Inhibition of Late Sodium Current by Mexiletine
A Novel Pharmotherapeutical Approach in Timothy Syndrome

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Background—Timothy syndrome (TS) is a rare long-QT syndrome caused by CACNA1C mutations G406R in exon 8A (TS1) and G402S/G406R in exon 8 (TS2). Management of TS is a challenge and prognosis is poor. This study aimed to explore the inheritance pattern and mechanism of an I_{Na} blocker, mexiletine, to improve clinical manifestations in TS.

Methods and Results—A 2-year-old Chinese girl with a typical TS1 phenotype underwent candidate gene screening. Qualitative and quantitative cloning sequence and analyses for mosaicism were performed on family members. Therapeutic effects of mexiletine were evaluated using ECG and Holter monitoring. The electrophysiological effect of mexiletine was evaluated in a TS model using rabbit ventricular wedges. The proband with severe syndactyly and delayed language skills was identified harboring a G406R mutation in CACNA1C. Her baseline ECG showed markedly prolonged QTc, 2:1 AV block and macro-T wave alternans. G406R was absent in her mother but expressed in her father’s oral mucosa, sperm, and white blood cells, indicating a mosaic carrier. Although asymptomatic, he exhibited mild QTc prolongation (470–490 ms) and syndactyly. Mexiletine shortened QTc from 584 to 515 ms, blunted QT–RR relationship, and abolished 2:1 AV block and T wave alternans in the girl. In in vitro studies, mexiletine inhibited late I_{Na} with IC50 of 17.6±1.9 μmol/L and attenuated brady-dependent QT prolongation and reduced QT–RR slope in the TS model using BayK 8644.

Conclusions—Mexiletine shortened QTc, attenuated QT–RR slope, abolished 2:1 AV block and T wave alternans in a TS1 patient and TS model via inhibition of late I_{Na}. (Circ Arrhythm Electrophysiol. 2013;6:614-622.)

Key Words: atrioventricular block ■ late sodium current ■ LQT8 ■ mexiletine ■ T wave alternans ■ Timothy syndrome

Timothy syndrome (TS), also known as long QT (LQT8), is a rare and severe form of LQT syndrome (LQTS). It is characterized by multiorgan system dysfunction, including malignant arrhythmias, syndactyly, immunodeficiency, intermittent hypoglycemia, developmental delay, autism, and dysmorphic facial features. Because of markedly delayed ventricular repolarization, patients with TS often present with functional 2:1 AV block (AVB), T wave alternans (TWA), and ventricular arrhythmias.

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TS is caused by mutations on CACNA1C which encodes L-type calcium channel Cav1.2. Two types of TS have been defined according to the mutation sites: G406R in exon 8A (TS1) and G402S/G406R in exon 8 (TS2). Both mutations impair inactivation of L-type calcium current (I_{Ca,L}), leading to a sustained inward Ca^{2+} current during action potential plateau phase. Sicouri et al1 reported that enhancement of Ca^{2+} influx by BayK 8644, which mimics the gain-of-function of I_{Ca,L} in TS, prolonged ventricular repolarization and also resulted in the development of delayed after depolarizations capable of initiating ventricular arrhythmias. With a severe phenotype and poor prognosis, the management of TS has been challenging. Implantable cardioverter defibrillators have been shown to be effective in terminating ventricular fibrillation, but the benefit of implantable cardioverter defibrillators could be offset by the higher rate of complications in young children with TS because of body size and particular susceptibility to infections caused by autoimmune deficiency. Therefore, an alternative drug approach in TS has been clinically studied. However, TS is rare, a validated drug therapy has not yet been established. Because TS is associated with gain-of-function in I_{Ca,L}, reduction of I_{Ca,L} influx by calcium channel blockers was expected to accelerate ventricular repolarization and reduce intracellular Ca^{2+} loading, and, therefore, to be antiarrhythmic. However, verapamil, a specific I_{Ca,L} blocker,
failed to shorten QTc. In the study by Shah et al., verapamil was shown to initially reduce the incidence of ventricular arrhythmias, but the addition of ranolazine was required to suppress frequent episodes of ventricular arrhythmias and implantable cardioverter defibrillator shocks. Our recent basic study indicates that the late sodium current (INa,L) plays a central role in rate adaptation of ventricular repolarization and contributes importantly to amplified brady-dependent mechanisms. It is, therefore, reasonable to speculate that QT prolongation in LQTS regardless of the underlying ionic and cellular mechanism of mexiletine targets multiple ion channels.

In the present study, we identified a 2-year-old Chinese girl with the typical TS1 phenotype of syndactyly, QT prolongation, 2:1 AVB, and TWA. Genetic testing confirmed TS1 subtype. We also tested the clinical therapeutic efficacy of mexiletine as a potential INa,L blocker and compared it with propranolol and diltiazem. Significant improvement of TS1 ECG manifestations after use of mexiletine, ie, disappearance of 2:1 AVB and TWA, prompted us to explore further the underlying ionic and cellular mechanism of mexiletine in an experimental TS model.

Materials and Methods
A 2-year-old girl with typical TS1 phenotypes, including syndactyly, marked QT prolongation, 2:1 AVB, and TWA was enrolled in the Chinese National Channelopathy Register Study. Informed consents, approved by the Ethics Committee of Peking University People’s Hospital, were obtained from the proband’s parents and additional second-degree family relatives.

Genetic Analysis
Genomic DNA from the proband and her parents was extracted from whole blood sample in accordance with standard protocols. All samples underwent polymerase chain reaction (PCR) amplification and direct sequencing. PCR products were purified by vacuum pump Axygene PCR. Direct sequencing was carried out with BigDye Terminator DNA sequencing kit (version 3.1) and 3730XL DNA Analyzer. The sequence of PCR primer pairs was designed based on reference or redesigned using Primer 3 (CANCNA1C: NM_000238; KCNQ1: NM_000218.2; KCNH2: NM_000238; SCN5A: NM_198056.2).

In addition, oral mucosa DNA samples were obtained from the parents and other second-degree family members of the proband, and sperm DNA (Beijing CoWin Biotech, Beijing, China) was collected from the proband’s father. Specific primers for exon 8A were designed to amplify the mutated allele, making the first nucleotide of third backward nucleotide with no match to both wild and mutant (forward: 5′-TgTTgAgCggTAAgCTgAC-3′; reverse: 5′-TCCtCtGGtCCtCtAATCT-3′). Cloning sequencing and fluorescence quantitative PCR technique were performed to determine the quantitative distribution of the mutant allele in suspected family carriers.

ECG and Holter Monitoring
A 12-lead ECG was obtained at baseline and 2 hours after each dose of medication. The QT interval was measured on lead II or V5. Heart rate–corrected QT (QTc) was calculated using Bazett formula (QTc = QT/RR). Bidirectional T waves were included, but U waves were excluded in the QT measurements. Holter monitoring was performed on the day before medication and 1 week after. The QT/RR slope was calculated and compared between baseline and drug therapy on the basis of Holter recording data. The proband’s rhythm was also monitored on telemetry during her hospitalizations.

The effects of propranolol (a β-adrenergic receptor blocker), mexiletine (a sodium channel blocker), and diltiazem (a calcium channel blocker) were studied to determine whether each could serve as a potential therapeutic agent in TS1.

Basic Electrophysiological Methods
Arterially Perfused Rabbit Left Ventricular Wedge Preparation and Electrophysiological Recordings
Surgical preparation of the rabbit left ventricular (LV) wedge has been described in detail in previous publications. The preparation was placed in a small tissue bath and arterially perfused with Tyrode solution containing 4 mmol/L K+ buffered with 95% O2 and 5% CO2 (temperature, 35.7±0.1°C). The preparations were placed at basic cycle length of 500, 1000, and 2000 ms.

A transmural ECG signal was recorded using extracellular silver/silver chloride electrodes placed in the Tyrode solution bathing; the preparation was 1.0 to 1.5 cm from the epicardial and endocardial surfaces. Transmembrane action potentials were recorded from the endocardium (Endo) using floating glass microelectrodes.

The experimental TS model of the rabbit LV wedge preparation was created by constant perfusion of the preparation with 1 μmol/L BayK 8644 during the entire length of the experiment to mimic the gain-of-function in INa,L. The effect of mexiletine on ventricular repolarization (QT) and arrhythmias (ventricular tachycardia defined as consecutive nonsustained ventricular beats ≥3 or ectopic beats) in the experimental TS model was investigated by adding mexiletine to the Tyrode solution in the presence of BayK 8644. The incidences of arrhythmias 30 minutes before and after adding mexiletine were compared.

Isolated Rabbit Ventricular Myocytes and INa,L and INa,U Recording
Single ventricular myocytes were isolated enzymatically from New Zealand white rabbits (2.3–2.8 kg) of either sex using a method described previously. The fast sodium current (INa,F) and late sodium current (INa,L) were recorded at a temperature of 35.7°C using whole-cell patch clamp techniques. Command pulses were generated with a Digidata 1320A and pClamp 8 software (Axon Instruments, Foster City, CA). Pipettes with 2 to 3 mol/LΩ resistance after filling with a pipette solution were used. Liquid junction potentials were zeroed before the formation of membrane seal. Series resistance was compensated electronically by 70% to 80%. The method and protocol to record INa,F, INa,L, and INa,U have been described in detail in our previous publications.

Statistical Analysis
The values are reported as mean±SD in the clinical data and mean±SEM in the animal data. The n in the clinical data represents number of observations, and n in the basic experimental data represents number of rabbits or myocytes. The independent t test was performed for statistical analysis of the differences in the clinical data (QTc and QT–RR slope) between pre and post treatments with mexiletine. The paired t test was used for statistical analysis of the basic experimental data between the paired samples. Fisher exact test was used for the comparison between pre and post treatments for event incidences.

Results
Clinical Characteristics
The proband, a 2-year-old Chinese female child, presented with complete bilateral syndactyly of 2 to 3–4–5 fingers and cutaneously syndactyly of 2 to 3 left toes (Figure 1A). Telemetry and Holter monitoring revealed significant fluctuated changes in T wave morphology, QT interval, and AV
conduction abnormalities; QTc intervals fluctuated from 531 to 615 ms. Although 2:1 AVB (Figure 1B) and macro-TWA (Figure 1C) could occur at any time, they occurred more often during nocturnal sleep when the heart rate decreased.

An echocardiography revealed a patent foramen ovale and marginal LV hypertrophy. The child exhibited a normal level of intelligence and cognitive ability except for delayed language skill for age.

Bilateral cutaneous syndactyly of 3 to 4 fingers and 1 to 2 toes were noted in the proband’s father. Although the father had slightly delayed language development at early age, he had no other developmental delays. His QTc was mildly to moderately prolonged at 470 to 490 ms.

**Genetic Pattern**

Genetic testing identified a c.1216G>A transition resulting in the p.Gly406Arg (G406R) missense mutation in exon 8A on CACNA1C (Figure 1D) in the proband. In addition, she carried 2 polymorphisms, including KCNQ1-G643S (allele frequency of A=5.9% in controls of 744) and SCN5A-A29A (allele frequency G=55.9%; 38/68 in unrelated normal individuals).

DNA samples from the parents’ peripheral blood and oral mucosa showed no abnormality in the proband’s mother, but the presence of a superimposed minor A peak at nucleotide 1216 (Figure 2A) in her father’s samples. Further testing with specific primers showed that the A rather than the G signal was the major peak, confirming paternal somatic mosaicism (Figure 2B). To further investigate the possibility of germline mosaicism, we analyzed the father’s sperm DNA samples; the result proved positive (Figure 2C). Somatic mosaic testing on oral mucosa DNA sample of proband’s second-degree paternal family relatives was all negative (Figure 2D).

Via cloning sequencing technique, we identified the A1216 in 5 clones of 45 colonies, indicating that ≈22.22% of the oral mucosa cells carried the mutant allele in proband’s father. The percentage of affected clones for his blood and sperm were 17.02 (4 clones of 47 colonies) and 3.75 (3 clones of 80 colonies).

**Effects of Mexiletine on QT, 2:1 AV block, TWA, and QT–RR Relationship in the TS1 Patient**

A low-dose mexiletine (9 mg/kg per day) was initiated at admission when the proband’s 12-lead ECG revealed QTc of 600 ms and 2:1 AVB (Figure 3A). After the third dosage of mexiletine, 2:1 AVB resolved and TWA became less prominent. Mexiletine also attenuated the phasic changes in T wave morphologies. To determine whether those ECG improvements were by chance, mexiletine was replaced by propranolol (1.25 mg/kg per day). However, bradycardia (heart

![Figure 1. Phenotype and genotype characteristics of TS1 proband. A, Syndactyly of 2 to 3-4-5 fingers and cutaneously syndactyly of 2 to 3 left toes. X-ray confirmed complete syndactyly of both hands. B, Holter tracings demonstrated marked QT prolongation, functional 2:1 AV block with the blocked P wave landed on the ascending limb of T wave. C, Macro–T wave alternans. D, Electropherogram of DNA sequences derived from peripheral blood samples of the proband: a heterozygous G/A at nucleotide position 1216 (pink arrow) as c.1216G>A transition resulting in the p.Gly406Arg (G406R) missense mutation in exon 8A of the Cav1.2 L-type calcium channel gene, CACNA1C.](http://circep.ahajournals.org/doi/fig/10.1161/CIRCEP.113.001541)
rate, 55 beats per minute) occurred and the QTc lengthened to 588 ms 24 hours after propranolol administration. As a consequence, 2:1 AVB reappeared and TWA became prominent. Surprisingly, diltiazem (4 mg 3 times daily), an ICa,L blocker, exhibited a similar effect to that of propranolol. Therefore, both drugs were discontinued, and reinitiating mexiletine abolished 2:1 AVB and attenuated TWA. At a higher dose (12.5 mg/kg per day), mexiletine shortened mean QTc (Figure 3B) from 584±32 ms (531–615 ms) at baseline to 516±17 ms (494–542 ms; P=0.001). Each of the mean QTc values before (n=5) and after (n=6) mexiletine therapy were calculated on the basis of the separate consecutive 12-lead ECG recordings on different days.

The effects of mexiletine on the QT–RR relationship are shown in Figure 4. Mexiletine blunted the QT–RR relationship and significantly reduced the QT–RR slope from 443±59 ms/s at baseline to 320±42 ms/s (P=0.007) on the basis of 5 separate Holter recordings on different days before and after mexiletine therapy.

Six months after initial treatment with mexiletine, the patient successfully underwent her first syndactyly repair surgery on a maintenance dose of mexiletine (12.5 mg/kg per day). During her 1-week hospital stay, neither ventricular arrhythmias nor 2:1 AVB or significant TWA were detected on the telemetry. The operation under general anesthesia was also uneventful, and no arrhythmias were observed.

**Effect of Mexiletine on I_{Na} and I_{Ca,L} in the Isolated Rabbit Ventricular Myocytes**

Clinical observations that mexiletine improved ECG manifestations of TS1 patient indicated that mexiletine may have exerted its therapeutic effects via inhibition of I_{Na,L}. The effects of mexiletine on I_{Na,L} and fast sodium current (I_{Na,S}) were studied and compared with the isolated rabbit ventricular myocytes. As shown in Figure 5A through 5D, IC_{50} of mexiletine to inhibit I_{Na,L} was significantly lower than its IC_{50} on I_{Na,S} (17.6±1.9 versus 34.6±2.9 μmol/L; n=4 myocytes in each group; P=0.003), indicating that mexiletine selectively blocked I_{Na,L}.

The effect of mexiletine on I_{Ca,L} was also investigated in the isolated rabbit ventricular myocytes. As shown in Figure 5E and 5F, mexiletine at concentrations ≤100 μmol/L exhibited no significant effect on I_{Ca,L} compared with the time-matched control: reduction of I_{Ca,L} by 8.5±0.8% in the presence of 100 μmol/L mexiletine versus 8.0±0.7% in the time-matched control (n=4 myocytes in each group; P=0.36).

**Effects of Mexiletine in the TS Model of the Rabbit LV Wedge Preparation**

The experimental TS model using the rabbit LV wedge was created by perfusing the preparation with BayK 8644 to mimic the gain-of-function of I_{Ca,L}. BayK 8644 at 1 μmol/L significantly prolonged the QT interval from 304±11 ms at control to 437±32 ms (n=4 rabbits; P=0.011) at a basic cycle length of 2000 ms. Mexiletine at 30 μmol/L attenuated QT prolongation induced by BayK 8644 particularly at a basic cycle length of 2000 ms, resulting in a decrease in the QT–RR slope and ΔQT among different pacing rates (Figure 6).

There were intermittent runs of spontaneous ventricular tachycardia in groups and ectopic beats in 3 of 4 rabbits after perfusion of BayK 8644. However, no tordades de pointes occurred. Interestingly, BayK 8644 also induced macroscopic T wave changes in the rabbit LV wedge preparation similar to those observed in the TS1 patient, although the clinical T wave changes occurred with a much shorter phasic cycle length (Figure 7). Mexiletine (30 μmol/L), which was added into the perfusate containing BayK 8644 (1 μmol/L), completely abolished BayK 8644–induced ventricular tachycardia and ectopic beats in all these 3 rabbits (P=0.143). In addition, the phasic T wave changes were also attenuated by mexiletine.
Another interesting finding was the effect of BayK 8644 on contractility, which reflects intracellular calcium loading (Figure 8). BayK 8644 at 1 μmol/L markedly increased the contractility by 176±19% ($P=0.027; n=4$ rabbits), but abolished the positive staircase phenomenon in 4 of 4 rabbits. In other words, BayK 8644 blunted contractility strength–interval relationship. Mexiletine significantly reduced the increase in contractility induced by BayK 8644 but without restoring the staircase phenomenon.

### Discussion

TS is a rare subtype of LQTS. To date, only 32 TS cases have been reported worldwide. In this study, we identified the first case of TS in Chinese by genetic analysis and explored potential drug therapies for this malignant syndrome. The major novel findings of our study include: (1) a uncommon mosaicism in both germline and partial somatic inheritance for the CACNA1C-G406R mutation in TS; (2) worsening of functional 2:1 AVB and TWA in TS by use of either propranolol (a

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**Figure 3.** A, 12-Lead ECG of the TS1 patient was obtained immediately after initiation of the first dose of mexiletine. Marked QT prolongation (QTc, 600 ms) was accompanied by 2:1 AVB (P waves marked by arrows). B, mexiletine (12.5 mg/kg per d) significantly briefed the QT interval (QTc, 495 ms) and abolished 2:1 AVB.

**Figure 4.** Effects of mexiletine on the QT–RR relationship. The data were collected from 5 separate Holter recordings ($\times24$ hours each) each before and after the treatment of mexiletine. The minimal interval between 2 consecutive Holters was 3 days; **$P=0.007$.**
β-adrenergic receptor blocker) or diltiazem (a calcium channel blocker); and (3) abolishment of 2:1 AVB and TWA in TS by mexiletine via inhibition of \( \text{INa,L} \).

Two types of TS have been defined on the basis of 2 mutations (G406R on exon 8a and G402S/G406R on exon 8).\(^1\)\(^,\)\(^2\) Recently, Gillis et al.\(^1\)\(^5\) identified another novel mutation (p.Ala1473Gly) on exon 36 of \( \text{CACNA1C} \), which expands the TS-related mutations to 3. Somatic mosaicism is defined as the presence of genetically distinct populations of somatic cells in a given organism.\(^1\)\(^6\) To the best of our knowledge, there have only been 2 studies that showed mosaicism in TS. Splawski et al\(^1\)\(^,\)\(^2\) published the first study in 2004.\(^1\) Etheridge et al\(^1\)\(^3\) recently found that the father of a TS proband who exhibited a mild TS phenotype (complete cutaneous syndactyly and asymptomatic LQTS) was genetically mosaic.\(^1\)\(^3\) Similarly, the father of the index patient has bilateral cutaneous syndactyly and a mildly prolonged QT interval (QTc, 470–490ms). Further genetic mosaicism quantitative analysis confirmed that he has 3% to 22% mutant-type somatic and germline cells. Such an existence of mosaicism further emphasized the importance of a mosaic examination, specifically if parents anticipate having additional children, as a germline mosaicism would suggest an increase in probability of giving birth to another genetically affected child.

TS is one of the most severe types of LQTS, and its high mortality at a very young age is likely caused by cardiac arrhythmias, precipitated by infections, severe illnesses, or anesthesia.\(^1\) Different treatment approaches in TS have been attempted. Because QT prolongation and associated arrhythmogenesis in TS is gain-of-function in \( \text{ICa,L} \), a therapeutic role of \( \text{ICa,L} \) blockers was expected. However, verapamil, a specific \( \text{ICa,L} \) blocker, had little effect on the QTc interval in a TS2 patient.\(^5\)\(^,\)\(^6\) In a recent study, verapamil actually increased the frequency of TdP in an infant with TS.\(^1\)\(^3\) Our finding for the \( \text{ICa,L} \) blocker, diltiazem, indicates similar findings to that study, as it worsened 2:1 AVB and TWA. The mechanism underlying the failure of \( \text{ICa,L} \) blockers in TS is unclear. Experience with other channelopathies indicates that the altered function of a mutant ion channel may not necessarily be corrected by a specific blocker or agonist targeting on the channel. For example, in short QT syndrome caused by mutations in \( \text{IKr} \) channel, some of the classical \( \text{IKr} \) blockers fail to correct \( \text{IKr} \) and the QT interval.\(^1\)\(^7\)\(^,\)\(^8\) Mutant ionic channels may have altered binding properties and respond differently to drugs.

2:1 AVB in our TS case occurred likely in ventricular myocardium with excessively prolonged repolarization time instead of AV node, which is why mexiletine could abolish 2:1 AVB. Bradycardia induced by propranolol in our patient may facilitate 2:1 AVB in the setting of markedly prolonged QT interval. A recent study showed that β-adrenergic blockers, including propranolol, could shorten QTc in patients with LQT1 and LQT2, an effect thought to be related to the inhibitory effect of β-adrenergic blockers on sodium channels.\(^1\)\(^9\) However, propranolol blocks \( \text{INa,L} \) with an \( \text{IC50} \) of 10.3 μmol/L,\(^2\)\(^0\) which is ≈100 folds higher than the plasma concentrations of propranolol required for a β-blocking effect.\(^3\)\(^1\)\(^2\) Because sympathetic stimulation delays ventricular repolarization in both LQT1 and

![Figure 5](https://example.com/fig5.png)
LQT2,23 an alternative explanation is that β-blockers shorten QTc in LQT1 and LQT2 mainly via reducing sympathetic tones. In a recent report, the baseline ECG of a TS infant on propranolol exhibited prominent TWA.24

Our study indicates that inhibition of I_{Na,L} is a promising pharmacotherapeutic approach in TS. I_{Na,L} plays a central role in rate adaptation of ventricular repolarization. Inhibition of I_{Na,L} blunts bradycardia-dependent QT prolongation and leads to resolution of early after depolarization induced by I_{K1} blockers.7,25 Previous basic studies and clinical observations have shown that ranolazine, an antiangina drug, suppressed ventricular arrhythmias in TS.4,5 Although ranolazine blocks multiple ion channels involved in ventricular depolarization and repolarization, it exerts its antiarrhythmic action in TS probably via inhibition of I_{Na,L}. In the present study, we chose mexiletine instead of ranolazine as an I_{Na,L} blocker in treatment of TS mainly because ranolazine also blocks I_{K1} and may potentially cause further QT prolongation and worsen 2:1 AVB. A very recent case report also shows abolition of 2:1 AVB by mexiletine.14

**Figure 6.** Effect of mexiletine in a TS model of the rabbit left ventricular wedge preparation. Gain-of-function in I_{Na,L} in TS was mimicked by constant perfusion of the preparation with 1 µmol/L BayK 8644. A, ECG tracings were recorded under control perfusion, in the presence of BayK 8644 or BayK 8644+mexiletine. B, Mexiletine shortened the QT interval significantly during slower pacing rates (basic cycle lengths [BCLs] of 1000 and 2000 ms), therefore blunting the QT–BCL relationship (C). Error bars: mean±SEM, *P=0.017 between control and BayK 8644; and *P=0.023 between BayK 8644 and BayK 8644+mexiletine.

**Figure 7.** A, Phasic changes in T wave morphologies in the TS1 patient before use of mexiletine. B, Similar changes in T waves induced by BayK 8644 in the rabbit left ventricular (LV) wedge preparation. Note that the phasic cycle length was longer in the wedge preparation.
Mexiletine is a sodium channel blocker that blocks $I_{Na,L}$ preferentially without a significant effect on $I_{Ca,L}$ (Figure 5). In addition to its effect to shorten the QT interval, a blunted QT–RR relationship by mexiletine also plays an important role in abolishment of 2:1 AVB in our patient with TS. As shown in the rabbit ventricular wedge preparation, mexiletine shortened the QT interval more significantly at slower pacing rates and, therefore, reducing ΔQT during a wide range of pacing cycle lengths. Marked changes in ventricular repolarization during transition from tachycardia to bradycardia or from bradycardia to tachycardia may be responsible for 2:1 AVB in LQTS. A blunted QT–RR relationship would be expected to produce a smaller and more gradual change in QT during transition in heart rates, in which functional 2:1 AVB unlikely occurs at the level of ventricular myocardium.

However, mexiletine as a sodium channel blocker may reduce intracellular Ca$^{2+}$ overloading in TS via Na$^+$–Ca$^{2+}$ exchange, which is supported by the finding that mexiletine attenuated the increase in contractility, an index of intracellular Ca$^{2+}$ level, by BayK 8644 in the rabbit ventricular wedge preparation. The data obtained in iPSC from a TS patient suggested delayed after depolarizations as the trigger for ventricular arrhythmias. This explains why mexiletine suppressed ventricular arrhythmias induced by BayK 8644 in the wedge preparation, which occurred in groups without a change in QRS direction, and attenuated TWA and phasic T wave, a phenomenon that is associated with intracellular Ca$^{2+}$ overloading, in our patient with TS.

**Clinical Significance**

Our study validates a novel pharmotherapeutical approach in a TS patient with 2:1 AVB and prominent TWA. Abolishment of 2:1 AVB and prominent TWA by mexiletine via inhibition of $I_{Na,L}$ would be expected to reduce arrhythmic risks of the patients with TS because marked bradycardia because of 2:1 AVB or prominent TWA may facilitate the development of ventricular arrhythmias. Our patient with TS successfully underwent syndactyly repair surgery under general anesthesia without any arrhythmias, a procedure that may be associated with a high risk for cardiac arrest. Our patient is currently aged 3.5 years (the average life span of LQT8 is 2.5 years) and is free of any symptoms. We think that other patients with TS, particularly those who are not candidates for placement of pacemakers or intracardiac defibrillator, might also benefit from the treatment of mexiletine.

With the general prognosis of TS being poor and uncertain, our approach may bring a new hope to other patients with TS, their parents, and physicians.

**Study Limitations**

We did not test the effect of mexiletine on the mutant L-type calcium channels. Therefore, a possibility of mexiletine to inhibit the mutant $I_{Ca,L}$ cannot be completely ruled out. Propranolol was initiated for our patient at a relatively low dose at which β-adrenergic blockade was likely dominant and associated with worsening 2:1 AV block and TWA. But the therapeutic role of propranolol in TS cannot be disqualified on the basis of only 1 observation.

In conclusion, our study indicates that inhibition of $I_{Na,L}$ is a novel pharmotherapeutical approach in TS. Mexiletine as a sodium channel blocker with preferential inhibition of $I_{Na,L}$ is a promising candidate drug. In addition, the present study also emphasizes the importance of mosaicism detection in the first-degree family members of a TS index patient using specifically designed primers.

**Sources of Funding**

This study was supported by National Natural Science Foundation of China (NSFC-81170089 and NSFC-81070162), National 985-Program (BMU 201000057), National Basic Research Program of China (973 Program, 2007CB512002), Doctoral Program of Higher Education of China (20110001110046), and the Sharpe-Strumia Research Foundation (SSRF2011-24 and SSRF2012).

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**Figure 8.** BayK 8644 (1 µmol/L) produced a marked increase in contractility and abolished the positive staircase phenomenon (ie, enhancement of contractility during faster heart rates). Mexiletine (30 µmol/L) reduced the increase in contractility induced by BayK 8644 without restoring the positive staircase phenomenon.
Disclosures
None.

References


CLINICAL PERSPECTIVE

Delayed ventricular repolarization regardless of the underlying causes delays inactivation of late sodium current (I_{Na,L}), an inward ion current that contributes importantly to rate adaptation of repolarization. Therefore, I_{Na,L} is expected to be a pharmacotherapeutic target for the treatment of a variety of long-QT syndromes. Our present study serves as a successful example translating this important concept into clinical application. Despite the fact that LQT8 is caused by a gain-of-function in L-type calcium channel, mexiletine not only shortened the QT, but also blunted its rate-dependency via selective blockade of I_{Na,L}, resulting in abolishment of 2:1 atrioventricular block and attenuation of T wave alternans. This information may break a new ground in the management of different types of long QT syndromes. For patients with congenital long-QT syndrome who are intolerant to β-adrenergic blockers such as those patients with asthma or marked sinus bradycardia or 2:1 atrioventricular block secondary to excessively prolonged ventricular repolarization, a selective I_{Na,L} blocker could be a substitute for the β-blockers in prevention of cardiac events. However, the selective I_{Na,L} blockers could be conveniently used for acutely terminating torsade de pointes in the emergency room, the telemetry floor, or intensive care unit. Although validation of these broader clinical applications of the I_{Na,L} blockers requires further clinical studies in a large population of patients, the promising results of the present study clearly point out clinical therapeutic values of the I_{Na,L} blockers in long-QT syndrome that is not necessarily related to the gain-of-function in I_{Na} per se.
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Circ Arrhythm Electrophysiol. 2013;6:614-622; originally published online April 11, 2013; doi: 10.1161/CIRCEP.113.000092

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