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Specific Therapy Based on the Genotype and Cellular Mechanism in Inherited Cardiac Arrhythmias. Long QT Syndrome and Brugada Syndrome

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Abstract

Seven forms of congenital long QT syndrome (LQTS) caused by mutations in ion channel genes have been identified. Genotype-phenotype correlation in clinical and experimental studies involving arterially-perfused canine left ventricular wedges suggest that β -blockers are protective in LQT1, less so in LQT2, but not protective in LQT3. A class IB sodium channel blocker, mexiletine, is most effective in abbreviating QT interval in LQT3, but effectively reduces transmural dispersion of repolarization (TDR) and prevents the development of Torsade de Pointes (TdP) in all 3 models, suggesting its potential as an adjunctive therapy in LQT1 and LQT2. High concentrations of intravenous nicorandil, a potassium channel opener, have been shown to be capable of decreasing QT and TDR, and preventing TdP in LQT1 and LQT2 but not in LQT3. The calcium channel blocker, verapamil, has also been suggested as adjunctive therapy for LQT1, LQT2 and possibly LQT3.

Experimental data using right ventricular wedge preparations suggest that a prominent transient outward current (I_{to})-mediated action potential (AP) notch and a loss of AP dome in epicardium, but not in endocardium, give rise to a transmural voltage gradient, resulting in ST segment elevation and the induction of ventricular fibrillation (VF), characteristics of the Brugada syndrome. Since the maintenance of the AP dome is determined by the balance of currents active at the end of phase 1 of the AP, any intervention that reduces the outward current or boosts inward current at the end of phase I may normalize the ST segment elevation and suppress VF. Such interventions are candidates for pharmacological therapy of the Brugada syndrome. The infusion of isoproterenol, a β -adrenergic stimulant, strongly augments L-type calcium current (I_{Ca-L}), and is the first choice for suppressing electrical storms associated with Brugada syndrome. Quinidine, by virtue of its actions to block I_{to} , has been proposed as adjunctive therapy, with an implantable cardioverter defibrillator as backup. Oral denopamine, atropine or cilostazol all increase I_{Ca-L} , and for this reason may be effective in reducing episodes of VF.

INTRODUCTION

The past decade has witnessed significant advances in molecular genetics that have established a link between a number of inherited cardiac arrhythmias and mutations in genes encoding for ion channels or other membrane components. Most inherited cardiac arrhythmias have been linked to ion channelopathies giving rise to primary electrical diseases, including the long QT syndrome [1,2], Brugada syndrome [3], idiopathic ventricular fibrillation, cardiac conduction

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defect (Lenegre disease) [4], catecholaminergic polymorphic ventricular tachycardia [5,6], familial atrial fibrillation [7], familial sick sinus syndrome [8], familial Wolff-Parkinson-White syndrome [9], and short QT syndrome [10].

Seven genotypes have been identified in the congenital form of the long QT syndrome (LQTS). Genotype-phenotype relationships have been delineated in congenital LQTS, and genotype-specific therapies have been proposed based on experimental and clinical data.

SCN5A, the gene encoding for the α subunit of the sodium channel, is the only gene thus far linked to the Brugada syndrome [3]. Recent studies have elucidated the cellular basis for the Brugada syndrome, which is characterized by an ST segment elevation in leads V1 – V3 and a high incidence of ventricular fibrillation (VF), and have suggested specific therapy based on these cellular mechanisms. Our focus in this Mini review is on the pharmacologic approach to therapy of the long QT and Brugada syndromes with an assessment of the potential for gene-specific therapy.

LONG QT SYNDROME

Congenital LQTS is characterized by QT prolongation in the electrocardiogram (ECG) and polymorphic ventricular tachycardia known as Torsade de Pointes (TdP), which often leads to syncope and sudden cardiac death [11-14]. Physical exercise and emotional states often precipitate syncope and/or sudden cardiac death in patients with congenital LQTS [11-15]. Accordingly, β -blockers are indicated for prevention of cardiac events in LQTS patients [16]. However, cardiac events occasionally appear at rest or during sleep without arousal, in which case β -blockers are usually ineffective [16]. Recent molecular genetic studies have provided an understanding of the basis for these phenotypic distinctions. Seven forms of congenital LQTS have been identified due to mutations in genes encoding for potassium and sodium channels or membrane components located on chromosomes 3, 4, 7, 11, 17 and 21 [17-19]. Mutations in *KCNQ1* and *KCNE1*, α and β subunits of the potassium channel gene, respectively, are responsible for defects in the slowly activating component of the delayed rectifier potassium current (I_{KS}) underlying the LQT1 and LQT5 forms of LQTS [20,21]. Similarly, mutations in *KCNH2* and *KCNE2* cause defects in the rapidly activating component of the delayed rectifier potassium current (I_{Kr}) responsible for the LQT2 and LQT6 forms [22,23]. Mutations in *SCN5A*, the gene that encodes the α subunit of the sodium channel, result in an increase in the late sodium current (I_{Na}) responsible for LQT3 [24]. Recently, mutations in *KCNJ2*, which encodes for the inward rectifier potassium current (I_{K1}), were shown to cause QT prolongation, periodic paralysis and dysmorphic features underlying Andersen's syndrome (LQT7) [18]. Moreover, a mutation in *Ankyrin-B*, a member of a family of versatile membrane adapters, was recently reported to result in the intracellular Ca^{2+} overload, underlying LQT 4 syndrome [19]. It is noteworthy that causative mutations can be identified in 60 - 70 % of clinically affected LQTS probands. Congenital LQTS is responsible for at least a part of the cases of sudden infant death syndrome (SIDS) [25], some of which possess *SCN5A* mutations [26,27].

Genotype-phenotype correlation can contribute to optimal management and genotype-specific approach to therapy of patients with LQTS [28-30]. Since LQT1, LQT2 and LQT3 syndromes comprise more than 90 % of genotyped patients [17], genotype-phenotype data are most abundant for these syndromes.

Genotype-Specific Clinical Characteristics

Moss and co-workers identified genotype-specific T wave morphologies in the ECG. Broad-based prolonged T waves were found most frequently in LQT1 syndrome, low-amplitude T waves with a notched or bifurcated configuration in LQT2 syndrome, and late-appearing T

waves with a long isoelectric ST-segment in LQT3 syndrome [31]. The genotype-specific T wave pattern in a resting ECG in the LQT1, LQT2 and LQT3 forms was further evaluated by Zhang *et al.*, and numerous exceptions were reported for all 3 genotypes [32]. To overcome this, Takenaka *et al.* reported that exercise treadmill testing could unmask the characteristic T wave patterns in LQT1 (broad-based T waves) and LQT2 (notched T waves) patients [33]. A characteristic T wave pattern has not been reported in LQT5 and LQT6 syndromes. TU abnormalities such as biphasic T waves following long pauses have been reported in LQT4 and LQT7 syndromes [18,19].

Experimental models of LQTS involving the arterially-perfused canine left ventricular wedge preparations have delineated the cellular basis for T wave patterns characteristic of LQT1, LQT2 and LQT3 syndromes [34-42]. Chromanol 293B, a specific I_{Ks} blocker, was used to mimic LQT1 syndrome [35,40-42], whereas d-sotalol, an I_{Kr} blocker, in the presence of hypokalemia was used to simulate LQT2 syndrome [34,36,40-42]. ATX-II was used to augment late I_{Na} , mimicking LQT3 syndrome [34,39-42]. In all 3 models, differences in the time course of ventricular repolarization of the epicardial, mid-myocardial (M) and endocardial cells create voltage gradients across the ventricular wall responsible for the specific T wave patterns.

Genotype-Specific Response to Sympathetic Stimulation

Genotype-specific triggers of cardiac events were also reported for LQT1, LQT2 and LQT3 syndromes [29,43-45], and these are probably due to the genotype-specific response of repolarization to sympathetic stimulation. In LQT1 syndrome, cardiac events are more frequently observed during exercise (62 %) than in LQT2 (13 %) or LQT3 (13 %) syndromes [29]. Swimming is a specific trigger of LQT1 syndrome [45]. In LQT2 syndrome, cardiac events can also occur during exercise (13 %) or during sleep/rest (15 %) [29]. Often, a sudden startle in the form of an auditory stimulus (telephone ring, alarm clock, ambulance siren, etc.) is a specific trigger of LQT2 syndrome [43,44]. Cardiac events are more frequently observed during postpartum periods in LQT2 syndrome than in LQT1 syndrome [46]. In contrast, cardiac events occur principally during sleep/rest (39 %) in LQT3 syndrome, and exercise-related cardiac events are rare (13 %) [29].

Clinical studies by our group and others suggest that sympathetic stimulation with epinephrine infusion or exercise testing produces genotype-specific responses of the QT interval [33, 47-52]. The corrected QT (QTc) interval is prolonged at peak epinephrine effect when the heart rate is maximally increased, and remains prolonged at steady state epinephrine effect in LQT1 patients [48,52]. The QTc interval is also prolonged at peak epinephrine effect in LQT2 patients, but returns to close to baseline levels at steady state epinephrine effect [48]. In contrast, QTc is less prolonged at peak epinephrine effect in LQT3 patients than in either LQT1 or LQT2 patients, and is abbreviated below baseline levels at steady state epinephrine effect [48].

Our experimental data using arterially-perfused wedge preparations also suggest a genotype-specific response of the action potential duration (APD) and transmural dispersion of repolarization (TDR) to β -adrenergic stimulation in the 3 LQTS models [35,41,50]. In the LQT1 model, β -adrenergic stimulation prolongs the QT interval and the APD of M cells but abbreviates those of epicardial and endocardial cells, resulting in a **persistent increase** in the QT interval and the TDR (Fig. 1A) [41]. In the LQT2 model, isoproterenol initially prolongs and then abbreviates the QT interval and the APD of M cells to the control level, whereas the APD of epicardial and endocardial cells is always abbreviated, leading to a **transient increase** in the QT interval and the TDR (Fig. 1B) [41]. In the LQT3 model, isoproterenol produces a persistent abbreviation of the QT interval and the APD of the 3 cell types, resulting in a **persistent decrease** of the QT interval and TDR (Fig. 1C) [41]. The **persistent increase** in the QT interval and the TDR during β -adrenergic stimulation may create an

arrhythmogenic substrate, and is consistent with the greater sensitivity of LQT1 patients to sympathetic stimulation. The **transient increase** of the QT interval and TDR following increased sympathetic activity is consistent with the nature of TdP, which is often observed following a startle. The **persistent decrease** of the QT interval and TDR during β -adrenergic stimulation in the LQT3 model explains why cardiac events occur more frequently during sleep/rest when sympathetic tone is low in LQT3 patients.

Genotype-Specific Therapy

Preliminary clinical studies indicate the possibility for genotype-specific therapy based on abbreviations of the QT interval by agents or other interventions in congenital LQTS [29,53]. However, the ability to abbreviate the QT interval does not necessarily determine the effectiveness of an intervention to reduce arrhythmic risk or sudden cardiac death. Our experimental studies employing pharmacological models of LQTS in arterially-perfused wedge preparations have provided a quantitative assessment of genotype-specific therapies for congenital forms of LQTS (Table 1) [34-42].

1. β -Blockers—A β -Blocker is the first choice of therapy in patients with congenital LQTS, when the genotype cannot be identified [16]. The international registry of LQTS reported that β -blockers reduce the incidence of syncope and sudden cardiac death in patients with congenital LQTS, especially in LQT1 patients (80 %) [29]. β -blockers are less effective in LQT2 and LQT3 patients. Data from wedge studies suggest that, propranolol, a β -blocker, completely suppresses the effect of isoproterenol to persistently increase TDR and to induce TdP in the LQT1 model [35,41]. In the LQT2 model, propranolol also totally prevents the transient effect of isoproterenol to increase TDR and to induce TdP [41], indicating that moderate effectiveness of β -blockers in LQT2 syndrome. However, LQT2 models can develop TdP in the absence of isoproterenol unlike LQT1, explaining why β blockade is not as protective in LQT2 as it is in LQT1. In LQT3 models, sympathetic stimulation with isoproterenol persistently decreases TDR and suppresses TdP [41]. Propranolol antagonizes these protective effects of isoproterenol, suggesting that β -blockers are not protective in LQT3 patients.

2. Sodium Channel Blockers—Schwartz *et al.* initially reported that mexiletine, a class IB sodium channel blocker that blocks late I_{Na} , abbreviates the QT interval in LQT3 patients more effectively than in LQT2 patients [53]. However, QT shortening by class IB drugs does not reflect their efficacy in reducing arrhythmic risk. Experimental data from wedge studies indicates that mexiletine is more effective in abbreviating the QT interval in the LQT3 model than in the LQT1 or LQT2 model (Fig. 2) [34,35], but that the drug reduces TDR and suppresses the development of TdP equally in the LQT1, LQT2 and LQT3 models (Fig. 2) [34,35]. This effect of mexiletine to reduce TDR in all three models is attributable to the intrinsically larger late I_{Na} in M cells than in epicardial or endocardial cells [54]. Block of late I_{Na} by mexiletine limits the ability of QT prolonging forces to increase the APD of the M cell. Our data suggest that mexiletine, a class IB sodium channel blocker, may be given consideration as first line therapy in LQT3 patients. However, because of a lack of prospective clinical trials mainly due to small number of LQT3 patients, mexiletine should be used at the moment in the presence of β -blockers or under the backup of an implantable cardioverter-defibrillator (ICD) even in LQT3 patients.

A class IC sodium channel blocker, flecainide, is reported to be effective in abbreviating QT interval in LQT3 patients with a specific mutation (D1790G) in *SCN5A* [55]. However, class IC sodium channel blockers might elicit a Brugada phenotype in LQT3 patients [56], therefore should not be used in general in LQT3 syndrome except for that with the specific *SCN5A* mutation.

3. Potassium Supplement—Compton and co-workers demonstrated that exogenously administered potassium corrects repolarization abnormalities in LQT2 patients with I_{K_r} defects [57]. More recently, longterm oral potassium administration was reported to improve repolarization abnormalities in LQT2 patients [58]. Acute intravenous treatment with potassium is especially effective in suppressing TdP. Experimental data from the wedge have also shown that an increase in extracellular potassium can limit the development of an arrhythmogenic substrate under long QT conditions, due principally to its action to increase I_{K_r} and I_{K_1} and limit the potency of I_{K_r} blockers [36].

4. Potassium Channel Openers—Our previous clinical study using monophasic action potential (MAP) recordings showed that intravenous administration of nicorandil, a potassium channel opener, reduces epinephrine-induced prolongation of the QT interval and MAP duration in LQT1 patients with I_{K_s} defects [59]. Nicorandil was also shown to suppress epinephrine-induced early afterdepolarizations (EADs) [59]. Experimental data from wedge studies suggest that nicorandil (2 - 20 $\mu\text{mol/L}$) abbreviates QT interval and APD of the 3 cell types in the 3 models [42]. High concentrations (10 - 20 $\mu\text{mol/L}$) completely reverse the effects of chromanol 293B+isoproterenol and those of d-sotalol to increase APD and TDR, and to induce TdP in the LQT1 and LQT2 models [42]. In contrast, 20 $\mu\text{mol/L}$ nicorandil reverses only 50% of the effect of ATX-II and fails to completely suppress TdP in the LQT3 model [42]. Our data suggest that potassium channel openers may be effective when LQTS is secondary to reduced I_{K_s} (LQT1) or I_{K_r} (LQT2) but not when it is due to augmented late I_{Na} (LQT3). Oral dosing of nicorandil leads to blood levels in the range of 0.2 to 0.3 $\mu\text{mol/L}$, whereas intravenous injection can raise plasma levels to 4 $\mu\text{mol/L}$. Therefore, intravenously but not orally administered nicorandil may be of therapeutic value in suppressing repetitive episodes of TdP in patients with LQT1 and LQT2 syndromes, but less so in those with LQT3.

5. Calcium Channel Blockers—Our previous clinical studies involving MAP recordings indicated that verapamil, a blocker of L-type calcium current (I_{Ca-L}), is effective in abbreviating the QT interval and MAP duration as well as abolishing epinephrine-induced EADs in patients with congenital LQTS [60]. Thereafter, most of our LQTS patients in the study were shown to be linked to LQT1 or LQT2 syndrome. Our recent experimental data employing the wedge preparations also demonstrated that verapamil effectively decreases the QT interval and TDR and suppresses EADs and TdP in a combination of congenital and acquired LQTS (LQT1 + LQT2) (Fig. 3) [61]. Although data of the effect of verapamil in the LQT3 model is still lacking, calcium channel blockers may be useful for adjunctive therapy in LQT1, LQT2 (Fig. 4) and probably LQT3 patients. It is noteworthy that verapamil, like many other calcium channel blockers, is also a potent inhibitor of late I_{Na} .

6. Pacemaker Therapy—An increase of heart rate with exercise abbreviates the QT interval more effectively in LQT3 patients than in LQT2 patients [53]. Our previous MAP studies demonstrated that atrial pacing without sympathetic stimulation shortens the QT interval and MAP duration more significantly in patients with LQTS than in control patients [62]. Our experimental data from the wedges showed that the APD-, QT- and TDR- rate relations are much steeper in the LQT3 model than in the LQT1 or LQT2 model, possibly due to slow kinetics of reactivation of late I_{Na} [34,35]. However, the APD-rate relations in the 3 models are all steeper than under baseline conditions, suggesting that pacemaker therapy may also be useful in LQT1 and LQT2 patients, although it is likely to be most effective in LQT3 patients.

BRUGADA SYNDROME

In 1992, Pedro and Josep Brugada described 8 patients with a history of aborted sudden cardiac death due to VF and a distinct ECG pattern, consisting of right bundle branch block (RBBB) and ST segment elevation in the right precordial leads (V1 - V3) in the absence of any structural

heart disease [63-72]. Brugada syndrome is more commonly observed in Asian countries, including Thailand and Japan than in the U.S. and European countries [73-75]. In 1998, Chen and co-workers reported the first and only gene mutation linked to Brugada Syndrome in *SCN5A*, which encodes for the α subunit of the cardiac sodium channel [3]. The *SCN5A* mutations causing Brugada phenotype generally result in a reduction in the availability of I_{Na} (loss of function). More than five dozen distinct mutations in *SCN5A* gene have been so far identified, and all mutations display an autosomal dominant mode of transmission. Thus, males and females are expected to inherit the defective gene equally. However, more than 80% of Brugada probands are adult males. Two specific types of ST segment elevation are observed in patients with this syndrome; coved and saddleback type ST segment elevation. Although the magnitude and pattern of ST segment elevation is dynamic, waxing and waning day-to-day [76], the coved type ST segment elevation is of importance in relation to a higher incidence of VF and sudden cardiac death [69-72,77].

Cellular Mechanism for Brugada Phenotype

A transient outward current (I_{to})-mediated phase 1 notch of the action potential (AP) is reported to be greater in the epicardium than in the endocardium in many species between the late 1980s and early 1990s [78-82]. Antzelevitch's group used the canine right ventricle and suggested that the prominent I_{to} -mediated phase 1 AP notch and subsequent loss of the AP dome (all-or-none repolarization) in the epicardium but not in the endocardium contribute to a significant voltage gradient transmurally during ventricular activation [78,79]. Moreover, they demonstrated that heterogeneous loss of the AP dome in the epicardium produces a premature beat via a mechanism of phase 2 reentry in isolated sheets of canine right ventricle [83]. Around the same time, Brugada syndrome was reported as a specific clinical entity, which seemed to be a clinical counterpart to the mechanism of all-or-none repolarization and phase 2 reentry [63].

Direct experimental evidence for the cellular mechanism of ST segment elevation and VF in Brugada syndrome was obtained by the same group using an arterially-perfused canine right ventricular wedge preparation [84,85]. Their data showed that the I_{to} -mediated AP notch and the loss of AP dome in the epicardium, but not endocardium of the right ventricular outflow tract, gives rise to a transmural voltage gradient. This results in ST segment elevation in leads V1 - V3 and the induction of VF due to phase 2 reentry [85]. J point elevation or saddleback-type ST segment elevation is created by the transmural voltage gradient due to a large phase 1 notch in the epicardium but not in the endocardium (Fig. 5B). The coved-type ST segment elevation and the terminal negative T wave, which are more malignant signs, are secondary to further accentuated phase 1 notch, greater prolongation of epicardial APD, and a resultant reversed transmural voltage gradient (Fig. 5C). Loss of the AP dome in the epicardium further accentuates ST segment elevation (Fig. 5D). A variety of agents including antiarrhythmic and autonomic agents modulate ST segment elevation and the prevalence of VF in right ventricular wedge preparations. Exposure to pinacidil, a potassium channel opener, produces a transmural voltage gradient between epicardial and endocardial cells and ST segment elevation in the transmural ECG. A combination with pilsicainide, a class IC sodium channel blocker and terfenadine, an $ICa-L$ blocker, also induces a transmural voltage gradient, coved-type ST segment elevation, and the terminal negative T wave in the ECG (Fig. 5C). As an autonomic agent, acetylcholine, a parasympathetic agonist, also induces ST segment elevation probably due to its blocking effect of $ICa-L$. In contrast, isoproterenol, a β -adrenergic agonist, strongly augments $ICa-L$, restores the epicardial dome and attenuates ST segment elevation (Fig. 5E). The relatively selective I_{to} blocker, 4-aminopyridine (4-AP), and the less selective I_{to} blocker, quinidine, also restore the epicardial dome and decrease the phase 1 AP notch, thus decreasing or eliminating ST segment elevation (Fig. 6). In right ventricular wedge preparations, heterogeneous loss of the AP dome in the epicardium results in a marked epicardial dispersion

of repolarization (EDR) (Fig. 6B and 7A), giving rise to a premature beat due to phase 2 reentry, which then precipitates VF (Fig. 7B and 7C). The episodes of VF induced in this model are also successfully suppressed by I_{to} blockade with 4-AP or quinidine.

Specific Therapy Based on Cellular Mechanisms

Since the maintenance of the AP dome is determined by the balance of currents active at the end of phase 1 of AP (principally I_{to} and I_{Ca-L}), any interventions that increase outward currents (e.g. I_{to} , adenosine tri-phosphate sensitive potassium current [I_{K-ATP}], I_{Ks} , I_{Kr}) or decrease inward currents (e.g. I_{Ca-L} , fast I_{Na}) at the end of phase 1 can accentuate ST segment elevation, as found in Brugada patients. Among these interventions, ST segment elevation is unmasked or amplified most by class IC sodium channel blockers secondary to their strong effect to block fast I_{Na} . Therefore, class IC sodium channel blockers are used as a diagnostic tool to unmask latent Brugada syndrome with transient or non-spontaneous ST segment elevation [86-89]. In addition to sodium channel blockers, considerable drugs and conditions that cause an outward shift in current active at the end of phase 1 AP are reported to induce transient ST segment elevation like that in Brugada syndrome, which is described as an “acquired” form of Brugada syndrome [90]. These include calcium channel blockers, β -blockers, first-generation histaminic H1 receptor antagonists, and psychotropic drugs including tricyclic antidepressants, phenothiazine, and selective serotonin reuptake inhibitors.

On the other hand, agents that reduce outward currents (e.g. I_{to} , I_{K-ATP} , I_{Ks} , I_{Kr}) or boost inward currents (e.g. I_{Ca-L}) at the end of phase 1 of AP can attenuate ST segment elevation and suppress episodes of VT/VF. Such agents are candidates for a pharmacological approach to therapy of the Brugada syndrome (Table 2). Based on current data, an ICD should be implanted in Brugada patients with a history of cardiac arrest/aborted sudden cardiac death or syncope (symptomatic Brugada syndrome), because of a high recurrence rate of cardiac events during follow-up periods after the first cardiac event [64,69,71,72,91]. The indication of ICD is still controversial in patients with asymptomatic Brugada syndrome who have no history of cardiac arrest/aborted sudden cardiac death and syncope [69,71]. Only under backup with ICD therapy, should adjunctive pharmacological treatment be considered in symptomatic Brugada patients to reduce the incidence of VF episodes. Quinidine is the only oral antiarrhythmic agents which may be of therapeutic value [92,93]. Although quinidine is classified as a IA sodium channel blocker, it improves ST segment elevation as a result of its relatively strong I_{to} blocking effect [94]. Denopamine, an oral adrenergic stimulant, or oral atropine, an anti-cholinergic agent, increases I_{Ca-L} , and may be a choice for pharmaceutical therapy [95]. More recently, cilostazol, a phosphodiesterase III inhibitor, was reported to reduce ST segment elevation probably due to its effect to increase I_{Ca-L} and heart rate [96]. During electrical storm associated with repetitive episodes of VF, continuous infusion of isoproterenol, a β -adrenergic agonist (0.005 – 0.02 $\mu\text{g/kg/min}$ or 20 % increase of heart rate), is the first choice of therapy (Fig. 8) [97]. Injections of atropine may be another choice, although the effect is short-lived. Based on the cellular mechanism responsible for Brugada phenotype, a cardio-selective I_{to} blocker would be an ideal pharmaceutical approach, and the development of such a drug will be most welcome [98].

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REFERENCES

References 99-101 are related articles recently published in Current Pharmaceutical Design.

1. Keating M, Atkinson D, Dunn C, Timothy K, Vincent GM, Leppert M. Linkage of a cardiac arrhythmia, the long QT syndrome, and the Harvey ras-1 gene. *Science* 1991;252:704–706. [PubMed: 1673802]
2. Donger CD, Denjoy I, Berthet M, Neyroud N, Cruaud C, Bennaceur M, et al. KVLQT1 C-terminal missense mutation causes a forme fruste long-QT syndrome. *Circulation* 1997;96:2778–2781. [PubMed: 9386136]
3. Chen Q, Kirsch GE, Zhang D, Brugada R, Brugada J, Brugada P, et al. Genetic basis and molecular mechanisms for idiopathic ventricular fibrillation. *Nature* 1998;392:293–296. [PubMed: 9521325]
4. Schott JJ, Alshinawi C, Kyndt F, Probst V, Hooftje TM, Hulsbeek M, et al. Cardiac conduction defects associate with mutations in SCN5A. *Nat Genet* 1999;23:20–21. [PubMed: 10471492]
5. Priori SG, Napolitano C, Tiso N, Memmi M, Vignati G, Bloise R, et al. Mutations in the Cardiac Ryanodine Receptor Gene (hRyR2) Underlie Catecholaminergic Polymorphic Ventricular Tachycardia. *Circulation* 2001;103:196–200. [PubMed: 11208676]
6. Laitinen PJ, Brown KM, Piippo K, Swan H, Devaney JM, Brahmabhatt B, et al. Mutations of the cardiac ryanodine receptor (RyR2) gene in familial polymorphic ventricular tachycardia. *Circulation* 2001;103:485–490. [PubMed: 11157710]
7. Chen YH, Xu SJ, Bendahhou S, Wang XL, Wang Y, Xu WY, et al. KCNQ1 gain-of-function mutation in familial atrial fibrillation. *Science* 2003;299:251–254. [PubMed: 12522511]
8. Veldkamp MW, Wilders R, Baarscheer A, Zegers JG, Bezzina CR, Wilde AA. Contribution of sodium channel mutations to bradycardia and sinus node dysfunction in LQT3 families. *Circ Res* 2003;92:976–983. [PubMed: 12676817]
9. Gollob MH, Green MS, Tang AS, Gollob T, Karibe A, Ali Hassan AS, et al. Identification of a gene responsible for familial Wolff-Parkinson-White syndrome. *N Engl J Med* 200;344:1823–1831. [PubMed: 11407343]
10. Brugada R, Hong K, Dumaine R, Cordeiro J, Gaita F, Borggrefe M, et al. Sudden death associated with short-QT syndrome linked to mutations in HERG. *Circulation* 2004;109:30–35. [PubMed: 14676148]
11. Schwartz PJ, Periti M, Malliani A. The long QT syndrome. *Am Heart J* 1975;89:378–390. [PubMed: 234667]
12. Moss AJ, Schwartz PJ, Crampton RS, Locati E, Carleen E. The long QT syndrome: a prospective international study. *Circulation* 1985;71:17–21. [PubMed: 2856865]
13. Zipes DP. The long QT interval syndrome. A Rosetta stone for sympathetic related ventricular tachyarrhythmias. *Circulation* 1991;84:1414–1419. [PubMed: 1760020]
14. Roden DM, Lazzara R, Rosen MR, Schwartz PJ, Towbin JA, Vincent GM, et al. Multiple mechanisms in the long-QT syndrome: Current knowledge, gaps, and future directions. *Circulation* 1996;94:1996–2012. [PubMed: 8873679]
15. Shimizu W, Ohe T, Kurita T, Takaki H, Aihara N, Kamakura S, et al. Early Afterdepolarizations induced by isoproterenol in patients with congenital long QT syndrome. *Circulation* 1991;84:1915–1923. [PubMed: 1657447]
16. Moss AJ, Zareba W, Hall WJ, Schwartz PJ, Crampton RS, Benhorin J, et al. Effectiveness and limitations of beta-blocker therapy in congenital long-QT syndrome. *Circulation* 2000;101:616–623. [PubMed: 10673253]
17. Splawski I, Shen J, Timothy KW, Lehmann MH, Priori S, Robinson JL, et al. Spectrum of mutations in long-QT syndrome genes. KVLQT1, HERG, SCN5A, KCNE1, and KCNE2. *Circulation* 2000;102:1178–1185. [PubMed: 10973849]
18. Plaster NM, Tawil R, Tristani-Firouzi M, Canun S, Bendahhou S, Tsunoda A, et al. Mutations in Kir2.1 cause the developmental and episodic electrical phenotypes of Andersen's syndrome. *Cell* 2001;105:511–519. [PubMed: 11371347]
19. Mohler PJ, Schott JJ, Gramolini AO, Dilly KW, Guatimosim S, DuBell WH, et al. Ankyrin-B mutation causes type 4 long-QT cardiac arrhythmia and sudden cardiac death. *Nature* 2003;421:634–639. [PubMed: 12571597]

20. Sanguinetti MC, Curran ME, Zou A, Shen J, Spector PS, Atkinson DL, et al. Coassembly of KvLQT1 and minK (IsK) proteins to form cardiac I_{Ks} potassium channel. *Nature* 1996;384:80–83. [PubMed: 8900283]
21. Barhanin J, Lesage F, Guillemare E, Fink M, Lazdunski M, Romey G. KvLQT1 and IsK (minK) proteins associate to form the I_{Ks}, cardiac potassium current. *Nature* 1996;384:78–80. [PubMed: 8900282]
22. Sanguinetti MC, Jiang C, Curran ME, Keating MT. A mechanistic link between an inherited and an acquired cardiac arrhythmia: HERG encodes the I_{Kr}, potassium channel. *Cell* 1995;81:299–307. [PubMed: 7736582]
23. Abbott GW, Sesti F, Splawski I, Buck ME, Lehmann MH, Timothy KW, et al. MiRP1 forms IKr potassium channels with HERG and is associated with cardiac arrhythmia. *Cell* 1999;97:175–187. [PubMed: 10219239]
24. Wang Q, Shen J, Splawski I, Atkinson DL, Li ZZ, Robinson JL, et al. SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. *Cell* 1995;80:805–811. [PubMed: 7889574]
25. Schwartz PJ, Stramba-Badiale M, Segantini A, Austoni P, Bosi G, Giorgetti R, et al. Prolongation of the QT interval and the sudden infant death syndrome. *N Engl J Med* 1998;338:1709–1714. [PubMed: 9624190]
26. Schwartz PJ, Priori SO, Dumaine R, Napolitano C, Antzelevitch C, Stramba-Badiale M, et al. A molecular link between the sudden infant death syndrome and the long-QT syndrome. *N Engl J Med* 2000;343:262–267. [PubMed: 10911008]
27. Ackerman MJ, Siu BL, Sturner WQ, Tester DJ, Valdivia CR, Makielski JC, et al. Postmortem molecular analysis of SCN5A defects in sudden infant death syndrome. *JAMA* 2001;286:2264–2269. [PubMed: 11710892]
28. Zareba W, Moss AJ, Schwartz PJ, Vincent GM, Robinson JL, Priori SG, et al. Influence of the genotype on the clinical course of the long-QT syndrome. *N Engl J Med* 1998;339:960–965.
29. Schwartz PJ, Priori SG, Spazzolini C, Moss AJ, Vincent GM, Napolitano C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation* 2001;103:89–95. [PubMed: 11136691]
30. Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, et al. Risk stratification in the long-QT syndrome. *N Engl J Med* 2003;348:1866–1874. [PubMed: 12736279]
31. Moss AJ, Zareba W, Benhorin J, Locati EH, Hall WJ, Robinson JL, et al. ECG T-wave patterns in genetically distinct forms of the hereditary long QT syndrome. *Circulation* 1995;92:2929–2934. [PubMed: 7586261]
32. Zhang L, Timothy KW, Vincent GM, Lehmann MH, Fox J, Giuli LC, et al. Spectrum of ST-T-wave patterns and repolarization parameters in congenital long-QT syndrome: ECG findings identify genotypes. *Circulation* 2000;102:2849–2855. [PubMed: 11104743]
33. Takenaka K, Ai T, Shimizu W, Kobori A, Ninomiya T, Otani H, et al. Exercise stress test amplifies genotype-phenotype correlation in the LQT1 and LQT2 forms of the long QT syndrome. *Circulation* 2003;107:838–844. [PubMed: 12591753]
34. Shimizu W, Antzelevitch C. Sodium channel block with mexiletine is effective in reducing dispersion of repolarization and preventing torsade de pointes in LQT2 and LQT3 models of the long-QT syndrome. *Circulation* 1997;96:2038–2047. [PubMed: 9323097]
35. Shimizu W, Antzelevitch C. Cellular basis for the electrocardiographic features of the LQT1 form of the long QT syndrome: Effects of β -adrenergic agonists, antagonists and sodium channel blockers on transmural dispersion of repolarization and torsade de pointes. *Circulation* 1998;98:2314–2322. [PubMed: 9826320]
36. Yan GX, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long QT syndrome. *Circulation* 1998;98:1928–1936. [PubMed: 9799215]
37. Antzelevitch, C.; Yan, GX.; Shimizu, W.; Burashnikov, A. Electrical heterogeneity, the ECG, and cardiac arrhythmias. In: Zipes, DP.; Jalife, J., editors. *Cardiac Electrophysiology: From Cell to Bedside*. 3rd edition. Saunders WB. Co.; Philadelphia: 1999. p. 222-238.
38. Antzelevitch C, Shimizu W, Yan GX, Sicouri S, Weissenberger J, Nesterenko V, et al. The M cell: Its contribution to the ECG and to normal and abnormal electrical function of the heart. *J Cardiovasc Electrophysiol* 1999;10:1124–1152. [PubMed: 10466495]

39. Shimizu W, Antzelevitch C. Cellular and ionic basis for T wave alternans under long QT conditions. *Circulation* 1999;99:1499–1507. [PubMed: 10086976]
40. Shimizu W, Antzelevitch C. Cellular basis for long QT, transmural dispersion of repolarization and Torsade de Pointes in the long QT syndrome. *J Electrocardiol* 1999;32:177–184. [PubMed: 10688323]
41. Shimizu W, Antzelevitch C. Differential effects of beta-adrenergic agonists and antagonists in LQT1, LQT2 and LQT3 models of the long QT syndrome. *J Am Coll Cardiol* 2000;35:778–786. [PubMed: 10716483]
42. Shimizu W, Antzelevitch C. Effects of a K⁺ channel opener to reduce transmural dispersion of repolarization and prevent Torsade de Pointes in LQT1, LQT2 and LQT3 models of the long-QT syndrome. *Circulation* 2000;102:706–712. [PubMed: 10931813]
43. Moss AJ, Robinson JL, Gessman L, Gillespie R, Zareba W, Schwartz PJ, et al. Comparison of clinical and genetic variables of cardiac events associated with loud noise versus swimming among subjects with the long QT syndrome. *Am J Cardiol* 1999;84:876–879. [PubMed: 10532503]
44. Wilde AAM, Jongbloed RJE, Doevendans PA, Duren DR, Hauer RNW, van Langen IM, et al. Auditory stimuli as a trigger for arrhythmic events differentiate HERG-related (LQT2) patients from KVLQT1-related patients (LQT1). *J Am Coll Cardiol* 1999;33:327–332. [PubMed: 9973011]
45. Ackerman MJ, Tester DJ, Porter CJ. Swimming, a gene-specific arrhythmogenic trigger for inherited long QT syndrome. *Mayo Clin Proc* 1999;74:1088–1094. [PubMed: 10560595]
46. Khositseth A, Tester DJ, Will ML, Bell CM, Ackerman MJ. Identification of a common genetic substrate underlying postpartum cardiac events in congenital long QT syndrome. *Heart Rhythm* 2004;1:60–64. [PubMed: 15851119]
47. Tanabe Y, Inagaki M, Kurita T, Nagaya N, Taguchi A, Suyama K, et al. Sympathetic stimulation produces a greater increase in both transmural and spatial dispersion of repolarization in LQT1 than LQT2 forms of congenital long QT syndrome. *J Am Coll Cardiol* 2001;37:911–919. [PubMed: 11693770]
48. Noda T, Takaki H, Kurita T, Suyama K, Nagaya N, Taguchi A, et al. Gene-specific response of dynamic ventricular repolarization to sympathetic stimulation in LQT1, LQT2 and LQT3 forms of congenital long QT syndrome. *Eur Heart J* 2002;23:975–983. [PubMed: 12069453]
49. Ackerman MJ, Khositseth A, Tester DJ, Hejlik JB, Shen WK, Porter CB. Epinephrine-induced QT interval prolongation: a gene-specific paradoxical response in congenital long QT syndrome. *Mayo Clin Proc* 2002;77:413–421. [PubMed: 12004990]
50. Shimizu W. Effects of sympathetic stimulation on various repolarization indices in the congenital long QT syndrome. *Ann Noninvasive Electrocardiol* 2002;4:332–342. [PubMed: 12431311]
51. Shimizu W, Tanabe Y, Aiba T, Inagaki M, Kurita T, Suyama K, et al. Differential effects of β -blockade on dispersion of repolarization in absence and presence of sympathetic stimulation between LQT1 and LQT2 forms of congenital long QT syndrome. *J Am Coll Cardiol* 2002;39:1984–1991. [PubMed: 12084597]
52. Shimizu W, Noda T, Takaki H, Kurita T, Nagaya N, Satomi K, et al. Epinephrine unmasks latent mutation carriers with LQT1 form of congenital long QT syndrome. *J Am Coll Cardiol* 2003;41:633–642. [PubMed: 12598076]
53. Schwartz PJ, Priori SG, Locati EH, Napolitano C, Cantu F, Towbin JA, et al. Long QT syndrome patients with mutations of the SCN5A and HERG genes have differential responses to Na⁺ channel blockade and to increases in heart rate: Implications for gene-specific therapy. *Circulation* 1995;92:3381–3386. [PubMed: 8521555]
54. Zygmunt AC, Eddlestone GT, Thomas GP, Nesterenko VV, Antzelevitch C. Larger late sodium conductance in M cells contributes to electrical heterogeneity in canine ventricle. *Am J Physiol Heart Circ Physiol* 2001;281:H689–697. [PubMed: 11454573]
55. Benhorin J, Taub R, Goldmit M, Kerem B, Kass RS, Windman I, et al. Effects of flecainide in patients with new SCN5A mutation: mutation-specific therapy for long-QT syndrome? *Circulation* 2000;101:1698–1706. [PubMed: 10758053]
56. Priori SG, Napolitano C, Schwartz PJ, Bloise R, Crotti L, Ronchetti E. The elusive link between LQT3 and Brugada syndrome: the role of flecainide challenge. *Circulation* 2000;102:945–947. [PubMed: 10961955]

57. Compton SJ, Lux RL, Ramsey MR, Strellich KR, Sanguinetti MC, Green LS, et al. Genetically defined therapy of inherited long-QT syndrome. Correction of abnormal repolarization by potassium. *Circulation* 1996;94:1018–1022. [PubMed: 8790040]
58. Etheridge SP, Compton SJ, Tristani-Firouzi M, Mason JW. A new oral therapy for long QT syndrome: long-term oral potassium improves repolarization in patients with HERG mutations. *J Am Coll Cardiol* 2003;42:1777–1782. [PubMed: 14642687]
59. Shimizu W, Kurita T, Matsuo K, Aihara N, Kamakura S, Towbin JA, et al. Improvement of repolarization abnormalities by a K⁺ channel opener in the LQT1 form of congenital long QT syndrome. *Circulation* 1998;97:1581–1588. [PubMed: 9593563]
60. Shimizu W, Ohe T, Kurita T, Kawade M, Arakaki Y, Aihara N, et al. Effects of verapamil and propranolol on early afterdepolarizations and ventricular arrhythmias induced by epinephrine in congenital long QT syndrome. *J Am Coll Cardiol* 1995;26:1299–1309. [PubMed: 7594047]
61. Aiba T, Shimizu W, Hidaka I, Uemura K, Sunagawa K. Verapamil suppresses torsade de pointes by reducing transmural dispersion of repolarization and preventing early afterdepolarization in acquired model of long-QT syndrome. *Circulation* 2002;106(Suppl):1–22.
62. Hirao H, Shimizu W, Kurita T, Aihara N, Kamakura S, Shimomura K. Frequency-dependent electrophysiologic properties of ventricular repolarization in patients with congenital long QT syndrome. *J Am Coll Cardiol* 1996;28:1269–1277. [PubMed: 8890826]
63. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome: a multicenter report. *J Am Coll Cardiol* 1992;20:1391–1396. [PubMed: 1309182]
64. Brugada J, Brugada R, Brugada P. Right bundle-branch block and ST-segment elevation in leads V₁ through V₃. A marker for sudden death in patients without demonstrable structural heart disease. *Circulation* 1998;97:457–460. [PubMed: 9490240]
65. Gussak I, Antzelevitch C, Bjerregaard P, Towbin JA, Chaitman BR. The brugada syndrome: clinical, electrophysiological and genetic aspects. *J Am Coll Cardiol* 1999;33:5–15. [PubMed: 9935001]
66. Alings M, Wilde A. “Brugada” syndrome: Clinical data and suggested pathophysiological mechanism. *Circulation* 1999;99:666–673. [PubMed: 9950665]
67. Antzelevitch, C.; Brugada, P.; Brugada, J.; Brugada, R.; Nademanee, K.; Towbin, JA. The Brugada Syndrome. In: Camm, J., editor. *Clinical Approaches to Tachyarrhythmias*. Futura Publishing Company, Inc.; Armonk, NY: 1999. p. 1-99.
68. Antzelevitch C, Brugada P, Brugada J, Brugada R, Shimizu W, Gussak I, et al. Brugada syndrome. A decade of progress. *Circ Res* 2002;91:1114–1118. [PubMed: 12480811]
69. Priori SG, Napolitano C, Gasparini M, Pappone C, Della Bella P, Giordano U, et al. Natural history of Brugada syndrome: insights for risk stratification and management. *Circulation* 2002;105:1342–1347. [PubMed: 11901046]
70. Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, et al. Proposed diagnostic criteria for the Brugada syndrome: consensus report. *Circulation* 2002;106:2514–2519. [PubMed: 12417552]
71. Brugada J, Brugada R, Antzelevitch C, Towbin J, Nademanee K, Brugada P. Long-term follow-up of individuals with the electrocardiographic pattern of right bundle-branch block and ST-segment elevation in precordial leads V₁ to V₃. *Circulation* 2002;105:73–78. [PubMed: 11772879]
72. Brugada J, Brugada R, Brugada P. Determinants of sudden cardiac death in individuals with the electrocardiographic pattern of Brugada syndrome and no previous cardiac arrest. *Circulation* 2003;108:3092–3096. [PubMed: 14623800]
73. Nademanee K, Veerakul G, Nimmannit S, Chaowakul V, Bhuripanyo K, Likittanasombat K, et al. Arrhythmogenic marker for the sudden unexplained death syndrome in Thai men. *Circulation* 1997;96:2595–2600. [PubMed: 9355899]
74. Miyazaki T, Mitamura H, Miyoshi S, Soejima K, Aizawa Y, Ogawa S. Autonomic and antiarrhythmic drug modulation of ST segment elevation in patients with Brugada syndrome. *J Am Coll Cardiol* 1996;27:1061–1070. [PubMed: 8609322]
75. Vatta M, Dumaine R, Varghese G, Richard TA, Shimizu W, Aihara N, et al. Genetic and biophysical basis of sudden unexplained nocturnal death syndrome (SUNDS), a disease allelic to Brugada syndrome. *Hum Mol Genet* 2002;11:337–345. [PubMed: 11823453]

76. Matsuo K, Shimizu W, Kurita T, Inagaki M, Aihara N, Kamakura S. Dynamic changes of 12-lead electrocardiograms in a patient with Brugada syndrome. *J Cardiovasc Electrophysiol* 1998;9:508–512. [PubMed: 9607459]
77. Atarashi H, Ogawa S, Harumi K, Hayakawa H, Sugimoto T, Okada R, et al. Characteristics of patients with right bundle branch block and ST-segment elevation in right precordial leads. *Am J Cardiol* 1996;78:581–583. [PubMed: 8806350]
78. Litovsky SH, Antzelevitch C. Transient outward current prominent in canine ventricular epicardium but not endocardium. *Circ Res* 1988;62:116–126. [PubMed: 2826039]
79. Antzelevitch C, Sicouri S, Litovsky SH, Lukas A, Krishnan SC, Di Diego JM, et al. Heterogeneity within the ventricular wall. Electrophysiology and pharmacology of epicardial, endocardial, and M cells. *Circ Res* 1991;69:1427–1449. [PubMed: 1659499]
80. Furukawa T, Myerburg RJ, Furukawa N, Bassett AL, Kimura S. Differences in transient outward currents of feline endocardial and epicardial myocytes. *Circ Res* 1990;67:1287–1291. [PubMed: 2225360]
81. Fedida D, Giles WR. Regional variations in action potentials and transient outward current in myocytes isolated from rabbit left ventricle. *J Physiol (Lond)* 1991;442:191–209. [PubMed: 1665856]
82. Wettwer E, Amos GJ, Posival H, Ravens U. Transient outward current in human ventricular myocytes of subepicardial and subendocardial origin. *Circ Res* 1994;75:473–482. [PubMed: 8062421]
83. Krishnan SC, Antzelevitch C. Flecainide-induced arrhythmia in canine ventricular epicardium: Phase 2 Reentry? *Circulation* 1993;87:562–5729. [PubMed: 8425300]
84. Yan GX, Antzelevitch C. Cellular basis for the electrocardiographic J wave. *Circulation* 1996;93:372–379. [PubMed: 8548912]
85. Yan GX, Antzelevitch C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST segment elevation. *Circulation* 1999;100:1660–1666. [PubMed: 10517739]
86. Brugada R, Brugada J, Antzelevitch C, Kirsch GE, Potenza D, Towbin JA, et al. Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts. *Circulation* 2000;101:510–515. [PubMed: 10662748]
87. Shimizu W, Matsuo K, Takagi M, Tanabe Y, Aiba T, Taguchi A, et al. Body surface distribution and response to drugs of ST segment elevation in the Brugada syndrome: Clinical implication of 87-leads body surface potential mapping and its application to 12-leads electrocardiograms. *J Cardiovasc Electrophysiol* 2000;11:396–404. [PubMed: 10809492]
88. Shimizu W, Antzelevitch C, Suyama K, Kurita T, Taguchi A, Aihara N, et al. Effect of sodium channel blockers on ST segment, QRS duration, and corrected QT interval in patients with Brugada syndrome. *J Cardiovasc Electrophysiol* 2000;11:1320–1329. [PubMed: 11196553]
89. Morita H, Morita ST, Nagase S, Banba K, Nishii N, Tani Y, et al. Ventricular arrhythmia induced by sodium channel blocker in patients with Brugada syndrome. *J Am Coll Cardiol* 2003;42:1624–1631. [PubMed: 14607450]
90. Goldgran-Toledano D, Sideris G, Kevorkian JP. Overdose of cyclic antidepressants and the Brugada syndrome. *N Engl J Med* 2002;346:1591–1592. [PubMed: 12015405]
91. Kanda M, Shimizu W, Matsuo K, Nagaya N, Taguchi A, Suyama K, et al. Electrophysiologic characteristics and implication of induced ventricular fibrillation in symptomatic patients with Brugada syndrome. *J Am Coll Cardiol* 2002;39:1799–1805.
92. Belhassen B, Viskin S, Fish R, Glick A, Setbon I, Eldar M. Effects of electrophysiologic-guided therapy with Class IA antiarrhythmic drugs on the long-term outcome of patients with idiopathic ventricular fibrillation with or without the Brugada syndrome. *J Cardiovasc Electrophysiol* 1999;10:1301–1312. [PubMed: 10515552]
93. Hermida JS, Denjoy I, Clerc J, Extramiana F, Jarry G, Milliez P, et al. Hydroquinidine therapy in Brugada syndrome. *J Am Coll Cardiol* 2004;43:1853–1860. [PubMed: 15145111]
94. Alings M, Dekker L, Sadee A, Wilde A. Quinidine induced electrocardiographic normalization in two patients with Brugada syndrome. *PACE* 2001;24:1420–1422. [PubMed: 11584468]
95. Shimizu W, Kamakura S. Catecholamines in children with congenital long QT syndrome and Brugada syndrome. *J Electrocardiol* 2001;34:173–175. [PubMed: 11781952]

96. Tsuchiya T, Ashikaga K, Honda T, Arita M. Prevention of ventricular fibrillation by cilostazol, an oral phosphodiesterase inhibitor, in a patient with Brugada syndrome. *J Cardiovasc Electrophysiol* 2002;13:698–701. [PubMed: 12139296]
97. Suzuki H, Torigoe K, Numata O, Yazaki S. Infant case with a malignant form of Brugada syndrome. *J Cardiovasc Electrophysiol* 2000;11:1277–1280. [PubMed: 11083249]
98. Antzelevitch C, Brugada P, Brugada J, Brugada R, Towbin JA, Nademanee K. Brugada syndrome: 1992-2002: a historical perspective. *J Am Coll Cardiol* 2003;41:1665–1671. [PubMed: 12767644]
99. Lombardi F, Terranova P. Hypertension and concurrent arrhythmias. *Curr Pharm Design* 2003;9(21): 1703–13.
100. Perrella MA, Yet SF. Role of heme oxygenase-1 in cardiovascular function. *Curr Pharm Design* 2003;9(30):2479–87.
101. Takano H, Ohtsuka M, Akazawa H, Toko H, Harada M, Hasegawa H, et al. Pleiotropic effects of cytokines on acute myocardial infarction: G-CSF as a novel therapy for acute myocardial infarction. *Curr Pharm Design* 2003;9(14):1121–7.

Fig. (1).

Differential effect of isoproterenol (Iso), a β -agonist, on the QT interval and the action potential duration (APD) in the LQT1, LQT2 and LQT3 models of the arterially-perfused canine left ventricular wedge preparations. Shown are superimposed action potentials recorded simultaneously from M and epicardial (Epi) cells together with a transmural ECG at a BCL of 2000 msec. In the LQT1 model with chromanol 293B, Iso dramatically prolongs the APD of the M cells (2 minutes) and maintains this as the effect approaches a steady state (10 minutes), whereas the APD of the Epi cells is always abbreviated, resulting in a **persistent increase** in the QT interval and the transmural dispersion of repolarization (TDR) (A). In the LQT2 model with d-sotalol, Iso initially prolongs (2 minutes) and then abbreviates the APD of the M cells to the control level (10 minutes), whereas the APD of the Epi cells is always abbreviated, resulting in a **transient increase** in the QT interval and the TDR (B). In the LQT3 model with ATX-II, Iso always abbreviates the APD of both cells, resulting in a **persistent decrease** in the QT interval and the TDR (C). Modified from [41] with permission.

Fig. (2).

Dose-dependent effects of mexiletine (Mex) on action potential duration (APD) and QT interval in the chromanol 293B+isoproterenol (LQT1, **A**), d-sotalol (LQT2, **B**) and ATX-II (LQT3, **C**) models of the arterially-perfused canine left ventricular wedge preparations. Each trace shows superimposed action potentials recorded simultaneously from M and epicardial (Epi) regions, together with a transmural ECG. BCL=2000 msec. Mexiletine (2 to 20 $\mu\text{mol/L}$) dose-dependently abbreviates the APD of both cells as well as the QT interval; 20 $\mu\text{mol/L}$ mexiletine completely reverses the effect of ATX-II to prolong the QT interval, APD and to increase the transmural dispersion of repolarization (TDR) in the LQT3 model (**C**). Although 20 $\mu\text{mol/L}$ mexiletine does not reverse the effect of the drugs to prolong the QT interval and APD in the LQT1 (**A**) and LQT2 (**B**) models, the effect of mexiletine to abbreviate the APD is clearly greater in the M cell than in the Epi cell. Mexiletine thus decreases TDR. Modified from [34,35] with permission.

Fig. (3).

Dose-dependent effects of verapamil on action potential duration (APD) and QT interval in a combination of congenital and acquired LQTS model (LQT1 + LQT2). Shown are transmembrane action potentials simultaneously recorded from epicardial (Epi) and M regions together with a transmural ECG using the arterially-perfused feline left ventricular wedge preparations (BCL=2000 msec.). Verapamil (0.1 to 5 $\mu\text{mol/L}$) dose-dependently abbreviates APD of the Epi and M regions as well as the QT interval. Verapamil preferentially abbreviates the Epi APD compared to the APD of the M region, thus normalizing the inverted T wave and decreasing transmural dispersion of repolarization to control levels.

Fig. (4).

Effect of verapamil, an L-type calcium blocker, to suppress Torsade de Pointes (TdP) in a patient with LQT2 form of congenital long QT syndrome. **A:** Spontaneously induced TdP. **B:** Injection of verapamil (3 mg) totally prevents the episodes of TdP. The 12-lead ECG shows low-amplitude T waves with a notched configuration in leads I, II, III, aVF, V4, V5 and V6, consistent with the T wave pattern in LQT2 syndrome.

Fig. (5).

Cellular basis for ST-segment elevation and effect of isoproterenol, a β -adrenergic agonist, in a Brugada model employing an arterially perfused canine right ventricular wedge preparation. Shown are transmembrane action potentials (APs) simultaneously recorded from the epicardial (Epi) and endocardial (Endo) sites together with a transmural ECG (BCL=2000 msec). **A:** Control. **B:** Terfenadine (5 μ mol/L) accentuates phase 1 notch in Epi but not in Endo, causes J point elevation. **C:** Additional pilsicainide (5 μ mol/L) produces further accentuation of phase 1 notch, a greater prolongation of Epi AP, and a reversed transmural voltage gradient, giving rise to coved-type ST segment elevation with a terminal negative T wave. **D:** Further accentuation of phase 1 notch in Epi AP causes loss of AP dome, thus further accentuates ST-segment elevation in the ECG. **E:** Isoproterenol (0.02 μ g/min) restores AP dome in Epi and attenuates the ST segment elevation.

Fig. (6).

Effect of 4-aminopyridine (4-AP), a selective blocker of transient outward current (I_{to}), in a Brugada model using an arterially perfused canine right ventricular wedge preparation. Shown are transmembrane action potentials (APs) simultaneously recorded from 2 epicardial sites (Epi 1 and Epi 2) and 1 endocardial site (Endo) together with a transmural ECG (BCL=2000 msec). **A:** In control, phase 1 AP notch in Epi but not in Endo is associated with a J wave in the ECG. **B:** A combination of pinacidil (2 μ mol/L), terfenadine (5 μ mol/L), and pilsicainide (5 μ mol/L) produces a loss of AP dome in Epi 1 but not in Epi 2, results in a marked epicardial dispersion of repolarization (EDR), and a coved-type ST segment elevation and a negative T wave in the ECG. **C:** 4-AP (2 μ mol/L) restores the AP dome, decreases the phase 1 AP notch, and normalizes the ST-segment elevation.

Fig. (7).

Ventricular premature beat (PVC) and polymorphic ventricular tachycardia via phase 2 reentry in a Brugada model employing an arterially perfused canine right ventricular wedge preparation. Shown are transmembrane action potentials (APs) recorded simultaneously from one endocardial (Endo) and 2 epicardial (Epi 1 and Epi 2) sites together with a transmural ECG (BCL=2000 msec). A combined administration of pinacidil (2 $\mu\text{mol/L}$), terfenadine (5 $\mu\text{mol/L}$), and pilsicainide (5 $\mu\text{mol/L}$) causes heterogeneous loss of AP dome in Epi, giving rise to coved-type ST-segment elevation and increasing epicardial dispersion of repolarization (EDR) (A). Electrotonic propagation from the site where the dome is restored (Epi 1) to the site where it is lost (Epi 2) develops PVC due to a mechanism of phase 2 reentry (B), which triggered a spontaneous polymorphic ventricular tachycardia (C).

Fig. (8).

Effect of isoproterenol, a β -adrenergic agonist, during electrical storm of ventricular fibrillation (VF) in a patient with Brugada syndrome. **A:** The 12-lead ECG at baseline shows coved-type ST segment or prominent J wave in leads V1 and V2. **B:** Spontaneous VF is recorded by Holter monitoring. **C:** Continuous infusion of isoproterenol (0.004 $\mu\text{g/kg/min}$) attenuates the amplitude of ST segment elevation and J wave, and totally suppresses VF.

Table 1
Genotype-Specific Therapy Based on Experimental Data in LQT Syndrome

	LQT1 (LQT5)	LQT2 (LQT6)	LQT3
Sensitivity to Sympathetic Stimulation	+++++ (Sustained ↑ in TDR)	+++ (Transient ↑ in TDR)	– (↓ in TDR)
Torsade de Pointes	Exercise-related (Swimming)	Startle (Alarm Clock) Postpartum periods	Sleep / Rest
β-blockers	+++++	+++	–
Class IB sodium channel blockers	+++	+++++	+++++
Potassium channel openers	++	++	–
Calcium channel blockers	+++	+++	++?
Pacemaker	++	++	+++++

TDR, Transmural dispersion of repolarization. +++++ means most effective.

Table 2
Specific Therapy Based on Cellular Mechanism in Brugada Syndrome

Essential Therapy
Implantable cardioverter defibrillator (ICD)
Adjunctive Oral Therapy
Quinidine (I_{to} blockade)
Denopamine (I_{Ca} augmentation)
Atropine (I_{Ca} augmentation)
Cilostazol (I_{Ca} augmentation)
Acute Intravenous Therapy (Electrical storm of VF)
Isoproterenol (I_{Ca} augmentation, 0.005 - 0.02 $\mu\text{g/kg/min}$ or 20% increase of HR)
Atropine (I_{Ca} augmentation)

HR, Heart rate; I_{Ca} L-type calcium current; I_{to} , transient outward current; VF, Ventricular fibrillation.