Effect of beta-blockers on QT dynamics in the long QT syndrome: measuring the benefit

Matthew T. Bennett1*, Lorne J. Gula2, George J. Klein2, Allan C. Skanes2, Raymond Yee2, Peter Leong-Sit2, Ishvinder Chattha2, Raymond Sy3, Douglas L. Jones2,4, and Andrew D. Krahn1

1Division of Cardiology, Department of Medicine, University of British Columbia, Arrhythmia Service, 9th Floor, Gordon & Leslie Diamond Health Care Centre, 2775 Laurel Street, Vancouver, BC, Canada V5Z 1M9; 2Division of Cardiology, Department of Medicine, University of Western Ontario, London, ON, Canada N6G 2V4; 3Department of Cardiology, Royal Prince Alfred Hospital, Sydney, NSW 2050, Australia; and 4Department of Physiology and Pharmacology, University of Western Ontario, London, ON, Canada N6G 2V4

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Aims
Beta-blockers are the standard of care for the treatment of long QT syndrome (LQTS), and have been shown to reduce recurrent syncope and mortality in patients with type 1 LQTS (LQT1). Although beta-blockers have minimal effect on the resting corrected QT interval, their effect on the dynamics of the non-corrected QT interval is unknown, and may provide insight into their protective effects.

Methods and results
Twenty-three patients from eight families with genetically distinct mutations for LQT1 performed exercise stress testing before and after beta-blockade. One hundred and fifty-two QT, QTc, and Tpeak – Tend intervals were measured before starting beta-blockers and compared with those at matched identical cycle lengths following beta-blockade. Beta-blockers demonstrated heart-rate-dependent effects on the QT and QTc intervals. In the slowest heart rate tertile (< 90 b.p.m.), beta-blockade increased the QT and QTc intervals (QT: 405 vs. 409 ms; P = 0.06; QTc: 459 vs. 464 ms; P = 0.06). In the fastest heart rate tertile (> 100 b.p.m.), the use of beta-blocker was associated with a reduction in both the QT and QTc intervals (QT: 367 vs. 358 ms; P = 0.0001; QTc: 500 vs. 486 ms; P < 0.0001). The Tpeak – Tend interval showed minimal change at slower heart rates (< 90 b.p.m.) (93 vs. 87 ms; P = NS) and at faster heart rates (> 100 b.p.m.) (87 vs. 84 ms; P = NS) following beta-blockade.

Conclusion
Beta-blockers have heart-rate-dependent effects on the QT and QTc intervals in LQTS. They appear to increase the QT and QTc intervals at slower heart rates and shorten them at faster heart rates during exercise.

Keywords
QT interval • Beta-blocker • Exercise testing • Long QT syndrome • Electrocardiography

Introduction
Long QT syndrome (LQTS) is an inherited disorder characterized by QT prolongation, ventricular arrhythmias, and sudden cardiac death. Type 1 long QT syndrome (LQT1) is the most common cause of congenital LQTS. Type 1 long QT syndrome is caused by a mutation of the KCNQ1 gene on chromosome 11. This results in a reduction of function of the slowly activating delayed rectifier potassium channel (\(I_{Ks}\)).12 The resultant electrophysiological effects, which are presumed to predispose to torsades de pointes, are prolongation of ventricular repolarization and an increase in the transmural dispersion of repolarization (TDR).3

Syncope and sudden death in LQT1 occur more commonly during physical activity or emotion and, as such, are presumed to be associated with high heart rates.4,5 Beta-blockers are recommended for all patients with LQTS,6 as they are effective in reducing mortality and syncope in these patients.7 The specific mechanisms by which beta-blockers decrease mortality are unclear. They have been shown to prevent both the QT prolongation and increases in TDR produced by isoproterenol in a canine wedge preparation model.8 In previous human studies, beta-blockers have had variable effects on the QT and Tpeak – Tend intervals measured both at rest and during 24 h Holter monitoring.7,9 The aim of the current study was to analyse the effect of beta-blockers on the QT, QTc,
and T_{peak}–T_{end} at identical heart rates during structured exercise testing.

**Methods**

**Patients**

Participants in this study were recruited from patients who had been referred to the Arrhythmia Clinic at the University of Western Ontario. This study was approved by the Research Ethics Board at the University of Western Ontario. Patients were included in the study if they had genetically proven LQT1, underwent exercise testing before and after beta-blockade, and provided written informed consent to participate. All patients had previously undergone genetic testing for LQTS as they or their family members were the probands with the LQTS phenotype. Patients were initiated on beta-blockade (usually bisoprolol 2.5 mg daily) for 1 month, and then increased (usually to 5 mg daily). Repeat exercise testing was performed after at least 2 months of beta-blocker therapy, and the dose was adjusted to target a 30 b.p.m. fall in peak exercise heart rate.

**Exercise testing**

Patients underwent exercise testing in the form of a gradual bicycle ergometry test. During the bicycle ergometry test, standard 12-lead electrocardiograms were acquired prior to exercise and then continuously during exercise. From a baseline of 30 W, the workload was increased in increments of 20 W every minute to a symptom-limited output. Exercise stress testing was then repeated at least 1 month following the institution of beta-blockade in an identical manner. All stress tests were recorded digitally at a paper speed of 25 mm/s using the GE Marquette Case V5.02 system.

**Electrocardiogram analysis**

For each test, the QT and T_{peak}–T_{end} intervals were manually measured in sinus rhythm/tachycardia after each 50 ms RR interval shortening from the longest to shortest cycle length from tests with continuous analysis. The QT interval was defined as the time interval between QRS onset and the intersection of the isoelectric line and the tangent of the maximal downward slope of the T-wave (Figure 1). In cases where there were two peaks, the second peak was included in the measurement if it was larger in amplitude than, and merged with the first peak. If the second peak was smaller in amplitude or did not merge with the first peak, the second peak was defined as a U-wave and was not included in the measurement. The T_{peak}–T_{end} was calculated by subtracting the interval from the peak of the R-wave to the peak of the T-wave from the QT interval in patients whose QRS duration did not change during the stress tests. All 12 leads were compared and the longest interpretable QT interval was used for analysis; typically, Lead II or a lateral precordial lead (V5). Where possible, a mean of three consecutive QT intervals at a stable RR interval was used.

To isolate the QT effects from heart rate, QT intervals were compared at matching heart rates before and after beta-blocker to obviate the need for rate correction. The overlapping intervals from stress tests before and after beta-blockade usually included the intervals between the heart rate at rest in the pre-beta-blocker group to the heart rate at maximal exercise in the post-beta-blocker group. These results were then stratified by heart rate tertiles (<90 b.p.m., 90–100 b.p.m., and >100 b.p.m.). Where appropriate, the QT interval was corrected for heart rate (QTc) using Bazett’s (QTcB) or Fridericia’s formula (QTcF). Measurements were carried out by two investigators (M.T.B., I.S.C.) who were blinded to the results of the intervals from the matching stress tests and whether stress tests were acquired before or after beta-blockade.

**Statistics**

Continuous variables were compared by use of a two-tailed Student’s t-test for continuous variables and χ^2 test for categorical variables. Analysis was corrected for repeated measures using a mixed regression model, with standard methods for combining multiple data points from individual samples. Statistical analysis was performed using SAS software version 9.2 (SAS Institute by the authors (L.J.G.). P-values < 0.05 were considered significant. All results are expressed as mean ± standard deviation. All authors had full access to the data and take full responsibility for its integrity. All authors have read and agreed to the manuscript as written.

**Results**

Twenty-three subjects from eight families with KCNH2 mutations associated with LQT1 were included in the study (Table 1). These mutations resulted in abnormalities in the I_{Ks} in the transmembrane portion (n = 19), N-terminal (n = 2), and C-terminal (n = 2). Supplementary material online, Appendix 1 details the patient’s specific mutations.

A total of 152 QT, QTc, and T_{peak}–T_{end} intervals were measured. The beta-blocker used was bisoprolol with a mean dose of 5 mg daily.
(SD = 1.83). Four patients were not taking 5 mg daily (two patients in each group < and >5 mg daily). Beta-blockers reduced the resting and peak heart rate (both P < 0.001), but had no effect on the peak workload (153 vs. 148 W).

**Effect of beta-blockade on QT interval**
Beta-blockers demonstrated a differential effect on the QT interval when adjusted for heart rate when analysing matched sets by heart rate tertile (Figure 2). The mean QT interval was shorter following administration of beta-blocker therapy (386 ± 29 vs. 382 ± 35 ms; *P* = 0.0092). In the slowest heart rate (<90 b.p.m.), beta-blockade increased the QT interval (405 ± 21 vs. 409 ± 24 ms; *P* = 0.06). In the fastest heart rate (>100 b.p.m.), the use of beta-blocker was associated with a reduction in QT interval (367 ± 22 vs. 358 ± 23 ms; *P* < 0.0001) (Table 2).

**Effect of beta-blockade on QTc interval**
The effect of beta-blockade on the QTc interval had similar effects when stratified by heart rate tertile and analysed by matched sets. The QTc interval shortened following beta-blockade (QTcB: 482 ± 32 vs. 476 ± 26 ms; *P* = 0.0023; QTcF: 447 ± 24 vs. 442 ± 22 ms; *P* = 0.01). This was due to a reduction in QTc interval of the faster heart rate group (>100 b.p.m.) (QTcB: 500 ± 27 vs. 486 ± 24 ms; *P* < 0.0001; QTcF: 451 ± 23 vs. 437 ± 19 ms; *P* < 0.0004). In the slowest heart rate tertile (<90 b.p.m.), beta-blockade showed a trend towards an increased QTc interval (QTcB: 459 ± 23 vs. 464 ± 24 ms; *P* = 0.06; QTcF: 440 ± 20 vs. 445 ± 22 ms; *P* = 0.06) (Table 2).

**Effect of beta-blockade on Tpeak–Tend interval**
Overall, the mean Tpeak–Tend interval shortened before vs. after beta-blockade (90 ± 19 vs. 85 ± 15 ms; *P* = 0.015). However, there were no changes seen in Tpeak–Tend interval in the slower heart rate subgroup (<90 b.p.m.) (93 ± 21 vs. 87 ± 13 ms; *P* = 0.09) nor in the fastest heart rate subgroup (>100 b.p.m.) (87 ± 20 vs. 84 ± 14 ms; *P* = NS) following the use of beta-blocker (Table 2).

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics</th>
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<tbody>
<tr>
<td><strong>Age (± SD, years)</strong></td>
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<tr>
<td><strong>Male</strong></td>
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<tr>
<td><strong>Genetic profile (%)</strong></td>
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<tr>
<td><strong>Resting parameters</strong></td>
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<tr>
<td><strong>Heart rate (b.p.m.)</strong></td>
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<tr>
<td><strong>QT interval (ms)</strong></td>
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<tr>
<td><strong>QTc interval (ms)</strong></td>
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<tr>
<td><strong>Peak workload (W)</strong></td>
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**Figure 2** Effect of beta-blockers on the QT interval with exercise.

**Table 2** Change following beta-blockers

<table>
<thead>
<tr>
<th></th>
<th>QT</th>
<th>QTc</th>
<th>Tpeak–Tend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>-3.86</td>
<td>-5.76</td>
<td>-4.21</td>
</tr>
<tr>
<td>HR &lt; 90 b.p.m.</td>
<td>4.11*</td>
<td>4.61*</td>
<td>-5.18</td>
</tr>
<tr>
<td>HR &gt; 100 b.p.m.</td>
<td>-9.84*</td>
<td>-13.86*</td>
<td>-3.44</td>
</tr>
</tbody>
</table>

*P* < 0.001 (beta-blocker’s effects in high vs. low intensity zones).

**Discussion**
The major finding of this study was that beta-blockers have differential effects on the QT and QTc intervals depending on the heart rate in LQT1. Both the QT and QTc intervals shortened following beta-blockade at exercise-induced faster heart rates, and lengthened following beta-blockade at slower heart rates. This finding is in keeping with the known ability of beta-blockers to attenuate tachycardia-associated events in patients with LQTS. The observations extend our previous report that beta-blockers normalise hysteresis in LQTS, a comparison of the QT interval during recovery with a matched exercise QT. The current study was devised to explore the mechanism of benefit of beta-blockers in LQTS patients.

Our results are concordant with those from previous canine wedge preparation models of LQTS. Shimizu and Antzelevitch examined the effects of both beta-agonists and beta-antagonists in a LQT1 model with Chromanol 293B in an arterially perfused canine wedge preparations. They analysed the effects of isoproterenol and propranolol on the action potential duration (APD) and TDR. Prior to isoproterenol, propranolol had minimal effects on the QT interval and TDR at lower concentrations. Isoproterenol prolonged the QT interval by prolonging the APD in the M cell layer. Importantly, the QT prolonging effects of
isoproterenol on the APD were prevented by pre-treatment with propranolol. These findings are consistent with our findings that beta-blocker shortened the QT interval at higher heart rates in patients with LQT1.

Viitasalo et al.9 examined the effects on QT interval of beta-blockers in patients with LQT1 who had undergone 24 h Holter monitoring. In their study of 24 patients with LQT1, they measured QT intervals and compared them to matched heart rates from Holter monitors following the administration of beta-blockade. They found that overall beta-blocker had little effect on mean QT interval at each heart rate. However, when the maximum QT interval from the range of QT intervals for each heart rate was assessed, beta-blockers had a heart-rate-dependent differential effect on the QT interval duration. At faster heart rates, beta-blockers shortened the maximum QT interval, whereas at slower heart rates beta-blockers lengthened the maximum QT interval. We believe that these results are consistent with our findings as the maximum QT interval is most likely to occur during an exercise stress test where the heart rate is expected to change quickly. Our study adds to these results by allowing the measurement of QT intervals during a brief, structured test.

Moss et al.1 also examined the effect of beta-blockers on the rate corrected QT interval in 23 patients who had had a resting electrocardiogram both before and after beta-blockade, and did not see a difference in the corrected QTc after beta-blockade. This is a calculated value that attempts to correct for heart rate. The current study eliminated heart rate correction to permit direct comparison of QT intervals at identical heart rates across a breadth of heart rates.

More recently, Gemma et al.27 have further assessed the effect of beta-blocker on repolarization dynamics. They analysed the effect of beta-blockers on the QT and T_{peak}–T_{end} intervals during exercise-induced tachycardia (100–110 b.p.m.) in 10 patients with LQT1 and found that at these heart rates, the QT shortened after beta-blockade. These findings are consistent with the current study. In addition, we were able to add to this observation by demonstrating the effects of beta-blockade on repolarization dynamics across a breadth of heart rates.

Beta-blockers are very effective at reducing syncope and mortality in patients with LQT1, where events typically occur with exertion.7,26,28–31 Baseline heart rate and maximal heart rate during exertion are common targets of therapy. If further studies support that beta-blocker-induced QT shortening reduces clinical events, QT shortening at higher heart rates may also become a useful target in clinical practice.

Limitations

The current study examined the effects of beta-blockade during structured exercise by comparing QT intervals at identical heart rates before and after beta-blocker therapy. A higher workload is required to obtain the same heart rate after beta-blocker therapy. As such, some of the observed effects may be due to the differences in stage and duration of exercise between the tests, even though the overall workload was similar between tests. In addition, although clinical events correlate with the degree of QT prolongation, it remains speculative whether the observed shortening is causally linked to beta-blocker efficacy.32–36

The beta-blocker used within this study was bisoprolol as this was the current practice of our arrhythmia clinic physicians at the time of patient inclusion due to its duration of action, ease of accessibility (propranolol had previously not been available in Canada at this time), and cardioselectivity. We acknowledge that bisoprolol may not be the current beta-blocker of choice for LQTS in other clinics and that this may reduce the generalizability of our findings. Our findings, however, are consistent with those found in other studies using other beta-blockers.7,9,27

Conclusion

Beta-blockers have differential heart-rate-dependent effects on the QT and QTc intervals in patients with LQT1. Beta-blockers decrease the QT and QTc intervals at rapid heart rates, and may lengthen them at slower heart rates. These effects may explain their protective effect in LQTS.

Supplementary material

Supplementary material is available at Europace online.

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Conflict of interest: none declared.

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