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Effects of β-blockers on ventricular repolarization documented by 24-hour electrocardiography in long QT syndrome type 2

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BACKGROUND Long QT syndrome (LQTS) is an inherited arrhythmia disorder characterized by ventricular repolarization abnormalities and a risk of sudden cardiac death. The electrophysiological components generating the high risk of arrhythmias in LQTS are prolonged repolarization, increased dispersion of repolarization, and early afterdepolarizations, which are clinically estimated as QT interval, T-wave peak to T-wave end (TPE) interval, and T2/T1-wave amplitude ratio, respectively. In experimental LQTS type 2 (LQT2) models, β-blockers decrease dispersion of repolarization and prevent early afterdepolarizations. In clinical studies in patients with LQT2 , β-blockers are more effective against exercise-induced than arousal-induced cardiac events.

OBJECTIVES The aim of the study was to investigate the effects of β-blocker therapy on repolarization properties in LQT2.

METHODS QT and TPE intervals and maximal T2/T1-wave amplitude ratios recorded by 24-hour electrocardiograms before and during β-blocker therapy were evaluated in 25 patients with LQT2.

RESULTS β-Blocker therapy decreased the maximal T2/T1-wave amplitude ratio from 2.9 ± 1.1 to 1.8 ± 0.7 ($P < .001$), but did not change the pause-induced T2/T1-wave amplitude ratio. Under medication, abrupt maximal TPE intervals were shorter at heart rates of ≥75 beats/min and maximal QT intervals were shorter at a heart rate of 100 beats/min.

CONCLUSION β-Blockers stabilize ventricular repolarization in LQT2 by reducing electrocardiographic early afterdepolarizations and by reducing abrupt prolongation of electrocardiographic dispersion of repolarization and ventricular repolarization duration at elevated heart rates. The effect of β-blockers on pause-induced electrocardiographic early afterdepolarizations is weak. The findings provide electrocardiographic explanation for the protective effects of β-blockers against exercise-induced cardiac events in LQT2.

KEYWORDS Long QT syndrome type 2; β-Blocker; 24-Hour electrocardiogram; Dispersion of repolarization; Early afterdepolarization

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Introduction

Long QT syndrome (LQTS) is an inherited channelopathy characterized by abnormalities in ventricular repolarization and the risk of sudden cardiac death.[1,2] LQTS type 2 (LQT2), the second most prevalent type of LQTS, is caused by a mutation in the *KCNH2* gene that leads to an impaired function of potassium ion channel and decreased activity of rapid delayed rectifier potassium current (I_{Kr}).[2,3] Abnormal channel function causes ventricular repolarization prolongation, increased dispersion of repolarization (DR), and early afterdepolarizations (EAs) predisposing to torsades de pointes (TdP), typically during arousal in patients with LQT2.[4–6] In an experimental LQT2 model, blocking of I_{Kr} increased DR and introduction of sympathetic stimulus further transiently increased DR and incidence of TdP.[7] Propranolol inhibited DR and TdP during sympathetic stimulation in LQTS models.[4,7]

The T-wave peak to T-wave end (TPE) interval and the ratio of the U-wave (T2-wave) to T-wave (T1-wave) amplitude of an electrocardiogram (ECG) have been used for clinically estimating DR and EA, respectively.[5,8,9] A previous study showed that symptomatic patients with LQT2 had a higher maximal T2/T1-wave ratio on 24-hour ECG than did

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asymptomatic subjects.[10] In a 24-hour ECG study in patients with LQTS type 1 (LQT1), β-blockers were shown to decrease the maximal T2/T1-wave amplitude ratio and to shorten the maximal QT end and TPE intervals at elevated heart rates.[11] In LQT2, however, the knowledge concerning effects of β-blockers on electrocardiographic repolarization properties is limited. In clinical studies, the high efficacy of β-blockers in LQT1 is well established, but in LQT2 their effect against arrhythmias, especially those triggered by arousal, appears suboptimal.[6,12,13]

The aim of the present study was to investigate the effects of β-blockers on dynamic ECG repolarization patterns recorded by 24-hour ECGs in patients with LQT2. Our working hypothesis was that treatment with β-blockers would decrease the maximal T2/T1-wave amplitude ratio. We also postulated that β-blocker therapy might shorten TPE intervals and decrease abrupt lengthening of QT intervals at elevated heart rates.

Methods

Study subjects

The study subjects comprised a consecutive series of 25 LQT2 patients (10 probands) with 12 different *KCNH2* mutations (Online Supplemental Table S1), all examined at the Department of Cardiology, Helsinki University Hospital. The selection of the β-blocker was made by the responsible physician. The goal of the β-blocker medication was to reach a therapeutic dose without side effects. Subjects were not using other medications known to influence cardiac repolarization. All subjects had a sinus rhythm without conduction abnormalities, and they did not show symptoms or signs of other cardiac disease on clinical examination. The study protocol was approved by Finnish Medicines Agency (FIMEA) and the ethical review committee of Helsinki University Hospital. A written informed consent was obtained from the subjects. The research reported in this article adhered to the ethical principles of the Declaration of Helsinki.

24-Hour ECG recordings

All study subjects underwent a 24-hour ECG recording (model 8500, Marquette Electronics Inc., Milwaukee, WI) before and a second recording during a tolerable dose of β-blocker therapy. The minimum time from β-blocker initiation to second 24-hour ECG recording was 4 weeks. Normal daily activities were encouraged during both recordings. The recordings were initially processed with the Marquette 8000 Holter Analysis System to label the QRS complexes as normal, ventricular extrasystoles, or aberrant complexes. The ECG data were then transferred to a computer platform to further analyze QT and TPE intervals and T-wave amplitudes.

Measurements of QT and TPE intervals and T1- and T2-wave amplitudes

Previously described methods were used to determine T-wave fiducial points.[14,15] All measurements were obtained using modified lead V_5. In this study, we determined the highest amplitude peak of the T1-wave as the T-wave peak even in the presence of a higher T2-wave in the case of bifid T-waves. In QT interval measurements, a later higher peak of bifid T-waves was regarded as a T2-wave and included in the QT interval. A later lower peak was included in the QT duration if the deflection remained merged with the earlier deflection irrespective of peak-to-peak interval time; otherwise, it was regarded as a U-wave. Negative T-waves and T-waves with an amplitude of <0.1 mV were excluded from the measurements.

The highest T2-wave amplitudes and highest T2/T1-wave amplitude ratios on 24-hour ECG recordings were manually searched for using the superimposed scan.[10] Next, we measured manually each individual's maximal T2-wave amplitude and maximal T2/T1-wave amplitude ratio from the ECG strip at the speed of 50 mm/s and at the amplitude calibration of 0.1 mV/mm as a mean of 5 consecutive beats by using an unaveraged signal. For subjects with maximal T2/T1-wave amplitude ratio < 1, a value of 1 was used as the individual maximum for technical reasons. Pause-induced T2/T1-wave amplitude ratios >1 were separately measured manually from 1 beat after any pause including both sinus pauses and postextrasystolic pauses. Examples of QT and TPE interval and maximal T2/T1-wave amplitude ratio measurements are provided in Online Supplemental Figures S1 and S2.

Data analyses and definitions

All QT and TPE interval values from each 24-hour ECG were plotted against preceding R-R intervals as described previously (Figure 1).[15,16] Maximal diurnal QT peak, QT end, and TPE intervals were checked and measured manually as a mean of 5 consecutive beats from an unaveraged signal. We computed the median values of the QT peak, QT end, and TPE intervals against R-R intervals in R-R steps of 10 ms. To analyze the rate dependence of the QT end intervals, we recorded these intervals at stable heart rates in R-R steps of 10 ms as described previously.[11,15] We present the median and maximal QT end intervals as well as the median and maximal TPE intervals of all beats during 24-hour ECG recordings against R-R intervals with R-R steps of 50 ms (from 500 to 700 ms) or 100 ms (from 700 to 1400 ms). The maximal QT end and TPE intervals at specified R-R intervals were visually inspected before automated measuring, and the median QT end and TPE intervals were calculated after removal of outliers from the scatter plots (Figure 1).

Capacity to change TPE interval was defined as the difference between maximal TPE and median TPE intervals as described previously.[17] We present the mean capacity to change the TPE interval at R-R intervals of 550–800 ms with R-R steps of 50 ms (from 550 to 700 ms) or 100 ms (from 700 to 800 ms). Nighttime values (from ~10 PM to 8 AM), including each individual's awakening estimated as increase in heart rate, of QT end and TPE intervals and maximal T2/T1-wave amplitude ratios were analyzed

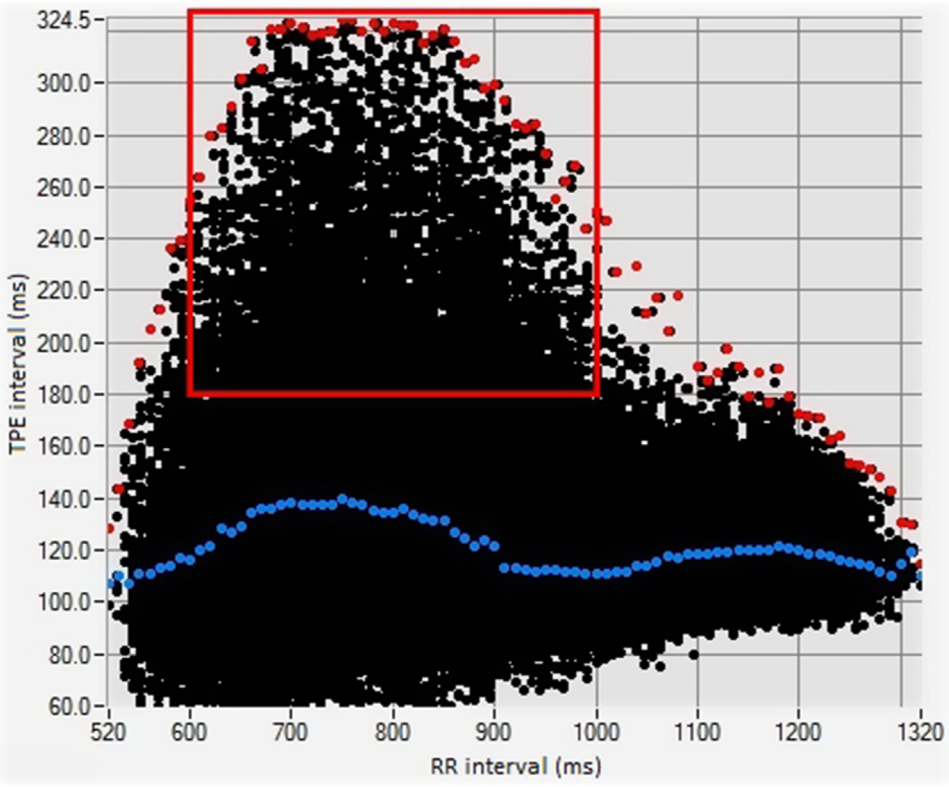

Figure 1 Example of TPE intervals plotted against preceding R-R intervals from a 24-hour ECG recorded before β-blocker treatment in a patient with long QT syndrome type 2. The *red dots* represent maximal and *blue dots* median TPE intervals against R-R intervals in R-R steps of 10 ms. The *red rectangle* encloses the area in which most of the bifid T-waves of this patient appeared in the ECG signal. ECG = electrocardiogram; TPE = T-wave peak to T-wave end.

separately. Data were processed and analyzed without the investigator knowing the presence or absence of β-blocker therapy.

Statistical analyses

Data are presented as mean ± SD. Continuous variables before and during β-blocker therapy were compared using the paired samples *t* test or Wilcoxon rank-sum test. Comparing QT end and TPE intervals before and during β-blocker therapy at specified R-R intervals was limited to 500–1400 ms because of missing values at shorter and longer R-R intervals. A 2-tailed *P* value of $<.05$ was interpreted as statistically significant. SPSS version 27 (IBM Corporation, Armonk, NY) was used for all statistical tests.

Results

Clinical characteristics and baseline ECGs

The clinical and baseline ECG characteristics of the 25 study subjects are presented in Table 1 and Table 2, respectively. Eleven subjects (44%) were symptomatic, and the most common trigger for cardiac events was startle or emotion. β-Blockers reduced the mean heart rate, confirming the effective use of the β-blocker ($P < .001$). QT interval adjusted for heart rate using Fridericia's cubic root formula was similar before vs during β-blocker therapy ($P = .66$). Applying Bazett's square root formula, the QT interval (QTc) appeared shorter during therapy ($P = .01$), presumably because this formula undercorrects measured QT values at low heart rates.[18] TPE intervals and T-wave amplitudes were similar in baseline ECGs before and during β-blocker therapy.

QT intervals on 24-hour ECGs

In the 24-hour ECG recordings, treatment with β-blockers had no influence on median QT peak ($P = .59$) or QT end

Table 1 Clinical characteristics of 25 patients with LQT2

Characteristic	Value
Age (y)	34.2 ± 14.6
Men/women	11 (44%)/14 (56%)
Cardiac event	11 (44)
Cardiac arrest	1 (4)
Syncope	10 (40)
Triggers for cardiac events	
Startle or emotion	7 (64)
Exercise	2 (18)
Rest or sleep	2 (18)
β-Blocker therapy	
Bisoprolol	20 (80)
Dose (mg/kg)	0.05 ± 0.03
Propranolol	4 (16)
Dose (mg/kg)	1.8 ± 0.7
Atenolol	1 (4)
Dose (mg/kg)	0.7

Values are presented as mean ± SD or n (%).
LQT2 = long QT syndrome type 2.

Table 2 Characteristics of baseline ECGs

Characteristic	Before BB	During BB	*P*
Heart rate (beats/min)	70 ± 14	55 ± 7	<.001
QTfc interval (Fridericia's formula) (ms)	470 ± 42	466 ± 36	.66
QTc interval (Bazett's formula) (ms)	481 ± 38	459 ± 37	.01
TPE interval in lead V_5 (ms)	106 ± 29	99 ± 20	.43
Maximal TPE interval in any lead (ms)	130 ± 47	114 ± 35	.29
T-wave amplitude in lead V_5 (ms)	0.27 ± 0.14	0.24 ± 0.14	.60
Maximal T-wave amplitude in any lead (ms)	0.45 ± 0.24	0.37 ± 0.20	.28

Values are presented as mean ± SD.

BB = β-blocker; ECG = electrocardiogram; QTc = QT interval adjusted for heart rate using Bazett's square root formula; QTfc = QT interval adjusted for heart rate using Fridericia's cubic root formula; TPE = T-wave peak to T-wave end.

(P = .70) intervals at a heart rate of 60 beats/min (Table 3). Diurnal maximal QT peak (P = .14) and QT end (P = .41) intervals also remained similar. Figure 2 shows the behavior of the QT end intervals measured at stable heart rates and of the maximal QT end intervals, demonstrating the capacity of QT intervals to prolong from stable state values to momentary maximal values, which typically associates with abrupt heart rate accelerations. β-Blocker therapy showed no effect on QT end intervals measured at stable heart rates, whereas the maximal QT end interval was shorter at an R-R interval of 600 ms during treatment (P = .02).

TPE intervals on 24-hour ECGs

The median TPE interval at a heart rate of 60 beats/min was unchanged and the diurnal maximal TPE interval showed a tendency (P = .10) toward shorter values during β-blocker therapy (Table 3). Figure 3 shows the behavior of the median and maximal TPE intervals at specified R-R intervals. β-Blocker therapy showed no statistically significant effect on median TPE intervals at any given heart rate, whereas maximal TPE intervals were shorter at higher heart rates (R-R intervals from 550 to 800 ms). Figure 3 shows that the capacity to change the TPE interval (difference between maximal and median TPE intervals) appeared at a wide range of R-R intervals both before and during therapy. Treatment with β-blockers reduced the capacity to change the TPE interval at R-R intervals of 550–800 ms (mean 119 ms vs 81 ms before and during therapy, respectively; P = .03).

T2-wave amplitudes and T2/T1-wave amplitude ratios on 24-hour ECGs

During 24-hour ECG recordings, β-blocker treatment decreased the maximal T2-wave amplitude from 0.45 ± 0.26 to 0.32 ± 0.25 mV (P = .04) (Table 3). The maximal T2/T1-wave amplitude ratio was >1 in 24 subjects (96%) before and in 19 subjects (76%) during β-blocker therapy. β-Blocker therapy decreased the maximal T2/T1-wave amplitude ratio from 2.9 ± 1.1 to 1.8 ± 0.7 (P < .001) (Figure 4; Online Supplemental Figure S2), and the heart rates preceding the maximal values were 94 ± 23 beats/min before and 81 ± 19 beats/min during therapy (P = .11). The decrease in maximal T2/T1-wave amplitude ratio was present in 23 of 25 patients (92%), and it was observed

Table 3 Effects of β-blockers on 24-hour ECG parameters in 25 patients with LQT2

Characteristic	Before BB	During BB	*P*
Minimal HR (beats/min)	46 ± 8	42 ± 6	.05
Mean HR (beats/min)	73 ± 10	61 ± 9	<.001
Maximal HR (beats/min)	133 ± 20	115 ± 23	.006
Median QT peak interval at an HR of 60 beats/min (ms)	366 ± 49	373 ± 45	.59
Median QT end interval at an HR of 60 beats/min (ms)	506 ± 49	511 ± 44	.70
Median TPE interval (ms)	137 ± 23	131 ± 17	.30
Maximal QT peak interval (ms)	436 ± 60	463 ± 65	.14
Maximal QT end interval (ms)	630 ± 76	647 ± 72	.41
Maximal TPE interval (ms)	291 ± 58	266 ± 51	.10
Maximal T2-wave amplitude (mV)	0.45 ± 0.26	0.32 ± 0.25	.04
Men (n = 11)	0.53 ± 0.23	0.42 ± 0.32	.36
Women (n = 14)	0.39 ± 0.27	0.25 ± 0.14	.09
Maximal T2/T1-wave amplitude ratio	2.95 ± 1.13	1.81 ± 0.69	<.001
Men (n = 11)	3.06 ± 1.24	1.82 ± 0.75	.01
Women (n = 14)	2.86 ± 1.08	1.80 ± 0.67	.004

Values are presented as mean ± SD.

BB = β-blocker; ECG = electrocardiogram; HR = heart rate; LQT2 = long QT syndrome type 2; TPE = T-wave peak to T-wave end.

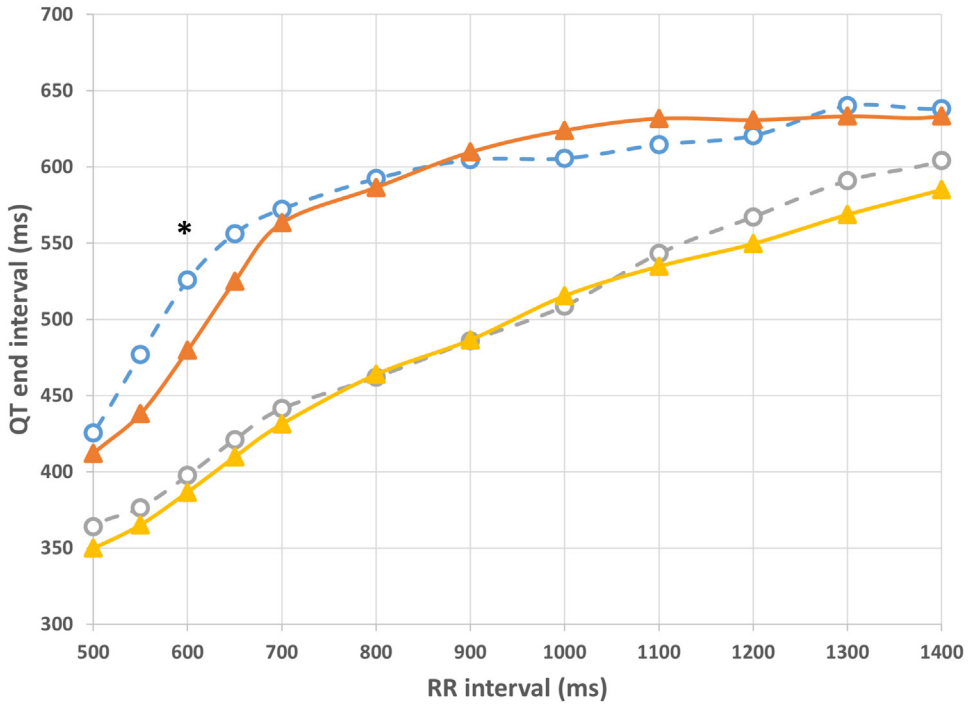

Figure 2 Maximal QT end intervals (2 *upper lines*) and median QT end intervals at stable heart rates (2 *lower lines*) from all 24-hour electrocardiogram recordings before (*broken lines*) and during (*solid lines*) β-blocker therapy at specified R-R intervals. *$P < .05$ for maximal QT end intervals before vs during β-blocker therapy at an R-R interval of 600 ms.

separately in both men and women. A pause-induced T2/T1-wave amplitude ratio of >1 was recorded in 13 patients (52%) before and in 13 patients during β-blocker therapy with the mean T2/T1-wave amplitude ratios of 1.9 ± 0.5 and 1.7 ± 0.4 in these patients, respectively ($P = .15$).

A comparison of the maximal TPE intervals and maximal T2/T1-wave amplitude ratios during heart rate acceleration vs deceleration at comparable R-R intervals with and without β-blocker therapy revealed no significant differences between the groups.

Nighttime measurements

Nighttime values of QT end intervals measured at stable heart rates and maximal QT end intervals at specified R-R intervals were similar before vs during β-blocker treatment (data not shown). Median TPE intervals remained unchanged, and maximal TPE intervals showed a tendency toward shorter values during β-blocker therapy (R-R interval of 700 ms: 235 ms vs 201 ms; $P = .06$ and R-R interval of 800 ms: 242 ms vs 211 ms; $P = .07$). During nocturnal bradycardia with a heart rate of <60 beats/min, 4 of 25 patients showed a trend of increased maximal TPE interval during treatment, but the study sample size was limited to draw conclusions about the possible dual effect of β-blocker therapy in some patients with LQT2. The nighttime maximal T2/T1-wave amplitude ratios before and during therapy were 2.2 ± 1.2 and 1.6 ± 0.7 ($P = .08$), respectively, and the heart rates preceding the maximal values were 81 ± 22 and 75 ± 12 beats/min ($P = .73$), respectively.

Discussion

Main findings

The present study shows that β-blockers decrease the maximal T2/T1-wave amplitude ratio and, at elevated heart rates, shorten the maximal QT end and TPE intervals in LQT2. The effect of β-blockers on pause-induced electrocardiographic EAs is weak. This is the first investigation to provide a detailed 24-hour electrocardiographic insight into the favorable effects of β-blockers on ventricular repolarization in patients with LQT2.

EAs and induction of TdP in experimental LQTS models, T2/T1-wave amplitude ratio in patients with LQT2, and effects of β-blockers

In LQTS, the occurrence of EAs and increased DR have been described as the trigger and the substrate for TdP, respectively.[5,7,19,20] Several experimental and clinical LQTS studies have revealed the key role of EAs in the induction of TdP.[21,22] Using monophasic action potential recordings, isoproterenol was shown to prolong the monophasic action potential duration, increase the amplitude of the late component of the T-wave to U-wave complex, and induce EAs.[22] In addition, using the experimental model of LQT2, Gbadebo et al[5] showed that the increase in U/T-wave amplitude ratio occurred before TdP onset. Prolonged repolarization associates with increased refractoriness, enhancements of the Na^+/Ca^{2+} exchange current, and triggering of EAs by reactivation of the L-type Ca^{2+} channels.[19,22] While EAs seem to be the

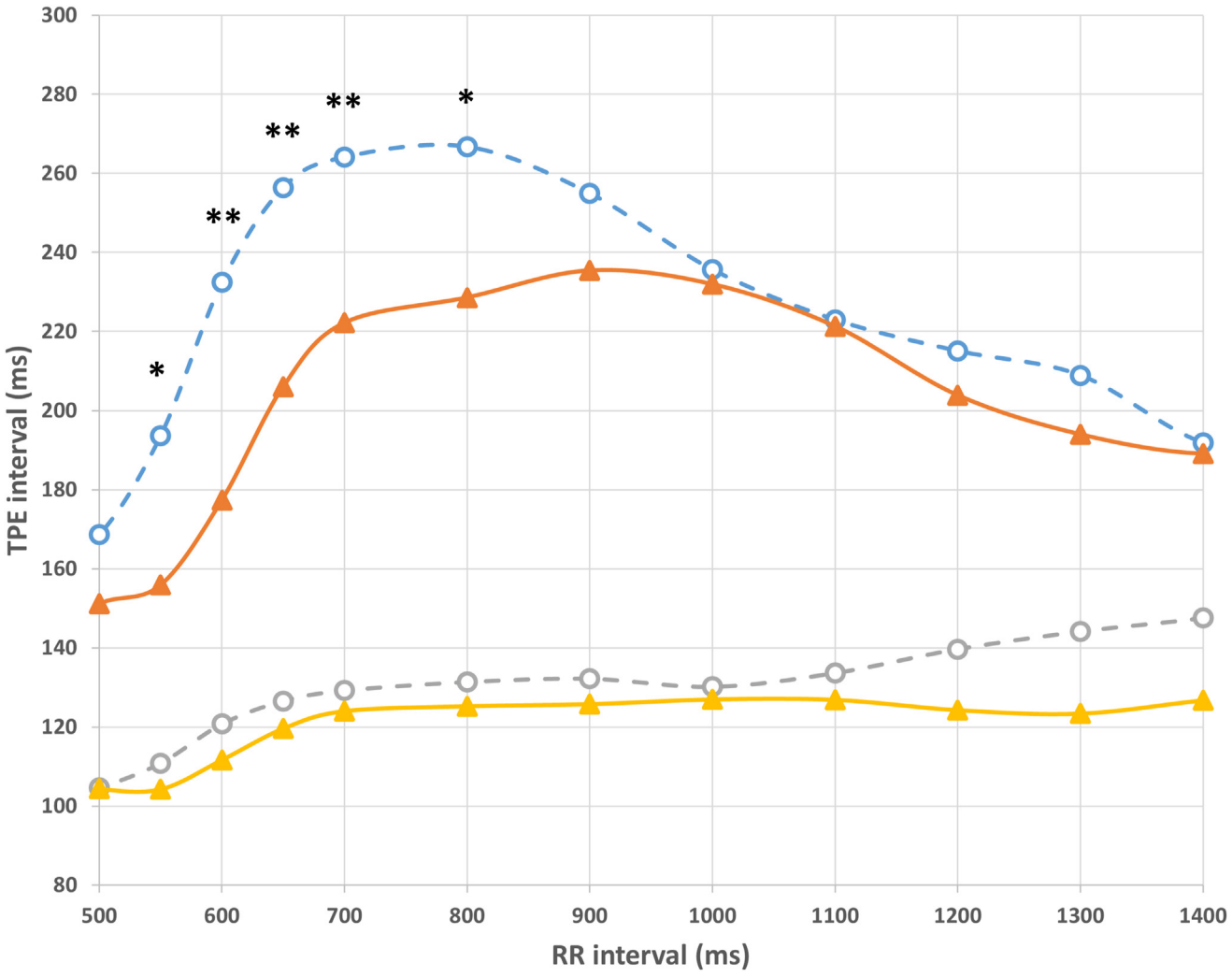

Figure 3 Maximal TPE intervals (2 *upper lines*) and median TPE intervals (2 *lower lines*) from all 24-hour electrocardiogram recordings before (*broken lines*) and during (*solid lines*) β-blocker therapy at specified R-R intervals. *$P < .05$ and **$P < .01$ for maximal TPE intervals before vs during β-blocker therapy at R-R intervals of 550–800 ms. TPE = T-wave peak to T-wave end.

trigger for TdP, a reentrant mechanism is likely responsible for maintaining TdP.[23]

In this study, β-blocker therapy decreased the maximal T2/T1-wave amplitude ratio in patients with LQT2. Heart rates immediately preceding the maximal T2/T1-wave amplitude ratios were higher than the mean diurnal heart rates but lower than commonly seen during exercise. The present findings were similar as we earlier observed in patients with LQT1.[11] In contrast, we did not find an effect of β-blockers on the typical pause-induced T2/T1-wave amplitude ratio in patients with LQT2. Previously, we have also reported that increased T2/T1-wave amplitude ratio associated with a higher risk of cardiac events.[10] In the heart, G_s protein coupled to β_1-adrenergic receptor activates L-type Ca^{2+} channels,[24,25] which conversely may explain the protective effect of β_1-adrenergic receptor antagonists (β-blockers) in preventing EAs. Since the maximal T2/T1-wave amplitude ratio is regarded as the electrocardiographic counterpart of EA,[5] the findings of the present study indicate that β-blockers suppress EAs and prevent induction of TdP at elevated heart rates in LQT2 whereas β-blockers' effect on pause-induced EAs is weak.

DR in experimental LQTS models, TPE interval in patients with LQT2, and effects of β-blockers

Evidence from experimental studies suggested that under baseline conditions I_{Kr} is the dominant component of repolarization and that the dominant repolarization current shifts from I_{Kr} to slow delayed rectifier potassium current during β-adrenergic stimulation.[26,27] An experimental study reported that reduction in I_{Kr} (LQT2 model) increased DR even in the absence of β-adrenergic stimulation at baseline, whereas reduction in slow delayed rectifier potassium current (LQT1 model) increased DR only after introduction of β-adrenergic stimulation.[7] In addition, experimental studies have shown that measurement of the TPE interval from precordial leads can be used for clinically estimating DR.[7–9] In a previous clinical study, patients with LQT2 showed a

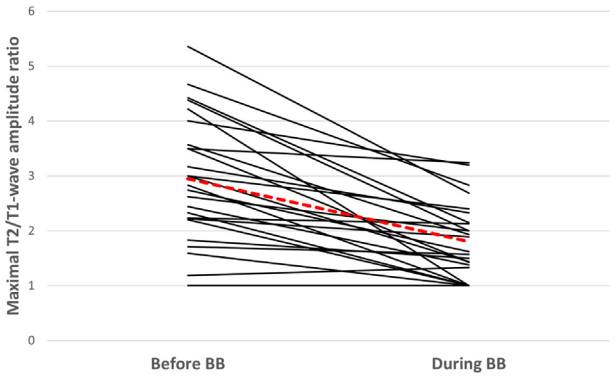

Figure 4 Maximal T2/T1-wave amplitude ratios during 24-hour electrocardiograms before and during BB ($P < .001$). The *red broken line* shows the mean values. The maximal T2/T1-wave amplitude ratio was ≤1 in 1 subject (4%) before and in 6 subjects (24%) during BB. BB = β-blocker.

capacity to increase electrocardiographic DR at a wide range of heart rates.[16]

In the present study, we observed that β-blocker therapy reduced abrupt prolongations of maximal TPE intervals at elevated heart rates. This finding is similar to what we observed in patients with LQT1 earlier.[11] However, we observed no reduction in electrocardiographic DR at low heart rates, indicating a lower effectiveness of β-blockers against nonexercise cardiac events, which are more often seen in LQT2 than in LQT1. Our findings are also in accordance with the previous findings by Shimizu et al[4] and by Tanabe et al,[20] who, by using 87-lead body-surface ECGs, observed that in patients with LQT2 epinephrine infusion increased electrocardiographic DR whereas propranolol attenuated the influence of epinephrine. To our knowledge, the reduction in the capacity to increase electrocardiographic DR in response to β-blocker therapy that was observed in the present study has not been reported previously.

QT interval and effects of β-blockers

A previous experimental study on LQT2 human-induced pluripotent stem cell–derived cardiomyocytes showed only marginal shortening in action potential duration in response to propranolol.[28] In a body surface resting ECG study in patients with LQT2, β-blockers had no significant effect on QTc values, and a large international clinical study reported only minimal effects on QTc values in patients with LQT2.[4,29] In line with the previous studies, we observed no significant effect of β-blockers on QT intervals measured at stable heart rates during 24-hour ECG recordings. In contrast, we noticed shortening in maximal QT intervals at abruptly elevated heart rates, similarly to a previous LQT1 study,[11] indicating a shortening effect of β-blockers on the QT interval duration in sudden adrenergic circumstances in LQT2, as well. One clinical study comprising high-risk patients with LQT1 and LQT2 with markedly increased QTc values reported decrease in QTc intervals after initiating β-blocker therapy in these high-risk patients.[30]

Prevention of cardiac events with β-blockers in LQT2

In clinical studies, the protective effects of β-blockers against cardiac events have been suboptimal in LQT2.[6,12,13] The efficacy of β-blockers in patients with LQT2 was investigated in more detail by cardiac event triggers, showing that therapy associated with a pronounced reduction in the risk of exercise-triggered events but might not protect against arousal-triggered or nonarousal/nonexercise events.[6]

In the present study, the decrease induced by β-blockers in the maximal T2/T1-wave amplitude ratio and in the maximal TPE and QT intervals occurred at elevated heart rates, implying a likely preceding adrenergic stimulus. During nighttime, the corresponding electrocardiographic effects of β-blockers were weak. The present results provide electrocardiographic evidence, and supplement the previous experimental and clinical studies,[4,6,7,13,24,31] that in LQT2 β-blockers are most effective against exercise-induced EAs and thus against exercise-triggered cardiac events. However, the most frequent trigger of cardiac events in patients with LQT2 – startle – typically induces a sudden decrease in heart rate.[32] Importantly, pause-induced EA augmentation is the electrophysiological feature in LQT2 rather than in LQT1,[33] and similarly pause-induced TdP onset[34,35] is predominant in LQT2 but rare in LQT1.[36] Therefore, our results indicate that β-blockers' weak effect against pause-induced EAs may explain their lower effectiveness in LQT2 than in LQT1.

Study limitations

The present study included 25 patients, and more detailed gender-specific or even mutation-specific analyses need to be addressed in larger studies. The β-blocker medication was not uniform among our patients, and the limited sample size precluded the investigation of possible differential electrocardiographic effects between different types of β-blockers. Similarly, a comparison of potassium levels between the users of different types of β-blockers was infeasible because of sample size. Nadolol and a long-acting preparation of propranolol are not available in Finland. Although patients were encouraged to maintain their normal daily activities, the evaluation of ventricular repolarization during strenuous physical exercise was beyond the scope of the present study. Clinical circumstances and triggering factors (eg, auditory stimulus or exercise) preceding the maximal QT end or TPE intervals, or maximal T2/T1-wave amplitude ratios, were unavailable for the present study. Postextrasystolic pauses could not be analyzed separately because patients exhibited only a few extrasystoles. We cannot rule out that some patients with LQT2 may show increased electrocardiographic DR during nocturnal bradycardia with β-blocker therapy.

The TPE interval was proposed as an index of transmural repolarization on the basis of the results of wedge preparations.[8] In the intact heart, however, the TPE interval was shown to be an index of total DR.[9] Thus, transmural DR in

experimental LQT2 models using wedge preparations cannot be directly extrapolated to the intact human heart. Nevertheless, our simplification of the electrophysiology of the TPE interval does not invalidate our finding that β-blocker therapy reduced abrupt prolongations of maximal TPE intervals and thus reduced abrupt prolongations of electrocardiographic DR at elevated heart rates in patients with LQT2.

Conclusion

This study presents detailed electrocardiographic effects of β-blockers on ventricular repolarization recorded by 24-hour ECGs in patients with LQT2. β-Blockers stabilize ventricular repolarization by reducing abrupt increases in electrocardiographic EAs, DR, and ventricular repolarization duration at elevated heart rates. Thus, in conditions in which preceding sympathetic activations are likely β-blockers suppress the 3 electrophysiological components necessary to trigger and sustain TdP. β-Blockers' effect on pause-induced electrocardiographic EAs is weak, which may explain their lower effectiveness in LQT2 than in LQT1. The findings complement the previous experimental and clinical studies by providing electrocardiographic explanation for the suboptimal protective effects of β-blockers in LQT2.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2022.04.028.

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