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Effects of Beta-Blocker Therapy on Ventricular Repolarization Documented by 24-h Electrocardiography in Patients With Type 1 Long-QT Syndrome

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OBJECTIVES We tested the hypothesis that in long-QT syndrome (LQT) type 1 (LQT1), beta-blocker therapy may decrease both the diurnal maximal T-wave peak to T-wave end interval (TPE) and the maximal ratio between late and early T-wave peak amplitude (T2/T1 ratio), which are electrocardiographic counterparts of transmural dispersion of repolarization (TDR) and early afterdepolarizations (EA), respectively.

BACKGROUND Ventricular repolarization duration and increased TDR and EAs are the three electrophysiological components generating the high risk of ventricular arrhythmias and sudden death in the inherited LQT. In the most prevalent LQT1 form of LQT, treatment with beta-blockers reduces serious arrhythmia events dramatically without a known influence on QT interval duration. In experimental LQT1 models, beta-blockers decrease TDR and prevent EAs.

METHODS We reviewed 24-h electrocardiographic recordings obtained before and during the treatment with beta-blockers from 24 genotyped LQT1 patients to record maximal TPE intervals and T2/T1 ratios as well as maximal and rate-adapted QT intervals using a computer-assisted program.

RESULTS Treatment with beta-blockers decreased the maximal diurnal T2/T1 amplitude ratio from 3.0 ± 1.0 to 2.2 ± 0.6 ($p = 0.002$). Beta-blockers also decreased both maximal TPE intervals and abrupt maximal QT intervals at heart rates higher than 85 beats/min, whereas QT intervals measured at steady-state conditions remained unchanged.

CONCLUSIONS Prevention of abrupt increases of electrocardiographic TDR, EA, and ventricular repolarization duration at elevated heart rates may explain the favorable clinical effects of beta-blockers in LQT1. (J Am Coll Cardiol 2006;48:747–53) © 2006 by the American College of Cardiology Foundation

Long-QT syndrome (LQT) type 1 (LQT1), the most prevalent type of inherited LQT syndrome, is caused by mutations leading to decreased activity in the I_{Ks} potassium current (1). As electrophysiological consequences of the potassium ion channel mutations, ventricular repolarization is prolonged, transmural dispersion of repolarization (TDR) is increased, and early afterdepolarizations (EA) may appear (2). These three electrophysiological components expose patients with LQT1 to torsades de pointes (TdP), which often lead to syncope or sudden death typically associated with physical exercise or psychological stress (3). Beta-blocker treatment has dramatically reduced cardiac events in LQT1 (4,5). Although beta-blockers' favorable effects in LQT1 patients are expected to depend on normalization of ventricular repolarization, no consistent effect of beta-blockers on QT interval duration has been reported so far. In an experimental LQT1 model, on the other hand, propranolol had little or no effect on the duration of action potential and QT interval, whereas during strong sympathetic stimulation propranolol inhibited TDR to increase and prevented the induction of TdP (6,7). In addition, although Moss et al. (8) reported a significant reduction of cardiac events in LQT1 patients during the beta-blocker therapy, they observed only minimal changes in rate-corrected QTc intervals in their patients' rest electrocardiograms (ECGs). One may assume, therefore, that beta-blockers' clinical effects cannot be detected by measuring only QT intervals at rest. Of the three electrophysiological components necessary to trigger and sustain TdP, TDR as clinically evaluated by the T-wave peak to T-wave end (TPE) interval (9) and EA as clinically evaluated by the ratio of U-wave (T2-wave) to T-wave (T1-wave) amplitude (10) are in LQT1 abrupt, presumably autonomically mediated phenomena and therefore are suitable to be evaluated using ambulatory ECG recordings (11,12).

The purpose of this study was to explore the effects of beta-blocker treatment on the dynamic ECG repolarization recognized by 24-h recordings in molecularly defined LQT1 patients. We hypothesized that treatment with beta-blockers would decrease abrupt lengthening of TPE intervals as well as would decrease high T2-wave to T1-wave amplitude ratios in LQT1 patients. We also hypothesized that beta-blocker treatment might decrease

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Abbreviations and Acronyms

ECG = electrocardiogram/electrocardiographic
LQT1 = long-QT syndrome type 1
LQT2 = long-QT syndrome type 2
TdP = torsades de pointes
TDR = transmural dispersion of repolarization
TPE = T-wave peak to T-wave end interval

abrupt lengthening of QT intervals at elevated heart rates.

METHODS

Study subjects. We studied 24 patients with the LQT1 genotype consisting of 10 different KCNQ1 mutations. Thirteen patients were symptomatic, and 11 were their family members and were so far asymptomatic (Table 1). The patients were from consecutive series genotyped at the Helsinki University Central Hospital who had available 24-h ECG recordings both before the treatment and during the treatment with a beta-blocker. The specific beta-blocker used, and the dose, was at the discretion of the treating physician (Table 1). The baseline ECG and 24-h recording were obtained at the same visit before the treatment. During the treatment with a tolerable dose of a beta-blocker, the second ECG and 24-h recording were obtained. No patient took any other medication known to influence cardiac repolarization. All study subjects were in sinus rhythm, did not show bundle-branch block, and did not have symptoms or signs of other cardiac disease on clinical examination. Similar normal daily activities were encouraged during both recordings. The ethical review committee of the institute approved the study, and informed consent was obtained from all participants.

Table 1. Clinical and ECG Characteristics of the Patients: Effects of Beta-Blockers on Baseline ECG Parameters

Variables	LQT1 Patients (n = 24)		
Age, yrs	23 ± 13		
Men/women	8/16		
Cardiac events, n (%)	13 (54)		
Cardiac arrest	2 (8)		
Syncope	11 (46)		
Triggers for cardiac events, n (%)			
Exercise	11 (85)		
Emotion	2 (15)		
Beta-blocker therapy			
Propranolol, n	18		
Dose, mg/kg	1.9 ± 0.9		
Atenolol, n	3		
Dose, mg/kg	1.1 ± 0.3		
Bisoprolol, n	3		
Dose, mg/kg	0.1 ± 0.01		
	Before Beta-Blocker	**Under Beta-Blocker**	**p Value**
Baseline ECG			
Heart rate, beats/min	74 ± 15	58 ± 9	<0.001
QTfc (Fridericia formula), ms	472 ± 31	460 ± 27	0.39
QTc (Bazett formula), ms	482 ± 32	457 ± 28	0.002
TPE interval in lead V_5, ms	77 ± 17	76 ± 9	0.67
Maximal TPE interval in any lead, ms	99 ± 39	98 ± 34	1.00
T-wave amplitude in lead V_5, mV	0.4 ± 0.2	0.4 ± 0.2	1.00
Maximal T-wave amplitude in any lead, mV	0.6 ± 0.2	0.6 ± 0.2	0.77

ECG = electrocardiogram/electrocardiographic; LQT1 = long-QT syndrome type 1; TPE = T-wave peak to T-wave end interval.

Holter monitor recordings and analyses. All study subjects underwent two 24-h ECG recordings (model 8500, Marquette Electronics Inc., Milwaukee, Wisconsin). The tapes were initially analyzed with a Marquette 8000 Holter Analysis system (version 5.8 software) to label the QRS complexes to normal, ventricular extrasystoles, or aberrant complexes. The ECG data were then transferred to a personal computer for further analysis of T waves and QT intervals.

Measurement of QT and TPE intervals and the T1- and T2-wave amplitudes. To measure the QT interval durations from the 24-h ECG recordings, we used previously described methods for determination of T-wave fiducial points (13) and for measurement of QT intervals (14). In this study, we determined the highest amplitude peak of the deflections during repolarization as the peak of the T-wave. In QT interval measurements, bifid T waves showing a time interval of ≤0.15 s between the highest peak and the later lower peak were calculated into the QT duration (Fig. 1, top); otherwise, the later lower peak was not included into the QT duration (Fig. 1, middle) (15). Thus, QT interval measurements always include T2 waves that are of higher amplitude than T1 waves (Fig. 1, bottom).

To measure the T1 and T2 peaks of the T-wave, we reviewed the morphology of T waves in the 24-h ECG recordings using the superimposed scan. We then looked for the highest T2-wave amplitudes and highest T2/T1 amplitude ratios meeting the criteria of grade III bifid T waves in the approach presented by Lehman et al. (15) and printed the samples on chart paper for detailed analysis as described earlier in detail (12). Finally, we measured the maximal T2/T1 amplitude ratios manually from the ECG strips at the paper speed of 50 mm/s and with the amplitude calibration of 0.1 mV/mm using modified lead V_5. We recorded the maximal T2-wave amplitudes and maximal T2/T1 amplitude value as the mean of 5 consecutive beats for each individual if ≥1.1, otherwise we used the value of 1 as the individual maximum (Fig. 1, bottom).

Data analyses and definitions. The QT and TPE intervals were analyzed by plotting all of the measured QT and TPE values recorded during 24 h against the preceding respective RR intervals as described previously (11,14). We first determined diurnal maximal QT peak, QT end, and TPE intervals. We also recorded maximal QT end and TPE intervals at different RR intervals with RR steps of 50 ms (from 500 to 700 ms) or with RR steps of 100 ms (from 700

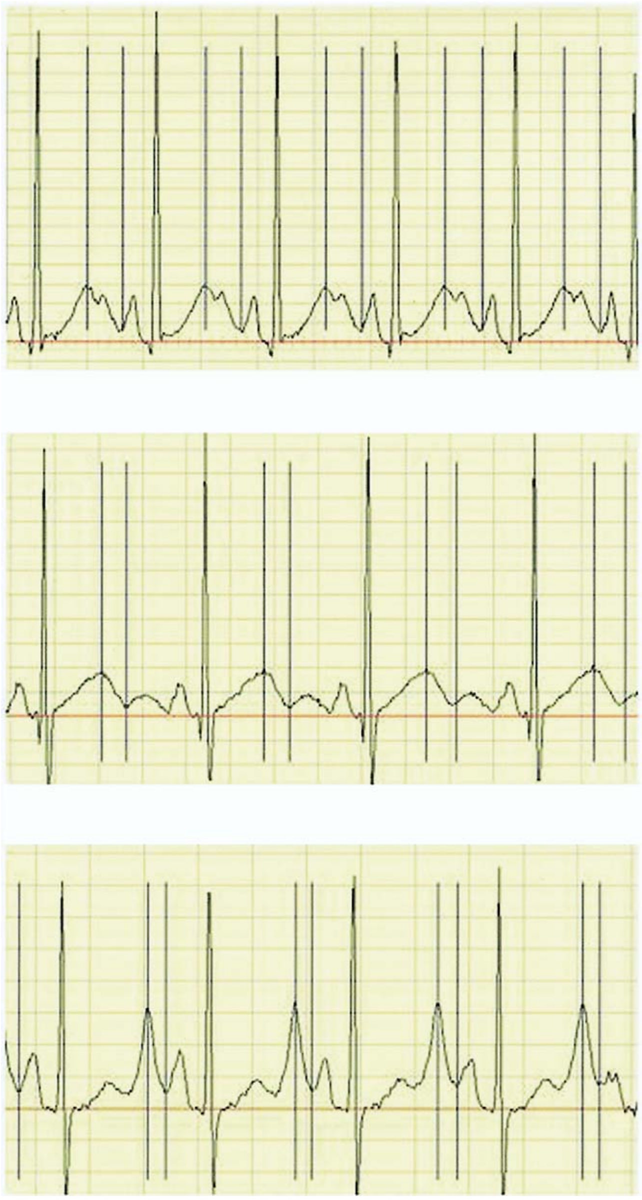

Figure 1. The measurement of QT end and T-wave peak to T-wave end (TPE) intervals as well as the T2/T1-wave amplitude ratio in cases with bifid T waves. **Vertical lines** show the peak and the end of the T wave; see text for details. In the **top panel**, with an interpeak difference of 0.08 s, the second peak is a part of the T-wave. In the **middle panel**, with an interpeak difference of 0.2 s, the second peak is a U wave. In the **bottom panel** the interpeak difference is 0.18 s, but because the second peak is higher it is interpreted as a T2-wave with a T2/T1-wave amplitude ratio of 3.7.

to 1,400 ms). All of the maximal QT and TPE intervals were determined and checked visually by use of the unaveraged ECG signal, with three or more consecutive acceptable measurements. We computed the median values of the QT peak, QT end, and TPE intervals against RR intervals in RR steps of 10 ms. To analyze the rate dependence of the QT end intervals, we recorded these intervals at stable heart rates in RR steps of 10 ms (14). We present the median TPE values of all beats during 24 h against RR intervals with RR steps similarly to maximal TPE values.

The baseline QT interval was measured in lead II from 12-lead ECGs and adjusted for heart rate using the Bazett and Fridericia formulas, giving QTc and QTfc values, respectively.

All measurements and analyses were performed without the investigator knowing the presence or absence of the beta-blocker medication.

Statistical analyses. Data are presented as mean ± SD. Comparison of the continuous variables before and during beta-blocker therapy was performed using the Student *t* test for paired data. Analysis of variance for repeated measurements was used for both QT and TPE intervals with two within-group variables (RR intervals and medication) to estimate the effects of medication on QT and TPE intervals. These analyses were performed up to RR intervals of 600 ms because of missing values at short RR intervals. Statistical significance was defined as $p < 0.05$. The SPSS version 13.0 (SPSS Inc., Chicago, Illinois) was used for data analysis.

RESULTS

Effects of beta-blockers on heart rates. Beta-blockers reduced the heart rate of each study subject, confirming the use of the beta-blocker. In 24-h recordings, both minimal and mean as well as maximal heart rates were significantly lower during beta-blocker therapy than before the therapy (Table 2).

Effects of beta-blockers on repolarization parameters in baseline ECG. Baseline QTfc intervals adjusted using the Fridericia cubic root formula did not change significantly when compared before and after starting beta-blocker therapy (Table 1). When using the Bazett square root adjusting formula, corresponding QTc intervals seemed to shorten with decreased heart rates during beta-blocker treatment, presumably because this formula undercorrects measured QT values at low heart rates (16) (Table 1). The TPE intervals or T-wave amplitudes did not change after starting beta-blocker therapy (Table 1).

Effects of beta-blockers on repolarization parameters in 24-h ECG. QT INTERVALS. Treatment with beta-blockers had no influence on the median QT peak or median QT end intervals determined at heart rate of 60 beats/min (Table 2). Beta-blocker treatment prolonged both maximal diurnal QT peak and maximal diurnal QT end intervals (Table 2). Figure 2 shows the maximal QT end values and the QT end values measured at stable heart rates. The figure highlights the behavior of the RR interval-related QT end intervals to prolong from the state of stable rates to maximal momentary values that typically are associated with abrupt heart rate accelerations. The beta-blocker treatment had little effect on the QT end interval duration measured at any specified stable heart rates, whereas the beta-blocker treatment shortened the transient maximal QT end intervals at elevated heart rates (Fig. 2). At low heart rates, the beta-blocker treatment tended to prolong the transient maximal QT end intervals (Fig. 2). Both men and women showed

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Table 2. Effects of Beta-Blockers on 24-h ECG Parameters in 24 LQT1 Patients

Measure	Before Beta-Blocker	Under Beta-Blocker	p Value
Minimal heart rate, beats/min	47 ± 8	43 ± 6	0.02
Mean heart rate, beats/min	74 ± 10	64 ± 8	<0.001
Maximal heart rate, beats/min	132 ± 17	114 ± 15	<0.001
Median QT peak interval at heart rate of 60 beats/min, ms	394 ± 24	396 ± 27	0.61
Median QT end interval at heart rate of 60 beats/min, ms	482 ± 26	486 ± 26	0.12
Maximal QT peak interval, ms	454 ± 38	475 ± 42	0.02
Maximal QT end interval, ms	565 ± 54	584 ± 62	0.03
Median T-wave peak to T-wave end interval, ms	89 ± 12	92 ± 18	0.29
Maximal T-wave peak to T-wave end interval, ms	195 ± 57	176 ± 66	0.09
Maximal T2-wave amplitude, mV	0.57 ± 0.26	0.36 ± 0.18	0.001
Male (n = 8)	0.51 ± 0.31	0.34 ± 0.18	0.12
Female (n = 16)	0.59 ± 0.25	0.37 ± 0.19	0.003
Maximal T2/T1-wave amplitude ratio	3.0 ± 1.0	2.2 ± 0.6	0.002
Male (n = 8)	2.5 ± 0.8	2.0 ± 0.5	0.10
Female (n = 16)	3.3 ± 1.1	2.4 ± 0.6	0.008

Abbreviations as in Table 1.

similar effects of the beta-blocker treatment on the behavior of the maximal QT end interval (data not shown).

TPE intervals. Figure 3 shows the maximal as well as the median TPE interval values at specified RR intervals before and during the beta-blocker treatment. At RR intervals of 700 ms or less (heart rates higher than 85 beats/min), the maximal TPE interval values were shorter during the treatment than before the treatment. At low heart rates, LQT1 patients tended to show longer maximal TPE intervals during the beta-blocker treatment than before the treatment (Fig. 3). Both men and women showed similar effects of the beta-blocker treatment on the TPE interval behavior (data not shown).

T2/T1 wave amplitude ratio. The treatment with beta-blockers decreased the diurnal maximal T2-wave amplitudes in the study group, with both men and women showing the same tendency (Table 2). The maximal T2/T1-wave amplitude ratio decreased from 3.0 ± 1.0 to 2.2 ± 0.6 ($p = 0.002$), with 19 (79%) patients showing a decrease, whereas only 5 (21%) patients showed an increase or no change (Fig. 4). In symptomatic patients (n = 13) the maximal T2/T1-wave amplitude ratio decreased from 3.6 ± 0.8 to 2.4 ± 0.6 ($p = 0.003$), whereas in asymptomatic patients (n = 11) the change was not statistically significant (2.3 ± 0.9 to 2.0 ± 0.5, respectively; $p = 0.26$). The maximal heart rate during the preceding 30 s before the maximal T2/T1-wave amplitude ratio was lower during the beta-blocker treatment (93 ± 15 beats/min) than before the treatment (107 ± 14 beats/min) ($p < 0.001$).

DISCUSSION

Main findings. The present results show that treatment with beta-blockers decreases the maximal diurnal T2/T1-wave amplitude ratio in symptomatic LQT1 patients. Beta-blockers also decrease abrupt lengthening of both QT and

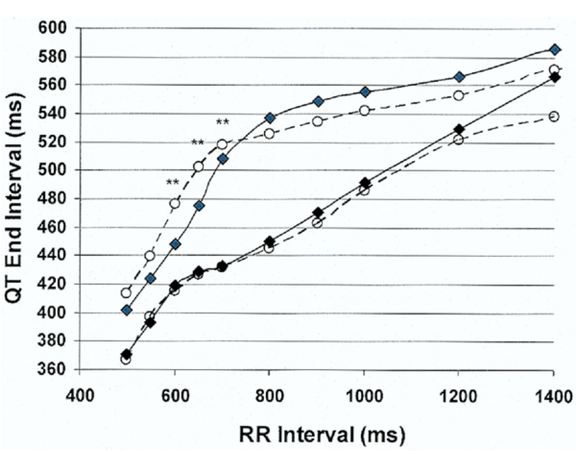

Figure 2. Maximal QT end intervals **(higher two lines)** and QT end intervals at stable heart rates **(lower two lines)** at specified heart rates before the treatment with beta-blockers **(broken lines)** and during the treatment with beta-blockers **(solid lines)** in 24 long-QT syndrome type 1 (LQT1) patients. **$p < 0.01$ before the treatment versus during the treatment with beta-blockers at RR intervals from 600 to 700 ms.

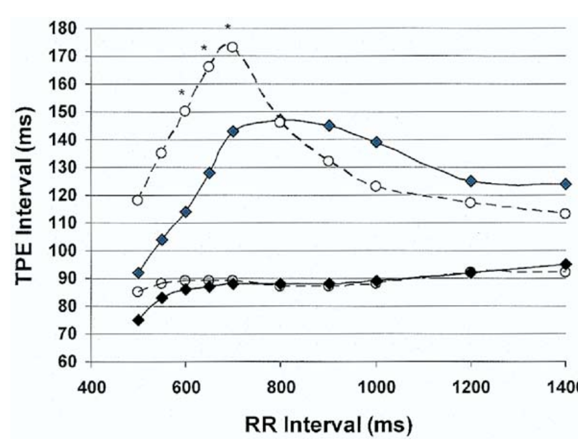

Figure 3. Maximal T-wave peak to T-wave end (TPE) intervals **(higher two lines)** and median TPE intervals, calculated from all beats **(lower two lines)**, at specified heart rates before the treatment with beta-blockers **(broken lines)** and during the treatment with beta-blockers **(solid lines)** in 24 long-QT syndrome type 1 (LQT1) patients. *$p < 0.05$ before the treatment versus during the treatment with beta-blockers at RR intervals from 600 to 700 ms.

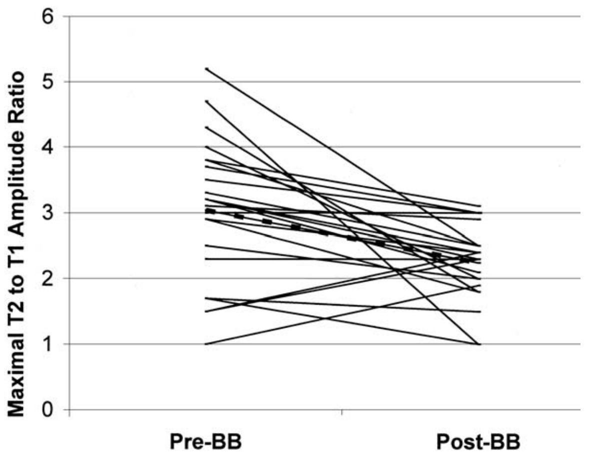

Figure 4. Maximal T2/T1-wave amplitude ratios during 24-h before (pre-BB) and during (post-BB) the treatment with beta-blockers in 24 long-QT syndrome type 1 (LQT1) patients. The **broken line** shows the average values.

TPE intervals at elevated heart rates in LQT1 patients. The observed ECG effects of beta-blockers in LQT1 patients temporally coincide with likely preceding sympathetic activations.

EAs and induction of TdP in experimental LQT1 models, T2/T1-wave amplitude ratio in LQT1 patients, and effects of beta-blockers. Several experimental and clinical observations using monophasic action potential recordings suggest a key role for EA-induced triggered activity in the genesis of TdP (17–19). Experimental evidence supports the hypothesis that an EA-induced triggered response initiates TdP but that the arrhythmia is maintained by a re-entrant mechanism (20–22). Inward currents through I_{Ca-L} (23) or through sodium-calcium exchange (24) have suggested being responsible for the development of EAs. In addition, experimental studies using an LQT2 model showed that the ratio of T2/T1-wave amplitude could be used as an ECG parameter to predict the acute onset of TdP (10). In a recent clinical study, symptomatic LQT1 and LQT2 patients showed episodes of higher T2/T1-wave amplitude ratios than asymptomatic patients with similar genotypes at abruptly elevated heart rates in 24-h ECG recordings (12).

In this study we found that beta-blocker therapy decreased maximal amplitudes of high T2 waves. Also the maximal T2/T1-wave amplitude ratios, abruptly present in LQT1 patients at elevated heart rates (12), decreased during the beta-blocker treatment. In symptomatic patients with the highest maximal T2/T1-wave amplitude ratios at baseline, this ratio during the beta-blocker treatment decreased to similar values previously observed in asymptomatic patients (12). Supposing that the maximal T2/T1-wave amplitude ratio is the ECG counterpart of EA (10), the present findings are in accordance with previous experimental studies by Shimizu and Antzelevitch (6) showing that propranolol suppressed the induction of TdP by sympathetic stimulation in the LQT1 model. The effect of beta-blockers is likely to be mediated by decreasing I_{Ca-L} activity as well as by preventing catecholamines from binding to beta-adrenergic receptors (19). Recently, Nakagava et al. (25) observed that autonomic blockade with propranolol and atropine prevented isoproterenol to induce transient TU-wave abnormalities (high T2 waves) in normal subjects. In patients with LQT1, the effect of beta-blockers on the T2-wave amplitude and on the T2/T1-wave amplitude ratio has not been previously described.

TDR in experimental LQT1 models and TPE interval in LQT1 patients: effects of beta-blockers. In experimental LQT1 models, I_{Ks} block prolongs action potential durations homogeneously across the ventricular wall and TDR does not change significantly, but beta-adrenergic stimulation with isoproterenol increases TDR dramatically (6). This may be explained by a larger augmentation of I_{Ks} by isoproterenol in epicardial and endocardial cells than in M cells, in which I_{Ks} is weaker (6). The result is abbreviation of epicardial but not of midmyocardial action potential durations, giving rise to increased TDR and prolonged TPE intervals. In addition, experimental studies have shown that the TPE interval measured in precordial leads serves as an index of TDR across the ventricle (6,7). In previous clinical studies in LQT1 patients, sympathetic stimulation with epinephrine markedly prolonged the TPE interval (26), and at elevated heart rates during 24-h ECG recordings LQT1 patients showed abrupt increases of the TPE interval (11).

In the present study we found that treatment with beta-blockers diminished the abrupt prolongations of TPE intervals at elevated heart rates. This finding is in accordance with a previous finding by Shimizu et al. (27), who, by using rest ECGs, observed that propranolol completely suppressed the influence of epinephrine in increasing the rate-corrected TPE interval in LQT1 patients. Earlier experimental studies by Shimizu and Antzelevitch (6,7) showed that beta-blockade inhibits the sympathetically induced transient prolongation of the M cell action potential duration and thus inhibits the increase of TDR.

We observed also that beta-blocker therapy tended to prolong abrupt maximal TPE interval values at low heart rates in LQT1 patients. In fact, the therapy with beta-blockers changed the behavior of the maximal TPE values from the LQT1 type (caused by I_{Ks} defect) toward the behavior previously observed in LQT2 patients (with I_{Kr} defect) (11). Because our patients showed only KCNQ1 mutations, our findings may suggest that at low heart rates the beta-blockers might have a weak decreasing effect on the activity of I_{Kr} potassium channels in the presence of reduced I_{Ks} channel activity. Previously it has been postulated that cyclic adenosine monophosphate may activate the HERG channel, thus beta-adrenergic blocking agents might act by interrupting the effect of cyclic adenosine monophosphate on I_{Kr} channel function (28).

Effects of beta-blockers on QT interval behavior in experimental LQT1 models and in LQT1 patients. In experimental LQT1 models, therapeutic concentrations of

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propranolol had no significant effect on the QT interval duration (6). In a large international study, Moss et al. (8) reported that beta-blocker therapy had only minimal effects on the QTc interval in LQT1 patients. In accordance with previous experimental and clinical studies, we observed no significant changes in the QT end interval duration measured at stable heart rates during 24-h ECG recordings. On the other hand, we observed that beta-blocker treatment inhibited LQT1 patients to transiently show long QT end values at abruptly elevated heart rates. We emphasize that in our approach, the maximal QT end intervals recorded at each specified heart rate typically associate with abrupt, presumably autonomically mediated heart rate accelerations. Thus, the effect of the beta-blocker therapy on the QT interval in LQT1 patients may also be concentrated at occasions coinciding with abrupt sympathetic activations.

The present observations in LQT1 patients suggest that treatment with beta-blockers may increase both maximal QT end and maximal TPE intervals at low heart rates. This finding may further explain the benefits of combining the use of continuous cardiac pacing with beta-blocker treatment in high-risk patients with LQT1 syndrome (29,30).

Study limitations. Our study compares TPE intervals, high T2 waves, and the behavior of QT end intervals determined before and during treatment with beta-blockers in a limited number of LQT1 patients with 10 different KCNQ1 mutations. Thus, although our findings showed shortened maximal TPE and QT end intervals and decreased maximal T2/T1-wave amplitude ratios, which all are expected to be favorable signs of diminished arrhythmia risk in LQT1 patients, the clinical significance of the present findings to predict the benefit of beta-blocker treatment in LQT1 patients remains unclear until results from large prospective follow-up studies are available. Possible different effects of beta-blocker treatment between men and women need to be addressed in a separate larger study. During 24-h ECG recordings the patients are at their usual daily activities, and therefore our approach leaves the evaluation of the effects of beta-blocker treatment on the ventricular repolarization during strenuous exercise beyond the scope of this study. The ECG measures used in this study give only an approximation for evaluating the electrophysiologic effects of beta-blockers on ventricular repolarization.

Conclusions. This study shows detailed effects of beta-blocker treatment on the ECG ventricular repolarization in patients with LQT1 syndrome. At elevated heart rates, beta-blockers seem to decrease abrupt increases of QT interval durations and of TPE intervals as well as to decrease maximal T2/T1-wave amplitude ratios. Thus, in conditions in which preceding sympathetic activations are likely, beta-blockers have effects on the 3 electrophysiological components necessary to trigger and sustain TdP. These findings are in strong accord with the clinical experience of the reduction of cardiac events in LQT1 patients using beta-blocking medication (4,5,8), giving insight on explanations of the favorable effects of beta-blockers, particularly in this genotype.

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