Journal of Toxicology: Clinical Toxicology

ISSN: 0731-3810 (Print) (Online) Journal homepage: http://www.tandfonline.com/loi/ictx19

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**To cite this article:** Lewis S. Nelson (2002) Toxicologic Myocardial Sensitization, Journal of Toxicology: Clinical Toxicology, 40:7, 867-879, DOI: 10.1081/CLT-120016958

**To link to this article:** http://dx.doi.org/10.1081/CLT-120016958

Published online: 26 Nov 2002.

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Journal of Toxicology
CLINICAL TOXICOLOGY
Vol. 40, No. 7, pp. 867–879, 2002

ARTICLE

# Toxicologic Myocardial Sensitization*

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**ABSTRACT**

*Drug-induced polymorphic ventricular tachycardia (torsades de pointes) may lead to syncope or sudden cardiac death. One mechanism by which drugs and toxins may predispose to the development of this malignant dysrhythmia is through their ability to produce myocardial sensitization. The concept of myocardial sensitization actually represents a series of events involving altered cellular repolarization produced by blockade of myocardial potassium channels. Altered potassium ion flow raises the likelihood that an ectopic beat will occur via an early afterdepolarization and simultaneously alters the myocardial tissue to make it favorable for reentrant dysrhythmias, such as torsades de pointes, to propagate. Alternatively, calcium overload of the myocyte produces ectopy by causing delayed afterdepolarizations, which if the substrate for reentry is present, will result in ventricular tachycardia. This paper discusses the mechanisms underlying the production of both the altered myocardial substrate and the afterdepolarizations.*

***Key Words:*** *Torsades de pointes; Dysrhythmia (drug-induced dysrhythmia); Potassium channel; Afterdepolarization*

## INTRODUCTION

The rhythmic activity of the heart is the earliest sign of fetal development. From the time of its first beat, the heart beats flawlessly about 37 million times annually. Fortunately, in the vast majority of people the heart performs this way throughout life. Occasionally, the complex electrochemical system that is responsible for cardiac contraction misfires, resulting in ectopy or the formation of a dysrhythmia. These dysrhythmias may be

*Presented at the 2001 American Board of Applied Toxicology Symposium at the North American Congress of Clinical Toxicology, Montreal, Canada.



DOI: 10.1081/CLT-120016958
0731-3810 (Print); 1097-9875 (Online)

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imperceptible to the individual or may, result in palpitations, dizziness, or syncope. Rarely, the failure of a consequential dysrhythmia to terminate may result in sudden cardiac death.

Most cardiac dysrhythmias occur in patients with underlying structural heart disease, particularly ischemic disease. In a young healthy population sudden cardiac death is statistically a rare occurrence, a large number of cases in absolute terms occur annually.[1] Given the frequent inability to identify a structural cause for their sudden dysrhythmic death, it is likely that a proportion of these deaths are drug-induced.[2]

The concept of drug-induced syncope and death were first recognized in the 1920s in patients taking therapeutic doses of quinidine.[3] However, the link between syncope and cardiac dysrhythmias waited more than 40 years.[4] Several well-intended studies, most prominently the Cardiac Arrhythmia Suppression Trial (CAST), noted that sudden cardiac death with antidysrhythmic therapy was higher than occurred in a control population, suggesting consequential prodysrhythmic effect of certain drugs.[5] Over the past decade several prominent drugs have had warnings affixed to their package inserts or were removed from the market entirely due to their propensity to cause potentially lethal cardiac dysrhythmias, particularly torsades de pointes (Table 1). In several circumstances, years passed before the connection was made between the use of a specific drug and the development of dysrhythmia. In contrast with the CAST, and of particular concern, was that these drugs were primarily indicated for nonlife-threatening, noncardiac conditions.

Ventricular fibrillation is probably the final common pathway of most sudden cardiac death, but rhythm disturbances may begin with monomorphic or polymorphic ventricular tachycardia. Torsades de pointes, a rhythm formally described in 1966 but recognized well before, is a form of polymorphic ventricular tachycardia that is identified electrocardiographically by the changing amplitude and direction of the QRS complex as it rotates about the isoelectric line. Because the rhythm is sudden in onset and nonperfusing, it typically produces syncope without a prodrome. Fortunately, due to the tendency of this rhythm to remit spontaneously, most patients suffer only syncope. Under conditions in which torsades de pointes does not terminate, however, degeneration into ventricular tachycardia and fibrillation is likely to occur.

***Table 1***

*Some Drugs Reported to Either Prolong the QT Interval or Produce Torsades de Pointes*

| |
|---|
| Antidepressants: |
| Tricyclics: amitriptyline, desipramine, doxepin, imipramine, |
| Nontricyclics: venlafaxine |
| Antidysrhythmics: |
| Type Ia: disopyramide, procainamide, quinidine |
| Other: amiodarone, dofetilide, flecainide, ibutilide, sotalol |
| Antihistamines: astemizole, terfenadine |
| Arsenic trioxide (Trisenox) |
| Antipyschotics: |
| 1st generation: chlorpromazine, mesoridazine, thioridazine |
| Butyrophenones: droperidol, haloperidol |
| Atypicals: quetiapine, risperidone, ziprasidone |
| Cisapride |
| Erythromycin |
| Fluoroquinolones: gatifloxin, grepafloxacin, levofloxacin, |
| moxifloxacin |
| Foscarnet |
| Levomethadyl (α-L-acetylmethadol, LAAM) |
| Pentamidine |
| Tacrolimus |
| Tamoxifen |
| Trimethoprim/sulfamethoxazole |
| Triptans: naratriptan, sumatriptan, zolmitriptan |

Not every drug is included; the association for some of the drugs cited remain unproved. Several have been removed from sale, had dispensing restrictions imposed, or had a boxed or bolded warning affixed. See the following websites for a more complete list of drugs associated with QT prolongation (www.qtdrugs.org) or torsade de pointes (www.torsade.org). Also visit the website of the FDA (www.fda.gov) for current warnings and information.

## INTRODUCTION TO MYOCARDIAL SENSITIZATION

Whether due to underlying structural heart disease or drug-induced functional heart disease several pathophysiologic abnormalities must occur simultaneously to result in ventricular tachycardia. Thus, a single abnormality is insufficient to produce a dysrhythmia but rather it renders the heart "sensitized," awaiting a second process to occur concomitantly and thereby initiate the life-threatening dysrhythmia (Fig. 1).

Historically, the toxicologic concept of myocardial sensitization is most closely associated with halogenated hydrocarbons. However, as the understanding of cardiac electrophysiology expands, it is apparent that many drugs and toxins share common mechanisms through which they sensitize the heart and induce dysrhythmias. This distinction likely relates to the situational nature of hydrocarbon-induced dysrhythmias (i.e., physical exertion or excitation shortly following drug use) compared to the apparently unprompted dysrhythmias following

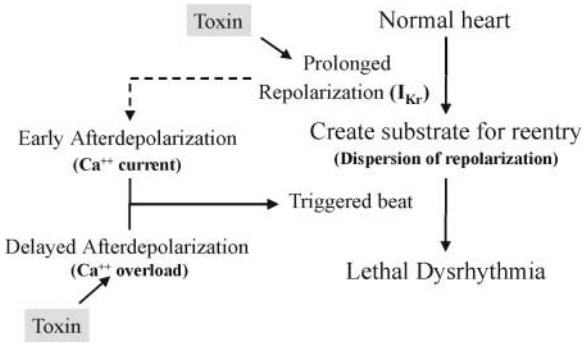


**Figure 1.** The concept of pharmacologic myocardial sensitization. Toxins or drugs may sensitize the heart by prolonging repolarization, most commonly by blocking the potassium current $I_{Kr}$. This creates a substrate for a reentrant dysrhythmia, such as torsade de pointes, which may occur following an appropriate trigger. The trigger is frequently an early or a late afterdepolarization, which may also develop due to exposure to toxins or drugs.

most myocardial sensitizing drugs. The term sensitized is used herein to suggest a heart—both prone to spontaneous discharge (e.g., triggered beat) and having the ability to propagate the discharge (e.g., favorable substrate for reentry). This paper focuses on the concept of myocardial sensitization as it occurs in most cases of drug-induced dysrhythmia. The normal physiology is reviewed and the focus of the remainder of the work is on drugs and toxins that affect the QTc interval and their clinical consequences.

## NORMAL ELECTROPHYSIOLOGY

### Depolarization

Under normal conditions, an impulse, generated by the sinoatrial (SA) node, is carried through the ventricular myocardium by the fast conducting tissue of the His-Purkinje system. Within the ventricular myocardium, intercellular connections activate cells locally allowing rapid and near simultaneous depolarization and contraction of the entire heart.

The initial step in cellular depolarization is the opening of fast $Na^+$ channels from their resting state, which allows the rapid influx of $Na^+$ ions down their concentration gradient (Fig. 2A). This raises the intracellular potential, from its resting level near $-90$ mV to peak at $+30$ mV. After a brief period of time the fast $Na^+$ channels assume an inactivated conformation, a state from which they cannot be reopened, although a small persistent inward $Na^+$ current continues through a slowly inactivating subset of $Na^+$ channels. This inactivation of the fast $Na^+$ channels accounts for the absolute refractory period of the myocyte, a time during which the cell cannot be depolarized again. Over time, and with cellular repolarization, the $Na^+$ channels progressively transform back to their resting state, from which reactivation is possible. During the transition to the resting state, when a sufficient subset of $Na^+$ channels have regained the resting conformation, the myocyte enters a relative refractory period (Fig. 3). During this period a larger-than-normal stimulus, needed to open a greater proportion of available $Na^+$ channels than normally required, can induce a cellular depolarization.

### Plateau

As the upstroke of the action potential depolarizes the cell past $-40$ mV, L-type voltage-gated $Ca^{2+}$ channels are activated, as are voltage-gated outward potassium channels (Fig. 2B). The competing effects of the inward $Ca^{2+}$ current and the outward $K^+$ current through $I_{Kr}$ maintain cellular depolarization for a prolonged period of time, visible as the plateau of the action potential. This plateau is unique to cardiac myocytes and is not present in other excitable cells such as neurons. It most likely exists in myocytes to allow time for cellular contraction.

### Contraction

Myocyte contraction is $Ca^{2+}$ dependent; that is, $Ca^{2+}$ interacts with troponin and liberates its inhibition of actin allowing progressive actin/myosin overlap to rapidly shorten the cell. The sarcoplasmic reticulum is the organelle that both harbors the intracellular $Ca^{2+}$ between contractions and releases it upon myocyte depolarization in the process known as excitation–contraction coupling. Release of sarcoplasmic $Ca^{2+}$ is itself $Ca^{2+}$ dependent (i.e., $Ca^{2+}$-induced $Ca^{2+}$ release). Specifically, influx of $Ca^{2+}$ through the L-type $Ca^{2+}$ channel during depolarization and the plateau phases triggers the dose-dependent release of sarcoplasmic $Ca^{2+}$ through interactions with $Ca^{2+}$ release channels on the sarcoplasmic reticulum, known as ryanodine receptors.

### Repolarization

Repolarization, or return of the transmembrane potential towards $-90$ mV, occurs during phase 3 of the action potential (Fig. 2E). During this period, inward

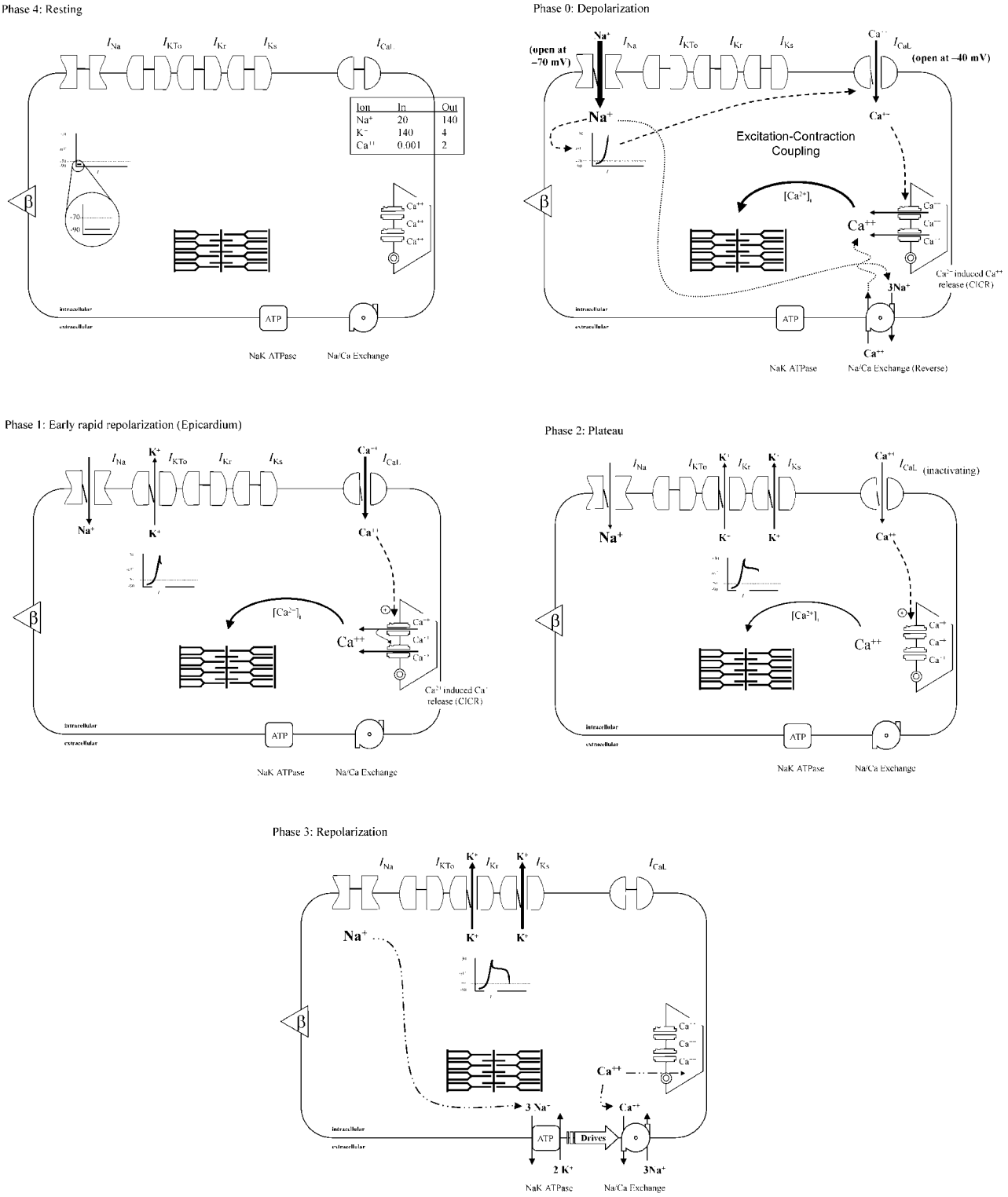


**Figure 2.** Electrophysiology of ventricular myocardial or Purkinje cells. See text for details.

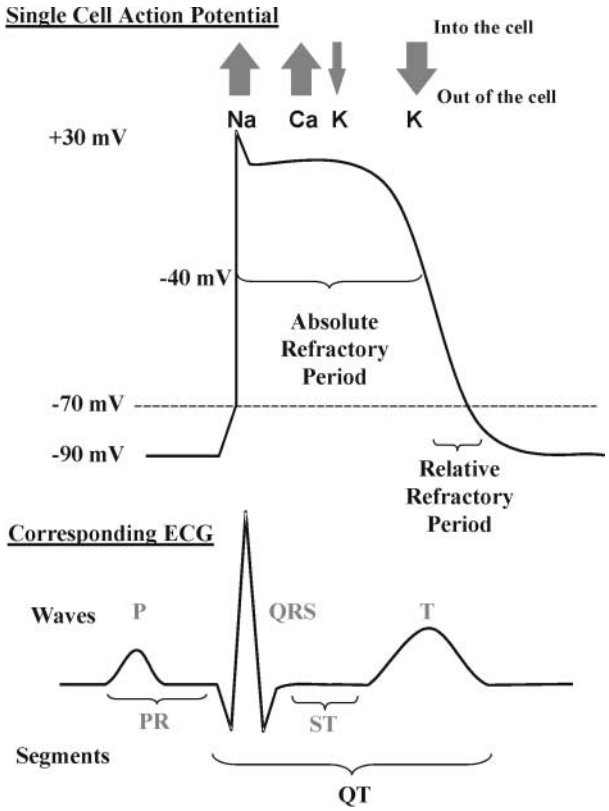


**Figure 3.** Relationship of ventricular myocyte or purkinje cell action potential to the waveform identified on the electrocardiogram. The approximate locations of the refractory periods are noted.

$Ca^{2+}$ flow slows as the L-type $Ca^{2+}$ channel inactivates (in a time and voltage-dependent manner) and flow through $I_{Kr}$ continues unabated. Furthermore, three intracellular $Na^+$ ions are electrogenically pumped against their gradients via the $Na^+/K^+$ ATPase in exchange for two extracellular $K^+$ ions. Simultaneously, intracellular $Ca^{2+}$ is both actively pumped into the sarcoplasmic reticulum and electrogenically exchanged with extracellular $Na^+$ in a 3:1 molar ratio, or a 3:2 charge ratio. Although the characteristics of cellular depolarization appear to be nearly identical between all ventricular myocardial cells, repolarization normally varies regionally throughout the heart. The variability exists because of the different circumstances under which different cells must function. As an example of the need for nonuniform repolarization, the endocardial cells contract for the longest period of time, and must therefore repolarize more slowly than the epicardial cells. It is thus apparent that this nonuniformity is necessary for the normal functioning of the heart. This regional difference in repolarization, also termed nonuniform refractoriness or the dispersion of repolarization, is measured on the ECG as the QT dispersion, or the difference between the longest and shortest QT durations. There is a normal dispersion of repolarization, and its alteration in either direction may prove clinically consequential as detailed below.[6]

## ABNORMAL ELECTROPHYSIOLOGY: ACTION POTENTIAL DURATION PROLONGATION

Under normal conditions, depolarization, plateau, and repolarization require about 300 milliseconds, but when conditions prolong the duration of repolarization, a long QT syndrome (LQTS) develops. Physiologically, bradycardia prolongs the action potential duration, while tachycardia shortens it. Action potential duration prolongation, as described below, may provide either the substrate for reentry or induce a triggered beat, or both, which potentially results in ventricular tachycardia. Drug-induced prolongation of the ventricular action potential and QT duration may occur through two predominant mechanisms: delayed inactivation of $Na^+$ channels and $K^+$ channel blockade.

### Delayed Inactivation of $Na^+$ Channels

Prevention of closure of the myocardial $Na^+$ channels results in a persistent inward depolarizing current. Typically, the less substantial delayed inward $Na^+$ component fails to inactivate, as persistent activation of the fast inward $Na^+$ current is incompatible with life. By loading the myocyte with excessive $Na^+$, repolarization of the cell by $Na^+/K^+$ ATPase is delayed while the additional $Na^+$ is actively excreted. Drugs and toxins that prolong the QT through this manner include aconitine, from *Aconitum* sp. (monkshood)[7] and grayanotoxin, from plants of the Rhododendron family. The antidysrhythmic agent ibutilide has as its primary mechanism, the ability to delay the inactivation of cardiac $Na^+$ channels, an effect that accounts for the high rate of ibutilide-associated dysrhythmias. A congenital LQTS (known as LQT3), due to a gain-of-function alteration in the $Na^+$ channel caused by mutation in the gene SCN5A, results in early childhood death from ventricular dysrhythmias.[8]

### Potassium Channel Blockade

Because of their logical role in myocyte function, sodium and calcium channel functions are not difficult to conceptualize. However, the electrophysiologic roles of the various potassium channels are less intuitive. There are three general types of myocardial potassium channels:[9] (1) an inwardly rectifying current,* which flows through $I_{K1}$, maintains the normal resting potential at $-90$ mV; (2) a rapidly inactivating, or transient, potassium channel ($I_{to}$) that facilitates initial repolarization of the cell, thus creating the notch in the action potential (Fig. 2C). The distribution and function of these channels is not uniform across the myocardium, which accounts for the different shapes of the action potentials of the epicardial and endocardial cells (Fig. 4);[10] (3) the delayed rectifier channels ($I_K$), which can be divided into two distinct populations: rapid ($I_{Kr}$) and slow ($I_{Ks}$). $I_{Kr}$ is the current most frequently implicated in drug-induced myocardial sensitization.

$I_{Kr}$ represents the current carried by the channel expressed by the human ether-a-go-go related gene (HERG). HERG actually encodes the α-subunit and the coalescence of four α-subunits creates a channel with a large hydrophobic cavity.[11–13] The spaciousness and hydrophobicity of this pore may explain why $I_{Kr}$ is the target of so many diverse agents; the channel has been termed "promiscuous" for this reason.[14,15] Furthermore, its paradoxical inactivation under conditions of low extracellular $K^+$, which should theoretically increase the outward driving force for $K^+$ and shorten the QT, explains why hypokalemia prolongs the QT interval and increases the risk of torsades de pointes. Drug-induced inhibition of $I_{Kr}$ represents an iatrogenic version of the inherited abnormality in the HERG gene that is responsible for the congenital long QT syndrome (LQT2). This syndrome is associated with dysrhythmias during times of emotional stress, and has an interesting predilection to be triggered by auditory stimuli.[16] This latter effect may in some way relate to the fact that a gene product identical to $I_{Kr}$ is involved in hearing, also explaining the association of LQT2 with congenital deafness.[17]

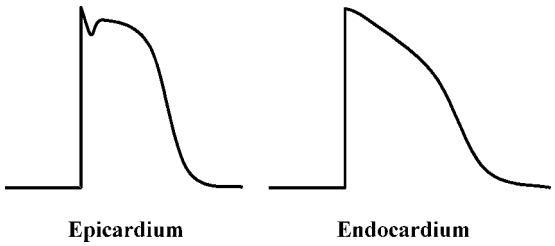


**Figure 4.** Schematic comparison of the action potentials expected in epicardial and endocardial myocytes. The differences in the pattern and duration of repolarization are important factors in the production of myocardial sensitization by drugs and toxins. Adapted from Ref. [10].

### $Na^+$ Channel Blockers

It is noteworthy that prolongation of depolarization, as occurs following overdose of sodium channel blocking drugs (e.g., tricyclic antidepressant), is a common toxicologic cause of electrocardiographic QT prolongation. However, while in most of these patients the QT prolongation represents QRS prolongation, at high doses drug-induced blockade of $I_{Kr}$ may also occur.[18] Furthermore, as with other pharmacologic agents, inhibition of sodium current may introduce increased heterogeneity in the overall action potential configuration, leading to dysrhythmia formation.[19] This effect may in fact be involved with the increased risk of sudden cardiac death noted in CAST with the use of encainide and flecainide.[5] That is, under the drug-induced conditions favorable to reentry, an ischemic event may be the trigger for sudden cardiac death, turning a nonlife-threatening event into a lethal one (see below).[20] Interestingly, a recently defined genetic abnormality of the $Na^+$ channel, the Brugada syndrome, imparts the risk of sudden cardiac death following $Na^+$ channel blockade.[21,22]

### Sequelae of Prolonged Repolarization

There are two important sequelae of the prolonged duration of the action potential: (1) the dispersion of repolarization increases (providing the substrate for reentry) and (2) afterdepolarizations develop (which produce triggered beats). In fact, it is the simultaneous occurrence of these two events that ultimately accounts for the development of ventricular dysrhythmias. Interestingly, although both of these effects may also occur independently, prolongation of the action potential provides a unifying basis for many drug-induced dysrhythmias.

*Rectification is the property of changing conductance with changes in voltage. Specifically, inward rectification suggests that ion conduction increases through a channel as the cellular potential becomes more negative, or during hyperpolarization.

## Dispersion of Repolarization

As mentioned earlier, repolarization is not normally uniform across the myocardium but rather is predictably heterogeneous. Prolongation of repolarization by an identical amount in all myocardial tissue would not increase the dispersion of repolarization and therefore would not, in theory, be dysrhythmogenic. However, drugs and toxins typically increase the dispersion of repolarization nonuniformly across the myocardium.[23] This likely relates to the varying ion channel compositions of cells within the different myocardial layers and the dissimilar effects of agents on these ion channels. The increased dispersion of repolarization, through the production of conduction blocks and other abnormal conduction pathways, produces the substrate for reentry.[24,25] Reentry, or the circus movement of electrical impulses within the myocardium, is critical to the production of tachydysrhythmias.

A vast array of halogenated hydrocarbons can experimentally induce cardiac dysrhythmias.[26] Additionally, there is clear clinical evidence of a similar in humans. During the 1960s there were epidemic deaths of children from "sniffing glue" or other means of hydrocarbon inebriation[27] and such deaths continue to occur today. Similarly, in a study of outpatient anesthesia, the risk in children of dysrhythmia formation was substantial when halothane, a halogenated hydrocarbon, was used as the anesthetic agent.[28] Interestingly, the use of a related agent, sevoflurane, was associated with significantly less cardiotoxicity.[28] In support of their role in sudden sniffing death, volatile hydrocarbons variably increase both QT duration[29] and dispersion[30] in healthy patients undergoing inhalational anesthesia for noncardiac procedures. Although animal models have documented their occurrence for decades and inhalational hydrocarbons are a common means by which to induce experimental dysrhythmias,[31,32] only recently has a unifying mechanism become evident. Since it is unlikely that there is a specific receptor capable of binding so many structurally different molecules, it is expected that the effect is due to the physicochemical properties of the class of agents.[33] Most implicated hydrocarbons are hydrophobic (e.g., aromatic or halogenated) and the common hydrophilic hydrocarbons, such as ethanol, do not share their dysrhythmic propensity. The promiscuity of the $I_{Kr}$ channel for various blocking drugs and toxins likely relates specifically to the aromatic hydrophobic lining of its S6 domain[15,34] and the large size of the channel vestibule.[13]

The link between the dispersion of repolarization induced by these agents and the development of life-threatening dysrhythmias is the related occurrence of afterdepolarizations, which may be either early or delayed (see below). Thus, in the before-mentioned study of pediatric dental anesthesia nearly all dysrhythmias occurred during tooth extraction or emergence, periods when circulating catecholamines, which produce delayed afterdepolarizations, were likely to be greatest.[28] Similarly, exogenous epinephrine is often administered to produce dysrhythmias in experimental models of halogenated hydrocarbon sensitization.[35]

## Triggered Activity: Afterdepolarizations

Early afterdepolarizations (EAD) are oscillations in the membrane potential that occur either toward the end of the plateau phase or during repolarization of an action potential. They are more readily induced in cells of the His-Purkinje system although other myocardial cells may also be capable of developing afterdepolarization. This may be particularly true for cells of the mid-myocardial layer, or M cells, due to their more marked sensitivity than other myocardial cells to QT prolonging agents.[36,37] It is suggested that, given their substantial mass compared with the His-Purkinje cells, that EADs in the M cells account for the electrocardiographic U wave often noted in patients with QT prolongation.[38]

Drug-induced blockade of $I_{Kr}$, by prolonging repolarization, provides the foundation for EAD formation (Fig. 5). Since prolonged repolarization is associated with more gradual repolarization than normal, the membrane potential remains at any given electrical potential for a longer period of time. For the L-type $Ca^{2+}$ channels, which also undergo time-dependent conversion to the resting state, the prolongation of repolarization allows these same channels to reacquire the resting state. If a sufficient proportion of L-type $Ca^{2+}$ channels convert to their resting state while the cellular potential remains within an appropriate range, these channels may reopen.[39] Entry of $Ca^{2+}$ via these reopened $Ca^{2+}$ channels produce an EAD, and the subsequent depolarization of the myocyte membrane, if of sufficient magnitude, can produce a conducted beat, or a premature ventricular contraction (PVC). The importance of the $Ca^{2+}$ channel in the ultimate production of EADs is highlighted by amiodarone. Although amiodarone, a class III antidysrhythmic agent, dramatically prolongs the action potential duration, unlike other class III drugs, it is rarely associated with the production of EADs and ventricular dysrhythmias. This paradoxical effect is

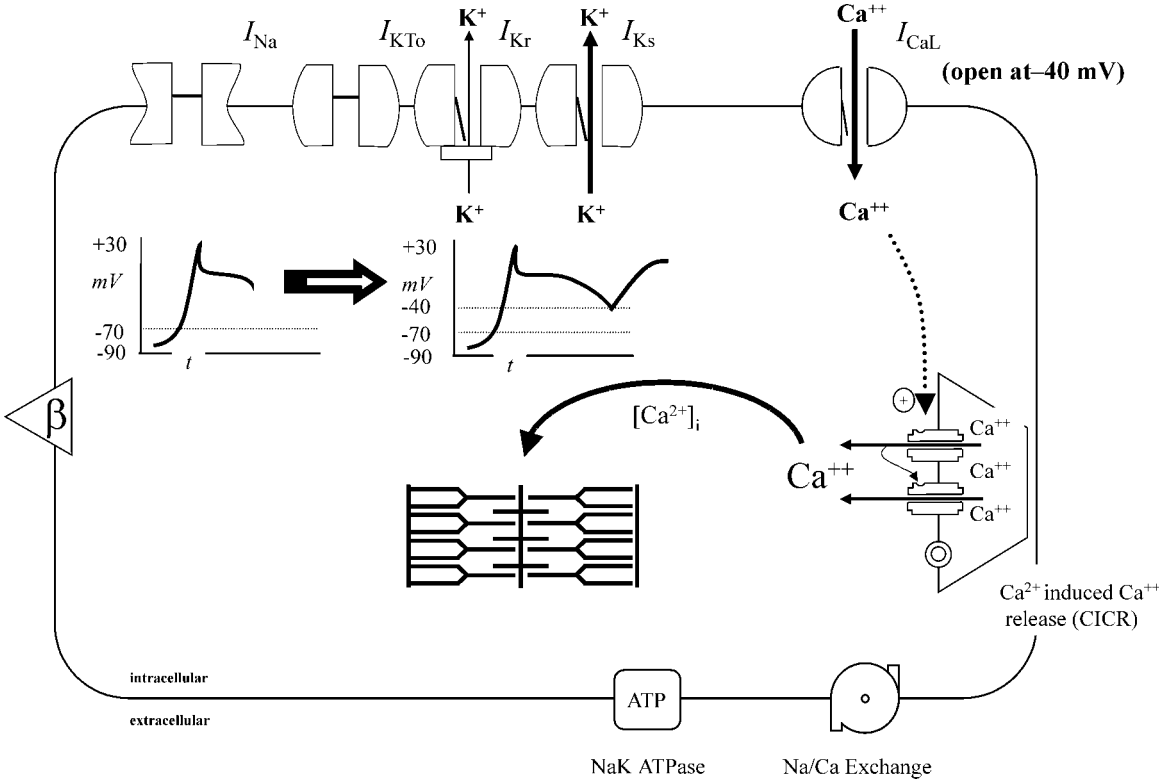


**Figure 5.** The mechanism of drug-induced blockade of $I_{Kr}$ producing an early afterdepolarization. See text for complete explanation.

explained by the complex receptor pharmacology of the drug, specifically its blockade of the L-type $Ca^{2+}$ channel[40] and its relatively favorable effects on the uniform dispersion of repolarization.[41] Similarly, the importance of $I_{Kr}$ to this process is highlighted by a model in which experimental overexpression of HERG ($I_{Kr}$) channels prevents EAD formation by speeding repolarization.[42]

In most cases, prior to the onset of a malignant dysrhythmia there is a short–long cardiac cycle, generally the result of a brief bigeminal rhythm, caused by an EAD (i.e., a PVC coupled to a sinus beat).[43] This abnormal beat propagates in regions with normal action potentials but is inhibited in regions with prolonged action potential duration and thus extinguishes (n.b. this same effect forms the basis for the antidysrhythmic effects of drugs). When the substrate is properly prepared for reentry (i.e., increased dispersion of repolarization), the PVC becomes the trigger for ventricular tachycardia. This is commonly referred to as the "R on T" phenomenon.

Delayed afterdepolarizations (DAD) are oscillations in the membrane potential that occur after the completion of cellular repolarization. If the oscillation depolarizes the cell sufficiently to reach threshold potential, rapid and complete cellular depolarization occurs. The ionic basis of delayed afterdepolarizations appears to be spontaneous release of $Ca^{2+}$ from an overloaded sarcoplasmic reticulum (Fig. 6); that is, the presence of excess $Ca^{2+}$ during repolarization results in the stimulated release of sarcoplasmic $Ca^{2+}$ through effects on the ryanodine receptor, analogous to $Ca^{2+}$-induced $Ca^{2+}$ release. However, this per se, does not account for the afterdepolarization, since charge in this case is merely being shifted between two intracellular compartments. Rather, the elevated intracellular $Ca^{2+}$ concentration activates an inward current through the $Na^+/Ca^{2+}$ exchange mechanism described earlier. This electrogenic exchange results in an inward flow of positive charge and accounts for the oscillation. An analogous congenital syndrome, caused by mutations in the ryanodine receptor gene (i.e., RyR2), results in catecholaminergic (exertional) sudden cardiac death.[44,45]

The Digitalis Investigation Group (DIG) compared the benefit of digoxin to placebo in patients with congestive heart failure (CHF) who were in sinus

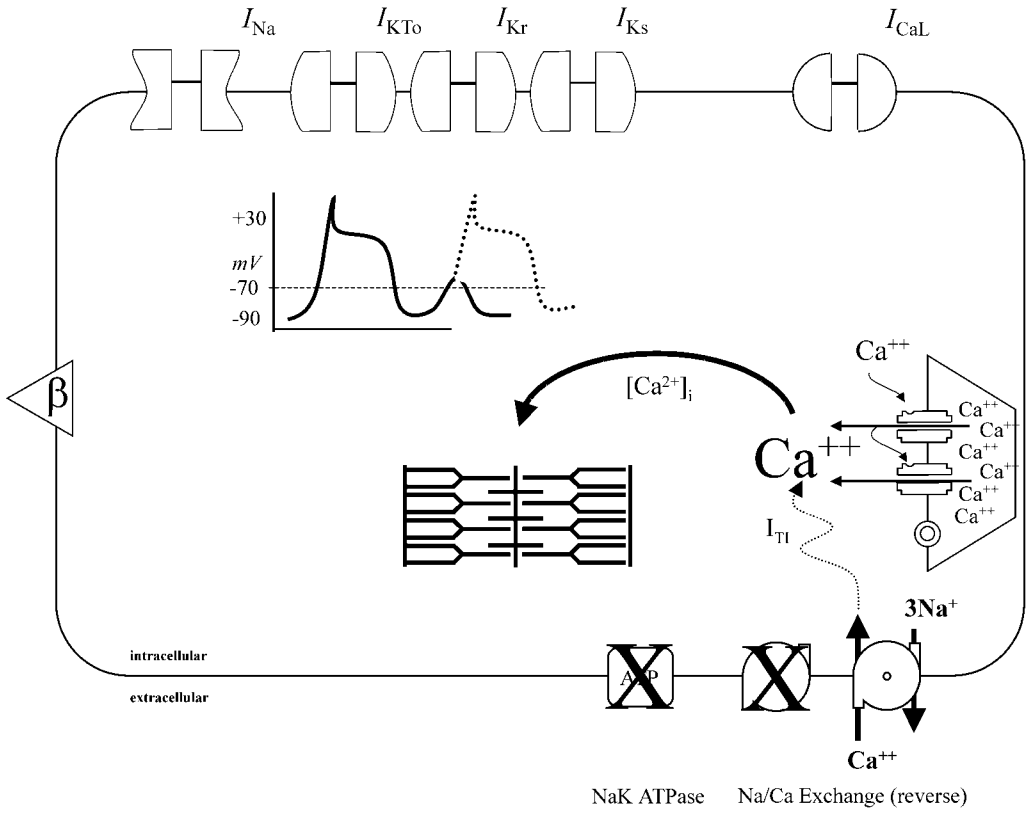


**Figure 6.** The mechanism of drug-induced (e.g., digoxin) $Ca^{2+}$ overload resulting in a delayed afterdepolarization. Excessive intracellular $Ca^{2+}$ stimulated the release of more $Ca^{2+}$ from the sarcoplasmic reticulum. In addition, the excess $Ca^{2+}$ is exchanged for $Na^+$ by reverse function of the Na/Ca exchange mechanism, depolarizing the cell by producing a transient inward current, $I_{TI}$. See text for complete explanation.

rhythm.[46] Although the investigators noted a reduced admission rate for and death due to CHF, they also discovered a significantly increased [presumed] dysrhythmic death rate in the digoxin group. Digoxin-related ventricular dysrhythmias are generally heralded by the presence of frequent PVCs, which represent electrocardiographic manifestations of delayed afterdepolarizations. In these patients, unlike in those with $I_{Kr}$ blockade, the complete conditions for dysrhythmia formation are not created by digoxin (i.e., digoxin does not create a substrate for reentry). However, given the presence of underlying ischemic or other heart disease in most digoxin-using patients, the substrate for reentry does, in fact, exist. Thus, digoxin may be considered a myocardial sensitizing agent. This model also explains the sensitivity of the heart to both internal pacing interventions[47] and to exogenous $Ca^{2+}$ salt administration.

Similarly, β-adrenergic agonists are dysrhythmogenic not through altering repolarization but rather by initiating DADs. These are most significant when the substrate for reentry is present, as occurs when a user of halogenated hydrocarbons is startled and releases endogenous epinephrine. $\beta_1$-adrenergic receptors and $\beta_2$-adrenergic receptors both couple to $G_s$, a stimulatory protein linked to adenyl cyclase. $G_s$ triggers the conversion of ATP to cAMP, which activates protein kinase A (PKA). PKA in turn, phosphorylates several critical intramyocardial sites, the two most relevant being the L-type $Ca^{2+}$ channel and the ryanodine receptor. Thus, β-agonism raises the intracytoplasmic calcium concentration and produces myocardial sensitization in a manner analogous to digoxin. A potent argument for the role of β agonism in causing fatal ventricular dysrhythmias is the benefit (in reduced risk of sudden death) derived from the popular use of β-antagonists.[48] Similarly, the Survival With Oral D-sotalol (SWORD) trial, in which D-sotalol was

administered to suppress ventricular ectopic beats, was stopped prematurely due to an increase in mortality in the treatment group.[49] D-sotalol is a pure class III antidysrhythmic agent ($K^+$ channel blocker) that does not have any of the β-adrenergic antagonist effect of the racemic D,L mixture. The racemic mixture, presumably due to the β-blocking effect of the L-isomer, is not associated with an increased risk of ventricular dysrhythmia.

## TORSADES DE POINTES (POLYMORPHIC VENTRICULAR TACHYCARDIA ASSOCIATED WITH QT PROLONGATION)

The specific description of torsades de pointes was made by Dessertenne,[50] 2 years after the suggestion by Selzer and Wray[4] that quinidine syncope was produced by self-terminating ventricular fibrillation.[51] Although the exact method by which torsades de pointes produces its unique electrocardiographic effects remains controversial it may be due to either competing dysrhythmogenic foci or the production of coexisting spiral waves of depolarization.[52] Experimental models generally support the latter, and suggest that following the first ectopic beat, the subsequent beats are due to reentrant excitation of a rotating wavefront.[53,54] The dysrhythmia terminates when competing wavefronts extinguish one another.[52,54]

Most occurrences of torsades de pointes are preceded by pauses, or long–short intervals, and are thus termed "pause dependent."[55] This is documented experimentally and using Holter monitoring,[56] and is commonly due to post-extrasystolic pauses. In patients with congenital LQTSs, the bradycardia that accompanies sleep may produce pauses sufficient to trigger torsades de pointes;[16] this event has also been offered as one possible etiology of sudden infant death syndrome.

## TREATMENT

The therapy required by patients poisoned by myocardial sensitizing drugs and toxin depends on the particular pathophysiologic mechanism (i.e., ischemia, $K^+$ channel blockade) and the specific clinical manifestations (i.e., cardiac arrest vs. dysrhythmia with life-sustaining vital signs). In any patient, immediate withdrawal of the potential cause and the correction of hypokalemia, hypocalcemia, and hypomagnesemia, if present, is always the initial step.

Patients with immediately life-threatening dysrhythmias require immediate cardioversion. In the presence of nonperfusing rhythms, such as ventricular fibrillation, pulseless ventricular tachycardia, or torsades de pointes, unsynchronized electrical defibrillation is the treatment of choice. Neither overdrive pacing nor magnesium sulfate, commonly recommended for the prevention of the recurrence of torsades de pointes, is likely an appropriate therapy for nonterminating torsades de pointes.

Once the patient's rhythm converts the goal of therapy is to prevent recurrence of the dysrhythmia. Eliminating the substrate or the trigger for the dysrhythmia, or both, is the goal of therapy. Intravenous magnesium sulfate is a simple, benign, and highly effective intervention to suppress EADs. The likely mechanism is blockade of the myocardial L-type $Ca^{2+}$ channel, which prevents $Ca^{2+}$ influx should calcium channels reactivate during a prolonged repolarization period. As noted, this is a purported advantage of amiodarone as well. It should be noted that $Mg^{2+}$ therapy does not shorten the QT interval.

Stable patients with ventricular tachycardia may benefit from a trial of antidysrhythmic drugs such as lidocaine or amiodarone, although the use of these agents in this particular setting is not well studied. β-Adrenergic antagonists are commonly recommended as initial therapy for patients with drug-induced torsades de pointes. They derive their benefit largely by eliminating the trigger for dysrhythmia formation (i.e., afterdepolarization) but they do not effect to any substantial degree the substrate.

Elimination of both the substrate and the trigger for dysrhythmogenesis may be achieved by normalizing a prolonged action potential duration (i.e., QT interval), which has the dual effect of reducing dispersion of repolarization (the substrate) and suppressing EADs (a trigger). Action potential shortening may be done by raising the patient's heart rate either with overdrive pacing (i.e., pacing higher than the intrinsic heart rate) or by administering a β-agonist, typically isoproterenol. Raising the heart rate increases the amplitude of $I_{Ks}$, which partially counteracts the electrophysiologic effects $I_{Kr}$ blockade. However, tachycardia, particularly that produced by β-agonism, may cause ventricular dysrhythmias by raising the intracellular $Ca^{2+}$ concentration, which predisposes to the development of DADs. Thus, this form of therapy is a delicate balance of antidysrhythmic and prodysrhythmic forces and not widely used.

Theoretically, class Ib sodium channel blockers may be useful by reducing inward $Na^+$ influx and shortening

action potential duration. Similarly, calcium channel blockers, such as diltiazem, should effectively suppress EADs. However, neither of these therapies is consistently effective and therefore they are not routinely recommended. Raising the extracellular (serum) $K^+$ slightly above normal, which reduces QT dispersion and prolongation in quinidine-using patients,[57] may be beneficial but is also not routinely recommended because of the very narrow therapeutic index of potassium.

Patients with drug-induced QT prolongation may have normal QT at baseline. The reason that some patients develop QT prolongation in response to certain $I_{Kr}$ blocking drugs while others do not remains unknown, and the incidence of such sensitivity is unknown. It is possible that as yet unidentified mutations in these channel proteins may underlie this sensitivity.[58] Patients who develop QT prolongation or torsades de pointes with either a class Ia antidysrhythmic agent or any agent that blocks $I_{Kr}$, should be given $I_{Kr}$ blockers very cautiously, if at all.[55,59]

## IMPLICATIONS/CONCLUSIONS

Underlying the ability to identify the prodysrhythmic potential of many drugs prior to marketing was the lack of both an adequate experimental model and extensive premarketing testing.[60] A related limitation of drug development is that the patient population is often considered pharmacokinetically and pharmacodynamically homogenous, while in reality significant interindividual differences are present.[60] Pharmacological alterations due to organ dysfunction are often considered initially, while genetic polymorphisms, which remain relatively poorly understood, and drug interactions cannot be readily systematically evaluated. Screening using $I_{Kr}$ model systems or animal models[32] performed prior to marketing may provide insight into the likelihood that a drug will cause torsades de pointes, suggesting the need for enhanced postmarketing surveillance.[61] Furthermore, there is evidence that risk factor analysis may predict the development of torsades de pointes.[60] Although women are at greater risk than men,[62] this may be an impractical marker. However, genotypic analysis may ultimately prove useful in identifying patients who are carriers of mutant ion channel genes or those with incomplete penetrance,[16] in whom the risk of $I_{Kr}$ blockade may be most concerning.

## REFERENCES

1. Huikuri, H.V.; Castellanos, A.; Myerburg, R.J. Sudden Death Due to Cardiac Arrhythmias. N. Engl. J. Med. **2001**, *345*, 1473–1482.
2. Roden, D.; Woosley, R.; Primm, R. Incidence and Clinical Features of the Quinidine-Associated Long QT Syndrome, Implications for Patient Care. Am. Heart J. **1986**, *111*, 1088–1093.
3. Wenckebach, K.F. Cinchona Derivatives in the Treatment of Heart Disorders. J. Am. Med. Assoc. **1923**, *81*, 472–474.
4. Selzer, A.; Wray, H.W. Quinidine Syncope, Paroxysmal Ventricular Fibrillations Occurring During Treatment of Chronic Atrial Arrhythmias. Circulation **1964**, *30*, 17–26.
5. CAST Investigators. Preliminary Report, Effect of Encainide and Flecainide on Mortality in a Randomized Trial of Arrhythmia Suppression After Myocardial Infarction. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. N. Engl. J. Med. **1989**, *321*, 406–412.
6. Schouten, E.G.; Dekker, J.M.; Meppelink, P.; Kok, F.J.; Vandenbroucke, J.P.; Pool, J. QT Interval Prolongation Predicts Cardiovascular Mortality in an Apparently Healthy Population. Circulation **1991**, *84*, 1516–1523.
7. Sawanobori, T.; Adaniya, H.; Hirano, Y.; Hiraoka, M. Effects of Antiarrhythmic Agents and $Mg^{2+}$ on Aconitine-Induced Arrhythmias. Jpn. Heart J. **1996**, *37*, 709–718.
8. Viskin, S. Long QT Syndromes and Torsades de Pointes. Lancet **1999**, *354*, 1625–1633.
9. Tristani-Firouzi, M.; Chen, J.; Mitcheson, J.S.; Sanguinetti, M.C. Molecular Biology of K(+) Channels and Their Role in Cardiac Arrhythmias. Am. J. Med. **2001**, *110*, 50–59.
10. Wettwer, E.; Amos, G.J.; Posival, H.; Ravens, U. Transient Outward Current in Human Ventricular Myocytes of Subepicardial and Subendocardial Origin. Circ. Res. **1994**, *75*, 473–482.
11. del Camino, D.; Holmgren, M.; Liu, Y.; Yellen, G. Blocker Protection in the Pore of a Voltage-Gated $K^+$ Channel and Its Structural Implications. Nature **2000**, *403*, 321–325.
12. Lees-Miller, J.P.; Duan, Y.; Teng, G.Q.; Duff, H.J. Molecular Determinant of High Affinity Dofetilide Binding to HERG1 Expressed in Xenopus Oocytes, Involvement of S6 Sites. Mol. Pharmacol. **2000**, *57*, 367–374.
13. Mitcheson, J.S.; Chen, J.; Sanguinetti, M.C. Trapping of a Methanesulfonanilide by Closure of the HERG Potassium Channel Activation Gate. J. Gen. Physiol. **2000**, *115*, 229–239.
14. Keating, M.T.; Sanguinetti, M.C. Molecular and Cellular Mechanisms of Cardiac Arrhythmias. Cell **2001**, *104*, 569–580.
15. Mitcheson, J.S.; Chen, J.; Lin, M.; Culberson, C.; Sanguinetti, M.C. A Structural Basis for Drug-Induced

Long QT Syndrome. Proc. Natl Acad. Sci. **2000**, *97*, 12329–12333.

16. Schwartz, P.J.; Priori, S.G.; Spazzolini, C.; Moss, A.J.; Vincent, G.M.; Napolitano, C.; Denjoy, I.; Guicheney, P.; Breithardt, G.; Keating, M.T.; Towbin, J.A.; Beggs, A.H.; Brink, P.; Wilde, A.A.; Toivonen, L.; Zareba, W.; Robinson, J.L.; Timothy, K.W.; Corfield, V.; Wattanasirichaigoon, D.; Corbett, C.; Haverkamp, W.; Schulze-Bahr, E.; Lehmann, M.H.; Schwartz, K.; Coumel, P.; Bloise, R. Genotype–Phenotype Correlation in the Long-QT Syndrome, Gene-Specific Triggers for Life-Threatening Arrhythmias. Circulation **2001**, *103*, 89–95.
17. Splawski, I.; Timothy, K.W.; Vincent, G.M.; Atkinson, D.L.; Keating, M.T. Molecular Basis of the Long-QT Syndrome Associated with Deafness. N. Engl. J. Med. **1997**, *336*, 1562–1567.
18. Teschemacher, A.G.; Seward, E.P.; Hancox, J.C.; Witchel, H.J. Inhibition of the Current of Heterologously Expressed HERG Potassium Channels by Imipramine and Amitriptyline. Br. J. Pharmacol. **1999**, *128*, 479–485.
19. Krishnan, S.C.; Antzelevitch, C. Sodium Channel Block Produces Opposite Electrophysiological Effects in Canine Ventricular Epicardium and Endocardium. Circ. Res. **1991**, *69*, 277–291.
20. Greenberg, H.M.; Dwyer, E.M., Jr.; Hochman, J.S.; Steinberg, J.S.; Echt, D.S.; Peters, R.W. Interaction of Ischaemia and Encainide/Flecainide Treatment, a Proposed Mechanism for the Increased Mortality in CAST I. Br. Heart J. **1995**, *74*, 631–635.
21. Goldgran-Toledano, D.; Sideris, G.; Kevorkian, J.P. Overdose of Cyclic Antidepressants and the Brugada Syndrome. N. Engl. J. Med. **2002**, *346*, 1591–1592.
22. Gussak, I.; Antzelevitch, C.; Bjerregaard, P.; Towbin, J.A.; Chaitman, B.R. The Brugada Syndrome, Clinical; Electrophysiologic and Genetic Aspects. J. Am. Coll. Cardiol. **1999**, *33*, 5–15.
23. Surawicz, B. Electrophysiologic Substrate of Torsades de Pointes, Dispersion of Repolarization or Early Afterdepolarizations. J. Am. Coll. Cardiol. **1989**, *14*, 172–184.
24. Yan, G.X.; Wu, Y.; Liu, T.; Wang, J.; Marinchak, R.A.; Kowey, P.R. Phase 2 Early Afterdepolarizations as a Trigger of Polymorphic Ventricular Tachycardia in Acquired Long-QT Syndrome. Direct Evidence from Intracellular Recordings in the Intact Left Ventricular Wall. Circulation **2001**, *103*, 2851–2856.
25. Wang, Y.; Rudy, Y. Action Potential Propagation in Inhomogeneous Cardiac Tissue, Safety Factor Considerations and Ionic Mechanism. Am. J. Physiol. Heart Circ. Physiol. **2000**, *278*, H1019–H1029.
26. Reinhardt, C.F.; Mullin, L.S.; Maxfield, M.E. Epinephrine-Induced Cardiac Arrhythmia Potential of Some Common Industrial Solvents. J. Occup. Med. **1973**, *15*, 953–955.
27. Bass, M. Sudden Sniffing Death. J. Am. Med. Assoc. **1970**, *21*, 2075–2079.
28. Blayney, M.R.; Malins, A.F.; Cooper, G.M. Cardiac Arrhythmias in Children During Outpatient General Anaesthesia for Dentistry, a Prospective Randomised Trial. Lancet **1999**, *354*, 1864–1866.
29. Güler, N.; Kati, I.; Demirel, C.B.; Bilge, M.; Eryonucu, B.; Topai, C. The Effects of Volatile Anesthetics on the Q-Tc Interval. J. Cardiothorac. Vasc. Anesth. **2001**, *15*, 188–191.
30. Güler, N.; Bilge, M.; Eryonucu, B.; Kati, I.; Demirel, C.B. The Effects of Halothane and Sevoflurane on QT Dispersion. Acta Cardiol. **1999**, *54*, 311–315.
31. Hayashi, Y.; Sumikawa, K.; Kamibayashi, T.; Yamatodani, A.; Mammoto, T.; Kuro, M.; Yoshiya, I. Selective β1- and β2-Adrenoceptor Blockade on Epinephrine-Induced Arrhythmias in Halothane Anaesthetized Dogs. Can. J. Anaesth. **1992**, *39*, 873–876.
32. Yamamoto, K.; Tamura, T.; Imai, R.; Yamamoto, M. Acute Canine Model for Drug-Induced Torsadess de Pointes in Drug Safety Evaluation—Influences of Anesthesia and Validation with Quinidine and Astemizole. Toxicol. Sci. **2001**, *60*, 165–176.
33. Clark, D.G.; Tinston, D.J. Correlation of the Cardiac Sensitizing Potential of Halogenated Hydrocarbons with Their Physicochemical Properties. Br. J. Pharmacol. **1973**, *49*, 355–357.
34. Kiehn, J.; Wible, B.; Lacerda, A.E.; Brown, A.M. Mapping the Block of a Cloned Human Inward Rectifier Potassium Channel by Dofetilide. Mol. Pharmacol. **1996**, *50*, 380–387.
35. Zhang, S.; Todoroki, S.; Urechino, H.; Morooka, H.; Makita, T.; Shibata, O.; Sumikawa, K. Role of Potassium Channels in Halothane–Epinephrine Arrhythmias. Res. Commun. Mol. Pathol. Pharmacol. **1998**, *100*, 339–350.
36. Liu, D.W.; Antzelevitch, C. Characteristics of the Delayed Rectifier Current ($I_{kr}$ and $I_{ks}$) in Canine Ventricular Epicardial; Midmyocardial; and Endocardial Myocytes. A Weaker $I_{ks}$ Contributes to the Longer Action Potential of the M Cell. Circ. Res. **1995**, *76*, 351–365.
37. Viswanathan, P.C.; Rudy, Y. Pause Induced Early Afterdepolarizations in the Long QT Syndrome, a Simulation Study. Cardiovasc. Res. **1999**, *42*, 530–542.
38. Antzelevitch, C.; Sicouri, S. Clinical Relevance of Cardiac Arrhythmias Generated by Afterdepolarizations, Role of M Cells in the Generation of U Waves; Triggered Activity and Torsades de Pointes. J. Am. Coll. Cardiol. **1994**, *23*, 259–277.
39. January, C.T.; Riddle, J.M. Early Afterdepolarizations. Mechanism of Induction and Block. A Role for L-Type $Ca^{2+}$ Current. Circ. Res. **1989**, *64*, 977–990.
40. Hii, J.T.; Wyse, D.G.; Gillis, A.M.; Duff, H.J.; Solylo, M.A.; Mitchell, L.B. Precordial QT Interval Dispersion as a Marker of Torsades de Pointes. Disparate Effects of Class Ia Antiarrhythmic Drugs and Amiodarone. Circulation **1992**, *86*, 1376–1382.

41. Kodama, I.; Kamiya, K.; Toyama, J. Cellular Electrophysiology of Amiodarone. Cardiovasc. Res. **1997**, *35*, 13–29.
42. Nuss, H.B.; Marban, E.; Johns, D.C. Overexpression of a Human Potassium Channel Suppresses Cardiac Hyperexcitability in Rabbit Ventricular Myocytes. J. Clin. Investig. **1999**, *103*, 889–896.
43. Roden, D.M.; Anderson, M.E. The Pause That Refreshes; or Does It? Mechanisms in Torsadess de Pointes. Heart **2000**, *84*, 235–237.
44. Marks, A.R. Ryanodine Receptors/Calcium Release Channels in Heart Failure and Sudden Cardiac Death. J. Mol. Cell Cardiol. **2001**, *33*, 615–624.
45. Priori, S.G.; Napolitano, C.; Tiso, N.; Memmi, M.; Vignati, G.; Bloise, R.; Sorrentino, V.V.; Danieli, G.A. Mutations in the Cardiac Ryanodine Receptor Gene (hRyR2) Underlie Catecholaminergic Polymorphic Ventricular Tachycardia. Circulation **2001**, *103*, 196–200.
46. Digitalis Investigation Group. The Effect of Digoxin on Mortality and Morbidity in Patients with Heart Failure. N. Engl. J. Med. **1997**, *336*, 525–533.
47. Taboulet, P.; Baud, F.J.; Bismuth, C.; Vicaut, E. Acute Digitalis Intoxication—Is Pacing Still Appropriate? J. Toxicol. Clin. Toxicol. **1993**, *31*, 261–273.
48. Ogunyankin, K.O.; Singh, B.N. Mortality Reduction by Antiadrenergic Modulation of Arrhythmogenic Substrate, Significance of Combining Beta Blockers and Amiodarone. Am. J. Cardiol. **1999**, *84*, 76R–82R.
49. Waldo, A.L.; Camm, A.J.; deRuyter, H.; Friedman, P.L.; MacNeil, D.J.; Pauls, J.F.; Pitt, B.; Pratt, C.M.; Schwartz, P.J.; Veltri, E.P. Effect of d-Sotalol on Mortality in Patients with Left Ventricular Dysfunction After Recent and Remote Myocardial Infarction. The SWORD Investigators. Survival with Oral d-Sotalol. Lancet **1996**, *348*, 7–12.
50. Dessertenne, F. La Tachycardie Ventriculaire à deux Foyers Opposés Variables. Arch. Mal. Cœur. **1966**, *59*, 263–272.
51. Natttel, S. Experimental Evidence for Proarrhythmic Effects of Antiarrhythmic Drugs. Circ. Res. **1998**, *37*, 567–577.
52. El-Sherif, N.; Caref, E.B.; Chinushi, M.; Restivo, M. Mechanism of Arrhythmogenicity of the Short–Long Cardiac Sequence That Precedes Ventricular Tachyarrhythmias in the Long QT Syndrome. J. Am. Coll. Cardiol. **1999**, *33*, 1415–1423.
53. Asano, Y.; Davidenko, J.M.; Baxter, W.T.; Gray, R.A.; Jalife, J. Optical Mapping of Drug-Induced Polymorphic Arrhythmias and Torsades de Pointes in the Isolated Rabbit Heart. J. Am. Coll. Cardiol. **1997**, *29*, 831–842.
54. El-Sherif, N.; Chinushi, M.; Caref, E.B.; Restivo, M. Electrophysiological Mechanism of the Characteristic Electrocardiographic Morphology of Torsades de Pointes Tachyarrhythmias in the Long-QT Syndrome. Detailed Analysis of Ventricular Tridimensional Activation Patterns. Circulation **1997**, *96*, 4392–4399.
55. Viskin, S.; Belhassen, B. Polymorphic Ventricular Tachyarrhythmias in the Absence of Organic Heart Disease, Classification; Differential Diagnosis; and Implications for Therapy. Progr. Cardiovasc. Dis. **1998**, *41*, 17–34.
56. Locati, E.H.; Maison-Blanche, P.; Dejode, P.; Cauchemez, B.; Coumel, P. Spontaneous Sequences of Onset of Torsades de Pointes in Patients with Acquired Prolonged Repolarization. Quantitative Analysis of Holter Recordings. J. Am. Coll. Cardiol. **1995**, *25*, 1564–1575.
57. Choy, A.M.; Lang, C.C.; Chomsky, D.M.; Rayos, G.H.; Wilson, J.R.; Roden, D.M. Normalization of Acquired QT Prolongation in Humans by Intravenous Potassium. Circulation **1997**, *96*, 2149–2154.
58. Napolitano, C.; Schwartz, P.J.; Brown, A.M.; Ronchetti, E.; Bianchi, L.; Pinnavaia, A.; Acquaro, G.; Priori, S.G. Evidence for a Cardiac Ion Channel Mutation Underlying Drug-Induced QT Prolongation and Life-Threatening Arrhythmias. J. Cardiovasc. Electrophysiol. **2000**, *11*, 691–696.
59. Nattel, S.; Ranger, S.; Talajic, M.; Lemery, R.; Roy, D. Erythromycin-Induced Long QT Syndrome. Concordance with Quinidine and Underlying Cellular Electrophysiologic Mechanism. Am. J. Med. **1990**, *89*, 235–238.
60. Roden, D.M. Taking the "Idio" Out of "Idiosyncratic," Predicting Torsadess de Pointes. Pacing Clin. Electrophysiol. **1998**, *21*, 1029–1034.
61. Yang, T.; Snyders, D.; Roden, D. Drug Block of $I_{Kr}$, Model Systems and Relevance to Human Arrhythmias. J. Cardiovasc. Pharmacol. **2001**, *38*, 737–744.
62. Makkar, R.R.; Fromm, B.S.; Steinman, R.T.; Meissner, M.D.; Lehmann, M.H. Female Gender as a Risk Factor for Torsadess de Pointes Associated with Cardiovascular Drugs. J. Am. Med. Assoc. **1993**, *270*, 2590–2597.