Role of β_1 -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 β -blockade, 20–25% of patients continue to have syncopal episodes and remain at high risk for sudden cardiac death. In some patients refractory to β -blockade, the recurrence of arrhythmias is successfully prevented by left stellate ganglionectomy, and also by labetalol, a nonselective β -blockade with β_1 -blocking action. These observations suggest that not only β -adrenoceptors, but also β_1 -adrenoceptors, play an important pathogenic role, especially under sympathetic stimulation, in LQTS. The clinical effects of β_1 -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 (QT) and from the QRS onset to the peak of the T wave (QTp). Using the Bruce protocol, an exercise test was performed after administration of β -blockade alone and again after administration of β_1 -blockade. The following were compared: (1) Bazett-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 β_1 -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 β_1 -blockade. The QTpc was unchanged in any situation. Consequently, QTc–QTpc was significantly shortened by β_1 -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 β_1 -blockade. The findings suggest that the addition of β_1 -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 β_1 -blockade may be beneficial to prevent cardiac events in LQTS patients in whom ventricular arrhythmia is resistant to β -blockade. (*Jpn Circ J* 2001; 65: 654–658)

Key Words: β_1 -Blockade; β -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),¹ HERG (LQT2),² KCNE1 (minK)^{3,4} and MiRP1⁵) and the cardiac sodium channel gene SCN5A (LQT3).⁶ 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.⁷ Beta-blockade prevents new syncopal episodes in 75–80% of patients with congenital LQTS,^{8–10} but, despite full-dose β -blockade,

20–25% of patients continue to have syncopal episodes and remain at high risk for sudden cardiac death.¹¹ LQT3 patients can be included among these patients resistant to β -blockade.^{12,13} 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 β -blockade is unsuccessful underscores the potential role of β_1 -adrenoceptors.¹¹ Ben-David and Zipes reported that β_1 -adrenoceptor stimulation increased the cesium-induced EAD amplitude and induced ventricular tachycardia occurrence and they postulated that for some patients with LQTS, β_1 -rather than β -adrenoceptor stimulation is more arrhythmogenic.¹⁴

In the present study, we hypothesized that not only β -adrenoceptors but also β_1 -adrenoceptors play an important role in the pathogenic effects in LQTS and so we investigated the effect of β_1 -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;

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

Patient no.	Age (years) /sex	Clinical symptoms	Type of heredity	Genotype	QT (ms)	QTc (ms ^{1/2})	Therapy
1	22/F	Syncope, Tdp(+)	Romano-Ward	NI	560	480	Propranolol 60 mg (+ mexiletine 300 mg)
2	57/F	Syncope, Tdp(+)	Romano-Ward	NE	540	520	Propranolol 60 mg
3	34/F	Syncope, Tdp(+)	Romano-Ward	NI	520	500	Propranolol 50 mg
4	15/M	Asymptomatic Tdp(-)	sporadic	NI	500	450	Propranolol 60 mg
5	54/F	Syncope, Tdp(+)	sporadic	NE	500	540	Propranolol 30 mg
6	25/F	Syncope, Tdp(+)	sporadic	NE	520	500	Propranolol 30 mg
7	24/M	Syncope, Tdp(+)	sporadic	NE	540	600	Propranolol 90 mg
8	23/M	Asymptomatic Tdp(-)	sporadic	NI	540	510	Atenolol 50 mg
					523±21	513±44	

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

Table 2 Changes in Parameter Caused by 1-Blockade

	-blocker	-blocker + 1-blocker	p value
HR			
Supine	54±6	57±6	0.429
Standing	62±10	67±15	0.163
Peak Ex	113±18	110±14	0.553
SBP			
Supine	122±15	111±15	0.004
Standing	122±26	103±21	0.041
Peak Ex	134±10	129±22	0.522
QT			
Supine	523±37	488±26	0.004
Standing	509±35	449±32	<0.001
Post Ex	462±43	438±40	0.021
QTc			
Supine	498±23	486±23	0.198
Standing	523±21	483±22	0.004
Post Ex	521±30	490±39	0.004
QTp			
Supine	407±14	390±27	0.246
Standing	381±23	367±40	0.130
Post Ex	343±45	343±51	0.946
QTpc			
Supine	382±10	384±42	0.912
Standing	398±41	378±43	0.173
Post Ex	392±68	386±78	0.643
QTc-QTpc			
Supine	119±24	106±35	0.254
Standing	131±36	105±37	0.028
Post Ex	132±29	102±31	0.001

HR, heart rate; SBP, systolic blood pressure.

mean age, 31±15 (range, 15–57) years) with a diagnosis of LQTS based on the previously established criteria.¹⁵ Seven of the patients had a history of syncope and/or cardiac arrest, and spontaneous torsade de pointes was also documented in these patients.

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

Fig 1. Changes in parameters with 1-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 1-blockade are shown. QTc was shortened, especially in the early recovery phase after exercise, but QTpc did not change before or after 1-blockade. Consequently, QTc-QTpc were markedly shortened after 1-blockade.

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. The QTp interval was calculated as the interval between the onset of earliest QRS deflection to the peak 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 3 QT–HR Relation During Exercise (QT=b-mHR)

	-blocker	-blocker + 1-blocker	p value
Slope	-2.23 ± 0.38	-2.93 ± 0.76	0.009
Intercept	614 ± 49	656 ± 78	0.056
r value	0.968 ± 0.017	0.951 ± 0.026	0.058

Fig2. QT interval–heart rate relation during treadmill exercise before (●) and after (○) 1-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 1-blockade compared with before 1-blockade.

recorded at a paper speed of 25 mm/s with a calibration of 10 mm/mV, and the longest QT and QTp intervals in the leads II, V4 and V5 were used for the analysis.

Regression Analysis

According to a previous report,¹⁶ the relationship between the QT interval and HR can be examined during exercise by means of linear regression and the slope is compared before and after 1-blockade.

Drug Protocol

The control treadmill test was performed during -blockade (propranolol [30–90 mg] or atenolol [50 mg]) (Table 1). After additional treatment with 1-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 $\pm$ SD. Significant differences were determined using paired and unpaired t tests. The level of significance was $p < 0.05$.

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 -blockade. After -blockade, none of the patients, except one, had a syncopal attack. In the one patient (patient 1), syncopal attack recurred despite full -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).

Response of Blood Pressure and HR After the Addition of 1-Blockade

After 1-blockade, HR did not change in the supine or standing positions before exercise, or at peak exercise. However, 1-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 1-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 additional 1-blockade treatment (Table 2). Because the QTpc 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 1-blockade (Table 2). On the other hand, 1-blockade did not change the QTc–QTpc in the supine position before exercise. Fig 1 shows representative data of the changes in parameters by 1-blockade in patient 5.

QT–HR Relation During Exercise (Table 3)

After the addition of 1-blockade, the linear regression curve became steeper, and the slope 'm' changed from -2.23 ± 0.38 to -2.93 ± 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).

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 -adrenoceptor stimulation in triggering and/or maintaining torsade de pointes in patients with LQTS^{15,17} and -blockade has been used as the first treatment. However, some patients are refractory to -blockade and require left stellate ganglionectomy,¹¹ which suggests that the 1-adrenergic activity is arrhythmogenic. This hypothesis is reinforced by the fact that labetalol hydrochloride, a non-selective -blockade with 1-blocking properties, has been shown to be effective for patients with LQTS who are refractory to pure -blockade, although it was reported in only a single patient!⁸

In the present study, we investigated the role of 1-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!¹⁹ 1-adrenoceptors, predominantly the 1 subtype,^{20,21} have been demonstrated in human ventricular muscle!²²

1-Adrenoceptor and the QT Interval in LQTS

In animal models, the mechanism of the prolongation of the action potential caused by 1-adrenoceptor stimulation has been attributed to an increase in the L-type calcium current (I_{Ca})²³ but subsequent studies have failed to demonstrate any effect of 1-adrenergic stimulation on I_{Ca} ^{24,25} and have instead demonstrated an 1-adrenergic inhibition of the outward (I_{to})^{24,26} and delayed rectifier potassium $I_{K}^{24,27,28}$ currents. In the present study, the QT intervals in the stand-

ing position and early recovery phase were prolonged, but that prolongation was inhibited by 1-blockade, which is consistent with studies in which 1-adrenergic stimulation prolonged the action potential duration^{20,21} 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,^{14,29} 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,³⁰ but the QT interval is modulated by a number of additional factors^{31–33} and correction by the Bazett formula might result in some limitations.^{34–36} Recently, Kligfield et al reported that the QT interval and heart rate (or cycle length) during exercise testing were linearly correlated!⁶ 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 I_{Ks} or the cAMP-activated chloride current (I_{Cl-cAMP}) or I_{Ca-L} to the adrenergic drive.³⁷ In the present study, we found that the slope of the QT interval–HR relation during exercise became steeper after 1-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_{Ca-L}.³³ An increase in the K⁺-channels,³⁸ including I_{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 1-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.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 1-blockade. However, Burashnikov and Antzelevitch reported that 1-adrenoceptor stimulation produces opposite effects on M cells and Purkinje fibers; that is, 1-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.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.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 1-blockade was uniformly observed in the 8 patients.

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