Mechanisms and Risk Factors for Proarrhythmia With Type Ia Compared With Ic Antiarrhythmic Drug Therapy

Joseph H. Levine, MD, Joel Morganroth, MD, and Alan H. Kadish, MD

Antiarrhythmic drugs have been known for many years to commonly aggravate existing arrhythmias and induce new ventricular arrhythmias de novo; however, only recently has the true frequency been recognized. This phenomenon is now termed "proarrhythmia" and has been documented for all antiarrhythmic agents currently in use. Proarrhythmia may involve the creation or exacerbation of supraventricular or ventricular arrhythmias, and this discussion will focus on the latter arrhythmia. A variety of definitions have been applied to "proarrhythmia," and these include an increase in the frequency of premature ventricular contraction and the conversion of nonsustained to sustained ventricular arrhythmias. Two specific syndromes of new, sustained ventricular tachycardia have been described: 1) polymorphic ventricular tachycardia associated with QT interval prolongation and 2) incessant, wide complex tachycardia (Figure 1). The risk factors for the development of those syndromes have been described (Table 1), and their frequency differs with different antiarrhythmic drugs. The mechanisms of proarrhythmia are less well understood. However, the interaction between the basic mechanisms of ventricular arrhythmia and the electrophysiologic actions of antiarrhythmic drugs may help to explain the association of certain syndromes of proarrhythmia with particular classes of antiarrhythmic drugs.

Basic Mechanisms of Arrhythmia

Arrhythmias have been broadly classified into those that arise as a result of abnormal impulse initiation (abnormal automaticity and triggered activity) and those that arise as a result of abnormal impulse conduction (reentry).

Enhanced automaticity may be abnormal. In this case, phase 4 diastolic depolarization leads to abnormal impulse initiation. In Figure 2, panel A, is a schematic of an intracellular action potential recording that exhibits abnormal automaticity. Note the slow phase 4 decay in transmembrane potential that results in the generation of another action potential when threshold voltage (dashed line) is reached. Automaticity may be normal as in the case of normal sinus node function or may be abnormal when caused by myocardial injury, ischemia, catecholamines, or other pharmacologic agents. Antiarrhythmic agents can alter the time course of phase 4 diastolic depolarization or the level of threshold voltage.

Triggered activity is abnormal impulse initiation that results from a preceding impulse. It differs from automaticity in that without this preceding impulse, no electrical activity would occur. Triggered activity results from afterdepolarizations that reach threshold. The afterdepolarizations are secondary depolarizations arising during phase 2 or 3 (early afterdepolarizations) or phase 4 (delayed afterdepolarizations) of the cardiac action potential (Figure 2, Panel B). Delayed afterdepolarizations have been noted in a variety of cardiac tissues exposed to conditions favoring intracellular calcium overload (cardiac glycosides, catecholamines, low extracellular potassium, and hypoxia). Early afterdepolarizations, on the other hand, are present in cardiac tissues under conditions favoring prolongation of repolarization (slow pacing rates, low extracellular potassium, quinidine, barium, and cesium chloride).

Figure 3 is a diagrammatic representation of one type of a reentrant pathway. Although other types of reentry such as the leading circle model as described by Allesie et al have been recognized in recent years, classic reentry as described by Mines involves an anatomic barrier. The stippled portion in Figure 3, Panel B, represents diseased myocardium that exhibits unidirectional block. An impulse traveling from point a to c finds a branching point at...
point b. Under normal conditions, the impulse will travel over both branches, and the impulse will collide at point c (Figure 3, Panel A). When unidirectional block and slow conduction (stippled area) are present, the impulse will block antegrade in the diseased myocardium, travel down the alternative pathway to point c, and then travel slowly retrograde through the diseased pathway (Figure 3, Panel B). If the time delay is sufficient and if the myocardium at point b is no longer refractory, the impulse can reenter the circuit, and a reentrant rhythm could result.

Any of these arrhythmia mechanisms could be responsible for spontaneous and drug-induced arrhythmias. Antiarrhythmic drugs could potentiate an arrhythmia mechanism already existing or create the electrophysiologic substrate for an arrhythmia based on a new mechanism.

**Probable Mechanisms of Ventricular Tachycardia in Humans**

The mechanisms of sustained ventricular tachyarrhythmias have been best studied for those arrhythmias that arise in the setting of chronic ischemic heart disease. The principles in this setting may well apply to other settings in which diseased or scarred myocardium is the substrate for the arrhythmia. Although arrhythmias may be due to abnormal automaticity, triggered activity, or reentry, the available data support a reentrant mechanism for most clinical, sustained ventricular arrhythmias in patients with chronic coronary artery disease. The evidence supporting reentry in this setting is based on 1) the ability to reproducibly initiate and terminate the tachycardia by programmed electrical stimulation, 2) the response of the tachycardia to stimulation, and 3) the results of activation mapping. The substrate for these arrhythmias in humans is not unlike that in canine infarction models; there are similar patterns of behavior of the tachycardia to programmed electrical stimulation and to pharmacologic intervention. In these animal models, the presence of and determinants of slow conduction have been determined, and, in addition, reentry has been confirmed as an arrhythmia mechanism.

### Table 1. Risk Factors for the Development of Sustained Proarrhythmia in Response to Type Ia and Ic Drugs

<table>
<thead>
<tr>
<th>Polymorphic ventricular tachycardia (type Ia drugs)</th>
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<tbody>
<tr>
<td>Increased QT interval</td>
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<tr>
<td>Electrolyte disturbance (↓ K⁺, ↓ Mg²⁺)</td>
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<tr>
<td>Bradycardia/pauses</td>
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<tr>
<td>Congestive heart failure</td>
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<tr>
<td>Incessant, wide complex tachycardia (type Ic drugs)</td>
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<tr>
<td>Sustained ventricular tachycardia (preexisting)</td>
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<tr>
<td>Congestive heart failure</td>
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<td>High dose rate of administering Ic agents</td>
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The same techniques have been applied in humans, and preliminary data suggest the presence of both macroreentrant and microreentrant\textsuperscript{20,21} circuits in hearts of patients with ventricular tachycardia. Thus, most evidence from clinical data in humans and from experimental data on animal models supports reentry as the underlying mechanism for the most clinically occurring ventricular dysrhythmias arising from chronically scarred ventricular tissues.

The goals of antiarrhythmic action in this setting may be twofold. First, if an agent can convert unidirectional to bidirectional block, then the abnormal limb is removed, and reentry can no longer occur. Second, if myocardial refractoriness is lengthened, then the impulse traveling retrograde may find the myocardium at point b (Figure 3) still refractory, and again, reentry can no longer be sustained. Antiarrhythmic agents may convert unidirectional to bidirectional block by depressing myocardial conduction through blockade of sodium channels\textsuperscript{22} (type I antiarrhythmic drugs) or by altering cell-to-cell coupling (amiodarone).\textsuperscript{23} They may affect refractoriness through effects

<table>
<thead>
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<th>TABLE 2. Membrane Effects of Antiarrhythmic Drugs</th>
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<tr>
<td>Antiarrhythmic drug class*</td>
</tr>
<tr>
<td>Ia</td>
</tr>
<tr>
<td>Ib</td>
</tr>
<tr>
<td>Ic</td>
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<tr>
<td>III</td>
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</tbody>
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+, +++, +++ indicate strength of effect.

*Class II (\(\beta\)-blockers) and class IV (calcium channel blockers) have little or no effect on sodium channels.
Potential Mechanisms Underlying Drug-Induced Proarrhythmia Characterized as Torsades de Pointes

Quinidine is the antiarrhythmic agent most commonly implicated in causing proarrhythmia manifesting as polymorphic ventricular tachycardia and torsades de pointes. This clinical type of proarrhythmia, however, has been well described as occurring during the use of other antiarrhythmic agents; specifically, procainamide, disopyramide, and amiodarone. In addition, this clinical syndrome has also been recognized as a complication of treatment with a variety of other agents including antidepressant drugs, psychotropic drugs such as phenothiazines, and other miscellaneous drugs. The proarrhythmic potential of the particular drug may be increased by concomitant electrolyte disturbances, particularly hypokalemia and occasionally hypomagnesemia. A common factor in each case is that use of these agents results in prolongation of action potential duration and in refractoriness at the cellular level. This prolongation of the time course of repolarization results in prolongation of the QT interval (or more precisely, the JT component of the QT interval) on the surface electrocardiogram. Our hypothesis is that this prolongation of repolarization predisposes toward early afterdepolarizations and toward the development of triggered activity at the cellular level that, in turn, is clinically manifest as polymorphic ventricular tachycardia. Direct and indirect evidence exists suggesting that this notion is correct. Furthermore, the clinical manifestations of this type of proarrhythmia are predicted from and are concordant with those of triggered activity mediated by early afterdepolarization.

Indirect evidence supporting this hypothesis comes from in vitro studies of the effect of quinidine on canine myocardium and Purkinje fibers. Quinidine administration is well established to result in prolongation of action potential duration. Recent experimental data suggest that the combination of slow pacing rates, low extracellular potassium, and quinidine results in the genesis of early afterdepolarizations and triggered activity in canine Purkinje fibers in vitro. It has also been demonstrated that other agents, such as cesium, that prolong repolarization through potassium channel blockade may lead to an acquired prolonged QT syndrome and torsades de pointes in vivo. Early afterdepolarizations have been identified in this setting and have been implicated in the genesis of the arrhythmias, including torsades de pointes. These findings have been recently extended to humans. Alterations in repolarization consistent in configuration and characteristics with early afterdepolarizations have been recorded from the ventricles of patients during drug-induced polymorphic ventricular tachycardia and have been associated with the genesis of arrhythmias in these patients.

If this hypothesis is correct, there should be a concordance of the clinical manifestations of drug-induced polymorphic ventricular tachycardia and the characteristics of triggered activity mediated by early afterdepolarization. These relations are shown in Table 3. As noted, conditions favoring prolongation of repolarization (slow pacing or slow heart rates), hypokalemia, hypomagnesemia, or increased calcium channel activity (by calcium channel agonists and catecholamines) may lead to early afterdepolarizations and triggered activity in vitro. These same factors are associated with exacerbation of drug-induced polymorphic ventricular tachycardia in patients. Specifically, bradycardia, a long-short initiation sequence, and electrolyte abnormalities are known risk factors for the development of drug-induced polymorphic ventricular tachycardia in patients. In addition, antiarrhythmic agents associated with prolongation of repolarization and the QT interval should be most commonly associated with this type of proarrhythmic response. This is, in fact, what has been seen clinically; that is, use of type Ia antiarrhythmic agents (quinidine, procainamide, and disopyramide) and amiodarone are most commonly associated with drug-induced polymorphic ventricular tachycardia. On the other hand, this type of proarrhythmia is uncommon during use of type Ib and Ic antiarrhythmic agents, which do not lead to significant prolongation of repolarization or the QT interval. Conversely, elevated magnesium and fast pacing rates, which are associated with suppression of early afterdepolarizations and triggered activity in vitro and in vivo, have been found to ameliorate drug-induced polymorphic ventricular tachycardia in patients, and these form the cornerstones of supportive therapy for this type of proarrhythmia. In addition, patients prone to drug-induced torsades de pointes may have a greater predisposition toward
repolarization abnormalities. Preliminary clinical data further indicate that patients exhibiting type Ia proarrhythmia manifest as polymorphic ventricular tachycardia may have a defect in myocardial repolarization that may represent a form fruste or latent form of the long QT syndrome.\textsuperscript{48} Several factors affecting repolarization, therefore, may coexist and may be additive in leading to this type of proarrhythmia. In summary, the clinical features of polymorphic ventricular tachycardia induced by type Ia agents are consistent with those expected of an arrhythmia due to triggered activity mediated by early afterdepolarizations.

**Potential Mechanisms of Proarrhythmia Manifest as Incessant, Monomorphic, Wide Complex, Ventricular Tachycardia**

The mechanisms that form the basis for proarrhythmia manifest as incessant, wide complex, monomorphic, complex ventricular tachycardia are less well understood. Our hypothesis is that incessant, monomorphic, wide complex ventricular tachycardia is caused by incessant reentry and that the clinical manifestations of this type of proarrhythmia can be predicted from the basic electrophysiologic mechanism. Although incessant tachycardias could be automatic in origin, the origin of at least one type of incessant tachycardia—the permanent form of functional reciprocating tachycardia—has been shown to be reentrant.\textsuperscript{49} As noted, reentrant tachyarrhythmias require the proper balance of slow conduction and refactoriness to allow them to be sustained (Figure 3). The subendocardial and lateral borders of infarctions may have surviving cells interspersed with areas of fibrosis in which slow conduction may be present.\textsuperscript{18} In patients with spontaneous ventricular tachycardia, many such areas of potential reentrant circuits may exist because there is often a large border zone between normal and infarcted myocardium; in fact, many patients manifest several patterns of ventricular tachycardia that may arise from several foci.\textsuperscript{50} In some cases, these potential reentrant circuits may not exhibit enough conduction delay in the slow conducting limb to cause a sufficient time delay to allow the normal myocardium (point b in Figure 3) to recover excitation and sustain a reentrant circuit.

All type I antiarrhythmic drugs possess sodium channel blocking characteristics and, in turn, depress myocardial conduction. In addition to exerting effects on manifest reentrant circuits, these drugs may also affect the potential reentrant circuits at the diseased or scarred limb of myocardium where insufficient conduction delay is present to allow reentry to sustain. In this case, sodium channel blockade may result in one of three effects: 1) to depress conduction sufficiently to result in bidirectional block, 2) to only minimally depress conduction and, hence, not potentiating reentry, or 3) to depress conduction in the abnormal, scarred myocardium sufficiently to allow the normal myocardium (point b in Figure 3) to recover its excitability and thereby favor reentry. This third possibility would convert a potential reentrant circuit into a manifest one. Frame and Rhee\textsuperscript{51} recently showed in an in vitro model that single premature ventricular beats often fail to sustain reentry because an inadequate degree of slow conduction is present to allow recovery of tissue excitability at the site of unidirectional block.\textsuperscript{51} Drugs that produce marked slowing of conduction such as type Ic agents may potentiate reentry in this model. Drugs that prolong repolarization and slow conduction (type Ia agents) may counteract this proarrhythmic effect by lengthening refractoriness sufficiently to block even a more slowly conducting impulse. Inherent in this scheme is the hypothesis that unidirectional block, a second requirement for reentrant pathways, is also present. This block may be due to nonuniform recovery of excitability in the presence of premature beats, anatomic factors in the healed infarct, depressed conduction in marginal areas caused by sodium channel blocking drugs, or concealed retrograde penetration of one limb of the reentrant circuit caused by spontaneous or drug-induced slowing of conduction.

The mechanisms proposed for incessant, monomorphic, wide complex ventricular tachycardia are consistent with the clinical syndrome in humans. If conduction delay resulting in potentiation of reentry is the mechanism underlying the incessant tachycardia form of proarrhythmia, then drugs that have a large degree of sodium channel blockade but that have minimal effects on action potential duration and refractoriness should be the agents most likely to result in incessant reentry. This is, in fact, the case clinically. Although all agents have been associated with proarrhythmia manifested as incessant monomorphic ventricular tachycardia, the class Ic drugs (encainide and flecainide) are, by far, the most commonly implicated.\textsuperscript{6,7,52} These agents are the most potent sodium channel blockers, but they only minimally affect action potential duration and, in turn, the JT interval and refractoriness.\textsuperscript{26} Type Ia agents (quinidine, procainamide, and disopyramide), on the other hand, are less potent sodium channel blockers and also lead to prolongation of action potential duration and refractoriness; therefore, these agents, which lead to a more balanced prolongation of conduction time and refractoriness, should be less likely to result in potentiation of reentry and, in fact, are much less commonly implicated in this type of proarrhythmia. Finally, the class Ib agents (lidocaine, tocainide, and mexiletine), which are the least potent sodium channel blockers, should and, in fact, clinically have the least potential to cause incessant, monomorphic, wide complex ventricular tachycardia as a proarrhythmic response.\textsuperscript{4}

A second characteristic of this type of proarrhythmia is also explained by the proposed mechanism. Incessant, monomorphic, wide complex ventricular tachycardia occurs most frequently in patients who have a history of ventricular tachycardia that arises from a structurally abnormal heart. On the other
hand, this type of proarrhythmic response is unusual in the absence of structural heart disease.\textsuperscript{52,53} If incessant reentry due to converting potential reentrant into reentrant circuits is the mechanism for incessant, monomorphic, wide complex tachycardia, then the more potential reentrant circuits that are present, the greater will be the chance of proarrhythmia. This is what is noted clinically. Conversely, our proposed mechanism of triggered activity mediated by early afterdepolarization for polymorphic ventricular tachycardia induced by type Ia agents, is not dependent on the presence of potential reentrant circuits or on a maximal interface of normal and scarred myocardium and, as such, is consistent with the finding of this type of proarrhythmia even in the subgroup of patients without structural heart disease. Although there may be some association between left ventricular dysfunction and proarrhythmia induced by type Ia agents,\textsuperscript{54} several reports describe torsade de pointes in patients with relatively normal ejection fractions.\textsuperscript{28,54}

Incessant reentry also may explain the response to various interventions of proarrhythmia associated with type Ic antiarrhythmic drug use manifested as incessant, monomorphic, wide complex tachycardia. Neither defibrillation nor overdrive would be expected to have an effect because the tachycardias would likely recur immediately. Clinically, this type of proarrhythmia is generally resistant to these maneuvers and usually persists until the particular inciting drug is cleared.

Summary

Proarrhythmia defined as the exacerbation of existing arrhythmias or the genesis of new arrhythmias de novo may result from any antiarrhythmic agent. The two general clinical syndromes of sustained arrhythmias that result appear to have distinct clinical properties that are consistent with the proposed basic mechanisms of arrhythmogenesis. Torsades de pointes occurs most commonly in association with administration of type Ia antiarrhythmic agents and has characteristics most consistent with triggered activity mediated by early afterdepolarization. Conversely, incessant, sustained, monomorphic, wide complex ventricular tachycardia occurs most commonly in association with type Ic antiarrhythmic agents and has characteristics most consistent with incessant reentry. These general subdivisions are probably oversimplified, and in fact, much overlap likely exists. In addition, these proposed mechanisms may not apply to other forms of proarrhythmia such as an increased frequency of isolated ventricular premature couplets or repetitive forms. Furthermore, proarrhythmia may also occur during treatment of supraventricular arrhythmias; although some of these described syndromes are consistent with incessant reentry, the clinical syndromes are not sufficiently defined to better characterize potential mechanisms. Further investigation, therefore, is needed to better define the mechanisms in question, but the mechanisms proposed in this article help to provide a rational approach toward understanding and dealing with clinical proarrhythmia.

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References

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