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Pharmacological approach to the treatment of long and short QT syndromes[☆]

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Abstract

Inherited channelopathies have received increasing attention in recent years. The past decade has witnessed impressive progress in our understanding of the molecular and cellular basis of arrhythmogenesis associated with inherited channelopathies. An imbalance in ionic forces induced by these channelopathies affects the duration of ventricular repolarization and amplifies the intrinsic electrical heterogeneity of the myocardium, creating an arrhythmogenic milieu. Today, many of the channelopathies have been linked to mutations in specific genes encoding either components of ion channels or membrane or regulatory proteins. Many of the channelopathies are genetically heterogeneous with a variable degree of expression of the disease. Defining the molecular basis of channelopathies can have a profound impact on patient management, particularly in cases in which genotype-specific pharmacotherapy is available.

The long QT syndrome (LQTS) is one of the first identified and most studied channelopathies where abnormal prolongation of ventricular repolarization predisposes an individual to life threatening ventricular arrhythmia called Torsade de Pointes. On the other hand of the spectrum, molecular defects favoring premature repolarization lead to Short QT syndrome (SQTS), a recently described inherited channelopathy. Both of these channelopathies are associated with a high risk of sudden cardiac death due to malignant ventricular arrhythmia. Whereas pharmacological therapy is first line treatment for LQTS, defibrillators are considered as primary treatment for SQTS. This review provides a comprehensive review of the molecular genetics, clinical features, genotype–phenotype correlations and genotype-specific approach to pharmacotherapy of these two mirror-image channelopathies, SQTS and LQTS.

Keywords

Sudden cardiac death; Arrhythmias; Electrophysiology; Pharmacology Inherited channelopathy

1. Introduction

The QT interval is an electrocardiographic index of ventricular repolarization and a measure of the duration of the ventricular action potential. Acquired or congenital defects in a particular ion channel can seriously alter the balance of currents that determines repolarization of the action potential, thus predisposing to the development of cardiac arrhythmias. Inherited channelopathies have received increasing attention in recent years as an important etiology of sudden cardiac death (SCD) in individuals with structurally normal hearts. With clinical

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presentation relatively early in life, channelopathies are now considered one of the possible etiologies of sudden infant death syndrome (SIDS). The past decade has witnessed exciting advances in our understanding of the molecular and cellular basis of arrhythmogenesis associated with inherited channelopathies.

Congenital long QT syndrome (LQTS) was one of the first described and hence most studied channelopathies. Since its initial description in 1957 by Jervell (Jervell & Lange-Nielsen, 1957), a great deal of progress has been achieved in elucidating the genetic and molecular basis for arrhythmogenesis in LQTS. Thus far, mutations in 10 different genes have been identified and the disease has shown strong genotype-phenotype correlation.

The Short QT syndrome (SQTS), first described in 2000 by Gussak et al. (2000), is understandably less well studied. This notwithstanding, mutations in five different genes encoding a variety of ion channels have been identified.

Both, LQTS and SQTS are associated with high risk of sudden cardiac death. Pharmacotherapy is considered first line of therapy in LQTS, whereas an implantable cardioverter defibrillator (ICD) is considered first line therapy for SQTS. This review provides an in depth assessment of current and future pharmacological therapies for these mirror image channelopathies based on our present knowledge of mechanisms associated with their clinical and genetic presentation.

2. The long QT syndrome

The congenital LQTS is characterized by abnormally prolonged ventricular repolarization and high incidence of polymorphic ventricular tachycardia known as Torsade de Pointes (TdP), which is often self-limited but can degenerate in ventricular fibrillation, thus leading to sudden cardiac death (Schwartz et al., 1975; Moss et al., 1985; Zipes, 1991; Roden et al., 1996). The incidence of congenital LQTS is estimated as 1:3000. It was first described clinically and electrocardiographically in 1957 by Jervell as a familial trait with congenital deafness associated with unusually long QT intervals and high incidence of sudden cardiac death. This autosomal recessive syndrome is referred to as Jervell–Lange-Nielsen Syndrome (JLN) (Jervell & Lange-Nielsen, 1957). In 1964, Romano and Wards reported a similar but more common variant of LQTS without congenital deafness—a syndrome called Romano–Ward syndrome (Romano et al., 1963). An international registry of LQTS patients was established in 1979 and the first causal mutation was identified in 1991. Since then, about 500 different mutations in 10 different genes have been identified as causing LQTS.

2.1. Molecular genetics of LQTS

Today, LQTS is best described as genetically heterogeneous disease with a variable degree of penetrance in the expression of the disease. The disease was previously classified based on mode of inheritance—homozygous (Jervell–Lange-Nielsen syndrome/JLN—with deafness) or heterozygous (Romano–Ward Syndrome—without deafness). The newer more detailed classification scheme is based on the genetic mutation involved. Ten forms of congenital LQTS have been identified due to mutations in genes encoding for potassium channels, sodium channels or membrane components located on chromosome 3, 4, 6, 7, 11, 17 and 21 (Table 1) (Andersen et al., 1971; Tawil et al., 1994; Splawski et al., 2000; Plaster et al., 2001; Mohler et al., 2003; Splawski et al., 2004; Vatta et al., 2006; Medeiros-Domingo et al., 2007).

Loss of function mutation in *KCNQ1* and *KCNE1* genes, which encode the α and β subunits of the slowly activating delayed rectifier potassium current (I_{Ks}), are responsible for subtypes of LQTS known as LQT1 and LQT5, respectively (Barhanin et al., 1996; Sanguinetti et al., 1996). Similarly, loss of function mutations in *KCNH2* and *KCNE2* genes which encode the

α and β (MiRP1) subunit of the rapidly activating delayed rectifier potassium current (I_{Kr}) is responsible for LQT2 and LQT6 subtypes (Sanguinetti et al., 1995; Abbott et al., 1999). The channelopathies involving mutant subunits generally have milder manifestation of the disease as compared to one involving the pore forming principle subunit. Loss of function mutations in the *KCNJ2* gene, which encodes the inward rectifier potassium channel Kir2.1 (I_{K1} current) has been reported to lead to long QT interval on ECG in association with periodic paralysis and dysmorphic features (Andersen et al., 1971; Tawil et al., 1994). This syndrome is termed Anderson–Tawil syndrome, also referred to as LQT7.

In contrast, LQT3 is caused by gain of function mutations in *SCN5A*, the gene that encodes the cardiac sodium channel α subunit. These mutations in *SCN5A* lead to defective inactivation of the sodium channels causing an increase in late Na channel current (late I_{Na}) (Wang et al., 1995). Similarly, gain of function mutations in the *CACNA1C* gene, which encodes the L-type calcium channel $Ca_v1.2$, leads to multi-organ disease including prolongation of QT interval, immunodeficiency and autism (Splawski et al., 2004). This syndrome is termed Timothy syndrome or LQT8.

Mutations in *ANKB*, the gene encoding the anchoring β subunit ANK2 (a structural protein that joins myocyte membrane proteins with cytoskeleton proteins) have been linked to LQT4. Mutations in *ANKB* has been shown to lead to intra-cellular calcium overload that contributes to arrhythmogenesis in LQT4 (Mohler et al., 2003). Similarly mutation of *CAV3*, which encodes caveolin-3 (an important structural protein of caveola—an invagination of the plasma membrane), alters the biophysical properties of $Na_v1.5$ sodium channels, generating another phenotype of LQTS termed LQT9 (Vatta et al., 2006). Mutations in *SCN4B*, the gene encoding $\beta 4$ subunit of the sodium channel has recently been reported to be associated with severe prolongation of the QT interval, atrio-ventricular block and fetal bradycardia (Medeiros-Domingo et al., 2007). This subtype is referred to as LQT10. It is noteworthy that causative mutations can be identified in approximately 75% of LQTS cases only, indicating additional genetic heterogeneity of the syndrome. LQT1 is the most common accounting for 30 to 35% of cases, followed by LQT2 (25–30% cases) and LQT3 (5 to 10% cases) (Splawski et al., 2000).

The JLN syndrome corresponds to LQT1 and LQT5 or a combination of the two and is characteristically associated with congenital deafness (Schwartz et al., 2006). The more common form, Romano–Ward syndrome includes LQT1 through LQT10 and is not associated with deafness. Mode of inheritance is autosomal recessive in JLN syndrome and it is caused by homozygous or compound heterozygous mutations that reduced I_{Ks} . On the other hand Romano–Ward syndrome shows an autosomal dominant mode of inheritance.

2.2. Genotype–phenotype correlation in LQTS

Genotypic heterogeneity of LQTS confers broad phenotypic heterogeneity to LQTS subtypes. The different genotypic subtypes of LQTS differ significantly in terms of clinical presentation, ST-T morphology, arrhythmogenic triggers, the response to traditional treatment and the risk of sudden cardiac death (Zareba et al., 1998; Schwartz et al., 2001; Priori et al., 2003). Genotype–phenotype correlations are helpful in risk stratification as well as in optimal management of LQTS. Since, LQT1-3 comprise more than 90% of genotyped patients, genotype–phenotype data are most abundant for these syndromes.

2.2.1. Genotype specific clinical features—Common to all genotypes is the LQTS patient who is asymptomatic but was diagnosed because of an ECG done as a part of routine check up or as a part of screening of the family of an individual with LQTS. LQTS may initially present at any age. Fetal bradycardia is one of the first signs of intrauterine LQTS and it is frequently associated with hydrops fetalis and fetal losses during third trimester (Chang et al.,

2002; Miller et al., 2004). The patient may present with recurrent syncope and is frequently misdiagnosed as seizures in young individuals. SCD is not an unusual presentation. LQTS is thought to account for at least 5% cases of sudden infant death syndrome (SIDS) (Schwartz et al., 1998). Tester and Ackerman recently reported that mutations associated with LQTS are found in 20% of cases of sudden unexplained death in young individuals at postmortem genetic autopsy (Tester & Ackerman, 2007). Most patients typically have a family history of SCD or recurrent syncope. As described above, patients with JLN subtype of LQTS characteristically have congenital deafness.

Anderson–Tawil syndrome (LQT7) and Timothy syndrome (LQT8) patients characteristically demonstrate certain somatic features typical to their genotype. In addition to long QT syndrome, Anderson–Tawil syndrome is associated with periodic paralysis and dysmorphic features like short stature, scoliosis, clinodactylia, hypertelorism, low implantation of the ears, micrognathia and an ample forehead (Andersen et al., 1971; Tawil et al., 1994). Similarly, Timothy syndrome is characterized by cardiac malformations, intermittent immunological deficiency, hypoglycemia, autism and interdigital fusions (Splawski et al., 2004).

2.2.2. Genotype specific ECG features—Genotype specific ST-T wave morphology was first reported by Moss et al. (1995) who highlighted the difference in the shapes of T waves of the ECG among the three most common genotypes. Broad-based prolongation of the T waves is more commonly observed in LQT1, whereas low-amplitude T waves with a notched or bifurcated configuration are seen more frequently in LQT2. LQT3 patients often show prolonged iso-electric ST-segment with late-appearing T waves. These T wave features were further analyzed by Zhang et al. (2000), and numerous exceptions were reported in all three genotypes, and the T wave pattern varied greatly with time even in the same patient with one specific mutation. The genotype–phenotype ECG correlation has about 70 to 80% sensitivity and specificity for LQT1 and LQT2. However it is much lower for LQT3. Family grouped ECG has been shown to improve genotype–phenotype correlation. This characteristic difference in T wave morphology may be further delineated by treadmill exercise testing or catecholamine infusion in LQT1 and LQT2, as demonstrated by Takenaka et al. (2003). Also, Priori et al. (2003) has reported that QTc is generally longer in LQT2 and LQT3 as compared to LQT1. Biphasic T waves following long pauses are commonly observed in the LQT4 (Plaster et al., 2001). Patient with LQT7 generally shows normal or near normal QT interval and the U waves are usually prominent and separated from the T wave (Mohler et al., 2003). Recently reported LQT10 appears to be associated with extremely long QT interval (>600 ms), fetal bradycardia and atrio-ventricular block (Medeiros-Domingo et al., 2007).

2.2.3. Genotype specific triggers of arrhythmic events—Though TdP is the most common arrhythmia seen in all subtypes of LQTS, genotype-specific triggers and onset of TdP has been reported in patients with the LQT1, LQT2 and LQT3 (Ackerman et al., 1999; Moss et al., 1999; Wilde et al., 1999; Schwartz et al., 2001; Tan et al., 2006). Schwartz et al. (2001) first reported genotype-specific triggers for cardiac events in patients with LQT1, LQT2 and LQT3. In LQT1 cardiac events most frequently occur during exercise (62%) but only rarely during sleep and rest (3%) (Schwartz et al., 2001). Swimming is a common trigger in LQT1 (Ackerman et al., 1999). On the other hand, in LQT3 cardiac events principally occur during sleep and rest (39%), and less frequently during exercise (13%) (Schwartz et al., 2001). In the middle of the spectrum, in LQT2 patients, cardiac events occur equally during exercise (13%) or during sleep/rest (15%). Often, a sudden startle in the form of an auditory stimulus (a telephone, alarm clock, ambulance siren, etc.) is a specific trigger in LQT2 (Wilde et al., 1999). It has been noted that the risk of ventricular arrhythmia decreases during pregnancy, although a higher post-partum vulnerability to cardiac events is reported in LQTS, especially the LQT2 subtype (Khositseth et al., 2004). It has also been reported that pause-dependence of TdP is predominant in LQT2 patient and rare in LQT1 and LQT3 (Tan et al.,

2006). Similarly, exercise or mental stress has been reported to be a trigger for ventricular arrhythmias in LQT4 patients (Mohler et al., 2003) and hypokalemia is often associated with frequent ventricular arrhythmia in LQT7 (Plaster et al., 2001). Information on genotype-specific triggers can enable physicians to take patient-tailored approach in recommending physical and sports related activities and avoiding specific triggers in LQTS patients.

2.2.4. Genotype specific response to sympathetic stimulation and exercises—

β adrenergic influences have been shown to elicit dramatically different responses in experimental models of LQT1-3 (Shimizu & Antzelevitch, 2000a), and to predict the clinical response to sympathetic influences in these LQTS genotypes. Sympathetic stimulation either in the form of exercise or infusion of epinephrine has been shown to produce different and genotype-specific changes in QT interval (Tanabe et al., 2001; Ackerman et al., 2002; Noda et al., 2002; Shimizu et al., 2002, 2003; Takenaka et al., 2003). This differential response is quite specific and can sometime be helpful in diagnosis of borderline cases and risk stratification of asymptomatic cases. Patients with LQT1 prolong their QTc interval at peak epinephrine effect (approximately 1 minute) and QTc remains prolonged at a steady state (Noda et al., 2002; Shimizu et al., 2003). In patients with LQT2, QTc interval is also prolonged at peak epinephrine effect but returns to close to baseline at steady-state (Noda et al., 2002). In contrast, QTc is less prolonged at peak epinephrine effect in LQT3 patients and abbreviates below baseline levels once steady state is achieved (Noda et al., 2002).

A similar differential response is observed during exercise. LQT1 patients fail to achieve their maximum heart rate and paradoxically increase their QT interval (Swan et al., 1999; Takenaka et al., 2003). LQT2 patients are able to achieve maximal heart rate and changes in QT interval are negligible (Swan et al., 1999; Takenaka et al., 2003). In contrast, patients with LQT3 have a normal physiological response to exercise and abbreviate their QT interval below baseline values (Schwartz et al., 1995).

2.3. Genotype–phenotype correlation—experimental explanation

Experimental preparations in the form of arterially-perfused canine left ventricular wedge preparations have been helpful in delineating the cellular basis of the characteristic phenotypic T wave morphologies as well as genotype-specific response to sympathetic stimuli in LQT1, LQT2 and LQT3 (Shimizu & Antzelevitch, 1997, 1998; Yan & Antzelevitch, 1998; Antzelevitch et al., 1999; Shimizu & Antzelevitch, 1999a,b, 2000a). In these studies, chromanol 293B (specific I_{Ks} blocker), d-sotalol (specific I_{Kr} blocker) and ATX-II (used to augment late I_{Na}) were used to create the experimental conditions mimicking LQT1, LQT2 and LQT3, respectively (Fig. 1). In all three models, differences in time course of repolarization of the three principle ventricular cell types (epicardial, endocardial and M cells) lead to inscription of different T wave morphologies specific to a particular genotype. Infusion of isoproterenol mimicking the experimental conditions of sympathetic stimulation produces a differential response similar to that observed clinically (Shimizu & Antzelevitch, 1998, 2000a). In the LQT1 model, addition of isoproterenol abbreviates the action potential duration (APD) of epicardial and endocardial cells but not that of M cells, leading to persistent increase in QT interval and transmural dispersion of repolarization (TDR) (Shimizu & Antzelevitch, 2000a). In the LQT2 model, isoproterenol initially prolongs and then abbreviates the APD of the M cells, whereas APD of epicardial and endocardial cells are always abbreviated, leading to transient increase in QT interval and TDR (Shimizu & Antzelevitch, 2000a). In the LQT3 model, isoproterenol produces a persistent abbreviation of APD of all three cell type leading to abbreviation of QT interval and TDR (Shimizu & Antzelevitch, 2000a).

The persistent increase in QT interval and TDR during sympathetic stimulation creates an arrhythmogenic environment, accounting for the greater sensitivity of LQT1 patients to

exercise and swimming. Similarly, a transient increase of the QT interval and TDR during sympathetic stimuli creates the sequence of short and long cycles, which mimics the mode of onset of TdP observed in LQT2 patients following a startle. On the other hand, in the LQT3 model, increase in QT interval and TDR are least pronounced under the condition of sympathetic stimulation and most pronounced in the absence of isoproterenol. This explains the higher incidence of TdP at rest and during sleep in LQT3 patient and the low incidence of arrhythmia under condition of exercise.

2.4. Genotype-specific approach to pharmacotherapy

LQTS is a potentially lethal disease with 13% incidence of cardiac arrest and sudden death among untreated patients (Priori et al., 2003). Genotype of the disease has strong influence on the overall prognosis as the locus of the causative mutation, in addition to QTc interval, has been shown to be an independent predictor of cardiac events. The incidence of the first cardiac event prior to age 40 is highest in LQT2 patients (46%) followed by LQT3 (42%) and LQT1 (30%) (Priori et al., 2003). Sex also affects the probability of a first cardiac event, with higher incidence of cardiac events in females than in males, particularly in mutations at the LQT2 locus. In contrast, male LQT3 patients have a higher event rate compared to females (Priori et al., 2003). In general, male patients are younger than female patients at first cardiac event. In a recent report from Hobbs et al., who analyzed risk of sudden death in 2772 adolescents with LQTS, patients with QTc>530 ms, history of syncope in the last 10 years and male patients between 10 to 12 years of age were at higher risk of cardiac arrest as compared to their counterparts (Hobbs et al., 2006). Another recent study evaluating 812 mutation-confirmed LQTS patients of age>18 found that female gender, QTc interval>500 ms, LQT2 genotype and interim syncopal events during follow-up were associated with significantly increased risk of life-threatening cardiac events in adulthood (Sauer et al., 2007). Although there is variability in relative risk of sudden death in patient with LQTS in different population studies, it is very clear that in a given patient, interaction between genotype, gender and QTc interval confers arrhythmic risk, specific to the particular patient.

2.4.1. β -blockers— β -blockers remain the first choice of therapy for LQTS irrespective of the genotype (Moss et al., 2000), although their benefit in LQT3 has not been demonstrated. Therapy with β -blocker in LQTS cuts down the risk of cardiac events in excess of 60% (Sauer et al., 2007). They are especially effective in LQT1 cases in which arrhythmic events are strongly influenced by the state of sympathetic nervous system. Clinical data from the International Registry of LQTS reported that β -blockers are more effective in prevention of arrhythmic symptoms and sudden cardiac death in LQT1 patients (81%) than in LQT2 (59%) or LQT3 (50%) (Schwartz et al., 2001). Despite their proven efficacy, about 10% patients with LQT1, 23% of patients with LQT2 and 32% patients with LQT3 still develop cardiac events while taking adequate β -blocker therapy (Priori et al., 2004). In particular, patients with LQT3 fail to derive adequate benefit from β -blocker therapy as sympathetic stimulation has little if any contribution to arrhythmogenesis in LQT3. In fact, β -blocker therapy should be used with caution in LQT3 patients, as extremely low heart rate will increase the dispersion of repolarization in LQT3 that may facilitate TdP.

Consistent with clinical observations, data from left ventricular wedge studies indicate that in the LQT1 model, propranolol completely suppresses the isoproterenol induced augmentation of TDR and hence completely suppresses TdP (Shimizu & Antzelevitch, 1998, 2000a), whereas in the LQT2 model, propranolol blocks the transient effects of isoproterenol (transient increase in TDR followed by decrease in TDR) and shows moderate effectiveness in preventing the induction of TdP (Shimizu & Antzelevitch, 2000a). In the LQT3 model, the effects of sympathetic stimulation/isoproterenol are antiarrhythmic (decrease in QT interval as well as

TDR) and propranolol antagonizes the protective effects of adrenergic stimulation (Shimizu & Antzelevitch, 2000a).

2.4.2. Sodium channel blocker—LQT3 subtype of LQTS is caused by mutations in sodium channel causing failure of the channel to inactivate leading to a persistent increase in late I_{Na} during phase 2 of the action potential, which is responsible for QT prolongation. So, it is intuitive that blockade of I_{Na} might be of therapeutic benefit, especially in this subtype of LQTS. Schwartz et al. (1995) was first to report genotype-specific treatment in LQTS with mexiletine, a class IB sodium channel blocker which blocks the late I_{Na} current and hence abbreviates the QT interval in LQT3 patients. While the benefits of Class IB agents are clearly apparent in experimental models of LQT3, data from studies utilizing the perfused-wedge preparation indicate that mexiletine is also effective in abbreviating the TDR and suppressing TdP in LQT1 and LQT2 models (Fig. 2) (Shimizu & Antzelevitch, 1997, 1998). The antiarrhythmic effect of mexiletine is attributed to reduction of TDR in all three models, secondary to preferential abbreviation of APD of M cells which in-trinsically possesses stronger late I_{Na} (Zygmunt et al., 2001). Recent studies involving the ventricular wedge model demonstrate that blockade of late I_{Na} is of therapeutic value in Timothy syndrome or LQT8, as well (Sicouri et al., 2007). In this wedge model of LQT8 created by exposure to BayK 8644, ranolazine, a late I_{Na} blocker, completely prevented ST-T wave alternans, early afterdepolarizations (EAD) and ventricular tachycardia. Because it is the most potent blocker of late I_{Na} , ranolazine is likely to be of therapeutic value in LQT3 as well as in all forms of LQTS.

Another class IC sodium channel blocker, flecainide has been reported to be effective in one of the variants of LQT3 with a specific mutation (D1790G) in SCN5A (Benhorin et al., 2000). Sodium channel blockade by flecainide in this subgroup of patients increased the heart rate, abbreviated heart rate-corrected repolarization duration parameters, suppressed alternations in T wave and abbreviated the QT interval. However, class IC sodium channel blockers should not be used in all LQT3 patients as it can elicit a Brugada phenotype in some patients (Priori et al., 2000). Its benefit in the wide variety of mutations that lead to LQT3 has not been established.

Experimental data supporting use of I_{Na} channel blockade is very promising but unfortunately has not been validated in prospective clinical trials mainly due to the limited number of patients, particularly LQT3. At the present time, sodium channel blockers warrant some consideration as an adjunct to β -blockade therapy in patients with LQT3, until further clinical data are available.

2.4.3. Potassium supplement—Serum potassium plays an important role in determining the duration of the action potential because both I_{Kr} and I_{K1} are sensitive to extracellular potassium levels, displaying increased conductance as a function of increased $[K^+]_o$. Compton and coworkers tested this hypothesis in patients with LQT2 and demonstrated that administration of oral potassium to raise plasma concentration by 1.5 mEq/l above the baseline can reduce resting QTc interval by 24%, improve QT-RR relationship towards normal and normalize T wave morphology (Compton et al., 1996). A few years later, the same group of investigators reported long term efficacy of the regimen (Etheridge et al., 2003). Though supplemental potassium corrects the repolarization abnormality in LQT2 patients, whether these effects translate into protection against arrhythmia remains to be determined by long term clinical trial. Effects of potassium supplement are related to its action to increase I_{Kr} and I_{K1} and also by limiting the potency of the I_{Kr} blocker as suggested by experimental data from the wedge preparation (Yan & Antzelevitch, 1998).

2.4.4. Potassium channel openers—As outlined above, five out of 10 subtypes of LQTS are caused by mutations which eventually lead to reduction in net outward potassium current. Increasing this outward potassium current to augment repolarization forces can be an effective therapy in LQTS, especially when due to mutations in potassium channels. In fact, experimental data have supported the role of potassium channel opener in treatment of LQTS. Administration of intravenous nicorandil, a potassium channel opener, reduces the epinephrine-induced QT prolongation and suppresses EADs in LQT1 patients with an I_{Ks} defect (Shimizu et al., 1998). Experimental studies involving left ventricular wedge suggest that nicorandil (2 to 20 $\mu\text{mol/L}$) abbreviates the QT interval and APD of all three cell types in models of LQT1-3 (Shimizu & Antzelevitch, 2000b). At high concentration (10 to 20 $\mu\text{mol/L}$) nicorandil completely reverses the effects of chromanol293B+isoproterenol (LQT1 model) and d-sotalol (LQT2 model) and prevents TdP (Shimizu & Antzelevitch, 2000b). In contrast, it is far less effective (50%) in reversing ATX-II-induced (LQT3 model) increase in QT interval and fails to completely suppress TdP (Shimizu & Antzelevitch, 2000b). These experimental data support the role of nicorandil in LQT1 and LQT2 and less so in LQT3.

The recent availability of novel HERG current enhancers has generated a great deal interest as well. HERG blockade is the major determinant of drug-induced QT prolongation and TdP. The first drug in this class, RPR260243, was shown to reverse dofetilide-induced APD prolongation in guinea pig myocytes (Kang et al., 2005). More potent than the first agent, PD-118057 was found to reduce the APD of endocardial and epicardial cells and abbreviate the QT interval when infused alone in rabbit left ventricular wedge (Zhou et al., 2005). PD-118057 at 3 $\mu\text{mol/L}$ concentration prevented the dofetilide induced APD and QT prolongation and abolished EADs (Zhou et al., 2005). Similarly, the I_{Ks} enhancer benzodiazepine L3 has been shown to reverse dofetilide-induced APD prolongation and EADs in rabbit endocardial myocytes, suggesting its possible therapeutic role in LQT2 (Xu et al., 2002). It should be kept in mind that the potential role of these potassium channel agonists in the therapeutic management of LQTS is thus far supported only by experimental data.

2.4.5. Calcium channel blockers—Calcium influx through L-type calcium channel plays a significant role in maintaining the plateau phase of action potential and hence contributes importantly to duration of action potential and QT interval. Therefore, administration of calcium channel blocker is a logical strategy in all types of LQTS and more so in LQT8/Timothy syndrome caused by a gain of function in calcium channel current. The first report of the role of verapamil, a blocker of L-type calcium channel in LQTS, was provided by Shimizu et al. (1995). In the clinical study involving recording of monophasic action potential (MAP) in eight patients with LQTS, verapamil effectively abbreviated MAP duration and suppressed epinephrine-induced EADs (Shimizu et al., 1995). At the bench side, recent studies employing left ventricular wedge technique also demonstrated that verapamil effectively abbreviates QT interval and TDR and suppresses TdP in models of congenital and acquired LQTS (LQT1 +LQT2) (Aiba et al., 2005). Although there are no available data about the effects of verapamil in LQT3, calcium channel blockers might be of more if not same benefit in LQT3 patients as verapamil like many other calcium channel blocker is also an inhibitor of late I_{Na} . This property of verapamil can offer dual benefit to LQT3 patients by directly targeting the underlying genetic defect in addition to blockade of late I_{Na} .

Calcium channel blocking effect of verapamil should be of particular benefit in LQT8/Timothy syndrome. Because of the scarcity of such patients, the role of calcium channel blocker in Timothy syndrome has not been demonstrated except in one case report (Jacobs et al., 2006). Although supported by experimental science, population studies supporting a role for calcium channel blockers in LQTS is still lacking and at this time they might best be used as an adjunct to β -blocker therapy in LQTS.

2.4.6. Correction of the trafficking defects—Cardiac ion channels consist of proteins and glycoproteins that form transmembrane pores that permit the flow of particular ions at particular conductance. Proper function of these proteins requires their transport to the cardiac cell membrane. Defects in such transport, referred to as trafficking defects, reduces the availability of normally functioning ion channels on the cell surface and hence can affect the amplitude of the corresponding current. Such trafficking defects have recently received significant attention in pathogenesis of LQTS, especially in case of LQT2 (Anderson et al., 2006; Zhou et al., 1998) and cases of LQT1 (Gouas et al., 2004). Zhou et al. (1998) first reported trafficking defects related to the expression of I_{Kr} as a disease-causing mechanism with certain mutations associated with LQT2. Correction of these defects by culturing cells at lower temperature (27 °C) or in presence of agents like E4031, astemizole or cisapride (Zhou et al., 1999) was shown to restore function. However, most of these compounds have intrinsic HERG blocking properties which counterbalanced their corrective effects on trafficking. Nevertheless, the study opened new possible approaches in the treatment of LQTS —‘correction of trafficking defects’. Ongoing search of compound that corrects the trafficking defects without HERG blocking properties has revealed two compounds. Rajamani, Anderson, Anson, and January (2002) first reported that fexofenadine, a metabolite of terfenadine, can rescue such defective trafficking without blocking HERG current, in certain missense mutations associated with LQT2. Similarly, Delisle et al. (2003) reported that thapsigargin, an inhibitor of sarcoplasmic/endoplasmic reticulum Ca^{+} -ATPase, also have similar properties. The role of defective trafficking was further emphasized recently in a large in vitro study by Anderson et al. (2006). These investigators tested 34 missense mutations associated with LQT2 for trafficking defects and concluded that about 82% of those mutations reduced the HERG current by a class 2 trafficking defect mechanism, which could be corrected by reducing temperature to 27 °C or with drugs like E-4031 and thapsigargin.

Current experimental data strongly support the role of trafficking errors in pathogenesis of LQTS and its possible implication in development of genotype-specific future pharmacologic therapy. It should be emphasized that these findings are tested only in vitro in single cell models and it may be long before they are validated and available for treating the patients at bedside.

2.4.7. Gap junction coupling enhancers—Gap junctions are composed of intercellular channels that allow the transfer of electrical current and small molecules between two cardiac cells. Connexin-43 is a major constituent protein of these gap junctions (Saffitz et al., 1995). It is clear that intrinsic heterogeneity of myocardium is more pronounced when cells are electrically uncoupled and they become less pronounced in intact tissue where cells are closely coupled (Anyukhovsky et al., 1999; Viswanathan & Rudy, 2000). Conditions associated with heart failure and hypertrophy are associated with uncoupling of gap junctions (Armoundas & Tomaselli, 2003). Enhancing gap junction coupling is thought to be capable of reducing the intrinsic heterogeneity of myocardium, and thus provide an antiarrhythmic effect, especially under the conditions in which dispersion of repolarization is augmented as in LQTS. Promising results were obtained when this hypothesis was tested in a model of LQT3 created by ATX-II in the rabbit left ventricular wedge preparation (Quan et al., 2007). Enhancing the gap junction by infusion of AAP10 (a gap junction enhancer) significantly reduced the QT interval, TDR and incidence of TdP in this model. Interestingly, the ATX-II-induced increase in QT interval and TDR was associated with an increase in the non-phosphorylated form of connexin-43 while the effects of AAP10 were associated with an increase in the phosphorylated form of connexin-43 (Quan et al., 2007).

2.4.8. Pacemaker and defibrillator therapy—The repolarization abnormalities in congenital LQTS are attenuated by increasing the heart rate with atrial pacing without sympathetic stimulation, which provides another approach to therapy (Hirao et al., 1996). Abbreviation of QT interval with exercise is most pronounced in LQT3 as compared to LQT1

and LQT2 because of the steeper QT-RR relationship (Schwartz et al., 1995; Shimizu & Antzelevitch, 1997, 1998). Moreover, LQT3 patients are at highest risk of TdP when heart rate is slow. Accordingly, pacemaker therapy is thought to be most beneficial in patients with LQT3 and less so in LQT1 and LQT2. Pause-dependent TdP is more prevalent in LQT2 patients than in the other forms and hence pacemaker therapy may be of therapeutic value in preventing TdP by suppressing pauses in LQT2 patients. In a population study, Eldar et al. (1992) reported reduced incidence of cardiac events with combined therapy of β -blocker and continued pacing over follow up period of 4 to 5 years. When pacemaker is implanted in LQTS patient, frequency regulation function must be on to prevent post-extrasystolic pause. The utility of such “rate-smoothing” algorithms was further highlighted by Viskin and colleagues (Viskin, Fish, Roth, & Copperman, 1998; Viskin, Glikson, Fish, Glick, Copperman, & Saxon, 2000). An implantable cardio-verter-defibrillator (ICD) is indicated for LQTS patients with high risk of sudden cardiac death (aborted cardiac arrest or repetitive episodes of syncope despite pharmacologic and other therapies) (Zareba et al., 2003).

2.4.9. Left cardiac sympathetic denervation—The sympathetic nervous system has strong influence on arrhythmogenesis in LQTS as described above, and hence sympathetic denervation has been explored as an alternative approach to therapy, an effort pioneered by Schwartz and coworkers. Schwartz et al. (2004) reported results of left cardiac sympathetic denervation (LCSD) in 147 high risk LQTS patients. LCSD abbreviated the QT interval and reduced cardiac events by 91%. LCSD appears to be more effective in LQT1 and LQT3 patients as compared to LQT2. At the present time, this therapy is reserved for only those LQTS patients who remain symptomatic with recurrent TdP or syncope despite adequate pharmacological and interventional electrophysiological management in terms of pacemaker and defibrillators.

3. The Short QT syndrome

It is only recently that attention has been focused on the arrhythmogenic significance of abbreviated QT intervals. The mirror image disorder of LQTS—the congenital SQTS is a relatively young disorder added to the growing list of inherited channelopathies in 2000 (Gussak et al., 2000). SQTS is characterized by abnormally short QT interval on ECG (<360 ms) in association with high incidence of sudden cardiac death (Gussak et al., 2000, 2003; Gussak & Bjerregaard, 2005). Initially describe by Gussak et al. (2000) as a new clinical entity, the familial nature of the disease and its arrhythmogenic potential was confirmed by Gaita et al. (2003) in 2003 with description of six patients of SQTS in two unrelated European families with family history of sudden death associated with short QT interval in the ECG. Since its initial introduction in 2000, significant progress has been achieved in terms of defining the clinical, genetic and ionic basis of the disease and approaches to therapy.

3.1. Molecular genetics of SQTS

Similar to LQTS, SQTS is also genetically heterogeneous disease and thus far mutations in five different genes (Table 1) encoding different cardiac ion channels located on chromosome 7, 10, 11, 12 and 17 have been identified, and the corresponding syndromes have been termed SQT1 to SQT5 depending of chronology of discovery (Brugada et al., 2004; Bellocq et al., 2004; Priori et al., 2005; Antzelevitch et al., 2007). Interestingly, four of those genes are the same as those involved in LQTS; however mutations leading to SQTS have the net effect of increasing rather than decreasing depolarizing forces. To date, SQT1, SQT3, SQT4, and SQT5 has been reported in familial cases and SQT2 is reported only in a sporadic setting. In familial cases, the disease is generally seen in each generation of family and both sexes, suggesting autosomal dominant mode of inheritance. As in the case of LQTS, in many patients no genetic mutation could be found, pointing towards genetic heterogeneity.

A mutation in *KCNH2* was the first reported gene mutation associated with SQTs (Brugada et al., 2004). In contrast to LQT2, mutations in *KCNH2* associated with SQT1 is a gain of function mutation leading to an increase in I_{Kr} . The N588K mutation in *KCNH2* led to loss of normal rectification of I_{Kr} at physiological range of voltages resulting in large gain of function during phase 2 and 3 of the action potential, leading to marked abbreviation of action potential. Interestingly, N588K mutation reduced the affinity of the I_{Kr} channel for class III antiarrhythmic drugs like d-sotalol, which has direct implications in the treatment of SQT1 (discussed below in the pharmacotherapy section). This was followed by the discovery a gain of function mutation in *KCNQ1* by Bellocq et al. (2004) in a single sporadic case of a 70 year old man with a history of resuscitated ventricular fibrillation and short QT interval on ECG. V307L mutation in *KCNQ1* resulted in -20 mV shift of the half-activation potential and acceleration of the activation kinetics leading to activation of mutant channels at more negative potentials leading to marked gain of function of I_{Ks} and abbreviation of the action potential. SQT2 is a mirror image of LQT1, with the mutation in *KCNQ1* leading to a gain of function of I_{Ks} in SQT2, but to a loss of function in LQT1. Similarly, a gain of function mutation in *KCNJ2* was identified by Priori et al. (2005) in a familial setting in an asymptomatic 5 year old child and 35 year old father who showed extremely short QT interval on ECG. Heterologous expression of the mutant channel showed that the genetic mutation caused a significant augmentation of I_{K1} responsible for abbreviation of action potential and QT interval.

Recently, the first loss of function mutation leading to SQTs was described by our group (Antzelevitch et al., 2007). This new clinical entity is associated with mutation in *CACNA1C* and *CACNB2b* genes which encode the pore forming $Ca_v1.2$ α_1 and β -subunit, respectively. Interestingly, this new clinical entity (which has been termed SQT4 and SQT5 respectively) is characterized by Brugada type ST elevation in V_1 and V_2 in addition to short QT intervals (330–370 ms) on the ECG. Heterologous expression of the mutant channels revealed a loss of function in L-type of calcium current, responsible for an abbreviation of the plateau phase of action potential and the QT interval. In one case, that of the A39V mutation in *CACNA1C*, the decrease in inward calcium current expression was found to be due to defective trafficking.

3.2. Genotype–phenotype correlation

As with LQTS, there has been a great deal of interest in establishing genotype–phenotype correlation in SQTs. A major limitation has been the scarcity of SQTs families worldwide. Based on available literature there are approximately 50 SQTs patients, representing a dozen families and several sporadic cases. In many of the cases, genetic mutations are either not reported or not found. One subtype of SQTs, SQT2, is thus far reported only in a sporadic setting. The majority of patients who are tested genetically have been found to have mutation in *KCNH2*-SQT1, with N588K as a hot spot. Due to above factors, despite great interest, robust genotype–phenotype linkage is still not possible in SQTs.

3.3. Clinical presentation

As with LQTS, clinical presentation of SQTs patients is highly heterogeneous, with a great deal of variation in presenting symptom and clinical course of the disease between different families and even among members of the same family. In the largest available case series of SQTs, Giustetto et al. (2006) reported clinical presentation of 29 patients with SQTs. Approximately 25% of patients had a mutation in *KCNH2* (SQT1) and no mutation was found in rest of the patients. In this group of patients, the first manifestation of disease was seen as early as the first month of life to as late as 62 years of age. Mutations in *KCNQ1* and *KCNJ2* were not detected and *CACNA1C* and *CACNB2b* were not screened. The oldest patient in this group was 80 year old male who was asymptomatic. About 62% of the patients were symptomatic. Cardiac arrest was the most frequently (34%) reported symptom and in about 28% patient it was the first clinical presentation. Cardiac arrest had occurred in the first month

of life in two patients, suggesting that SQTs may be one of the causes of sudden infant death syndrome (SIDS). Palpitation was second most frequently reported symptom (31%) followed by syncope (24%). Atrial fibrillation was the first presenting symptom in 17% of patients. Many patients had frequent ventricular extrasystoles. Approximately 38% of patients were asymptomatic and were diagnosed due to family history, suggesting that disease may manifest at any age and it may be concealed until first presentation, which in many cases is cardiac arrest. Strong family history of arrhythmic symptoms including SCD is a common finding reported in the familial subtype of the SQTs.

The only reported patient of SQT2 is a 70 year old male who was successfully resuscitated after an episode of ventricular fibrillation (Bellocq et al., 2004). There are two reported cases of SQT3—a 5 year old female child who was asymptomatic and a 35 year old father, who had frequent episodes of sudden awakening at night with seizure like activity followed by shortness of breath and palpitations (Priori, 2005).

SQT4 has thus far been reported in two different patients of two unrelated families (Antzelevitch et al., 2007). A 41 year old male with a family history of SCD, who presented with atrial fibrillation and a QTc of 346 ms. The second patient with SQT4 was a 44 year male with family history of syncope and SCD, who was recently also diagnosed with fascioscapulohumeral muscular dystrophy. SQT5 has been described in seven patients belonging to a family of European descent (Antzelevitch et al., 2007). The proband, a 25 year old male presented with a QTc of 330 ms and had an episode of aborted sudden cardiac death. His 23 year old brother had frequent syncope as well. The rest of the family was asymptomatic.

ECG in SQTs is characterized by abnormally short QT interval, commonly <360 ms with a range of 220 to 360 ms (Gaita et al., 2003; Giustetto et al., 2006; Gussak et al., 2000). Another common finding on the ECG of SQT1-3 patients is tall, symmetrical or asymmetrical peaked T wave in precordial leads. T waves could be positive or negative. Another distinctive feature is a relatively prolonged $T_{\text{peak}}-T_{\text{end}}$ interval suggestive of augmented TDR. Asymmetric T wave with less steep ascending limb followed by a rapid descending limb has been reported in cases of SQT3 (Priori et al., 2005). The ST segment is short or even absent in most of cases and T wave originates from the S wave. Impaired QT-RR relationship/rate independence of QT interval has been reported thus far in the setting of SQT1 and SQT4. In addition to the classical ECG features of SQTs, patients with SQT4 and SQT5 demonstrate Brugada type ST elevation in precordial leads V1 and V2 at baseline or after administration of ajmaline (Antzelevitch et al., 2007). Also, QTc intervals are relatively longer (around 330 to 360 ms) in cases of SQT4 and SQT5 as compared to the other subtypes.

The role of the autonomic nervous system in arrhythmogenesis in SQTs is not clear. Clinically, episodes of ventricular fibrillation have been reported at rest, during sleep, during intensive exercises, following a loud noise and even during daily activities (Giustetto et al., 2006). It is suggested that likelihood of arrhythmia is higher at rest as TDR which plays a key role in arrhythmogenesis in SQTs, is more pronounced at lower heart rates.

Paroxysmal atrial fibrillation is often a complication of SQTs. The association of AF with SQTs was apparent in the very first publication of the syndrome by Gussak and workers (Gussak et al., 2000). Giustetto et al. (2006) reported that 31% of patients diagnosed with SQTs have AF.

Information about genotype–phenotype correlation in SQTs available to date is less robust and more speculative, primarily because of the scarcity of data. Variability of presentation of the disease in patients with the same mutation and even among members of the same family, suggest that in addition to genetic heterogeneity there may be great variability in the expression

of the disease due to environmental factors or additional genetic variations, as is the case in LQTS.

3.4. Treatment of SQTS

Risk stratification as well as the approach to treatment is not fully established for this syndrome as yet. SQTS patients are at a high risk of SCD due to malignant ventricular arrhythmia and implantation of an ICD is recommended for all patients with SQTS for primary prevention of SCD, unless contraindicated or refused by the patient (Bjerregaard & Gussak, 2005b). Because the sensitivity of EP study for inducibility of VF is only 50%, the decision to implant an ICD should be based on clinical grounds, including the presence of a short QT interval, in conjunction with arrhythmic symptoms or manifestations and a strong family history of SCD (Giustetto et al., 2006; Schimpf et al., 2005). Because implantation of an ICD is problematic in young children, a pharmacologic solution (discussed below) may be helpful as a bridge to ICD therapy.

SQTS patients receiving an ICD are at an increased risk for inappropriate shocks due to the detection of short coupled and tall peaked T waves. Schimpf et al. (2003) observed inappropriate shocks due to oversensing in 3 of 5 patients who received an ICD for SQTS. Device algorithms that permit reduced sensitivity and linear or programmable decay after the R wave to avoid oversensing of the T wave may reduce the possibility of inappropriate therapy. Caution must be exercised to avoid programming modifications that prevent the detection of ventricular arrhythmias.

3.4.1. Genotype specific pharmacological therapy—Although ICD is the mainstay of therapy for SQTS, pharmacological therapy is helpful as a bridge to ICD implantation in young children, as an alternative in patients refusing an ICD, and as an adjunct to ICD therapy in individuals experiencing frequent appropriate therapy.

Data regarding pharmacological therapy in SQTS are very limited and the majority pertains to patients with SQT1 (Gaita et al., 2004). Pharmacotherapy of SQTS would appear to be fairly straightforward since many of the traditional antiarrhythmics can act to prolong action potential duration via inhibition of I_{Kr} and thus antagonize the increase in net depolarizing current produced by the genetic defects. However, this logical approach proved to be less than straightforward when first implemented in the clinic. Attempts to prolong the QT interval using the selective I_{Kr} blocker, d-sotalol, in SQT1 patients met with failure (Gaita et al., 2004). Heterologous expression studies revealed that the N588K mutation in *KCNH2* not only increases I_{Kr} density but also reduces the affinity of the channel to class III antiarrhythmics such as d-sotalol by 20-fold (Brugada et al., 2004). Similarly, the affinity of another selective I_{Kr} blocker, E-4031, was shown to be reduced (McPate et al., 2006). The reduced sensitivity to the I_{Kr} blockers was attributed to the +90 mV shift in the voltage-dependence of inactivation of HERG channels (Cordeiro et al., 2005). The inactivated state of the channel normally stabilizes the interaction of the channel with most I_{Kr} blockers. Thus, failure of rectification of current due to loss of inactivation of the channel rendered the I_{Kr} blockers in N588K *KCNH2* channels largely ineffective (Brugada et al., 2004; Cordeiro et al., 2005; MCPate et al., 2006). Consistent with this observation, heterologous expression showed that affinity of mutant channel to open state channel blockers like quinidine was relatively high (Wolpert et al., 2005; MCPate et al., 2006). The N588K mutation reduced the affinity of quinidine for the I_{Kr} channel by only 5.8-fold. More recently, MCPate et al. (2006) showed that N588K mutation reduced affinity of I_{Kr} channel for disopyramide by only 1.5 fold, suggesting that disopyramide may be another potential therapeutic agent for treatment of SQTS.

Clinical studies by Gaita et al. (2004) concurrent with the *in vitro* observations demonstrated the efficacy of quinidine in patients with SQTS. These investigators tested four different

antiarrhythmic drugs including flecainide, sotalol, ibutilide and hydroquinidine to determine whether they could prolong the QT interval in to normal range and prevent arrhythmia recurrence. Only hydroquinidine caused QT prolongation to the normal range, increased ventricular ERP and rendered VF non inducible, whereas the Class IC and III antiarrhythmic drugs failed to do so. Moreover, quinidine also restored QT-RR relationship towards the normal range (Wolpert et al., 2005). In a one year follow up, patient treated with hydroquinidine remained asymptomatic and no further episodes of ventricular arrhythmia were detected. Recently, Schimpf et al. (2007) reported clinical efficacy of disopyramide in two patients with SQT1, consistent with the experimental data from heterologous expression of N588K *KCNH2* mutant channels. Administration oral administration of disopyramide in these patients increased the QT interval and ventricular refractory period and abbreviated the $T_{peak}-T_{end}$ interval.

The efficacy of quinidine and disopyramide may also be attributable to their ability to block K channels other than I_{Kr} , including I_{to} , I_{K1} and especially I_{Ks} . Although the effectiveness of quinidine and disopyramide has only been demonstrated in SQT1, there is reason to believe that they may be effective in the other forms of SQTs. In fact, prolongation of QT interval with by quinidine has been reported in one patient with SQT4 (Antzelevitch et al., 2007). Unlike SQT1, other class III anti-arrhythmic agents, including d-sotalol, are likely to prove clinically useful in other forms of SQTs. Amiodarone has been shown to prevent the incidence of arrhythmia and prolong the QT interval in one patient however genetic and electrophysiologic testing data are not available in that patient (Lu et al., 2006).

Some SQTs patients exhibit only atrial fibrillation (Hong et al., 2005). In such cases, propafenone has been shown to be effective in preventing frequent paroxysms of AF with no recurrence of arrhythmia for more than two years, and without any effect on QT interval (Bjerregaard & Gussak, 2005a).

4. Conclusion

Recent advances in molecular genetics and cellular electro-physiology have significantly improved our understanding of inherited channelopathies. LQTS was identified first followed by discovery of catecholaminergic ventricular tachycardia, Brugada syndrome and finally by SQTs. Each of these channelopathies has been linked to specific genetic mutation and strong genotype–phenotype correlation is observed in some cases. As this list of inherited channelopathies grows, the list of patients labeled as ‘Idiopathic Ventricular Fibrillation’ will shrink further. Our ability to more precisely diagnose and develop gene-specific treatments will continue to advance as we gain further knowledge about the molecular and genetic basis underlying the diverse phenotypic expression of these syndromes.

Abbreviations

APD	Action potential duration
EAD	Early afterdepolarization
JLN	Jervell–Lange-Nielsen syndrome
LQTS	Long QT syndrome
LCSD	

Left cardiac sympathetic denervation

SQTS

Short QT syndrome

SCD

Sudden cardiac death

SIDS

Sudden infant death syndrome

TDR

Transmural dispersion of repolarization

TdP

Torsade de pointes

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Fig. 1.

Transmembrane action potentials and transmurals electrocardiograms (ECG) in control and LQT1 (A), LQT2 (B), and LQT3 (C) models of LQTS (arterially-perfused canine left ventricular wedge preparations). Isoproterenol+chromanol 293B—an I_{Ks} blocker, d-sotalol+low $[K^+]_o$, and ATX-II—an agent that slows inactivation of late I_{Na} are used to mimic the LQT1, LQT2 and LQT3 syndromes, respectively. Panels A–C depict action potentials simultaneously recorded from endocardial (Endo), M and epicardial (Epi) sites together with a transmural ECG. BCL=2000 ms. Transmural dispersion of repolarization across the ventricular wall, defined as the difference in the repolarization time between M and epicardial cells, is denoted below the ECG traces. Panels D–F: effect of isoproterenol in the LQT1, LQT2 and LQT3 models. In LQT1, isoproterenol (Iso) produces a persistent prolongation of the APD₉₀ of the M cell and of the QT interval (at both 2 and 10 min), whereas the APD₉₀ of the epicardial cell is always abbreviated, resulting in a persistent increase in TDR (D). In LQT2, isoproterenol initially prolongs (2 min) and then abbreviates the QT interval and the APD₉₀ of the M cell to the control level (10 min), whereas the APD₉₀ of epicardial cell is always abbreviated, resulting in a transient increase in TDR (E). In LQT3, isoproterenol produced a persistent abbreviation of the QT interval and the APD₉₀ of both M and epicardial cells (at both 2 and 10 min), resulting in a persistent decrease in TDR (F). * $p < .0005$ vs. Control; † $p < .0005$, ‡ $p < .005$, †† $p < .05$, vs. 293B, d-sotalol (d-Sot) or ATX-II. Modified from references (Shimizu & Antzelevitch, 1997, 1998, 2000a) with permission.

Fig. 2.

Dose dependent effects of mexiletine (Mex) on APD and QT interval in chromanol 293B +isoproterenol (Iso) (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 ms. 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 effects of ATX-II to prolong the QT interval, APD and to increase the TDR in the LQT3 model (**C**). Although 20 $\mu\text{mol/L}$ mexiletine does not completely reverse the effect of the drug to prolong the QT interval and APD in the LQT1 (**A**) and LQT2 (**B**) models, mexiletine was effective in markedly reducing TDR due to a greater abbreviation of the APD of the M cell than that of Epi. Modified from references (Shimizu & Antzelevitch, 1997, 1998) with permission.

Table 1
Inherited disorders caused by ion channelopathies affecting QT interval duration

Rhythm	Inheritance	Locus	Ion	Channel	Gene/protein
Long QT syndrome	TdP	AD	11p15 7q35 3p21 4q25 21q22 21q22 17q23 6q8A 3p25 11q23.3 11p15 21q22 7q35 11p15 17q23.1-24.2 12p13.3 10p12.33	I _{Ks} I _{Kr} I _{Na} I _{Ks} I _{Kr} I _{K1} I _{Ca} I _{Na} I _{Na} I _{Ks} I _{Kr} I _{Ks} I _{K1} I _{Ca} I _{Ca}	KCNQ1, KvLQT1 KCNH2, HERG SCN5A, Na _v 1.5 ANKB, ANK2 KCNK1, minK KCNK2, MiRP1 KCNJ2, Kir 2.1 CACNA1C, Ca _v 1.2 CAV3, Cavolin-3 SCN4B, Na _v β4 KCNQ1, KvLQT1 KCNK1, minK KCNH2, HERG KCNQ1, KvLQT1 KCNJ2, Kir2.1 CACNA1C, Ca _v 1.2 CACNB2b, Ca _v β _{2b}
LQT syndrome (JLN)	(Andersen-Tawil Syndrome) (Timothy Syndrome)				
Short QT syndrome	TdP VT/VF	AD AD AD AD			

Abbreviations: AD: autosomal dominant, AR: autosomal recessive, JLN: Jervell and Lange-Nielsen, LQT: Long QT, RW: Romano-Ward, TdP: Torsade de Pointes, VT: ventricular fibrillation, VT: ventricular tachycardia.