Role of ß1-Blockade in Congenital Long QT Syndrome
— Investigation by Exercise Stress Test —

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Beta-blockade is widely reported to reduce the incidence of syncope in 75–80% of patients with congenital long QT syndrome (LQTS). However, despite full-dose ß-blockade, 20–25% of patients continue to have syncopal episodes and remain at high risk for sudden cardiac death. In some patients refractory to ß-blockade, the recurrence of arrhythmias is successfully prevented by left stellate ganglionectomy, and also by labetalol, a nonselective ß-blockade with ß1-blocking action. These observations suggest that not only ß-adrenoceptors, but also ß1-adrenoceptors, play an important pathogenic role, especially under sympathetic stimulation, in LQTS. The clinical effects of ß1-blockade in congenital LQTS were investigated in 8 patients with familial or sporadic LQTS. Two measurements of the QT interval were taken, from the QRS onset to the T wave offset (QTp). Using the Bruce protocol, an exercise test was performed after administration of ß-blockade alone and again after administration of ß1-blockade. The following were compared: (1) Bazzet-corrected QT (QTc) and QTp (QTpc) intervals in the supine and standing position before exercise and in the early recovery phase after exercise; and (2) the slopes (reflecting the dynamic change in the QT interval during exercise) of the QT interval to heart rate were obtained from the linear regression during the exercise test. In the supine position before exercise, there was no change in the QTc before or after the addition of ß1-blockade (498±23 vs 486±23 ms [NS]). However, in the upright position before exercise and in the early recovery phase after exercise, QTc was significantly shortened from 523±21 to 483±22 ms (p<0.01), and from 521±30 to 490±39 ms (p<0.01), respectively, by ß1-blockade. The QTpc was unchanged in any situation. Consequently, QTc–QTpc was significantly shortened by ß1-blockade in the upright position before exercise and in the early recovery phase after exercise (131±36 to 105±37 ms [p<0.05], and 132±29 to 102±31 ms [p<0.01], respectively). The slopes of the QT interval–heart rate relation by linear regression became significantly steeper from –2.23±0.38 to –2.93±0.76 (p<0.01) with the addition of ß1-blockade. The findings suggest that the addition of ß1-blockade attenuated the exercise-induced prolongation of the QT interval and that the rate adaptation of the QT interval to heart rate during exercise was improved. This indicates that additional treatment with ß1-blockade may be beneficial to prevent cardiac events in LQTS patients in whom ventricular arrhythmia is resistant to ß-blockade.

Key Words: ß1-Blockade; ß1-Blockade; QT interval; Ventricular tachyarrhythmia

Recent genetic analysis has identified 5 forms of the congenital long QT syndrome (LQTS) caused by mutations in ion channel genes, including 3 cardiac potassium channel genes (KvLQT1 (LQT1), HERG (LQT2), KCNE1 (minK)) and the cardiac sodium channel gene SCN5A (LQT3). The malignant ventricular tachyarrhythmias associated with LQTS, especially LQT1 and LQT2, are known to be elicited by a sudden increase in sympathetic activity, and catecholamines in the form of isoproterenol, norepinephrine and epinephrine, as well as stellate ganglion stimulation, have been used in attempts to provoke the ventricular tachyarrhythmias initiated by early afterdepolarization (EAD) and/or increased dispersion of ventricular repolarization? Beta-blockade prevents new syncopal episodes in 75–80% of patients with congenital LQTS but, despite full-dose ß-blockade, 20–25% of patients continue to have syncopal episodes and remain at high risk for sudden cardiac death; thus, LQT3 patients can be included among these patients resistant to ß-blockade. The fact that surgical interruption of the left stellate ganglion reduces the incidence of syncope and sudden death in some patients with idiopathic LQTS in whom ß-blockade is unsuccessful underscores the potential role of ß-adrenoceptors. Ben-David and Zipes reported that ß1-adrenoceptor stimulation increased the cesium-induced EAD amplitude and induced ventricular tachycardia occurrence and they postulated that for some patients with LQTS, ß1-rather than ß-adrenoceptor stimulation is more arrhythmogenic.

In the present study, we hypothesized that not only ß-adrenoceptors but also ß1-adrenoceptors play an important role in the pathogenic effects in LQTS and so we investigated the effect of ß1-blockade on the QT interval using an exercise test in patients with LQTS.

Methods

Patients
The study group comprised 8 patients (5 females, 3 males;
Exercise Protocol and Measurement of ECG

Informed consent was obtained from all subjects. The exercise stress test was performed using the Bruce protocol and terminated when the heart rate (HR) reached 120 beats/min to avoid the possible induction of ventricular arrhythmia. The QT and corrected QT (QTc) intervals were measured in the supine and upright positions before exercise and 3 min (early recovery phase) after exercise. The QT interval was measured from the onset of the earliest QRS deflection to the end of the T wave, which was determined by drawing a tangent to the steepest portion on the downslope of the T wave. If the U wave and/or next P wave was superimposed on the end of the T wave, the QT interval was measured to the nadir of the T wave, and the QT minus QTp (QT – QTp) interval was also analyzed as the terminal component of the T wave. The ECG was

Table 1 Clinical Characteristics of the Study Population of Patients With Long QT Syndrome

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Clinical symptoms</th>
<th>Type of heredity</th>
<th>Genotype</th>
<th>QT (ms)</th>
<th>QTc (ms)</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22/F</td>
<td>Syncope, Tdp(+)</td>
<td>Romano-Ward</td>
<td>NI</td>
<td>560</td>
<td>480</td>
<td>Propranolol 60 mg (+mexiletine 300 mg)</td>
</tr>
<tr>
<td>2</td>
<td>57/F</td>
<td>Syncope, Tdp(+)</td>
<td>Romano-Ward</td>
<td>NE</td>
<td>540</td>
<td>520</td>
<td>Propranolol 60 mg</td>
</tr>
<tr>
<td>3</td>
<td>34/F</td>
<td>Syncope, Tdp(+)</td>
<td>Romano-Ward</td>
<td>NE</td>
<td>520</td>
<td>500</td>
<td>Propranolol 50 mg</td>
</tr>
<tr>
<td>4</td>
<td>15/M</td>
<td>Asymptomatic Tdp(–)</td>
<td>sporadic</td>
<td>NI</td>
<td>500</td>
<td>450</td>
<td>Propranolol 60 mg</td>
</tr>
<tr>
<td>5</td>
<td>54/F</td>
<td>Syncope, Tdp(+)</td>
<td>sporadic</td>
<td>NE</td>
<td>500</td>
<td>540</td>
<td>Propranolol 30 mg</td>
</tr>
<tr>
<td>6</td>
<td>25/F</td>
<td>Syncope, Tdp(+)</td>
<td>sporadic</td>
<td>NE</td>
<td>520</td>
<td>500</td>
<td>Propranolol 30 mg</td>
</tr>
<tr>
<td>7</td>
<td>24/M</td>
<td>Syncope, Tdp(+)</td>
<td>sporadic</td>
<td>NE</td>
<td>540</td>
<td>600</td>
<td>Propranolol 90 mg</td>
</tr>
<tr>
<td>8</td>
<td>23/M</td>
<td>Asymptomatic Tdp(–)</td>
<td>sporadic</td>
<td>NI</td>
<td>540</td>
<td>510</td>
<td>Atenolol 50 mg</td>
</tr>
</tbody>
</table>

Tdp, torsade de pointes; NI, not identified; NE, not examined.

Fig 1. Changes in parameters with ß-blockade in patient 5. The surface ECG in lead II in the supine and standing positions before exercise and in the early recovery phase after exercise, and before and after ß-blockade are shown. QTc was shortened, especially in the early recovery phase after exercise, but QTpc did not change before or after ß-blockade. Consequently, QTc – QTpc were markedly shortened after ß-blockade.
by means of linear regression and the slope is compared with before exercise tests. The level of significance was \( p<0.05 \). Differences were determined using paired and unpaired t tests. After the addition of \( \beta \)-blockade did not change the QTc interval in the supine position before exercise, but in the upright position before exercise and in the early recovery phase after exercise, it was significantly shortened by the additional \( \beta \)-blockade treatment (Table 2). Because the QTc did not change, the QTc – QTpc, (ie, the duration of the terminal component of the T wave) in the upright position before exercise and in the early recovery phase after exercise was significantly shortened by the addition of \( \beta \)-blockade (Table 2). On the other hand, \( \beta \)-blockade did not change the QTc – QTpc in the supine position before exercise. Fig 1 shows representative data of the changes in parameters by \( \beta \)-blockade in patient 5.

### Results

**Clinical Characteristics (Table 1)**

Three patients (nos. 1–3) had family members with LQTS and sudden cardiac death. All patients had a prolonged QTc interval and the mean QT and QTc intervals were 523±21 ms and 513±44 ms, respectively, before \( \beta \)-blockade. After \( \beta \)-blockade, none of the patients, except one, had a syncopal attack. In the one patient (patient 1), syncopal attack recurred despite full \( \beta \)-blockade and mexiletine, and therefore a defibrillator device was implanted. Routine blood examinations and left ventricular function evaluated by 2-D echocardiograms were both normal in all patients. Genetic analyses, including KvLQT1, HERG, SCN5A and KCNE1 were performed in 4 patients (nos. 1,3,4,8), but no abnormality was identified (Table 1).

**Regression Analysis**

According to a previous report, the relationship between the QT interval and HR can be examined during exercise by means of linear regression and the slope is compared with before and after \( \beta \)-blockade.

**Drug Protocol**

The control treadmill test was performed during \( \beta \)-blockade (propranolol [30–90 mg] or atenolol [50 mg]) (Table 1). After additional treatment with \( \beta \)-blockade (doxazosin; 2 mg/day) for 1 week, the treadmill test was repeated until the exercise stress reached the same stage as the first study.

**Statistical Analysis**

Data are expressed as mean value ± SD. Significant differences were determined using paired and unpaired t tests. The level of significance was \( p<0.05 \).

### Discussion

Adrenergic stimulation can modify repolarization and may produce arrhythmias in normal subjects and patients with LQTS. Recently, many experimental and clinical studies have highlighted the role of \( \beta \)-adrenergic stimulation in triggering and/or maintaining torsade de pointes in patients with LQTS. \( \beta \)-blockade has been used as the first treatment. However, some patients are refractory to \( \beta \)-blockade and require left stellate ganglionectomy, which suggests that the \( \beta \)-adrenergic activity is arrhythmogenic. This hypothesis is reinforced by the fact that labetalol hydrochloride, a non-selective \( \beta \)-blockade with \( \beta \)-blocking properties, has been shown to be effective for patients with LQTS who are refractory to pure \( \beta \)-blockade, although it was reported in only a single patient.

In the present study, we investigated the role of \( \beta \)-blockade in LQTS using an exercise test on a treadmill, because plasma norepinephrine levels rise with exercise and continue to be higher in the early recovery phase, with a half-life of 2.8 min \( \beta \)-adrenoceptors, predominantly the \( \beta_1 \) subtype, have been demonstrated in human ventricular muscle.

### Table 3 QT–HR Relation During Exercise (QT=b-mHR)

<table>
<thead>
<tr>
<th></th>
<th>( \beta )-blocker</th>
<th>( \beta )-blocker + Dox</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope</td>
<td>(-2.2±0.38)</td>
<td>(-2.9±0.76)</td>
<td>0.009</td>
</tr>
<tr>
<td>Intercept</td>
<td>(614±49)</td>
<td>(656±78)</td>
<td>0.056</td>
</tr>
<tr>
<td>r value</td>
<td>(0.968±0.017)</td>
<td>(0.95±0.026)</td>
<td>0.058</td>
</tr>
</tbody>
</table>

Fig 2. QT interval–heart rate relation during treadmill exercise before (○) and after (□) \( \beta \)-blockade. An inverse relation with strong linear correlation was shown in both situations (\( r=-0.98 \) vs –0.94), and the slope of regression becomes steeper after \( \beta \)-blockade compared with before \( \beta \)-blockade.

### Response of Blood Pressure and HR After the Addition of \( \beta \)-Blockade

After \( \beta \)-blockade, HR did not change in the supine or standing positions before exercise, or at peak exercise. However, \( \beta \)-blockade significantly decreased systolic blood pressure (BP) both in the supine and upright position before exercise, but no statistical difference was observed at peak exercise (Table 2).

### Response of the QTc and QTpc Intervals to the Addition of \( \beta \)-Blockade

Alpha-1-blockade did not change the QTc interval in the supine position before exercise, but in the upright position before exercise and in the early recovery phase after exercise, it was significantly shortened by the addition of \( \beta \)-blockade (Table 2). On the other hand, \( \beta \)-blockade did not change the QTc – QTpc in the supine position before exercise. Fig 1 shows representative data of the changes in parameters by \( \beta \)-blockade in patient 5.

**QT–HR Relation During Exercise (Table 3)**

After the addition of \( \beta \)-blockade, the linear regression curve became steeper, and the slope ‘\( m \)’ changed from –2.2±0.38 to –2.9±0.76 ms (beats/min) (\( p<0.01 \)), and the intercept point changed from 614±49 to 656±78 ms (\( p=0.056 \)). A representative case is shown in Fig 2 (patient 2).
ing position and early recovery phase were prolonged, but that prolongation was inhibited by β-blockade, which is consistent with studies in which β-adrenergic stimulation prolonged the action potential duration\(^\text{19,21}\). QT prolongation while standing as well as during the early recovery phase would be due to enhanced sympathetic activity and consequently, as mentioned in previous reports\(^\text{15,29}\), may be associated with the occurrence of EAD during exercise.

**QT Interval and HR Relation During Exercise in LQTS**

Shortening of the QT interval with increased HR is a normal response\(^\text{20}\), but the QT interval is modulated by a number of additional factors\(^\text{31–33}\) and correction by the Bazett formula might result in some limitations\(^\text{34–36}\). Recently, Klügfeldt et al reported that the QT interval and heart rate (or cycle length) during exercise testing were linearly correlated\(^\text{10}\). In LQTS, there are abnormal QT responses, which are the failure of the QT to shorten and lengthening of the QTc interval with adrenergic stimulation, including exercise. This failure in shortening of the action potential duration might be caused by an abnormal response of IKs or the cAMP-activated chloride current \(I_{\text{Cl-cAMP}}\) or \(I_{\text{Ca-L}}\) to the adrenergic drive\(^\text{27}\). In the present study, we found that the slope of the QT interval–HR relation during exercise became steeper after β-blockade, which implies an improvement in the rate of adaptation of the QT interval. The details of this mechanism remain unknown; however, it may be related to the suppression of the enhanced response of \(I_{\text{Ca-L}}\).\(^\text{33}\) An increase in the \(K^+\)-channels,\(^\text{38}\) including \(I_{\text{to}}\) is another possibility.

**Significance of the Shortening of the Duration of the Terminal Component of the T Wave**

The present data showed a shortening of the duration of the terminal component of the T wave by β-blockade. In canine experimental models, Shimizu and Antzelevitch showed that the peak of the T wave in the ECG was coincident with the end of the repolarization of the epicardial myocytes, whereas the end of the T wave was coincident with that of the M region.\(^\text{39}\) If this can be applied to human patients with LQTS, our data show that the repolarization of the M cell was preferentially abbreviated by β-blockade. However, Burashnikov and Antzelevitch reported that β-adrenoceptor stimulation produces opposite effects on M cells and Purkinje fibers; that is, β-adrenoceptor agonists abbreviate the action potential duration of the M cells and prolonged the action potential duration of the Purkinje fibers in the canine ventricular cell.\(^\text{40}\) This suggests that the prolongation of the duration of the terminal component of the T wave is related to something other than M cells (eg, Purkinje fibers), but more direct evidence is needed.

**Study Limitations**

Recent studies have shown that congenital LQTS is a primary electrical disease caused by mutations in specific ion channel genes.\(^\text{34}\) In particular, in LQT1 and LQT2 adrenergic stimulation plays an important role in the electrophysiological pathogenesis. However, only 30–40% of familial LQTS cases have been identified by genotype, and it is not easy to identify the genotype in sporadic patients. In the present study, 4 of the 8 patients underwent genetic analysis, but no abnormal genes were found. So we could not specify the abnormal gene in each patient, but the response to β-blockade was uniformly observed in the 8 patients.

**Acknowledgments**

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