recent data from the PIAF, RACE, AFFIRM, STAF, and HOT-CAFE trials strongly suggest that patients with AF and other risk factors for stroke continue to be at risk for stroke even when maintained in sinus rhythm.[20–24] It is possible that these patients may be having undetected episodes of paroxysmal AF, placing them at risk for stroke. Consequently, the updated treatment guidelines for AF recommend that chronic antithrombotic therapy be considered for all patients with AF and risk factors for stroke regardless of whether or not they remain in sinus rhythm.[15] Figure 19–6 is an algorithm for preventing thromboembolism in patients with AF.

The second form of chronic therapy to be considered is antiarrhythmic drugs to prevent recurrences of AF. With some exceptions (e.g., postoperative situations or transient states of high sympathetic tone), AF often recurs after initial cardioversion because most patients have irreversible, underlying heart or lung disease. Large atrial size, poor LV function, and the presence of long-standing AF are factors that make the restoration and maintenance of sinus

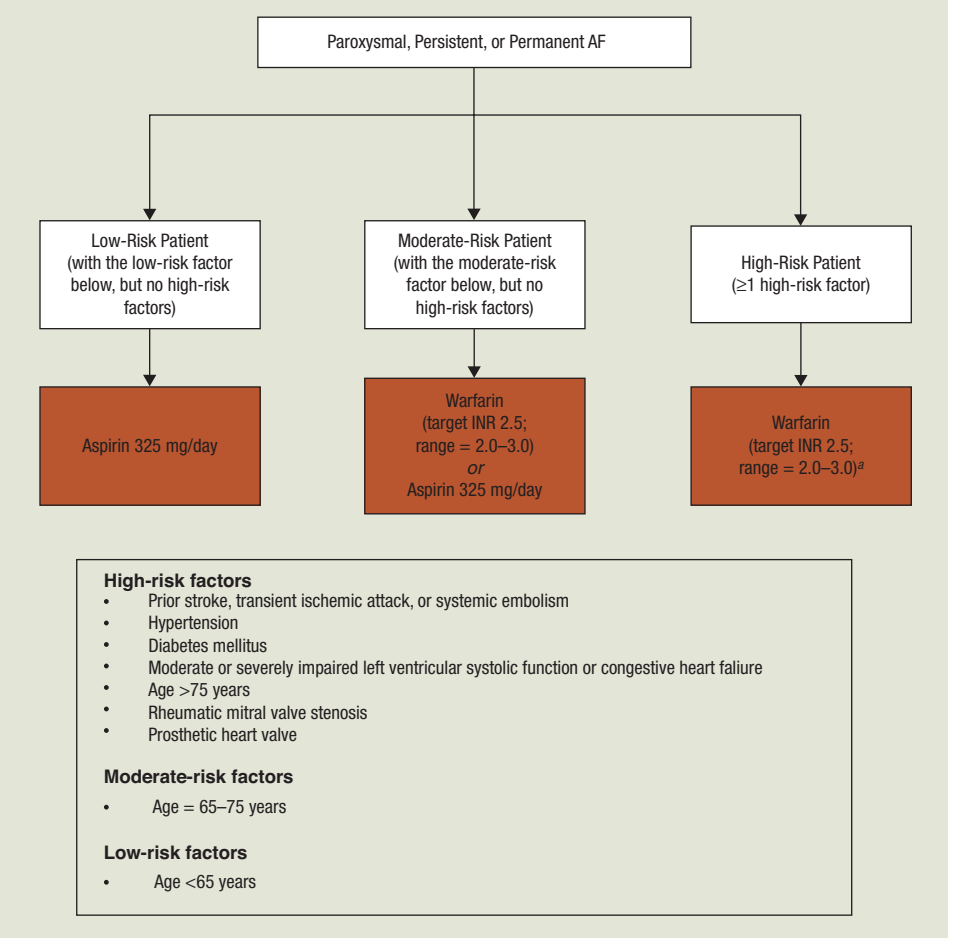

FIGURE 19-6. Algorithm for the prevention of thromboembolism in paroxysmal, persistent, or permanent atrial fibrillation. [a]The target INR for patients with prosthetic heart valves should be based upon the type of valve that is present. (AF, atrial fibrillation; INR, international normalized ratio.)

rhythm difficult if not impossible. Nevertheless, historically, many clinicians have aggressively attempted to maintain sinus rhythm by prescribing oral antiarrhythmic drugs (usually quinidine) to prevent these recurrences despite the fact that only small studies with conflicting results existed evaluating this approach. To evaluate the efficacy of quinidine in preventing AF, a well-known meta-analysis of the existing literature was completed.[31] This meta-analysis demonstrated that indeed more patients remain in sinus rhythm with quinidine therapy (compared to placebo); however, approximately 50% have recurrences of AF within a year despite quinidine. However, this reported effectiveness was at the cost of an associated increase in mortality (presumably due, in part, to proarrhythmia) in the quinidine-treated patients. These disturbing results (published soon after the CAST[32]) became widely quoted and highly visible, making clinicians question the wisdom of long-term prevention of recurrences of AF with antiarrhythmic drugs. Although the results were questioned because some of the reported causes of death in the treated patients could not be directly attributed to quinidine, subsequent studies[33] tended to support the findings of the meta-analysis.

These results coupled with the recent findings of the PIAF, RACE, AFFIRM, STAF, and HOT-CAFE trials question the need to use antiarrhythmic drugs to prevent recurrences of AF.[20–24] Perhaps this practice should now be totally abandoned, allowing patients to remain in AF once recurrences happen and only using strategies to control rate and prevent thromboembolism. Although it is true that these data have certainly led to a less-aggressive approach, patients with paroxysmal AF who continue to have intolerable symptoms during recurrences do require antiarrhythmic drugs to prevent these symptomatic attacks.

According to the recent treatment guidelines for AF, the type Ic or type III antiarrhythmic drugs are reasonable to consider to maintain patients in sinus rhythm (Table 19–9).[15] The role of the type Ia antiarrhythmic drugs for maintenance of sinus rhythm has been deemphasized throughout these updated guidelines as they are considered less effective or incompletely studied compared to the type Ic and type III agents. Realistically, however, these agents can still be considered as last-line therapy in patients without structural heart disease and in patients with hypertension (without significant LV hypertrophy) or coronary artery disease (with normal LV systolic function).

TABLE 19-9 Guidelines for Selecting Antiarrhythmic Drug Therapy for Maintenance of Sinus Rhythm in Patients with Recurrent Paroxysmal or Recurrent Persistent Atrial Fibrillation

No structural heart disease[a]
First line: flecainide, propafenone, or sotalol
Second line: amiodarone or dofetilide (catheter ablation could also be considered as an alternative to antiarrhythmic therapy)
Heart failure[a]
First line: amiodarone or dofetilide
Second line: catheter ablation
Coronary artery disease[a]
First line: sotalol (to be used only if patients have normal LV systolic function)
Second line: amiodarone or dofetilide (catheter ablation could also be considered as an alternative to antiarrhythmic therapy)
Hypertension[a]
Presence of significant LVH
First line: amiodarone
Second line: catheter ablation
Absence of significant LVH:
First line: flecainide, propafenone, or sotalol
Second line: amiodarone or dofetilide (catheter ablation could also be considered as an alternative to antiarrhythmic therapy)

LV, left ventricular; LVH, left ventricular hypertrophy.
[a]Drugs are listed alphabetically and not in order of suggested use.

The type Ic antiarrhythmics, flecainide and propafenone, are effective for maintaining sinus rhythm. However, because of the increased risk for proarrhythmia, these drugs should be avoided in patients with structural heart disease.

Although all of the oral type III antiarrhythmic drugs have demonstrated efficacy in preventing recurrences of AF, amiodarone is clearly the most effective agent and is now the most frequently chosen despite its impressive organ toxicity.[11] Since 2000, the superiority of amiodarone over other antiarrhythmics for maintaining patients in sinus rhythm has been demonstrated in a number of clinical trials. In the Canadian Trial of Atrial Fibrillation, amiodarone was significantly more effective than sotalol or propafenone in maintaining sinus rhythm in patients with persistent or paroxysmal AF.[34] Furthermore, in a substudy of the AFFIRM trial, amiodarone appeared to be the most effective antiarrhythmic agent of those used in the study.[35] In the more recently published Sotalol Amiodarone Atrial Fibrillation Efficacy Trial, amiodarone and sotalol were equally effective at converting AF to sinus rhythm.[36] However, amiodarone was significantly more effective than sotalol at maintaining sinus rhythm in all patient subgroups, except for those with ischemic heart disease where the efficacy of these two drugs was comparable.

Although sotalol is not effective for conversion of AF, it is an effective agent for maintaining sinus rhythm. Sotalol has been shown to be at least as effective as quinidine or propafenone in preventing recurrences of AF.[34,37] However, treatment with either quinidine or sotalol is associated with a similar incidence of TdP. Because this form of proarrhythmia primarily occurs with higher doses of sotalol (quinidine usually causes TdP at low or therapeutic concentrations), it may be more easily predicted and therefore avoided. Nonetheless, sotalol may increase mortality in patients with AF similar to quinidine; however, this requires further study.[38]

Dofetilide is effective in preventing recurrences of AF[39] but has not been directly compared with either amiodarone or sotalol. In a large, multicenter trial,[40] dofetilide (dose adjusted for renal function and QT interval) was more effective than placebo in maintaining sinus rhythm (approximately 35% to 50% at 1 year). The efficacy of dofetilide for the maintenance of sinus rhythm has also specifically been demonstrated in patients with LV dysfunction.[41] Like sotalol and quinidine, dofetilide also has significant potential to cause TdP (in a dose-related fashion).

Overall, the use of antiarrhythmic drug therapy to maintain sinus rhythm is reasonable to consider in patients with recurrent paroxysmal or persistent AF who develop intolerable symptoms during episodes of AF. As with cardioversion, the selection of an antiarrhythmic drug for maintaining sinus rhythm should be based on whether the patient has structural heart disease.[15] For those patients with no underlying structural heart disease, flecainide, propafenone, or sotalol should be considered initially because they have the most optimal long-term safety profile. However, amiodarone or dofetilide could be used as alternative therapy if the patient fails or does not tolerate one of these initial antiarrhythmic drugs. In the presence of structural heart disease, flecainide and propafenone, should be avoided because of the risk of proarrhythmia. If LV dysfunction is present (LVEF ≤40%), amiodarone should be considered the antiarrhythmic of choice. Dofetilide can be used as an alternative if patients develop intolerable side effects with amiodarone. In patients with coronary artery disease, sotalol can be used initially, provided that the patient's LV function is normal. Amiodarone or dofetilide could be used as an alternative therapy if the patient fails or does not tolerate sotalol. The presence of LV hypertrophy may predispose the myocardium to proarrhythmic events. Because of its low proarrhythmic potential, amiodarone should be considered first-line therapy in these patients.

Nondrug forms of therapy, designed to maintain sinus rhythm are becoming increasingly popular treatment options for patients with AF or atrial flutter. For patients who have "pure" (i.e., not associated with concurrent AF) type I atrial flutter, ablation of the reentrant substrate with radiofrequency current is highly effective (~80%)[42] and can be considered first-line treatment of atrial flutter to prevent recurrences.[43] For patients with AF, an innovative surgical procedure, referred to as the "maze" operation, has been used for more than a decade.[44] Because of its highly complex and invasive nature, the maze procedure is often reserved for highly drug-refractory patients. Over the past several years, most of the emerging data in the literature regarding nondrug treatment of AF have primarily focused on the safety and efficacy of catheter ablation techniques. Patients with AF have been found to have arrhythmogenic foci that occur in atrial tissue near and within the pulmonary veins. During the ablation procedure, radiofrequency energy can be delivered to these areas in an attempt to abolish the foci. Historically, this procedure was often considered last-line therapy for patients who had failed all antiarrhythmic drugs, including amiodarone. However, in some of the recent trials, the use of catheter ablation in patients with AF has been associated with a significant reduction in recurrent episodes of AF and an improvement in quality of life when compared with antiarrhythmic drug therapy.[45,46] There is even some evidence[47] to suggest that this procedure may be superior to antiarrhythmic drugs as first-line therapy of symptomatic AF; however, these results will have to be validated in larger trials. Based on this recent data, the guidelines now recommend that catheter ablation be considered as a reasonable treatment alternative for patients with symptomatic episodes of recurrent AF who fail or do not tolerate at least one antiarrhythmic drug.[15] This procedure is not without its risks, as major complications, such as pulmonary vein stenosis, thromboembolic events, cardiac tamponade, and new atrial flutter, have been reported in up to 6% of patients.[48]

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA CAUSED BY REENTRY

Paroxysmal supraventricular tachycardia arising by reentrant mechanisms includes those arrhythmias caused by AV nodal reentry, AV reentry incorporating an anomalous AV pathway, SA nodal reentry, and intraatrial reentry. Atrioventricular nodal reentry and AV reentry are by far the most common of these tachycardias. 5

Mechanisms

The underlying substrate of AV nodal reentry is the functional division of the AV node into two (or more) longitudinal conduction pathways or "dual" AV nodal pathways.[49] Most clinicians now believe that there are not two distinct anatomic pathways inside the AV node itself; rather, it is likely that a fan-like network of perinodal fibers inserts into the AV node and represents the second pathway. The two pathways possess key differences in conduction characteristics: one is a fast conducting pathway with a relatively long refractory period (fast pathway), and the other is a slower conducting pathway with a shorter refractory period (slow pathway). The presence of dual pathways does not necessarily imply that the patient will have clinical PSVT. In fact, it is estimated that between 10% and 50% of patients have discernible dual pathways but the incidence of PSVT is considerably lower.[49] Sustenance of the tachycardia depends on the critical electrophysiologic discrepancies and the ability of one pathway (usually the slow) to allow repetitive antegrade conduction, and the ability of the other pathway (usually the fast) to allow repetitive retrograde conduction. During sinus rhythm, a patient with dual pathways conducts supraventricular impulses antegrade through both pathways. Electrical activity reaches the distal common pathway at the level of or above the His bundle and continues to depolarize the ventricles in an antegrade direction. Conduction proceeds via the two pathways but reaches the distal common pathway first through the

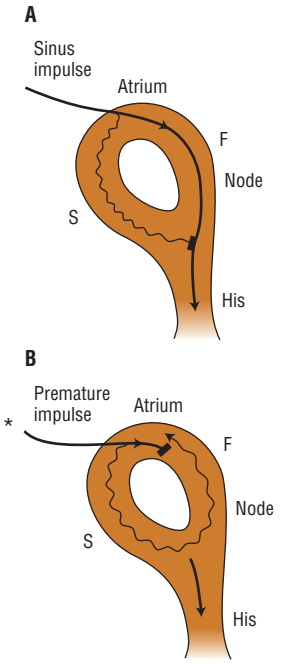

FIGURE 19-7. Reentry mechanism of dual AV nodal pathway PSVT. *A.* Sinus rhythm: The impulse travels from the atrium through the fast pathway *(F)* and then to the His-Purkinje system *(His)*. The impulse also travels through the slow pathway *(S)* but is stopped when refractory tissue is encountered. *B.* Dual AV nodal reentry: A critically timed premature impulse (*) is stopped in the fast pathway (because of prolonged refractoriness) but is able to travel antegrade down the slow pathway and retrograde through the fast pathway.

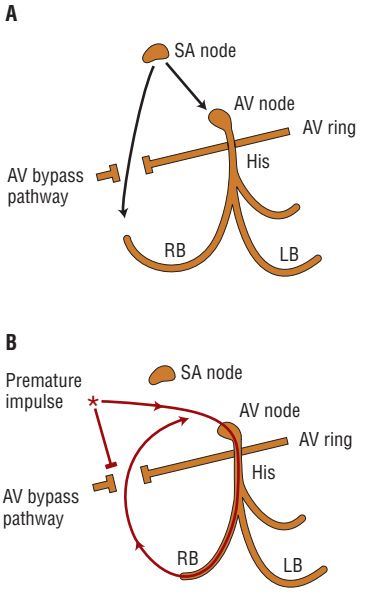

FIGURE 19-8. Reentry mechanism for AV accessory pathway PSVT in Wolff-Parkinson-White syndrome. *A.* Sinus rhythm: The impulse travels from the atrium to the ventricle by two pathways—the AV node and an accessory bypass pathway. *B.* AV reentry: A critically timed premature impulse (*) is stopped in the Kent bundle (because of prolonged refractoriness) but travels antegrade through the AV node and retrograde through the Kent bundle. (AV, atrioventricular; His, His-Purkinje system; LB, left bundle-branch; RB, right bundle-branch; SA, sinoatrial.)

fast AV nodal route (Fig. 19–7). For this reason, a short PR interval is sometimes observed during sinus rhythm.

Paroxysmal supraventricular tachycardia caused by AV nodal reentry may occur by the following sequence of events. The occurrence of an appropriately timed premature impulse penetrates the AV node, but is blocked in the fast pathway that is still refractory from the previous beat. However, the slow pathway, which has a shorter refractory period, permits antegrade conduction of the premature impulse. By the time the impulse has reached the distal common pathway, the fast pathway has recovered its excitability and now will permit retrograde conduction. The impulse reaches the common proximal pathway, preceded by an excitable gap of tissue, and reenters the slow pathway. A reentrant circuit that does not require atrial or ventricular tissue is completed within (or nearly so) the AV node, and a tachycardia is thereby initiated (see Fig. 19–7). The common form of this tachycardia uses the slow pathway for antegrade conduction and the fast pathway for retrograde conduction; an uncommon form exists in which the reentrant impulse travels in the opposite direction.

Atrioventricular reentrant tachycardia depends upon the presence of an anomalous, or accessory, extranodal pathway that bypasses the normal AV conduction pathway. Several different types of accessory pathways have been described, depending on the specific anatomic areas they connect (e.g., AV bundles or nodoventricular tracts); some are also referred to as eponyms, such as the Kent bundle. A Kent bundle is an extranodal AV connection that is associated with WPW syndrome. During sinus rhythm (Fig. 19–8), patients with WPW syndrome depolarize the ventricles simultaneously through both AV pathways (AV nodal pathway and the Kent bundle), creating a fusion pattern on the early portion of the QRS complex (delta wave). The degree of ventricular "preexcitation" depends on the contribution of antegrade ventricular activation through the accessory pathway. Patients may have an accessory pathway that is not evident on ECG, which is referred to as a "concealed" Kent bundle. These concealed accessory pathways are often incapable of antegrade conduction and can only accept electrical stimulation in a retrograde fashion. The electrocardiographic expression of preexcitation (delta wave) depends on the location of the accessory pathway, the distance from the wavefront of sinus activation and the conduction characteristics of the various structures involved. It should be noted that (similar to patients with dual AV nodal pathways) not all patients with preexcitation with an accessory AV pathway are capable of having clinical PSVT.

Patients with an accessory AV pathway may have three forms of supraventricular tachycardia: orthodromic reentry, antidromic reentry, and/or AF or atrial flutter. Atrioventricular reentrant PSVT usually occurs by the following sequence of events. Analogous to AV nodal reentry, two pathways (the normal AV nodal pathway and the accessory AV pathway) exist that have different electrophysiologic characteristics. The AV nodal pathway usually has a relatively slower conduction velocity and shorter refractory period, and the accessory pathway has a faster conduction velocity and a longer refractory period. A critically timed premature impulse may be blocked in the accessory pathway because this area is still refractory from the previous sinus beat. However, the AV nodal pathway, with a relatively shorter refractory period, may accept antegrade conduction of the premature impulse. Meanwhile, the accessory pathway may recover its excitability and now allow retrograde conduction. A macroreentrant tachycardia is thereby initiated in which the antegrade pathway is the AV nodal pathway; the distal common pathway is the ventricle; the retrograde pathway the accessory pathway; and the proximal common pathway is the atrium (see Fig. 19–8). This sequence of events (down the node, up the Kent bundle), termed *orthodromic PSVT*, is the common variety of reentry in patients with an accessory AV pathway, resulting in a narrow QRS tachycardia. In the uncommon variety, conduction proceeds in the opposite direction (down the Kent bundle, up the node), resulting in a wide QRS tachycardia, which is termed *antidromic PSVT*. Patients with WPW syndrome can have a third type of tachycardia, namely AF. The occurrence of AF in the setting of an accessory AV pathway (i.e., WPW syndrome) can be extremely serious and has been documented. As AF is an extremely

rapid atrial tachycardia, conduction can proceed down the accessory AV pathway, resulting in a very fast ventricular response or even VF. Unlike the AV nodal pathway, the refractory period of the accessory bundle shortens in response to rapid stimulation rates.

Sinus node reentry and intraatrial reentry occur less commonly and are not as well-described as AV nodal reentry and AV reentry. Aside from a characteristic abrupt onset and termination, coupled with subtle changes in P-wave morphology, these tachycardias can be difficult to diagnose. Electrophysiologic studies may be necessary to determine the ultimate mechanism of the PSVT.

Management

Both pharmacologic and nonpharmacologic methods have been used to treat patients with PSVT. Drugs used in the treatment of PSVT can be divided into three broad categories: (a) those that directly or indirectly increase vagal tone to the AV node (e.g., digoxin); (b) those that depress conduction through slow, calcium-dependent tissue (e.g., adenosine, β-blockers, and CCBs); and (c) those that depress conduction through fast, sodium-dependent tissue (e.g., quinidine, procainamide, disopyramide, and flecainide). Drugs within these categories alter the electrophysiologic characteristics of the reentrant substrate so that PSVT cannot be sustained.[50,51] In PSVT caused by AV nodal reentry, type I antiarrhythmic drugs, such as procainamide, act primarily on the retrograde fast pathway. Digoxin and β-blockers may work on either the retrograde fast or the antegrade slow limb. Verapamil, diltiazem, and adenosine prolong conduction time and increase refractoriness primarily in the slow antegrade pathway of the reentrant loop. In PSVT caused by AV reentry incorporating an extranodal pathway, type I drugs increase refractoriness in the fast accessory pathway or within the His-Purkinje system. β-blockers, digoxin, adenosine, and verapamil all act by their effects on the AV nodal (antegrade, slow) portion of the reentrant circuit. Regardless of the mechanism, treatment measures are directed at first terminating an acute episode of PSVT and then preventing symptomatic recurrences of the arrhythmia.

For those patients with PSVT who present with severe symptoms (syncope, near syncope, angina, or severe HF), synchronized DCC is the treatment of choice. Even at low energy levels (such as 25 joules), DCC is almost always effective in quickly restoring sinus rhythm and correcting symptomatic hypotension. Patients with only mild to moderate symptoms usually do not require DCC and nondrug measures that increase vagal tone to the AV node can be used initially. Unilateral carotid sinus massage, Valsalva maneuver, ice water facial immersion, induced retching, and other more elaborate vagomimetic measures are often successful in terminating PSVT, although carotid massage and Valsalva maneuver are the simplest, least obtrusive, and most frequently used of these techniques.

In the event that vagal maneuvers fail (approximately 80% of acute episodes) in those patients with tolerable symptoms, drug therapy is the next option. Figure 19–9 shows a therapeutic approach to the acute treatment of the different forms of reentrant PSVT. 6 This approach is based on analysis of the electrocardiographic characteristics of the rhythm because PSVT is not always discernible from other

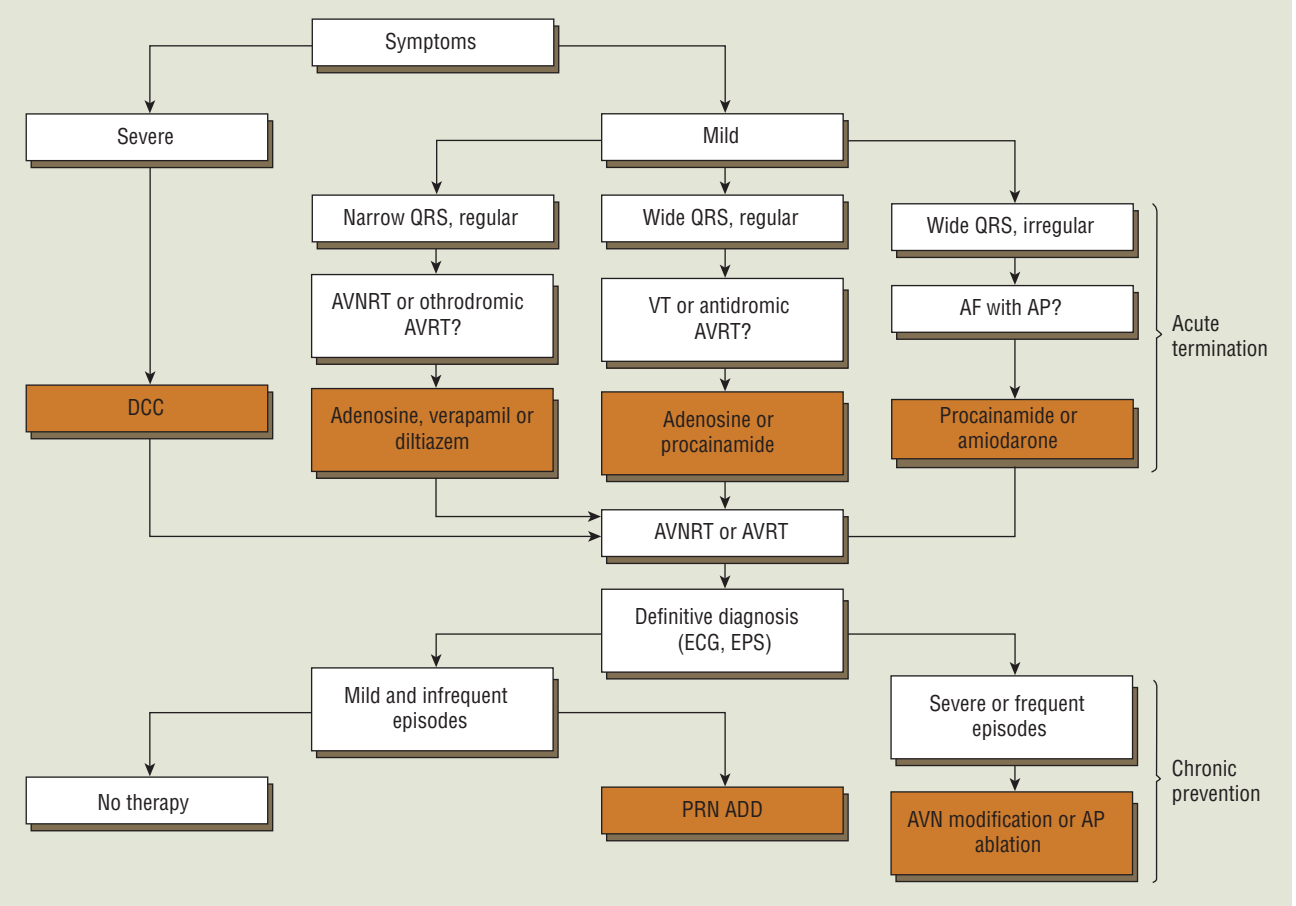

FIGURE 19-9. Algorithm for the treatment of acute *(top portion)* paroxysmal supraventricular tachycardia and chronic prevention of recurrences *(bottom portion)*. *Note:* For empiric bridge therapy prior to radiofrequency ablation procedures, calcium channel blockers (or other AV nodal blockers) should not be used if the patient has AV reentry with an accessory pathway. (AAD, antiarrhythmic drugs; AF, atrial fibrillation; AP, accessory pathway; AV, atrioventricular; AVN, atrioventricular nodal; AVNRT, atrioventricular nodal reentrant tachycardia; AVRT, atrioventricular reentrant tachycardia; DCC, direct current cardioversion; ECG, electrocardiographic monitoring; EPS, electrophysiologic studies; PRN, as needed; VT, ventricular tachycardia.)

arrhythmias, and some forms of PSVT require different treatment. In patients with a narrow QRS, regular arrhythmia (AV nodal reentry or orthodromic AV reentry), IV verapamil (5 to 10 mg), IV diltiazem (15 to 25 mg), or adenosine (6 to 12 mg) are all equally efficacious. Approximately 80% to 90% of PSVT episodes will revert to sinus rhythm within 5 minutes of IV verapamil, diltiazem, or adenosine therapy.[52] Both verapamil and diltiazem have the advantage in terms of cost, being available in generic formulations; whereas adenosine (although it has a higher frequency of side effects) may be safer because of its ultrashort duration of action. Adenosine should not be used in patients with severe asthma because of the potential risk of bronchospasm. The most recent guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care from the AHA,[53] and practice guidelines from the ACC/AHA/ESC,[43] promote adenosine as the drug of first choice in patients with PSVT. 5 These recommendations are particularly important when treating a patient who presents with a wide QRS, regular tachycardia that may be VT or PSVT (antidromic AV reentry or as a result of aberrancy). Because of its short duration of action (seconds), adenosine will not cause the severe and prolonged hemodynamic compromise seen in patients with VT who were mistakenly treated with verapamil and suffer from its negative inotropic effects and vasodilator properties.[54] If, in fact, the arrhythmia is PSVT, adenosine will likely terminate it. An alternative treatment for this type of patient is IV procainamide, which works on the fast, sodium-dependent extranodal pathway, and is also effective for VT. Likewise, IV procainamide, or perhaps amiodarone (particularly in patients with LV dysfunction), should be used for the patient who presents with a wide QRS, irregular arrhythmia that is hemodynamically stable.[53] This rhythm could represent AF with rapid ventricular activation occurring primarily through an extranodal pathway. Administration of IV verapamil, diltiazem, digoxin, or adenosine to these patients could result in a paradoxical increase in ventricular response, causing severe symptoms requiring cardioversion. Consequently, these agents are considered contraindicated in this specific setting.

Once the acute episode of PSVT is terminated, a decision on long-term preventive therapy must follow. Most patients require long-term therapy; preventive treatment is indicated if: (a) frequent episodes occur that necessitate therapeutic intervention (i.e., emergency room visits or interference with the patient's lifestyle), or (b) infrequent but severely symptomatic symptoms occur. For those patients in whom a preventive treatment is deemed necessary, two methods of management have been used: preventive drug therapy and ablation.

Antiarrhythmic drugs are no longer the treatment of choice to prevent recurrences of reentrant PSVT for the following reasons: (a) life-long treatment is necessary in these generally young, but otherwise healthy, individuals; (b) there are few, if any, large controlled or comparative trials to assist the clinician in rationally choosing effective agents, and most importantly; (c) other nondrug treatments are clearly more effective. Nevertheless, occasionally one must resort to the use of drug therapy in these patients. A trial-and-error approach on an ambulatory basis may be considered for those patients with frequently recurrent, mildly symptomatic PSVT. Ambulatory electrocardiographic recordings (Holter) or telephonic transmissions of cardiac rhythm (event monitors) can be used to objectively document the efficacy or failure of drug therapy. Drugs known to be effective in preventing recurrences of PSVT are the AV nodal-blocking agents (digoxin, β-blockers, nondihydropyridine CCBs, and combinations of these agents) and the type Ic antiarrhythmic drugs (flecainide, propafenone). Agents such as quinidine, disopyramide, amiodarone, and dofetilide, although effective in some patients, should be discouraged because of the risk of toxicity with long-term treatment. One concept that can serve as an aid to arriving at an effective regimen is that there are patterns of drug response in patients with PSVT; in other words, the tachycardia behaves as if it has a "weak link." Patients who respond to agents that act on one limb of the reentrant loop are less likely to respond to drugs that block conduction on the other limb. For instance, in a patient with AV nodal reentry, one may first choose a nondihydropyridine CCB or β-blocker (to affect the antegrade, slow pathway). If symptomatic recurrences are subsequently documented, it may be prudent to switch to a type Ic agent (to affect the retrograde, fast pathway) in an attempt to find the weak link or susceptible pathway. Patients with evidence of preexcitation (delta waves during sinus rhythm) should not be treated with only AV nodal-blocking agents. If AF were to occur, these agents would facilitate rapid conduction over the accessory pathway. The trial-and-error method for determining drug effectiveness in this setting has inherent shortcomings. If the PSVT episodes are infrequent, a considerable time period may be consumed before an effective regimen is realized, or if the patient has moderate to severe symptoms associated with PSVT, he/she may experience several troublesome episodes before the correct agent is identified. Consequently, a method of serial testing of antiarrhythmic agents by invasive electrophysiologic techniques has been used to determine effective long-term therapy in those patients with sporadic and/or symptomatic PSVT and this method represents another strategy to find an effective antiarrhythmic regimen. Using this method, the patient's clinical tachycardia is replicated in the laboratory by inserting appropriately timed, premature extra stimuli via a transvenous right-heart catheter. The patient is first studied off of antiarrhythmic therapy; induction of the tachycardia by premature stimuli by programmed stimulation serves as a control study. Then, over a period of several days, specific drugs are administered in a serial fashion and tested for efficacy in preventing the induction of PSVT.[50] The goal is to find an effective drug regimen in a short period of time, obviating the recurrence of highly symptomatic or rare episodes that may occur in the trial-and-error method. Occasionally, one encounters a patient with uncommon and very-well-tolerated recurrences of PSVT. Similar to those with paroxysmal AF, self-administered, single-dose oral therapy (i.e., the "pill-in-the-pocket" strategy) has been shown effective. Specifically, 120 mg of oral diltiazem coupled with 80 mg of oral propranolol has been shown to be superior to single-dose flecainide in terminating PSVT, decreasing the need to visit the emergency department for treatment.[55] Nonetheless, *all* forms of drug treatment designed to prevent or terminate the arrhythmia by self-administered therapy should probably be avoided in most patients because of the superior efficacy of nondrug treatment strategies.

Transcutaneous catheter ablation using radiofrequency current on the PSVT substrate has dramatically altered the traditional treatment of these patients (Fig. 19–10). 5 Radiofrequency energy delivered through a transvenous or arterial catheter causes small, discrete lesions through thermal energy. During invasive electrophysiologic studies, portions of the reentrant circuit can be located (or "mapped") by the use of a number of catheters. Once this is completed, radiofrequency energy is applied, creating thermal injury in the tissue necessary for reentry. In this way, the substrate for reentry is destroyed, "curing" the patient of recurrent episodes of PSVT and obviating the need for chronic drug therapy. Historically, ablation procedures were reserved for drug-refractory patients because they necessitated open-heart surgery. However, breakthroughs in technology initially included transvenous catheter approaches, followed by the use of radiofrequency (rather than direct current) energy. Complications, although unusual, include tamponade, pericarditis, valvular insufficiency, and AV block. Radiofrequency ablation is highly effective, preventing the recurrences of PSVT in 85% to 98% of patients.[56,57] The procedure was originally used in patients with WPW syndrome.[56] In these patients, the extranodal pathway is most often located at the left lateral free

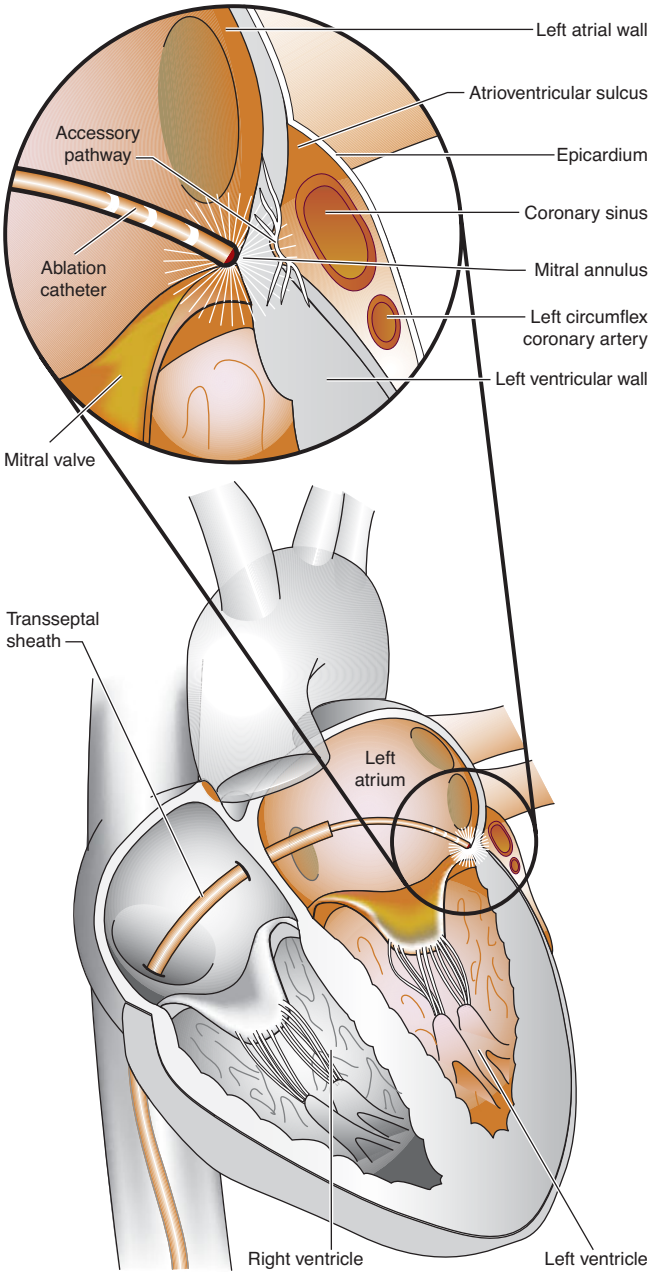

FIGURE 19-10. Drawing showing catheter placement for radiofrequency ablation of a left lateral free wall accessory pathway. Here, a venous (atrial) transseptal puncture to gain access to the Kent bundle is shown; a retrograde arterial approach has also been used. *(From Lerman BB, Basson CT. High risk patients with ventricular preexcitation: A pendulum in motion. N Engl J Med 2003;349:1787–1789, with permission.)*

wall of the left ventricle (Fig. 19–10). After the pathway is located, the catheter is put as close to the site as possible and radiofrequency current is applied to make small burns in the tissue. Ablation of the extranodal connection occurs promptly and evidence of preexcitation (delta waves) disappears. Thereafter, a similar approach was developed for patients with AV nodal reentry, placing the catheter in the coronary sinus, proximal to the AV node.[57] The preferred method in these individuals is to apply small amounts of radiofrequency current to the slow pathway of the reentrant circuit in order to modify its properties enough so that PSVT can not recur.

It has been suggested that *all* patients with symptomatic PSVT undergo radiofrequency catheter ablation.[58] This is because it is highly effective and curative, rarely results in complications, and obviates the need for chronic antiarrhythmic drug therapy. In other words, it should be considered in *any* patient who would previously be considered for chronic antiarrhythmic drug treatment. Radiofrequency ablation is also a cost-effective approach (in the long-term) because, if effective, the costs of drugs and repeated hospital visits are avoided. In one cost-effectiveness analysis, radiofrequency ablation improved quality of life and reduced lifetime medical expenditures by nearly $30,000 compared to chronic drug treatment.[59]

AUTOMATIC ATRIAL TACHYCARDIAS

Automatic atrial tachycardias, such as multifocal atrial tachycardia, appear to arise from supraventricular foci that have enhanced automatic properties.[60] It is presumed that multifocal atrial tachycardia is the result of multiple ectopic atrial pacemakers, which account for the variable and differing P-wave morphology. In unifocal atrial tachycardia (more often referred to as ectopic atrial tachycardia), a single P-wave morphology, different from that of sinus rhythm, is recorded. In either case, the underlying, precipitating disorder present in the majority (60% to 80%) of these patients is severe pulmonary disease. Other disease states associated with these arrhythmias include acute infection (pneumonia and sepsis) and dilated congestive cardiomyopathy. It should be noted that young patients without associated precipitating factors might rarely present with rapid atrial tachycardias from unknown etiologies. In these cases, long-standing tachycardias cause the cardiomyopathic state. Effective treatment of the tachycardia may result in reversal of the LV dysfunction. Traditionally, many factors (i.e., electrolyte disturbances, hypoxia, catecholamines, and tissue stretch) may cause an elevated slope of phase 4 depolarization and theoretically result in abnormal heightened automaticity. Noteworthy is that many of these factors are often clinically present in patients with concurrent pulmonary disease and automatic atrial tachycardia. However, it appears that triggered activity (i.e., LADs) is a more likely mechanism in the genesis of these tachycardias. Atrial tachycardias with AV block or a slow ventricular response should alert the clinician to the possibility of digitalis toxicity.

The first step in the treatment of automatic atrial tachycardia is to correct the underlying, precipitating factors.[60] One should ensure proper oxygenation and ventilation and correct acid–base or electrolyte disturbances. These measures alone may result in the return of sinus rhythm, but in some cases, the tachycardia will persist. Patients with an asymptomatic atrial tachycardia and a relatively slow ventricular rate usually require no drug therapy. In symptomatic patients, medical therapy can be tailored to either control ventricular rate or to restore sinus rhythm. Type I antiarrhythmic drugs, such as procainamide and quinidine, are only occasionally effective in restoring sinus rhythm, and are usually not considered first-line therapy. Direct-current cardioversion is ineffective in restoring sinus rhythm, and the use of programmed stimulation will not replicate the clinical tachycardia; consequently, serial drug testing is of no value. The use of IV β-blockers to slow ventricular rate is usually contraindicated because of the frequent coexistence of bronchospastic pulmonary disease or decompensated HF. Digoxin has been used but is controversial because of its ability to increase the automatic properties of atrial tissue and the high sympathetic state of these patients frequently overrides the vagotonic effects of digoxin, rendering it ineffective. Nondihydropyridine CCBs, such as verapamil, are most effective and are now considered first-line drug therapy.[61] Interestingly, verapamil seems to decrease ventricular rate by altering atrial automaticity, not by slowing AV nodal conduction.[61] Intravenous magnesium (independent of serum magnesium) can also be effective, but high doses are required and its effects are transient, rendering it impractical.[60] Both verapamil and parenteral magnesium probably act by suppressing calcium-mediated LADs.

CLINICAL PRESENTATION: VENTRICULAR ARRHYTHMIAS

Premature Ventricular Contractions

- Premature ventricular contractions are non-life-threatening and usually asymptomatic. Occasionally, patients will complain of palpitations or uncomfortable heart beats. Since the PVC, by definition, occurs early and the ventricle contracts when it is incompletely filled, patients do not feel the PVC. Rather, the next beat (after the PVC and a compensatory pause) is usually responsible for the patient's symptoms.

Ventricular Tachycardia

- The symptoms of VT (monomorphic VT or TdP), if prolonged (i.e., sustained), can vary from nearly completely asymptomatic to pulseless, hemodynamic collapse. Fast heart rates and underlying poor LV function will result in more severe symptoms. Symptoms of nonsustained, self-terminating VT also correlate with duration of episodes (e.g., patients with 15-second episodes will be more symptomatic than those with 3-beat episodes).

Ventricular Fibrillation

- By definition, VF results in hemodynamic collapse, syncope, and cardiac arrest. Cardiac output and blood pressure are not recordable.

VENTRICULAR ARRHYTHMIAS

The common ventricular arrhythmias include: (a) PVCs, (b) VT, and (c) VF. These arrhythmias may result in a wide variety of symptoms. Premature ventricular complexes often cause no symptoms or only mild palpitations. Ventricular tachycardia may be a life-threatening situation associated with hemodynamic collapse or may be totally asymptomatic. Ventricular fibrillation, by definition, is an acute medical emergency necessitating CPR.

PREMATURE VENTRICULAR COMPLEXES AND PREVENTION OF SUDDEN CARDIAC DEATH

Premature ventricular complexes are very common ventricular rhythm disturbances that occur in patients with or without structural heart disease. Experimental models show that premature ventricular depolarizations may be elicited by abnormal automaticity, triggered activity, or by reentrant mechanisms. It is well known that PVCs are commonly observed in apparently healthy individuals; in these patients, the PVCs seem to have little if any prognostic significance. Premature ventricular contractions occur more frequently and in more complex forms in patients with structural heart disease than in healthy individuals. The prognostic meaning of PVCs has been well studied in patients with MI (acute or remote) with several consistent themes. Patients with some forms of PVCs are at higher risk for "sudden death" than if they did not have these minor rhythm disturbances. Sudden cardiac death can be defined as unexpected death occurring in a patient within 1 hour of experiencing symptoms. Studies of patients who experienced SCD (and happened to be wearing an electrocardiographic monitor at the time) often demonstrate the cause to be VF preceded by a short run of VT and frequent PVCs.[62] Therein lies the basis of the so-called "PVC hypothesis" (i.e., preventing more minor arrhythmias, such as PVCs, may prevent the occurrence of SCD).

Significance

Historically, investigators promoted the concept that patients in the acute phase of MI may have types of PVCs that are predictive of VF and SCD. These types of PVCs were referred to as "warning arrhythmias" and included frequent ventricular ectopy (more than 5 beats/min), multiform configuration (different morphology), couplets (two in a row), and R-on-T phenomenon (PVCs occurring during the repolarization phase of the preceding sinus beat in the vulnerable period of ventricular recovery). However, as a result of using continuous electrocardiographic monitoring techniques, it has become apparent that almost all patients have warning arrhythmias in the acute infarct setting. In those patients who experience VF, warning arrhythmias are no more common than in those without VF. Consequently, warning arrhythmias observed during acute MI are neither sensitive nor specific for determining which patients will have VF. Thus, there is little need to direct drug therapy specifically at PVC suppression in these particular patients. Studies show that effective prevention of VF in the acute infarct setting may be achieved without the abolition of PVCs.

Conversely, data strongly imply that PVCs documented in the convalescence period of MI do carry important long-term prognostic significance.[63] Premature ventricular complexes occurring after a MI seem to be a risk factor for patient death that is independent of the degree of LV dysfunction or the extent of coronary atherosclerosis. Ruberman et al.[63] employed a simple classification of PVCs: simple or benign (infrequent and monomorphic) versus "complex" (≥5 PVCs/min, couplets, R-on-T beats, and multiform). These investigators found that the presence of complex (but not simple) ventricular ectopy in the setting of ischemic heart disease was associated with a higher incidence of overall mortality and cardiac death. One can see that within the controversy of the significance of PVCs is a basic question: Are complex forms of PVCs simply an unimportant marker of underlying structural heart disease or are PVCs an important electrical disorder that should be addressed independently?

Because PVCs without associated structural heart disease, in apparently healthy individuals, carry little or no risk, drug therapy is unnecessary. However, because of the prognostic significance of complex PVCs in patients with structural heart disease, the use of antiarrhythmic drug therapy to suppress them has been controversial. Historically, many supported the aggressive use of antiarrhythmic drug therapy designed to suppress a high percentage of PVCs, based on the underlying premise of eliminating a risk factor for SCD in patients with coronary disease (namely the presence of complex PVCs). However, others favored a more conservative approach and disregarded drug therapy in the absence of significant symptoms. An important study, the CAST,[32] abruptly put an end to this debate in noteworthy fashion and its results are reviewed below because of its great historical significance and lingering impact.

The Cardiac Arrhythmia Suppression Trial

The CAST[32,64] was initiated by the National Institutes of Health in 1987 to determine if suppression of ventricular ectopy with encainide, flecainide, or moricizine could decrease the incidence of death from arrhythmia in patients who had suffered a MI. 7 Entrance criteria included documented MI between 6 days and 2 years prior to enrollment, and ≥6 PVCs per hour (associated with no or minimal symptoms) without runs of VT greater than 15 beats in length. Also, patients were required to have a LVEF ≤55% if recruited within 90 days of MI or ≤40% if recruited 90 days or more after infarction. Patients with a LVEF <30% were randomized only to encainide or moricizine. Patients were randomized to receive drug therapy or placebo after demonstrating PVC suppression with one of the agents. The drug and dose were determined during an open-label, dose-titration phase that preceded randomization.

In April 1989, a routine, preliminary review of the study by the Safety and Monitoring Board revealed alarming results and the study was interrupted. The results showed that compared to placebo, treatment with encainide or flecainide was associated with a significantly higher rate of total mortality and death due to arrhyth-

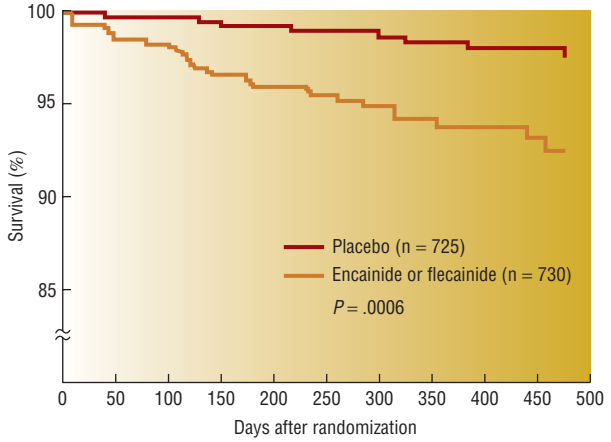

FIGURE 19-11. Life table curves from the Cardiac Arrhythmia Suppression Trial (CAST), specifically for patients receiving encainide or flecainide *(lighter line)* and matching placebo *(darker line)*. Note the divergent slopes of each line, implying a sustained risk of death (presumed proarrhythmia). *(From The CAST Investigators. Preliminary report: Effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 1989;321:406–412, with permission.)*

mia, presumably caused by proarrhythmia (Fig. 19–11). Analysis of the moricizine arm indicated neither harm nor benefit from this therapy; therefore, only this portion of the study was allowed to continue as CAST II.[64] However, in July 1991, CAST II was also prematurely stopped because there was a trend toward an increase in mortality in moricizine-treated patients. This increase in mortality was primarily observed during the initiation of moricizine therapy (dose-titration phase) but not during the chronic treatment phase. The overall results of the two CASTs conclusively prove that that the use of antiarrhythmic drug therapy (beyond the general use of β-blocking agents) to suppress PVCs in patients after a MI does not improve survival and is most likely detrimental. These studies also put into perspective the risk associated with the use of antiarrhythmic therapy and the need to carefully select only those patients with a defined therapeutic benefit.

Even though the CAST was conducted nearly 2 decades ago, it is considered one of the most important trials ever undertaken and has had a tremendous influence on the overall approach to the treatment of arrhythmias, as well as a far-reaching impact on new drug development. The results of the CAST have clearly had a negative influence on the long-term use of all antiarrhythmics, causing a broad skepticism in the risk-versus-benefit analysis of this class of drugs. Consequently, pharmaceutical companies have shifted their drug discovery and investigative efforts away from potent sodium channel blockers. As immediate fallout, encainide was withdrawn from the market, and another type Ic agent, indecainide, was not even brought to market despite approval by the Food and Drug Administration. The findings of the CAST also provided additional fuel for the pursuit of nondrug therapies for arrhythmias, such as ablation and implantable devices.

Despite the discouraging results of the CAST, post-MI patients with complex ventricular ectopy remain at risk for death. Other drugs, besides the type Ic agents, have been studied, including sotalol. Sotalol is marketed as a racemic mixture of a *d* and *l* isomer: both are type III potassium blockers but the *l* isomer has β-blocking actions. Chronic therapy with *d*-sotalol was studied in patients with remote MI complicated by complex ectopy in the Survival With Oral *d*-Sotalol trial.[65] Unlike the CAST, *d*-sotalol treatment was not designed to cause PVC suppression, yet (like the CAST) the trial was halted prematurely because of excessive mortality in the treatment arm. Again, the presumed reason for this observation was *d*-sotalol–related proarrhythmia. Currently, only two antiarrhythmic drugs have been shown *not* to increase mortality with long-term use: amiodarone and dofetilide. A number of trials[66,67] have shown amiodarone to decrease the incidence of sudden (or arrhythmic) death, but not total mortality, in post-MI patients with complex ventricular ectopy. A meta-analysis of all trials (6,553 combined patients) demonstrated a reduction in total mortality (by 13%) with long-term amiodarone therapy.[68] It is unclear if these findings can be attributed to one property (e.g., β-blocking) or a combination of amiodarone's complex pharmacologic effects on conduction. Noteworthy is that in two major studies, patients treated with amiodarone *and* a β-blocker generally did better than when no β-blocker was used.[66,67] Clearly, because of its impressive adverse effect profile and its inability to improve survival, amiodarone cannot routinely be recommended in patients with heart disease such as remote MI and complex PVCs. Two randomized, controlled trials[69,70] showed that chronic therapy with dofetilide has no effect on overall mortality in patients who have suffered MI with LV dysfunction. Dofetilide (not approved for prevention of sudden death) caused TdP in approximately 5% of patients, necessitating a protocol amendment with dosage adjustments during both trials (particularly in those with renal disease because its primary route of elimination is through the kidney).

How should the clinician approach the patient with documented asymptomatic PVCs? Clearly, attempts to suppress asymptomatic PVCs should not be made with any antiarrhythmic drug. Indeed, those patients who are at risk for arrhythmic death (recent MI, LV dysfunction, complex PVCs) should not be routinely given *any* type I or III antiarrhythmic agent.[71] If these patients have symptomatic PVCs, chronic drug therapy should be limited to the use of β-blockers. The use of β-blockers in post-MI patients is associated with a decrease in the incidence of total mortality and SCD, especially in the presence of LV dysfunction. These agents can also be used in patients without underlying structural heart disease to suppress symptomatic PVCs. 7

VENTRICULAR TACHYCARDIA

Mechanisms and Types of VT

Ventricular tachycardia is a wide QRS tachycardia that may acutely occur as a result of metabolic abnormalities, ischemia, or drug toxicity, or chronically recur as a paroxysmal form. On electrocardiographic inspection, VT may appear as either repetitive monomorphic or polymorphic ventricular complexes. The definition of VT is three or more consecutive PVCs occurring at a rate greater than 100 beats/min. An acute episode of VT may be precipitated by severe electrolyte abnormalities (hypokalemia), hypoxemia, or digitalis toxicity, or (most commonly) may occur during an acute MI or ischemia complicated by HF. In these cases, correction of the underlying precipitating factors will usually prevent further recurrences of VT. As an example, if VT occurs during the first 24 hours of an acute MI, it will probably not reappear on a chronic basis after the infarcted area has been reperfused or healed with scar formation. This form of acute VT may be caused by a transient reentrant mechanism within temporarily ischemic or dying ventricular tissue. In contrast, some patients have a chronic recurrent form of VT that is almost always associated with some type of underlying structural heart disease. Common examples are paroxysmal VT associated with idiopathic dilated cardiomyopathy or remote MI with a LV aneurysm. Indeed, severe LV dysfunction and aneurysm formation are risk factors for the development of VT on a recurrent basis after MI. In chronic, recurrent VT, microreentry within the distal Purkinje network is presumed to be responsible for the underlying substrate in a large majority of patients (see Fig. 19–3). Theoretically, electrophysiologic discrepancies occur as a result of structural damage and heart disease within the ventricular conducting system. The reentrant circuit may possess both anatomically determined and functional properties coursing through

normal tissue, damaged (but not dead) tissue and islands of necrosed tissue. In a minority of patients, macro-reentrant circuits may be responsible for recurrent VT, including reentry incorporating the bundle branches.

Patients with acute VT associated with a precipitating factor often suffer severe symptoms, requiring immediate treatment measures. Chronic recurrent VT may also cause severe hemodynamic compromise, but may also be associated with only mild symptoms, which are generally well tolerated. Sustained VT is that which requires therapeutic intervention to restore a stable rhythm or persists for a relatively long time (usually longer than 30 seconds). Nonsustained VT is that which self-terminates after a brief duration (usually less than 30 seconds). If the patient has VT more frequently than sinus rhythm (i.e., VT is the dominant rhythm), this is referred to as incessant VT. In monomorphic VT, the QRS complexes are similar in morphologic characteristics from beat to beat. In polymorphic VT, the QRS complexes vary in shape between beats. A characteristic type of polymorphic VT, in which the QRS complexes appear to undulate around a central axis and is associated with evidence of delayed ventricular repolarization (long QT interval or prominent U waves), is referred to as TdP.

Most but not all forms of recurrent VT occur in patients with extensive structural heart disease. Ventricular tachycardia occurring in a patient without structural heart disease is sometimes referred to as "idiopathic VT" and may take several forms.[72–74] Fascicular tachycardia arises from a fascicle of the left bundle branch (usually posterior) and is usually not associated with severe underlying structural heart disease. In distinct contrast to the common form of recurrent VT associated with extensive structural heart disease, nondihydropyridine CCBs (but not adenosine) are effective in terminating an acute episode of fascicular VT. Ventricular outflow tract tachycardia (usually originating from the right ventricular outflow tract) originates from near the pulmonic valve (or uncommonly the aortic valve) and also occurs in patients with normal LV function without discernible cardiac disease.[74] Unlike other forms of VT, right ventricular outflow tract tachycardia often terminates with adenosine and may be prevented with β-blockers and/or nondihydropyridine CCBs.

Some unusual forms of VT are congenital or heritable (Table 19–10). Torsade de pointes can be associated with heritable defects in the flux of ions that govern ventricular repolarization. Although nine syndromes and genetic mutations have been described, the more common examples are long QT syndrome 1 (depressed I_{Ks}), long QT syndrome 2 (depressed I_{Kr}), and long QT syndrome 3 (enhanced inward sodium ion flux during repolarization).[75,76] Polymorphic VT (without a long QT interval) or VF may also occur as a result of a heritable defect in the sodium channel. This is the case in Brugada syndrome, described as a typical ECG pattern (ST-segment elevation in leads V_1 to V_3) in sinus rhythm associated with SCD, commonly in males of Asian descent.[77] It is estimated that Brugada syndrome accounts for approximately 40% of all cases of VF in patients without heart disease.

Management

Consider the patient with the more common form of sustained monomorphic VT (i.e., those with structural heart disease, usually ischemic in nature). Like other rapid tachycardias, the initial management of an acute episode of VT (with a pulse) requires a quick assessment of the patient's status and symptoms. If severe symptoms are present (i.e., severe hypotension, angina, pulmonary edema), synchronized DCC should be delivered immediately to attempt to restore sinus rhythm. An investigation should be made into possible precipitating factors and these should be corrected if possible. The diagnosis of acute MI should be entertained. If the episode of VT is thought to be an isolated electrical event associated with a transient initiating factor (such as acute myocardial ischemia or digitalis toxicity), there is no need for long-term antiarrhythmic therapy once the precipitating factors are corrected (e.g., an infarct has been reperfused and healed and the patient is stable). Nevertheless, the patient should be monitored closely for possible recurrences of VT.

Patients presenting with an acute episode of VT (with a pulse) associated with only mild symptoms can be initially treated with antiarrhythmic drugs (synchronized DCC should be readily available). The reader is referred to the most recent guidelines for CPR and emergency cardiovascular care put forth by the AHA.[53] Intravenous amiodarone is now recommended as first-line antiarrhythmic therapy in this situation. Intravenous procainamide or lidocaine are suitable alternatives, although in one small study comparing these two agents, procainamide was shown to be superior in terminating VT.[78] Synchronized DCC should be delivered if the patient's status deteriorates, VT degenerates to VF (would be unsynchronized in this situation), or drug therapy fails.

Once an acute episode of sustained VT has been successfully terminated by electrical or pharmacologic means and an acute MI has been ruled out, the possibility of a patient having recurrent episodes of VT should be considered. Evidence for the possibility of VT recurrence can often be gleaned from invasive electrophysiologic studies using programmed ventricular stimulation. The management of the patient with chronic, recurrent, sustained VT deserves considerable attention. Because these patients are at extremely high risk for death, trial-and-error attempts to find effective therapy are unwarranted. To gain some objective evidence of a response to a specific antiarrhythmic regimen, serial testing of these drugs using the following two surrogate end points has been used: (a) inability to induce sustained VT with programmed extrastimuli by invasive electrophysiologic studies and (b) suppression of ventricular ectopic beats by serial 24-hour continuous electrocardiographic (Holter) monitoring. These two strategies have been compared[79,80] but largely abandoned for several reasons. First, the yield for finding an effective drug is low. For instance, sustained monomorphic VT can be rendered noninducible or nonsustained by programmed stimulation protocols in only 20% to 25% of patients. Therefore, the clinician frequently must search for other therapeutic options or settle for other treatment end

TABLE 19-10 Heritable Polymorphic Ventricular Tachycardia

Syndrome	Channel Defect	Mutant Gene	Characteristics	Treatment
$LQTS_1$	$\downarrow I_{Ks}$	KVLQT1	SCD/TdP with exercise	BB/ICD
$LQTS_2$	$\downarrow I_{Kr}$	HERG	SCD/TdP with arousal	BB/ICD
$LQTS_3$	$\uparrow I_{Na}^+$ during plateau/repolarization	SCN5A	SCD/TdP at rest/sleep	Flecainide Mexiletine/ICD
Brugada	$\downarrow I_{Na}^+$	SCN5A	SCD/PMVT or VF at rest/sleep in Asian males	ICD/quinidine

BB, β-blocker; ICD, implantable cardioverter-defibrillator; LQTS, long QT syndrome; PMVT, polymorphic ventricular tachycardia; SCD, sudden death; TdP, torsade de pointes; VF, ventricular fibrillation.

Note: LQTS can be provoked by potassium channel blockers (e.g., quinidine, sotalol) and Brugada syndrome can be provoked by potent sodium channel blockers (e.g., cocaine, flecainide). $LQTS_3$ and Brugada syndrome may coexist.

points such as slower and more tolerable inducible VT. Second, amiodarone is clearly the most effective (approximately 50% effective after 2 years) agent in patients with recurrent VT; however, electrophysiologic drug testing does not necessarily predict the clinical efficacy of amiodarone. Patients may have continued inducibility of VT on amiodarone despite long-term success. Indeed, empiric amiodarone has been compared to therapy (with other agents) guided by electrophysiologic testing in patients at high risk for recurrent VT.[81] In this trial, amiodarone therapy without invasive testing was superior in preventing SCD and recurrences of severe ventricular arrhythmias at all time points. Third, the recurrence rate of life-threatening VT is high (20% to 50% per year depending on the drug chosen), regardless of the method of acute drug testing. Fourth, is the substantial side-effect profile of the type I and type III antiarrhythmic agents referred to previously. Lastly, and perhaps most importantly, is the impressive demonstrated effectiveness of nondrug approaches to the treatment of recurrent VT/VF.[82] For instance, some forms of recurrent VT are amenable to catheter ablation therapy using radiofrequency current. This approach is highly effective (approximately 90%) in idiopathic VT (right ventricular outflow tract or fascicular VT), but less so in recurrent VT associated with a cardiomyopathic process or remote MI with LV aneurysm. In the latter patients, ablation is usually regarded as second-line therapy after other methods have failed.

The Implantable Cardioverter-Defibrillator The introduction of and advances in the ICD (Fig. 19–12) have obviated the need for serial drug testing (by invasive or noninvasive methods).[83] 8 Numerous advancements in device technology have allowed the ICD to become smaller, less invasive to implant, and programmable. Early ICDs required a thoracotomy to place the generator in the abdomen, whereas with the newer, smaller models, the leads are implanted transvenously with the generator placed into the pectoral region in a manner similar to cardiac pacemakers. Modern ICDs now employ a "tiered-therapy approach" meaning that overdrive pacing (i.e., antitachycardia pacing) can be attempted first to terminate the tachyarrhythmia (no painful shock delivered), followed by low-energy cardioversion, and, finally, by painful, high-energy defibrillation shocks. In addition, backup antibradycardia pacing and extended battery lives have made these newer devices much more attractive. All models store recordings during delivery of pacing shocks; this is extremely important in discerning appropriate from inappropriate shocks (i.e., delivers shock for AF with rapid ventricular rate) and in documenting true recurrences of the patient's tachycardia.

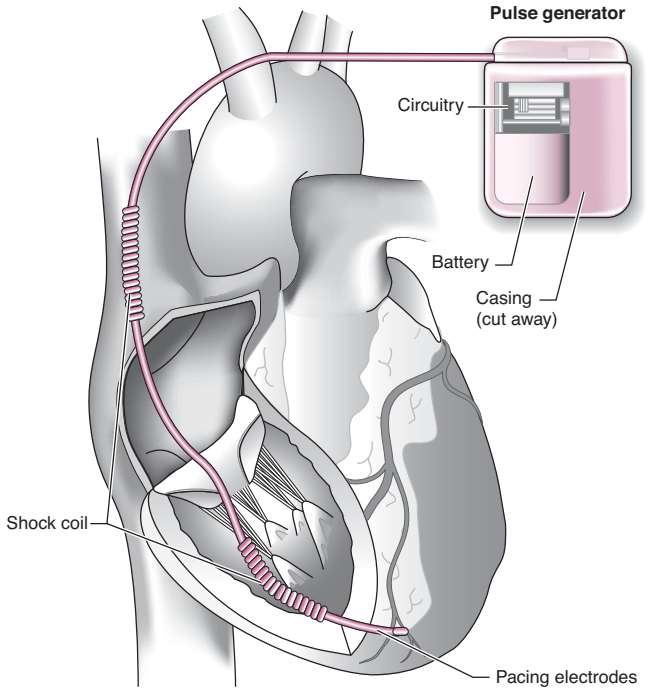

FIGURE 19-12. Drawing showing implantable cardioverter defibrillator. *(From reference 83 with permission.)*

Although the ICD is a highly effective method for preventing SCD due to recurrent VT or VF,[84] several problems remain. First, the device itself, implantation procedure, electrophysiologic studies, hospitalization, and physician fees are costly. Given that the indications for receiving an ICD have significantly expanded over the past several years, the total cost associated with the implantation of this device is likely to place a great burden on the healthcare system. Second, many patients (as high as 70% of patients) end up receiving antiarrhythmic drugs (usually amiodarone or sotalol) in addition to the ICD.[85,86] Antiarrhythmic drugs can be initiated in these patients for a number of reasons, including: (a) decreasing the frequency of VT/VF episodes to subsequently reduce the frequency of appropriate shocks; (b) reducing the rate of VT so that it can be terminated with antitachycardia pacing; and (c) decreasing episodes of supraventricular arrhythmias (e.g., AF, atrial flutter) that may trigger inappropriate shocks. As result of these potential benefits, the concomitant use of antiarrhythmic drugs can minimize patient discomfort and prolong the battery life of the ICD. The decision to initiate concomitant antiarrhythmic therapy should be individualized, with treatment usually being reserved for those with frequent shocks because of VT or AF. If antiarrhythmic drugs are added to ICD therapy, one should note that many agents alter defibrillation thresholds; consequently, the device should be reprogrammed to account for this alteration.[87]

Secondary Prevention of Sudden Cardiac Death Over the past decade, numerous trials have established the ICD as a superior treatment over antiarrhythmic therapy not only for the secondary prevention of SCD in patients who have been resuscitated from cardiac arrest or had sustained VT ("secondary prevention"), but also for the prevention of an initial episode of SCD in certain high-risk patient populations ("primary prevention"). With regard to the use of ICDs for secondary prevention, the results of three trials, the Antiarrhythmics Versus Implantable Defibrillators (AVID), Cardiac Arrest Study Hamburg (CASH), and Canadian Implantable Defibrillator Study (CIDS), definitively support this device as first-line therapy in this patient population.[88–90] Of these, the AVID trial was the largest, randomizing more than 1,000 patients with resuscitated VF, sustained VT with syncope, or hemodynamically significant sustained VT (with LVEF ≤40%) to either an ICD or antiarrhythmic drugs (~95% receiving amiodarone at discharge).[88] The trial was stopped early because of a demonstrated superiority of the ICD; patients in the ICD group had a better overall survival when compared to those in the antiarrhythmic drug group (75% vs. 64%, respectively, at 3 years). Although they were smaller trials, both CASH and CIDS demonstrated the efficacy of an ICD compared with amiodarone in patients with a history of sustained VT or VF, with the ICD reducing overall mortality by 20% to 25%.[89,90] Despite the high costs, the results of AVID, CASH, and CIDS provide strong support for the aggressive use of the ICD in patients who are at high risk for recurrent, life-threatening ventricular arrhythmias. Implantation of an ICD can be cost-effective, particularly in patients with poor LV function. Although nearly all clinicians now consider the ICD as first-line treatment for secondary prevention of SCD, there is at least one possible patient group that may do as well with antiarrhythmic drug therapy alone. In the AVID trial, there was no difference in survival between ICD and antiarrhytmic drug treatment in patients with mild LV dysfunction (LVEF >35%), which suggests that long-term amiodarone therapy may be appropriate to use in this lower-risk patient population.[88] However, because this data was obtained from a post-hoc analysis, additional trials need to be performed to confirm these findings.

Primary Prevention of Sudden Cardiac Death Over the past decade, the above trials have established the ICD as an effective treatment for the secondary prevention of SCD in patients who have previously suffered a documented episode of VT or VF. Most of the studies that have been performed in the past several years have focused on the efficacy of the ICD for primary prevention in patients deemed to be at high risk for SCD.[91–94]

One of the patient populations that appears to be at high risk for a first episode of SCD are those with a prior MI, LV dysfunction, and nonsustained VT. The use of antiarrhythmic drugs to prevent SCD in this high-risk group has been significantly limited by the results of the CAST and other similar trials that have collectively demonstrated that these drugs may actually increase the risk of mortality in these patients. As a result of these trials, clinicians have sought a more clearly defined strategy for risk stratification in these patients before initiating drug therapy.

Traditionally, there are three strategies to approach the treatment of nonsustained VT: (a) conservative (i.e., no antiarrhythmic drug treatment beyond β-blockers), (b) empiric amiodarone, and (c) aggressive (i.e., electrophysiologic studies with possible insertion of an ICD) (Fig. 19–13). 9 A number of early studies[95,96] suggested that tests such as electrophysiologic studies could be used to determine long-term risk in patients with nonsustained VT. For instance, Wilbur et al.[95] demonstrated that post-MI patients with nonsustained VT and inducible sustained VT after programmed stimulation were at increased risk for subsequent VT/VF or SCD compared to those in whom sustained VT could not be induced. These data provided the basis for the Multicenter Automatic Defibrillator Implantation Trial (MADIT) and the Multicenter Unsustained Tachycardia Trial (MUSTT).[91,92] The MADIT was the first of these trials to be conducted to evaluate the efficacy of ICD therapy in this high-risk patient population. Specifically, this trial randomized patients with a previous MI, LVEF ≤36%, asymptomatic nonsustained VT, and inducible VT that was not suppressed with the use of IV procainamide to receive an ICD or conventional medical therapy (74% of patients in this particular group received amiodarone).[91] This trial was terminated prematurely after a significant survival benefit was detected in the ICD group. The findings of the MADIT were subsequently supported by those of the MUSTT. In the MUSTT, patients with a history of MI, LVEF ≤40%, asymptomatic nonsustained VT, and inducible sustained VT were randomized to the conservative approach (no antiarrhythmic drug therapy beyond β-blockers) or electrophysiologically-guided therapy (antiarrhythmic drugs and/or ICD).[92] The results showed that the conservative approach had a significantly higher event rate (cardiac arrest or death from arrhythmia). However, when the results of the electrophysiologically-guided group were further stratified, those receiving only antiarrhythmic drugs (no ICD) were no different in terms of outcomes than those who received no treatment. In other words, only those treated with an ICD had a significantly lower event rate and greater survival. One problem with the MUSTT, however, is that because of when the trial was initiated (1989), nearly 50% of patients received type I antiarrhythmic drugs or drugs that are now known not to improve survival in patients with coronary artery disease, LV dysfunction, and ventricular arrhythmias; only 10% of patients received the most effective agent in this setting, amiodarone. Based on the results of the MADIT and MUSTT, it is reasonable for patients with coronary artery disease, LV dysfunction, and nonsustained VT to undergo electrophysiologic testing;[97] that is, invasive electrophysiologic studies with programmed stimulation are used to determine risk and guide subsequent therapy. If these patients do not have inducible sustained VT/VF, chronic antiarrhythmic drug therapy is unnecessary; however, if these patients do have inducible sustained VT/VF, implantation of an ICD is warranted.

Although the MADIT and MUSTT provided clinicians with important information regarding risk stratification, both of these trials targeted patients who had a history of nonsustained VT. The results of two landmark trials, the MADIT II and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), have provided clinicians with additional information regarding the treatment of other groups of high-risk patients who have no prior history of ventricular arrhythmia (see Fig. 19–13).[93,94] In the MADIT II, patients with a prior MI and LVEF ≤30% were randomized to receive either an ICD or conventional therapy (routine post-MI and HF therapy).[93] Neither a history of ventricular arrhythmia nor electrophysiologic testing was required for inclusion in this study. Patients in the ICD group experienced a significant reduction in mortality when compared to the conventional therapy group; the reduction in mortality in the ICD group was primarily due to a reduction in arrhythmic death. Whereas the MADIT, MUSTT, and MADIT II limited enrollment to patients with ischemic cardiomyopathy, the SCD-HeFT is the largest trial, to date, to evaluate the efficacy of an ICD in a nonischemic HF population. In this trial, patients with NYHA class II or III HF (of either ischemic or nonischemic etiology) and LVEF ≤35% were randomized to receive placebo, amiodarone, or an ICD.[94] All patients were treated with appropriate HF therapies, as indicated. Implantation of an ICD resulted in a significantly lower mortality rate compared to treatment with either placebo or amiodarone (there was no difference between placebo and amiodarone). The survival benefits of the ICD were observed regardless of the etiology of the HF.

Overall, as the ICD trials have evolved over the past decade, the indications for implanting these devices have significantly expanded (Table 19–11).[97] Based on the results of the MUSTT, MADIT, MADIT II, and SCD-HeFT, many patients will be eligible for an ICD. 9 In fact, just based on the results of the MADIT II and SCD-HeFT alone, it is estimated that an additional 500,000 Medicare beneficiaries will now qualify for implantation of an ICD for primary prevention of SCD.

VENTRICULAR PROARRHYTHMIA

All antiarrhythmic agents have the potential to aggravate existing arrhythmias or to cause new arrhythmias. It is believed that antiarrhythmic drugs may cause proarrhythmia in 5% to 20% of patients.[10] Although drug-induced arrhythmias have been recognized for several years, only recently has this adverse effect gained widespread attention. Many definitions for proarrhythmia have been proposed; however, in the simplest terms, it indicates the development of a significant new arrhythmia (such as VT, VF, or TdP) or worsening of an existing arrhythmia (episodes are longer, faster, or more frequent). As with all arrhythmias, the consequences of proarrhythmia are varied. Some patients who develop proarrhythmia may be totally asymptomatic, others may notice a worsening of symptoms, and some may die suddenly from this side effect. The development of proarrhythmia results from the same mechanisms that cause arrhythmias in general (e.g., quinidine-induced TdP due to EADs) or from an alteration in the underlying substrate due to the antiarrhythmic agent (e.g., development of an accelerated tachycardia caused by flecainide which decreases conduction velocity without significantly altering the refractory period) (see Fig. 19–4).[10] The diagnosis of proarrhythmia is sometimes difficult to make because of the variable nature of the underlying arrhythmias. However, in all cases, the agent should be discontinued if proarrhythmia is detected or suspected.

Incessant Monomorphic VT

The prototypical form of proarrhythmia caused by the type Ic antiarrhythmic drugs is a rapid, sustained, monomorphic VT with a characteristic sinusoidal QRS pattern that is often resistant to resuscitation with cardioversion or overdrive pacing. 10 It is sometimes referred to as sinusoidal or incessant VT and is the result of excessive sodium

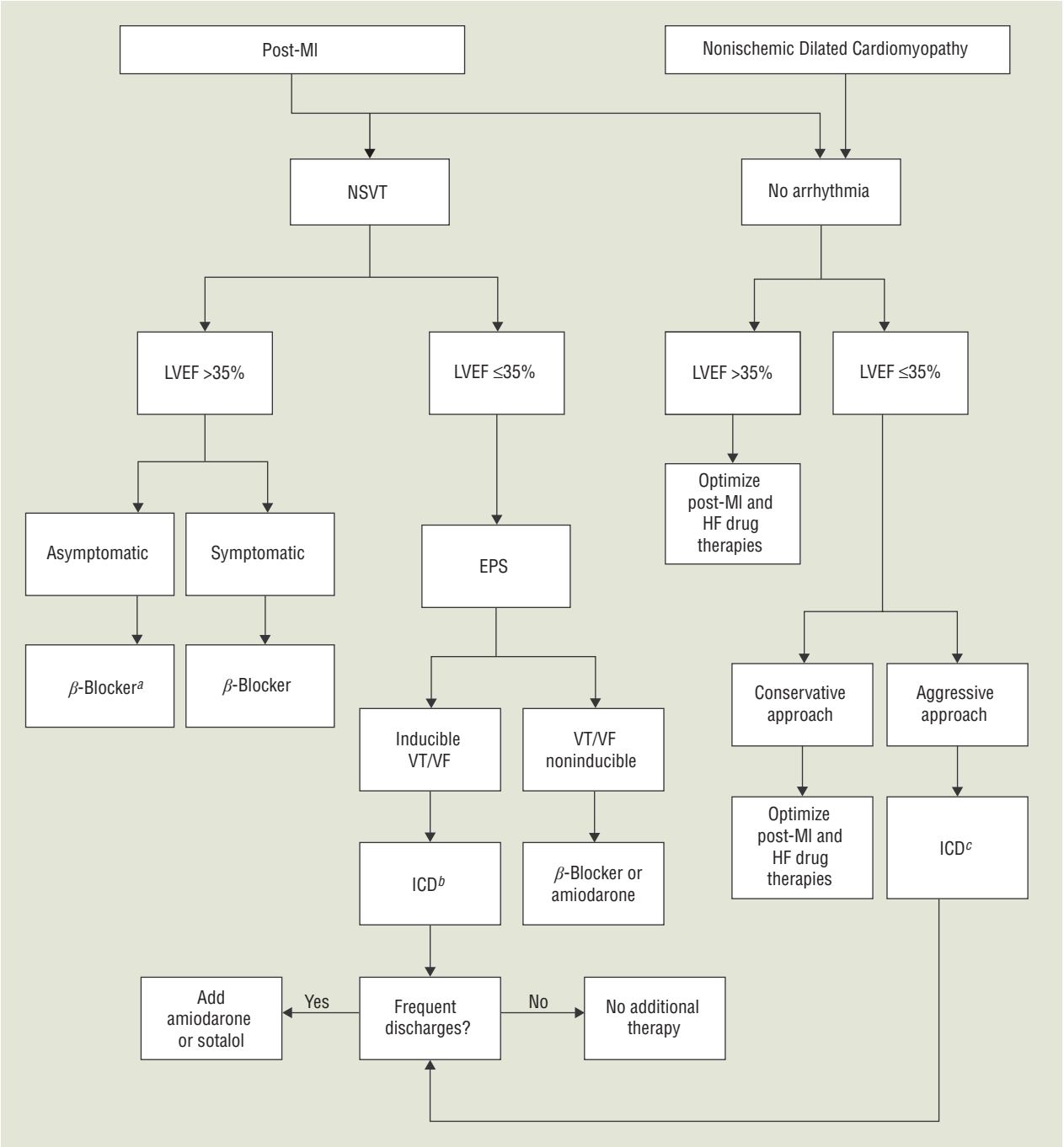

FIGURE 19-13. Algorithm for the primary prevention of sudden cardiac death in patients with a history of myocardial infarction or with a nonischemic dilated cardiomyopathy. [a]In these patients, the β-blocker is being used to reduce post-MI mortality. [b]Patients should be >40 days post-MI prior to insertion of ICD. [c]Patients with an ischemic cardiomyopathy should be >40 days post-MI prior to insertion of ICD. (EPS, electrophysiologic study; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSVT, nonsustained VT; VF, ventricular fibrillation; VT, ventricular tachycardia.)

channel blockade and slowed conduction. Sinusoidal VT caused by the type Ic drugs was thought to occur within the first several days of drug initiation; however, the results of the CAST indicate that the risk for this type of proarrhythmia may exist as long as the agent is continued. Factors that definitely predispose a patient to this form of proarrhythmia are: (a) the presence of underlying ventricular arrhythmias, (b) ischemic heart disease, and (c) LV dysfunction. Provocation of proarrhythmia by the type Ic drugs is sometimes reported during exercise, which is most likely a result of augmented slowed conduction at rapid heart rates (i.e., rate-dependent sodium blockade). The incidence of proarrhythmia caused by type Ic drugs is greatest in patients with all three risk factors (approximately 10% to 20%) and extremely uncommon in those without risks, such as patients with supraventricular tachycardias and normal LV function. In one study, in patients with risk factors, the incidence of death due to proarrhythmia from encainide and flecainide was approximately the same as the chance of long-term effectiveness![98] Other factors that have a less well-defined association with proarrhythmia are elevated antiarrhythmic serum concentrations and rapid dosage escalation. It has been proposed that the presence of underlying ventricular conduction delays may also pose a risk for proarrhythmia. As mentioned earlier, this arrhythmia is resistant to resuscitation; however, some have had success with lidocaine (competes for sodium channel receptor) or sodium bicarbonate (reverses the excessive sodium channel blockade).

TABLE 19-11 Current Indications for ICD Implantation

Secondary prevention indications

1. Documented episode of cardiac arrest caused by VF (not a result of transient or reversible cause)[a]
2. Documented sustained VT, either spontaneous or induced at electrophysiologic study, not associated with an acute MI and not a result of transient or reversible cause

Primary prevention indications

1. Documented familial or inherited conditions with a high-risk of life-threatening VT (i.e., long QT syndrome, Brugada syndrome, or hypertrophic cardiomyopathy)
2. Coronary artery disease (with prior MI >40 days before ICD insertion), LVEF ≤35%, and sustained VT or VF induced at electrophysiologic study[a]
3. Prior MI (>40 days before ICD insertion) and LVEF ≤30%
4. Ischemic dilated cardiomyopathy, prior MI (>40 days before ICD insertion), NYHA class II or III HF, and LVEF ≤35%
5. Nonischemic dilated cardiomyopathy (>9 months), NYHA class II or III HF, and LVEF ≤35%
6. Nonischemic dilated cardiomyopathy (>3 months but <9 months), NYHA class II or III HF, and LVEF ≤35%
7. Patients meeting requirements for cardiac resynchronization therapy with NYHA class IV HF

HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; VF, ventricular fibrillation; VT, ventricular tachycardia.

[a]The electrophysiologic study must be performed >4 weeks after the MI.

Torsade de Pointes

As defined previously, TdP is a rapid form of polymorphic VT (Fig. 19–14) that is associated with evidence of delayed ventricular repolarization (long QT interval or prominent U waves) on ECG. It is important to note that most forms of polymorphic VT occurring in the setting of a normal QT interval are similar to monomorphic VT in terms of etiology and treatment strategies (thus, a long QT interval is crucial to the diagnosis of TdP). Much has been learned about the underlying etiology of TdP. Basic defects (genetic, drugs or diseases) that delay repolarization by influencing ion movement (usually by blocking potassium efflux) provoke EADs, preferentially in cells deep in the heart muscle (termed *M cells*), which, in turn, trigger reentry and TdP. Drugs that cause TdP usually delay ventricular repolarization in an inhomogeneous way (termed *dispersion of refractoriness*), which facilitates the formation of multiple reentrant loops in the ventricle.[99] Torsade de pointes may occur in association with hereditary syndromes or as an acquired form (i.e., a result of drugs or diseases). The underlying etiology in both cases is delayed ventricular repolarization due to blockade of potassium conductance. It is possible, however, that some individuals have a partially expressed form of these congenital syndromes but never suffer TdP unless some other external factor (drugs, diseases) further delays ventricular repolarization. Acquired forms of TdP are associated with electrolyte disturbances (hypokalemia or hypomagnesemia), subarachnoid hemorrhage, myocarditis, liquid protein diets, arsenic poisoning, hypothyroidism, or, most commonly, drug therapy (notably phenothiazines, antibiotics, antihistamines, antidepressants, and antiarrhythmics) (Table 19–12). 10

The type Ia antiarrhythmic drugs (especially quinidine) and type III I_{Kr} blockers are most notorious for precipitating TdP; the types Ib and Ic antiarrhythmic drugs rarely, if ever, cause TdP. Most antiarrhythmic drugs with I_{Kr} blocking activity cause TdP in approximately 2% to 4% of patients, with the exception being amiodarone (<1%). Risk factors and associated features of drug-induced TdP have been identified and can be summarized as follows[28,100]: (a) high dosages or plasma concentrations of the offending agent ("dose-related") (except for quinidine-induced TdP, which tends to occur more frequently at low-to-therapeutic concentrations); (b) concurrent structural heart disease (e.g., ischemic heart disease, HF, and/or LV hypertrophy); (c) evidence of mild delayed repolarization (prolonged QT interval) at baseline; (d) evidence of a prolonged QT interval shortly after initiation of the offending agent; (e) concomitant electrolyte disturbances such as hypokalemia or hypomagnesemia; (f) female gender; and (g) a characteristic long–short initiating sequence (so-called "pause" dependence) of the episode of TdP (see Fig. 19–14). However, none of these associations are absolute prerequisites to the occurrence of drug-induced TdP. For instance, although usually documented early in the course of therapy, patients may suffer TdP during chronic quinidine treatment.[101] The reason for quinidine's relatively unique propensity for causing TdP at relatively low dosages and concentrations requires explanation. Quinidine's ability to block I_{Kr} is clinically manifest at low concentrations; at higher

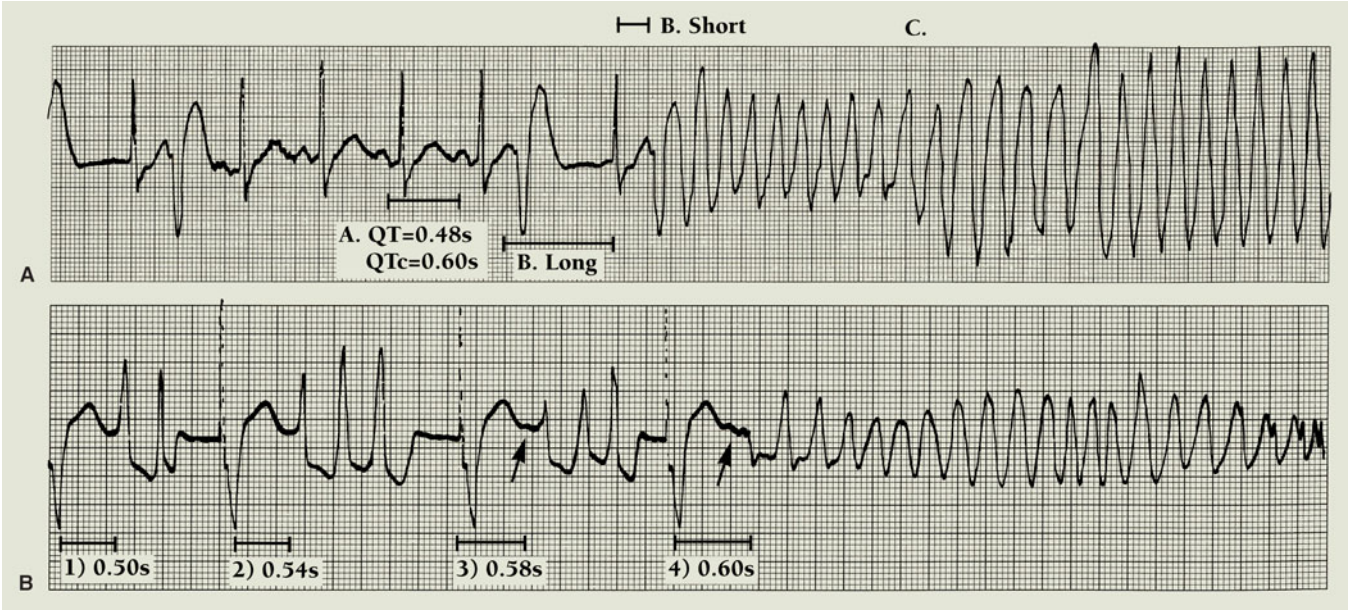

FIGURE 19-14. Torsade de pointes caused by quinidine. Note the presence of a couplet and two triplets following each extra systolic pause. The pause gets progressively longer until it is long enough to result in an episode of sustained torsade de pointes. Also, as the pause lengthens, discernible U waves (labeled ↑) (EADs?) begin to appear. The amplitude of the U wave is somewhat greater with the longest pause. *(From Bauman JL. Drug safety: Cardiac arrhythmias. Antihistamine update symposium. Hosp Med 1995;31:24, with permission.)*

concentrations its sodium-blocking properties predominate. Other agents that block I_{Kr} usually do so in a concentration-dependent fashion. The observation that most patients who suffer drug-induced TdP have evidence of mildly delayed repolarization (long QT intervals) even before they are prescribed the offending agent has stimulated a search for a potential genetically linked risk. Could it be that patients with drug-induced TdP have a partially expressed form of the congenital long QT syndrome? Indeed, it does appear that at least some of these patients with acquired drug-induced TdP appear to possess mutations of genes that encode for I_{Kr} or I_{Ks}.[100]

The common underlying electrophysiologic cause of TdP is a delay in ventricular repolarization (provoking EADs), which usually results from inhibition (drug-induced or genetic) of I_K current and manifests as QT interval prolongation on the ECG. Therefore, the extent of QT interval prolongation has been used as a measurement of risk of TdP; however, considerable controversy exists. Amiodarone, for example, commonly causes significant QT prolongation but is a relatively infrequent cause of TdP. Nonetheless, the QT interval should be measured and monitored in all patients prescribed drugs that have a high potential for causing TdP (see Table 19–12). Patients with a baseline QT_c interval (QT interval corrected for heart rate) >450 msec should not be given these agents; an increase in the QT_c interval to ≥560 msec after the initiation of the drug is an indication to discontinue the agent or, at least, to reduce its dosage and carefully observe and monitor. The QT_c interval can be calculated using Bazett's formula: $QT_c = QT\ measured/\sqrt{R\text{-}R\ interval}$.

Drug-induced TdP has become an extremely visible hazard plaguing new drugs, sometimes resulting in public health disasters. For instance, six drugs (cisapride, astemizole, terodiline, levomethadyl, grepafloxacin, and terfenadine) have been withdrawn from the market in the United States because of TdP. One of the most visible and striking examples was with regard to the popular nonsedating antihistamine, terfenadine. Terfenadine is a potent I_{Kr} blocker but is rapidly metabolized by CYP3A4 to an active moiety (fexofenadine) that is not associated with delayed repolarization. Consequently, in the presence of drugs that block the CYP3A4 isoenzyme (e.g., ketoconazole, erythromycin, diltiazem), accumulation of the parent compound, terfenadine, causes clinically significant blockade of I_{Kr} that could result in TdP and even death.[102] Because of experiences like this, all new drug entities under investigation are screened for their ability to block I_K and cause significant QT prolongation.

Acute treatment of TdP is different than treatment for the more common acute monomorphic VT. For an acute episode of TdP, most patients will require and respond to DCC. However, TdP tends to be paroxysmal in nature and often will rapidly recur after DCC. Therefore, after the initial restoration of a stable rhythm, therapy designed to prevent recurrences of TdP should be instituted. Drugs that further prolong repolarization such as IV procainamide are absolutely contraindicated. Lidocaine is usually ineffective. Although there are no true efficacy trials, IV magnesium sulfate, by suppressing EADs, is now considered the drug of choice in preventing recurrences of TdP.[103] If IV magnesium sulfate is ineffective, treatment strategies designed to increase heart rate, shorten ventricular repolarization, and prevent the pause dependency should be initiated. Either temporary transvenous pacing (105 to 120 beats/min) or pharmacologic pacing (isoproterenol or epinephrine infusion) can be initiated for this purpose. All agents that prolong QT interval should be discontinued and exacerbating factors (such as hypokalemia or hypomagnesemia) should be corrected.

TABLE 19-12 Potential Causes of QT Prolongation and Torsade de Pointes

Conditions
Congenital long QT syndromes
Myocarditis
Myocardial ischemia/infarction
Heart failure
Severe bradycardia (<50 beats/min)
Hypokalemia
Severe hypothermia
Hypomagnesemia
Severe starvation/liquid-protein diets
Subarachnoid hemorrhage
Drugs
Antiarrhythmic drugs
Quinidine
Procainamide (also *N*-acetylprocainamide)
Disopyramide
Amiodarone
Dofetilide
Sotalol
Ibutilide
Bepridil[a]
Psychotropics
Phenothiazines (e.g. thioridazine, mesoridazine, chlorpromazine)
Tricyclic and tetracyclic antidepressants
Haloperidol/droperidol
Pimozide
Atypical antipsychotics (e.g. quetiapine, ziprasidone)
Toxins
Organophosphate insecticides
Arsenic
Antihistamines
Terfenadine[a]
Astemizole[a]
Antibiotics
Pentamidine
Macrolides (erythromycin and clarithromycin)
Trimethoprim-sulfamethoxazole
Fluoroquinolones (grepafloxacin,[a] sparfloxacin,[a] moxifloxacin, gatifloxacin, gemifloxacin)
Voriconazole
Pain
Methadone
Levomethadyl[a]
Miscellaneous
Liquid-protein diets[b]
Corticosteroids[b]
Diuretics[b]
Quinine
Chloroquine
Chloral hydrate
Cisapride[a]
Terodiline[a]
Tacrolimus

[a] Withdrawn from market because of torsade de pointes.
[b] More than likely a result of severe electrolyte imbalance.
Note: For a complete list, see *www.qtdrugs.org*.

VENTRICULAR FIBRILLATION

Background and Prevention

Ventricular fibrillation is electrical anarchy of the ventricle resulting in no cardiac output and cardiovascular collapse. Death will ensue rapidly if effective treatment measures are not taken. Patients who die abruptly (within 1 hour of initial symptoms) and unexpectedly (i.e., "sudden death") usually have VF recorded at the time of death.[61] Sudden cardiac death accounts for about 330,000 deaths per year in the United States. Sudden cardiac death occurs most commonly in patients with ischemic heart disease and primary myocardial disease associated with LV dysfunction; it occurs less commonly in those with WPW syndrome or mitral valve prolapse, and occasionally in those without associated heart disease (e.g., Brugada syndrome). Patients who have SCD (not associated with acute MI) but survive because of

appropriate CPR, often have inducible sustained VT and/or VF during electrophysiologic studies. These individuals are at high risk for the recurrence of VT and/or VF.

In contrast, patients who have VF associated with acute MI (i.e., within the first 24 hours after symptoms) usually have little risk of recurrence. Of all patients who die as a result of an acute MI, approximately 50% die suddenly prior to hospitalization. Ventricular fibrillation associated with acute MI can be subdivided into two types: primary VF and complicated or secondary VF. Primary VF occurs in an uncomplicated MI not associated with HF; secondary VF occurs in an MI complicated by HF. The time course, incidence, mechanisms, treatment, and complications of these two forms of VF are different. For example, approximately 2% to 6% of patients with acute MI suffer primary VF within 24 hours of chest pain, but the risk of VF declines rapidly over time and is nearly zero after the initial 24-hour period. Complicated or secondary VF does not follow such a predictable time course and may occur in the late infarction period. The premise of prophylactic antiarrhythmic drugs administered to all patients with uncomplicated MI is based on (a) the inability to predict which patients are at risk for primary VF and (b) the predictable time course of primary VF (in contrast to complicated VF). Of the prophylactic therapies used, lidocaine has been the most widely debated and studied. Lie et al.[104] performed the classic study showing the effectiveness of lidocaine in preventing primary VF. Although lidocaine significantly reduced the incidence of VF compared to placebo, there was no significant difference in mortality due to VF between the groups. This data, along with the effectiveness of rapidly instituted DCC in modern coronary care units with sophisticated monitoring techniques, have caused most to reject the notion of prophylactic lidocaine administration for all patients with uncomplicated MI. In support of this, two meta-analyses[105,106] concluded against the routine use of prophylactic lidocaine because of a possible increase in mortality in lidocaine-treated patients[105] as well as the declining incidence of primary VF documented in recent years (probably a result of the more aggressive and rapid use of β-blockers, thrombolytics, and percutaneous intervention for the treatment of acute coronary syndromes).[106]

The use of IV magnesium sulfate has also been entertained for the prevention of VF during the acute infarct period. Small trials implying its effectiveness were subsequently incorporated into a meta-analysis.[107] This meta-analysis found a decrease in the incidence of VT/VF and a reduction in total mortality with magnesium therapy. A subsequent large multicenter trial[108] found similar results, although most of the reduction in mortality was (surprisingly) attributed to HF deaths rather than to deaths caused by ventricular arrhythmia. These results would lead one to conclude that magnesium sulfate should be routinely administered to patients with suspected MI because of its ease of administration and safety. However, data from another large trial apparently has verified no such effectiveness of magnesium therapy in this setting.[109] Hence, prophylactic magnesium cannot be recommended. Indeed, no therapy (lidocaine, magnesium, or other antiarrhythmic drugs) has shown a conclusive benefit to prevent VF in the acute infarct period and no form of therapy can be recommended at this time.

Acute Management

A patient with pulseless VT or VF (with or without associated myocardial ischemia) should be managed according to the most recent AHA guidelines for CPR and emergency cardiovascular care.[53] To summarize, in patients with an unwitnessed arrest, five cycles (or 2 minutes) of CPR (one cycle of CPR = 30 chest compressions followed by 2 breaths) should be given before defibrillation. When the arrest is witnessed, and a defibrillator is readily available, defibrillation should be instituted immediately after two rescue breaths are provided; in these patients, there is no need for an initial period of CPR. Because of the increased availability of biphasic defibrillators which have a higher first-shock efficacy than monophasic defibrillators, delivery of only one shock at a time is recommended. For biphasic defibrillators, the dose of the shock to be used is device-specific; however, 200 joules can be used as the default if the effective dose range of the device is unknown. For all subsequent shocks, the initial dose or a higher dose can be used. If a monophasic defibrillator is used, 360 joules should be used for the initial as well as all subsequent shocks. After delivery of the initial shock, five cycles of CPR should be delivered, followed by a check of the patient's pulse and rhythm. If pulseless VT/VF is still present, another shock can be delivered, followed by five cycles of CPR. This general sequence of providing shocks followed by CPR can be followed as long as the patient remains in pulseless VT/VF.

Although there is very little, if any, evidence that demonstrates an increased survival rate with either vasopressor or antiarrhythmic agents in patients with pulseless VT/VF, these drugs still continue to play a role in the management of these ventricular arrhythmias.[53] To minimize interruptions in chest compressions, any vasopressor or antiarrhythmic administered during the course of the cardiac arrest should be given during CPR either before or after a shock. With regard to vasopressor therapy, either epinephrine or vasopressin can be administered if pulseless VT/VF persists after delivery of one or two shocks plus CPR. More specifically, epinephrine can be administered every 3 to 5 minutes while the patient remains in pulseless VT/VF. Alternatively, one dose of vasopressin can be given to replace either the first or second dose of epinephrine. In a recent comparative trial, patients with out-of-hospital cardiac arrest (60% with asystole or pulseless electrical activity, 40% with VF) were randomized to receive up to two doses of either vasopressin or epinephrine, followed by an additional dose of epinephrine if a stable rhythm was not restored.[110] Overall, no significant differences were observed between the treatment groups with regard to the end points of survival to hospital admission or survival to hospital discharge (in patients with asystole, however, vasopressin was superior for both of these end points).

If pulseless VT/VF persists after delivery of two or three shocks plus CPR and after administration of a vasopressor, antiarrhythmic therapy can then be initiated.[53] It appears clear from the most recent AHA guidelines for CPR and emergency cardiovascular care that IV amiodarone continues to be the antiarrhythmic drug of first choice in patients with pulseless VT/VF. Amiodarone's status as the first-line antiarrhythmic drug during pulseless VT/VF (and lidocaine's resulting role as second-line antiarrhythmic therapy) is the result of (a) a lack of data demonstrating the effectiveness of other antiarrhythmic agents; (b) the Amiodarone in Out-of-Hospital Resuscitation of Refractory Sustained Ventricular Tachyarrhythmias (ARREST) trial;[111] and (c) the Amiodarone versus Lidocaine in Prehospital Ventricular Fibrillation Evaluation (ALIVE) trial.[112] In the ARREST trial,[111] significantly more patients with out-of-hospital pulseless VT/VF who received 300 mg of IV amiodarone survived to hospital admission than did a corresponding placebo group. Noteworthy was that survival to hospital discharge was no different between the groups (although the study was not powered to determine this end point). In the ALIVE trial,[112] IV amiodarone was significantly more effective than lidocaine in increasing survival to hospital admission in patients with out-of-hospital VF. Again, there were no differences in survival to hospital discharge between the groups. Nonetheless, the results of these trials stimulated a change (away from lidocaine and toward amiodarone) in the treatment of pulseless VT/VF. In the event that a patient remains in pulseless VT/VF despite the administration of IV amiodarone and/or lidocaine, it is interesting to note that IV procainamide is no longer recommended in the treatment algorithm because of limited evidence and the need for a prolonged infusion.[53]

Once the patient is successfully resuscitated, antiarrhythmics should be continued until the patient's rhythm and overall status is stable. If the episode of pulseless VT/VF was associated with acute ischemia, long-term antiarrhythmic drugs are probably unnecessary provided that the patient undergoes successful revascularization; however, the patient should be monitored closely for recurrence of VT and/or VF. If, on the other hand, the pulseless VT/VF was not associated with acute MI (or a known precipitating factor), the patient should undergo ICD implantation.

BRADYARRHYTHMIAS

SINUS NODE DYSFUNCTION

The previous sections reviewed the pathophysiology and treatment of tachyarrhythmias, and this section serves to briefly consider the bradyarrhythmias. For the most part, the symptoms of bradyarrhythmias result from a decline in cardiac output. Because cardiac output decreases as heart rate decreases (to a point), patients with bradyarrhythmias may experience symptoms in association with hypotension, such as dizziness, syncope, fatigue, and confusion. If LV dysfunction exists, patients may experience worsening HF symptoms. Except in the case of recurrent syncope, symptoms associated with bradyarrhythmias are often subtle and nonspecific.

SINUS BRADYCARDIA

Sinus bradyarrhythmias (heart rate <60 beats/min) is a common finding, especially in young, athletically active individuals, and usually is neither symptomatic nor requires therapeutic intervention. On the other hand, some patients, particularly the elderly, have sinus node dysfunction. This may be the result of underlying structural heart disease and the normal aging process which, over time, attenuate SA nodal function. Sick sinus syndrome refers to this process resulting in symptomatic sinus bradycardia and/or periods of sinus arrest.[113,114] Sinus node dysfunction is usually reflective of diffuse conduction disease, and accompanying AV block is relatively common. Furthermore, symptomatic bradyarrhythmias may be accompanied by alternating periods of paroxysmal tachycardias such as AF. In this instance, AF sometimes presents with a rather slow ventricular response (in the absence of AV nodal blocking drugs) because of diffuse conduction disease. The occurrence of alternating bradyarrhythmias and tachyarrhythmias is referred to as the "tachy-brady syndrome." The occurrence of paroxysmal AF in a patient with sinus node dysfunction may be a result of underlying structural heart disease with atrial dysfunction or to atrial escape in response to reduced sinus node automaticity. In fact, because the rate of impulse generation by the sinus node is generally depressed or may fail altogether, other automatic pacemakers within the conduction system may "rescue" the sinus node. These rescue rhythms often present as paroxysmal atrial rhythms (e.g., AF) or as a junctional escape rhythm.

The treatment of sinus node dysfunction involves the elimination of symptomatic bradycardia and the possibility of managing alternating tachycardias such as AF. In general, the long-term therapy of choice is a permanent ventricular pacemaker. Dual-chamber, rate-adaptive chronic pacing clearly improves symptoms and overall quality of life and decreases the incidence of paroxysmal AF and systemic embolism.[113] Drugs that are commonly employed to treat supraventricular tachycardias should be used with caution, if at all, in the absence of a functioning pacemaker. Antiarrhythmic drugs prescribed to prevent recurrences of AF may also suppress the escape or rescue rhythms that appear in severe sinus bradycardia or sinus arrest. In this way, these drugs may transform an asymptomatic patient with bradycardia into a symptomatic one. It is also important to remember that the addition of type I antiarrhythmic agents can affect pacemaker threshold and result in loss of capture if the pacemaker is not appropriately interrogated and adjusted.[87] Other drugs that depress SA or AV nodal function, such as β-blockers and nondihydropyridine CCBs, may also significantly exacerbate bradycardia. Even agents with indirect sympatholytic actions, such as methyldopa and clonidine, may worsen sinus node dysfunction. The use of digoxin in these patients is controversial, but in most cases, it can be used safely.

Other Causes

Another reason for paroxysmal bradycardia and sinus arrest that is not directly due to sinus node dysfunction is carotid-sinus hypersensitivity.[115,116] Again, this syndrome occurs commonly in the aged with underlying structural heart disease, and may precipitate falls and hip fractures. Symptoms occur when the carotid sinus is stimulated, resulting in an accentuated baroreceptor reflex. Often, however, symptoms are not well correlated with the obvious physical manipulation of the carotid sinus (in the lateral neck region). Patients may experience intermittent episodes of dizziness or syncope because of sinus arrest caused by increased vagal tone and sympathetic withdrawal (the cardioinhibitory type), a drop in systemic blood pressure caused by sympathetic withdrawal (the vasodepressor type), or both (mixed cardioinhibitory and vasodepressor types). The diagnosis can be confirmed by performing carotid-sinus massage with electrocardiographic and blood pressure monitoring in controlled conditions. Symptomatic carotid-sinus hypersensitivity should also be treated with permanent pacemaker therapy.[115] However, some patients, particularly those with a significant vasodepressor component, still experience syncope or dizziness. The choice of definitive drug therapy in this situation is marred by the lack of controlled trials although α-adrenergic stimulants such as midodrine are often tried in addition to the pacemaker.[116]

Vasovagal syndrome, by causing bradycardia, sinus arrest, and/or hypotension, is the cause of syncope in many patients who present with recurrent fainting of unknown origin.[117–119] By history, many individuals can recount rare instances of fainting spells at times of duress or fear. These are most often caused by vasovagal syncope. However, some have extremely frequent, unexpected syncopal episodes that interfere with the patient's quality of life and cause physical danger (sometimes referred to as neurocardiogenic syncope syndrome or malignant vasovagal syndrome). Vasovagal syncope is presumed to be a neurally mediated, paradoxical reaction involving stimulation of cardiac mechanoreceptors (i.e., Bezold-Jarisch reflex). Forceful contraction of the ventricle (e.g., as with adrenergic stimulation) coupled with low ventricular volumes (e.g., with upright posture or dehydration) provide a powerful stimulus for cardiac mechanoreceptors. Syncope results from the spontaneous development of transient hypotension (sympathetic withdrawal) and bradycardia (vagotonia). However, the true mechanism of vasovagal syncope remains to be definitively determined. For instance, patients with denervated hearts (e.g., heart transplant recipients) can still experience this form of syncope. This observation has led some to question the ultimate role of the Bezold-Jarisch reflex in these patients. Regardless, patients believed to have frequent episodes of vasovagal syncope have been evaluated and diagnosed using the upright body-tilt test,[121] a potent stimulus for the development of vasovagal symptoms. Although commonly used, the sensitivity and reproducibility of this test has been questioned.[120]

Traditionally, oral β-blockers, such as metoprolol, were frequently chosen as the drugs of choice in preventing episodes of vasovagal syncope. Although these agents may seem inappropriate to treat a syndrome resulting from vasodilation and bradycardia, the therapeutic approach is designed to block an inappropriate vasovagal reaction (i.e., they inhibit the sympathetic surge that causes forceful ventricular contraction and precedes the onset of hypotension and bradycardia). To most clinicians' surprise, most controlled trials of the use of β-blockers in patients with severe vasovagal syncope have shown no

effect compared to placebo in preventing syncopal episodes.[122] Some trials have suggested that β-blockers are more effective and should be used in older patients (>40 years of age) with vasovagal syncope rather than the relatively young.[123] Other drugs that have been used successfully (with or without β-blockers) include mineralocorticoids as volume expanders (fludrocortisone), anticholinergic agents (scopolamine patches, disopyramide), α-adrenergic agonists (midodrine), adenosine analogs (theophylline, dipyridamole), and selective serotonin receptor antagonists (sertraline, paroxetine).[124] Permanent pacing has been used for patients with malignant vasovagal syncope but its routine use is controversial. Chronic pacing has been used with some success but should be reserved for drug-refractory patients.[118,119] Because of the questionable effectiveness of β-blockers and the paucity of controlled or comparative trials, there is not a true drug of choice for severe vasovagal syncope and clinicians are left with choosing agents and judging clinical effectiveness in individual patients on a case-by-case basis.

ATRIOVENTRICULAR BLOCK

Conduction delay or block may occur in any area of the AV conduction system: the AV node, the His bundle, or the bundle branches. Atrioventricular block is usually categorized into three different types based on ECG findings (Table 19–13). First-degree AV block is 1:1 AV conduction with a prolonged PR interval. Second-degree AV block is divided into two forms: Mobitz I AV block (Wenckebach periodicity) is less than 1:1 AV conduction with progressively lengthening PR intervals until a ventricular complex is dropped; Mobitz II AV block is intermittently dropped ventricular beats in a random fashion without progressive PR lengthening. Third-degree AV block is complete heart block where AV conduction is totally absent (AV dissociation). By using intracardiac His bundle ECGs, the actual site of conduction delay/block can be correlated to the above diagnosis. First-degree AV block usually represents prolonged conduction in the AV node. Mobitz I, second-degree AV block is also usually caused by prolonged conduction in the AV node. Indeed, Wenckebach periodicity is a normal AV nodal response to rapid supraventricular stimulation or high vagal tone. In contrast, Mobitz II AV block is usually caused by conduction disease below the AV node (i.e., His bundle). Third-degree AV block may be caused by disease at any level of the AV conduction system: complete AV nodal block, His bundle block, or trifascicular block. In this situation, the ventricle beats independently of the atria (AV dissociation), and the rate of ventricular activation and QRS configuration are determined by the site of AV block. The usual degree of automaticity of ventricular pacemakers progressively declines as impulses move down the conduction system. Therefore, the ventricular escape rate in cases of trifascicular block will be significantly less than complete AV nodal block.

Atrioventricular block may be found in patients without underlying structural heart disease such as trained athletes or during sleep when vagal tone is high. Also, AV block may be transient where the underlying etiology is reversible such as in myocarditis, myocardial ischemia, after cardiovascular surgery, or during drug therapy. β-blockers, digoxin, or nondihydropyridine CCBs may cause AV block, primarily in the AV nodal area. Type I antiarrhythmic agents may exacerbate conduction delays below the level of the AV node (sodium-dependent tissue). In other cases, AV block may be irreversible, such as that caused by acute MI, rare degenerative diseases, primary myocardial disease, or congenital forms.

If patients with Mobitz II AV block or third-degree AV block develop signs or symptoms of poor perfusion (e.g., altered mental status, chest pain, hypotension, shock) associated with bradycardia or AV block, transcutaneous pacing should be initiated immediately.[53,125] Intravenous atropine (0.5 mg given every 3 to 5 minutes, up to 3 mg total dose) should be given as the leads for pacing are being placed. Drugs such as atropine will facilitate the effectiveness of transcutaneous pacing. In the past, isoproterenol infusion was frequently chosen for this purpose but is now not recommended because of its vasodilating properties and its ability to increase myocardial oxygen consumption (particularly during acute MI). If patients do not respond to atropine, transcutaneous pacing is usually indicated. Sympathomimetic infusions such as epinephrine (2 to 10 mcg/min) or dopamine (2 to 10 mcg/kg/min) can also be used in the event of atropine failure and are particularly effective in sinus bradycardia/arrest and AV nodal block. These agents usually do not help when the site of AV block is below the AV node (e.g., Mobitz II or trifascicular AV block). If patients with bradycardia or AV block present with signs and symptoms of adequate perfusion, no therapy other than close observation is recommended.

Patients with chronic symptomatic AV block should be treated with the insertion of a permanent pacemaker. Patients without symptoms can sometimes be followed closely without the need for a pacemaker. The reader is referred for more detail to the national consensus guidelines for pacemaker implantation, which were last updated in 2002.[125] Because symptoms often correlate with the ventricular rate and the ventricular rate corresponds to the site of block, pacemaker therapy is usually necessary in distal AV blocks such as those occurring in the His bundle or the bundle branches. Patients with acute MI and evidence of new AV block or conduction disturbances will often require the insertion of a temporary transvenous pacemaker. Atrioventricular block more commonly occurs as a complication of inferior wall infarcts because of high vagal innervation at this site, and the coronary blood flow to the nodal areas usually supplies the inferior wall. However, the AV block may only be transient, obviating the need for permanent pacing. In patients with chronic AV conduction disturbances, intracardiac recordings (His bundle ECGs) are sometimes used to document the actual site of block and define the potential need for and specific type of pacemaker therapy.

TABLE 19-13 Forms of Atrioventricular Block

Type	Criteria	Site of Block
First-degree block	Prolonged PR interval (>0.2 sec); 1:1 AV conduction	Usually AVN
Second-degree block		
Mobitz I	Progressive PR prolongation until QRS is dropped; <1:1 AV conduction	AVN
Mobitz II	Random nonconducted beats (absence of QRS); <1:1 AV conduction	Below AVN
Third-degree block	AV dissociation Absence of AV conduction	AVN or below

AV, atrioventricular; AVN, atrioventricular node.

EVALUATION OF THERAPEUTIC AND ECONOMIC OUTCOMES

Generally, patients who suffer from tachyarrhythmias can be monitored for one or several possible therapeutic outcomes. Obviously, the presence or recurrence of any arrhythmia can be documented by electrocardiographic means (e.g., surface ECG, Holter monitor, or event monitor). Furthermore, patients may experience a decrease in blood pressure that may result in symptoms ranging from lightheadedness to abrupt syncope, depending on the rate of the arrhythmia and the status of the underlying heart disease. For some patients, the potential alteration in hemodynamics may result in death if the arrhythmia is not detected and treated immediately. Besides these clinical outcomes, many patients with tachyarrhythmias experience alterations in quality of life as a result of recurrent symptoms of the

TABLE 19-14 Arrhythmia Outcomes

Mortality
Total, all-cause
Arrhythmic death (i.e., sudden cardiac death)
Recurrences documented by electrocardiogram
Time to recurrence
Frequency of recurrences
Tolerance
Symptoms
Blood pressure
Rate of tachycardia
Surrogate markers of efficacy such as:
Number of premature ventricular contractions/day
Inducibility of tachycardia with programmed stimulation
Necessity of nondrug interventions (e.g., ICD)
ICD shocks
Side effects of drugs/treatment complications
Quality of life
Economics
Outcomes specific to tachycardia (e.g., systemic embolism in atrial fibrillation)

ICD, implantable cardioverter-defibrillator.

arrhythmia or from side effects of therapy. And, finally, there are the economic considerations of medical or surgical intervention, continued medical care, and chronic drug or nondrug treatment.[126,127] Most of the studies are limited to the use of nondrug therapies such as the ICD or radiofrequency ablation.[43,97] Because that technology is rapidly evolving, what is not very cost-effective now, indeed may be cost-effective in the next several years. For example, original cost-effectiveness analysis of the ICD showed it to be highly sensitive to the life of the generator, yet newer-generation devices have made significant advances in not only the size, but also with regard to battery life. More recent data on the effect of the ICD on mortality coupled with the declining costs of an ICD imply that the device is indeed cost-effective in certain subsets of patients, not unlike well-proven drug therapies used for other disorders.[97] Other nondrug treatments, such as radiofrequency ablation, for PSVT not only improve quality of life, but also save money on medical expenditures compared to chronic drug therapy.[43]

There are some therapeutic outcomes that are unique to certain arrhythmias. For instance, patients with AF or atrial flutter need to be monitored for thromboembolism and for complications of anticoagulation therapy (bleeding, drug interactions) prescribed to prevent thromboembolic events. However, the most important monitoring parameters for most patients fall into the following categories: (a) mortality (total and arrhythmic), (b) arrhythmia recurrence (duration, frequency, symptoms), (c) hemodynamic consequences (heart rate, blood pressure, symptoms), and (d) treatment complications (need for alternative or additional drugs, devices, surgery) (Table 19–14). When evaluating the arrhythmia literature, care should be taken to consider real outcomes. For example, total mortality is more meaningful than only SCD rates; it is possible an intervention prevents arrhythmic death but patients die from other causes, leaving all-cause mortality unaltered. Likewise, surrogate markers of drug efficacy (e.g., noninducible tachycardia, suppression of minor arrhythmias) should be judged with a degree of skepticism. One should ask: Did the treatment make patients live longer (reduce mortality)? Did it make them feel better (improve humanistic outcomes or quality of life)? Was it economically worth it (cost-effective)?

ABBREVIATIONS

ACC: American College of Cardiology

AF: atrial fibrillation

AFFIRM: Atrial Fibrillation Follow-up Investigation of Rhythm Management

AHA: American Heart Association

ALIVE: Amiodarone versus Lidocaine in Prehospital Ventricular Fibrillation Evaluation

ARREST: Amiodarone in Out-of-Hospital Resuscitation of Refractory Sustained Ventricular Tachycardia trial

AV: atrioventricular

AVID: Antiarrhythmics Versus Implantable Defibrillators trial

CASH: Cardiac Arrest Study Hamburg

CAST: Cardiac Arrhythmia Suppression Trial

CCB: calcium channel blocker

CIDS: Canadian Implantable Defibrillator Study

CPR: cardiopulmonary resuscitation

CYP: cytochrome P450

DCC: direct-current cardioversion

EADs: early after-depolarizations

ECG: electrocardiogram

ESC: European Society of Cardiology

HF: heart failure

HOT-CAFE: How to Treat Chronic Atrial Fibrillation trial

ICD: implantable cardioverter-defibrillator

INR: international normalized ratio

IV: intravenous

LADs: late after-depolarizations

LV: left ventricular

LVEF: left ventricular ejection fraction

MADIT: Multicenter Automatic Defibrillator Implantation Trial

MI: myocardial infarction

MUSTT: Multicenter Unsustained Tachycardia Trial

NYHA: New York Heart Association

PIAF: Pharmacological Intervention in Atrial Fibrillation trial

PSVT: paroxysmal supraventricular tachycardia

PVCs: premature ventricular complexes

RACE: Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation trial

RMP: resting membrane potential

SA: sinoatrial

SCD: sudden cardiac death

SCD-HeFT: Sudden Cardiac Death in Heart Failure Trial

STAF: Strategies of Treatment of Atrial Fibrillation trial

TdP: torsade de pointes

TEE: transesophageal echocardiography

VF: ventricular fibrillation

VT: ventricular tachycardia

WPW: Wolff-Parkinson-White syndrome

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