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Beta-blockers protect against dispersion of repolarization during exercise in congenital long-QT syndrome type 1

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Abstract

Introduction—Beta-blocker therapy reduces syncope and sudden death in long-QT syndrome type 1 (LQT1), but the mechanism of protection is incompletely understood. This study tested the hypothesis that beta-blockade reduces QT prolongation and dispersion of repolarization, measured as the T peak-to-end interval (T_{pe}), during exercise and recovery in LQT1 patients.

Methods and Results—QT and T_{pe} were measured in 10 LQT1 patients (33 ± 13 yrs) and 35 normal subjects (32 ± 12 yrs) during exercise tests on and off beta-blockade. In LQT1 patients, beta-blockade reduced QT (391 ± 25 msec vs. 375 ± 26 msec, $p = 0.04$ during exercise; 419 ± 41 msec vs. 391 ± 39 msec, $p = 0.02$ during recovery) and markedly reduced T_{pe} (91 ± 26 msec vs. 67 ± 19 msec, $p = 0.03$ during exercise; 103 ± 26 msec vs. 78 ± 11 msec, $p = 0.02$ during recovery). In contrast, in normal subjects, beta-blockade had no effect on QT (320 ± 17 msec vs. 317 ± 16 msec, $p = 0.29$ during exercise; 317 ± 13 msec vs. 315 ± 14 msec, $p = 0.15$ during recovery) and mildly reduced T_{pe} (69 ± 13 msec vs. 61 ± 11 msec, $p = 0.01$ during exercise; 77 ± 19 msec vs. 68 ± 14 msec, $p < 0.001$ during recovery).

Conclusion—In LQT1 patients, beta-blockers reduced QT and T_{pe} during exercise and recovery, supporting the theory that beta-blocker therapy protects LQT1 patients by reducing dispersion of repolarization during exercise and recovery.

Keywords

Long-QT Syndrome; Beta-Blocker Therapy; Tpeak-end; Dispersion of Ventricular Repolarization; Sudden death

INTRODUCTION

Congenital long-QT syndrome (LQTS) is a genetically heterogeneous group of cardiac repolarization disorders characterized by prolongation of the QT interval and a propensity to develop syncope or sudden cardiac death due to the malignant ventricular arrhythmia known as torsades de pointes (TdP). In long-QT syndrome type 1 (LQT1), the commonest form of LQTS, affected patients often develop TdP during or shortly after exercise. Whereas in normal subjects the QT interval shortens as the heart rate (HR) increases, in LQT1 the QT interval fails to shorten adequately during exercise^{1–3} or epinephrine infusion^{4–7}. These

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exercise-induced repolarization responses are thought to play a role in the mechanism of arrhythmogenesis in LQT1.

Beta-blocker therapy (BB) significantly reduces the occurrence of syncope and sudden cardiac death in LQT1 patients^{8–10}, although a small subset of LQT1 patients continues to have syncope or sudden death despite BB. Identification of these high-risk, BB-resistant patients, who could benefit from implantable cardioverter-defibrillator therapy, remains a challenge for the clinician. Several parameters are available to help clinicians assess the response to BB in LQT1 patients, such as resting and peak exercise HR, and recurrence of syncope despite BB. In many centers, serial exercise testing is performed routinely in LQT1 patients, but whether such testing can be used to confirm a protective effect of BB has not been established. Specifically, whether BB results in a measurable change in abnormal repolarization during exercise and recovery (i.e., during greatest susceptibility to arrhythmias) in LQTS patients remains controversial based on conflicting published data^{11–13}. Thus, it is not clear whether BB actually improves abnormal repolarization, or whether BB simply blunts the maximal HR LQT1 patients may achieve during exercise. Furthermore, QT interval duration may be a less specific marker of the risk of developing TdP than measures such as the ECG interval from the peak to the end of the T wave (T_{pe})^{14–20}, thought to represent global dispersion of repolarization, a reflection of electrical inhomogeneity and repolarization gradients within the ventricular myocardium.

Deviation from a normal range of the T_{pe} interval has been shown to be a marker of arrhythmogenesis^{16,19,21}, and the T_{pe} is prolonged by sympathetic stimulation in both congenital^{14,22–26} and acquired²⁷ LQTS patients but not in normal subjects²⁸. Shimizu showed that BB prevents T_{pe} prolongation with epinephrine infusion in LQT1 subjects²⁶. However, whether BB prevents T_{pe} prolongation during symptom-limited exercise in LQT1 subjects is not known. We hypothesized that BB would protect against exercise-induced prolongation of QT and T_{pe} in LQT1 subjects, and that BB would have no significant effect on these parameters in normal subjects.

METHODS

Study population

The institutional review board at MetroHealth Medical Center approved the protocol, and all subjects provided written informed consent. Participants included 10 genotype-proven LQT1 subjects from 7 different families and 35 age- and gender-matched normal subjects (Table 1). An effort was made to recruit 3–4 control subjects for each LQT1 subject, matched by gender and within a 5-year age span. Normal subjects were required to complete a screening questionnaire. Subjects were excluded if they had known cardiac disease, diabetes mellitus, hypertension, severe allergic reaction, asthma requiring treatment, pregnancy, inability to provide informed consent, inability to walk on a treadmill, or use of medications other than oral contraceptives, acetaminophen, non-steroidal anti-inflammatory drugs, or thyroid replacement. All control subjects had normal resting electrocardiograms.

Experimental protocol

LQT1 subjects completed a symptom-limited exercise treadmill test (ETT) prior to initiation of BB and again on their maintenance dose of BB. The target dose of BB was 2–3 mg/kg/day of long-acting propranolol or 1–2 mg/kg/day of nadolol. If these were not well-tolerated, metoprolol succinate or atenolol were given. Normal subjects completed an ETT following 2 weeks of treatment with long-acting propranolol, as well as following 2 weeks of treatment with matching placebo, dosed in a random-order, double-blind fashion. Propranolol was

dosed 80 mg/day for the first week and, depending on tolerance, increased to 160 mg/day for the second week.

ECG Recordings

Digital 12-lead ECG data were recorded continuously throughout the rest, exercise, and recovery stages using a CH 2000 or HearTwave system (Cambridge Heart, Inc., Tewksbury, MA). Selected tracings corresponding to rest, peak exercise, and 1 minute into recovery were printed for QT measurements or transferred to a personal computer in pdf format for T_{pe} measurements. For each tracing, Adobe PhotoshopTM was used to perform the following editing functions: (1) enlarging the image 600–700% its original size, (2) cropping the image to include 2.5 seconds in the desired lead only, and (3) de-identification. Because lead V6 may best represent the transmural axis of the heart²⁹, lead V6 was used for measurement of T_{pe} whenever possible. When the end of the T wave was not discernable in lead V6, T_{pe} was measured in lead V5, or, if not possible, as in one patient, in lead II. After blinding of the investigators to genotype and BB status, the RR, QT and T_{pe} intervals were defined by using Adobe PhotoshopTM to draw an isoelectric line, a T_{end} using the standard tangent method²⁹, and a T_{peak} line. Using commercially available digital screen calipers (IconicoTM), between 2 and 5 measurements were made per ECG tracing, depending on heart rate and number of complexes in the 2.5 second interval (Figure 1).

QT Interval Analysis

Due to the limitations associated with the use of HR correction formulae for QT measurement, we sought to compare QT at matched HR. ECG tracings were selected during exercise and recovery at rates between 100–110 bpm (peak HR limited by maximal achieved HR on BB) and both an isoelectric line and a tangent line were used to define the end of the T wave. The QT interval was manually measured in lead II using standard calipers. Measurements were made by a single observer, blinded to LQTS/control status and to beta-blocker use.

Statistical Analysis

For QT interval analysis, the uncorrected QT interval was compared before and after BB at matched HR, in normal subjects and in LQT1 patients. For T_{pe} analysis, mean values were plotted against stage of exercise. Paired t-tests were used to compare the means for each group before and after BB. A p-value of <0.05 was considered statistically significant.

RESULTS

Table 1 shows the baseline characteristics of the study subjects. The LQT1 subjects and controls were matched for age and gender. The mean QT interval was longer among LQT1 subjects and 4 of 10 had a history of syncope. Five subjects received long-acting propranolol (mean dose 2.73 mg/kg/day), 3 received nadolol (mean dose 1.4 mg/kg/day), 1 received atenolol (1.5 mg/kg/day), and 1 received metoprolol succinate (0.33 mg/kg/day). Of the 35 normal subjects, 34 were taking long-acting propranolol at 160 mg/day and 1 was taking 80 mg/day (dose limited by tolerance) for a mean dose of 2.23 mg/kg/day.

Effect of beta-blocker therapy on QT interval

BB reduced QT during exercise and recovery in LQT1 patients but not in normal subjects (Figures 2 and 3). During exercise, normal subjects had QT interval 320 ± 17 msec before BB vs. 317 ± 16 msec after BB at mean HR 106 ± 3 bpm ($p = 0.29$), and LQT1 subjects had QT interval 391 ± 25 msec before BB vs. 375 ± 26 msec after BB at mean HR 106 ± 4 bpm ($p = 0.04$). During recovery, normal subjects had QT interval 317 ± 13 msec before BB vs.

315 ± 14 msec after BB at mean HR 105 ± 2 bpm ($p = 0.15$), and LQT1 subjects had QT interval 419 ± 41 msec before BB vs. 391 ± 39 msec after BB at mean HR 106 ± 5 bpm ($p = 0.02$). Although the mean reduction in QT interval (16 msec during exercise and 28 msec during recovery) with BB reached statistical significance, the magnitude of the effect of BB was not uniform across the group of LQT1 subjects, and the QT interval actually increased with BB in 1 subject (figure 4). We observed variability in the QT response to BB even among members of a single family, even when all members of the family had achieved their target dose of BB (Table 2).

Effect of beta-blocker therapy on T_{pe} interval

BB markedly reduced T_{pe} in LQT1 patients and mildly reduced T_{pe} in normal subjects during exercise and recovery (Figure 5). The peak exercise T_{pe} was 69 ± 13 msec before BB vs. 61 ± 11 msec after BB ($p = 0.01$) in normal subjects, and 91 ± 26 msec before BB vs. 67 ± 19 msec after BB ($p = 0.03$) in LQT1 subjects. At 1 minute into recovery the T_{pe} was 77 ± 19 msec before BB vs. 68 ± 14 msec after BB ($p < 0.001$) in normal subjects, and 103 ± 26 msec before BB vs. 78 ± 11 msec after BB ($p = 0.02$) in LQT1 subjects. Resting T_{pe} was not significantly different between LQT1 patients and normal subjects, and resting T_{pe} was not reduced by BB in either group. Resting T_{pe} was 74 ± 13 msec before BB vs. 72 ± 13 msec after BB ($p = 0.18$) in normal subjects, and 82 ± 33 msec before BB vs. 70 ± 8 msec after BB ($p = 0.27$) in LQT1 subjects.

DISCUSSION

In the current study, we determined the effect of BB on abnormal repolarization during exercise in LQT1 subjects. We found that BB both shortened QT and substantially reduced T_{pe} , effectively normalizing this measure of dispersion of repolarization. These findings help to clarify the mechanism whereby BB reduces the risk of TdP in LQT1: our findings support the hypothesis that BB reduces abnormal QT prolongation and protects against dispersion of repolarization in LQT1 subjects during exercise and recovery, the time period of greatest arrhythmic risk.

Effect of beta-blocker therapy on QT interval

There are conflicting data in the existing literature as to whether BB results in a shortening of the QT interval at a given HR in LQT1 subjects. Moss et al¹¹ reported a reduction in *resting* QTc (20 msec) by BB in a cohort of 23 LQT1 patients, but this effect did not reach statistical significance. Kaltman et al¹² found no significant difference in QTc during exercise with BB among non-genotyped patients. Wong et al¹³ reported a decrease in QTc during exercise in LQT1 subjects treated with BB, but this did not reach statistical significance ($p = 0.07$) and the peak exercise HR was significantly lower in the BB group. Sy³⁰ et al noted that the maximal exercise QTc during exercise was not significantly different in LQT1 and LQT2 patients on BB versus those naïve to BB. Since Bazett's HR correction formula, which tends to overestimate QTc at elevated HR, is not optimally suited for assessing the effect of BB on QT, we compared QT at matched HR before and after BB, during the ascending and descending limbs of the graded exercise test. This methodology precluded comparing the QT at peak HR before BB to the QT at peak HR after BB, since subjects did not achieve the same HR after BB. By comparing QT at matched HR, we found that BB resulted in QT values that either stayed the same or decreased during exercise and recovery in 90% of LQT1 subjects.

In general, subjects whose QT interval was longer before BB had a greater reduction in QT with BB, and the 1 patient whose QT increased with BB (+20 msec) had the *shortest* QT interval before BB (360 msec). Thus, although BB appears to reduce QT modestly in the

majority of LQT1 subjects, our data illustrate the variability of phenotypic expression of QT prolongation and response to BB even among family members with identical mutations (Table 2). BB did not significantly affect QT in normal subjects, and there was a significantly smaller variability in normal subjects than in LQT1 subjects (reduction of QT by 3 ± 14 msec in normal vs. 16 ± 22 msec in LQT1 during exercise, $p = 0.02$; reduction of QT by 2 ± 8 msec in normal vs. 28 ± 30 msec in LQT1 during recovery, $p < 0.001$).

Effect of beta-blocker therapy on T_{pe} interval in normal subjects

In our cohort of normal subjects, the T_{pe} did not change significantly during exercise, and T_{pe} values at rest and during exercise were identical to those previously reported in non-beta-blocked subjects²⁸. Interestingly, although BB did not affect the T_{pe} in normal subjects at rest, BB shortened the T_{pe} during exercise and recovery to values significantly lower than those observed in non-beta-blocked normal subjects. These findings suggest that BB results in more efficient terminal repolarization during exercise and recovery even in normal subjects. It is known that the risk of sudden cardiac arrest is increased during and after vigorous exercise^{31,32}, and it is possible that this increased risk might be related to increased global dispersion of repolarization that may reach clinically significant levels in some individuals.

Effect of beta-blocker therapy on T_{pe} interval in LQT1 subjects

The resting T_{pe} values in LQT1 subjects did not differ significantly from those seen in normal subjects, but LQT1 subjects exhibited marked T_{pe} prolongation during exercise and recovery. BB normalized the T_{pe} response to exercise and recovery in LQT1 subjects to values seen in normal subjects without BB. These findings provide strong evidence to suggest that BB offers a protective effect in LQT1 by decreasing global dispersion of ventricular repolarization to a level seen in normal subjects.

Our observation that LQT1 subjects have abnormal T_{pe} prolongation during exercise that is prevented by BB extends the findings of Shimizu and Antzelevitch³³. In their canine wedge model of LQT1, isoproterenol infusion increased QT, transmural dispersion of repolarization, and inducibility of ventricular arrhythmia, and this effect was completely suppressed in the presence of BB. While it is true that T_{pe} measured on the surface ECG is not equivalent to transmural dispersion of repolarization^{17,18,20} there is evidence to support the theory that the T_{pe} interval reflects *global* ventricular dispersion of repolarization^{16–19}. Our data provide clinical evidence to support the theory that BB prevents the abnormal exercise-induced increase in global dispersion of repolarization in LQT1 subjects. Our finding has practical application, since both QT and T_{pe} can be measured easily on clinical exercise test data, and a salutatory effect of BB on abnormal repolarization can be confirmed. We speculate that the dose of BB required to reduce T_{pe} and QT may vary between patients, and that repeated exercise testing may allow the clinician to judge whether a therapeutic or protective dose has been achieved. It is tempting to speculate that failure of BB to normalize T_{pe} in LQT1 patients during exercise may be indicative of an inadequate protective effect. Larger studies will be needed to test this hypothesis.

Limitations

The most significant limitation to this study is the limited sample size. Our enrollment of LQT1 patients was limited by the number of patients who underwent a baseline exercise test prior to initiation of beta-blocker therapy and subsequently were found to have LQT1 mutations. We follow other LQT1 patients who were already started on beta-blocker therapy prior to their initial evaluation in our center, but we thought it would be unethical to discontinue their beta-blocker therapy to obtain drug-free exercise test data. Despite the small number of subjects, however, we were able to show a significant effect of BB on QT

interval and on T_{pe} in LQT1 subjects. Another limitation is the potential error that is associated with manual measurement of ECG data. However, with the measurements made by an investigator blinded to subject status (LQT1 vs. control and BB exposure vs. no BB) we showed significant reduction in both QT and T_{pe} in LQT1 subjects during exercise and recovery. A further limitation was the use of multiple BB agents in the LQT1 patients. This is a reflection of variations in clinical practice style and, in some cases, reflects what medication regimen was best tolerated by the individual patient. The clinical goal was long acting propranolol 2–4 mg/kg/day or nadolol 1–2 mg/kg/day, depending on tolerance. Patients who did not tolerate either of these received alternative beta blockers. When we designed a uniform protocol for our control subjects, we estimated that a daily dose of 160 mg of long acting propranolol would give at least 2 mg/kg/day, the target dose for our patients. Of our 35 control subjects, only one was limited to 80 mg due to symptoms; the other 34 tolerated 160 mg daily. An argument could be made that our control subjects were treated “better” than some of the LQT1 patients who did not tolerate the preferred beta blocker. Yet, despite the use of multiple kinds of BB in the LQT1 patients, we were able to demonstrate normalization of T_{pe} during exercise.

CONCLUSIONS

In LQT1 subjects, BB reduced the QT interval during exercise, but not to values seen in normal subjects. In contrast, LQT1 subjects displayed marked T_{pe} prolongation during exercise and BB suppressed this effect, resulting in mean T_{pe} values identical to those seen in normal subjects without BB. These findings suggest that BB reduces arrhythmogenic dispersion of ventricular repolarization in LQT1 subjects, and that this is likely a key mechanism by which BB reduces the risk of syncope and sudden cardiac arrest in this population. The use of exercise testing to monitor the T_{pe} response to BB in LQT1 may add useful risk stratification information, as LQT1 subjects with persistent exercise-induced T_{pe} prolongation despite BB may be at increased risk of syncope or sudden cardiac arrest. A larger sample of patients with long term follow-up data will be necessary to determine whether this is true.

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Abbreviations

BB	beta-blocker therapy
LQT1	long QT syndrome type 1
T_{pe}	the interval from the peak of the T-wave to the end of the T-wave
TdP	torsades de pointes

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Figure 1. Example of T_{pe} measurement, in which a best-fit tangent line was drawn to the isoelectric line, and T_{pe} interval was defined by drawing a vertical line from the T_{peak} to the isoelectric line.

QT at Matched HR During Exercise

Figure 2.

QT at matched HR (106 ± 3 bpm) during exercise in normal subjects = 320 ± 17 msec before BB and 317 ± 16 msec after BB; $p = 0.29$. QT at matched HR (106 ± 4 bpm) in LQT1 subjects = 391 ± 25 msec before BB and 375 ± 26 msec after BB; $p = 0.04$.

QT at Matched HR During Recovery

Figure 3.

QT at matched HR (105 ± 2 bpm) during recovery in normal subjects = 317 ± 13 msec before BB and 315 ± 14 msec after BB; $p = 0.15$. QT at matched HR (106 ± 5 bpm) = 419 ± 41 msec before BB and 391 ± 39 msec after BB; $p = 0.02$.

Figure 4.

QT at matched HR during exercise and recovery before and after BB. Solid dots represent individual LQT1 subjects and open dots represent mean values for 35 normal subjects.

Figure 5.

T_{pe} at rest, peak exercise, and 1 minute into recovery in normal subjects and LQT1 subjects on and off BB. * $p < 0.05$ for comparison of off vs. on BB between paired samples of normal or LQT1 subjects.

Table 1

Baseline Characteristic	Normal Subjects (n=35)	LTQ1 (n=10)	P Value
Age (Years)	32±12	33±13	0.92
Sex (Male)	15 (43%)	4 (40%)	0.87
History of Syncope	No=35	Yes=4, No=6	NA
Mean BB dose (mg/day)	Propranolol: 158	Propranolol (n = 5): 184 Nadolol (n = 3): 60 Metoprolol Succinate (n = 1): 25 Atenolol (n = 1): 100	0.06*
Resting HR off BB (bpm)	70±11	74±14	0.45
Resting QTc off BB (msec)	401±26	477±35	< 0.001
Resting Tpe off BB (msec)	74±13	82±33	0.45

* Applies to propranolol weight-based dose

Table 2

Subject	Syncope (Before BB)	Mutation	Effect of BB on QT During Exercise (msec)
1	Yes	S225L	0
2	Yes	S349W	-20
3	Yes	S349W	-50
4	No	S349W	-30
5	No	A150fs+132x	+20
6	Yes	G325R	0
7	No	G325R	-10
8	No	A344E	0
9	No	T587M	-30
10	No	R518x	-40