



Pathophysiology of the long QT syndrome

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INTRODUCTION

The long QT syndrome (LQTS) is the phenotypic description of a group of disorders that are defined by two characteristics:

- Prolongation of the QT interval
- A characteristic arrhythmia, polymorphic ventricular tachycardia

The LQTS can be congenital, as an inherited disorder usually involving a mutation of an ion channel gene, or can be acquired as an adverse response to medication, metabolic abnormalities, or bradyarrhythmias ([table 1](#)) [1,2]. Torsades de pointes (TdP) or "twisting of points" is the specific type of polymorphic ventricular tachycardia (VT) associated with either form of the LQTS.

There are some pathophysiologic differences between the acquired and congenital forms of the LQTS.

- In the acquired form, polymorphic VT is most commonly precipitated by a characteristic sequence of long-short RR intervals. This interval is normally caused by a ventricular premature beat followed by a compensatory pause ([waveform 1](#)). Polymorphic VT can similarly occur in association with bradycardia or frequent pauses; as a result, the acquired form of LQTS is called "pause-dependent" LQTS [3].
- In the inherited or congenital form, particularly with certain genotypes, TdP typically follows

a sudden adrenergic surge. Such patients are considered to have "catecholamine-dependent" LQTS [3].

However, these distinctions are not absolute. As an example, one observational study of 15 patients with congenital LQTS documented "pause-dependent" TdP, which is more characteristic of the acquired form, in 14 [4].

The pathophysiology of the long QT syndromes will be reviewed here. The causes, genetics, diagnosis, prognosis, and management are discussed separately. (See ["Congenital long QT syndrome: Epidemiology and clinical manifestations"](#) and ["Congenital long QT syndrome: Diagnosis"](#) and ["Genetics of congenital and acquired long QT syndrome"](#) and ["Congenital long QT syndrome: Treatment"](#) and ["Acquired long QT syndrome: Definitions, causes, and pathophysiology"](#) and ["Acquired long QT syndrome: Clinical manifestations, diagnosis, and management"](#).)

PATHOPHYSIOLOGY

Although the relatively simple clinical definition of LQTS applies to both acquired and the variety of congenital forms, the pathophysiology of the disorder is complex, incompletely understood, and probably varies among patients. Two leading pathophysiologic hypotheses have emerged to explain commonly observed features of LQTS:

- Extensive and growing clinical and genetic evidence supports the importance of derangements in cardiac ion flows, resulting in prolongation of the action potential ([figure 1](#)). Based upon these data, congenital LQTS is considered a disease of ion channels. (See ["Genetics of congenital and acquired long QT syndrome"](#).)
- The observation that the immediate trigger for TdP in the inherited form is often a sudden surge in sympathetic tone (a feature not seen in the acquired form) led to the hypothesis that the congenital LQTS may be caused by an imbalance in the sympathetic innervation of the heart.

Derangements in ion flow — One of the leading pathophysiologic hypotheses focuses on derangements in cardiac ion flow, leading to increases in the action potential duration, early afterdepolarizations and triggered activity. The latter change can be due both to an increase in time for repolarization and to oscillations in membrane potential called early afterdepolarizations (EADs) which are a form of triggered activity. Abnormalities in ion flow that prolong the action

potential duration may lead to arrhythmias via reentrant mechanisms as described below.

The normal action potential — An understanding of normal cardiac cell electrophysiology is required in order to fully appreciate the proposed alteration in ion currents and electrophysiologic mechanisms which may underlie the long QT syndromes. The normal action potential (AP) is composed of the following five phases, beginning with phase four ([figure 2](#) and [figure 3](#) and [movie 1](#)). (See "[Cardiac excitability, mechanisms of arrhythmia, and action of antiarrhythmic drugs](#)".)

- Phase 4 represents the normal **diastolic** resting membrane potential of myocardial cells. Myocardial ventricular cell membranes during diastole are polarized at -90 mv (ie, the resting membrane potential), which largely represents the equilibrium potential for potassium. This occurs because most resting cardiac cell membranes are much more permeable to potassium than to sodium ions.
- Phase 0 occurs when the membrane potential reaches -60 mv. A rapid inward flow of sodium ions through the fast sodium channels ensues and **depolarizes** the cell membrane. Inward current during phase 0 is also sustained by activation of L and T type calcium channels.
- Phase 1 represents an initial repolarization after the overshoot of phase 0 and is caused by a transient outward potassium current.
- Phase 2 is called the plateau phase, because it represents an equilibrium between the inward calcium and delayed sodium currents and the outward potassium current (known as the delayed rectifier potassium current).
- Phase 3 represents the rapid repolarization which occurs when outward potassium current dominates over the decaying inward calcium current. Repolarization is predominantly effected through the outward (delayed) rectifying potassium current. These channels open in response to depolarization and allow potassium to flow out of cells and repolarize the membrane potential toward its resting level. The QT interval on the surface electrocardiogram is determined by the activity of these channels.

Prolonged repolarization and EADs — Prolongation of the QT interval may be associated with the presence of early afterdepolarizations (EADs). EADs are single or multiple oscillations of the membrane potential that can occur during phase 2 or 3 of the action potential. EADs occur in association with prolongation of the repolarization phase of the action potential.

Prolongation of repolarization results from a **net reduction in the outward current**, due to an increase in inward current, a decrease in outward current, or both. This may occur by one or more of three ionic mechanisms:

- Activation of a delayed sodium current which occurs early during repolarization. This is the mechanism responsible for the QT prolongation seen with the drug [ibutilide](#) [5].
- An increased inward calcium current. Increases in intracellular calcium are caused by an elevation in transsarcolemmal calcium current due to either catecholamines or a rise in the extracellular calcium concentration.

If occurring in phase 2 of the action potential, EADs are thought to be caused by increased inward current through L-type calcium channels [6] or through the sodium-calcium exchanger [7]. Depolarizing currents occurring late in phase 3 are thought to be due to inward currents through T-type calcium channels or sodium channels [8].

- A decreased outward potassium current. This decreased outward current can be caused by either class IA or III antiarrhythmic drugs ([figure 2](#)). Class IA agents ([quinidine](#), [procainamide](#), and [disopyramide](#)) block the outward delayed rectifier potassium current; in contrast, class III antiarrhythmic drugs (such as [sotalol](#)) block the rapid component of the delayed outward rectifier with a minimal effect on the inward rectifier current.

Triggered activity — Triggered responses or triggered activity are EADs that reach threshold potential, depolarize cell membranes, and result in additional action potentials. Propagation of these triggered responses produce ventricular premature depolarizations that may initiate polymorphic VT (TdP) in susceptible subjects. EADs and triggered responses are particularly easy to induce in Purkinje fibers and M cells, a group of cells in the left ventricular free wall which have recently been identified as the site of EAD-induced triggered activity after exposure to drugs such as [quinidine](#), [sotalol](#), and [erythromycin](#) (see below) [9,10].

Common precipitants of EADs and triggered activity — The development of EADs is potentiated by bradycardia, hypokalemia, hypomagnesemia and a long list of medications (see ["Acquired long QT syndrome: Definitions, causes, and pathophysiology", section on 'Medications'](#)). A few notable examples deserve emphasis:

- Bradycardia – Slow heart rates are associated with increased inactivation of the outward repolarizing potassium current and a reduction in the Na-K-ATPase pump outward current (3 Na out/2 K in = net outward positive current). Slow heart rates also enhance the activity

of certain antiarrhythmic drugs on repolarization (ie, repolarization and the QT interval are more prolonged). This property is called reverse use dependence and can lead to ion fluxes that facilitate EADs and TdP.

- Hypokalemia – Low potassium levels lead to decreased outward repolarizing current via reductions in electrogenic Na-K-ATPase pump activity and outward potassium channel activity.
- Antiarrhythmic drugs – Class IA antiarrhythmic agents block both sodium and potassium channels, while the class III drugs block the potassium channels ([table 1](#)). Blockade of sodium channels would be expected to shorten the action potential duration, whereas blockade of potassium channels should prolong the action potential duration. At slow heart rates and low to normal concentrations of Class IA drugs, the potassium channel blocking activity predominates over the effect on the sodium channel [[11](#)]. Therefore, EADs and TdP are more frequently seen with nontoxic levels of [quinidine](#); supratherapeutic levels lead to increased sodium channel blocking activity and are rarely associated with QT prolongation and TdP.

d,l-Sotalol (a class III antiarrhythmic drug with beta blocking activity) and the pure class III agents, such as d-sotalol (and probably [dofetilide](#)), are potassium channel blockers that cause QT prolongation and are associated with TdP. Proarrhythmia, primarily TdP, occur in 2 to 7 percent of patients taking d,l-sotalol at doses of at least 320 mg/day; this complication is dose-dependent [[12](#)].

d-Sotalol, the isomer of d,l-sotalol, is a pure class III agent that does not affect beta adrenergic receptors. It is associated with an increased rate of arrhythmias, including TdP as shown in the SWORD (Survival With Oral D-sotalol) trial [[13](#)]. These findings led to the withdrawal of d-sotalol from the market.

Like other class III antiarrhythmic agents, [ibutilide](#) prolongs the time for repolarization in atrial and ventricular myocardium [[14](#)]. This effect is mediated by activation of a slow, delayed inward sodium current that occurs early during repolarization [[5](#)]. This is different from other class III agents which act by inhibiting outward potassium currents. In one report, nonsustained TdP occurred in 2.7 percent of patients treated with ibutilide, while a sustained event was seen in 1.7 percent [[15](#)].

[Amiodarone](#), a complex antiarrhythmic agent with potassium channel blocking activity, causes

QT prolongation but is rarely associated with TdP. This disparate result may be due to the drug's multiple actions, including the blockade of sodium, potassium, and calcium channels, and of alpha and beta adrenergic receptors. (See "[Cardiac excitability, mechanisms of arrhythmia, and action of antiarrhythmic drugs](#)".)

The degree of drug-induced blockade of the rapidly activating delayed rectifier current appears to be dependent upon the extracellular potassium concentration [16]. Low extracellular potassium increases the drug block, while there is relative resistance to block when extracellular potassium levels are elevated as may occur with myocardial ischemia or rapid heart rates. This relationship may explain the reverse use-dependent effect of these drugs, ie, the degree of prolongation of repolarization is reduced as the stimulation rate increases.

- [Ketoconazole](#) or [erythromycin](#) – Ketoconazole and erythromycin both inhibit CYP3A. Individuals with low CYP3A activity may therefore be unable to oxidize drugs such as terfenadine, astemizole (both of which have been taken off the market), or [disopyramide](#) when they are concurrently taking ketoconazole or erythromycin. These effects may lead to QT prolongation, resulting in TdP [17]. In addition, erythromycin alone can cause QT prolongation and TdP [10,18].
- HIV infection – QT prolongation and TdP have been reported in patients with HIV infection, even in the absence of drug therapy. In one study, 29 percent of hospitalized patients with HIV infection had QT prolongation [19]. Postulated mechanisms include myocarditis, a subclinical cardiomyopathy, or autonomic neuropathy [20].

Increased sympathetic activity — Evidence supporting the significance of sympathetic activity in LQTS includes observations on the impact of the stellate ganglia. The activity of the left sympathetic stellate ganglion is greater than that of the right ganglion in normal individuals. In addition, the left stellate ganglion innervates the majority of the ventricle [12,21].

Increased activity of the left stellate ganglion or reduced activity of the right stellate ganglion leads to increased sympathetic innervation of the heart. Studies in both animals and humans have demonstrated that right stellectomy or stimulation of the left stellate ganglion both prolong the QT interval and alter T wave morphology in a manner that mimics the surface ECG found in patients with LQTS. Furthermore, in a computer model sympathetic stimulation facilitated the induction of TdP by a number of mechanisms, including [22]:

- Decreasing the refractory period

- Permitting earlier premature stimulation
- Allowing reentry in the presence of the shorter refractory period

In addition, sympathetic stimulation can also facilitate the induction of triggered activity and early after potentials. (See '[Prolonged repolarization and EADs](#)' above.)

Indirect clinical evidence also supports the hypothesis that increased sympathetic activity may underlie the pathophysiology of congenital LQTS. One study found that an infusion of [epinephrine](#) increased both transmural and spatial dispersion of repolarization in patients with LQTS; this effect was more pronounced in LQT1 compared to LQT2, possibly explaining why LQT1 patients are more sensitive to sympathetic stimulation [23]. In addition, antiadrenergic therapies, including beta blockers and left sympathectomy, substantially reduce the risk of TdP in patients with LQTS, despite the fact that they do not shorten the QT interval [21]. (See "[Genetics of congenital and acquired long QT syndrome](#)" and "[Congenital long QT syndrome: Treatment](#)".)

Additional support for the role of enhanced sympathetic activity comes from a study in which the heart rate was increased by atrial pacing in the absence of sympathetic stimulation [24]. In this setting, the QT interval shortened and QT dispersion (as determined by monophasic action potential duration) decreased in both control and LQTS patients. An infusion of [epinephrine](#) during atrial pacing blunted these effects on repolarization in the patients with LQTS but not the controls.

Dispersion of repolarization and reentry — Both the dispersion of repolarization and reentry may be other potential mechanisms for the development of TdP. Dispersion of repolarization refers to an inhomogeneity in repolarization or recovery of excitability in a region of myocardium. A specific population of cells in the myocardium, called M cells, demonstrate marked prolongation of action potential duration in response to drugs such as [quinidine](#), [sotalol](#), and [erythromycin](#) [9,10]. Dispersion of repolarization could therefore occur in response to these drugs if the action potential is prolonged in M cells but not in the surrounding myocardium. The result is a functional block in the M cell region, providing the necessary milieu for the development of a reentrant arrhythmia [9].

Initiation and maintenance of VT — EADs and triggered activity are thought to be the most common initiating mechanism for the ventricular ectopy and polymorphic VT associated with long QT intervals [17,25]. Alterations in sympathetic activity and dispersion of repolarization probably contribute to the electrophysiologic milieu that facilitates malignant arrhythmias, at least

in certain cases.

Maintenance of a sustained ventricular arrhythmia may be due to repeated triggered responses, although reentry or abnormal automaticity could also be responsible. In an animal model using a voltage sensitive dye and high resolution video imaging of electrical waves, drug-induced polymorphic VT resulted from beat to beat changes in wave propagation patterns initiated by EADs or EAD-induced nonstationary vortex-like reentrant activity ([waveform 2](#)) [26].

In another animal study, TdP consistently arose as a focal activity within the subendocardium, while subsequent beats were due to reentrant excitation in the form of rotating vortices [27]. The VT ended when reentry terminated. The changing QRS axis usually coincided with the transient bifurcation of a predominantly single rotating vortex into two simultaneous vortices, involving the right and left ventricles separately. The bifurcation resulted from the development of functional conduction block within the right ventricle. In other cases, the axis shift was due to a single localized circuit which varied in location and orientation.

SUMMARY

It is likely that the prolonged QT interval seen in the congenital LQTS is the result of an abnormality in an ion channel and therefore in ion conductance. Observations in the genetic forms of the LQTS are consistent with this hypothesis. (See "[Genetics of congenital and acquired long QT syndrome](#)".)

The ensuing delay in repolarization and an associated dispersion of heterogeneity may serve as the substrate upon which the following may occur:

- Heightened sympathetic tone can initiate the development of EADs and triggered activity.
- Reentry may result with the initiation and, in some instances, maintenance of an arrhythmia.

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Topic 955 Version 9.0

GRAPHICS

Some reported causes and potentiators of the long QT syndrome*

Congenital	Acquired (continued)
Jervell and Lange-Nielsen syndrome (including "channelopathies")	Antihistamines
Romano-Ward syndrome	Astemizole [§] , bilastine [¶] , hydroxyzine, terfenadine [§]
Idiopathic	Antineoplastic drugs [◇]
Acquired	<ul style="list-style-type: none"> High risk: Arsenic trioxide, ivosidenib, lenvatinib, vandetanib Moderate risk: Ceritinib, crizotinib, dasatinib, encorafenib, gilteritinib, inotuzumab, ozogamicin, midostaurin, nilotinib, osimertinib, ribociclib, toremifene, vemurafenib
Metabolic disorders	Analgesic, anesthetic, and sedative drugs
Hypokalemia	Anesthetic/sedative: Chloral hydrate, propofol
Hypomagnesemia	Opioids: Buprenorphine [¥] , hydrocodone, loperamide [‡] (in overdose), methadone
Hypocalcemia	Bronchodilators (beta₂-agonists)
Starvation	Arformoterol, albuterol, formoterol, levalbuterol, indacaterol, olodaterol, salmeterol, terbutaline, vilanterol
Anorexia nervosa	Diuretics
Liquid protein diets	Via electrolyte changes (especially hypokalemia or hypomagnesemia)
Hypothyroidism	Gastrointestinal drugs [◇]
Bradyarrhythmias	Antidiarrheal: Loperamide [‡] (in overdose)
Sinus node dysfunction	Antiemetics:
Atrioventricular (AV) block: Second- or third-degree	<ul style="list-style-type: none"> Moderate risk: Droperidol, ondansetron (risk with IV use greater than oral) Low to moderate risk: Granisetron, dolasetron, hydroxyzine, tropisetron[¶]
Androgen deprivation therapy (GnRH agonist/antagonist therapy or bilateral surgical orchiectomy)	Promotility:
Antiarrhythmic drugs	<ul style="list-style-type: none"> High risk: Cisapride (restricted availability) Moderate risk: Domperidone[¶] Low to moderate risk (rare reports): Metoclopramide
Quinidine, procainamide, disopyramide	Proton pump inhibitors: Chronic use leading to hypomagnesemia (rare)
Flecainide, pilsicainide [¶] , propafenone	Neurologic drugs
Amiodarone ^Δ , dronedarone, vernakalant [¶]	Apomorphine, deutetrabenazine, donepezil, ezogabine, fingolimod, pimavanserin, tetrabenazine
Sotalol	
Dofetilide, ibutilide	
Antianginal drugs	
Ranolazine, ivabradine [¶]	
Anticholinergic drugs (antimuscarinics)	
Solifenacin, tolterodine	
Anti-infective drugs [◇]	
Antimalarial:	
<ul style="list-style-type: none"> High risk: Delamanid[¶], quinidine, quinine Moderate risk: Chloroquine, halofantrine, piperazine 	
Antituberculous:	
<ul style="list-style-type: none"> High risk: Bedaquiline 	

<p>Azole antifungals:</p> <ul style="list-style-type: none"> Moderate risk: Fluconazole, voriconazole Low to moderate risk: Itraconazole 	<p>Psychotropic drugs</p> <p>Antipsychotics: ◇</p> <ul style="list-style-type: none"> High risk: Chlorpromazine, IV haloperidol, ziprasidone Moderate risk: Amisulpride ¶, clozapine, flupentixol ¶, haloperidol (oral), olanzapine, quetiapine, risperidone, thioridazine Low to moderate risk: Asenapine, iloperidone, paliperidone, pimavanserin <p>Tricyclic and tetracyclic antidepressants (TCAs; including doxepin) †</p> <p>Selective serotonin reuptake inhibitors (lower risk than TCAs): Citalopram, escitalopram, fluoxetine (less than citalopram)</p> <p>Others:</p> <ul style="list-style-type: none"> Atomoxetine, trazodone, valbenazine <p>Vasodilator drugs</p> <p>Bepidil §, cilostazol</p> <p>Other drugs and herbs</p> <p>Miscellaneous: Anagrelide, alfuzosin, cocaine, eliglustat, gadobenate dimeglumine, lofexidine, mifepristone, papaverine (intracoronary), pasireotide, probucol §, terlipressin ¶</p> <p>Herbs: Cinchona (contains quinine), licorice extract (glycyrrhizin) in overuse leading to electrolyte changes</p> <p>Other factors</p> <p>Myocardial ischemia or infarction, especially with prominent T-wave inversions</p> <p>Intracranial disease</p> <p>HIV infection</p> <p>Hypothermia</p> <p>Toxic exposure: Organophosphate insecticides</p>
Clofazimine (moderate risk)	
<p>Fluoroquinolones (systemic):</p> <ul style="list-style-type: none"> Moderate risk: Gemifloxacin ¶, levofloxacin, moxifloxacin, sparfloxacin ¶ Low to moderate risk: Ciprofloxacin, norfloxacin, ofloxacin 	
Foscarnet (low to moderate risk)	
<p>HIV antiretrovirals:</p> <ul style="list-style-type: none"> Moderate risk: Saquinavir Low to moderate risk: Efavirenz, lopinavir-ritonavir rilpivirine 	
<p>Macrolide antibiotics:</p> <ul style="list-style-type: none"> Moderate risk: Azithromycin, erythromycin, clarithromycin Low to moderate risk: Roxithromycin, telithromycin 	
Pentamidine (intravenous), moderate risk	
<p>Pentavalent antimonials (antiparasitic/antiprotozoal):</p> <ul style="list-style-type: none"> Moderate risk: Meglumine antimoniate, sodium stibogluconate 	
Telavancin (low to moderate risk)	

This is not a complete list of all corrected QT interval (QTc)-prolonging drugs and does not include drugs with either a minor degree or isolated association(s) with QTc prolongation that appear to be safe in most patients, but may need to be avoided in patients with congenital long QT syndrome depending upon clinical circumstances. A more complete list of such drugs is available at the Credible Meds website.

IV: intravenous.

* The list of medications and other factors capable of prolonging the QTc represents an evolving area of clinical research. In some cases of long QTc, two or more factors may be involved.

¶ Not available in the United States.

Δ In contrast with other class III antiarrhythmic drugs, amiodarone is rarely associated with torsades de pointes (TdP); refer to accompanying text within UpToDate topic reviews of acquired long QT syndrome.

◇ Classifications based upon US Food & Drug Administration guidance: Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs – Questions and Answers; Guidance for Industry US Food and Drug Administration, June 2017 (revision 2) available at:

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073161.pdf>.

The use of other classification criteria may lead to some agents being classified differently by other sources.

§ Removed from market in most countries due to adverse cardiovascular effects.

¥ Although product labeling for buprenorphine analgesics warn of QTc prolongation at doses exceeding those recommended, data for buprenorphine in usual doses for treatment of opioid use disorder are reassuring, and it appears to be a suitable alternative for patients with significant QTc prolongation due to methadone. Refer to the UpToDate topic reviews of opioid intoxication and opioid use disorder for detail.

‡ Over-the-counter; available without a prescription.

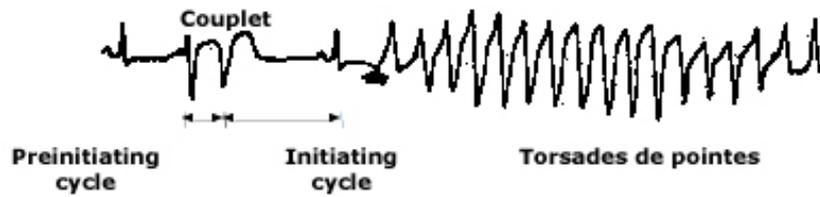
† Several of the cyclic antidepressants have not been adequately tested for QTc prolongation risk.

Data from:

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Graphic 57431 Version 98.0

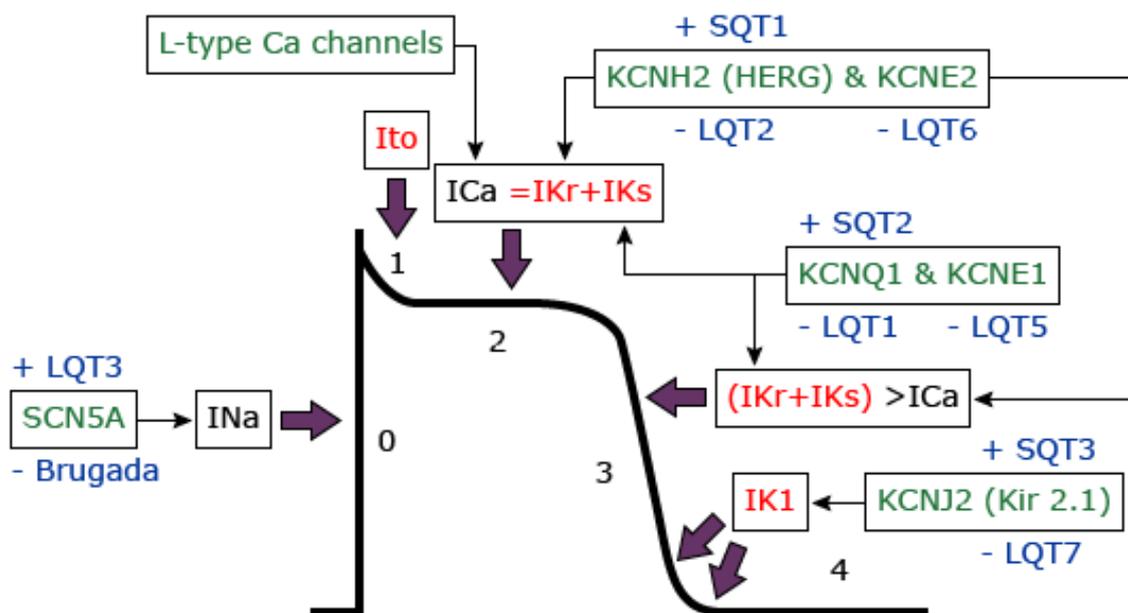
Single lead electrocardiogram (ECG) showing torsades de pointes



The electrocardiographic rhythm strip shows torsades de pointes, a polymorphic ventricular tachycardia associated with QT prolongation. There is a short, preinitiating RR interval due to a ventricular couplet, which is followed by a long, initiating cycle resulting from the compensatory pause after the couplet.

Graphic 73827 Version 4.0

Molecular basis for the long QT syndrome



Ion channels contributing to the cardiac action potential and the impact of genetic mutations.

+: gain-of-function mutation; -: dominant negative or loss-of-function mutation; LQT: long-QT syndrome; Ito: transient outward current; INa: inward sodium current; ICa: inward calcium current; IKr: rapid component of delayed rectifier current; IKs: slow component of delayed rectifier current; IK1: inward rectifier current; SQT: short-QT syndrome.

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Action potential currents

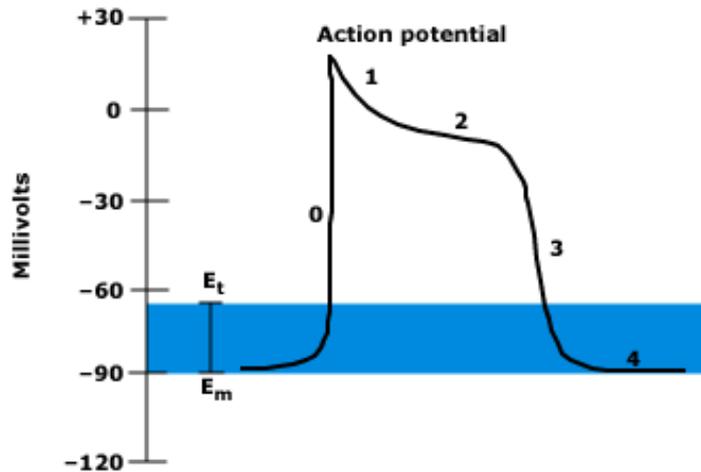
	Name		Gene	Protein
Inward depolarizing currents				
	I_{Na}	Voltage-dependent sodium	<i>SCN5A</i>	Nav1.5
	I_{Ca-L}	L-Type calcium	<i>CACNL1A1(α1c)</i>	CaV1.2
	I_{Ca-T}	T-Type calcium	<i>CACNA1H(α1h)</i>	CaV3.2
	I_{NaCaex}	Sodium calcium exchanger	<i>SLC8A1(NCX1)</i>	
Outward repolarizing currents				
	I_{to1}	Transient outward potassium	<i>KCND3, KCNA4</i>	KV4.3, KV1.4
	I_{to2}	Calcium activated chloride	?	?
	I_{Kr}	Rapid delayed rectifier potassium	<i>KCNH2 (HERG)</i>	KV11.1
	I_{Ks}	Slow delayed rectifier potassium	<i>KCNQ1 (KVLQT1)</i>	KV7.1
	I_{Kur}	Ultrarapid delayed rectifier potassium	<i>KCNA5</i>	KV1.5
	I_{Kp}	Plateau potassium	<i>KCNK1 (TWIK1)</i>	K2p1.1
	I_{K1}	Inward rectifier potassium	<i>KCNJ2, KCNJ12</i>	KIR2.1, KIR2.2
	I_{KAch}	Acetylcholine activated potassium	<i>KCNJ3, KCNJ5</i>	KIR3.1, KIR3.4
	I_{KATP}	ATP-sensitive potassium	<i>KCNJ11</i>	KIR6.2
	I_f	Pacemaker	<i>HCN2, HCN4</i>	
	$I_{NaKATPase}$	Sodium potassium ATPase pump	<i>ATP1A1</i>	

Major cardiac ion currents and channels responsible for a ventricular action potential are shown with their common name, abbreviation, and the gene and protein for the alpha subunit that forms the pore or transporter. The diagram on the left shows the time course of amplitude of each current during the action potential, but does not accurately reflect amplitudes relative to each of the other currents. This summary represents a ventricular myocyte, and lists only the major ion channels. The currents and their molecular nature vary within regions of the ventricles, and in atria, and other specialized cells such as nodal and Purkinje. Ion channels exist as part of multi-molecular complexes including beta subunits and other associated regulatory proteins which are also not shown.

Courtesy of Jonathan C Makielski, MD, FACC.

Graphic 70771 Version 4.0

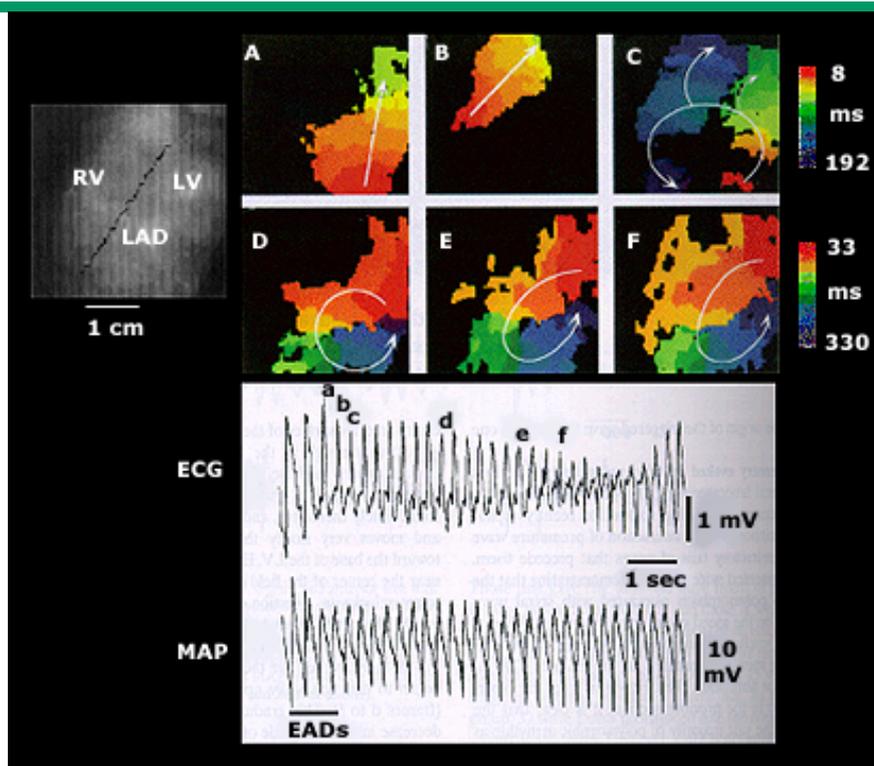
Myocardial action potential



Representation of a ventricular action potential. There are 5 phases of the action potential beginning with phase 0, rapid depolarization by sodium influx. Phase 1 is a rapid repolarization via potassium efflux followed by phase 2 or the plateau phase. The plateau phase results from entry of calcium into the cell and potassium efflux. Phase 3 repolarization is dominated by potassium currents which polarize the cell and potassium inward rectifier maintains the resting potential or phase 4. See text for full description.

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Mechanism of torsades de pointes



The top panels A-F are examples of epicardial isochrone maps obtained from the surface of the anterior left ventricular (LV) wall and free wall of the right ventricle (RV) during an episode of quinidine-induced torsades de pointes. Each map corresponds to a QRS deflection of the surface ECG and simultaneous monophasic action potential (MAP). Early afterpotentials (EADs) result in triggered activity (panels A-C) which is followed by a long episode of spiral-like reentry (panels D-F). Panel C shows the first reentrant wave which is not stationary, but gradually shifts upward and to the right. This is associated with a gradual decrease in the QRS complex amplitude.

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Contributor Disclosures

Peter J Zimetbaum, MD Consultant/Advisory Boards: Abbott Medical [lecture on lead extraction]; In carda Pharmaceuticals [Atrial fibrillation (Novel antiarrhythmic drug in development)]; Medtronic [Atrial fibrillation (Linq)]. **Samuel Lévy, MD** Nothing to disclose **John K Triedman, MD** Consultant/Advisory Boards: Biosense Webster [Supraventricular and ventricular topics (EP mapping and ablation systems)]. **Samuel Asirvatham, MD** Grant/Research/Clinical Trial Support: Medtronic [Defibrillators (Implantable cardiac defibrillators)]; St Jude's [Sudden Cardiac Death]. Consultant/Advisory Boards: BioTronik [Defibrillators (Implantable cardiac defibrillators)]; Boston Scientific [Sudden Cardiac Death]. **Brian C Downey, MD, FACC** Nothing to disclose

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