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Treatment of patients with tachyarrhythmias has evolved dramatically over the last 40 years. Antiarrhythmic drugs were the mainstay of therapy until the late 1960s, when surgical therapy to cure, not just suppress tachyarrhythmias was developed. This mode was replaced by catheter ablation for better control or even cure of tachyarrhythmias in the 1980s. Catheter ablation has largely replaced surgical and drug therapy for patients who need treatment of supraventricular tachycardia (SVT) and ventricular tachycardia (VT) in the absence of structural heart disease. The implantable cardioverter-defibrillator (ICD) was introduced in the early 1980s and has become standard therapy for patients with serious ventricular arrhythmias in the presence of structural heart disease. Some patients require a combination of these forms of treatment (hybrid therapy, such as an ICD and antiarrhythmic drugs or surgery and an ICD); drug therapy can also affect ICD function, either positively or negatively. Drug therapy for arrhythmias, at one time the only option, has largely been replaced as the mainstay of therapy by ablation or implanted devices. However, in most patients, tachyarrhythmias are initially treated with antiarrhythmic drugs, and thus they continue to have a significant role.

PHARMACOLOGIC THERAPY

The principles of clinical pharmacokinetics and pharmacodynamics are discussed in [Chapter 9](#).

General Considerations Regarding Antiarrhythmic Drugs

Most of the antiarrhythmic drugs available ([Table 35-1](#)) can be classified according to whether they exert blocking actions predominantly on sodium, potassium, or calcium channels and whether they block receptors. The commonly used classification, that of Vaughan Williams, is limited because it is based on the electrophysiologic effects exerted by an arbitrary concentration of the drug, generally on a laboratory preparation of normal cardiac tissue. In reality, the actions of these drugs are complex and depend on tissue type, degree of acute or chronic damage, heart rate, membrane potential, ionic composition of the extracellular milieu, autonomic influence, genetics ([see Chapter 32](#)), age ([see Chapter 76](#)), and other factors ([see Table 35-1](#)). Many drugs exert more than one type of electrophysiologic effect or operate indirectly, such as by altering hemodynamics, myocardial metabolism, or autonomic neural transmission. Some drugs have active metabolites that exert effects different from those of the parent compound. Not all drugs in the same class have identical effects (e.g., amiodarone, sotalol, and ibutilide). Whereas all class III agents are dramatically different, some drugs in different classes have overlapping actions (e.g., class IA and class IC drugs). Thus, *in vitro* studies on healthy myocardium usually establish the properties of antiarrhythmic agents rather than their actual antiarrhythmic properties *in vivo*.

Despite its limitations, the Vaughan Williams classification is widely known and provides a useful communication shorthand, but the reader is cautioned that drug actions are more complex than those depicted by the classification. A more realistic view of antiarrhythmic agents is provided by the Sicilian gambit. This approach to drug classification is an attempt to identify the mechanisms of a particular arrhythmia, to determine the vulnerable parameter of the arrhythmia most susceptible to modification, to define the target most likely to affect the vulnerable parameter, and then to select a drug that will modify the target.¹ This concept provides a framework in which to consider antiarrhythmic drugs ([Table 35-2](#); also see [Table 35-1](#)).

Drug Classification

According to the Vaughan Williams classification, class I drugs predominantly block the fast sodium channel; they can also block potassium channels. They, in turn, are divided into three subgroups, classes IA, IB, and IC ([Table 35-3](#)).

Class IA

This class includes drugs that reduce V_{max} (rate of rise in action potential upstroke [phase 0]) and prolong the action potential duration (APD; [see Chapter 33](#))—quinidine, procainamide, and disopyramide. The kinetics of onset and offset of class IA drugs in blocking the Na^+ channel is of intermediate rapidity (less than 5 seconds) when compared with class IB and class IC agents.

Class IB

This class of drugs does not reduce V_{max} and shortens the APD—mexiletine, phenytoin, and lidocaine. The kinetics of onset and offset of these drugs in blocking the sodium channel is rapid (less than 500 milliseconds).

Class IC

This class of drugs, including flecainide and propafenone, can reduce V_{max} , primarily slow conduction velocity, and prolong refractoriness minimally. These drugs have slow onset and offset kinetics (10 to 20 seconds).

Class II

These drugs block beta-adrenergic receptors and include propranolol, metoprolol, nadolol, carvedilol, nebivolol, and timolol.

Class III

This class of drugs predominantly blocks potassium channels (such as I_{Kr}) and prolongs repolarization. Included are sotalol, amiodarone, dronedarone, and ibutilide.

Class IV

This class of drugs predominantly blocks the slow calcium channel ($I_{Ca,L}$)—verapamil, diltiazem, nifedipine, and others (felodipine blocks $I_{Ca,T}$).



TABLE 35-1 Actions of Drugs Used for the Treatment of Arrhythmias

DRUG	Channels			Receptors				Pumps		Predominant Clinical Effects			
	NA Fast	NA Medium	NA Slow	CA	K _R	K _S	α	β	M ₂	P	NA,K-ATPASE	LV FUNCTION	SINUS RATE
Quinidine		●A		○	○	○					—	↑	○
Procainamide		●I		○							↓	—	○
Disopyramide		●A		○		○					↓	Var	●
Ajmaline		●A									—	—↓	○
Lidocaine	○										—	—↓	○
Mexitilene	○										—	—	○
Phenytoin	○										—	—	○
Flecainide			●A		○						↓	—	○
Propafenone		●A			○		○				↓	↓	○
Propranolol	○						●				↓	↓	○
Nadolol							●				↓	↓	○
Amiodarone	○			○	●	○	○	○			—	↓	●
Dronedarone	○			○	●	○	○	○			—	↓	○
Sotalol				●			●				↓	↓	○
Ibutilide		Activator			○						—	↓	○
Dofetilide			●								—	—	○
Verapamil	○			●			○				↓	↓	○
Diltiazem				○							↓	↓	○
Adenosine								□			—	↓	○
Digoxin						○			●		↑	↓	○
Atropine							●				—	↑	○
Ranolazine	○		○								—	—	○

*Fast, medium, and slow refer to the kinetics of recovery from sodium channel blockade.

Relative potency of blockade or extracardiac side effect: ○ = low; ● = moderate; ●● = high.

□ = agonist; A = activated state blocker; I = inactivated state blocker.

— = minimal effect; ↑ = increase; ↓ = decrease; Var = variable effects.

K_R = rapid component of the delayed rectifier K⁺ current; K_S = slow component of the delayed rectifier K⁺ current; M₂ = muscarinic receptor subtype 2; P = A₁ purinergic receptor.

ATPase = adenosine triphosphatase; LV = left ventricular.

Modified from Schwartz PJ, Zaza A: Haemodynamic effects of a new multifactorial antihypertensive drug. Eur Heart J 13:26, 1992. Copyright © 1992. Reproduced by permission of the publisher W.B. Saunders Company Limited.

TABLE 35-2 Classification of Drug Actions on Arrhythmias Based on Modification of Vulnerable Parameter

MECHANISM	ARRHYTHMIA	VULNERABLE PARAMETER (EFFECT)	DRUGS (EFFECT)
Automaticity			
Enhanced normal	Inappropriate sinus tachycardia Some idiopathic VTs	Phase 4 depolarization (decrease)	Beta-adrenergic blocking agents Na ⁺ channel-blocking agents
Abnormal	Atrial tachycardia	Maximum diastolic potential (hyperpolarization) Phase 4 depolarization (decrease)	M ₂ agonist Ca ²⁺ or Na ⁺ channel-blocking agents M ₂ agonist
	Accelerated idioventricular rhythms	Phase 4 depolarization (decrease)	Ca ²⁺ or Na ⁺ channel-blocking agents
Triggered Activity			
EAD	Torsades de pointes	Action potential duration (shorten) EAD (suppress)	Beta-adrenergic agonists; vagolytic agents (increase rate) Ca ²⁺ channel-blocking agents; Mg ²⁺ ; β-adrenergic-blocking agents; ranolazine
DAD	Digitalis-induced arrhythmias	Calcium overload (unload) DAD (suppress)	Ca ²⁺ channel-blocking agents Na ⁺ channel-blocking agents
	RV outflow tract VT	Calcium overload (unload) DAD (suppress)	Beta-adrenergic blocking agents Ca ²⁺ channel-blocking agents; adenosine

TABLE 35-2 Classification of Drug Actions on Arrhythmias Based on Modification of Vulnerable Parameter—cont'd

MECHANISM	ARRHYTHMIA	VULNERABLE PARAMETER (EFFECT)	DRUGS (EFFECT)
Reentry—Na⁺ Channel Dependent			
Long excitable gap	Typical atrial flutter Circus movement tachycardia in WPW Sustained uniform VT	Conduction and excitability (depress) Conduction and excitability (depress) Conduction and excitability (depress)	Type IA, IC Na ⁺ channel-blocking agents Type IA, IC Na ⁺ channel-blocking agents Na ⁺ channel-blocking agents
Short excitable gap	Atypical atrial flutter AT Circus movement tachycardia in WPW Polymorphic and uniform VT Bundle branch reentry VF	Refractory period (prolong) Refractory period (prolong) Refractory period (prolong) Refractory period (prolong) Refractory period (prolong) Refractory period (prolong)	K ⁺ channel-blocking agents K ⁺ channel-blocking agents Amiodarone, sotalol Type IA Na ⁺ channel-blocking agents Type IA Na ⁺ channel-blocking agents; amiodarone
Reentry—Ca²⁺ Channel Dependent			
	AVNRT Circus movement tachycardia in WPW Verapamil-sensitive VT	Conduction and excitability (depress) Conduction and excitability (depress) Conduction and excitability (depress)	Ca ²⁺ channel-blocking agents Ca ²⁺ channel-blocking agents Ca ²⁺ channel-blocking agents

AT = atrial tachycardia; AVNRT = atrioventricular nodal reentrant tachycardia; DAD = delayed afterdepolarization; EAD = early afterdepolarization; M₂ = muscarinic receptor 2; RV = right ventricular; VT = ventricular tachycardia; WPW = Wolff-Parkinson-White syndrome.

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TABLE 35-3 In Vitro Electrophysiologic Characteristics of Antiarrhythmic Drugs

DRUG	APD	DV/DT	MDP	ERP	CV	PF PHASE 4	SN AUTO	CONTR	SI Curr	AUTONOMIC NERVOUS SYSTEM
Quinidine	↑	↓	0	↑	↓	↓	0	0	0	Antivagal; alpha blocker
Procainamide	↑	↓	0	↑	↓	↓	0	0	0	Slight antivagal
Disopyramide	↑	↓	0	↑	↓	↓	↓ 0 ↑	↓	0	Central: antivagal, antisynthetic
Ajmaline	↑	↓	0	↑	↓	↓	↓ 0	↓	0	Antivagal
Lidocaine	↓	0 ↓	0	↓	0 ↓	↓	0	0	0	0
Mexitilene	↓	0 ↓	0	↓	↓	↓	0	↓	0	0
Phenytoin	↓	↓ 0 ↑	0	↓	0	↓	0		0	0
Flecainide	0 ↑	↓	0	↑	↓↓	↓	0	↓	0	0
Propafenone	0 ↑	↓	0	↑	↓↓	↓	0	↓	0 ↓	Antisynthetic
Propranolol	0 ↓	0 ↓	0	↓	0	↓*	↓	↓	0 ↓	Antisynthetic
Amiodarone	↑	0 ↓	0	↑	↓	↓	↓	0 ↑	0	Antisynthetic
Dronedarone	↑	0 ↓	0	↑	↓	↓	↓	0 ↓	0	Antisynthetic
Sotalol	↑	0 ↓	0	↑	0	0 ↓	↓	↓	0 ↓	Antisynthetic
Ibutilide	↑	0	0	↑	0	0	↓	0	0	0
Dofetilide	↑	0	0	↑	0	0	0	0	0	0
Verapamil	↓	0	0	0	0	↓*	↓	↓	↓↓	? Block alpha receptors; enhance vagal
Adenosine	↑	0 ↓	More (-)	↑	0	0 ↓	↓	0	↓	Vagomimetic
Ranolazine	↑	0	0	↑	0	0	0	0	0	0

*With a background of sympathetic activity.

dV/dt = rate of rise of action potential; MDP = maximum diastolic potential; ERP = effective refractory period (longest S₁-S₂ interval at which S₂ fails to produce a response); CV = conduction velocity; PF = Purkinje fiber; SN Auto = sinus nodal automaticity; Contr = contractility; SI Curr = slow inward current.

Antiarrhythmic drugs appear to cross the cell membrane and interact with receptors in the membrane channels when the channels are in the rested, activated, or inactivated state (see Table 35-1 and Chapter 33), and each of these interactions is characterized by different association and dissociation rate constants of a drug on its receptor. Such interactions depend on voltage and time. Transitions among rested, activated, and inactivated states are governed by standard Hodgkin-Huxley-type equations. When the drug is bound (associated) to a receptor site at or very close to the ionic channel (the drug may not actually plug the channel), the channel cannot conduct, even in the activated state.

Use Dependence. Some drugs exert greater inhibitory effects on the upstroke of the action potential at more rapid rates of stimulation and after longer periods of stimulation, a characteristic called use dependence. Use dependence means that depression of V_{max} is greater after the channel has been "used" (i.e., after action potential depolarization rather than after a rest period). Agents in class IB exhibit fast kinetics of onset and offset or use-dependent block of the fast channel; that is, they bind and dissociate quickly from receptors. Class IC drugs have slow kinetics, and class IA drugs are intermediate. With increased time spent in diastole (slower rate), a greater proportion of receptors become drug free, and the drug exerts less effect. Unhealthy cells with reduced (i.e., abnormal) membrane potentials

recover more slowly from drug actions than do healthier cells with more negative (i.e., normal) membrane potentials.

Reverse Use Dependence. Some drugs exert greater effects at slow rates than at fast rates, a property known as reverse use dependence. This is particularly true for drugs that lengthen repolarization. The QT interval becomes more prolonged at slow rather than at fast rates. This effect is not what the ideal antiarrhythmic agent would do because prolongation of refractoriness should be increased at fast rates to interrupt or to prevent a tachycardia and should be minimal at slow rates to avoid precipitation of torsades de pointes.

Mechanisms of Arrhythmia Suppression. Given the fact that enhanced automaticity, triggered activity, or reentry can cause cardiac arrhythmias (see Chapter 33), mechanisms by which antiarrhythmic agents suppress arrhythmias can be postulated (see Table 35-2). Antiarrhythmic agents can slow the spontaneous discharge frequency of an automatic pacemaker by depressing the slope of diastolic depolarization, shifting the threshold voltage toward zero, or hyperpolarizing the resting membrane potential. Mechanisms whereby different drugs suppress normal or abnormal automaticity may not be the same. In general, however, most antiarrhythmic agents in therapeutic doses depress the automatic firing rate of spontaneously discharging ectopic sites while minimally affecting the discharge rate of the normal sinus node. Slow channel blockers such as verapamil, beta blockers such as propranolol, and some antiarrhythmic agents such as amiodarone also depress spontaneous discharge of the sinus node, whereas drugs that exert vagolytic effects, such as disopyramide and quinidine, can increase the sinus discharge rate. Drugs can also suppress early or delayed afterdepolarizations and eliminate triggered arrhythmias related to these mechanisms.

Reentry depends critically on the interrelationships between refractoriness and conduction velocity, the presence of unidirectional block in one of the pathways, and other factors that influence refractoriness and conduction, such as excitability (see Chapter 33). An antiarrhythmic agent can stop ongoing reentry that is already present or prevent it from starting if the drug depresses or, alternately, improves conduction. For example, improving conduction can (1) eliminate a unidirectional block so that reentry cannot begin or (2) facilitate conduction in the reentrant loop so that the returning wave front reenters too quickly, encounters cells that are still refractory, and is extinguished. A drug that depresses conduction can transform a unidirectional block into a bidirectional block and thus terminate reentry or prevent it from starting by creating an area of complete block in the reentrant pathway. Conversely, a drug that slows conduction without producing block or lengthening refractoriness significantly can promote reentry. Finally, most antiarrhythmic agents share the ability to prolong refractoriness relative to their effects on APD; that is, the ratio of the effective refractory period (ERP) to APD exceeds 1.0. If a drug prolongs the refractoriness of fibers in the reentrant pathway, the pathway may not recover excitability in time to be depolarized by the reentering impulse, and reentrant propagation ceases. The different types of reentry (see Chapter 33) influence the effects and effectiveness of a drug.

In considering the properties of a drug, it is important that the situation or model from which conclusions are drawn be defined with care. Electrophysiologic, hemodynamic, autonomic, pharmacokinetic, and adverse effects may all differ in normal subjects as compared with patients, in normal tissue as compared with abnormal tissue, in cardiac muscle as compared with specialized conduction fibers, and in atrium as opposed to ventricular muscle (Table 35-4).

Drug Metabolites. Drug metabolites can add to or alter the effects of the parent compound by exerting similar actions, competing with the parent compound, or mediating drug toxicity. Quinidine has at least four active metabolites but none with a potency exceeding that of the parent drug and none implicated in causing torsades de pointes. About 50% of procainamide is metabolized to *N*-acetylprocainamide (NAPA), which prolongs repolarization and is a less effective antiarrhythmic drug but competes with procainamide for renotubular secretory sites and can increase the parent drug's elimination half-life. Lidocaine's metabolite can compete with lidocaine for sodium channels and partially reverse block produced by lidocaine.

Pharmacogenetics. Genetically determined metabolic pathways account for many of the differences in patients' responses to some drugs (see Chapter 9).² The genetically determined activity of hepatic *N*-acetyltransferase regulates the development of antinuclear antibodies and lupus syndrome in response to procainamide. Slow acetylator phenotypes appear to be more prone than rapid acetylators to the development of lupus. The enzyme cytochrome P-450 (CYP450) is needed to metabolize propafenone, to hydroxylate several beta

blockers, and to biotransform flecainide. Lack of this enzyme (in ~7% of patients) reduces metabolism of the parent compound and thereby leads to increased plasma concentrations of the parent drug and reduced concentrations of metabolites. Propafenone is metabolized by CYP450 to a compound with slightly less antiarrhythmic and beta-adrenergic blocking effects, as well as fewer central nervous system side effects. Thus, poor metabolizers may experience more heart rate slowing and neurotoxicity than extensive metabolizers do.

Drugs such as rifampin, phenobarbital, and phenytoin induce the synthesis of larger amounts of CYP450, which leads to lower concentrations of the parent drugs because of extensive metabolism, whereas erythromycin, clarithromycin, fluoxetine, and grapefruit juice inhibit enzyme activity, which leads to accumulation of the parent compound. Cisapride, a gastric motility agent, blocks the delayed rectifier current I_{Kr} but does not prolong the QT interval significantly in most patients because of extensive metabolism. In patients who take an inhibitor of CYP450 (such as erythromycin) along with cisapride, the latter drug could accumulate and lead to QT prolongation and torsades de pointes.

Clinical Use

In treating cardiac rhythm disorders, most drugs are given on a daily basis (in one to three doses) to prevent episodes from occurring or, in some cases of atrial fibrillation, to control the ventricular rate. Efficacy can be judged in various ways, depending on the clinical circumstances. Symptom reduction (in the case of benign arrhythmias, such as most premature ventricular complexes [PVCs]) and electrocardiographic monitoring (long-term or event; see Chapter 34) are useful; electrophysiologic studies (EPSs) have been used in the past, with suppression of induction of electrical arrhythmia being the goal. However, this is rarely used currently. Interrogation of implanted device memory can also provide an indicator of the success of drug therapy.

In some patients, tachycardia episodes are infrequent enough (months between occurrences) and symptoms mild enough that reactive drug administration is more reasonable than chronic daily dosing. In this setting a patient takes a medication only after an episode has started in the hope that the tachycardia will terminate in response to the drug and a visit to a physician's office or emergency department can be avoided. This "pill in the pocket" strategy has worked well for some patients with atrial fibrillation who have been given one of various medications orally in a monitored setting to ensure safety, as well as efficacy, before allowing self-medication at home or elsewhere.

Side Effects

Antiarrhythmic drugs produce one group of side effects related to excessive dosage and plasma concentrations that result in both non-cardiac (e.g., neurologic defects) and cardiac (e.g., heart failure, some arrhythmias) toxicity and another group of side effects unrelated to plasma concentrations, which is termed *idiosyncratic*. Examples of the latter include amiodarone-induced pulmonary fibrosis and some arrhythmias, such as quinidine-induced torsades de pointes, which can occur in individuals with a forme fruste of long-QT syndrome (i.e., normal QT interval at rest but markedly prolonged interval in the presence of certain medications; see Chapters 9 and 32). In the future, it is likely that genetic differences will explain many idiosyncratic reactions.

Proarrhythmia

Drug-induced or drug-exacerbated cardiac arrhythmias (proarrhythmia) constitute a major clinical problem. Proarrhythmia can be manifested as an increase in frequency of a preexisting arrhythmia, sustaining of a previously nonsustained arrhythmia (even making it incessant), or development of arrhythmias that the patient has not previously experienced. Electrophysiologic mechanisms are probably related to prolongation of repolarization or an increase in its transmural dispersion, development of early afterdepolarizations with resultant torsades de pointes, and alterations in reentry pathways to initiate or to sustain tachyarrhythmias (see Chapter 33). Proarrhythmic events can occur in as many as 5% to 10% of patients receiving antiarrhythmic agents. Heart failure increases this risk.

TABLE 35-4 Clinical Use Information for Antiarrhythmic Agents

DRUG	Loading	Maintenance	Loading	Maintenance	TIME TO PEAK PLASMA CONCENTRATION (ORAL) (hr)	EFFECTIVE SERUM OR PLASMA CONCENTRATION (µg/mL)	HALF-LIFE (hr)	BIOAVAILABILITY (%)	MAJOR ROUTE OF ELIMINATION	PREGNANCY CLASS
Quinidine	6-10 mg/kg at 0-3.0 mg/kg/min	—	800-1000	300-600 q6h	1.5-3.0	3-6	5-9	60-80	Liver	C
Procainamide	6-13 mg/kg at 0.2-0.5 mg/kg/min	2-6 mg/min	500-1000	250-1000 q4-6h	1	4-10	3-5	70-85	Kidney	C
Disopyramide	1-2 mg/kg over 15-45 min*	1 mg/kg/hr*	N/A	100-300 q6-8h	1-2	2-5	8-9	80-90	Kidney	C
Lidocaine	1-3 mg/kg at 20-50 mg/min	1-4 mg/min	N/A	N/A	N/A	1-5	1-2	N/A	Liver	B
Mexiletine	500 mg*	0.5-1.0 g/24 hr*	400-600	150-300 q8-12h	2-4	0.75-2	10-17	90	Liver	C
Phenytoin	100 mg q5min for ≤1000 mg	N/A	1000	100-400 q12-24h	8-12	10-20	18-36	50-70	Liver	D
Flecainide	2 mg/kg*	100-200 q12h*	N/A	50-200 q12h	3-4	0.2-1.0	20	95	Liver	C
Propafenone	1-2 mg/kg*	N/A	600-900	150-300 q8-12h	1-3	0.2-3.0	5-8	25-75	Liver	C
Propranolol	0.25-0.5 mg q5min to ≤0.20 mg/kg	N/A	N/A	10-200 q6-8h	4	1-2.5	3-6	35-65	Liver	C
Amiodarone	15 mg/min for 10 min 1 mg/min for 3 hr 0.5 mg/min thereafter	0.5 mg/min	800-1600	200-600 qd qd for 7-14 days	Variable	0.5-1.5	56 days	25	Kidney	D
Dronedarone	N/A	N/A	N/A	400 mg q12h	3-4	0.3-0.6	13-19	70-90	Liver	X
Sotalol	10 mg over 1-2 min*	N/A	N/A	80-320 q12h	2.5-4	2.5	12	90-100	Kidney	B
Ibutilide	1 mg over 10 min	N/A	N/A	N/A	N/A	N/A	6	90	Kidney	C
Dofetilide	2-5 µg/kg infusion*	N/A	N/A	0.125-0.5 q12h	N/A	N/A	7-13	90	Kidney	C
Verapamil	5-10 mg over 1-2 min	0.005 mg/kg/min	N/A	80-120 q6-8h	1-2	0.10-0.15	3-8	10-35	Liver	C
Adenosine	6-18 mg (rapidly)	N/A	N/A	N/A	N/A	N/A	Seconds	100	Blood cells	C
Digoxin	0.5-1.0 mg	0.125-0.25 qd	0.5-1.0	0.125-0.25 qd	2-6	0.0008-0.002	36-48	60-80	Kidney	C
Ranolazine	N/A	N/A	N/A	500-1000 bid	4-6	N/A	7	60-75	Liver, Kidney	C

*Intravenous use investigational or unavailable in the United States.

Results presented may vary according to doses, disease state, and IV or oral administration.

Pregnancy class: A = controlled studies show no fetal risk; B = no controlled studies, but no evidence of fetal risk; fetal harm unlikely; C = fetal risk cannot be excluded; drug should be used only if potential benefits outweigh potential risk; D = definite fetal risk; drug should be avoided unless in a life-threatening situation or safer alternatives do not exist; X = contraindicated in pregnancy

Reduced left ventricular function, treatment with digitalis and diuretics, and a longer pretreatment QT interval characterize patients who experience drug-induced ventricular fibrillation (VF). The more commonly known proarrhythmic events occur within several days of beginning drug therapy or changing dosage and are represented by such developments as incessant VT, long-QT syndrome, and torsades de pointes. However, in CAST (Cardiac Arrhythmia Suppression Trial), researchers found that encainide and flecainide reduced spontaneous ventricular arrhythmias but were associated with a total mortality of 7.7%, as opposed to 3.0% in the group receiving placebo. Deaths were equally distributed throughout the treatment period, thus raising the important consideration that another type of proarrhythmic response can occur some time after the beginning of drug therapy. Such late proarrhythmic effects may be related to drug-induced exacerbation of the regional myocardial conduction delay caused by ischemia and to heterogeneous drug concentrations that can promote reentry. In coming years, a candidate antiarrhythmic compound's potential for proarrhythmia may be modeled computationally or tested in stem cells.³

The availability of catheter ablation (see later) and implantable devices (pacemakers and ICDs; [see Chapter 36](#)) to treat a wide variety of arrhythmias has largely relegated drug therapy to a secondary role in the treatment of serious arrhythmias. Drugs are still useful to prevent or to decrease the frequency of recurrences in patients who have relatively infrequent episodes of benign tachycardias, those who have had incomplete success with catheter ablation procedures, and patients with an ICD to decrease the frequency of shocks because of supraventricular or ventricular arrhythmias.

Antiarrhythmic Agents

Class IA Agents

Quinidine

Quinidine and quinine are isomeric alkaloids isolated from cinchona bark.⁴ Although quinidine shares the antimalarial, antipyretic, and vagolytic actions of quinine, only quinidine has electrophysiologic effects. It blocks several channels (rapid inward sodium channel, I_{Kr} , I_{to} , and to a lesser extent, the slow inward calcium channel, I_{Ks} , and the adenosine triphosphate (ATP)-sensitive potassium current [K_{ATP}]).

Electrophysiologic Actions. Quinidine exerts little effect on automaticity of the normal sinus node but suppresses automaticity in normal Purkinje fibers ([Table 35-5](#); see also [Tables 35-1, 35-2, and 35-3](#)). In patients with sick sinus syndrome, quinidine can depress sinus node automaticity. Quinidine produces early afterdepolarizations in experimental preparations and in humans, which may be responsible for torsades de pointes. Because of its significant anticholinergic effect and the reflex sympathetic stimulation resulting from alpha-adrenergic blockade, which causes peripheral vasodilation, quinidine can reflexly increase the sinus node discharge rate and improve atrioventricular (AV) nodal conduction. Quinidine prolongs repolarization, an effect that is more prominent at slow heart rates (reverse use dependence) because of block of I_{Kr} (as well as enhancing the late Na current). Faster rates result in more block of sodium channels and less unblocking because of a smaller percentage of time spent in a polarized state (use dependence). Isoproterenol can modulate the effects of quinidine on reentrant circuits in humans. Quinidine at higher doses inhibits the late Na current. As noted, quinidine blocks the transient outward current I_{to} , which is probably why it is effective in suppressing ventricular arrhythmias in Brugada syndrome ([see Chapter 9](#)).

Hemodynamic Effects. Quinidine induces vasodilation by blocking alpha-adrenergic receptors and can cause significant hypotension. It does not result in significant direct myocardial depression.

Pharmacokinetics. Plasma quinidine concentrations peak at approximately 3 to 4 hours after an oral dose of a quinidine gluconate preparation (see [Table 35-4](#)). Quinidine can be given intravenously if it is infused slowly, but intramuscular dosing should be avoided. Approximately 80% of plasma quinidine is protein bound, especially to alpha₁-acid glycoprotein. Both the liver and the kidneys remove quinidine; dose adjustments may be made to achieve appropriate serum concentrations. Its elimination half-life is 5 to 8 hours after oral administration. Quinidine's effect on repolarization and its overall efficacy vary directly with left ventricular function; at the same serum concentration, the QT interval is longer in women than in men.

DOSAGE AND ADMINISTRATION. The usual oral dose of quinidine sulfate for an adult is 300 to 600 mg four times daily, which results in a steady-state level within about 24 hours (see [Table 35-4](#)). A loading dose of 600 to 1000 mg produces an earlier effective concentration. Oral doses of the gluconate are about 30% higher than those of the sulfate. Important interactions with other drugs occur.

INDICATIONS. Quinidine is a versatile antiarrhythmic agent that was used previously to treat premature supraventricular and ventricular complexes and sustained tachyarrhythmias. However, because of its side effect profile and potential for causing torsades de pointes, as well as its limited usefulness in preventing VT and VF in most applications, its use has decreased greatly. In recent years, however, there has been an increase in interest in quinidine for treating primary VF, ventricular arrhythmias in patients with Brugada syndrome⁵ ([see Chapter 32](#)), and short-QT syndrome.⁶ Because it crosses the placenta, quinidine can be used to treat arrhythmias in the fetus.

ADVERSE EFFECTS. The most common adverse effects of chronic oral quinidine therapy are gastrointestinal and include nausea, vomiting, diarrhea, abdominal pain, and anorexia (milder with the gluconate form). Central nervous system toxicity includes tinnitus, hearing loss, visual disturbances, confusion, delirium, and psychosis (cinchonism). Allergic reactions include rash, fever, immune-mediated thrombocytopenia, hemolytic anemia, and rarely, anaphylaxis. Side effects may preclude long-term administration of quinidine in 30% to 40% of patients.

Quinidine can slow cardiac conduction, sometimes to the point of block, which is manifested as prolongation of the QRS duration or as sinoatrial or AV nodal conduction disturbances. Quinidine can produce syncope in 0.5% to 2.0% of patients, most often the result of a self-terminating episode of torsades de pointes. Quinidine prolongs the QT interval in most patients, regardless of whether ventricular arrhythmias occur, but significant QT prolongation (QT interval of 500 to 600 milliseconds) is often a characteristic of patients with quinidine-related syncope, who may have a genetic predisposition underlying such a response ([see Chapter 9](#)). Many of these patients are also receiving digitalis or diuretics or have hypokalemia; women are more susceptible than men. Importantly, syncope is unrelated to plasma concentrations of quinidine or the duration of therapy, although most episodes occur within the first 2 to 4 days of therapy, often after conversion of atrial fibrillation to sinus rhythm (for this reason the drug should not be taken on an intermittent basis). Therapy requires immediate discontinuation of use of the drug and avoidance of other drugs that have similar pharmacologic effects because cross-sensitivity exists in some patients. Magnesium given intravenously (2 g over a period of 1 to 2 minutes, followed by an infusion of 3 to 20 mg/min) is the initial drug treatment of choice. Atrial or ventricular pacing can be used to suppress the ventricular tachyarrhythmia, perhaps by suppressing early afterdepolarizations. When pacing is not available, isoproterenol can be given with caution. The arrhythmia gradually dissipates as quinidine is cleared and the QT interval returns to baseline.

Drugs that induce hepatic enzyme production, such as phenobarbital and phenytoin, can shorten the duration of action of quinidine by increasing its rate of elimination. Quinidine can increase plasma concentrations of flecainide by inhibiting the CYP450 enzyme system. Quinidine may elevate serum digoxin concentrations by decreasing its clearance and volume of distribution and the affinity of tissue receptors.

Procainamide

Electrophysiologic Actions. The cardiac actions of procainamide on automaticity, conduction, excitability, and membrane responsiveness resemble those of quinidine (see [Tables 35-1, 35-2, 35-3, and 35-5](#)). Procainamide predominantly blocks the inactivated state of I_{Na} . It also blocks I_{Kr} and $I_{K,ATP}$. Like quinidine, procainamide usually prolongs the ERP more than it prolongs the APD and thus may prevent reentry. Procainamide exerts the least anticholinergic effects among type IA drugs. It does not affect normal sinus node automaticity. In vitro, procainamide decreases abnormal automaticity, with less effect on triggered activity or catecholamine-enhanced normal automaticity. The electrophysiologic effects of NAPA, the major metabolite of procainamide, differ from those of the parent compound. NAPA, a K^+

**TABLE 35-5** In Vivo Electrophysiological Characteristics of Antiarrhythmic Drugs

DRUG	ELECTROCARDIOGRAPHIC MEASUREMENTS					ELECTROPHYSIOLOGIC MEASUREMENTS					
	SINUS RATE	PR	QRS	QT	JT	ERP-AVN	ERP-HPS	ERP-A	ERP-V	AH	HV
Quinidine	0 ↑	↓ 0 ↑	↑	↑	↑	0 ↑	↑	↑	↑	0 ↓	↑
Procainamide	0	0 ↑	↑	↑	↑	0 ↑	↑	↑	↑	0 ↑	↑
Disopyramide	↓ 0 ↑	↓ 0 ↑	↑	↑	↑	↑ 0	↑	↑	↑	↓ 0 ↑	↑
Ajmaline	0	0 ↑	↑	↑	↑	0	↑	↑	↑	↓ 0 ↑	↑
Lidocaine	0	0	0	0 ↓	↓	0 ↑	0 ↑	0	0	0 ↓	0 ↑
Mexiletine	0	0	0	0 ↓	↓	0 ↑	0 ↑	0	0	0 ↑	0 ↑
Phenytoin	0	0	0	0	0	0 ↓	↓	0	0	0 ↑	0
Flecainide	0 ↓	↑	↑	↑	0	↑	↑	↑	↑	↑	↑
Propafenone	0 ↓	↑	↑	↑	0	0 ↑	0 ↑	0 ↑	↑	↑	↑
Propranolol	↓	↑	0	0 ↓	0	↑	0	0	0	0	0
Amiodarone	↓	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
Dronedarone	↓	↑	↑	↑	↑	↑	↑	↑	↑	↑	0
Sotalol	↓	0 ↑	0	↑	↑	↑	↑	↑	↑	↑	0
Ibutilide	↓	0 ↓	0	↑	↑	0	0	↑	↑	0	0
Dofetilide	0	0	0	↑	↑	0	0	↑	↑	0	0
Verapamil	0 ↓	↑	0	0	0	↑	0	0	0	↑	0
Adenosine	↓ then ↑	↑	0	0	0	↑	0	↓	0	↑	0
Digoxin	↓	↑	0	0	↓	↑	0	↓	0	↑	0
Ranolazine	0	0	0	↑	↑	0	0	↑	↑	0	0

Results presented may vary according to tissue type, drug concentration, and autonomic tone.

↑ = increase; ↓ = decrease; 0 = no change; 0 ↑ or 0 ↓ = slight or inconsistent increase or decrease; A = atrium; AVN = AV node; HPS = His-Purkinje system; V = ventricle; AH = atrio-His interval (an index of AV nodal conduction); HV = His-ventricular interval (an index of His-Purkinje conduction); ERP = effective refractory period (longest S₁-S₂ interval at which S₂ fails to produce a response).

channel blocker (I_{Kr}), exerts a class III action and prolongs the APD of ventricular muscle and Purkinje fibers in a dose-dependent manner. High levels can produce early afterdepolarizations, triggered activity, and torsades de pointes.

Hemodynamic Effects. Procainamide can depress myocardial contractility in high concentrations. It does not produce alpha blockade but can result in peripheral vasodilation, possibly through anti-sympathetic effects on the brain or spinal cord, which can impair cardiovascular reflexes.

Pharmacokinetics. Oral administration produces a peak plasma concentration in around 1 hour. Approximately 80% of oral procainamide is bioavailable; the overall elimination half-life of procainamide is 3 to 5 hours, with 50% to 60% of the drug being eliminated by the kidneys and 10% to 30% by hepatic metabolism (see Table 35-4). The drug is acetylated to NAPA, which is excreted almost exclusively by the kidneys. As renal function decreases and in patients with heart failure, NAPA levels increase and, because of the risk for serious cardiotoxicity, need to be carefully monitored in these situations. NAPA has an elimination half-life of 7 to 8 hours, but the half-life exceeds 10 hours if high doses of procainamide are used. Increased age, congestive heart failure, and reduced creatinine clearance lower the clearance of procainamide and necessitate a reduced dosage.

DOSAGE AND ADMINISTRATION. Procainamide can be given by the oral, intravenous, or intramuscular route to achieve plasma concentrations in the range of 4 to 10 mg/mL and produce an antiarrhythmic effect (see Table 35-4). Several intravenous regimens have been used to administer procainamide; 25 to 50 mg can be given during a 1-minute period and then repeated every 5 minutes until the arrhythmia has been controlled, hypotension results, or the QRS complex is prolonged more than 50%. Doses of 10 to 15 mg/kg administered a rate of at 50 mg/min can also be used. With this method, the plasma concentration falls rapidly during the first 15 minutes after the loading dose, with parallel effects on refractoriness and conduction. A

constant-rate intravenous infusion of procainamide can be given at a dosage of 2 to 6 mg/min, depending on the patient's response.

Oral administration of procainamide requires a 3- to 4-hour dosing interval at a total daily dose of 2 to 6 g, with a steady-state concentration being reached within 1 day. When a loading dose is used, it should be twice the maintenance dose. Frequent dosing is required because of its short elimination half-life in normal subjects. For the extended-release forms of procainamide, dosing is at 6- to 12-hour intervals. Procainamide is well absorbed after intramuscular injection, with almost 100% of the dose bioavailable.

INDICATIONS. Procainamide is used to treat both supraventricular and ventricular arrhythmias in a manner comparable to that of quinidine. Although both drugs have similar electrophysiologic actions, either drug can effectively suppress a supraventricular or ventricular arrhythmia that is resistant to the other drug. Procainamide can be used to convert recent-onset atrial fibrillation to sinus rhythm. As with quinidine, prior treatment with beta or calcium channel blockers is recommended to prevent acceleration of the ventricular response during atrial flutter or fibrillation after procainamide therapy. Procainamide can block conduction in the accessory pathway of patients with Wolff-Parkinson-White syndrome and can be used in patients with atrial fibrillation and a rapid ventricular response related to conduction over the accessory pathway. It can produce His-Purkinje block (see Fig. 34-8) and is sometimes administered during an EPS to stress the His-Purkinje system and evaluate the need for a pacemaker. However, it should be used with caution in patients with evidence of His-Purkinje disease (bundle branch block) in whom a ventricular pacemaker is not readily available. Procainamide is more effective than lidocaine in acutely terminating sustained VT. Most consistently, procainamide slows the VT rate, a change correlated with the increase in QRS duration. The drug also has diagnostic application when given intravenously (10 mg/kg over

a 5- to 10-minute period). In patients with suspected Brugada syndrome who have normal findings on a resting electrocardiogram (ECG), drug infusion may result in the characteristic “Brugada sign,” whereas in patients with Wolff-Parkinson-White syndrome, the drug may cause sudden loss of preexcitation, a finding indicative of an accessory pathway with a long refractory period and suggesting low risk for a dangerously rapid ventricular rate during atrial fibrillation. Evidence for the latter point is mixed, however.

ADVERSE EFFECTS. Noncardiac adverse effects from administration of procainamide include rash, myalgia, digital vasculitis, and Raynaud phenomenon. Fever and agranulocytosis may be the result of hypersensitivity reactions, and the white blood cell and differential counts should be assessed at regular intervals. Gastrointestinal side effects are less frequent than with quinidine, and adverse central nervous system side effects are less frequent than with lidocaine. Toxic concentrations of procainamide can diminish myocardial performance and promote hypotension. Various conduction disturbances or ventricular tachyarrhythmias that are similar to those produced by quinidine can occur. NAPA can cause QT prolongation and torsades de pointes. In the absence of sinus node disease, procainamide does not adversely affect sinus node function. In patients with sinus node dysfunction, however, procainamide can prolong sinus node recovery time and worsen symptoms in some patients with bradycardia-tachycardia syndrome.

Arthralgia, fever, pleuropericarditis, hepatomegaly, and hemorrhagic pericardial effusion with tamponade have been described in a systemic lupus erythematosus (SLE)-like syndrome related to procainamide administration. The syndrome occurs more frequently and earlier in patients who are slow acetylators of procainamide and is genetically influenced (see Chapter 9). Acetylation of an aromatic amino group on procainamide to form NAPA appears to block the SLE-inducing effect. In 60% to 70% of patients who take procainamide on a chronic basis, antinuclear antibodies develop, with clinical symptoms occurring in 20% to 30%, but this is reversible when use of procainamide is stopped. Positive serologic test results are not necessarily a reason to discontinue drug therapy; however, the development of symptoms or a positive anti-DNA antibody indicates that drug therapy should be discontinued. Corticosteroid administration in these patients may eliminate the symptoms. In this syndrome, in contrast to naturally occurring SLE, the brain and kidneys are spared, and there is no predilection for women.

Disopyramide

Disopyramide has been approved in the United States for oral administration to treat patients with ventricular and supraventricular arrhythmias.

Electrophysiologic Actions. Although it is structurally different from quinidine and procainamide, disopyramide produces similar electrophysiologic effects; it causes use-dependent block of I_{Na} and non-use-dependent block of I_K (see Tables 35-1, 35-2, 35-3, and 35-5). Disopyramide also inhibits $I_{K,ATP}$; it does not affect calcium-dependent action potentials, except possibly at very high concentrations.

Disopyramide is a muscarinic blocker and can increase the sinus node discharge rate and shorten AV nodal conduction time and refractoriness when the nodes are under cholinergic (vagal) influence. Disopyramide can also slow the sinus node discharge rate by a direct action when given in high concentration and can significantly depress sinus node activity in patients with sinus node dysfunction. It exerts greater anticholinergic effects than quinidine does and does not appear to affect alpha or beta adrenoceptors. The drug prolongs atrial and ventricular refractory periods, but its effect on AV nodal conduction and refractoriness is not consistent. Disopyramide prolongs His-Purkinje conduction time, but infra-His block rarely occurs. It can be administered safely to patients who have first-degree AV delay and narrow QRS complexes.

Hemodynamic Effects. Disopyramide suppresses ventricular systolic performance and is a mild arterial vasodilator. The drug should generally be avoided in patients with reduced left ventricular systolic function because they tolerate its negative inotropic effects poorly.

Pharmacokinetics. Disopyramide is 80% to 90% absorbed, with a mean elimination half-life of 8 to 9 hours in healthy volunteers but almost 10 hours in patients with heart failure (see Table 35-4). Renal

insufficiency prolongs its elimination time. Thus, in patients with renal, hepatic, or cardiac insufficiency, loading and maintenance doses need to be reduced. Peak blood levels after oral administration occur in 1 to 2 hours. Approximately 50% of an oral dose is excreted unchanged in urine, with around 30% occurring as the mono-*N*-dealkylated metabolite. The metabolites appear to exert less effect than the parent compound does. Erythromycin inhibits its metabolism.

DOSAGE AND ADMINISTRATION. Doses are generally 100 to 200 mg orally every 6 hours, with a range of 400 to 1200 mg/day (see Table 35-4). A controlled-release preparation can be given as 200 to 300 mg every 12 hours.

INDICATIONS. Disopyramide appears to be comparable to quinidine and procainamide in reducing the frequency of PVCs and effectively preventing recurrence of VT in selected patients. Disopyramide has been combined with other drugs, such as mexiletine, to treat patients who do not respond or respond only partially to one drug.

Disopyramide helps prevent recurrence of atrial fibrillation after successful cardioversion as effectively as quinidine does and may terminate atrial flutter. In treating patients with atrial fibrillation, particularly atrial flutter, the ventricular rate must be controlled before disopyramide is administered, or the combination of a decrease in atrial rate with vagolytic effects on the AV node can result in 1:1 AV conduction during atrial flutter (see Chapter 38). Disopyramide may be useful in preventing episodes of neurally mediated syncope. It has been used in patients with hypertrophic cardiomyopathy.

ADVERSE EFFECTS. Three types of adverse effects follow disopyramide administration. The most common effects are related to the drug's potent parasympatholytic properties and include urinary hesitancy or retention, constipation, blurred vision, closed-angle glaucoma, and dry mouth. Symptoms are less with the sustained-release form. Second, disopyramide can produce ventricular tachyarrhythmias that are commonly associated with QT prolongation and torsades de pointes. Cross-sensitization to both quinidine and disopyramide occurs in some patients, and torsades de pointes can develop while receiving either drug. When drug-induced torsades de pointes occurs, agents that prolong the QT interval should be used cautiously or not at all. Finally, disopyramide can reduce contractility of the normal ventricle, but the depression of ventricular function is much more pronounced in patients with preexisting ventricular failure. Rarely, cardiovascular collapse can result.

Ajmaline

Ajmaline, a rauwolfia derivative, has been used extensively to treat patients with ventricular and supraventricular arrhythmias in Europe and Asia but is not available in the United States.

Electrophysiologic Actions. Like other type IA drugs, ajmaline produces use-dependent block of I_{Na} ; it also weakly blocks I_K . The drug has mild anticholinergic activity (see Tables 35-1, 35-2, 35-3, and 35-5).

Hemodynamic Effects. Ajmaline mildly suppresses ventricular systolic performance but does not affect peripheral resistance. It also inhibits platelet activity more potently than aspirin does.

Pharmacokinetics, Dosage, and Administration. Ajmaline is well absorbed with a mean elimination half-life of 13 minutes in most patients, thus making it poorly suited to long-term oral use. The dose for termination of acute arrhythmia is generally 50 mg intravenously infused over a period of 1 to 2 minutes (see Table 35-4).

Indications. Although it is useful for terminating SVTs by intravenous infusion, other medications have largely supplanted ajmaline for this purpose. The drug's use has evolved to that of a diagnostic tool. When administered intravenously at doses of 50 mg over a 3-minute period, or 10 mg/min, to a total dose of 1 mg/kg, ajmaline can have the following effects: (1) delta wave disappearance in patients with Wolff-Parkinson-White syndrome (indicating an accessory pathway anterograde ERP longer than 250 milliseconds); (2) ST-T abnormalities and interventricular conduction blocks in patients with occult chagasic cardiomyopathy; (3) heart block in patients with bundle branch block and syncope, but in whom no rhythm disturbance had been discovered; and (4) right precordial ST elevation in patients with suspected Brugada syndrome in whom findings on the resting ECG are normal. It is in this last setting that ajmaline is used most frequently.

Adverse Effects. Ajmaline can produce mild anticholinergic side effects, as well as mild depression of left ventricular systolic function, and can worsen AV conduction in patients with His-Purkinje disease. Rare occurrences of torsades de pointes have been reported. Ajmaline can cause an increase in the defibrillation threshold.

Class IB Agents

Lidocaine

Electrophysiologic Actions. Lidocaine blocks I_{Na} , predominantly in the open or possibly inactivated state. It has rapid onset and offset kinetics and does not affect normal sinus node automaticity in usual doses but does depress other normal and abnormal forms of automaticity, as well as early and late afterdepolarizations in Purkinje fibers *in vitro* (see Tables 35-1, 35-2, 35-3, and 35-5). Lidocaine has only a modest depressant effect on V_{max} ; however, faster rates of stimulation, reduced pH, increased extracellular K^+ concentration, and reduced membrane potential (changes that can result from ischemia) increase the ability of lidocaine to block I_{Na} . Lidocaine can convert areas of unidirectional block into bidirectional block during ischemia and inhibit the development of VF by preventing fragmentation of organized large wave fronts into heterogeneous wavelets.

Except in very high concentrations, lidocaine does not affect slow-channel-dependent action potentials despite its moderate suppression of the slow inward current. Lidocaine has little effect on atrial fibers and does not affect conduction in accessory pathways. Depressed automaticity or conduction can develop in patients with preexisting sinus node dysfunction, abnormal His-Purkinje conduction, or junctional or ventricular escape rhythms. Part of its effects may involve inhibition of cardiac sympathetic nerve activity.

Hemodynamic Effects. Clinically significant adverse hemodynamic effects are rarely noted at the usual drug concentrations unless left ventricular function is severely impaired.

Pharmacokinetics. Lidocaine is used only parenterally because oral administration results in extensive first-pass hepatic metabolism and unpredictable low plasma levels, as well as excessive metabolites that can produce toxicity (see Table 35-4). Hepatic metabolism of lidocaine depends on hepatic blood flow; severe hepatic disease or reduced hepatic blood flow, as in heart failure or shock, can markedly decrease the rate of lidocaine metabolism. Beta adrenoceptor blockers can decrease hepatic blood flow and increase the serum concentration of lidocaine. Prolonged infusion can reduce lidocaine clearance. Its elimination half-life averages 1 to 2 hours in normal subjects, longer than 4 hours in patients after uncomplicated myocardial infarction, longer than 10 hours in patients after myocardial infarction complicated by heart failure, and even longer in the presence of cardiogenic shock. Maintenance doses should be reduced by a third to a half in patients with low cardiac output. Lidocaine is 50% to 80% protein bound.

DOSAGE AND ADMINISTRATION. Although lidocaine can be given intramuscularly, the intravenous route is most commonly used, with an initial bolus of 1 to 2 mg/kg body weight at a rate of 20 to 50 mg/min and a second injection of half the initial dose 20 to 40 minutes later to maintain the therapeutic concentration (see Table 35-4).

If the initial bolus of lidocaine is ineffective, up to two more boluses of 1 mg/kg may be administered at 5-minute intervals. Patients who require more than one bolus to achieve a therapeutic effect have arrhythmias that respond only to higher lidocaine plasma concentrations, and a higher maintenance dose may be necessary to sustain these higher concentrations. Maintenance infusion rates in the range of 1 to 4 mg/min produce steady-state plasma levels of 1 to 5 mg/mL in patients with uncomplicated myocardial infarction, but these rates must be reduced during heart failure or shock because of the concomitant reduced hepatic blood flow. Higher doses are unlikely to provide additional benefit but do increase the risk for toxicity.

INDICATIONS. Lidocaine has moderate efficacy against ventricular arrhythmias of diverse causes; it is generally ineffective against supraventricular arrhythmias and rarely terminates monomorphic VT. Although once commonly used in an attempt to prevent VF in the first 2 days after acute myocardial infarction, its efficacy was not great, and because it can produce side effects and a possible increase in the risk for the development of asystole, such use is not recommended. Lidocaine has been effective in patients after coronary revascularization and in those resuscitated from out-of-hospital VF,

although amiodarone has been shown to yield higher rates of survival, at least to hospital admission.

ADVERSE EFFECTS. The most commonly reported adverse effects of lidocaine are dose-related manifestations of central nervous system toxicity: dizziness, paresthesias, confusion, delirium, stupor, coma, and seizures. Occasional sinus node depression and His-Purkinje block have been reported. Rarely, lidocaine can cause malignant hyperthermia.

Mexiletine

Mexiletine, a local anesthetic congener of lidocaine with anticonvulsant properties, is used for the oral treatment of patients with symptomatic ventricular arrhythmias.

Electrophysiologic Actions. Mexiletine is similar to lidocaine in many of its electrophysiologic actions. *In vitro*, mexiletine shortens the APD and ERP of Purkinje fibers and, to a lesser extent, ventricular muscle. It depresses the V_{max} of phase 0 by blocking I_{Na} , especially at faster rates, and depresses the automaticity of Purkinje fibers but not of the normal sinus node. Its onset and offset kinetics are rapid. Hypoxia or ischemia can increase its effects (see Tables 35-1, 35-2, 35-3, and 35-5).

Mexiletine can result in severe bradycardia and abnormal sinus node recovery time in patients with sinus node disease, but not in those with a normal sinus node. It does not affect AV nodal conduction and can depress His-Purkinje conduction, but not greatly, unless conduction was abnormal initially. Mexiletine does not appear to affect human atrial muscle. It does not affect the QT interval. It has been used in treating a variety of other disorders, including erythromelalgia (red, painful extremities) in children and myotonia.

Hemodynamic Effects. Mexiletine exerts no major hemodynamic effects on ventricular contractile performance or peripheral resistance.

Pharmacokinetics. Mexiletine is rapidly and almost completely absorbed after oral ingestion by volunteers, with peak plasma concentrations being attained in 2 to 4 hours (see Table 35-4). Its elimination half-life is approximately 10 hours in healthy subjects but 17 hours in patients after myocardial infarction. Therapeutic plasma levels of 0.5 to 2 mg/mL are maintained by oral doses of 200 to 300 mg every 6 to 8 hours. Absorption with less than a 10% first-pass hepatic effect occurs in the upper part of the small intestine and is delayed and incomplete in patients receiving narcotics or antacids. Approximately 70% of the drug is protein bound. The apparent volume of distribution is large because of extensive tissue uptake. Normally, mexiletine is eliminated metabolically by the liver, with less than 10% being excreted unchanged in urine. Doses should be reduced in patients with cirrhosis or left ventricular failure. Renal clearance of mexiletine decreases as urinary pH increases. Its known metabolites exert no electrophysiologic effects. Metabolism can be increased by phenytoin, phenobarbital, and rifampin and can be reduced by cimetidine.

DOSAGE AND ADMINISTRATION. The recommended starting dose is 200 mg orally every 8 hours when rapid arrhythmia control is not essential (see Table 35-4). Doses may be increased or decreased by 50 to 100 mg every 2 to 3 days and are better tolerated when given with food. The total daily dose should not exceed 1200 mg. In some patients, administration every 12 hours can be effective.

INDICATIONS. Mexiletine is a moderately effective antiarrhythmic agent for the treatment of acute and chronic ventricular tachyarrhythmias, but not SVTs. Success rates vary from 6% to 60% and can be increased in some patients if mexiletine is combined with other drugs such as procainamide, beta blockers, quinidine, disopyramide, propafenone, or amiodarone. Most studies show no clear superiority of mexiletine over other class I agents. Mexiletine may be very useful in children with congenital heart disease and serious ventricular arrhythmias. In treating patients with a long QT interval, mexiletine may be safer than drugs that increase the QT interval further, such as quinidine. Limited experience in treating subsets of patients with long-QT syndrome (LQT3, which is related to the SCN5A gene for the cardiac sodium channel) suggests a beneficial role (see Chapter 32).

ADVERSE EFFECTS. Up to 40% of patients may require a change in dose or discontinuation of mexiletine therapy as a result of adverse effects, including tremor, dysarthria, dizziness, paresthesia, diplopia, nystagmus, confusion, nausea, vomiting, and dyspepsia. Cardiovascular side effects are rare but include hypotension, bradycardia, and

exacerbation of arrhythmia. The adverse effects of mexiletine appear to be dose related, and toxic effects occur at plasma concentrations only slightly higher than therapeutic levels. Therefore, effective use of this antiarrhythmic drug requires careful titration of dose and monitoring of plasma concentration. Lidocaine should be avoided or the dose reduced in patients receiving mexiletine.

Phenytoin

Phenytoin was used originally to treat seizure disorders. Its value as an antiarrhythmic agent remains limited.

Electrophysiologic Actions. Phenytoin effectively abolishes abnormal automaticity caused by digitalis-induced delayed afterdepolarizations in cardiac Purkinje fibers and suppresses certain digitalis-induced arrhythmias in humans (see [Tables 35-1, 35-2, 35-3, and 35-5](#)). The rate of rise of action potentials initiated early in the relative refractory period is increased, as is membrane responsiveness, which possibly reduces the chance of impaired conduction and block. Phenytoin minimally affects the sinus discharge rate and AV conduction in humans. Some of phenytoin's antiarrhythmic effects may be neurally mediated because it can modulate both sympathetic and vagal efferent activity. It has no peripheral cholinergic- or beta-adrenergic blocking actions and minimal hemodynamic effect.

Pharmacokinetics. The pharmacokinetics of phenytoin is less than ideal. Absorption after oral administration is incomplete and varies with the brand of drug. Plasma concentrations peak 8 to 12 hours after an oral dose; 90% of the drug is protein bound (see [Table 35-4](#)). Phenytoin has limited solubility at physiologic pH, and intramuscular administration is associated with pain, muscle necrosis, sterile abscesses, and variable absorption. Therapeutic serum concentrations of phenytoin (10 to 20 mg/mL) are similar for the treatment of cardiac arrhythmias and epilepsy. Lower concentrations can suppress certain digitalis-induced arrhythmias.

Metabolism. More than 90% of a dose is hydroxylated in the liver to inactive compounds; significant genetically determined variation can occur. The elimination half-time of phenytoin is approximately 24 hours and can be slowed in the presence of liver disease or when it is administered concomitantly with drugs such as warfarin, isoniazid, and phenothiazines, which compete with phenytoin for hepatic enzymes. Because of the large number of medications that can increase or decrease phenytoin levels during chronic therapy, the plasma concentration of phenytoin should be determined frequently when changes are made in other medications. Phenytoin has concentration-dependent kinetics for elimination that can cause unexpected toxicity because disproportionately large changes in plasma concentration can follow dose increases.

Dosage and Administration

To achieve a therapeutic plasma concentration rapidly, 100 mg of phenytoin should be administered intravenously every 5 minutes until the arrhythmia is controlled, 1 g has been given, or adverse side effects result (see [Table 35-4](#)). In general, if phenytoin is going to control the arrhythmia, 700 to 1000 mg suffices. A large central vein should be used to avoid pain and the development of phlebitis produced by the drug's alkalotic vehicle. Orally, phenytoin is given as a loading dose of 1000 mg the first day, 500 mg on the second and third days, and 300 to 400 mg daily thereafter. Maintenance doses can generally be given once daily because of the long half-life of elimination.

Indications

Phenytoin has been used successfully to treat atrial and ventricular arrhythmias caused by digitalis toxicity but is much less effective in treating ventricular arrhythmias in patients with ischemic heart disease or with atrial arrhythmias not caused by digitalis toxicity.

Adverse Effects

The most common manifestations of phenytoin toxicity are central nervous system effects (nystagmus, ataxia, drowsiness, stupor, and coma) and correlate with increases in plasma drug concentration. Nausea, epigastric pain, and anorexia are also relatively common effects of phenytoin. Long-term administration can result in hyperglycemia, hypocalcemia, rash, megaloblastic anemia, gingival hypertrophy, lymph node hyperplasia (a syndrome resembling malignant lymphoma), peripheral neuropathy, pneumonitis, and drug-induced SLE.

Class IC Agents

Flecainide

Flecainide is approved by the U.S. Food and Drug Administration (FDA) to treat patients with life-threatening ventricular arrhythmias, as well as various supraventricular arrhythmias.

Electrophysiologic Actions. Flecainide exhibits marked use-dependent depressant effects on the rapid sodium channel by decreasing V_{max} and has slow onset and offset kinetics (see [Tables 35-1, 35-2, 35-3, and 35-5](#)). Drug dissociation from the sodium channel is slow, with time constants of 10 to 30 seconds (versus 4 to 8 seconds for quinidine and less than 1 second for lidocaine). Thus, marked drug effects can occur at physiologic heart rates. Flecainide shortens the duration of the Purkinje fiber action potential but prolongs it in ventricular muscle, actions that depending on the circumstances, could enhance or reduce electrical heterogeneity and create or suppress arrhythmias. Flecainide profoundly slows conduction in all cardiac fibers and, in high concentrations, inhibits the slow Ca^{2+} channel (see [Chapter 33](#)). Conduction time in the atria, ventricles, AV node, and His-Purkinje system is prolonged. Minimal increases in atrial or ventricular refractoriness or in the QT interval result. Anterograde and retrograde refractoriness in accessory pathways can increase significantly in a use-dependent fashion. Sinus node function remains unchanged in normal subjects but may be depressed in patients with sinus node dysfunction. Flecainide can facilitate or inhibit reentry and may transform atrial fibrillation to flutter. Pacing and defibrillation thresholds are characteristically slightly to significantly increased.

Hemodynamic Effects. Flecainide depresses cardiac performance, particularly in patients with compromised ventricular systolic function, and should be used cautiously or not at all in those with moderate or severe ventricular systolic dysfunction.

Pharmacokinetics. Flecainide is at least 90% absorbed, with peak plasma concentrations being achieved in 3 to 4 hours. Its elimination half-life in patients with ventricular arrhythmias is 20 hours, with 85% of the drug being excreted unchanged or as an inactive metabolite in urine (see [Table 35-4](#)). Its two major metabolites have less potency than the parent drug. Elimination is slower in patients with renal disease and heart failure, and doses should be reduced in these situations. Therapeutic plasma concentrations range from 0.2 to 1.0 mg/mL. Approximately 40% of the drug is protein bound. Increases in serum concentrations of digoxin (15% to 25%) and propranolol (30%) result during coadministration with flecainide. Propranolol, quinidine, and amiodarone may increase flecainide serum concentrations. Five to 7 days of dosing may be required to reach a steady-state concentration in some patients.

DOSAGE AND ADMINISTRATION. The starting dose is 100 mg every 12 hours, increased in increments of 50 mg twice daily, no sooner than every 3 to 4 days, until efficacy is achieved or an adverse effect is noted or to a maximum of 400 mg/day (see [Table 35-4](#)). Cardiac rhythm and QRS duration should be monitored after changes in dose.

INDICATIONS. Flecainide is indicated for the treatment of life-threatening ventricular tachyarrhythmias, SVTs, and paroxysmal atrial fibrillation. Encouraging experimental and early clinical data support its use for catecholaminergic polymorphic VT (see [Chapter 32](#)). Some experts have suggested that therapy should begin in the hospital while the ECG is being monitored because of the possibility of proarrhythmic events (see later). The dosage is adjusted to achieve the desired effect, but the serum concentration should not exceed 1.0 mg/mL. Flecainide is particularly effective in almost totally suppressing PVCs and short runs of nonsustained VT. As with other class I antiarrhythmic drugs, no data from controlled studies indicate that the drug favorably affects survival or sudden cardiac death, and data from CAST have indicated increased mortality in patients with coronary artery disease. Flecainide produces a use-dependent prolongation of VT cycle length, which can improve hemodynamic tolerance. Flecainide is also useful for various SVTs, such as atrial tachycardia (AT), flutter, and atrial fibrillation (including oral loading to terminate episodes acutely). When it is administered chronically, isoproterenol can reverse some of these effects. It is important to slow the ventricular rate before treatment of atrial fibrillation with flecainide to avoid the 1:1 AV conduction of slowed atrial flutter that may result from the effect of flecainide on fibrillation. Flecainide has been used to treat fetal

arrhythmias and arrhythmias in children. Flecainide administration can produce ST elevation in lead V₁, characteristic of Brugada syndrome, in susceptible patients (see Chapter 32) and has been used as a diagnostic tool in persons suspected of having this disorder.

ADVERSE EFFECTS. Proarrhythmic effects are some of the most important adverse effects of flecainide. Its marked slowing of conduction precludes its use in patients with second-degree AV block without a pacemaker and warrants cautious administration in patients with intraventricular conduction disorders. Worsening of existing ventricular arrhythmias or the onset of new ventricular arrhythmias can occur in 5% to 30% of patients, especially in those with preexisting sustained VT, cardiac decompensation, and higher doses of the drug. Failure of the flecainide-related arrhythmia to respond to therapy, including electrical cardioversion-defibrillation, may result in mortality as high as 10% in patients in whom proarrhythmic events develop. Negative inotropic effects can precipitate or worsen heart failure episodes. Patients with sinus node dysfunction may experience sinus arrest, and an increase in the pacing threshold may develop in those with pacemakers. In CAST, patients treated with flecainide had 5.1% mortality or nonfatal cardiac arrest versus 2.3% in the placebo group during a 10-month period. Mortality was highest in those with non-Q-wave infarction, frequent PVCs, and faster heart rates, thus raising the possibility of drug interaction with ischemia and electrical instability. Exercise can amplify the conduction slowing in the ventricle produced by flecainide and in some cases can precipitate a proarrhythmic response. Therefore, exercise testing has been recommended to screen for proarrhythmia (as well as occult ischemia). Central nervous system complaints, including confusion and irritability, represent the most frequent noncardiac adverse effects. The safety of flecainide during pregnancy has not been determined, although as noted previously, it is occasionally used to treat fetal arrhythmias. It is concentrated in breast milk to a level 2.5- to 4-fold higher than in plasma.

Propafenone

Propafenone has been approved by the FDA for the treatment of patients with life-threatening ventricular tachyarrhythmias, as well as atrial fibrillation.

Electrophysiologic Actions. Propafenone blocks the fast sodium current in a use-dependent manner in Purkinje fibers and to a lesser degree in ventricular muscle (see Tables 35-1, 35-2, 35-3, and 35-5). Its use-dependent effects contribute to its ability to terminate atrial fibrillation. Its dissociation constant from the receptor is slow, similar to that of flecainide. Effects are greater in ischemic than in normal tissue and with reduced membrane potentials. Propafenone decreases excitability and suppresses spontaneous automaticity and triggered activity. The drug is a weak blocker of I_{Kr} and beta-adrenergic receptors. Although ventricular refractoriness increases, slowing of conduction is the major effect. Propafenone has several active metabolites that exert electrophysiologic effects. It depresses sinus node automaticity, and the A-H, H-V, PR, and QRS intervals increase, as do the refractory periods of all tissues. The QT interval increases only as a function of increased QRS duration.

Hemodynamic Effects. Propafenone and 5-hydroxypropafenone exhibit negative inotropic properties at high concentrations. In patients with left ventricular ejection fractions exceeding 40%, the negative inotropic effects are well tolerated, but patients with preexisting left ventricular dysfunction and congestive heart failure may have symptomatic worsening of their hemodynamic status.

Pharmacokinetics. With more than 95% of the drug absorbed, the maximum plasma concentration of propafenone is achieved in 2 to 3 hours (see Table 35-4). Systemic bioavailability is dose dependent and ranges from 3% to 40% because of variable presystemic clearance. Bioavailability increases as the dose increases, and the plasma concentration is therefore not linearly related to dose. A 3-fold increase in dosage (300 to 900 mg/day) results in a 10-fold increase in plasma concentration, presumably because of saturation of hepatic metabolic mechanisms. Propafenone is 97% bound to alpha₁-acid glycoprotein, with an elimination half-life of 5 to 8 hours. Maximum therapeutic effects occur at serum concentrations of 0.2 to 1.5 mg/mL. The marked interpatient variability in pharmacokinetics and pharmacodynamics may be the result of genetically determined differences

in metabolism (see Chapter 9). Approximately 7% of the population are poor metabolizers and have an elimination half-life of 15 to 20 hours for the parent compound and almost no 5-hydroxypropafenone. The (+)-enantiomer provides nonspecific beta-adrenergic receptor blockade with 2.5% to 5% of the potency of propranolol, but because plasma propafenone concentrations may be 50 or more times higher than propranolol levels, these beta-blocking properties may be relevant. Poor metabolizers have a greater beta-adrenergic receptor-blocking effect than extensive metabolizers do.

DOSAGE AND ADMINISTRATION. Most patients respond to oral doses of 150 to 300 mg every 8 hours, not to exceed 1200 mg/day (see Table 35-4). Doses are similar for patients of both metabolizing phenotypes. A sustained-release form is available for the treatment of atrial fibrillation; dosing is 225 to 425 mg twice daily. Concomitant food administration increases its bioavailability, as does hepatic dysfunction. No good correlation between the plasma propafenone concentration and suppression of arrhythmia has been shown. Doses should not be increased more often than every 3 to 4 days. Propafenone increases plasma concentrations of warfarin, digoxin, and metoprolol.

INDICATIONS. Propafenone is indicated for the treatment of paroxysmal SVT, atrial fibrillation, and life-threatening ventricular tachyarrhythmias and effectively suppresses spontaneous PVCs and nonsustained and sustained VT.⁷ Acute termination of atrial fibrillation episodes occurred with a single 600-mg oral dose of propafenone in 76% of patients given the drug (twice the rate of those given placebo). It has been used effectively in the pediatric age group. Propafenone increases the pacing threshold but minimally affects the defibrillation threshold. The sinus rate during exercise is reduced.

ADVERSE EFFECTS. Minor noncardiac effects occur in approximately 15% of patients, with dizziness, disturbances in taste, and blurred vision being the most common and gastrointestinal side effects next. Exacerbation of bronchospastic lung disease can occur because of mild beta-blocking effects. Cardiovascular side effects develop in 10% to 15% of patients, including AV block, sinus node depression, and worsening of heart failure. Proarrhythmic responses, which occur more often in patients with a history of sustained VT and decreased ejection fractions, appear less commonly than with flecainide (\approx 5%). Applicability of data from CAST about flecainide to propafenone is not clear, but limiting the application of propafenone in a manner similar to that of other class IC drugs seems prudent. Its beta-blocking actions may make it different, however. The safety of propafenone administration during pregnancy has not been established (class C).

Moricizine

As of December 31, 2007, moricizine (Ethmozine) is no longer available in the United States.

Class II Agents

Beta Adrenoceptor-Blocking Agents

Although many beta adrenoceptor-blocking drugs have been approved for use in the United States, metoprolol, carvedilol, atenolol, propranolol, and esmolol have been most widely used to treat supraventricular and ventricular arrhythmias. Acebutolol, nadolol, timolol, betaxolol, pindolol, and bisoprolol have been used less extensively for the treatment of arrhythmias. Metoprolol, atenolol, carvedilol, timolol, and propranolol decrease overall mortality and sudden death after myocardial infarction (see Chapter 39). It is generally thought that beta blockers possess class effects and that when titrated to the proper dose, all can be used effectively to treat cardiac arrhythmias, hypertension, or other disorders. However, differences in pharmacokinetic or pharmacodynamic properties that confer safety, reduce adverse effects, or affect dosing intervals or drug interactions influence the choice of agent. For example, nadolol may be particularly effective in patients with long-QT syndrome (see Chapter 32). Also, some beta blockers, such as sotalol, pindolol, and carvedilol, exert unique actions in addition to beta receptor blockade.

Beta receptors can be separated into those that affect predominantly the heart (beta₁) and those that affect predominantly blood vessels and the bronchi (beta₂). In low doses, selective beta blockers can block beta₁ receptors more than they block beta₂ receptors and

might be preferable for the treatment of patients with pulmonary or peripheral vascular disease. In high doses, the “selective” beta₁ blockers also block beta₂ receptors. Carvedilol also exerts alpha-blocking effects and is used primarily in patients with heart failure (see Chapters 23 to 25). It is not an ideal agent for rate control in atrial fibrillation because of the alpha-blocking–induced hypotension that accompanies doses large enough to block the AV node.

Some beta blockers exert intrinsic sympathomimetic activity; that is, they slightly activate the beta receptor. These drugs appear to be as efficacious as beta blockers without intrinsic sympathomimetic actions and may cause less slowing of the heart rate at rest and less prolongation of AV nodal conduction time. They have been shown to induce less depression of left ventricular function than do beta blockers without intrinsic sympathomimetic activity. Beta blockers without intrinsic sympathomimetic activity have been shown to reduce mortality in patients after myocardial infarction, with nonselective agents possibly conferring slightly greater benefit (see Chapters 51 and 52).

The following discussion focuses on the use of propranolol as a prototypic antiarrhythmic agent but is generally applicable to other beta blockers.

Electrophysiologic Actions. Beta blockers exert an electrophysiologic action by competitively inhibiting binding of catecholamine at beta adrenoceptor sites, an effect almost entirely the result of the (−)-levorotatory stereoisomer, or by their quinidine-like or direct membrane-stabilizing action (see Tables 35-1, 35-2, 35-3, and 35-5). The latter is a local anesthetic effect that depresses I_{Na} and membrane responsiveness in cardiac Purkinje fibers, occurs at concentrations generally 10 times those necessary to produce beta blockade, and most likely plays an insignificant antiarrhythmic role. Thus, beta blockers exert their major effects in cells most actively stimulated by adrenergic actions. At a beta-blocking concentration, propranolol slows spontaneous automaticity in the sinus node or in Purkinje fibers that are being stimulated by adrenergic tone and produces an I_f block (see Chapter 33). Beta blockers also block the I_{Ca,L} stimulated by beta agonists. In the absence of adrenergic stimulation, only high concentrations of propranolol slow normal automaticity in Purkinje fibers, probably by a direct membrane action.

Concentrations that cause beta receptor blockade but no local anesthetic effects do not alter the normal resting membrane potential, maximum diastolic potential amplitude, V_{max}, repolarization, or refractoriness of atrial, Purkinje, or ventricular muscle cells in the absence of catecholamine stimulation. However, in the presence of isoproterenol, a relatively pure beta receptor stimulator, beta blockers reverse isoproterenol’s accelerating effects on repolarization. Propranolol reduces the amplitude of digitalis-induced delayed afterdepolarizations and suppresses triggered activity in Purkinje fibers.

Concentrations exceeding 3 mg/mL are required to depress V_{max}, action potential amplitude, membrane responsiveness, and conduction in normal atrial, ventricular, and Purkinje fibers without altering resting membrane potential. These effects probably result from depression of I_{Na}. Long-term administration of propranolol may lengthen the APD. Similar to the effects of lidocaine, acceleration of repolarization of Purkinje fibers is most marked in areas of the ventricular conduction system in which the APD is greatest.

Propranolol slows the sinus discharge rate in humans by 10% to 20%, although severe bradycardia occasionally results if the heart is particularly dependent on sympathetic tone or if sinus node dysfunction is present. The PR interval lengthens, as do AV nodal conduction time and AV nodal effective and functional refractory periods (at a constant heart rate), but refractoriness and conduction in the normal His-Purkinje system remain unchanged, even after high doses of propranolol. Therefore, therapeutic doses of propranolol in humans do not exert a direct depressant or “quinidine-like” action but influence cardiac electrophysiology through a beta-blocking action. Beta blockers do not affect conduction or repolarization in normal ventricular muscle, as evidenced by their lack of effect on the QRS complex and QT interval, respectively.

Because administration of beta blockers that do not have direct membrane action prevents many arrhythmias resulting from activation of the autonomic nervous system, it is thought that the beta-blocking action is responsible for their antiarrhythmic effects. Nevertheless, the possible importance of the direct membrane effect of some of these drugs cannot be discounted totally because beta blockers with direct membrane actions can affect the transmembrane potentials of

diseased cardiac fibers at much lower concentrations than are needed to affect normal fibers directly. However, indirect actions on the arrhythmogenic effects of ischemia are probably the most important.

Hemodynamic Effects. Beta blockers exert negative inotropic effects and can precipitate or worsen heart failure. However, beta blockers clearly improve survival in patients with heart failure (see Chapter 25). By blocking beta receptors, these drugs may allow unopposed alpha-adrenergic effects to produce peripheral vasoconstriction and exacerbate coronary artery spasm or pain from peripheral vascular disease in some patients.

Pharmacokinetics. Although various types of beta blockers exert similar pharmacologic effects, their pharmacokinetics differs substantially. Propranolol is almost 100% absorbed, but the effects of first-pass hepatic metabolism reduce its bioavailability to approximately 30% and produce significant interpatient variability in plasma concentration with a given dose (see Table 35-4). Reduced hepatic blood flow, as in patients with heart failure, decreases the hepatic extraction of propranolol; in these patients, propranolol may further decrease its own elimination rate by reducing cardiac output and hepatic blood flow. Beta blockers eliminated by the kidneys tend to have longer half-lives and exhibit less interpatient variability in drug concentration than do beta blockers metabolized by the liver.

DOSAGE AND ADMINISTRATION. The appropriate dose of propranolol is best determined by a measure of the patient’s physiologic response, such as changes in resting heart rate or prevention of exercise-induced sinus tachycardia, because wide individual differences exist between the observed physiologic effect and plasma concentration. For example, intravenous dosing is best achieved by titration of the dose to clinical effect, beginning with doses of 0.25 to 0.50 mg, increasing to 1.0 mg if necessary, and administering doses every 5 minutes until either a desired effect or toxicity is produced or a total of 0.15 to 0.20 mg/kg has been given. In many cases, the short-acting effects of esmolol are preferred. Orally, propranolol is given in four divided doses, usually ranging from 40 to 160 mg/day to more than 1 g/day (see Table 35-4). Some beta blockers, such as carvedilol and pindolol, need to be given twice daily; many are available as once-daily long-acting preparations. In general, if one agent in adequate doses does not produce the desired effect, other beta blockers will also be ineffective. Conversely, if one agent produces the desired physiologic effect but a side effect develops, another beta blocker can often be substituted successfully.

INDICATIONS. Arrhythmias associated with thyrotoxicosis or pheochromocytoma and arrhythmias largely related to excessive cardiac adrenergic stimulation, such as those initiated by exercise, emotion, or cocaine, often respond to beta blocker therapy. Beta-blocking drugs do not usually convert chronic atrial flutter or atrial fibrillation to normal sinus rhythm but may do so if the arrhythmia is of recent onset and in patients who have recently undergone cardiac surgery. The atrial rate during atrial flutter or fibrillation is not changed, but the ventricular response decreases because beta blockade prolongs AV nodal conduction time and refractoriness. Esmolol can be used intravenously for rapid control of the heart rate. For reentrant SVTs using the AV node as one of the reentrant pathways, such as AV nodal reentrant tachycardia (AVNRT) and orthodromic reciprocating tachycardia in Wolff-Parkinson-White syndrome or inappropriate sinus tachycardia, or for AT, beta blockers can slow or terminate the tachycardia and can be used prophylactically to prevent a recurrence. Combining beta blockers with digitalis, quinidine, or various other agents can be effective when the beta blocker as a single agent fails. Metoprolol and esmolol may be useful in patients with multifocal AT. These agents must be used with caution in patients with this arrhythmia, however, because a common setting for it is advanced lung disease, often with a bronchospastic component.

Beta blockers can be effective for digitalis-induced arrhythmias such as AT, nonparoxysmal AV junctional tachycardia, PVCs, or VT. If a significant degree of AV block is present during digitalis-induced arrhythmia, lidocaine or phenytoin may be preferable to propranolol. Beta blockers can also be useful to treat ventricular arrhythmias associated with prolonged-QT interval syndrome (see Chapter 32) and with mitral valve prolapse (see Chapter 63). For patients with

ischemic heart disease, beta blockers do not generally prevent the episodes of recurrent monomorphic VT that occur in the absence of acute ischemia. It is well accepted that several beta blockers reduce the incidence of both total and sudden death after myocardial infarction (see Chapters 51 and 52). The mechanism of this reduction in mortality is not entirely clear and may be related to reduction of the extent of ischemic damage, autonomic effects, a direct antiarrhythmic effect, or combinations of these factors. Beta blockers may have been protective against proarrhythmic responses in CAST.

ADVERSE EFFECTS. Adverse cardiovascular effects from beta blockers include unacceptable hypotension, bradycardia, and congestive heart failure. The bradycardia can be caused by sinus slowing or AV block. Sudden withdrawal of propranolol in patients with angina pectoris can precipitate or worsen angina and cardiac arrhythmias and cause acute myocardial infarction, possibly as a result of the heightened sensitivity to beta agonists caused by previous beta blockade (receptor upregulation). Heightened sensitivity may begin several days after cessation of beta blocker therapy and can last 5 or 6 days. Other adverse effects of beta blockers include worsening of asthma or chronic obstructive pulmonary disease, intermittent claudication, Raynaud phenomenon, mental depression, increased risk for hypoglycemia in insulin-dependent diabetic patients, easy fatigability, disturbingly vivid dreams or insomnia, and impaired sexual function. Many of these side effects were noted less frequently with the use of beta₁-selective agents, but even so-called cardioselective beta blockers can exacerbate asthma or diabetic control in individual patients.

Class III Agents

Amiodarone

Amiodarone is a benzofuran derivative approved by the FDA for the treatment of patients with life-threatening ventricular tachyarrhythmias when other drugs are ineffective or not tolerated. Dronedarone, a noniodinated derivative of amiodarone, is approved by the FDA for the treatment of atrial fibrillation (see later).

Electrophysiologic Actions. When it is chronically given orally, amiodarone prolongs the APD and refractoriness of all cardiac fibers without affecting resting membrane potential (see Tables 35-1, 35-2, 35-3, and 35-5 and Chapter 33). When acute effects are evaluated, amiodarone and its metabolite desethylamiodarone prolong the APD of ventricular muscle but shorten the APD of Purkinje fibers. Injected into the sinus and AV node arteries, amiodarone reduces sinus and junctional discharge rates and prolongs AV nodal conduction time. It depresses V_{max} in ventricular muscle in a rate- or use-dependent manner by blocking of inactivated sodium channels, an effect that is accentuated by depolarized and reduced by hyperpolarized membrane potentials. Amiodarone depresses conduction at fast rates more than at slow rates (use dependence), not only by depressing V_{max} but also by increasing resistance to passive current flow. It does not prolong repolarization more at slow than at fast rates (i.e., does not demonstrate reverse use dependence) but does exert time-dependent effects on refractoriness, which may in part explain its high antiarrhythmic efficacy and low incidence of torsades de pointes.

Desethylamiodarone has relatively greater effects on fast-channel tissue, which probably contributes notably to its antiarrhythmic efficacy. The delay in building up adequate concentrations of this metabolite may in part explain the delay in amiodarone's antiarrhythmic action.

Amiodarone noncompetitively antagonizes alpha and beta receptors and blocks conversion of thyroxine (T₄) to triiodothyronine (T₃), which may account for some of its electrophysiologic effects. Amiodarone exhibits slow-channel-blocking effects; with oral administration, it slows the sinus rate by 20% to 30% and prolongs the QT interval, at times changing the contour of the T wave and producing U waves.

The ERP of all cardiac tissues is prolonged. The H-V interval increases and the QRS duration lengthens, especially at fast rates. Amiodarone given intravenously modestly prolongs the refractory period of atrial and ventricular muscle. The PR interval and AV nodal conduction time lengthen. The duration of the QRS complex lengthens at increased rates but less than after oral amiodarone. Thus, a far less increase in prolongation of conduction time (except for the AV node), duration of repolarization, and refractoriness occurs after intravenous

administration than after the oral route. Considering these actions, it is clear that amiodarone has class I (blocks I_{Na}), class II (antiadrenergic), and class IV (blocks I_{Ca,L}) actions in addition to its class III effects (blocks I_K). Amiodarone's actions approximate those of a theoretically ideal drug that exhibits use-dependent Na⁺ channel blockade with fast diastolic recovery from block and use-dependent prolongation of the APD. It does not increase and may decrease QT dispersion. Catecholamines can partially reverse some of the effects of amiodarone.

Hemodynamic Effects. Amiodarone is a peripheral and coronary vasodilator. When administered intravenously (150 mg over a 10-minute period, then a 1-mg/min infusion), amiodarone decreases the heart rate, systemic vascular resistance, left ventricular contractile force, and left ventricular dP/dt. Oral doses of amiodarone sufficient to control cardiac arrhythmias do not depress the left ventricular ejection fraction, even in patients with reduced ejection fractions, and the ejection fraction and cardiac output may increase slightly. However, because of the antiadrenergic actions of amiodarone and because it does exert some negative inotropic action, it should be given cautiously, particularly intravenously, to patients with marginal cardiac compensation.

Pharmacokinetics. Amiodarone is slowly, variably, and incompletely absorbed, with a systemic bioavailability of 35% to 65% (see Table 35-4). Plasma concentrations peak 3 to 7 hours after a single oral dose. There is a minimal first-pass effect, thus indicating little hepatic extraction. Elimination is by hepatic excretion into bile with some enterohepatic recirculation. Extensive hepatic metabolism occurs, with desethylamiodarone being a major metabolite. Both accumulate extensively in the liver, lung, fat, "blue" skin, and other tissues. The concentration in myocardium is 10 to 50 times that found in plasma. Plasma clearance of amiodarone is low, and renal excretion is negligible. Doses need not be reduced in patients with renal disease. Amiodarone and desethylamiodarone are not dialyzable. The volume of distribution is large but variable, with an average of 60 L/kg. Amiodarone is highly protein bound (96%), crosses the placenta (10% to 50%), and is found in breast milk.

The onset of action after intravenous administration generally occurs within 1 to 2 hours. After oral administration, the onset of action may require 2 to 3 days, often 1 to 3 weeks, and on occasion even longer. Loading doses reduce this time interval. Plasma concentrations relate well to oral doses during chronic treatment and average approximately 0.5 mg/mL for each 100 mg/day at doses between 100 and 600 mg/day. Its elimination half-life is multiphasic, with an initial 50% reduction in plasma concentration 3 to 10 days after cessation of drug ingestion (probably representing elimination from well-perfused tissues), followed by a terminal half-life of 26 to 107 days (mean, 53 days), with most patients being in the 40- to 55-day range. To achieve a steady-state concentration without a loading dose takes about 265 days. Interpatient variability in these pharmacokinetic parameters mandates close monitoring of the patient. Therapeutic serum concentrations range from 1 to 2.5 mg/mL. Greater suppression of arrhythmias may occur with up to 3.5 mg/mL, but the risk for side effects increases.

DOSAGE AND ADMINISTRATION. An optimal dosing schedule for all patients has not been achieved. One recommended approach is to treat with 800 to 1200 mg/day for 1 to 3 weeks, 400 mg/day for the next several weeks, and finally after 2 to 3 months of treatment, a maintenance dose of 300 mg or less per day (see Table 35-4). Maintenance drug can be given once or twice daily and should be titrated to the lowest effective dose to minimize the occurrence of side effects; in general, the earlier during drug loading that arrhythmia control is achieved, the lower the maintenance dose can be. Doses as low as 100 mg/day can be effective in some patients. Regimens must be individualized for a given patient and clinical situation. To achieve more rapid loading and effect in emergencies, amiodarone can be administered intravenously at initial doses of 15 mg/min for 10 minutes, followed by 1 mg/min for 6 hours and then 0.5 mg/min for the remaining 18 hours and the next several days as necessary. Supplemental infusions of 150 mg over a 10-minute period can be used for breakthrough VT or VF. Intravenous infusions can be continued safely for 2 to 3 weeks. Intravenous amiodarone is generally well tolerated, even in patients with left ventricular dysfunction. Patients with depressed ejection fractions should receive intravenous amiodarone with great caution because of hypotension. High-dose oral loading (800 to 2000 mg/day to maintain trough serum

concentrations of 2 to 3 mg/mL) may suppress ventricular arrhythmias in 1 to 2 days.

INDICATIONS. Amiodarone has been used to suppress a wide spectrum of supraventricular and ventricular tachyarrhythmias in utero, in adults, and in children, including AV node and AV reentry junctional tachycardia, atrial flutter and fibrillation, VT and VF associated with coronary artery disease, and hypertrophic cardiomyopathy. Success rates vary widely, depending on the population of patients, arrhythmia, underlying heart disease, length of follow-up, definition and determination of success, and other factors. In general, however, the efficacy of amiodarone equals or exceeds that of all other antiarrhythmic agents and may be in the range of 60% to 80% for most supraventricular tachyarrhythmias and 40% to 60% for ventricular tachyarrhythmias. Amiodarone may be useful in improving survival in patients with hypertrophic cardiomyopathy, asymptomatic ventricular arrhythmias after myocardial infarction, and ventricular tachyarrhythmia during and after resuscitation from cardiac arrest. Amiodarone given before open heart surgery, as well as postoperatively, has been shown to decrease the incidence of postoperative atrial fibrillation. Amiodarone is superior to class I antiarrhythmic agents and sotalol in maintaining sinus rhythm in patients with recurrent atrial fibrillation.

Patients who have an ICD receive fewer shocks if they are treated with amiodarone than if treated with conventional drugs. Amiodarone has little effect on the pacing threshold but typically increases the electrical defibrillation threshold slightly.

Several prospective, randomized, controlled trials and meta-analyses have demonstrated improved survival with amiodarone therapy versus placebo; however, amiodarone has been proved to result in inferior survival in comparison to ICD therapy, and in the SCD-HeFT population (Class II or III heart failure; ejection fraction, 35%), survival of amiodarone-treated patients was no different from that of those treated with placebo. The drug may still be used adjunctively in ICD-treated patients to decrease the frequency of shocks from VT and VF episodes or to control supraventricular tachyarrhythmias that elicit device therapy (see Chapter 37). The drug can slow the ventricular rate during spontaneous VT episodes beneath the detection rate of the device; careful patient assessment and, occasionally, device reprogramming and testing are necessary. It also can be used to slow the ventricular rate during atrial fibrillation and atrial flutter.

Because of the serious nature of the arrhythmias being treated, the unusual pharmacokinetics of the drug, and its adverse effects, consideration should be given to starting amiodarone therapy with the patient hospitalized and monitored for at least several days. Combining other antiarrhythmic agents with amiodarone may improve efficacy in some patients.

ADVERSE EFFECTS. Adverse effects are reported by about 75% of patients treated with amiodarone for 5 years, and these effects compel stopping use of the drug in 18% to 37%. The most frequent side effects requiring drug discontinuation involve pulmonary and gastrointestinal complaints or abnormal test results. Most adverse effects are reversible with dose reduction or cessation of treatment. Adverse effects are more common when therapy is continued in the long term and at higher doses. Of the noncardiac adverse reactions, pulmonary toxicity is the most serious⁸; in one study it occurred in 33 of 573 patients between 6 days and 60 months of treatment, with three deaths. The mechanism is unclear but may involve a hypersensitivity reaction, widespread phospholipidosis, or both. Dyspnea, nonproductive cough, and fever are common symptoms, along with crackles on examination, hypoxia, abnormal gallium scan results, reduced diffusion capacity, and radiographic evidence of pulmonary infiltrates. Amiodarone must be discontinued if such pulmonary inflammatory changes occur. Corticosteroids can be tried, but no controlled studies have been done to support their use. Ten percent mortality results in patients with pulmonary inflammatory changes, often in those with unrecognized pulmonary involvement that is allowed to progress. Chest radiography and pulmonary function testing, including carbon monoxide diffusion capacity (DLCO), at 3-month intervals for the first year and then twice a year for several

years have been recommended. At maintenance doses lower than 300 mg/day, pulmonary toxicity is uncommon but can occur. Advanced age, high drug maintenance dose, and reduced predrug diffusion capacity are risk factors for the development of pulmonary toxicity. An unchanged DLCO on therapy may be a negative predictor of pulmonary toxicity.

Although asymptomatic elevations in liver enzyme levels are found in most patients, the drug is not stopped unless values exceed two or three times normal in a patient with initially normal values. Cirrhosis occurs uncommonly but may be fatal.⁹ Neurologic dysfunction, photosensitivity (perhaps minimized by sunscreens), bluish skin discoloration, gastroenterologic disturbances, and hyperthyroidism (1% to 2%) or hypothyroidism (2% to 4%) can occur.¹⁰ Because amiodarone appears to inhibit the peripheral conversion of T₄ to T₃, chemical changes result and are characterized by a slight increase in T₄, reverse T₃, and thyroid-stimulating hormone (TSH) and a slight decrease in T₃ levels. The reverse T₃ concentration has been used as an index of drug efficacy. During hypothyroidism the TSH level increases greatly, whereas the level of T₃ increases in hyperthyroidism. Thyroid function tests should be performed approximately every 3 months for the first year while amiodarone is being taken and once or twice yearly thereafter, sooner if symptoms develop that are consistent with thyroid dysfunction. Corneal microdeposits occur in almost 100% of adults receiving the drug longer than 6 months. More serious ocular reactions, including optic neuritis and atrophy with visual loss, have been reported but are rare, and causation by amiodarone has not been established.

Cardiac side effects include symptomatic bradycardias in approximately 2% of patients; worsening of ventricular tachyarrhythmias with the occasional development of torsades de pointes in 1% to 2%, possibly higher in women; and worsening of congestive heart failure in 2%. Possibly because of interactions with anesthetics, complications after open heart surgery, including pulmonary dysfunction, hypotension, severe bradycardia, hepatic dysfunction, and low cardiac output, have been noted by some investigators.

In general, the lowest possible maintenance dose of amiodarone that is still effective should be used to avoid significant adverse effects. Many supraventricular arrhythmias can be managed successfully with daily dosages of 200 mg or less, whereas ventricular arrhythmias generally require higher doses. Adverse effects are uncommon at dosages of 200 mg/day or less but still occur. Because of potential toxicity in various organ systems, special multidisciplinary amiodarone clinics have been used by some in an attempt to prevent adverse outcomes when the drug is used.

Important interactions with other drugs occur, and when given concomitantly with amiodarone, the doses of warfarin, digoxin, and other antiarrhythmic drugs should be reduced by a third to a half and the patient observed closely. Drugs with synergistic actions, such as beta blockers or calcium channel blockers, must be given cautiously. The safety of amiodarone during pregnancy has not been established, and it should be used in pregnant patients only if no alternatives exist.

Dronedarone

Dronedarone is approved by the FDA to facilitate maintenance of sinus rhythm in patients with atrial flutter and fibrillation.

Electrophysiologic Actions. Like amiodarone, dronedarone alters the activity of multiple cardiac ion channels (see Tables 35-1, 35-2, 35-3, and 35-5). It is a more potent blocker of the rapid sodium current than amiodarone is and exhibits similar effects on the L-type calcium current. Blockade of both the rapid and slow components of the delayed rectifier potassium current by dronedarone is also similar to that by amiodarone, whereas its effect on the atrial acetylcholine-activated potassium current and antiadrenergic effects (via noncompetitive binding) are significantly more potent than that of amiodarone. Sinus node function is depressed to a minor degree. Pacing and defibrillation thresholds are slightly increased.

Hemodynamic Effects. Dronedarone has little effect on cardiac performance except in patients with compromised ventricular systolic function and should not be used in those with clinical signs of heart failure.

Pharmacokinetics. Dronedarone is 70% to 90% absorbed after oral administration, with peak plasma concentrations being achieved in 3 to 4 hours; absorption is enhanced by food (see Table 35-4). Unlike the very long half-life of amiodarone, the elimination half-life of dronedarone is 13 to 19 hours, with 85% of the drug being excreted unchanged in feces and the remainder in urine. Dronedarone is metabolized by and slightly inhibits the activity of CYP3A4 (as well as CYP2D6) and should not be used in conjunction with other agents that strongly inhibit these enzyme systems. There is little warfarin interaction, but dronedarone increases serum levels of dabigatran.

DOSAGE AND ADMINISTRATION. The standard recommended dose is 400 mg every 12 hours with food (see Table 35-4). No parenteral form is currently available.

INDICATIONS. Dronedarone is indicated to facilitate cardioversion of atrial flutter or fibrillation or to maintain sinus rhythm after restoration of sinus rhythm. It is slightly less effective than amiodarone in these regards.¹¹ In the ANDROMEDA (Antiarrhythmic Trial with Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease) study, dronedarone-treated patients had a mortality rate more than twice that of placebo (8.1% versus 3.8%). Similarly, in the PALLAS (Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy) trial, patients with permanent atrial fibrillation who were taking dronedarone had a greater than twofold higher risk for death, stroke, systemic embolism, or myocardial infarction than did control patients.¹² Thus, the medication should not be used in patients with current or recent episodes of clinical heart failure or in those with permanent atrial fibrillation (as a rate control agent). Patients taking dronedarone should be evaluated periodically to ensure that permanent fibrillation or heart failure has not developed.

ADVERSE EFFECTS. A transient, predictable increase in serum creatinine, without adversely affecting actual glomerular filtration or other measures of renal function, occurs with standard dosing and is not a reason to alter the dose or to discontinue use of the drug. As noted, patients with New York Heart Association class III or IV heart failure, as well as those with permanent atrial fibrillation, should not be given the drug because these patients have higher mortality. Patients with severe liver dysfunction should not generally receive the drug. The QT interval is predictably prolonged, but proarrhythmic effects from this or other mechanisms are rare (although sinus bradycardia is sometimes seen). Rash, photosensitivity, nausea, diarrhea, dyspepsia, headache, and asthenia have occurred in treated patients at higher frequency than in controls. Absence of the iodine molecule appears to account for the lower prevalence of lung and thyroid toxicity in dronedarone-treated patients than in those taking amiodarone. Dronedarone should not be used during pregnancy (category X, evidence or risk of fetal harm) and is possibly unsafe for breast feeding.

Bretylium Tosylate

Bretylium is a quaternary ammonium compound that had been used parenterally in patients with life-threatening ventricular tachyarrhythmias. Because of poor efficacy, it is no longer manufactured or available in the United States.

Sotalol

Sotalol is a nonspecific beta adrenoceptor blocker without intrinsic sympathomimetic activity that prolongs repolarization. It is approved by the FDA to treat patients with life-threatening ventricular tachyarrhythmias and those with atrial fibrillation.

Electrophysiologic Actions. Both the *d*- and *l*-isomers have similar effects on prolonging repolarization, whereas the *l*-isomer is responsible for almost all the beta-blocking activity (see Tables 35-1, 35-2, 35-3, and 35-5). Sotalol does not block alpha adrenoceptors and does not block the sodium channel (no membrane-stabilizing effects) but does prolong atrial and ventricular repolarization times by reducing I_{Kr} , thus prolonging the plateau of the action potential. Action potential prolongation is greater at slower rates (reverse use dependence). Resting membrane potential, action potential amplitude, and V_{max} are not significantly altered. Sotalol prolongs atrial and ventricular refractoriness, A-H and QT intervals, and sinus cycle length (see Chapter 37).

Hemodynamics. Sotalol exerts a negative inotropic effect only through its beta-blocking action. Although it can increase the strength of contraction by prolonging repolarization, which occurs maximally at slow heart rates, the negative inotropic effects predominate. In patients with reduced cardiac function, sotalol can decrease the cardiac index, increase filling pressure, and precipitate overt heart failure. Therefore, it must be used cautiously in patients with marginal cardiac compensation but is well tolerated in those with normal cardiac function.

Pharmacokinetics. Sotalol is completely absorbed and not metabolized, thus making it 90% to 100% bioavailable. It is not bound to plasma proteins, is excreted unchanged primarily by the kidneys, and has an elimination half-life of 10 to 15 hours (see Table 35-4). Peak plasma concentrations occur 2.5 to 4 hours after oral ingestion. Over the dose range of 160 to 640 mg, sotalol displays dose proportionality with plasma concentration (usually in the range of 2.5 μ g/mL). The dose must be reduced in patients with renal disease. The beta-blocking effect is half-maximal at 80 mg/day and maximal at 320 mg/day.

DOSAGE. The typical oral dose is 80 to 160 mg every 12 hours, with 2 to 3 days being allowed between dose adjustments to attain a steady-state concentration and to monitor the ECG for arrhythmias and QT prolongation (see Table 35-4). Doses exceeding 320 mg/day can be used in patients when the potential benefits outweigh the risk for proarrhythmia. Because of its ability to significantly prolong the QT interval in some patients and cause torsades de pointes or provoke severe bradycardia, consideration should be given to inpatient initiation of the drug, especially in those with atrial fibrillation (in whom conversion to sinus bradycardia may cause syncope and/or further QT prolongation at slow rates), as well as in women (with longer baseline QT intervals).

INDICATIONS. Approved by the FDA to treat patients with ventricular tachyarrhythmias and atrial fibrillation, sotalol is also useful to prevent recurrence of a wide variety of SVTs, including atrial flutter, AT, AV node reentry, and AV reentry (see Chapter 37). It also slows the ventricular response to atrial tachyarrhythmias. It appears to be more effective than conventional antiarrhythmic drugs and may be comparable to amiodarone in the treatment of patients with ventricular tachyarrhythmias, as well as in prevention of recurrences of atrial fibrillation after cardioversion. It has been used successfully to decrease the incidence of atrial fibrillation after cardiac surgery.¹³ Sotalol may be effective in fetal and pediatric patients and young adults with congenital heart disease.¹⁴ Unlike most other antiarrhythmic drugs, it may decrease the frequency of ICD discharges and reduce the defibrillation threshold.

ADVERSE EFFECTS. Proarrhythmia is the most serious adverse effect. Overall, new or worsened ventricular tachyarrhythmias occur in approximately 4% of patients; this response is the result of torsades de pointes in around 2.5% but increases to 4% in patients with a history of sustained VT and is dose related (only 1.6% at 320 mg/day but 4.4% at 480 mg/day). This proarrhythmic effect was probably the cause of excess mortality in patients given *d*-sotalol (the enantiomer lacking a beta-blocking effect) after acute myocardial infarction in the SWORD (Survival With Oral *d*-Sotalol) trial. Other adverse effects commonly seen with other beta blockers also apply to sotalol. Sotalol should be used with caution or not at all in combination with other drugs that prolong the QT interval. However, such combinations have occasionally been used successfully.

Ibutilide

Ibutilide is an agent released for acute termination of episodes of atrial flutter and fibrillation (see Chapter 37).

Electrophysiologic Actions. Like other class III agents, ibutilide prolongs repolarization (see Tables 35-1, 35-2, 35-3, and 35-5). Although it is similar to other class III agents that block outward potassium currents, such as I_{Kr} , ibutilide is unique in that it also activates a slow inward sodium current. Administered intravenously, ibutilide causes mild slowing of the sinus rate and has minimal effects on AV conduction or QRS duration, but the QT interval is characteristically prolonged. Ibutilide has no significant effect on hemodynamics.

Pharmacokinetics. Ibutilide is administered intravenously and has a large volume of distribution (see Table 35-4). Clearance is

predominantly renal, with a drug half-life averaging 6 hours, but with considerable interpatient variability. Protein binding is approximately 40%. One of the drug's metabolites has weak class III effects.

DOSAGE AND ADMINISTRATION. Ibutilide is given as an intravenous infusion of 1 mg over a 10-minute period (see Table 35-4). It should not be given in the presence of a QTc interval longer than 440 milliseconds or other drugs that prolong the QT interval or in patients with uncorrected hypokalemia, hypomagnesemia, or bradycardia. A second 1-mg dose may be given after the first dose is finished if the arrhythmia persists. Patients must have continuous electrocardiographic monitoring throughout the dosing period and for 6 to 8 hours thereafter because of the risk for ventricular arrhythmias. Pretreatment with intravenous magnesium may decrease the risk for ventricular arrhythmias and enhance efficacy in treating some atrial arrhythmias.¹⁵ Up to 60% of patients with atrial fibrillation and 70% of those with atrial flutter convert to sinus rhythm after 2 mg of ibutilide has been administered.

INDICATIONS. Ibutilide is indicated for termination of an established episode of atrial flutter or fibrillation. It should not be used in patients with frequent short paroxysms of atrial fibrillation because it merely terminates episodes and is not useful for long-term prevention. Patients whose condition is hemodynamically unstable should proceed to direct-current cardioversion. Ibutilide has been used safely and effectively in patients who were already taking amiodarone or propafenone but should be used with caution in these cases. Ibutilide has been administered at the time of transthoracic electrical cardioversion to increase the likelihood of termination of atrial fibrillation. In one study, all 50 patients given ibutilide before attempted electrical cardioversion achieved sinus rhythm, whereas only 34 of 50 who did not receive the drug converted to sinus rhythm. Of note, all 16 patients who did not respond to electrical cardioversion without ibutilide were successfully electrically cardioverted to sinus rhythm when a second attempt was made after ibutilide pretreatment.

Ibutilide prolongs accessory pathway refractoriness and can temporarily slow the ventricular rate during preexcited atrial fibrillation. The drug can also occasionally terminate episodes of organized AT, as well as sustained, uniform-morphology VT.

ADVERSE EFFECTS. The most significant adverse effect of ibutilide is QT prolongation–related torsades de pointes, which occurs in approximately 2% of patients given the drug (twice as often in women as in men). This effect develops within the first 4 to 6 hours of dosing, after which the risk is negligible. Thus, patients in whom the drug is used must undergo electrocardiographic monitoring for up to 8 hours after dosing. This requirement can make the use of ibutilide in emergency departments or private offices problematic. The safety of ibutilide during pregnancy has not been well studied, and its use in this setting should be restricted to patients in whom no safer alternative exists.

Dofetilide

Dofetilide is approved for the acute conversion of atrial fibrillation to sinus rhythm, as well as for chronic suppression of recurrent atrial fibrillation.¹⁶

Electrophysiologic Actions. The sole electrophysiologic effect of dofetilide is block of the rapid component of the delayed rectifier potassium current (I_{Kr}), important in repolarization (see Tables 35-1, 35-2, 35-3, and 35-5). This effect is more prominent in the atria than in the ventricles—30% increase in the atrial refractory period versus 20% in the ventricle. The effect of dofetilide on I_{Kr} is prolongation of refractoriness without slowing conduction, which is believed to be largely responsible for its antiarrhythmic effect. It is also responsible for prolongation of the QT interval on the ECG, which averages 11% but can be much greater. This effect on the QT interval is dose dependent and linear. No other important electrocardiographic changes are observed with the drug. It has no significant hemodynamic effects. Dofetilide is more effective than quinidine at converting atrial fibrillation to sinus rhythm. Its long-term efficacy is similar to that of other agents.¹⁷

Pharmacokinetics. Orally administered dofetilide is absorbed well, and more than 90% is bioavailable. Its mean elimination half-life is 7 to 13 hours, with 50% to 60% of the drug being excreted unchanged

in urine (see Table 35-4). The remainder of the drug undergoes hepatic metabolism to inert compounds. Significant drug-drug interactions have been reported in patients taking dofetilide; cimetidine, verapamil, ketoconazole, and trimethoprim, alone or in combination with sulfamethoxazole, cause a significant elevation in the dofetilide serum concentration and should not be used with this drug.

DOSAGE AND ADMINISTRATION. Dofetilide is available only as an oral preparation. Dosing is from 0.125 to 0.5 mg twice daily and must be initiated in a hospital setting with continuous electrocardiographic monitoring to ensure that inordinate QT prolongation and torsades de pointes do not develop (see Table 35-4). Physicians must be specially certified to prescribe the drug. Its dosage must be decreased in the presence of impaired renal function or an increase in the QT interval of more than 15%, or 500 milliseconds. The drug should not be given to patients with a creatinine clearance lower than 20 mL/min or a baseline QTc interval longer than 440 milliseconds.

INDICATIONS. Oral dofetilide is indicated for prevention of episodes of supraventricular tachyarrhythmias, particularly atrial flutter and fibrillation. The role of dofetilide in the treatment of ventricular arrhythmias is less clear; it has been shown to decrease the defibrillation threshold in patients with an ICD, as well as decrease the frequency of ICD therapies for ventricular arrhythmias.¹⁸

ADVERSE EFFECTS. The most significant adverse effect of dofetilide is QT interval prolongation–related torsades de pointes, which occurs in 2% to 4% of patients given the drug. Risk is highest in patients with a baseline prolonged QT interval, in those who are hypokalemic, in those taking some other agent that prolongs repolarization, and after conversion from atrial fibrillation to sinus rhythm. Because the risk for torsades de pointes is highest at the time of drug initiation, it should be used continuously and not as intermittent outpatient dosing. The drug is otherwise well tolerated, with few side effects. Its use in pregnancy has not been studied extensively, and it should probably be avoided in this setting if possible.

Class IV Agents

Calcium Channel Antagonists: Verapamil and Diltiazem

Verapamil, a synthetic papaverine derivative, is the prototype of a class of drugs that block the slow calcium channel and reduce $I_{Ca,L}$ in cardiac muscle (see Chapter 33). Diltiazem has electrophysiologic actions similar to those of verapamil. Nifedipine and other dihydropyridine agents exhibit minimal electrophysiologic effects at clinically used doses; these drugs are not discussed here.

Electrophysiologic Actions. By blocking $I_{Ca,L}$ in all cardiac fibers, verapamil reduces the plateau height of the action potential, slightly shortens muscle action potential, and slightly prolongs Purkinje fiber action potential (see Tables 35-1, 35-2, 35-3, and 35-5). It does not appreciably affect the action potential amplitude, V_{max} of phase 0, or resting membrane voltage in cells that have fast-response characteristics related to I_{Na} (e.g., atrial and ventricular muscle, the His-Purkinje system). Verapamil suppresses slow responses elicited by various experimental methods, as well as sustained triggered activity and early and late afterdepolarizations. Verapamil and diltiazem suppress electrical activity in the normal sinus and AV nodes. Verapamil depresses the slope of diastolic depolarization in sinus node cells, V_{max} of phase 0, and maximum diastolic potential and prolongs conduction time and refractory periods of the AV node. The AV node-blocking effects of verapamil and diltiazem are more apparent at faster rates of stimulation (use dependence) and in depolarized fibers (voltage dependence). Verapamil slows activation of the slow channel and delays its recovery from inactivation.

Verapamil does exert some local anesthetic activity because the *d*-isomer of the clinically used racemic mixture exerts slight blocking effects on I_{Na} . The *l*-isomer blocks the slow inward current carried by calcium, as well as other ions, traveling through the slow channel. Verapamil does not affect calcium-activated adenosine triphosphatase, nor does it block beta receptors, but it may block alpha receptors and potentiate vagal effects on the AV node. Verapamil may also cause other effects that indirectly alter cardiac electrophysiology, such as decreasing platelet adhesiveness or reducing the extent of myocardial ischemia.

In humans, verapamil prolongs conduction time through the AV node (the A-H interval) and lengthens AV nodal anterograde and

retrograde refractory periods without affecting the P wave or QRS duration or the H-V interval. The spontaneous sinus rate may decrease slightly, an effect only partially reversed by atropine. More commonly, the sinus rate does not change significantly because verapamil causes peripheral vasodilation, transient hypotension, and reflex sympathetic stimulation, which mitigates any direct slowing effect that verapamil exerts on the sinus node. If verapamil is given to a patient who is also receiving a beta blocker, the sinus node discharge rate may slow because reflex sympathetic stimulation is blocked. Verapamil does not exert a significant direct effect on atrial or ventricular refractoriness or on the anterograde or retrograde properties of accessory pathways. However, reflex sympathetic stimulation after intravenous verapamil administration may increase the ventricular response over the accessory pathway during atrial fibrillation in patients with Wolff-Parkinson-White syndrome, sometimes dangerously so.

Hemodynamic Effects. Because verapamil interferes with excitation-contraction coupling, it inhibits vascular smooth muscle contraction and causes marked vasodilation in coronary and other peripheral vascular beds. The reflex sympathetic effects of verapamil may reduce its marked negative inotropic action on isolated cardiac muscle, but the direct myocardial depressant effects of verapamil may predominate when the drug is given in high doses. In patients with well-preserved left ventricular function, combined therapy with propranolol and verapamil appears to be well tolerated, but beta blockade can accentuate the hemodynamic depressant effects produced by oral verapamil. Patients with reduced left ventricular function may not tolerate the combined blockade of beta receptors and calcium channels; thus, in these patients, verapamil and propranolol should be used in combination either cautiously or not at all. Verapamil reduces myocardial oxygen demand while decreasing coronary vascular resistance. Such changes may be indirectly antiarrhythmic.

Peak alterations in hemodynamic variables occur 3 to 5 minutes after completion of a verapamil injection, with the major effects dissipating within 10 minutes. Systemic resistance and mean arterial pressure decrease, as does left ventricular dP/dt_{max} , and left ventricular end-diastolic pressure increases. Heart rate, cardiac index, and mean pulmonary artery pressure do not change significantly in individuals with normal resting left ventricular systolic function. Thus the afterload reduction produced by verapamil significantly counterbalances its negative inotropic action, so the cardiac index may not be reduced. In addition, when verapamil slows the ventricular rate in a patient with tachycardia, hemodynamics may also improve. Nevertheless, caution should be exercised in giving verapamil to patients with severe myocardial depression or those receiving beta blockers or disopyramide because hemodynamic deterioration may progress in some patients.

Pharmacokinetics. After single oral doses of verapamil, measurable prolongation of AV nodal conduction time occurs in 30 minutes and lasts 4 to 6 hours (see Table 35-4). After intravenous administration, AV nodal conduction delay occurs within 1 to 2 minutes and A-H interval prolongation is still detectable after 6 hours. After oral administration, absorption is almost complete, but its overall bioavailability of 20% to 35% suggests substantial first-pass metabolism in the liver, particularly of the *I*-isomer. The drug's elimination half-life is 3 to 7 hours, with up to 70% of the drug being excreted by the kidneys. Norverapamil is a major metabolite that may contribute to the electrophysiologic actions of verapamil. Serum protein binding is approximately 90%. With diltiazem, the percentage of heart rate reduction in atrial fibrillation is related to its plasma concentration.

DOSAGE AND ADMINISTRATION. For acute termination of SVT or rapid achievement of ventricular rate control during atrial fibrillation, the most commonly used intravenous dose of verapamil is 10 mg infused over a 1- to 2-minute period while cardiac rhythm and blood pressure are monitored (see Table 35-4). A second injection of an equal dose may be given 30 minutes later. The initial effect achieved with the first bolus injection, such as slowing of the ventricular response during atrial fibrillation, can be maintained by continuous infusion of the drug at a rate of 0.005 mg/kg/min. The oral dose is 240 to 480 mg/day in divided doses. Diltiazem is given intravenously at a dose of 0.25 mg/kg as a bolus over a 2-minute period, with a second dose in 15 minutes if necessary; because it is generally better tolerated (less hypotension) with long-term administration, such as for control of the ventricular rate during atrial fibrillation, diltiazem is preferred over verapamil in this setting. Significant hypotension resulting from intravenous diltiazem can be countered by volume expansion or the judicious use of a pure

vasoconstrictor agent such as phenylephrine. Orally, doses must be adjusted to the patient's needs, with a 120- to 360-mg range. Various long-acting preparations (once daily) are available for verapamil and diltiazem.

INDICATIONS. After simple vagal maneuvers have been tried and adenosine has been given, intravenous verapamil or diltiazem is the next treatment of choice for termination of sustained AV node reentry or orthodromic AV reciprocating tachycardia associated with an accessory pathway (see Chapter 37). Verapamil is as effective as adenosine for termination of these arrhythmias. Assuming that the patient is stable, verapamil should definitely be tried before termination is attempted by digitalis administration, pacing, electrical direct-current cardioversion, or acute blood pressure elevation with vasopressors. Verapamil and diltiazem terminate 60% to 90% or more episodes of paroxysmal SVT within several minutes. Verapamil may also be of use in some fetal SVTs. Although intravenous verapamil has been given along with intravenous propranolol, this combination should be used only with great caution because of combined adverse hemodynamic effects.

Verapamil and diltiazem decrease the ventricular response over the AV node during atrial fibrillation or atrial flutter, possibly converting a small number of episodes to sinus rhythm, particularly if the atrial flutter or fibrillation is of recent onset. In addition, verapamil may prevent early recurrence of atrial fibrillation after electrical cardioversion. Atrial fibrillation may develop in some patients with atrial flutter after verapamil administration. As noted earlier, in patients with preexcited ventricular complexes during atrial fibrillation associated with Wolff-Parkinson-White syndrome, intravenous verapamil may accelerate the ventricular response; therefore the intravenous route is contraindicated in this situation. Verapamil can terminate some ATs. Even though verapamil can often terminate an idiopathic left septal VT, hemodynamic collapse can occur if intravenous verapamil is given to patients with the more common forms of VT because they generally occur in the setting of decreased left ventricular systolic function. A general rule for avoiding complications, however, is to not administer verapamil intravenously to any patient with wide-QRS tachycardia unless one is absolutely certain of the nature of the tachycardia and its probable response to verapamil.

Orally, verapamil or diltiazem can prevent the recurrence of AV node reentrant and orthodromic AV reciprocating tachycardias associated with an accessory pathway, as well as help maintain a decreased ventricular response during atrial flutter or atrial fibrillation in patients without an accessory pathway. Verapamil has not generally been effective in treating patients who have recurrent ventricular tachyarrhythmias, although it may suppress some forms of VT, such as left septal VT (noted earlier). It may also be useful in about two thirds of patients with idiopathic VT that has a left bundle branch block morphology (right ventricular outflow tract origin), patients with hypertrophic cardiomyopathy who have experienced cardiac arrest, patients with a short-coupled variant of polymorphic VT, and patients with ventricular arrhythmias related to coronary artery spasm. Calcium channel blockers have not been shown to reduce mortality or to prevent sudden cardiac death in patients after acute myocardial infarction, except for diltiazem in those with non-ST-segment elevation infarctions (see Chapter 53).

ADVERSE EFFECTS. Verapamil must be used cautiously in patients with significant hemodynamic impairment or in those receiving beta blockers, as noted earlier. Hypotension, bradycardia, AV block, and asystole are more likely to occur when the drug is given to patients who are already receiving beta-blocking agents. Hemodynamic collapse has been noted in infants, and verapamil should be used cautiously in children younger than 1 year. Verapamil should also be used with caution in patients with sinus node abnormalities because marked depression of sinus node function or asystole can result in some of these patients. Intravenous isoproterenol, calcium, glucagon, dopamine, or atropine, which may be only partially effective, or temporary pacing may be necessary to counteract some of the adverse effects of verapamil. Isoproterenol may be more effective for the treatment of bradyarrhythmias, and calcium may be used for the treatment of hemodynamic dysfunction secondary to verapamil. AV

node depression is common in overdoses. Contraindications to the use of verapamil and diltiazem include the presence of advanced heart failure, second- or third-degree AV block without a pacemaker in place, atrial fibrillation and anterograde conduction over an accessory pathway, significant sinus node dysfunction, most VTs, cardiogenic shock, and other hypotensive states. Although these drugs should probably not be used in patients with overt heart failure, if it is caused by one of the supraventricular tachyarrhythmias noted earlier, verapamil or diltiazem may restore sinus rhythm or significantly decrease the ventricular rate and thereby lead to hemodynamic improvement. Finally, verapamil can decrease the excretion of digoxin by approximately 30%. Hepatotoxicity may occur on occasion. Verapamil crosses the placental barrier; its use in pregnancy has been associated with impaired uterine contraction, fetal bradycardia, and possibly fetal digital defects. It should therefore be used only if no effective alternatives exist.

Other Antiarrhythmic Agents

Adenosine

Adenosine is an endogenous nucleoside present throughout the body and has been approved by the FDA to treat patients with SVTs.

Electrophysiologic Actions. Adenosine interacts with A₁ receptors present on the extracellular surface of cardiac cells and activates K⁺ channels ($I_{K,Ach}$, $I_{K,Ado}$) in a fashion similar to that produced by acetylcholine (see **Tables 35-1, 35-2, 35-3, and 35-5**). The increase in K⁺ conductance shortens the atrial APD, hyperpolarizes the membrane potential, and decreases atrial contractility. Similar changes occur in the sinus and AV nodes. In contrast to these direct effects mediated through the guanine nucleotide regulatory proteins G_i and G_o, adenosine antagonizes catecholamine-stimulated adenylate cyclase to decrease accumulation of cyclic adenosine monophosphate and to decrease $I_{Ca,L}$ and the pacemaker current I_f in sinus node cells along with a decrease in \dot{V}_{max} . Shifts in the pacemaker site within the sinus node and sinus exit block may occur. Adenosine slows the sinus rate in humans, followed within seconds by a reflex increase in the sinus rate. In the AV node, adenosine produces transient prolongation of the A-H interval, often with transient first-, second-, or third-degree AV node block lasting up to a few seconds. The delay in AV nodal conduction is rate dependent. His-Purkinje conduction is not generally affected directly. Adenosine does not affect conduction in normal accessory pathways. Conduction may be blocked in unusual accessory pathways that have long conduction times or decremental conduction properties. Patients with heart transplants exhibit a supersensitive response to adenosine. Adenosine may mediate the phenomenon of ischemic preconditioning.

Pharmacokinetics. Adenosine is removed from the extracellular space by washout, enzymatically by degradation to inosine, by phosphorylation to adenosine monophosphate, or by reuptake into cells through a nucleoside transport system (see **Table 35-4**). The vascular endothelium and erythrocytes contain these elimination systems, which result in very rapid clearance of adenosine from the circulation. Its elimination half-life is 1 to 6 seconds. Most of adenosine's effects are produced during its first passage through the circulation. Important drug interactions occur; methylxanthines are competitive antagonists, and therapeutic concentrations of theophylline totally block the exogenous effects of adenosine. Dipyridamole is a nucleoside transport blocker that blocks reuptake of adenosine, thus delaying its clearance from the circulation or interstitial space and potentiating its effect. Smaller adenosine doses should be used in patients receiving dipyridamole.

DOSAGE AND ADMINISTRATION. To terminate tachycardia, a bolus of adenosine is rapidly injected intravenously at doses of 6 to 12 mg, followed by a flush (see **Table 35-4**). Pediatric dosing should be 0.1 to 0.3 mg/kg. When it is injected into a central vein and in patients after heart transplantation or those receiving dipyridamole, the initial dose should be reduced to 3 mg. Transient sinus slowing or AV node block results but lasts less than 5 seconds. Doses higher than 18 mg are unlikely to revert a tachycardia and should not be used.

INDICATIONS. Adenosine has become the drug of first choice to terminate an SVT acutely, such as AV node or AV reentry (see **Chapter 37**), and is useful in pediatric patients. Adenosine can produce AV nodal block or terminate ATs and sinus node reentry. It results in only

transient AV block during atrial flutter or fibrillation and is thus useful only for diagnosis, not therapy. Adenosine terminates a group of VTs whose maintenance depends on adrenergic drive, which is most often located in the right ventricular outflow tract but can be found at other sites as well; idiopathic left septal VT rarely responds, however. Adenosine has less potential than verapamil for lowering blood pressure should tachycardia persist after injection.

Doses as low as 2.5 mg terminate some tachycardias; doses of 12 mg or less terminate 92% of SVTs, usually within 30 seconds. Successful termination rates with adenosine are comparable to those achieved with verapamil. Because of its effectiveness and extremely short duration of action, adenosine is preferable to verapamil in most cases, particularly in patients who have previously received intravenous beta adrenoceptor blockers, in those with poorly compensated heart failure or severe hypotension, and in neonates. Verapamil might be chosen first in patients receiving drugs such as theophylline (which is known to interfere with adenosine's actions or metabolism), in patients with active bronchoconstriction, and in those with inadequate venous access.

Adenosine may be useful to help differentiate among causes of wide-QRS tachycardias because it terminates many SVTs with aberrancy or reveals the underlying atrial mechanism and does not block conduction over an accessory pathway or terminate most VTs. However, in rare cases adenosine terminates some VTs, characteristically those of right ventricular outflow tract origin as noted earlier, and therefore tachycardia termination is not completely diagnostic of an SVT. This agent may predispose to the development of atrial fibrillation and might transiently increase the ventricular response in patients with atrial fibrillation conducting over an accessory pathway. Adenosine may also be useful in differentiating conduction over the AV node from that over an accessory pathway during ablative procedures designed to interrupt the accessory pathway. However, this distinction is not absolute because adenosine can block conduction in slowly conducting accessory pathways and does not always produce block in the AV node.

ADVERSE EFFECTS. Transient side effects occur in almost 40% of patients with SVT given adenosine and most commonly consist of flushing, dyspnea, and chest pressure. These symptoms are fleeting, lasting less than 1 minute, and are well tolerated. PVCs, transient sinus bradycardia, sinus arrest, and AV block are common when an SVT is terminated abruptly. Atrial fibrillation is occasionally observed (12% in one study) with adenosine administration, perhaps because of the drug's effect in shortening atrial refractoriness. Induction of atrial fibrillation can be problematic in patients with Wolff-Parkinson-White syndrome and rapid AV conduction over the accessory pathway.

Digoxin

Cardiac actions of digitalis glycosides have been recognized for centuries. Digoxin is used for control of supraventricular arrhythmias, mainly control of the ventricular rate during atrial fibrillation. Use of digoxin has decreased because of the availability of agents with greater potency and a wider therapeutic to toxic drug concentration range.

Electrophysiologic Actions. Digoxin acts mainly through the autonomic nervous system, in particular, by enhancing both central and peripheral vagal tone. These actions are confined largely to slowing of the sinus node discharge rate, shortening of atrial refractoriness, and prolongation of AV nodal refractoriness (see **Tables 35-1, 35-2, 35-3, and 35-5**). Electrophysiologic effects on the His-Purkinje system and ventricular muscle are minimal, except with toxic concentrations. In studies of denervated hearts, digoxin has relatively little effect on the AV node and causes a mild increase in atrial refractoriness.

The sinus rate and P wave duration are minimally changed in most patients taking digoxin. The sinus rate may decrease in patients with heart failure whose left ventricular performance is improved by the drug; individuals with significant underlying sinus node disease also have slower sinus rates or even sinus arrest. Similarly, the PR interval is generally unchanged, except in patients with underlying AV node disease. The QRS and QT intervals are unaffected. The characteristic ST and T wave abnormalities seen with use of digoxin do not represent toxicity.

Pharmacokinetics. Intravenously administered digoxin yields some electrophysiologic effect within minutes, with a peak effect occurring after 1.5 to 3 hours (see Table 35-4). After oral dosing, the peak effect occurs in 4 to 6 hours. The extent of digoxin absorption after oral administration varies according to the preparation; tablet forms are 60% to 75% absorbed, whereas encapsulated gel forms are almost completely absorbed. Ingestion of cholestyramine or an antacid preparation at the same time as digoxin ingestion decreases its absorption. The serum half-life of digoxin is 36 to 48 hours, and the drug is excreted unchanged by the kidneys.

DOSAGE AND ADMINISTRATION. In acute loading doses of 0.5 to 1.0 mg, digoxin may be given orally or intravenously (see Table 35-4). Chronic daily oral dosing should be adjusted on the basis of clinical indications and the extent of renal dysfunction. Most patients require 0.125 to 0.25 mg/day as a single dose. However, as little as 0.125 mg every other day is needed in some patients undergoing renal dialysis, whereas young patients may require as much as 0.5 mg/day. Serum digoxin levels may be used to monitor compliance with therapy, as well as to determine whether digitalis toxicity is the cause of new symptoms compatible with the diagnosis. However, routine monitoring of digoxin levels is not warranted in patients whose ventricular rate is controlled during atrial fibrillation and who have no symptoms of toxicity.

INDICATIONS. Digoxin can be used intravenously to slow the ventricular rate during atrial fibrillation and flutter; it was formerly used in an attempt to convert SVTs to sinus rhythm, but its onset of action is much slower and its success rate less than that of adenosine, verapamil, or beta blockers. Thus it is now rarely used in this fashion. Digoxin is more commonly used orally to control the ventricular rate in permanent ("chronic") atrial fibrillation. When a patient with atrial fibrillation is at rest and vagal tone predominates, the ventricular rate can be maintained at between 60 and 100 beats/min in 40% to 60% of cases. However, when the patient begins to exercise, the decrease in vagal tone and increase in adrenergic tone combine to diminish the beneficial effects of digoxin on AV nodal conduction. Patients may experience a marked increase in ventricular rate with even mild exertion. Digoxin is therefore rarely used as a single agent to control the ventricular rate in atrial fibrillation. The drug has little ability to prevent episodes of paroxysmal atrial fibrillation or to control the ventricular rate during episodes and may even provoke episodes in patients with so-called vagal atrial fibrillation. Finally, digoxin is no more effective than placebo in terminating episodes of acute- or recent-onset atrial fibrillation.

ADVERSE EFFECTS. One major reason that use of digoxin has decreased is its potential for serious adverse effects and the narrow window between therapeutic and toxic concentrations. Digitalis toxicity produces various symptoms and signs, including headache, nausea and vomiting, altered color perception, halo vision, and generalized malaise. Less common but more serious than these are digitalis-related arrhythmias, which include bradycardias related to a markedly enhanced vagal effect (e.g., sinus bradycardia or arrest, AV node block) and tachyarrhythmias that may be caused by delayed afterdepolarization-mediated triggered activity (e.g., atrial, junctional, and fascicular or ventricular tachycardia). Worsening renal function, advanced age, hypokalemia, chronic lung disease, hypothyroidism, and amyloidosis increase a patient's sensitivity to digitalis-related arrhythmias. The diagnosis can be confirmed by determination of the serum digoxin level. Therapy for most bradycardias consists of withdrawal of digoxin; atropine or temporary pacing may be needed in symptomatic patients. Phenytoin can be used for control of atrial tachyarrhythmias, whereas lidocaine has been successful in treating infranodal tachycardias. Life-threatening arrhythmias can be treated with digoxin-specific antibody fragments. Electrical direct-current cardioversion should be performed only when absolutely necessary in a digitalis-toxic patient because life-threatening VT or VF can result and be very difficult to control. Some data incriminate digoxin in increasing mortality in patients with atrial fibrillation.

Ranolazine

Ranolazine, approved by the FDA for the treatment of chronic angina, has significant electrophysiologic properties. It has been shown to

decrease the incidence of atrial fibrillation, SVT, and ventricular arrhythmias relative to controls in trials of the drug's antianginal effects.

Electrophysiologic Actions. Ranolazine blocks I_{Kr} , as well as the late Na current; at higher concentrations, the L-type Ca current is mildly affected (see Tables 35-1, 35-2, 35-3, 35-5). The drug prolongs atrial and ventricular refractoriness and induces postrepolarization refractoriness; the P wave, PR interval, and QRS are unaffected, but the QT interval is mildly prolonged. Unlike other I_{Kr} -blocking drugs, ranolazine does not induce early afterdepolarizations.¹⁹ Its effects are more pronounced on atrial than on ventricular myocardium, and the drug shows great promise for the treatment of atrial fibrillation.

Hemodynamic Effects. Ranolazine has no important hemodynamic effects; it does not appear to produce meaningful changes in contractility or vascular resistance.

Pharmacokinetics. Absorption of orally administered ranolazine is mediated in part by the P-glycoprotein system, modulators of which may increase or decrease exposure to the drug. About 75% of a dose is bioavailable, with peak levels being reached in 2 to 5 hours (see Table 35-4). Absorption is not affected by food. Its half-life is approximately 7 hours; hepatic metabolism to minimally or wholly inactive products occurs via the CYP3A and, to a lesser extent, the CYPD4 pathways. Approximately 75% of the drug is excreted in urine, the remainder in feces.

DOSAGE AND ADMINISTRATION. The typical oral dose is 500 mg twice daily, to a maximum of 1000 mg twice daily. The dose should be decreased in the setting of moderate liver disease. It should not be used in conjunction with strong inhibitors of CYP3A, which could increase the drug's serum concentration threefold.

ADVERSE EFFECTS. The most widely known potential adverse effect of the drug is QTc prolongation, which averages 6 to 15 milliseconds (sometimes more in patients with severe liver failure), because of inhibition of I_{Kr} . Despite this effect on the QT interval, torsades de pointes is very rare. This is probably due in part to only modest QT prolongation combined with the drug's inhibition of the late inward Na current, which mitigates the QT effect. As noted above, ranolazine does not cause early afterdepolarizations or increases in transmural dispersion of refractoriness, which are believed to be prerequisites for torsades. Ranolazine produces a mild elevation in measured serum creatinine (0.1 mg/dL) without changing the actual glomerular filtration rate. The drug is pregnancy category C; its concentration in breast milk is unknown.

Antiarrhythmic Effects of Nonantiarrhythmic Drugs

Several medications commonly used for other indications also have some degree of antiarrhythmic effect. In some cases, physicians can use these drugs for their standard indications and achieve additional, although often small, amounts of benefit in treating the patient's rhythm disturbance. Among these drugs are angiotensin-converting enzyme inhibitors and angiotensin receptor-blocking agents, aldosterone antagonists such as eplerenone, statins and omega-3 fatty acids (prevention of sudden death), and these same classes of drugs with the addition of nondihydropyridine calcium channel blockers and ranolazine (less atrial fibrillation and perhaps VF).²⁰ The mechanisms whereby these drugs exert their attenuating effect on arrhythmias is not clear in most cases, and they should not be relied on as the sole form of antiarrhythmic therapy. In patients who have arrhythmias, as well as another disorder that requires drug therapy (hypertension, heart failure), one of these medications may be preferable to agents that treat the primary disorder but do not possess antiarrhythmic effects.

ELECTROTHERAPY FOR CARDIAC ARRHYTHMIAS

Direct-Current Electrical Cardioversion

Cardioversion is a general term used to indicate the termination of an arrhythmia, usually a tachyarrhythmia, by various means, including electrical, pharmacologic, or manual/surgical. Electrical

cardioversion refers to the delivery of an electrical shock to the heart to terminate a tachycardia, flutter, or fibrillation and includes the technique of both synchronous cardioversion (see below) and defibrillation. It offers obvious advantages over drug therapy because under conditions optimal for close supervision and monitoring, a precisely regulated “dose” of electricity can restore sinus rhythm immediately and safely. The distinction between supraventricular and ventricular tachyarrhythmias, crucial to the proper medical management of arrhythmias, becomes less significant, and the time-consuming titration of drugs with potential side effects is obviated.

Mechanisms. Electrical cardioversion is most effective in terminating tachycardias related to reentry, such as atrial flutter and many cases of atrial fibrillation, AV node reentry, reciprocating tachycardias associated with Wolff-Parkinson-White syndrome, most forms of VT, ventricular flutter, and VF. The electrical shock, by depolarizing all excitable myocardium and possibly by prolonging refractoriness, interrupts reentrant circuits and establishes electrical homogeneity, which terminates reentry. The mechanism by which a shock successfully terminates VF has not been completely explained. If the precipitating factors are no longer present, interruption of the tachyarrhythmia for only the brief time produced by the shock may prevent its return for long periods, even though the anatomic and electrophysiologic substrates required for the tachycardia are still present.

Tachycardias thought to be caused by disorders of impulse formation (automaticity) include parasystole, some forms of AT, ectopic junctional tachycardia (with or without digitalis toxicity), accelerated idioventricular rhythm, and relatively uncommon forms of VT (see Chapters 33 and 37). An attempt to cardiovert these tachycardias electrically is not indicated in most cases because they typically recur within seconds after the shock; release of endogenous catecholamines consequent to the shock may further exacerbate the arrhythmia. It has not been established whether cardioversion can terminate tachycardias caused by enhanced automaticity or triggered activity.

Technique. Synchronous cardioversion refers to a specific technique of delivering an electrical shock, usually of lower energy and timed to the QRS complex (“R wave”), to avoid the vulnerable period of the T wave. Before elective synchronous cardioversion, careful physical examination, including palpation of limb pulses and inspection of the chest wall and airway, should be performed. A 12-lead ECG is obtained before and after cardioversion, as well as a rhythm strip during the electroshock. The patient, who should be informed completely about what to expect, is in a fasting state and metabolically balanced; that is, respiratory function and electrolyte values should be normal, with no evidence of drug toxicity. Withholding of digitalis for several days before elective cardioversion in patients without clinical evidence of digitalis toxicity is not necessary, although patients in whom digitalis toxicity is suspected should not be electrically cardioverted until this situation has been corrected. Administration of maintenance antiarrhythmic drugs 1 to 2 days before planned electrical cardioversion of patients with atrial fibrillation can revert some patients to sinus rhythm, help prevent recurrence of atrial fibrillation once sinus rhythm is restored, and assist in determining the patient’s tolerance of the drug for long-term use.²¹ There is also evidence that statin drugs,²² as well as angiotensin-converting enzyme inhibitors and receptor blockers, may help prevent recurrence of fibrillation, especially in patients with ventricular dysfunction.

Self-adhesive patches applied in the standard apicoanterior or anteroposterior paddle positions have transthoracic impedances similar to those of paddles and are useful in elective synchronous cardioversions or other situations in which time is available for their

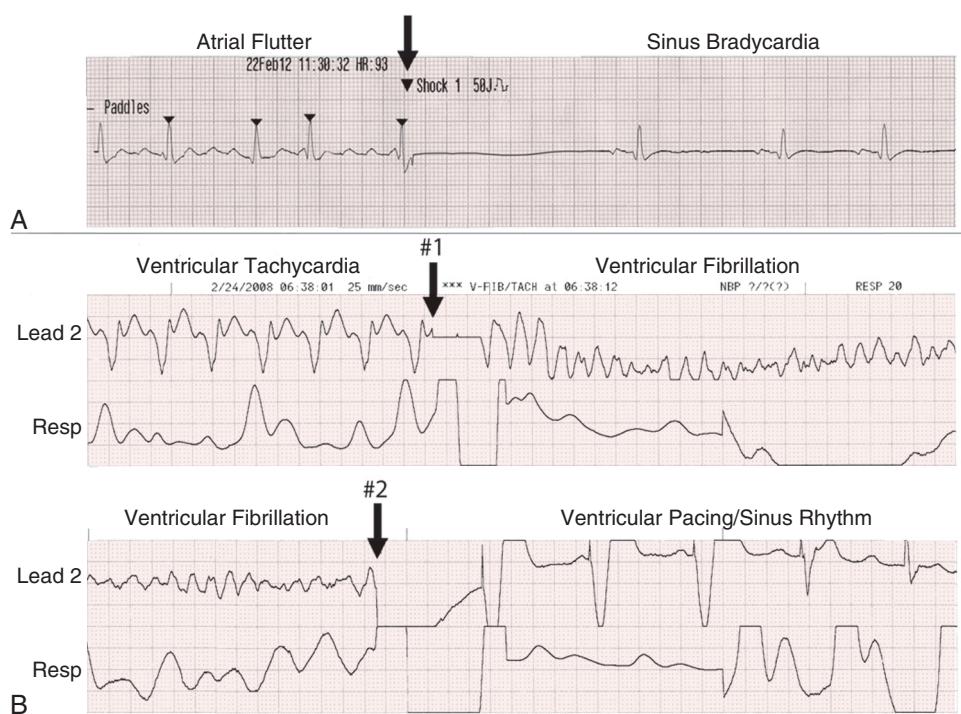


FIGURE 35-1 Cardioversions. In A, a synchronized shock (note the synchronization mark in the apex of the QRS complex [arrowhead]) during atrial flutter is followed by sinus bradycardia. In B, top panel, a shock (#1) is delivered during VT but asynchronously (on the T wave); this results in VF, which is then treated with a second, asynchronous shock (#2) that results in sinus rhythm with tracked ventricular pacing. Resp = respirations.

application. Patches 12 to 13 cm in diameter can be used to deliver maximum current to the heart, but the benefits of these patches versus patches 8 to 9 cm in diameter have not been clearly established. Larger patches may distribute the intracardiac current over a wider area and reduce shock-induced myocardial injury.

A synchronized shock (i.e., one delivered during the QRS complex; Fig. 35-1) is used for all cardioversions except for very rapid ventricular tachyarrhythmias, such as ventricular flutter or VF. For defibrillation of the latter, energies greater than those for synchronous cardioversion are required, and synchronization is not necessary because there is no vulnerable period of the T wave to avoid. Although generally minimal, shock-related myocardial damage increases directly with increases in applied energy, and thus the minimum effective shock should be used. Therefore, shocks are “titrated” when the clinical situation permits. Except for atrial fibrillation, shocks in the range of 25 to 50 J successfully terminate most SVTs and should be tried initially. If the shock is unsuccessful, a second shock of higher energy can be delivered. The starting level to terminate atrial fibrillation with older monophasic machines should be no less than 100 J, but with newer biphasic systems, a shock as low as 25 J may succeed.²³ Delivered energy can be increased in stepwise fashion; up to 360 J can be used safely. It is critical to remember to resynchronize the defibrillator to the QRS complex after an unsuccessful shock before delivery of another shock to avoid initiation of VF (machines typically revert to the asynchronous mode after each shock). Anteroposterior patches may have a higher efficacy rate by placing more of the atrial mass in the shock vector than is the case with apicoanterior patches. If a shock of 360 J fails to convert the rhythm, repeated shocks at the same energy may succeed by decreasing chest wall impedance; reversing patch polarity can occasionally help as well. Administration of ibutilide has been shown to facilitate electrical cardioversion of atrial fibrillation to sinus rhythm. Intracardiac or transesophageal defibrillation can be tried if all attempts at external cardioversion fail. For patients with stable VT, starting levels in the range of 25 to 50 J can be used. If there is some urgency to terminate the tachyarrhythmia, one can begin with higher energies. To terminate VF, 100 to 200 J (biphasic; 200 to 360 J with monophasic machines) is generally used, although much lower energies (<50 J) terminate VF when the shock is delivered soon after onset of the arrhythmia, for example, using adhesive patches in the electrophysiology laboratory.

During elective cardioversion, a short-acting barbiturate such as methohexitol, a sedative such as propofol, or an amnesic such as

diazepam or midazolam can be used. A physician skilled in airway management should be in attendance; an intravenous route should be established; and pulse oximetry, the ECG, and blood pressure should be monitored. All equipment necessary for emergency resuscitation should be immediately accessible. Before cardioversion, 100% oxygen may be administered for 5 to 15 minutes by nasal cannula or facemask and is continued throughout the procedure. Manual ventilation of the patient may be necessary to avoid hypoxia during periods of deepest sedation. Adequate sedation of the patient undergoing even urgent cardioversion is essential.

In up to 5% of patients with atrial fibrillation, sinus rhythm cannot be restored by external countershock despite all the preceding measures, including ibutilide pretreatment and biphasic shocks. It is important to distinguish between inability to attain sinus rhythm, indicating inadequate delivery of energy to the atria, and inability to maintain sinus rhythm after transient termination of fibrillation; the latter condition (early reinitiation of atrial fibrillation) does not respond to higher-energy shocks because fibrillation has already been terminated but quickly recurs. Pretreatment with an antiarrhythmic drug may help maintain sinus rhythm after subsequent shocks. Patients in whom atrial fibrillation simply cannot be terminated with an external shock tend to be very obese or have severe obstructive lung disease. In such cases, internal cardioversion can be performed with the use of specially configured catheters that have multiple large electrodes covering several centimeters of the distal portion of the catheter for distributing the shock energy. By standard percutaneous access, these catheters can be situated in the lateral part of the right atrium and coronary sinus to achieve a shock vector across most of the atrial mass. With such configurations, internal shocks of 2 to 15 J can terminate atrial fibrillation in more than 90% of patients whose arrhythmia is refractory to transthoracic shock. Esophageal cardioversion has also been reported. Rarely, simultaneous shocks from two defibrillators have been reported to terminate refractory VF.

Indications

As a rule, any nonsinus tachycardia that produces hypotension, congestive heart failure, mental status changes, or angina and does not respond promptly to medical management should be terminated electrically. Very rapid ventricular rates in patients with atrial fibrillation and Wolff-Parkinson-White syndrome are often best treated by electrical cardioversion. In almost all cases the patient's hemodynamic status improves after cardioversion. Rarely, a patient may experience hypotension, reduced cardiac output, or congestive heart failure after the shock. This problem may be related to complications of the cardioversion, such as embolic events, myocardial depression resulting from the anesthetic agent or the shock itself, hypoxia, lack of restoration of left atrial contraction despite return of electrical atrial systole, or postshock arrhythmias. Direct-current countershock of digitalis-induced tachyarrhythmias is contraindicated.

Favorable candidates for electrical cardioversion of atrial fibrillation include patients who (1) have symptomatic atrial fibrillation of less than 12 months' duration, (2) continue to have atrial fibrillation after the precipitating cause has been removed (e.g., after treatment of thyrotoxicosis), (3) have a rapid ventricular rate that is difficult to slow, or (4) have symptoms of decreased cardiac output (e.g., fatigue, lightheadedness, dyspnea) attributable to lack of atrial contraction's contribution to ventricular filling. In patients who have indications for chronic warfarin therapy to prevent stroke, the hope of avoiding anticoagulation by restoring sinus rhythm is not a reason to attempt cardioversion because these patients are still at increased risk for thromboembolic events. Several large trials have shown that maintenance of sinus rhythm confers no survival advantage over rate control and anticoagulation; thus, not all patients with newly discovered atrial fibrillation warrant an attempt at restoration of sinus rhythm. Treatment must be determined individually.

Unfavorable candidates include patients with (1) digitalis toxicity; (2) no symptoms and a well-controlled ventricular rate without therapy; (3) sinus node dysfunction and various unstable supraventricular tachyarrhythmias or bradyarrhythmias—often bradycardia-tachycardia syndrome—in whom atrial fibrillation finally develops and is maintained, which in essence represents a cure for sick sinus syndrome; (4) little or no symptomatic improvement with normal sinus rhythm who promptly revert to atrial fibrillation after

cardioversion despite drug therapy; (5) a large left atrium and long-standing atrial fibrillation; (6) episodes of atrial fibrillation that revert spontaneously to sinus rhythm; (7) no mechanical atrial systole after the return of electrical atrial systole; (8) atrial fibrillation and advanced heart block; (9) cardiac surgery planned in the near future; and (10) antiarrhythmic drug intolerance. Atrial fibrillation is more likely to recur after cardioversion in patients who have significant chronic obstructive lung disease, congestive heart failure, mitral valve disease (particularly mitral regurgitation), atrial fibrillation present longer than 1 year, and an enlarged left atrium (echocardiographic diameter larger than 4.5 cm).

In patients with atrial flutter, slowing the ventricular rate by administration of beta or calcium channel blockers or terminating the flutter with an antiarrhythmic agent may be difficult, and electrical cardioversion is often the initial treatment of choice. For patients with other types of SVT, electrical cardioversion may be used when (1) vagal maneuvers or simple medical management (e.g., intravenous adenosine and verapamil) has failed to terminate the tachycardia and (2) the clinical setting indicates that fairly prompt restoration of sinus rhythm is desirable because of hemodynamic decompensation or electrophysiologic consequences of the tachycardia. Similarly, in patients with VT, the hemodynamic and electrophysiologic consequences of the arrhythmias determine the need for and urgency of direct-current cardioversion. Electrical countershock is the initial treatment of choice for ventricular flutter or VF. Speed is essential (see Chapter 39).

If after the first shock, reversion of the arrhythmia to sinus rhythm does not occur, a higher energy level should be tried. When transient ventricular arrhythmias result after an unsuccessful shock, a bolus of lidocaine can be given before delivery of a shock at the next energy level. If sinus rhythm returns only transiently and is promptly supplanted by the tachycardia, a repeated shock can be tried, depending on the tachyarrhythmia being treated and its consequences. Administration of an antiarrhythmic agent intravenously may be useful before delivery of the next cardioversion shock (such as ibutilide for resistant atrial fibrillation). After cardioversion, the patient should be monitored, at least until full consciousness has been restored and preferably for an hour or more thereafter, depending on the duration of recovery from the particular form of sedation or anesthesia used. If ibutilide has been given, the ECG should be monitored for up to 8 hours because torsades de pointes can develop in the first few hours after administration.

Results

Electrical cardioversion restores sinus rhythm in up to 95% of patients, depending on the type of tachyarrhythmia. However, sinus rhythm remains after 12 months in less than a third to a half of patients with longstanding persistent atrial fibrillation. Thus, maintenance of sinus rhythm, once established, is the difficult problem, not immediate termination of the tachyarrhythmia. The likelihood of maintaining sinus rhythm depends on the particular arrhythmia, the presence of underlying heart disease, and the response to antiarrhythmic drug therapy. Atrial size often decreases after termination of atrial fibrillation and restoration of sinus rhythm, and functional capacity improves.

Complications

Arrhythmias induced by electrical cardioversion are generally caused by inadequate synchronization, with the shock occurring during the ST segment or T wave (see Fig. 35-1). On occasion, a properly synchronized shock can produce VF. Postshock arrhythmias are usually transient and do not require therapy. Asystole is rare and typically lasts no more than a few seconds before a sinus or junctional rhythm ensues; most defibrillators are also capable of transcutaneous pacing if needed. Embolic episodes are reported to occur in 1% to 3% of patients converted from atrial fibrillation to sinus rhythm. Prior therapeutic anticoagulation with warfarin (international normalized ratio [INR], 2.0 to 3.0) or newer agents such as dabigatran, rivaroxaban, or apixaban should be used consistently for at least 3 weeks by patients who have no contraindication to such therapy and

have had atrial fibrillation present for longer than 2 to 3 days or of indeterminate duration. It is important to note that 3 weeks of therapeutic anticoagulation is not the same as simply administering warfarin for 3 weeks because the warfarin dose may not achieve a therapeutic INR. The newer agents confer almost immediate anticoagulation (such that 3 weeks of treatment equals 3 weeks of anticoagulation). Anticoagulation for at least 4 weeks afterward is recommended because restoration of atrial mechanical function lags behind that of electrical systolic function, and thrombi can still form in largely akinetic atria, although they are electrocardiographically in sinus rhythm. Exclusion of left atrial thrombi by transesophageal echocardiography immediately before cardioversion may not always preclude embolism days or weeks after cardioversion of atrial fibrillation. Atrial thrombi can be present in patients with non-fibrillation-related atrial tachyarrhythmias, such as atrial flutter and AT in patients with congenital heart disease. The same precardioversion and postcardioversion anticoagulation recommendations apply to these patients, as well as to those with atrial fibrillation. Although direct-current shock has been demonstrated in animals to cause myocardial injury, studies in humans have indicated that elevations in myocardial enzymes after cardioversion are not common. ST-segment elevation, sometimes dramatic, can occur immediately after elective direct-current cardioversion and last for 1 to 2 minutes, although cardiac enzymes and myocardial scintigraphy may be unremarkable. ST elevation lasting longer than 2 minutes usually indicates myocardial injury unrelated to the shock. A decrease in serum K^+ and Mg^{2+} levels can occur after cardioversion of VT.

Cardioversion of VT can also be achieved by a chest thump. Its mechanism of termination is probably related to a mechanically induced PVC that interrupts a tachycardia circuit and may be related to commotio cordis (see Chapter 79). The thump cannot be timed very well and is probably effective only when delivered during a nonrefractory part of the cardiac cycle. The thump can alter a VT and possibly induce ventricular flutter or VF if it occurs during the vulnerable period of the T wave. Because there may be a slightly greater likelihood of converting a stable VT to VF than of terminating VT to sinus rhythm, chest thump cardioversion should not be attempted unless a defibrillator is simply unavailable.

Implantable Electrical Devices for Treatment of Cardiac Arrhythmias

Implantable devices that monitor the cardiac rhythm and can deliver competing pacing stimuli and low- and high-energy shocks have been used effectively in selected patients (see Chapter 36).

Ablation Therapy for Cardiac Arrhythmias

The purpose of catheter ablation is to destroy myocardial tissue by delivery of energy, generally electrical energy or cryoenergy, through electrodes on a catheter placed next to an area of the myocardium integrally related to onset or maintenance of the arrhythmia. For tachycardias with an apparent focal origin (e.g., automatic, triggered activity, microreentry), the focus itself (<5 mm in diameter) is targeted. In macroreentrant AT and VT, inexcitable scar tissue typically separates strands of surviving myocardium, and wave fronts propagate around these scars. The target for ablation is a narrow portion of myocardium between inexcitable areas (e.g., scar, valve annulus; Fig. 35-2). The first catheter ablation procedures were performed with direct-current shocks, but this energy source has been supplanted by radiofrequency (RF) energy, which is delivered from an external generator and destroys tissue by controlled heat production. Lasers and microwave energy sources have been used, but not commonly; cryothermal catheter ablation has been approved for use in

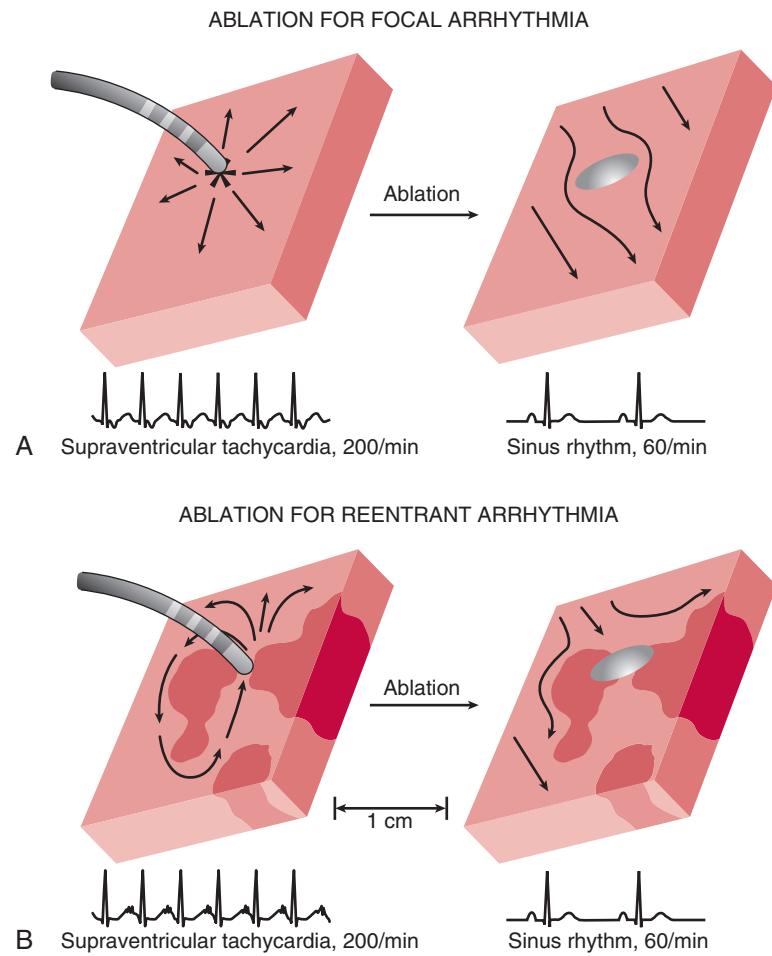


FIGURE 35-2 Strategies for catheter ablation. **A**, Focal tachycardia. At the left, SVT is caused by an atrial focus, with activation emanating in all directions. Ablation of the focus (right) eliminates the arrhythmia with minimal disruption of normal activation. **B**, Macroreentrant SVT in setting of previous atrial damage resulting in scar formation. During SVT (left), a wave front circulates around a scarred area and through a narrow isthmus between this and another area of scar. Ablation at this critical site (right) prevents further reentry.

humans. When a target tissue has been identified by EPS, the tip of the ablation catheter is maneuvered into apposition with this tissue. After stable catheter position and recordings have been ensured, RF energy is delivered between the catheter tip and an indifferent electrode, usually an electrocautery-type grounding pad on the skin of the patient's thigh. Because energies in the RF portion of the electromagnetic spectrum are poorly conducted by cardiac tissue, RF energy instead causes resistive heating in the cells close to the tip of the catheter (i.e., these cells transduce the electrical energy into thermal energy). When tissue temperature exceeds 50°C, irreversible cellular damage and tissue death occur. An expanding front of conducted heat emanates from the region of resistive heating while RF delivery continues over the next 30 seconds and results in the production of a homogeneous, roughly hemispheric lesion of coagulative necrosis 3 to 5 mm in diameter (Fig. 35-3). RF-induced heating of tissue that has inherent automaticity (e.g., His bundle, foci of automatic tachycardias) results in initial acceleration of a rhythm, whereas RF delivery during a reentrant arrhythmia typically causes slowing and termination of the arrhythmia. In most cases, RF delivery is painless, although ablation of atrial or right ventricular tissue can be uncomfortable for some patients.

Cooled-Tip Radiofrequency Ablation. In some situations the catheter can be delivered to the correct location, but conventional RF energy delivery cannot eliminate the tachycardia. In some of these cases the amount of damage—depth or breadth—caused by standard RF energy is inadequate. With the use of standard RF energy, power delivery is usually regulated to maintain a preset catheter tip

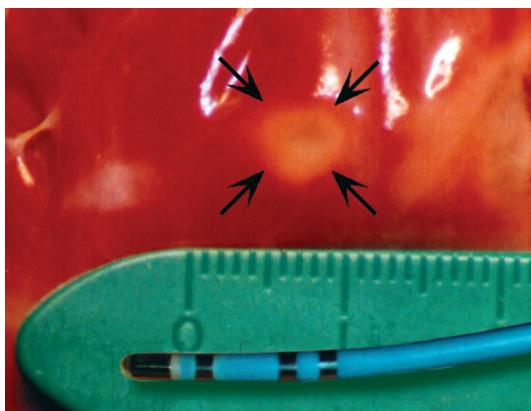


FIGURE 35-3 Radiofrequency lesion in human ventricular myocardium (explanted heart at the time of transplantation). A 30-second application of energy was made at the location denoted by arrows, with the tip of the catheter shown. The lesion is 5 mm in diameter and has a well-demarcated border. A central depression in the lesion results from partial desiccation of tissue.

temperature (typically, 55°C to 70°C). Tip temperatures higher than 90°C are associated with coagulation of blood elements on the electrode, which precludes further energy delivery and could also cause these elements to become detached and embolize. Cooling of the catheter tip by internal circulation of liquid or continuous fluid infusion through small holes in the tip electrode can prevent excessive heating of the tip and allow greater delivery of power, thus producing a larger lesion and potentially enhancing efficacy.²⁴ Cooled-tip ablation has been used to good advantage in cases in which standard (4-mm tip) catheter ablation has failed, as well as for primary therapy for atrial flutter and fibrillation and VT associated with structural heart disease, in which additional damage to already diseased areas is not harmful and may be required to achieve the desired result.

Catheter-delivered cryoablation causes tissue damage by freezing cellular structures. Nitrous oxide is delivered to the tip of the catheter, where it is allowed to boil and cool the tip electrode, after which the gas is circulated back to the delivery console. Catheter tip temperature can be regulated, with cooling to as low as -80°C. Cooling to 0°C causes reversible loss of function and can be used as a diagnostic test (i.e., termination of a tachycardia when the catheter is in contact with a group of cells critical to its perpetuation or determining its effect on normal conduction when close to the AV node). The catheter tip can then be cooled more deeply to produce permanent damage and thus cure of the arrhythmia. Cryoablation has been used for pulmonary vein isolation to treat paroxysmal atrial fibrillation by situating a collapsed balloon at the end of a catheter near a pulmonary vein ostium and inflating the balloon with nitrous oxide at -80°C. During cryoballoon occlusion of the vein for 3 to 4 minutes at a time, pulmonary vein isolation can usually be effected with one or two applications.²⁵ Real-time recordings can be done simultaneously to monitor conduction. Cryoablation appears to cause less endocardial damage than RF energy does and may thus engender less risk for thromboemboli after ablation, as well as less chance of esophageal injury with ablation of atrial fibrillation (although not eliminated); however, balloon cryotherapy to isolate right pulmonary veins for the treatment of atrial fibrillation has resulted in phrenic nerve injury, and care must be taken to establish the location of the phrenic nerve. Residual arrhythmias can result (Videos 35-1 and 35-2).



Radiofrequency Catheter Ablation of Accessory Pathways. **Location of Pathways.** The safety, efficacy, and cost-effectiveness of RF catheter ablation of an accessory AV pathway have made ablation the treatment of choice in most adult and many pediatric patients who have AV reentrant tachycardia (AVRT) or atrial flutter or fibrillation associated with a rapid ventricular response over the accessory pathway (see Chapter 37). When RF energy is delivered to an immature heart, the lesion size can increase as the heart grows; however, this has not been shown to cause problems later in life.

An EPS is performed initially to determine that the accessory pathway is part of the tachycardia circuit or capable of rapid AV conduction during atrial fibrillation and to localize the accessory pathway, the optimal site for ablation. Pathways can exist in the right or left free wall or the septum of the heart (Fig. 35-4). Septal accessory pathways are further classified as superoparaseptal, midseptal, and posteroseptal. Pathways classified as posteroseptal are posterior to

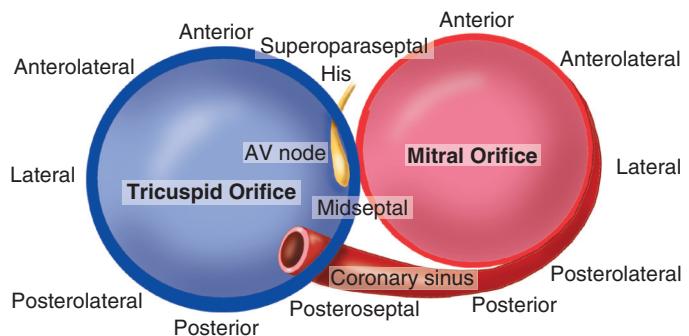


FIGURE 35-4 Locations of accessory pathways by anatomic region. The tricuspid and mitral valve annuli are depicted in a left anterior oblique view. Locations of the coronary sinus, AV node, and bundle of His are shown. Accessory pathways may connect the atrial to the ventricular myocardium in any of the regions shown.

the central fibrous body within the so-called pyramidal space, which is bounded by the posterior superior process of the left ventricle and the inferomedial aspects of both atria. Superoparaseptal pathways are found near the His bundle, and accessory pathway activation potential as well as His bundle potential can be recorded simultaneously from a catheter placed at the His bundle region. Midseptal pathways are close to the AV node and can usually be ablated from a right-sided approach; rarely, a left atrial approach is needed. Right posteroseptal pathways insert along the tricuspid ring in the vicinity of the coronary sinus ostium, whereas left posteroseptal pathways are further into the coronary sinus and may be located at a subepicardial site around the proximal coronary sinus, within a middle cardiac vein or coronary sinus diverticulum, or subendocardially along the ventricular aspect of the mitral annulus.

Pathways at all locations and in all age groups can be ablated successfully. Multiple pathways are present in about 5% of patients. Occasional pathways with epicardial locations may be more easily approached from within the coronary sinus. Rarely, pathways can connect an atrial appendage with adjacent ventricular epicardium, 2 cm or more from the AV groove.

Ablation Site. The optimal ablation site can be found by direct recordings of the accessory pathway (Fig. 35-5), although deflections that mimic accessory pathway potentials can be recorded at other sites. The ventricular insertion site can be determined by finding the site of the earliest onset of the ventricular electrogram in relation to the onset of the delta wave. Other helpful guidelines include unfiltered unipolar recordings that register a QS wave and an accessory pathway signal during preexcitation. A major ventricular potential synchronous with onset of the delta wave can be a target site in left-sided preexcitation, whereas earlier ventricular excitation in relation to the delta wave can be found for right-sided preexcitation. The atrial insertion site of manifest or concealed pathways (i.e., delta wave present or absent, respectively) can be found by locating the site showing the earliest atrial activation during retrograde conduction over the pathway. Reproducible mechanical inhibition of accessory pathway conduction during catheter manipulation and subthreshold stimulation has also been used to determine the optimal site. Accidental catheter trauma should be avoided, however, because it can hide the target for prolonged periods. Right free wall and superoparaseptal pathways are particularly susceptible to catheter trauma.

Left-sided accessory pathways typically cross the mitral annulus obliquely. Consequently, the earliest site of retrograde atrial activation and the earliest site of anterograde ventricular activation are not directly across the AV groove from each other (i.e., ventricular insertion closer to coronary sinus ostium). Identification of the earliest site of atrial activation is usually performed during orthodromic AVRT or relatively rapid ventricular pacing so that retrograde conduction using the AV node does not confuse assessment of the location of the earliest atrial activation.

Successful ablation sites should exhibit stable fluoroscopic and electrical characteristics. During sinus rhythm, local ventricular activation at the successful ablation site precedes onset of the delta wave on the ECG by 10 to 35 milliseconds; during orthodromic AVRT, the interval between onset of ventricular activation in any lead and local atrial activation is usually 70 to 90 milliseconds (see Fig. 35-5). When temperature-measuring ablation catheters are used, a stable rise in catheter tip temperature is a helpful indicator of catheter stability and adequate contact between the electrode and tissue. In such a case,

**VIDEO 35-1**

Macroseentrant left atrial tachycardia after pulmonary vein isolation (still image). The left atrium is viewed from the posterior perspective showing 4 pulmonary veins (PVs)—left (L), right (R), inferior (I), and superior (S). The color scheme indicates the sequence of activation (*red, orange, yellow, green, blue, and purple* before returning to red) during reentry around the right PV following isolation a few months earlier. *Gray regions* represent dense scarring.

VIDEO 35-2

Macroseentrant left atrial tachycardia after pulmonary vein isolation in the same patient as in Video 35-1. A moving *red band* indicates the advancing waveform of activation throughout one cycle of reentry. This can be seen traveling toward the bottom of the left atrium, then spreading to left and right, sweeping upward, and finally back to a relatively narrow region representing the diastolic corridor, before starting another cycle.

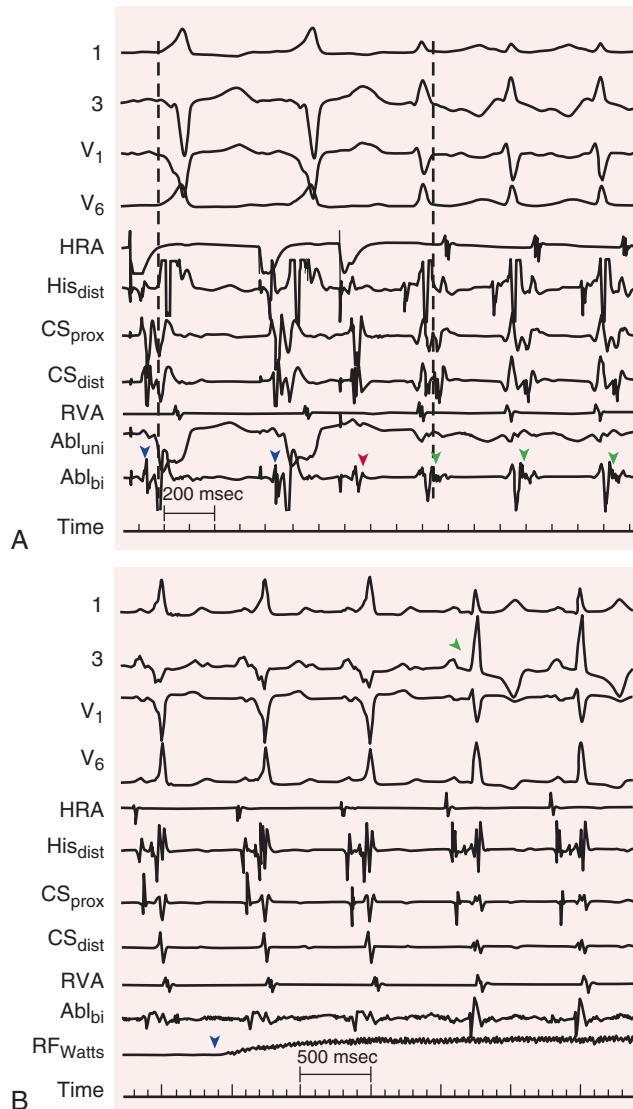


FIGURE 35-5 Wolff-Parkinson-White syndrome. Surface ECG leads 1, 3, V₁, and V₆ are shown, with intracardiac recordings from high right atrium (HRA), distal His (His_{dist}) bundle region, proximal (CS_{prox}) and distal (CS_{dist}) coronary sinus, right ventricular apex (RVA), and unipolar (Abl_{uni}) and bipolar (Abl_{bi}) tip electrodes of the ablation catheter. RF power in watts (RF_{Watts}) is also shown. **A**, Two beats of atrial pacing are conducted over the accessory pathway (blue arrowheads in the Abl_{bi} recording from the site of the accessory pathway) and resulted in a delta wave on the ECG; a premature atrial stimulus (center) encounters accessory pathway refractoriness (red arrowhead) and instead is conducted over the AV node and bundle of His and resulted in a narrow QRS complex and started an episode of AVRT. After each narrow QRS complex is an atrial deflection, the earliest portion of which is recorded at the ablation site (green arrowheads). **B**, Ablation of this pathway by delivery of RF energy from the ablation catheter tip. The blue arrowhead denotes the onset of delivery of RF energy; two QRS complexes later, the delta wave is abruptly lost (green arrowhead in lead 3) because of elimination of conduction over the accessory pathway.

tip temperature generally exceeds 50°C. The retrograde transseptal and transseptal approaches have been used with equal success to ablate accessory pathways located along the mitral annulus. Routine performance of an EPS weeks after the ablation procedure is not generally indicated but may be considered in patients who have a recurrent delta wave or symptoms of tachycardia. Catheter-delivered cryoablation can be useful in patients with septal accessory pathways (located near the AV node or His bundle). With use of this system, the catheter tip and adjacent tissue can be reversibly cooled to test a potential site. If accessory pathway conduction fails while normal AV conduction is preserved, deeper cooling can be performed at the site to complete the ablation. If, however, normal AV conduction is worsened, permanent damage is almost always averted by quickly allowing the catheter to rewarm.

Atriofascicular accessory pathways have connections consisting of a proximal, AV node-like portion, which is responsible for conduction

delay and decremental conduction properties, and a long distal segment located along the endocardial surface of the right ventricular free wall, which has electrophysiologic properties similar to those of the right bundle branch. The distal end of the right atriofascicular accessory pathway can insert into the apical region of the right ventricular free wall, close to the distal right bundle branch, or can actually fuse with the latter. Right atriofascicular accessory pathways might represent a duplication of the AV conduction system and can be localized for ablation by recording potentials from the rapidly conducting distal component, which crosses the tricuspid annulus (analogous to the His bundle) and extends to the apical region of the right ventricular free wall. Ablation at such a site on the annulus is usually successful; these pathways are very sensitive to catheter trauma, and the operator must use great care to avoid such trauma.

Indications

Ablation of accessory pathways is indicated in patients who have symptomatic AVRT that is drug resistant or who are drug intolerant or do not desire long-term drug therapy. It is also indicated in patients who have atrial fibrillation or other atrial tachyarrhythmias and a rapid ventricular response by means of an accessory pathway when the tachycardia is drug resistant or in those who are drug intolerant or do not desire long-term drug therapy. Other potential candidates with an accessory pathway include the following: (1) patients with AVRT or atrial fibrillation with rapid ventricular rates identified during an EPS for another arrhythmia; (2) asymptomatic patients with ventricular preexcitation whose livelihood, profession, important activities, insurability, or mental well-being and the public's safety would be affected by spontaneous tachyarrhythmias or by the presence of the electrocardiographic abnormality; (3) patients with atrial fibrillation and a controlled ventricular response by means of the accessory pathway; and (4) patients with a family history of sudden cardiac death. Controversy remains whether all patients with accessory pathways need treatment; however, ablation has such a high success rate and low complication rate that in most centers, patients who need any form of therapy are referred for catheter ablation.

Results

Currently, in the hands of an experienced operator, the success rate for accessory pathway ablation is greater than 95% (slightly less for right free wall pathways, in which stable catheter-tissue contact is more problematic), with a 2% recurrence rate after an apparently successful procedure. There is a 1% to 2% complication rate, including bleeding, vascular damage, myocardial perforation with cardiac tamponade, valve damage, stroke, and myocardial infarction. Heart block occurs in less than 3% of septal pathways. Procedure-related death is very rare.

Radiofrequency Catheter Modification of the Atrioventricular Node for Atrioventricular Nodal Reentrant Tachycardias

AV node reentry is a common cause of SVT episodes (see Chapters 33 and 37). Although controversy still exists about the exact nature of the tachycardia circuit, abundant evidence has indicated that two pathways in the region of the AV node participate, one with relatively fast conduction but long refractoriness and the other with shorter refractoriness but slower conduction. Premature atrial contractions can encounter refractoriness in the fast pathway, conduct down the slow pathway, and reenter the fast pathway retrogradely, thereby initiating AV nodal reentrant SVT (Fig. 35-6). Although this is the most common manifestation of AV node reentry, some patients have what appears to be propagation in the opposite direction in this circuit (anterograde fast, retrograde slow), as well as a “slow-slow” variant. Other, far less common types have been described. Two or more of these variants can exist in the same patient (Fig. 35-7).

Fast Pathway Ablation. Ablation can be performed to eliminate conduction in the fast pathway or the slow pathway. Currently, fast pathway ablation is rarely performed because it is associated with a prolonged PR interval, a higher recurrence rate (10% to 15%), and a slightly higher risk for complete AV block (2% to 5%) than with slow pathway ablation. One uncommon situation in which fast pathway

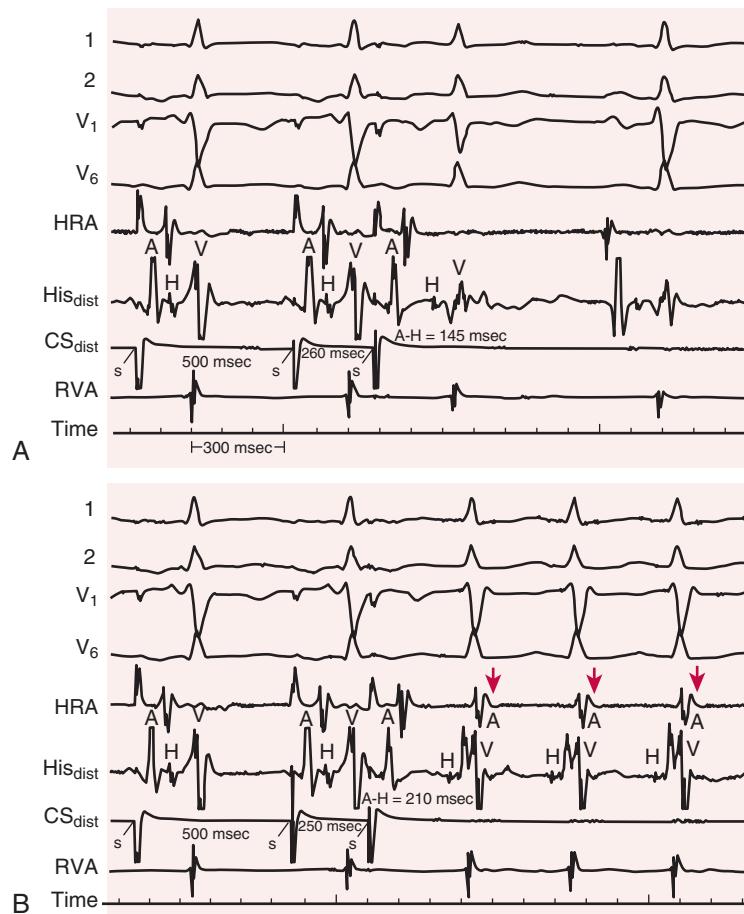


FIGURE 35-6 AV node reentry. **A**, Two atrial paced complexes from the coronary sinus (CS) are followed by an atrial premature stimulus at a coupling interval of 260 milliseconds and resulted in an A-H interval of 145 milliseconds. **B**, The same atrial drive train is followed by an atrial extrastimulus 10 milliseconds earlier than before (250 milliseconds). This resulted in a marked increase in the A-H interval to 210 milliseconds, after which AVNRT ensues because the extrastimulus encounters block in a “fast” AV node pathway, conducts down a “slow” pathway, and then conducts back up the fast pathway in a repeating fashion. Red arrowheads denote atrial electrograms coincident with QRS complexes, characteristic of the most common type of AV node reentry. Recording was done as in previous figures.

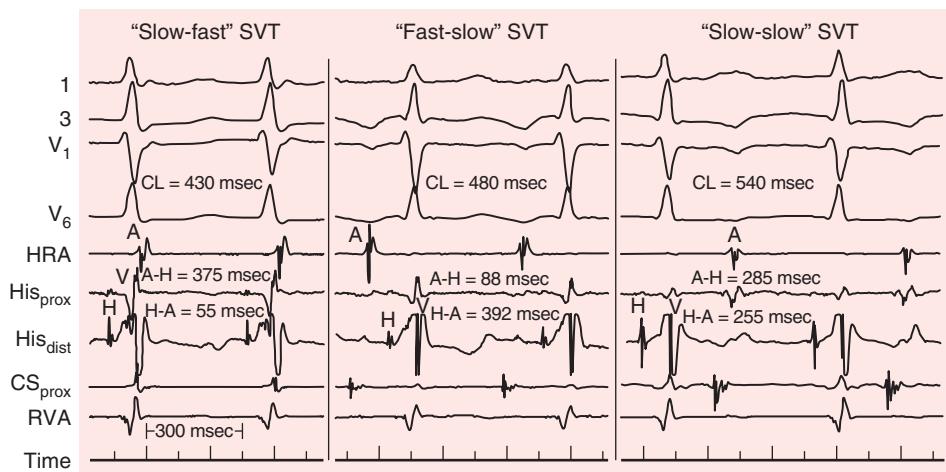


FIGURE 35-7 Three variants of AV node reentrant SVT in the same patient. **Left**, Most common type of AV node SVT (anterograde slow pathway, retrograde fast). Atrial activation is coincident with ventricular activation. **Center**, “Atypical” AV node reentry with anterograde fast pathway conduction and retrograde conduction over a slow pathway. **Right**, A rare variety is shown that consists of anterograde conduction over a slow pathway and retrograde conduction over a second slow pathway. Note the similar atrial activation sequences in the last two (coronary sinus before the right atrium), as distinct from that of slow-fast AV node reentry (coronary sinus and right atrial activation almost simultaneous). Note also the different P-QRS relationships, from simultaneous activation (left, short RP interval) to P in front of the QRS (middle, long RP interval) and P midway in the cardiac cycle (right). Recording was done as in previous figures. CL = cycle length.

ablation may be preferred is for patients who have a markedly prolonged PR interval at rest and no evidence of anterograde fast pathway conduction. In such cases, ablation of the anterograde slow pathway may produce complete AV block, whereas retrograde fast pathway ablation can eliminate SVT without altering AV conduction.

Slow Pathway Ablation. The slow pathway can be located by mapping along the posteromedial tricuspid annulus close to the coronary sinus os. Electrographic recordings are obtained with an atrial-to-ventricular electrogram ratio of less than 0.5 and either a multicomponent atrial electrogram or a recording of possible slow pathway potential. In the anatomic approach, target sites are selected fluoroscopically. A single RF application eliminates slow pathway conduction in many cases, but in others, serial RF lesions may be needed, starting at the most posterior site (near the coronary sinus os) and progressing to the more anterior locus (closer to the His bundle recording site). An accelerated junctional rhythm (**Fig. 35-8**) usually occurs when RF energy is applied at a site that will result in successful elimination of SVT. The success rate is equivalent with the anatomic and electrographic mapping approaches, and most often, combinations of both are used and yield success rates approaching 100%, with less than a 1% chance of complete heart block. Catheter-delivered cryoablation has been used for the treatment of AVNRT with excellent results and is considered by some to be safer than RF (less chance of permanent AV block) but in most series has a higher rate of SVT recurrence after apparent successful ablation.

Slow pathway ablation results in an increase in the anterograde AV block cycle length and AV node ERP without a change in the A-H interval or retrograde conduction properties of the AV node. Patients in whom slow pathway conduction is completely eliminated almost never have recurrent SVT episodes; approximately 40% of patients can have evidence of residual slow pathway function after successful elimination of sustained AVNRT, usually manifested as persistent dual-AV node physiology and single-AV node echoes during atrial extrastimulation. The surest endpoint for slow pathway ablation is elimination of sustained AVNRT, with and without an infusion of isoproterenol.

AVNRT recurs in approximately 5% of patients after slow pathway ablation; repeated ablation is almost always successful. In some patients, the ERP of the fast pathway decreases after slow pathway ablation, possibly because of electrotonic interaction between the two pathways. Atypical forms of reentry can result after ablation, as

can apparent parasympathetic denervation, and result in inappropriate sinus tachycardia.

At present, the slow pathway approach is the preferred method for ablation of typical AVNRT. Ablation of the slow pathway is also a safe and effective means for the treatment of atypical forms of AVNRT. In patients with AVNRT undergoing slow pathway ablation, junctional ectopy during application of the RF energy is a sensitive but nonspecific marker of successful ablation; it occurs in longer bursts at effective target sites than at ineffective sites. Ventriculoatrial conduction should be expected during the junctional ectopy, and poor ventriculoatrial conduction or actual block may herald subsequent anterograde AV block. Junctional ectopic rhythm is caused by heating of the AV node and does not occur with cryoablation.

Indications

RF catheter ablation for AVNRT can be considered in patients with recurrent, symptomatic, sustained AVNRT that is drug resistant or who are drug intolerant or do not desire long-term drug treatment. The procedure can also be considered for patients with sustained AVNRT identified during EPS or catheter ablation of another arrhythmia or when there is a finding of dual-AV node pathway physiology and atrial echoes but without AVNRT during EPS in patients suspected of having AVNRT clinically.

Results

Most centers currently use slow pathway ablation, which results in a procedural success rate of 98%, a recurrence rate of less than 2%, and an incidence of heart block requiring permanent pacing of 1% or less.

Ectopic Junctional Tachycardia

Ectopic junctional tachycardia is a rare form of SVT in which the ECG resembles that in AVNRT but is distinct in that (1) the mechanism is automatic, not reentrant and (2) the atrium is clearly not involved in the tachycardia. This disorder is most commonly observed in young healthy individuals, in women more often than in men, and is usually catecholamine dependent. Ablation must be carried out close to the His bundle, and the risk for heart block requiring pacemaker insertion exceeds 5%.

Radiofrequency Catheter Ablation of Arrhythmias Related to the Sinus Node

Reentry in or around the sinus node is an extremely uncommon arrhythmia characterized by episodes of tachycardia with a P wave identical to the sinus P wave, usually with a PR interval longer than in sinus; in physiologic sinus tachycardia, the PR interval remains normal or shortens because of similar catecholamine effects on the sinus and AV nodes. RF energy is applied around the region of the sinus node at sites of early activation, before onset of the P wave, until the tachycardia terminates.

Inappropriate sinus tachycardia is a syndrome characterized by high sinus rates with exercise and at rest. Patients complain of palpitations at all times of day that correlate with inappropriately high sinus rates. They may not respond well to beta blocker therapy because of lack of desired effect or occurrence of side effects. When the sinus node area is to be ablated, it can be identified anatomically and electrophysiologically, and ablative lesions are usually placed between the superior vena cava and crista terminalis at sites of early atrial activation. Intracardiac echocardiography can help in

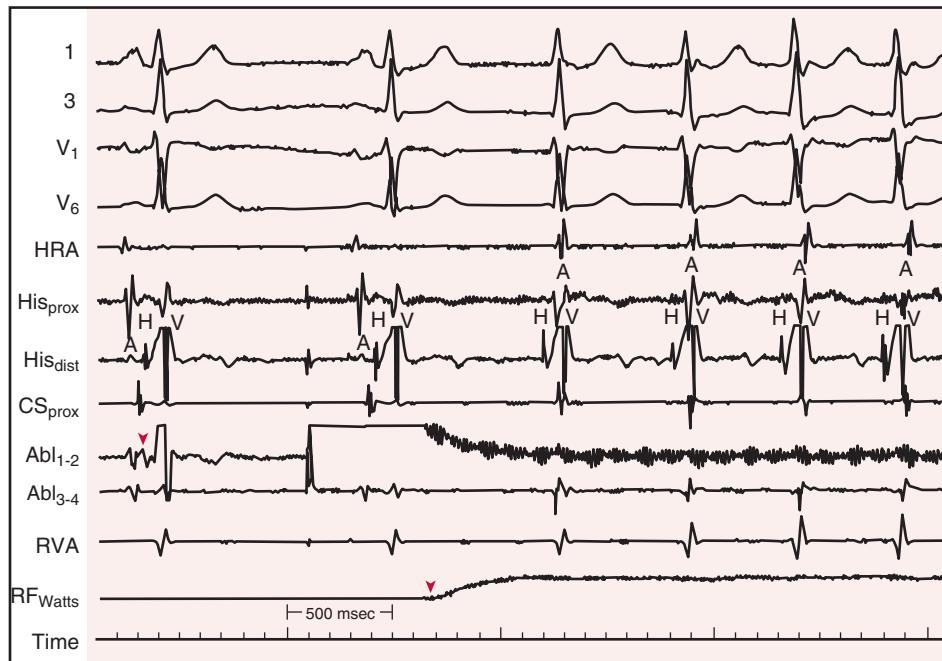


FIGURE 35-8 AV node slow pathway modification for cure of AV node reentrant SVT. The ablation recording (arrowhead in Abl₁₋₂) shows a slurred deflection between the atrial and ventricular electrogram components; this may represent the AV node slow pathway deflection (but it is not the bundle of His deflection, which is instead recorded from a separate catheter 15 mm away). Shortly after the onset of RF delivery (arrowhead in RF_{Watts}), an accelerated junctional rhythm begins and gradually speeds up further. Retrograde conduction is present during the junctional rhythm. Abl₃₋₄ = proximal electrode recording from ablation catheter. Recording was done as in previous figures.

defining the anatomy and in positioning the ablation catheter. Isoproterenol may be helpful in “forcing” the site of impulse formation to cells with the most rapid discharge rate. Care must be taken to apply RF energy at the most cephalad sites first; initial ablation performed farther down the crista terminalis does not alter the atrial rate at the time but can damage any subsidiary pacemaker regions that may be needed after the sinus node has eventually been ablated.

Indications

Catheter ablation for *paroxysmal* sinus node reentrant tachycardia can be performed in patients who have recurrent symptomatic episodes of sustained SVT that is drug resistant or who are drug intolerant or do not desire long-term drug treatment. Patients with *persistent* inappropriate sinus tachycardia should be considered for ablation only after clear failure of medical therapy because the results of ablation are often less than completely satisfactory. Whenever ablation is performed in the region of the sinus node, the patient should be apprised of the chance of needing a pacemaker after the procedure. Phrenic nerve damage and superior vena caval stenosis are also possibilities.

Results

Sinus node reentrant tachycardia can be ablated successfully in more than 90% of patients. The results are not as good for inappropriate sinus tachycardia; although a good technical result may be obtained at the time of the procedure, symptoms often persist because of recurrence of rapid sinus rates (at or near preablation rates) or for nonarrhythmic reasons. In some, after the atrial rate decreases, an inappropriately rapid junctional rhythm (80 to 90/min) is present; this may point to an overall increased sensitivity of cells with pacemaker capacity to catecholamines in these patients. Multiple ablation sessions are needed in some patients, and approximately 20% eventually undergo pacemaker implantation; however, not all these patients have relief of palpitations despite a normal heart rate.

Radiofrequency Catheter Ablation of Atrial Tachycardia

ATs are a heterogeneous group of disorders; causative factors include rapid discharge of a focus (focal tachycardia) and reentry. The former can occur in anyone, irrespective of the presence of structural abnormalities of the atria, whereas reentrant ATs almost always occur in the setting of structurally damaged atria. Symptoms vary from none, with relatively infrequent or slow ATs in patients without heart disease, to syncope (rapid AT with compromised cardiac function) or heart failure (incessant AT during a period of weeks or months). All forms of AT are amenable to catheter ablation (see Chapter 37).

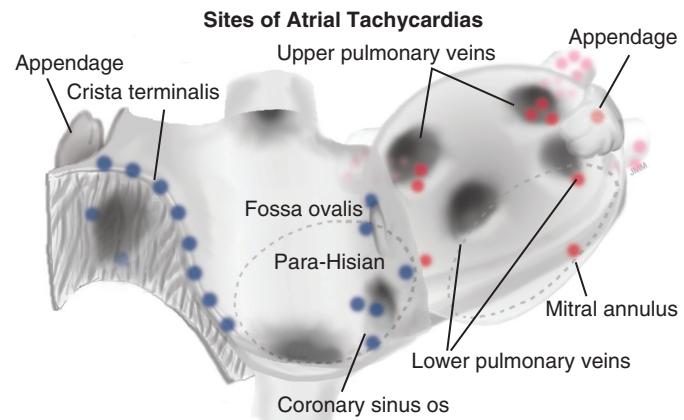


FIGURE 35-10 Locations of origins of focal ATs. The atria are viewed from the front with the right atrial free wall retracted to show the interior. Structures are labeled as shown; right atrial foci appear in shades of blue, left atrial foci in shades of red.

Focal Atrial Tachycardia. In focal ATs (automatic or triggered foci or microreentry), activation mapping is used to determine the site of the AT by recording the earliest onset of local activation. These tachycardias can behave capriciously and be practically noninducible during EPS despite the patient complaining of multiple daily episodes before the EPS. Approximately 10% of patients can have multiple atrial foci. Sites tend to cluster near the pulmonary veins in the left atrium and the mouths of the atrial appendages and along the crista terminalis on the right (Figs. 35-9A and 35-10; also see Fig. 34-14). Activation times at these sites typically occur only 15 to 40 milliseconds before onset of the P wave on the ECG. Care must be taken to avoid inadvertent damage to the phrenic nerve; its location can be determined by pacing at high current at a candidate site of ablation while observing for diaphragmatic contraction. Ablation should not be performed at a site at which this is seen, if at all possible.

Reentrant Atrial Tachycardia. As noted, these ATs occur more commonly in the setting of structural heart disease, especially after previous surgery involving an atrial incision (repair of congenital heart disease such as an atrial septal defect, Mustard or Senning repair of transposed great vessels, or one of a variety of Fontan repairs for tricuspid atresia and other disorders) or previous atrial ablation (e.g., for atrial fibrillation). The region of slow conduction is typically related to an end of an atriotomy or previous ablation scar, the location of which varies from patient to patient. Therefore, preprocedural review of operative and ablation procedure reports and careful electrophysiologic mapping are essential. Because reentry within a complete circuit is occurring, activation can be recorded throughout the entire cardiac cycle. The ablation strategy is to identify regions with mid-diastolic atrial activation during tachycardia (Fig. 35-11; also see Fig. 35-9B) that can be proved by pacing techniques to be integral to the tachycardia. Such sites are attractive ablation targets because they are composed of relatively few cells—hence, electrical silence on the surface ECG in diastole—and are thus more easily eliminated by the small amount of damage effected by a typical application of RF energy than other areas might be. Focal ablation of these sites can then be performed, but often tachycardia can still be initiated (usually at a slower rate) or recurs after the procedure. Because these sites are typically located at a relatively narrow zone between the ends of previous scars, surgical incisions, or ablation lines and another

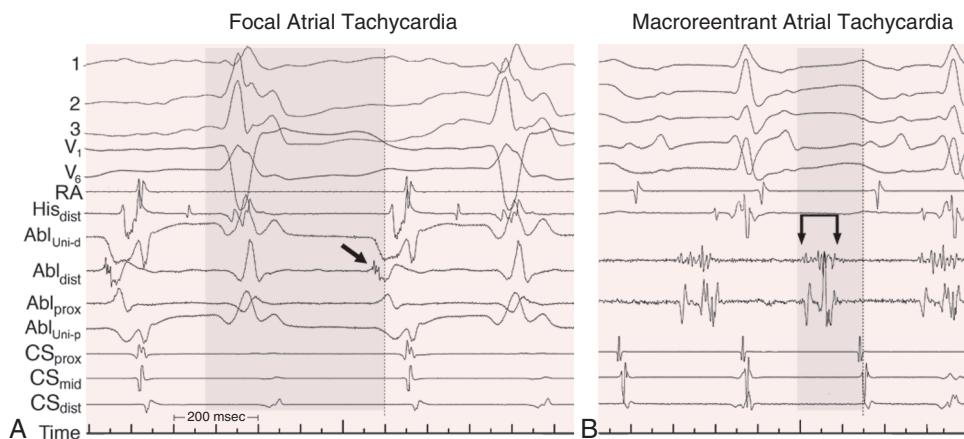


FIGURE 35-9 ATs. In both panels the interval from the end of one P wave to the beginning of the next (atrial diastole) is in gray. A dashed line denotes onset of the P wave during tachycardia. **A**, Focal AT arising in the right atrium. Two tachycardia complexes are shown; the earliest site found (Abl_{dist} , at which ablation eliminated the tachycardia) is shown as a multicomponent recording that starts only approximately 40 milliseconds before onset of the P wave. The unipolar recording ($\text{Abl}_{\text{Uni-d}}$) has a deep negative deflection (indicating propagation away from the electrode). The activation sequence of recordings is very different from that during sinus rhythm, in which the right atrial (RA) recording is at the onset of the P wave. **B**, Macroreentrant AT in a patient who had undergone repair of an atrial septal defect years earlier. The ablation catheter is in the posterior right atrium, where a fragmented signal (between arrows) is recorded that almost fills atrial diastole. Ablation at this site terminated the tachycardia. Recording was done as in previous figures.

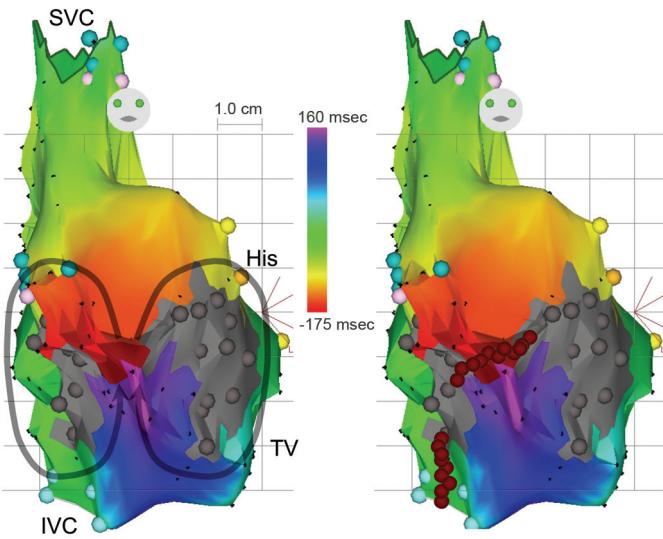


FIGURE 35-11 Reentrant AT. **Left**, An electroanatomic activation map of the right atrium is shown in a patient with a previous right atrial incision for closure of an atrial septal defect. Scar is shown as gray areas; arrows depict a double loop of reentry around scars with a common diastolic pathway between scars. The color bar at center shows progression of activation times during AT (from red through green, blue, and purple). The tachycardia cycle length (350 milliseconds) is almost entirely represented in the range of colors. **Right**, Red dots are ablation sites connecting scars (transecting diastolic pathway) and connecting one scar to the inferior vena cava (IVC) to preclude reentry around all barriers. His = His bundle; SVC = superior vena cava; TV = tricuspid valve.

nonconducting barrier (e.g., another scar, caval orifice, valve annulus), another technique is to make a line of ablative lesions from the end of the scar to the nearest electrical barrier. Reentry can thereby be prevented. This technique is analogous to that used in curing atrial flutter (see later). Because these patients frequently have extensive atrial disease with islands of scar that could serve as barriers for additional ATs, specialized mapping techniques may be needed to locate these regions and preemptively connect them with ablative lesions to prevent future AT episodes.

Indications

Catheter ablation for ATs should be considered in patients who have recurrent episodes of symptomatic sustained ATs that are drug resistant or who are drug intolerant or do not desire long-term drug treatment.

Results

Success rates for ablation of focal AT range from 80% to 95%, largely depending on the ability to induce episodes at EPS; when episodes can be initiated with pacing, isoproterenol, or other means, the AT can usually be ablated. Reentrant ATs, although more readily induced by an EPS, are often more difficult to eliminate completely; initial success rates are high (90%), but recurrences are seen in up to 20% of patients and necessitate drug therapy or another ablation procedure. Complications, which occur in 1% to 2% of patients, include phrenic nerve damage, cardiac tamponade, and heart block (with rare perinodal ATs).

Radiofrequency Catheter Ablation of Atrial Flutter. Atrial flutter may be defined electrocardiographically (most typically, negative sawtooth waves in leads II, III, and aVF at a rate of approximately 300 beats/min) or electrophysiologically (a rapid, organized macro-reentrant AT, the circuit for which is anatomically determined). Understanding of the reentrant pathway in all forms of atrial flutter is essential for development of an ablation strategy (see Chapter 37). Reentry in the right atrium, with the left atrium passively activated, constitutes the mechanism of the typical electrocardiographic variety of atrial flutter, with caudocranial activation along the right atrial septum and craniocaudal activation of the right atrial free wall

(**Fig. 35-12A**). Ablating tissue in a line between any two anatomic barriers that transects a portion of the circuit necessary for perpetuation of reentry can be curative. Typically, this is across the isthmus of atrial tissue between the inferior vena caval orifice and the tricuspid annulus (the cavotricuspid isthmus), a relatively narrow point in the circuit. Successful ablation can be accomplished at the point where the advancing flutter wave front enters this zone in the low inferolateral right atrium, near the exit of this zone at the inferomedial right atrium, or in between these sites. Locations for RF delivery can be guided anatomically or electrophysiologically. Less commonly, the direction of wave front propagation in this large right atrial circuit is reversed (“clockwise” flutter proceeding cephalad up the right atrial free wall and caudad down the septum with upright flutter waves in the inferior leads; **Fig. 35-12A**, right panel). This arrhythmia, which has been called atypical atrial flutter, can also be ablated by the same techniques as used for more typical atrial flutter. These two arrhythmias constitute cavotricuspid isthmus-dependent flutter and are distinct from other rapid atrial arrhythmias that may have a similar appearance on the ECG but use different (and often multiple) circuits in other parts of the right or left atrium. Ablation can be more difficult in these cases, which often occur in the setting of advanced lung disease or previous cardiac surgery or ablation. A common theme in these complex reentrant arrhythmias is the presence of an anatomically determined zone of inexcitability around which an electrical wave front can circulate. Specialized mapping tools and skills are necessary to achieve successful ablation in these cases.

In patients with atrial fibrillation, an antiarrhythmic drug can slow intra-atrial conduction to such an extent that atrial flutter results and fibrillation is no longer observed. In some of these patients, ablation of atrial flutter and having them continue to take the antiarrhythmic drug can prevent recurrences of these atrial arrhythmias.

The endpoint of atrial flutter ablation procedures was initially termination of atrial flutter, with RF application accompanied by noninducibility of the arrhythmia. However, with use of these criteria, up to 30% of patients had recurrent flutter because of lack of complete and permanent conduction block in the cavotricuspid isthmus. In the last several years the endpoint of ablation has changed to ensuring a line of bidirectional block in this region by pacing from opposite sides of the isthmus (**Fig. 35-12B**) or the use of other techniques. With use of these criteria, recurrence rates have fallen to less than 5%.

Indications

Candidates for RF catheter ablation include patients with recurrent episodes of atrial flutter that are drug resistant, those who are drug intolerant, and those who do not desire long-term drug therapy. Many patients who undergo atrial fibrillation ablation (see Chapter 38) also have episodes of flutter during the procedure that can be treated by ablation of the cavotricuspid isthmus at the same setting.

Results

Regardless of circuit location, atrial flutter can be ablated successfully in more than 90% of cases, although patients with complex right or left atrial flutter require more extensive and complex procedures. Recurrence rates are lower than 5% except in patients with extensive atrial disease, in whom new circuits can develop over time as new areas of conduction delay and block form. Complications are rare and include inadvertent heart block and phrenic nerve paralysis.

Ablation and Modification of Atrioventricular Conduction for Atrial Tachyarrhythmias

In some patients who have rapid ventricular rates despite optimal drug therapy during complex atrial tachyarrhythmias that are less amenable to ablation, RF ablation can be used to eliminate or to modify AV conduction and control the ventricular rates. To achieve this, a catheter is placed across the tricuspid valve and positioned to record a small His bundle electrogram associated with a large atrial electrogram. RF energy is applied until complete AV block has been achieved and is continued for an additional 30 to 60 seconds (**Fig. 35-13**). If no change in AV conduction is observed after 15 seconds of RF ablation despite good contact, the catheter is repositioned and the attempt repeated. In occasional patients, attempts at RF ablation via this right-sided heart approach fail to achieve heart block. These

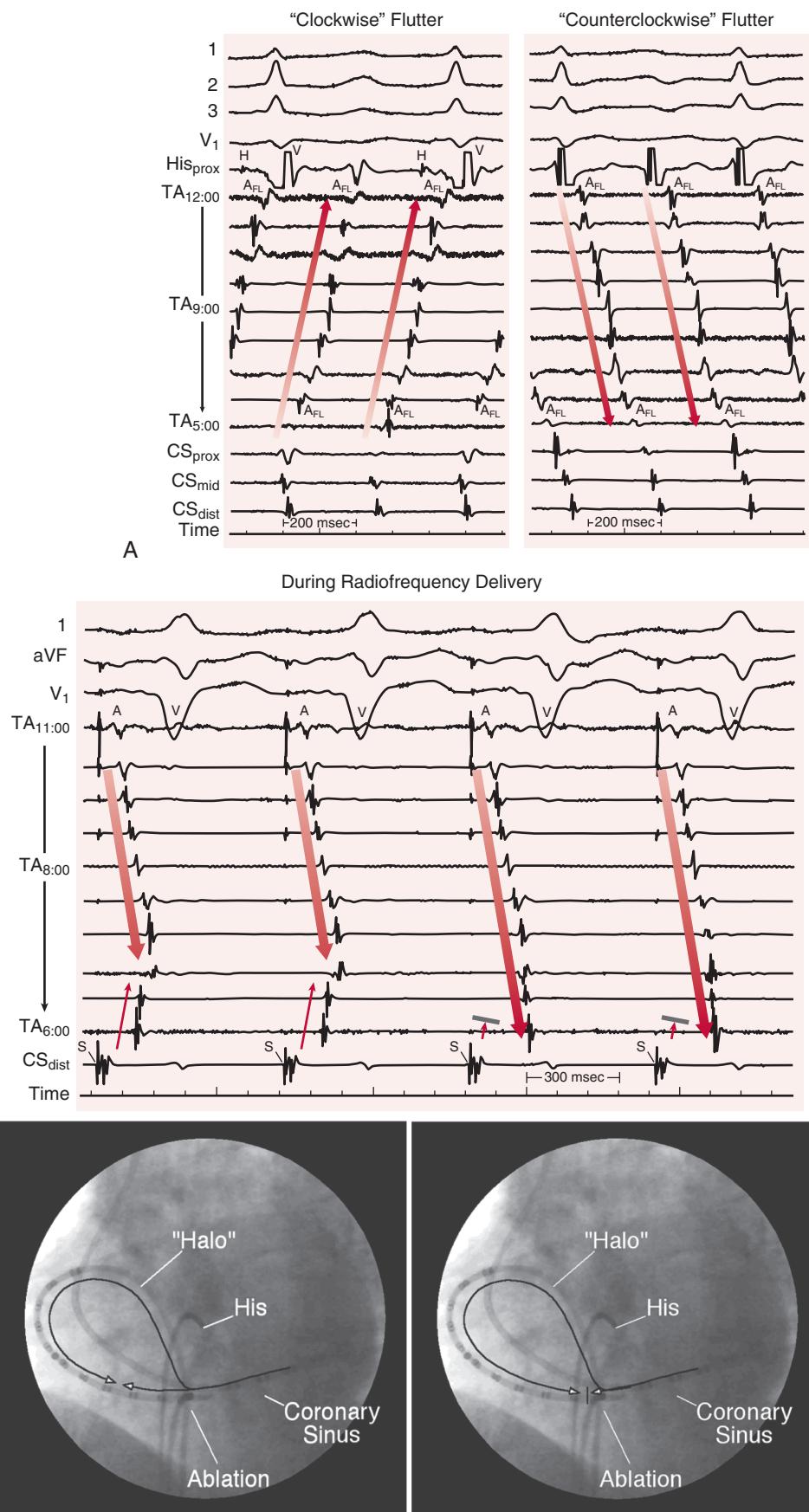


FIGURE 35-12 **A**, Two forms of atrial flutter in the same patient are shown. A halo catheter with 10 electrode pairs is situated on the atrial side of the tricuspid annulus (TA), with recording sites displayed from the top of the annulus (12:00) to the inferomedial aspect (5:00), as shown in the fluoroscopic views in **B**. On the left, the wave front of atrial activation proceeds in a clockwise fashion (arrows) along the annulus, whereas on the right, the direction of propagation is the reverse. **B**, Ablation of the isthmus of atrial tissue between the tricuspid annulus and the inferior vena caval orifice for cure of atrial flutter. Recordings are displayed from the multipolar catheter around much of the circumference of the tricuspid annulus (see the left anterior oblique fluoroscopic images). Ablation of this isthmus is performed during coronary sinus pacing. In the two beats on the left, atrial conduction proceeds in two directions around the tricuspid annulus, as indicated by arrows and recorded along the halo catheter. In the two beats on the right, ablation has interrupted conduction in the floor of the right atrium, thereby eliminating one path for transmission along the tricuspid annulus. The halo catheter now records conduction, proceeding all the way around the annulus. This finding demonstrates a unidirectional block in the isthmus; block in the other direction may be demonstrated by pacing from one of the halo electrodes and observing a similar lack of isthmus conduction. (The bundle of His recording in the right panel is lost because of catheter movement.)

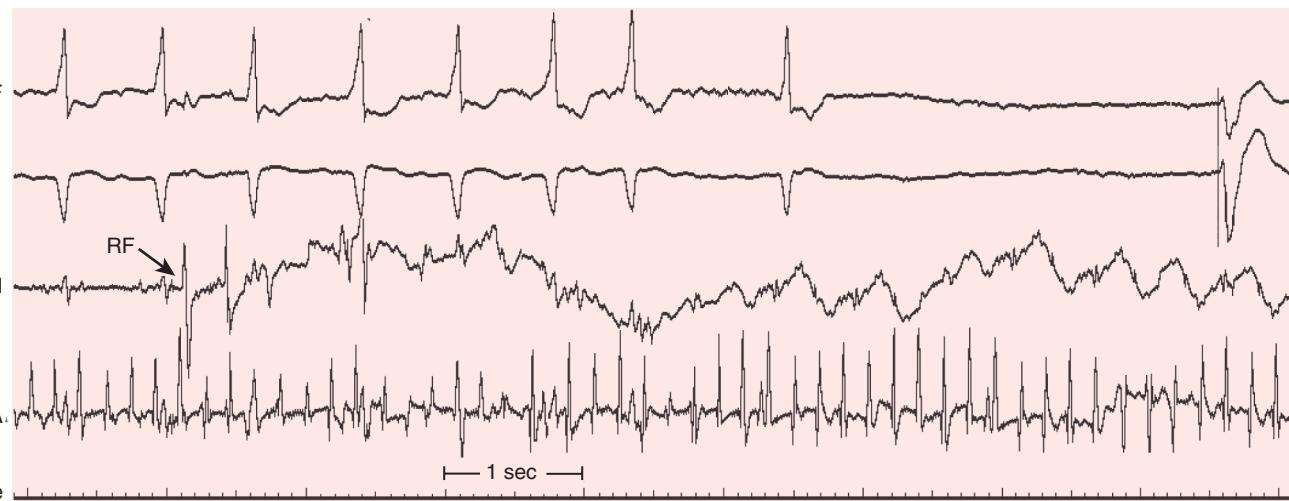


FIGURE 35-13 AV nodal ablation for rate control of atrial fibrillation (AF). The ECG shows rapidly conducted AF; application of RF energy (arrow) results in complete AV block within seconds, followed by a ventricular paced complex.

patients can undergo an attempt from the left ventricle with a catheter positioned along the posterior interventricular septum, just beneath the aortic valve, to record a large His bundle electrogram. Energy is applied between the catheter electrode and skin patch or between catheters in the left and right ventricles. Success rates currently approach 100%, with AV conduction recurring in less than 5% of cases. Improved left ventricular function can result from control of the ventricular rate during atrial fibrillation and withdrawal of rate-controlling medications with negative inotropic action. Permanent ventricular or AV pacing is required after ablation. With continuing advances in direct ablation of complex atrial arrhythmias, AV nodal ablation is less commonly used currently.

In some cases the AV junction can be modified to slow the ventricular rate without producing a complete AV block by ablation in the region of the slow pathway, as described in connection with AV node modification for AV node reentry. Initial success rates for slowing of the ventricular response are good; however, long-term results are less consistent. Some patients have a gradual increase in the ventricular rate to almost preablation levels, whereas late complete heart block may occur in others. Nonetheless, this procedure can be tried before producing a complete AV block.

Indications

Ablation and modification of AV conduction can be considered in the following cases: (1) patients with symptomatic atrial tachyarrhythmias who have inadequately controlled ventricular rates unless primary ablation of the atrial tachyarrhythmia is possible (especially when a permanent pacemaker is already present for treatment of bradycardia-tachycardia syndrome); (2) similar patients when drugs are not tolerated or patients do not wish to take them, even though the ventricular rate can be controlled; (3) patients with symptomatic, nonparoxysmal junctional tachycardia that is drug resistant or in whom drugs are not tolerated or are not desired; (4) patients resuscitated from sudden cardiac death related to atrial flutter or atrial fibrillation with a rapid ventricular response in the absence of an accessory pathway; and (5) patients with a dual-chamber pacemaker and a pacemaker-mediated tachycardia that cannot be treated effectively by drugs or by reprogramming of the pacemaker. The last three situations are rarely encountered.

Results

As noted before, successful interruption of AV conduction can be achieved in almost all cases; recurrent conduction is observed in less than 5%. Significant complications occur in 1% to 2%. In early studies, up to 4% of patients had an episode of sudden death after AV junction ablation despite adequate pacemaker function, presumably because

of relative bradycardia after long periods of rapid ventricular rates serving as the setting for repolarization-related ventricular arrhythmias. Since then, backup pacing rates are set to 80 to 90/min for the first 1 to 3 months after ablation in most cases, which has almost entirely eliminated this problem. Improvements in quality-of-life indices, as well as in cost-effectiveness, have been demonstrated for this procedure.

Radiofrequency Catheter Ablation of Atrial Fibrillation. See Chapters 37 and 38.

Radiofrequency Catheter Ablation of Ventricular Tachycardia

In general, the success rate for ablation of VTs is slightly lower than that for AV node reentry or AV reentry. This lower success rate may be related to the fact that this procedure is often a last resort in patients with drug-resistant VT and extensive structural heart disease, but it is also related to more difficult mapping in the ventricles. Furthermore, in the ideal case, induction of the VT must be reproducible, with uniform QRS morphology from beat to beat, and VT must be sustained and hemodynamically stable so that the patient can tolerate the VT long enough during the procedure to undergo the extensive mapping necessary to localize optimal ablation target sites. Patients with several electrocardiographically distinct, uniform morphologies of VT can still be candidates for ablation because in many cases a common reentrant pathway is shared by two or more VT morphologies. Also, the target for ablation must be fairly circumscribed and preferably endocardially situated, although cases of successful ablation only from the epicardial aspect have become more common. Very rapid VT, polymorphic VT, and infrequent, nonsustained episodes are less well suited to this form of therapy at this time (see later).

Location and Ablation. RF catheter ablation of VT can be divided into idiopathic VT, which occurs in patients with essentially structurally normal hearts; VT that occurs in various disease settings but without coronary artery disease; and VT in patients with coronary artery disease and usually previous myocardial infarction. In the first group, VTs can arise in either ventricle. Right ventricular tachycardias most commonly originate in the outflow tract and have a characteristic left bundle branch block-like, inferior axis morphology (see Chapter 37); less often, VTs arise in the inflow tract or free wall. Initiation of tachycardia can often be facilitated by catecholamines. Most left VTs are septal in origin and have a characteristic QRS configuration (i.e., right bundle branch block, superior axis); other VTs occur less commonly and arise from different areas of the left ventricle, including the left ventricular outflow tract and the aortic sinuses of Valsalva, and are similar in electrocardiographic appearance and clinical behavior to

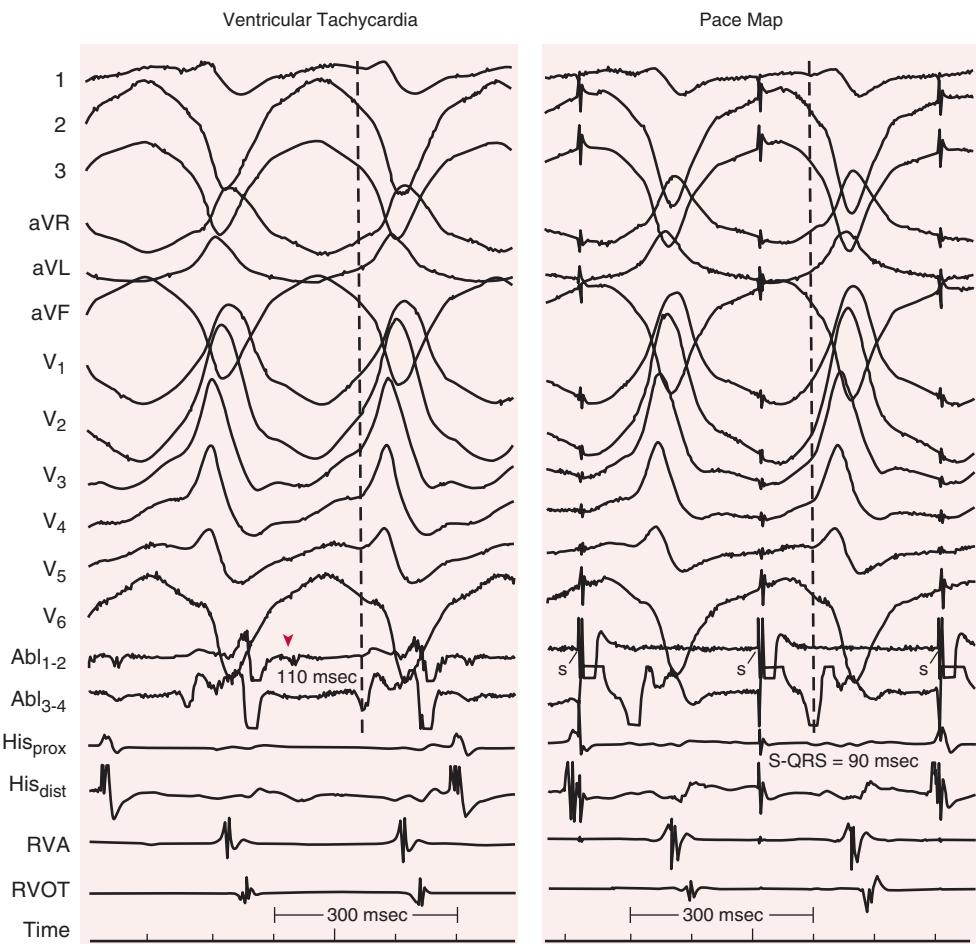


FIGURE 35-14 VT and pace mapping. All 12 surface ECG leads are shown, along with intracardiac recordings during VT. The Abl_{1,2} recording shows a small deflection occurring early in electrical diastole (arrowhead) 110 milliseconds before onset of the QRS (dashed line). In the right panel, pacing is performed from this site. This produces an identical QRS complex in each lead, with a stimulus-QRS onset interval similar to the electrogram-QRS onset interval during VT. Ablation at this site eliminated VT in 2 seconds. RVOT = right ventricular outflow tract.

those arising in the right ventricular outflow tract. Abnormal patterns of sympathetic innervation can be present in some. VTs in abnormal hearts without coronary artery disease can be the result of either intramyocardial or bundle branch reentry (see Chapter 37), most typically observed in patients with dilated cardiomyopathy or as a focal process. Epicardial foci and circuits are more common in this than in other groups. In patients with bundle branch reentry, ablation of the right bundle branch eliminates the tachycardia. VT can occur in patients with right ventricular dysplasia (see Chapter 32), sarcoidosis, Chagas disease, hypertrophic cardiomyopathy (see Chapter 66), and a host of other noncoronary disease states.

Activation mapping and pace mapping are effective in patients with idiopathic VTs to locate the site of origin of the VT. In activation mapping, the timing of endocardial electrograms sampled by the mapping catheter is compared with the onset of the surface QRS complex. Sites that are activated 20 to 40 milliseconds before onset of the surface QRS are near the origin of the VT (Fig. 35-14; also see Fig. 34-12). In idiopathic VT, ablation at a site at which the unipolar electrogram shows a QS complex may yield greater success than if an rS potential is observed (Fig. 35-15). Pace mapping involves stimulation of various ventricular sites to produce a QRS contour that duplicates the QRS contour of the spontaneous VT, thus establishing the apparent site of origin of the arrhythmia (see Fig. 35-14). This technique is limited by several methodologic problems but may be useful when the tachycardia cannot be initiated and when a 12-lead ECG has been obtained during the spontaneous VT. Presystolic Purkinje potentials, as well as very low-amplitude mid-diastolic signals, can be recorded during VT from sites at which ablation cures VT in most patients with left ventricular VTs that have a right bundle branch block superior axis. Localization of optimal ablation sites for VT in patients with coronary artery disease and previous infarction can be more challenging than in

patients with structurally normal hearts because of the altered anatomy and electrophysiology. Pace mapping has even lower sensitivity and specificity than for idiopathic VT. Furthermore, reentry circuits can sometimes be large and resistant to the relatively small lesions produced by RF catheter ablation in scarred endocardium.

In scar-based VT (e.g., after infarction, cardiomyopathies), finding of a protected region of diastolic activation used as a critical part of the reentrant circuit is desirable because ablation at this site has a good chance of eliminating the tachycardia (Fig. 35-16). As a result of the extensive derangement in electrophysiology caused by the previous damage (e.g., infarct, myopathy), many areas of the ventricle may have diastolic activation but may not be relevant to perpetuation of the VT. These “bystander sites” make activation mapping more difficult. Pacing techniques such as entrainment can be used to test whether a site is actually part of a circuit or is a bystander. Entrainment involves pacing for several seconds during a tachycardia at a rate slightly faster than the VT rate; after pacing is stopped and the same tachycardia resumes, the timing of the first complex relative to the last paced beat is an indicator of how close the pacing site is to a part of the VT circuit. During entrainment, part of the ventricle is activated by the paced wave front and part by the VT wave front being forced to exit earlier than it ordinarily would, thereby resulting in a fusion complex on the ECG. Pacing from within a critical portion of the circuit itself produces an exact QRS match with the VT; fusion

occurs only within the circuit and is “concealed” from being discerned on the surface ECG. Sites with a low-amplitude, isolated, mid-diastolic potential that cannot be dissociated from the tachycardia by pacing perturbations, at which entrainment with concealed fusion can be demonstrated, are highly likely to be successful ablation sites.

In a significant proportion of patients with VT and structural heart disease, activation mapping and entrainment cannot be performed because of poor hemodynamic tolerance of the arrhythmia or inability to initiate sustained tachycardia during an EPS. In these situations, additional methods can be used that are categorized as substrate mapping, in which areas of low electrical voltage or from which very delayed potentials are recorded during sinus rhythm or at which pacing closely replicates a known VT 12-lead ECG morphology (pace mapping) are targeted for ablation without needing any mapping during VT (Fig. 35-17). These methods have yielded very good results in many cases. In other cases, hemodynamic support in the form of catecholamine infusion, intra-aortic balloon counterpulsation, or a percutaneous temporary ventricular assist device or extracorporeal membrane oxygenation has been used to facilitate mapping during VT.²⁶

In patients without structural heart disease, only a single VT is usually present, and catheter ablation of that VT is most often curative. In patients with extensive structural heart disease, especially those with previous myocardial infarction, multiple VTs are usually present. Catheter ablation of a single VT in such patients may be only palliative and not eliminate the need for further antiarrhythmic therapy. The genesis of multiple tachycardia morphologies is not clear, although in some cases they are merely different manifestations of one circuit (e.g., different directions of wave front propagation or exit to the ventricle as a whole), and ablation of one may prevent recurrence of others. The presence of multiple VT morphologies contributes

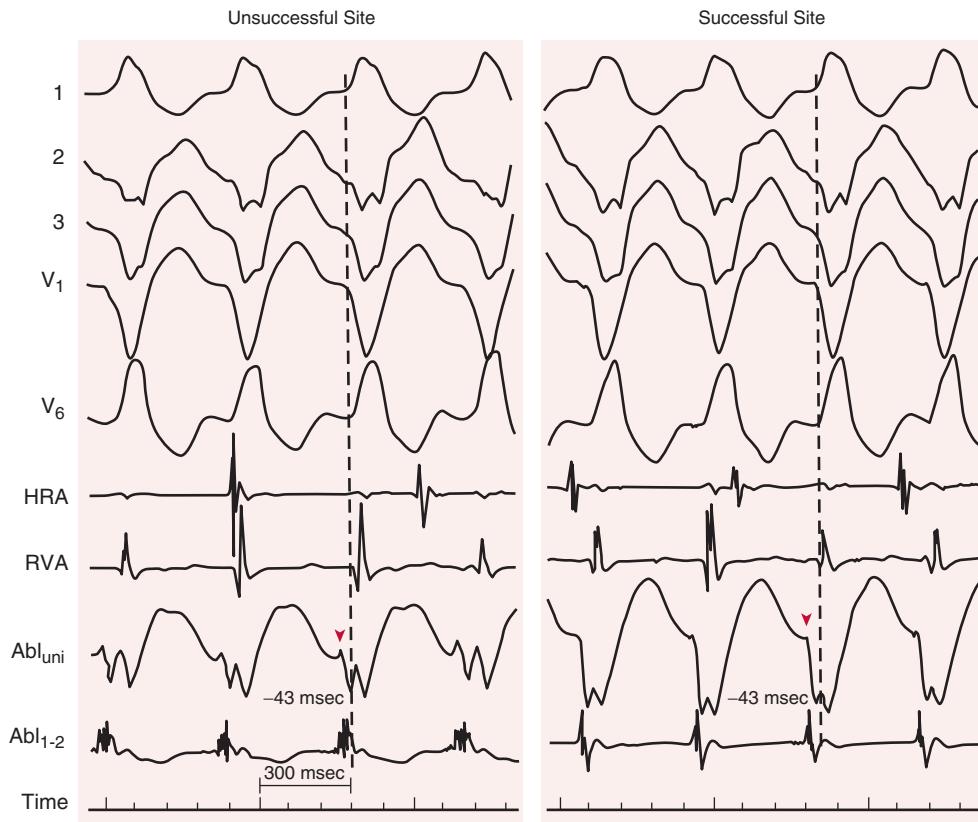


FIGURE 35-15 Recordings from unsuccessful and successful ablation sites in a patient with idiopathic VT arising in the inferior right ventricular wall. In the recordings from the unsuccessful ablation site, the unipolar signal (arrowhead) has a small r wave, which indicates that a portion of the wave front from the focus of tachycardia is approaching the site from elsewhere. At the successful site, the unipolar recording has a QS configuration, thus indicating that all depolarization is emanating from this site. In each site the bipolar recording (Abl₁₋₂) occurs an identical 43 milliseconds before onset of the QRS (dashed lines).

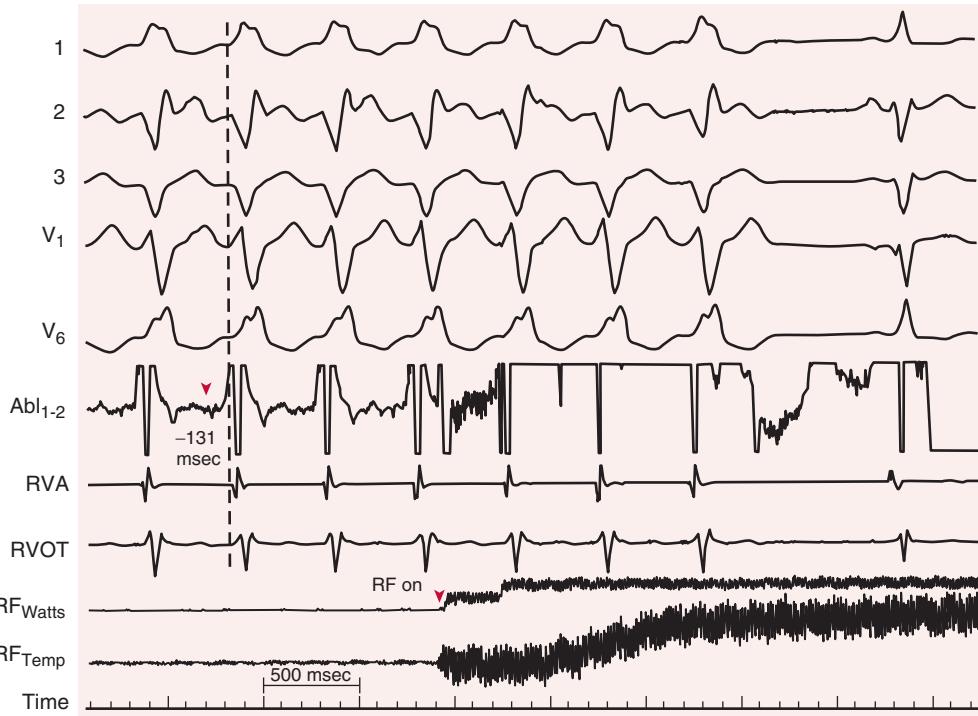


FIGURE 35-16 RF ablation of postinfarction VT. The electrogram in the ablation recording (Abl₁₋₂, arrowhead) precedes onset of the QRS (dashed line) by 131 milliseconds. Ablation here (RF on) results in slight deceleration of VT before termination in 1.3 seconds. Temperature monitored from the catheter tip had just peaked ($\approx 70^{\circ}\text{C}$) at the time that VT terminated. Recording was done as in previous figures.

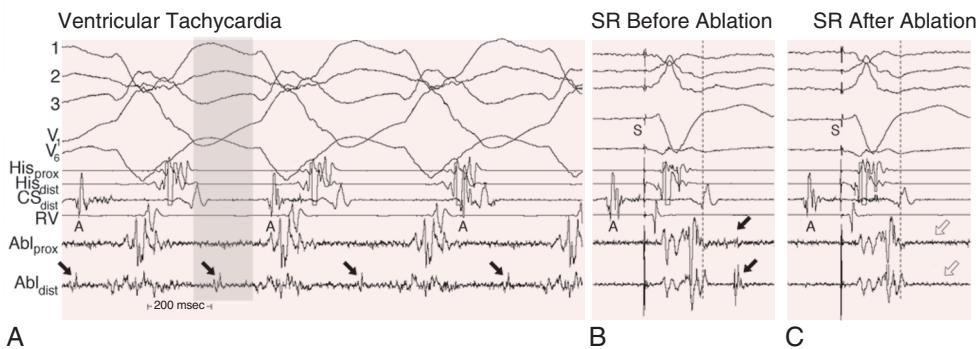


FIGURE 35-17 Mid-diastolic potentials during VT correlating with late potentials in sinus rhythm (SR). In **A**, VT is shown; diastole (from the end of one QRS complex to the beginning of the next) is shaded in gray. In the *Abl_{dist}* recording, a small, sharp signal is seen in mid-diastole that corresponds to a protected corridor of propagation. After termination of VT with pacing, recording at the same location shows a delayed (“late”) potential in SR with tracked ventricular pacing (black arrows; the dashed line denotes the end of the QRS complex). Ablation here eliminated the late potential (white arrows), as well as inducible VT. *A* = atrial recording; *S* = stimulus artifact.

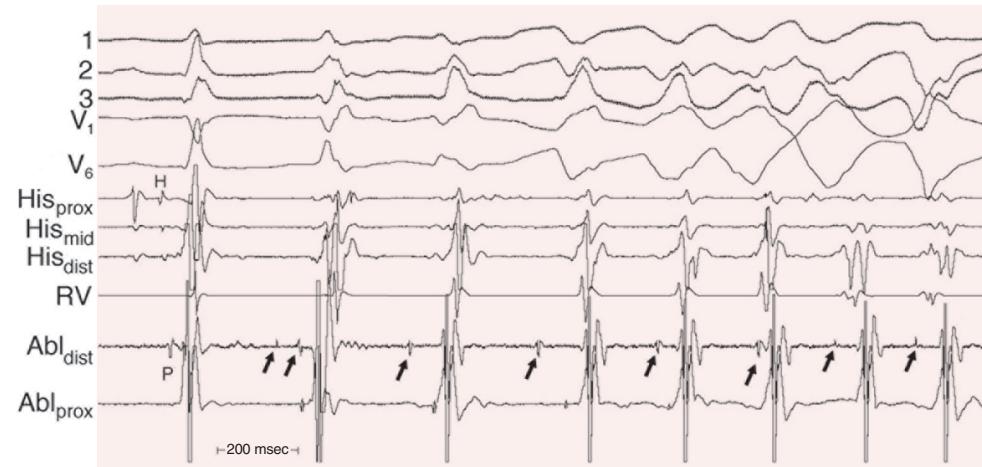


FIGURE 35-18 “Focal VF.” Recordings are shown from a patient with multiple episodes of VF in a day; a sinus rhythm complex, during which a Purkinje potential (*P*) is recorded from the *Abl* electrode, is followed by a premature complex from that site that is preceded by sharp Purkinje spikes (arrows) that continue to precede subsequent complexes of polymorphic VT that degenerated to VF. Ablation at this site eliminated recurrent episodes of VF.

to the difficulties in mapping and ablation of VT in these patients because pacing techniques used to validate recordings at potential sites of ablation may result in a change in morphology to another VT that does not arise in the same region.

After ablation of VT, ventricular stimulation is repeated to assess efficacy. In some cases, rapid polymorphic VT or VF is initiated. The clinical significance of these arrhythmias is unclear, but some evidence has suggested that they have a low likelihood of spontaneous occurrence during follow-up.

As noted earlier, most cases of polymorphic VT and VF are not currently amenable to ablation because of hemodynamic instability and beat-to-beat changes in activation sequence. However, some cases appear to have a focal source (similar to the focal sources of atrial fibrillation), and if the focus can be identified and ablated, further arrhythmia episodes can be prevented. In such cases, repeated episodes of arrhythmia have constant electrocardiographic features of the initiating beat or beats, thus suggesting a consistent source, which may be in either ventricle. The electrogram at sites of successful ablation often has very sharp presystolic potentials reminiscent of Purkinje potentials, with a 50- to 100-millisecond delay until onset of the QRS (Fig. 35-18).²⁷

Indications

Patients considered for RF catheter ablation of VT in the absence of structural heart disease are those with symptomatic, sustained monomorphic VT when the tachycardia is drug resistant, when the patient

is drug intolerant, or when the patient does not desire long-term drug therapy. Patients with structural heart disease who are candidates for ablation include those with bundle branch reentrant VT and those with sustained monomorphic VT and an ICD who are receiving multiple shocks not manageable by reprogramming or concomitant drug therapy. On occasion, nonsustained VT or even severely symptomatic PVCs require RF catheter ablation. In some of these cases, in which the ventricular ectopy occurs frequently, significant left ventricular systolic dysfunction has occurred (presumably similar to tachycardia-related cardiomyopathy). After successful ablation, ventricular function may improve significantly or even normalize.

Results

In patients with structurally normal hearts, the success rate of VT ablation is approximately 85%.²⁸ In patients with postinfarction VT, more than 70% no longer have recurrences of VT after the ablation procedure despite inducibility of rapid VT or VF (only \approx 30% of patients will have no inducible ventricular arrhythmia of any type and no spontaneous recurrences). Almost all these patients have an ICD, regardless of outcome. Significant complications occur in up to 3%, including vascular damage, heart block, worsening of heart failure, cardiac tamponade, stroke, and valve damage; death is rare but can occur in patients with severe coronary artery disease and/or systolic dysfunction.

New Mapping and Ablation Technologies

Multielectrode Mapping Systems. As noted earlier, many limitations of ablation are related to inadequate mapping. These problems include having only isolated premature complexes during the EPS as opposed to sustained tachycardias (in idiopathic AT and VT), nonsustained episodes of VT, poor hemodynamic tolerance of VT, and multiple VT morphologies. Standard mapping techniques sample single sites sequentially and are poorly suited to these situations. New mapping systems are available that enable sampling of many sites simultaneously and incorporate sophisticated computer algorithms for analysis and display of global maps. These mapping systems use various technologies ranging from multiple electrodes situated on each of several splines of a basket catheter (see Fig. 34-16), to the use of low-intensity electrical or magnetic fields to localize the tip of the catheter in the heart and record and plot activation times on a contour map of the chamber, to the use of complex mathematics to compute “virtual” electrograms recorded from a mesh electrode situated in the middle of a chamber cavity or on the body surface. Some of these systems are capable of generating activation maps of an entire chamber by using only one cardiac complex, an obvious advantage in patients with only rare premature complexes, nonsustained arrhythmias, or poor hemodynamic tolerance of sustained arrhythmias.

Epicardial Catheter Mapping. Although most VTs can be ablated from the endocardium, occasional cases are resistant to this therapy. In many of these cases, epicardial ablation may be successful. It is often needed in VT attributable to cardiomyopathy but less frequently in postinfarction patients and those without structural heart disease.

For gaining access to the pericardial space for epicardial mapping and ablation, a long spinal anesthesia needle is introduced from a subxiphoid approach under fluoroscopic guidance. As the pericardium is approached, a small amount of radiocontrast agent is injected. If the tip of the needle is still outside the pericardium, the dye stays where it is injected; when the pericardial space has been entered, the dye disperses and outlines the heart. A guidewire is introduced through the needle and a standard vascular introducer sheath is exchanged over the wire. The pericardial space is then accessible for a mapping/ablation catheter. The usual mapping techniques can then be applied. When a site is selected for possible ablation, coronary arteriography is usually warranted to avoid delivery of RF energy near a coronary artery. This is less important in cases of postinfarction VT because the VT substrate is typically in a region of previous transmural infarction. The technique can be used for patients who have previously undergone cardiac surgery, although adhesions may obliterate portions of the pericardial space; on occasion, a small subxiphoid incision is needed for better access and visualization of the space. The most frequent complication of epicardial mapping is pericarditis related to the ablation; cardiac tamponade is rare.

Chemical Ablation. Chemical ablation of an area of myocardium involved in a tachycardia with alcohol or phenol has been used to create AV block in patients not responding to catheter ablation and to eliminate AT and VT. Recurrences of tachycardia several days after apparently successful ablation are common. Excessive myocardial necrosis is the major complication, and alcohol ablation should be considered only when other ablative approaches fail or cannot be done.

Several other mapping/imaging techniques have been developed recently, including integration of a previously obtained computed tomography or magnetic resonance imaging study into computerized mapping systems and use of intracardiac ultrasound to construct a facsimile of the intracardiac anatomy in any chamber during ablation procedures to guide placement of anatomic ablation and reduce fluoroscopic exposure, use of algorithms to select complex fractionated atrial electrograms for ablation in patients with atrial fibrillation, and algorithms to assess the fidelity of pace maps with native tachycardia complexes.

SURGICAL THERAPY FOR TACHYARRHYTHMIAS

The objectives of a surgical approach to treatment of a tachycardia are to excise, isolate, or interrupt tissue in the heart critical for initiation, maintenance, or propagation of the tachycardia while preserving or even improving myocardial function. In addition to a direct surgical approach to the arrhythmia, indirect approaches such as

aneurysmectomy, coronary artery bypass grafting, and relief of valvular regurgitation or stenosis can be useful in selected patients by improving cardiac hemodynamics and myocardial blood supply. Cardiac sympathectomy alters adrenergic influences on the heart and has been effective in some patients, particularly those who have recurrent VT with long-QT syndrome despite beta blockade and catecholaminergic polymorphic VT.

Supraventricular Tachycardias

Surgical procedures exist for patients (adults and children) with AT, atrial flutter and fibrillation (see Chapter 38), AV node reentry, and AV reentry (Fig. 35-19). RF catheter ablation adequately treats most of these patients and thus has replaced direct surgical intervention, except for the occasional patient in whom RF catheter ablation fails or who is undergoing concomitant cardiovascular surgery. In some cases, a prior attempt at RF catheter ablation complicates surgery by obliterating the normal tissue planes that exist in the AV groove of the heart or by rendering tissues friable. On occasion, patients with ATs have multiple foci that require surgical intervention. Several surgical procedures have been developed to treat atrial fibrillation; these are reviewed in Chapter 38.

Ventricular Tachycardia

In contrast to patients with supraventricular arrhythmias, candidates for surgical therapy for ventricular arrhythmias often have severe left ventricular dysfunction, generally the result of coronary artery disease. The cause of the underlying heart disease influences the type of surgery performed. Candidates are patients with drug-resistant, symptomatic, recurrent ventricular tachyarrhythmias who ideally have a segmental wall motion abnormality (scar or aneurysm) with preserved residual left ventricular function, have not benefited from previous attempts at catheter ablation, or are not candidates for catheter ablation because of hemodynamic instability during VT or the presence of left ventricular thrombi (precluding endocardial catheter ablation). Poorer surgical results are obtained in patients with nonischemic cardiomyopathy.

Ischemic Heart Disease

In almost all patients who have VT associated with ischemic heart disease, the arrhythmia, regardless of its configuration on the surface ECG, arises in the left ventricle or on the left ventricular side of the interventricular septum. The electrocardiographic contour of the VT can change from a right bundle branch block to a left bundle branch block pattern without a change in the site of earliest diastolic activation, thus suggesting that the location of the circuit within the left

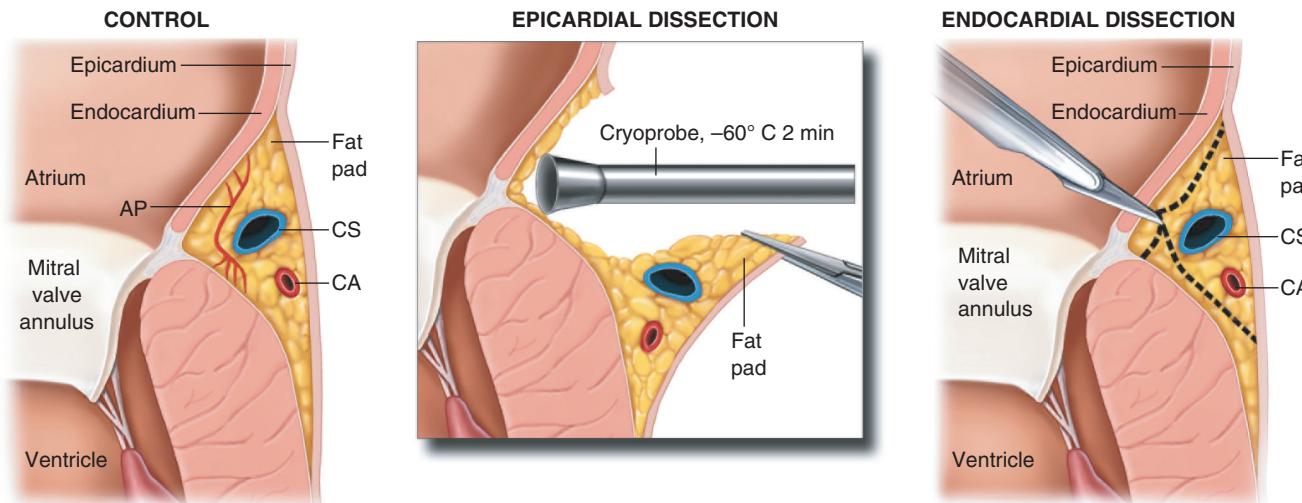


FIGURE 35-19 Schematic diagram showing the two approaches for surgical interruption of an accessory pathway. **Left**, Left AV groove and its vascular contents the coronary sinus (CS) and circumflex coronary artery (CA). Multiple accessory pathways (APs) course through the fat pad. **Middle**, Approach for epicardial dissection. **Right**, Endocardial dissection. Both approaches clear out the fat pad and interrupt any accessory pathways. (From Zipes DP: Cardiac electrophysiology: Promises and contributions. *J Am Coll Cardiol* 13:1329, 1989. Reprinted by permission of the American College of Cardiology.)

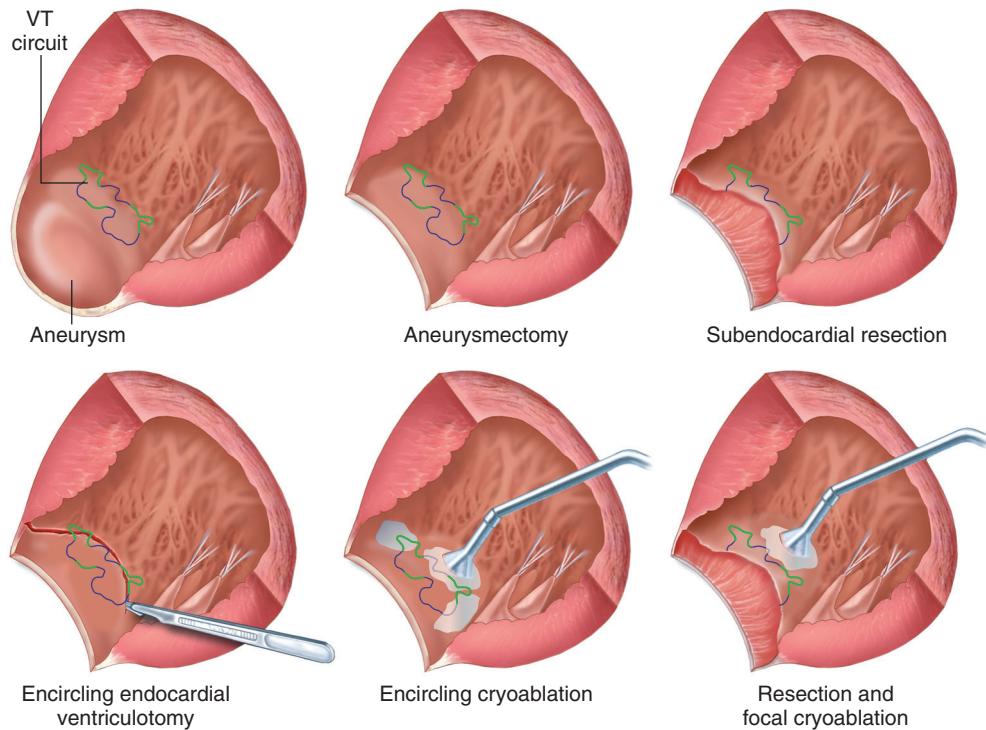


FIGURE 35-20 Schematic diagram showing surgical procedures for the treatment of postinfarction VT with a left ventricular aneurysm. A damaged left ventricle is depicted as opened along the lateral wall and showing the septum and papillary muscles. The tachycardia circuit (**upper left**) takes a meandering course near the point where the aneurysm meets normal myocardium and at times is superficial (purple lines) and at other times is coursing deeper (green lines). Simple aneurysmectomy that leaves a portion of the aneurysm for suturing often misses the circuit and thus does not cure the arrhythmia. By subendocardial resection, a layer of endocardium and subadjacent tissue is removed, including at least some of the tachycardia circuit. Such resection results in elimination of the tachycardia. Encircling endocardial ventriculotomy attempts to isolate the circuit electrically without removal of tissue, but it probably actually works by incising portions of the circuit. Cryoablation can be used to encircle the infarct zone or in combination with resection of damaged tissue too deep in the wall to be resected safely.

ventricle remains the same, often near the septum, but its exit pathway is altered.

Indirect surgical approaches, including cardiothoracic sympathectomy, coronary artery revascularization, and ventricular aneurysm or infarct resection with or without coronary artery bypass grafting, have been successful in no more than 20% to 30% of reported cases. Coronary artery bypass grafting as a primary therapeutic approach has generally been successful only in patients who experience rapid VT because of severe ischemia, as well as in patients with ischemia-related VF, but it can sometimes be useful in patients with coronary disease resuscitated from sudden death who have no inducible arrhythmias at EPS. These patients generally have a clear relationship between episodes of ventricular arrhythmia and immediately antecedent severe ischemia and have no evidence of infarction or minimal wall motion abnormalities but have preserved overall left ventricular function. Patients with sustained monomorphic VT or only polymorphic VT rarely have their arrhythmias affected by coronary bypass surgery, although it can reduce the frequency of the arrhythmic episodes in some patients and prevent new ischemic events.

Surgical Techniques. In general, two types of direct surgical procedures are used, resection and ablation (Fig. 35-20). The first direct surgical approach to VT was encircling endocardial ventriculotomy, which entails performing a transmural ventriculotomy to isolate areas of endocardial fibrosis that were recognized visually; this procedure is rarely used now. Another procedure, subendocardial resection, is based on data indicating that arrhythmias after myocardial infarction arise mostly at the subendocardial borders between normal and infarcted tissue. Subendocardial resection involves peeling off a 1- to 3-mm-thick layer of endocardium, often near the rim of an aneurysm, that has been demonstrated by mapping procedures to contain sites of mid-diastolic activation recorded during VT. Tachycardias arising from near the base of the papillary muscles are treated with a cryoprobe cooled to -70°C . Cryoablation can also be used to

isolate areas of the ventricle that cannot be resected and is often combined with resection. Lasers have also been used with good success, but the equipment is expensive and cumbersome.

Results. For ventricular tachyarrhythmias, operative mortality ranges from 5% to 10%; success, defined as the absence of recurrence of spontaneous ventricular arrhythmias, is achieved in 59% to 98% of patients. In experienced centers, operative mortality can be as low as 5% in stable patients undergoing elective procedures, with 85% to 95% of survivors being free of inducible or spontaneous ventricular tachyarrhythmias. Long-term recurrence rates range from 2% to 15% and correlate with results of the patient's postoperative electrophysiologic stimulation study. Operative survival is strongly influenced by the degree of left ventricular dysfunction.

Operative mortality for nonthoracotomy ICD implantation is far less than 1%, with an annual sudden cardiac death mortality rate of less than 2%. Because of the difference in operative survival and shorter hospital stay with ICD insertion than with direct surgery for VT and the success rates for catheter ablation in patients who have an ICD but experience frequent episodes of VT, few curative surgical procedures are now performed.

Electrophysiologic Studies

Preoperative Electrophysiologic Study. In patients for whom direct surgical therapy for VT is planned, a preoperative EPS is usually warranted. This study involves initiation of the VT and electrophysiologic mapping to localize the area to be resected, as is done with catheter ablation. Preoperative catheter mapping is contraindicated in patients with known left ventricular thrombi that might be dislodged by the mapping catheter.

Intraoperative Ventricular Mapping. Electrophysiologic mapping is also performed at the time of surgery, with the surgeon using a handheld probe or an electrode array coupled with computer techniques that instantaneously provide an overall activation map, cycle by cycle. The sequence of activation during VT can be plotted and the area of earliest activation determined. Resection or cryoablation of tissue from which these recordings are made usually cures the VT, thus indicating that they represent a critical portion of the reentrant circuit. When the earliest recordable endocardial electrical activity occurs less

than 30 milliseconds before onset of the QRS complex, the critical portions of the circuit may be in the interventricular septum or near the epicardium of the free wall. In some patients, intramural mapping using a plunge needle electrode can be useful. Most centers have used a strategy of "sequential" subendocardial resection in which VT is initiated, mapped, and ablated (resected or cryoablated) while the heart is warm and beating, and stimulation is repeated immediately. If VT can still be initiated, mapping and resection are also repeated until VT can no longer be initiated. Reentry around an inferior scar, with a critical diastolic pathway confined to an isthmus of ventricular muscle between the scar and mitral valve annulus, can be cured by cryoablation of this isthmus. Cure rates in this situation exceed 93%.

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