Assessment and treatment of ventricular tachyarrhythmias present extraordinary challenges to the clinician. Moreover, the prognosis for patients is quite variable with these characteristically sudden-onset, unpredictable, and transitory arrhythmias. In some patients, ventricular ectopic activity may be benign and without sequelae, but in other patients, comparable ectopy is a harbinger of ventricular fibrillation and sudden cardiac death. This subsection summarizes the practical aspects of evaluation and treatment of patients with ventricular arrhythmias.

**Pathophysiology**

Ventricular tachyarrhythmias are mediated by one of three basic mechanisms: reentry, abnormal automaticity, and triggering. Although causation cannot be directly determined in individual patients, experimental and clinical observations allow us to infer the mechanism underlying many ventricular arrhythmia syndromes encountered in practice.

**Reentrant ventricular tachycardia due to reentry**

Reentrant arrhythmias (also called circus movement tachycardias) are produced by a continuous circular or looping pattern of myocardial activation. Two features must be present for reentry to occur. The first is a barrier around which the wavefront circulates, either a fixed region of inexcitability caused by scarring or a dysfunctional region resulting from local refractoriness. The second feature required for reentry is unidirectional block at the entrance of the circuit. If activation spreads down both sides of the barrier, the impulses will collide distally and reentry will not occur. But if propagation is blocked in one limb and proceeds in an antegrade direction over the other, the activation wavefront may be capable of retrograde invasion of the initially blocked pathway, thereby initiating sustained reentry.

In patients with structural heart disease, most symptomatic ventricular arrhythmias are mediated by reentry. Sustained monomorphic ventricular tachycardia often occurs after transmural myocardial infarction. The arrhythmia usually arises in the border zone of the scar [see Figure 1]. The larger the extent of this heterogeneous border zone, the greater the probability of a circuit capable of mediating reentrant ventricular tachycardia. This is consistent with the observation that the risk of malignant ventricular arrhythmias is proportional to the volume of the scar and the severity of left ventricular dysfunction after myocardial infarction. Although they are controversial, experimental and clinical observations suggest that ventricular fibrillation is also a reentrant phenomenon. Unlike ventricular tachycardia, during which a single activation wavefront circulates around a fixed barrier, ventricular fibrillation is caused by multiple simultaneous rotors that travel around functional barriers of refractory tissue, moving continuously throughout the myocardium to create very rapid, irregular, and ineffective activation.

**Figure 1** Reentrant ventricular tachycardia usually arises as the result of reentry within the border zone of a myocardial infarction. This region consists of strands of viable myocytes interspersed with inexcitable fibrous tissue. Reentry begins when a wavefront of activation (1) encounters a bifurcation and blocks in one of the two pathways around an obstacle (2). The activation wavefront then conducts exclusively through the orthodromic pathway (3) and encounters a region of relatively slow conduction within the tachycardia circuit (4). The activation wavefront may exit from the tachycardia circuit at a site quite different from the entrance point (5). Although the antegrade limb of the circuit is initially refractory, it recovers excitability by the time it is depolarized by the reentrant wavefront (6). The activation wavefront reenters the orthodromic limb of the circuit, and the circus movement is established.
Like postinfarction arrhythmias, the ventricular tachycardia in patients with nonischemic cardiomyopathy is often the result of reentry in a zone of patchy fibrosis. However, in patients with left ventricular dilatation and slowed conduction in the specialized conduction system, the tachycardia may be mediated by bundle branch reentry: antegrade conduction over the right bundle branch, activation of the septum, and retrograde conduction over the left bundle branch [see Figure 2].6 Although an infrequent cause of ventricular tachycardia, bundle branch reentry is of interest to cardiac electrophysiologists because it can be cured by selective destruction of either the right or the left bundle branch by use of radiofrequency catheter ablation [see Subsection VII].

Ventricular tachycardia mediated by abnormal automaticity

Normal ventricular myocytes maintain a steady transmembrane resting potential of −80 to −90 mV, depolarizing only when stimulated by an activation wavefront. Extrinsic factors, such as electrolyte imbalance and ischemia, or intrinsic disease may reduce the resting potential and produce simultaneous diastolic depolarization (phase 4) [see Figure 3].

Unlike reentry, which can usually be induced and terminated by premature beats, automatic rhythms tend not to be influenced by pacing. Changes in heart rate at the onset of ventricular tachycardia may also provide insight into the arrhythmia mechanism. Reentrant tachycardias are usually stable because of a fixed conduction time around the circuit. In contrast, automaticity often shows warm-up, with progressive acceleration during the first few seconds of the tachycardia.

Abnormal automaticity may play a role in a number of clinical arrhythmia syndromes. An accelerated idioventricular rhythm (60 to 100 beats/min) or episodes of slow ventricular tachycardia (100 to 140 beats/min) occur in approximately 20% of patients who are monitored after transmural myocardial infarction.7 These slow-fast rhythms are probably the result of abnormal automaticity in ischemic Purkinje fibers.

More rapid ventricular tachycardia is also a frequent complication of acute ischemia, reperfusion, or both. These arrhythmias are often polymorphic, characterized by QRS complexes that change in amplitude and cycle length, with heart rates that may approach 300 beats/min. It is likely that abnormal automaticity in ischemic myocardium is responsible for many of these episodes.

Ventricular tachycardia occasionally occurs in patients without apparent structural heart disease.8 This idiopathic arrhythmia generally originates in the right ventricular outflow tract, just beneath the pulmonary valve. A number of observations suggest that it, too, is sometimes mediated by abnormal automaticity. It may develop spontaneously in response to increased adrenergic tone and, as a rule, cannot be induced or terminated by pacing. It may occur as a pattern of recurrent short bursts of tachycardia interspersed with equally short interludes of sinus rhythm, a pattern more consistent with automaticity than reentry.9

Ventricular tachycardia due to triggering

Early Afterdepolarization

Triggered activity, defined as premature activation caused by one or more preceding impulses, is the result of afterdepolarizations that occur either during (early afterdepolarization) or just after (delayed afterdepolarization) completion of the repolarization process [see Figure 4]. Factors that slow the heart rate tend to prolong the duration of depolarization, which is identified by a lengthened QT interval on the ECG, often sufficiently to bring early afterdepolarizations to threshold. Thus, triggered ventricu-
Arrhythmias mediated by delayed afterdepolarization are distinctly different from those associated with early afterdepolarizations and appear to be caused by abnormal accumulation and oscillation of cytosolic calcium concentration. The amplitude of these arrhythmias is augmented by acceleration rather than slowing of the heart rate. Delayed afterdepolarizations have been implicated in the genesis of ventricular tachycardia caused by digitalis toxicity and in some patients with ventricular tachycardia and no apparent structural heart disease. Verapamil may be therapeutic in this subset of patients. Although these arrhythmias have been recorded from surviving Purkinje fibers and infarcted canine myocardium, their role in clinical arrhythmias during and after myocardial infarction is less well established.

**Delayed Afterdepolarization**

Arrhythmias mediated by delayed afterdepolarization are characterized bradycardia dependent or pause dependent. Early afterdepolarizations have been produced experimentally under a variety of conditions, including ischemia, hypokalemia, and antiarrhythmic drug toxicity. The arrhythmias seen in these studies are bradycardia dependent and, typically, are both rapid and polymorphic. Slowing of the tachycardia rate just before spontaneous termination is another characteristic feature of early afterdepolarization-mediated ventricular tachycardia.

Although it is difficult to prove, it seems likely that early afterdepolarizations mediate a variety of clinical arrhythmias. Patients with the congenital long QT syndrome and patients with acquired QT prolongation produced by drugs (typically, class IA antiarrhythmic agents) or electrolyte depletion are at risk for a polymorphic ventricular tachycardia. As in the experimental situation, patients with QT prolongation tend to develop polymorphic ventricular tachycardia as a result of slowing of the heart rate, heart rate pauses, or sudden surges in adrenergic tone. Unlike rhythms mediated by automaticity or reentry, ventricular tachycardia in the setting of QT prolongation is almost always polymorphic, sometimes with the twisting pattern that characterizes torsade de pointes.

**Asymptomatic Ventricular Ectopy**

Ventricular ectopy is recorded in more than half of normal persons undergoing ambulatory electrocardiographic monitoring. Complex ectopy (multifocal premature ventricular complexes and nonsustained ventricular tachycardia) is less frequent but is still observed in 5% to 10% of healthy persons with no apparent heart disease. The prognostic significance of ventricular ectopy depends on the severity of left ventricular dysfunction. In the absence of structural heart disease, asymptomatic ventricular ectopic activity is benign, with no demonstrable risk of sudden death, even in the presence of ventricular tachycardia. In patients with structural heart disease, however, ventricular ectopic activity is associated with an increased risk of sudden cardiac death. This risk is markedly increased with progressive left ventricular dysfunction.

For example, postmyocardial infarction patients with a left ventricular ejection fraction greater than 40% who experience fewer than 10 ventricular premature complexes (VPCs) an hour after myocardial infarction have a mortality of 5% to 7% a year. Those patients who experience more than 10 VPCs an hour, however, have a mortality of 12% to 18%. The combination of a left ventricular ejection fraction of less than 40% and more than 10 VPCs an hour raises the annual mortality to between 27% and 40%.

**Figure 3** The resting transmembrane potential of the myocardial cell is created by active maintenance of sodium and potassium gradients. The cell is depolarized (phase 0) by an electrical stimulus that allows a sudden influx of sodium (Na⁺). Repolarization, phases 1 through 3, requires an early rapid chloride influx, a plateau phase mediated by calcium currents, and reestablishment of the resting transmembrane potential via potassium (K⁺) efflux. Between action potentials, the resting potential is designated as phase 4. In cells with automaticity, depolarization mediated by calcium (Ca²⁺) and Na⁺ currents may occur during phase 4, resulting in spontaneous generation of the next action potential. In normal ventricular myocytes, the resting potential during electrical diastole (phase 4) remains in the region of ~80 to ~90 mV. The rate of automatic firing is determined by the resting potential, the slope of phase 4, and the threshold potential.

**Figure 4** In ventricular tachycardia caused by triggering, prolongation of the action potential (and the QT interval) results in depolarization during phase 3. Such early afterdepolarizations are manifested as positive deflections at the end of the phase 2 plateau or during the phase 3 rapid repolarization of the action potential. If this deflection exceeds the threshold potential, one or more triggered beats will occur. Bradycardia-dependent torsade de pointes is an example of an arrhythmia caused by early afterdepolarizations. The electrocardiogram of a patient with quinidine intoxication reveals an extrasystole and polymorphic ventricular tachycardia.
The presence of frequent ventricular premature beats 7 to 10 days after myocardial infarction is associated with a fivefold increase in the risk of symptomatic or fatal arrhythmias during follow-up. Because many patients with frequent ectopy do not develop malignant ventricular arrhythmias, the positive predictive accuracy of this finding is only 16%. Conversely, because the majority of patients without frequent ectopy remain free of fatal arrhythmias, its absence is associated with a negative predictive accuracy of 82%. The occurrence of nonsustained ventricular tachycardia (fewer than three consecutive beats over a period of less than 30 seconds) during monitoring appears to confer an even greater risk than does the presence of frequent isolated ventricular premature beats.

The association between ambient ventricular ectopy and the risk of arrhythmic death is less well established in patients with nonischemic (i.e., valvular, hypertensive, or idiopathic) cardiomyopathy. However, most reports in the literature do suggest that the presence of high-grade ventricular arrhythmias, defined as multifocal VPCs or nonsustained ventricular tachycardia, confers an increased risk of sudden death that is independent of the severity of left ventricular dysfunction.

Because the significance of ventricular ectopy depends on the degree of ventricular function impairment, cardiac imaging should be part of the initial evaluation. Echocardiography is the most versatile test; it provides information regarding regional wall motion abnormalities and valvular lesions as well as the left ventricular ejection fraction. Radionuclide ventriculography also gives precise information regarding ejection fraction and may be of value in patients whose heart disease is already well characterized.

Another study that may be useful for estimating risk in patients with heart disease and ventricular ectopy is signal-averaged electrocardiography. This noninvasive test detects signals from areas of slow conduction in the arrhythmogenic regions on the periphery of a myocardial infarction. The surface electrocardiogram is recorded for approximately 250 beats, and the signal is averaged by a computer and filtered, resulting in dramatic reduction of the signal-to-noise ratio. This allows detection of low-amplitude, high-frequency late potentials that result from the activation of zones of slow conduction just after the offset of the QRS complex.

Low-amplitude, high-frequency late potentials are recorded in about one third of patients after myocardial infarction. These patients have a 20% incidence of life-threatening ventricular arrhythmias during the first year after infarction, compared with a 3% incidence in patients without late potentials. Signal-averaged ECG findings are independently predictive of adverse events after myocardial infarction and provide additional information regarding risks in patients with frequent ventricular premature contractions and impaired left ventricular function.

Electrophysiologic study can be used to assess the inducibility of sustained ventricular arrhythmias in patients with structural heart disease. Electrode catheters are introduced percutaneously into the venous system, usually via the femoral vein, and advanced under fluoroscopic guidance into the right ventricle. Programmed electrical stimulation is performed in an attempt to elicit ventricular tachycardia or fibrillation. This usually consists of a drive train at a constant paced cycle length followed by one, two, or three extra stimuli. The stimuli are introduced at progressively more premature coupling intervals until tachycardia is induced or the stimuli fail to capture as the result of local refractoriness.

The role of invasive electrophysiologic study for risk stratification in asymptomatic patients after myocardial infarction remains controversial. In about 20% of such patients, sustained monomorphic ventricular postinfarction tachycardia can be induced using programmed stimulation, and in an additional 10% to 15%, ventricular fibrillation can be produced. During follow-up, arrhythmic events occur in 5% of the noninducible patients, in 10% of patients with inducible ventricular fibrillation, and in 50% of patients with inducible ventricular tachycardia.

Although electrophysiologic study has reasonable sensitivity for prediction of subsequent arrhythmic events, the positive pre-
dichotic value of the test is probably no better than that of the signal-averaged ECG, especially when the latter is combined with measurements of left ventricular systolic function and quantification of ambient ectopy. Electrophysiologic study is invasive and relatively expensive. Moreover, there is no evidence to suggest that treatment of this group of patients with antiarrhythmic drugs improves survival. Thus, it is difficult to justify routine electrophysiologic testing in asymptomatic patients after myocardial infarction.

Electrophysiologic testing is of uncertain value for stratification of risk in patients with nonischemic cardiomyopathy and asymptomatic ventricular ectopy. In this population, induction of sustained monomorphic ventricular tachycardia is infrequent and does not appear to be predictive of subsequent sudden cardiac death.

**Syncope and Ventricular Arrhythmias**

Syncope, defined as transient loss of consciousness, is a common phenomenon, accounting for about 3% of all emergency room visits. Because the spells usually resolve by the time the patient is initially evaluated, determination of the cause of loss of consciousness is difficult but extremely important, because prognosis depends on the nature of the episode. If ventricular arrhythmias are detected during subsequent monitoring, additional evaluation should be undertaken to determine whether the syncope was produced by a paroxysm of ventricular tachycardia.

**History and physical examination**

A thorough history may provide important clues to the diagnosis of ventricular tachycardia. The onset of syncope mediated by ventricular tachycardia is usually abrupt, with only a brief prodrome of light-headedness or no premonitory symptoms at all. The absence of rapid heartbeat does not exclude the diagnosis, because only 60% of patients with documented sustained ventricular tachycardia experience this symptom. The duration of unconsciousness is brief, rarely lasting longer than several minutes. Because of the abrupt onset, traumatic injury is common.

Spontaneous movements during syncope often cause confusion and misdiagnosis. Cerebral hypoperfusion from any cause, including ventricular tachycardia, may produce one or more clonic jerks of the extremities. However, syncopal episodes differ from seizure activity in several respects: the movements in syncopal episodes are not reciprocating (tonic-clonic) and are much briefer in duration, and bladder or bowel incontinence rarely occurs.

Historical information regarding the patient’s condition after awakening is frequently overlooked but may be very helpful. Patients typically recover quickly from ventricular tachycardia-mediated syncope. Postictal confusion lasting longer than 5 minutes suggests a grand mal event rather than an arrhythmic one. Similarly, persistent residual malaise, nausea, and weakness are characteristic of a faint produced by the vasodepressor syndrome rather than arrhythmic syncope.

Ventricular tachycardia of sufficient rate or duration to produce loss of consciousness is rare in patients with normal ventricular function. Thus, patients in whom ventricular arrhythmias are identified after a syncopal episode must be thoroughly evaluated for structural heart disease. The presence of severe left ventricular dysfunction in these patients is associated with an ominous prognosis.

Patients with coronary artery disease, syncope, or ventricular arrhythmias require evaluation of myocardial ischemia with a functional study (e.g., thallium scintigraphy), coronary angiography, or both, in addition to quantification of ventricular function. Acute ischemia may precipitate rapid ventricular tachycardia that is sufficient to cause loss of consciousness. In such cases, exercise treadmill testing may induce ventricular ectopy, thereby suggesting the diagnosis, especially if premonitory symptoms are reproduced.

**Electrocardiography**

Signal-averaged electrocardiography plays a limited but important role in the evaluation of patients with syncope and ventricular arrhythmias. The positive predictive accuracy of this test is inadequate to confirm the diagnosis of an arrhythmic event. However, a negative result makes the possibility of sustained ventricular tachycardia unlikely enough that additional, more invasive studies are probably not justified.

Ambulatory electrocardiography is useful in selected patients with a history of syncope and ventricular arrhythmias. The yield of 24-hour or 48-hour Holter monitoring is low among patients with infrequent arrhythmic episodes, however. In such patients, a transtelephonic event recorder is more likely to provide diagnostic information. This device is worn by the patient for 4 to 6 weeks, continuously recording and storing approximately 90 seconds of the ECG in an endless loop. Immediately after presyncope or a syncopal spell, the patient presses the event button on the device to stop the recording and store the preceding ECG in memory. The output of the device is then transmitted over the telephone to a receiving station. This system has been shown to be more cost-effective than Holter monitoring and is preferable unless symptoms are present on a daily basis.

**Electrophysiologic tests**

Electrophysiologic testing can be useful in determining whether an episode of loss of consciousness was produced by ventricular tachycardia. Assessment of sinus node function and atrioventricular conduction should be performed during electrophysiologic testing even when ventricular tachycardia is suspected, because episodic bradyarrhythmias may produce spells with very similar symptoms.

The induction of sustained monomorphic ventricular tachycardia during programmed stimulation increases the probability that the patient’s spontaneous episode was mediated also by ventricular tachycardia. Several studies have shown a 2% to 27% rate of recurrent syncope in patients whose therapy is based on results of electrophysiologic testing, compared with 18% to 80% in those in whom the study was unrevealing or for whom no effective treatment could be found.

**Evaluation of the Patient Rescued from Cardiac Arrest**

Between 80% and 90% of patients who develop out-of-hospital cardiac arrest have as the precipitating event either primary ventricular fibrillation or a rapid ventricular tachycardia that degenerates into ventricular fibrillation. Bradyarrhythmic events occur occasionally, but when asystole is recorded as the initial rhythm, it is usually indicative of a prolonged downtime interval and is associated with a very poor prognosis.

The majority of patients who sustain cardiac arrest have structural heart disease. In industrialized societies, this is most often the result of coronary atherosclerosis. Studies of both victims and survivors of cardiac arrest show significant coronary obstruction in 75% to 80% of patients. Unfortunately, sudden cardiac death is the initial manifestation of coronary artery disease in 10% to 20%
of patients, making it the most common cause of mortality in adults younger than 65 years.20

Despite the close association between coronary artery disease and sudden cardiac death, acute myocardial infarction is an infrequent cause of cardiac arrest. Only about 20% of patients rescued from an episode of ventricular fibrillation have evidence of an evolving myocardial infarction during their subsequent hospitalization.21 The prognosis is favorable for cardiac arrest survivors in whom the event can be clearly linked to acute myocardial ischemia, with a recurrence rate of only 2% during the subsequent year. In contrast, patients with ventricular fibrillation not related to an ischemic event have an annual recurrence rate of greater than 20%, presumably because they have a chronic substrate capable of mediating malignant ventricular arrhythmias.20,21

All patients rescued from cardiac arrest require serial ECGs and enzyme measurements to determine whether the event was a consequence of acute myocardial infarction. Coronary angiography should be performed in all patients as well, except those in whom the precipitating factor has already been unequivocally identified.

**Electrocardiography**

Laboratory evaluation of patients rescued from cardiac arrest should be directed at the identification of specific reversible causative factors. The postresuscitation ECG may provide important information. A prolonged QT interval suggests the possibility of drug-induced torsade de pointes or the congenital long QT syndrome [see Subsection V]. Patients with WPW syndrome have an accessory connection linking the atrium and ventricle across either the mitral or the tricuspid annulus. A subset of patients with the WPW syndrome are capable of very rapid antegrade conduction over the accessory connection. If these patients develop atrial fibrillation, the ventricular response may be in excess of 300 beats/min and can degenerate into ventricular fibrillation.

**Laboratory tests**

The initial evaluation of serum electrolytes is sometimes revealing, because severe depletion of serum potassium, serum magnesium, or both may precipitate ventricular arrhythmias. Such depletions are characteristic of patients with congestive heart failure who are maintained on chronic diuretic therapy with inadequate electrolyte supplementation.

**Electrophysiologic tests**

Electrophysiologic study is an important part of the evaluation of the majority of cardiac arrest survivors in whom a reversible cause cannot be identified, including those with coronary artery disease, unless there is clear evidence for ischemia immediately preceding the event. The most specific end point of electrophysiologic study is the induction of sustained monomorphic ventricular tachycardia, which is more common in patients with a history of coronary artery disease and remote myocardial infarction than in those with other forms of structural heart disease. In a large series of cardiac arrest survivors undergoing electrophysiologic evaluation, slightly more than 42% of the survivors had inducible sustained monomorphic ventricular tachycardia, and either polymorphic ventricular tachycardia or ventricular fibrillation was induced in an additional 16%.20 These latter arrhythmias are less likely to be specific and reproducible than is stable monomorphic ventricular tachycardia.

**Pharmacologic Therapy**

As a result of changes in the medical care climate, more primary care practitioners bear direct responsibility for treatment decisions in patients with cardiac arrhythmias. The use of antiarrhythmic drugs in patients with ventricular arrhythmias presents a growing challenge, especially given that the medical literature contains reports of real and potential harm associated with the use of antiarrhythmic drugs. However, there have been advances in the understanding of electrophysiologic mechanisms of arrhythmias, there is an ever-growing and more powerful pharmacopoeia, and effective nonpharmacologic tools to prevent and treat ventricular arrhythmias are also emerging.

**Classification and mechanisms of antiarrhythmic drugs**

Antiarrhythmic drugs directly alter the electrophysiologic properties of myocardiocytes. Therefore, an understanding of basic cellular electrophysiology is critical for an informed use of these compounds [see Figure 6].

The most widely accepted classification of antiarrhythmic drugs, originally proposed by Vaughan Williams in 1970, involves four main classes of drugs, with the first further divided into three subgroups [see Table 1].24 This classification is based primarily on the ability of the drug to control arrhythmias by blocking ionic channels and currents. Few drugs demonstrate pure class effects, however, and other characteristics, such as influence of the drug on autonomic tone, contractility, and adverse effects, may be more important clinically and will be discussed as they pertain to individual drugs.

Class I agents inhibit the fast Na⁺ channel depolarization (phase 0) of the action potential, with resultant decreases in depolarization rate and conduction velocity [see Figure 6]. Agents in class IA (quinidine, procainamide, disopyramide, and moricizine) significantly lengthen both the action potential duration and the effective refractory period, achieved by the class I effect of Na⁺ channel inhibition and the lengthening of repolarization by K⁺ channel blockade, a class III effect.

Class IB drugs (lidocaine, mexiletine, tocainide, and phenytoin) are less powerful Na⁺ channel blockers and, unlike class IA agents, shorten the action potential duration and refractory period in normal ventricular tissue, probably by inhibition of a background Na⁺ current during phase 3 of the action potential.20,21 Recent evidence suggests that in ischemic tissue, lidocaine may also block an adenosine triphosphate (ATP)–dependent K⁺ channel, thus preventing ischemically mediated shortening of depolarization.27

Class IC drugs (flecainide and propafenone), the most potent Na⁺ channel blockers, markedly decrease phase 0 depolarization rate and conduction velocity. Unlike other class I agents, they have little effect on the action potential duration and the effective refractory period in ventricular myocardial cells, but they do shorten the action potential of the Purkinje fibers.20,22 This inhomogeneity of depolarization combined with marked slowing of conduction may contribute to the proarrhythmic effects of this class of drugs.

Class II agents are the beta-adrenergic antagonists. The efficacy of these drugs in the reduction of arrhythmia-related morbidity and mortality has become more evident in recent years, but the precise ionic bases for their salutary effects have not been fully elucidated. Beta-adrenergic antagonism has been shown to decrease spontaneous phase 4 depolarization and, therefore, to decrease adrenergically mediated automaticity, an effect that may be of particular importance in the prevention of ventricular arrhythmias during ischemia and reperfusion. Beta blockade also
### Table 1: Classification of Antiarrhythmic Drugs

<table>
<thead>
<tr>
<th>Class (Agents)</th>
<th>Action</th>
<th>I.V. Dosage</th>
<th>Oral Dosage</th>
<th>Route of Elimination</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I</strong></td>
<td>Inhibit membrane sodium channels; affect Purkinje fiber action potential during depolarization (phase 0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IA</strong></td>
<td>Quinidine</td>
<td>Slow the rate of rise of the action potential and prolong its duration; slow conduction; increase refractoriness</td>
<td>6–10 mg/kg (I.M. or I.V.) over 20 min</td>
<td>200–400 mg every 4–6 hr or every 8 hr (long-acting)</td>
<td>Hepatic</td>
</tr>
<tr>
<td></td>
<td>Procainamide</td>
<td></td>
<td>100 mg every 1–3 min to 500–1,000 mg; maintain at 2–6 mg/min</td>
<td>50 mg/kg/day in divided doses every 3–4 hr or every 6 hr</td>
<td>Renal</td>
</tr>
<tr>
<td></td>
<td>Disopyramide</td>
<td>100–200 mg every 6–8 hr</td>
<td>200–300 mg every 8 hr</td>
<td>Renal</td>
<td>Urinary retention, dry mouth, markedly LVF</td>
</tr>
<tr>
<td></td>
<td>Moricizine</td>
<td></td>
<td></td>
<td></td>
<td>Dizziness, nausea, headache, theophylline level, LVF</td>
</tr>
<tr>
<td><strong>IB</strong></td>
<td>Lidocaine</td>
<td>Shorten action potential duration; do not affect conduction or refractoriness</td>
<td>1–2 mg/kg at 50 mg/min; maintain at 1–4 mg/min</td>
<td>200–400 mg every 6–8 hr</td>
<td>Hepatic</td>
</tr>
<tr>
<td></td>
<td>Tocainide</td>
<td></td>
<td></td>
<td></td>
<td>CNS, GI, leukopenia</td>
</tr>
<tr>
<td></td>
<td>Mexiletine</td>
<td></td>
<td></td>
<td></td>
<td>CNS, GI, leukopenia</td>
</tr>
<tr>
<td><strong>IC</strong></td>
<td>Flecainide</td>
<td>Slow the rate of rise of the action potential and slow repolarization (phase 4); slow conduction; increase refractoriness</td>
<td>100–200 mg twice daily</td>
<td></td>
<td>Hepatic</td>
</tr>
<tr>
<td></td>
<td>Propafenone</td>
<td></td>
<td>150–300 mg every 8–12 hr</td>
<td></td>
<td>CNS, GI, ↓LVF, TDig</td>
</tr>
<tr>
<td><strong>II</strong></td>
<td>Beta blockers</td>
<td>Inhibit sympathetic activity; decrease automaticity; prolong atrioventricular conduction and refractoriness</td>
<td>500 µg/kg over 1–2 min; maintain at 25–200 µg/kg/min</td>
<td>Other beta blockers may be used</td>
<td>Hepatic</td>
</tr>
<tr>
<td></td>
<td>Esmolol</td>
<td></td>
<td></td>
<td></td>
<td>↓LVF, bradycardia, AV block, bronchospasm</td>
</tr>
<tr>
<td></td>
<td>Propranolol</td>
<td></td>
<td></td>
<td></td>
<td>↓LVF, bradycardia, positive ANA, lupuslike syndrome</td>
</tr>
<tr>
<td></td>
<td>Acebutolol</td>
<td></td>
<td></td>
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<tr>
<td><strong>III</strong></td>
<td>Amiodarone</td>
<td>Block potassium channels; predominantly prolong action potential duration, prolong repolarization, widen QRS complex, prolong QT interval, decrease automaticity and conduction, and prolong refractoriness</td>
<td>150 mg I.V. over 10 min, then 1 mg/min for 6 hr; maintain at 0.5 mg/min; overlap with initiation of oral treatment</td>
<td>800–1,600 mg/day for 7–21 days; maintain at 100–400 mg/day (higher doses may be needed)</td>
<td>Hepatic</td>
</tr>
<tr>
<td></td>
<td>Sotalol</td>
<td></td>
<td></td>
<td></td>
<td>Renal (dosing interval should be extended if creatinine clearance &lt; 60 ml/min)</td>
</tr>
<tr>
<td></td>
<td>Bretylium</td>
<td></td>
<td></td>
<td></td>
<td>↓LVF, bradycardia, fatigue and other side effects associated with beta blockers</td>
</tr>
<tr>
<td><strong>IV</strong></td>
<td>Verapamil</td>
<td>Slow calcium channel blockers; block the slow inward current; decrease automaticity and atrioventricular conduction</td>
<td>10–20 mg over 2–20 min; maintain at 5 µg/kg/min</td>
<td>80–120 mg every 6–8 hr; 240–360 mg once daily with sustained-release preparation (not approved for arrhythmias)</td>
<td>Hepatic</td>
</tr>
<tr>
<td></td>
<td>Diltiazem</td>
<td></td>
<td></td>
<td></td>
<td>Hepatic metabolism, renal excretion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypotension, LVF</td>
</tr>
</tbody>
</table>

*ANA*—antinuclear antibodies  *AV*—atrioventricular  *CNS*—central nervous system  *TDig*—elevation of serum digoxin level  *GI*—gastrointestinal (nausea, vomiting, diarrhea)  *LVF*—reduced left ventricular function  *SLE*—systemic lupus erythematosus  *VT*—ventricular tachycardia
results in the slowing of heart rate and decreased oxygen consumption, effects long recognized as desirable in myocardial infarction patients. Effects on the cardiac action potential differ in atrial, ventricular, and specialized conduction tissues. For example, conduction velocity is slowed most profoundly in specialized conduction tissue, resulting in prolongation of the PR interval, whereas action potential duration in ventricular myocardium is generally not affected.

The primary actions of class III agents (amiodarone, sotalol, and bretylium) are prolongation of depolarization, the action potential duration, and the effective refractory period by K+ channel blockade. These effects may prevent arrhythmias by decreasing the relative proportion of the cardiac cycle during which the myocardial cell is excitable and therefore susceptible to a triggering event. Reentrant tachycardias may be suppressed if the action potential duration becomes longer than the cycle length of the tachycardia circuit and if the leading edge of the wavefront suddenly impinges on inexcitable tissue. Use of class III agents is increasing because of proven efficacy and an incidence of proarrhythmia lower than that seen with class IA agents.

Class IV agents act by inhibiting the inward slow Ca2+ current, which may contribute to late afterdepolarizations and therefore to ventricular tachycardia. These Ca2+ channel blockers reduce afterdepolarizations and are useful in the treatment of idiopathic ventricular tachycardia. They have no appreciable effect on conduction velocity or repolarization and tend to evoke sympathetic activation. Thus, their role in the treatment of ventricular tachycardia in the setting of structural heart disease is limited.

Antiarrhythmic drugs in clinical use today have activity in multiple classes. For example, in addition to its class III effects, amiodarone also exhibits prominent Na+ channel blockade (class I), beta blockade (class II), and Ca2+ channel blockade (class IV). Sotalol is a racemic mixture of d and l isomers, both of which have a similar class III effect, whereas the l-isomer is essentially a beta blocker. d-Sotalol has been shown to increase mortality in patients with left ventricular dysfunction and recent myocardial infarction. The lower incidence of proarrhythmia seen with amiodarone or racemic sotalol therapy may be related to beneficial class II effects.

**Proarrhythmia**

Proarrhythmia refers to the worsening of an existing arrhythmia or the induction of a new one by an antiarrhythmic drug. Three types of proarrhythmia have been described: torsade de pointes (the most common), incessant ventricular tachycardia, and extremely wide complex ventricular rhythm.

**Torsade de Pointes**

Torsade de pointes is triggered by early afterdepolarizations in a setting of delayed repolarization and increased dispersion of refractoriness. Class IA and class III drugs, which prolong refractoriness (and thus the QT interval) by K+ channel blockade, provide the milieu for torsade de pointes. Drug-induced torsade de pointes is often pause dependent or bradycardia dependent, because the QT interval is longer at slower heart rates and after pauses. Exacerbating factors, such as hypokalemia, hypomagnesemia, and the concomitant use of other QT-prolonging drugs, are particularly important in this type of proarrhythmia.

**Incessant Ventricular Tachycardia**

Incessant ventricular tachycardia may be induced by drugs that markedly slow conduction (class IA and class IC) sufficiently to make the patient’s own ventricular tachycardia continuous. The arrhythmia is generally slower because of the drug effect, but it may become resistant to drugs or cardioversion, with potentially disastrous consequences in the presence of hemodynamic instability. This proarrhythmia is rarely associated with class IB drugs, which affect weaker Na+ channel blockades.

**Extremely Wide Complex Ventricular Rhythm**

Extremely wide complex ventricular rhythm is usually associated with class IC agents, also in the setting of structural heart disease, and has been linked to excessive plasma drug levels or a sudden change in dose. The arrhythmia is not thought to represent a preexisting reentrant tachycardia and easily degenerates to ventricular fibrillation.

**Efficacy and Outcomes of Antiarrhythmic Drug Use**

Suppression of ambient ventricular ectopy by an antiarrhythmic agent does not prevent future life-threatening arrhythmias. In fact, patients effectively treated with class IC agents in the Cardiac Arrhythmia Suppression Trial (CAST) had a greater risk of sudden cardiac death than those who received placebo, a finding that underlines the proarrhythmic potential of these agents. Conversely, beta blockers, agents that typically do not suppress ambient ectopy, appear to reduce the risk of malignant ventricular arrhythmias. A retrospective analysis of the CAST data showed that mortality related to arrhythmias, as well as from all causes, was reduced in patients who received beta blockers. The Electrophysiologic Study versus Electrocardiographic Monitoring (ESVEM) trial compared seven antiarrhythmic drugs and found that the risk of arrhythmia recurrence and cardiac mortality was greater with the class I agents than with sotalol.

As discussed above, patients with a history of myocardial infarction and ventricular arrhythmias have an increased risk of fatal arrhythmias during follow-up. Meta-analysis of 138 trials in-
Patients with a history of sustained monomorphic ventricular tachycardia who require coronary artery bypass grafting and who have a large discrete aneurysm may be considered for endocardial resection. Ideal candidates have well-preserved left ventricular function outside of the aneurysmal segment, which reduces the risk of postoperative congestive heart failure.

Although the transvenous ICD has replaced arrhythmia surgery as the definitive nonpharmacologic intervention for life-threatening ventricular arrhythmias, endocardial resection continues to play a small role for highly selected patients being considered for coronary artery bypass. Because the outcome depends critically on technique, this procedure should be performed only at experienced centers.

catheter ablation of ventricular tachycardia

The therapy of choice for reentrant supraventricular arrhythmias, radiofrequency catheter ablation also has an important role in selected patients with idiopathic ventricular tachycardia and bundle branch reentry, as well as in a subset of patients with ventricular tachycardia resulting from coronary artery disease [see Subsection VII].

The transvenous implantable cardioverter-defibrillator

The ICD automatically detects ventricular tachycardia or fibrillation and terminates the arrhythmia by overdrive pacing, high-energy shocks, or both. Since the first use of an ICD in a human, in 1980, the device has been used in over 100,000 patients worldwide.

All ICD systems contain three elements: the generator, rate-sensing leads, and electrodes to deliver high-energy shocks. In the early ICDs, conventional epicardial screw-in leads were used for rate sensing. Defibrillating shocks were delivered via wire-mesh patch electrodes applied directly to the epicardial surface. The generator was implanted subcutaneously in the abdomen. The implantation procedure required a thoracotomy and was associated with considerable morbidity and a perioperative mortality of 3% to 5%.42

Advances in hardware design have made the implantation procedure dramatically simpler and safer [see Figure 7]. In our institution, the median duration of ICD implantation has been reduced to 50 minutes, and the median postoperative stay is 24 hours. There have been no perioperative deaths in patients undergoing implantation of transvenous ICDs, and the incidence of major complications is less than 2%.43 Comparative results have recently been reported in studies of pectoral ICD implantation.

As with modern pacemakers, the current generation of ICDs are multiprogrammable, microprocessor-based devices capable of automatically detecting ventricular tachycardia or fibrillation on the basis of timing information. The heart rate and duration of a tachycardia episode that will trigger overdrive pacing or shock therapy can be programmed. Additional detection enhancements can be used to reduce the probability that inappropriate pacing or shock will be delivered during episodes of sinus tachycardia or atrial fibrillation that exceed the programmed rate cutoff. The device can also be programmed to initiate therapy only if the heart rate increases abruptly during one cycle and only if the rate variability during the episode is less than a specified amount.

The ICD’s output can also be tailored to suit patients’ individual needs. For patients with a history of primary ventricular fibrillation, the ICD is programmed to deliver high-energy shocks when it detects tachycardia. Patients with a history of stable monomorphic ventricular tachycardia may benefit from overdrive pace ter-

August 1999 Update

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The inability to reproduce the ventricular fibrillation or sustained hypotensive ventricular tachycardia remains a significant challenge and intolerable drug side effects. The originally described Jervell and Lange-Nielsen syndrome, an autosomal recessive disorder with associated deafness, has a male-to-female ratio of 1.06:1. The correct QT interval (QT/RR interval) exceeds 0.47 in children, 0.46 in men, or 0.48 in women. Other depolarization abnormalities are often present in the long QT syndrome. The T wave is flattened and may have a bifid, or double-hump, appearance. In addition, a prominent U wave may be seen. About one third of patients will have a resting heart rate of less than 60 beats/minute.

The Congenital Long QT Syndrome

A familial disorder with distinct clinical features, the congenital long QT syndrome usually presents as syncope (or, in rare instances, as cardiac arrest) during childhood or teenage years, mediated by recurrent bouts of rapid, polymorphic ventricular tachycardia. Many patients are incorrectly diagnosed with a grand mal seizure disorder. Loss of consciousness characteristically occurs with a sudden surge in adrenergic tone caused by abrupt physical, emotional, or auditory stimulation. There is often a family history of unexplained syncope or premature sudden cardiac death.

The hallmark of this disorder is abnormal prolongation of the QT interval on the ECG. Prolongation is present if the heart rate–corrected QT interval (QT/RR interval) exceeds 0.47 in children, 0.46 in men, or 0.48 in women. Other depolarization abnormalities are often present in the long QT syndrome. The T wave is flattened and may have a bifid, or double-hump, appearance. In addition, a prominent U wave may be seen. About one third of patients will have a resting heart rate of less than 60 beats/minute.

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proved to be quite rare. The more common Romano-Ward syndrome is an autosomal dominant disorder and is not associated with hearing loss. The relation between sympathetic activation and arrhythmias led to the hypothesis that an abnormality in cardiac sympathetic innervation was responsible for the syndrome. An alternative theory, for which there is now definitive evidence, postulates a primary defect in the ion channels mediating myocardial depolarization.

Studies of affected families have now defined the disorder’s molecular genetics. Linkage analyses have identified four distinct chromosomal loci associated with the disease. Remarkably, specific mutations have now been characterized at two of these loci. One mutation produces an abnormal sodium channel that has a small, persistent inward current. This inability of the depolarizing channel to completely turn off would be expected to prolong the plateau phase of the action potential and the QT interval. A second mutation produces a defective subunit in a repolarizing potassium channel (I_{Kr}). Dysfunctional or nonfunctional potassium channels would attenuate the outward current that returns the cell to resting potential after depolarization, thereby increasing action potential duration and the QT interval. Of note is that this same potassium channel is blocked by many of the antiarrhythmic drugs that are associated with torsade de points.

Evaluation of a patient with the long QT syndrome should include screening of all first-degree relatives. A careful history regarding unexplained syncope and a 12-lead ECG should be obtained. Although genetic testing of affected families is currently available only for research, it seems likely to become a clinical reality in the near future.

Holter monitoring, which should be performed in these patients, may reveal episodes of nonsustained ventricular tachycardia. Transient severe bradyarrhythmias and T wave alternans are also indicative of electrical instability. Exercise treadmill testing may sometimes be of value; absence of appropriate shortening of the QT interval during effort may help to confirm the diagnosis in questionable cases.

The prognosis for untreated long QT syndrome is poor. More than 50% of affected individuals have experienced loss of consciousness or cardiac arrest by 12 years of age. After the diagnosis has been established, the incidence of recurrent syncope is approximately 5% a year and incidence of sudden death is 1% a year. Prospective studies have identified risk factors for sudden death, which include congenital deafness, a history of syncope, female gender, and ventricular tachycardia during monitoring.

Antiadrenergic intervention with either beta-blocking drugs or surgical sympathectomy is the therapy of choice in the long QT syndrome. Although it has no direct effect on the primary disorder directly, reduction in cardiac sympathetic tone may reduce the amplitude of afterdepolarizations and, in turn, the likelihood that they will reach threshold and produce ventricular ectopy. Any patient or family member with QT prolongation and one or more risk factors should be treated with beta blockade sufficient to blunt the chronotropic response to exercise. For patients with recurrent symptoms or persistent nonsustained ventricular tachycardia despite pharmacologic beta blockade, left thoracic sympathectomy may be useful. The caudal half of the left stellate ganglion and the first four thoracic ganglia are generally removed via a supraclavicular approach. An alternative procedure for patients who fail to respond to beta blockers is permanently cardiac pacing, which may be especially helpful in patients whose ECG shows torsade de points in association with profound bradycardia. Finally, patients with a history of cardiac arrest who have had recurrences despite appropriate therapy or who have multiple risk factors should be considered for an ICD. Again, the device will not alter the natural history of the disorder, so it should be considered an adjunct to antiadrenergic interventions.

References


Acknowledgments
Figures 1, 2, and 7  Joseph Bloch, CMI.
Figures 3 through 6  Marcia Kammerer.