HEREDITARY ARRHYTHMIA CORNER

Gene-Specific Effect of Beta-Adrenergic Blockade on Corrected QT Interval in the Long QT Syndrome

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Background: In the long QT syndrome (LQTS) the effects of beta-blocker treatment on prevention of cardiac events differs according to the genotype. We aimed to assess the effect of beta-blocker treatment on QT/QTc duration in Type 1 LQTS (LQT1) and Type 2 LQTS (LQT2) patients.

Methods: 24-hour digital Holter ECG were recorded before and after beta-blocking therapy initiation in LQT1 ($n = 30$) and LQT2 patients ($n = 16$). QT duration was measured on consecutive 1-minute averaged QRS-T complexes leading to up to 1440 edited QT-RR pairs for each recording. We computed subject- and treatment-specific log/log QT/RR relationships which were used to correct the QT intervals. The QT duration was also evaluated at predefined heart rates and after correction using Bazett and Fridericia coefficients.

Results: At baseline, individual QT/RR coefficients were higher in LQT2 than in LQT1 patients (0.53 ± 0.10 vs. 0.40 ± 0.11 , $P < 0.001$) and QT1000 was longer in LQT2 than in LQT1 patients (521 ± 38 vs. 481 ± 39 ms, $P < 0.01$). Beta-blockers significantly prolonged the mean RR interval (from 827 ± 161 to 939 ± 197 ms, $P < 0.0001$). The individual QT/RR coefficients were not significantly modified by beta-blockers. Beta-blocker treatment was associated with a prolongation of the QT1000 interval (from 481 ± 39 to 498 ± 43 ms, $P < 0.01$) in LQT1 patients but with a shortening in LQT2 patients (from 521 ± 38 to 503 ± 32 ms, $P < 0.01$).

Conclusions: The effect of beta-adrenergic blockade on QTc duration is different in LQT1 and LQT2 patients. Our data suggest that, in LQT1 patients, the well-known positive effect of beta-blockade might be associated with a prolongation of QTc duration. The mechanisms of beta-blockade protection may be different in LQT1 and in LQT2 patients.

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long QT syndrome; beta-blocker; QT duration

Since its first description, more than 50 years ago, the inherited long QT syndrome (LQTS) has been recognized as one of the most prevalent genetic cardiac channelopathy associated with syncope, cardiac arrest and sudden cardiac death.¹ Accumulated clinical experience and data from the international LQTS registry have long demonstrated the efficacy of beta-blocker therapy in preventing cardiac events.^{2–6} Accordingly, beta-blockers are the mainstay therapy in LQTS patients.

The mechanisms by which beta-blockers prevent cardiac arrhythmic events in LQTS patients are less documented. The preventing effects of beta-blockers are generally thought to be related to attenuation of sympathetic stimulation, and according to the widely accepted concept of gene-specific arrhythmia triggers,⁷ the efficacy of beta-blockers differs between genotypes. Anti-adrenergic therapy provides the greatest protection in LQT1 patients who have cardiac arrhythmias

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mainly during exercise and elevated heart rates, but less in LQT2. Experimental data also suggest that the electrical properties of the ventricular repolarization are modulated by the autonomic nervous system and this autonomic modulation differs between type 1, type 2 and type 3 experimental models of the LQTS.⁸ The duration of the rate corrected QT interval (QTc) is a major risk factor for life threatening cardiac events⁴⁻⁹ and it is thus important to rigorously evaluate the effects of beta-blocker therapy on the QTc focusing on the impaired cardiac ion channel.

We aimed to test the hypothesis that the effects of beta-adrenergic blockade on the rate corrected QT interval are gene-specific, using digital ECG technology and individual QT rate correction.

PATIENTS AND METHODS

Patients

Enrollment in the Lariboisière Cardiac Channelopathy Registry started under the leadership of Philippe Coumel^{10,11} and for each patient the Registry includes personal demographic data, family history, channelopathy related symptoms (i.e., syncope, documented torsades de pointes or ventricular arrhythmias sudden cardiac death), genetic testing (after informed written consent) and mutation when available, and therapy (specifically beta-blocker treatment). In addition, the Registry is linked to an ECG database including 24-hour Holter recordings and resting ECG. Both Holter and resting ECG are in digital formats (ISHNE for Holter and XML for resting ECG).

At initiation of the present study, the Holter database included more than 1000 recordings from which we selected patients with (1) a positive genetic diagnosis and (2) Holter recording both before beta-blocker treatment initiation and on treatment. The query provided 50 patients, 30 LQT1, 16 LQT2, 2 LQT3 and 2 Jervel Lange Nielsen patients. Given the sample sizes, only data from LQT1 (n = 30 patients; 7 C-loop mutations, 24 families,) and LQT2 (n = 16 patients, 11 families) patients were analyzed.

Holter ECG recordings Analysis

24-hour digital ECG recordings (Ela Medical, Sorin Group, Le Plessis Robinson, France) were edited to ensure that all cardiac beats of sinus

origin were accurately identified excluding ectopic beats as well as artifacts. Fully edited recordings were then transferred in ISHNE format to a dedicated software (WinAtrec 8.00, AMPS LLC, New York, NY, USA) for quantitative ECG analysis. The methods have been previously described in Refs. 12-17. Briefly, consecutive 1-minute averaged QRS-T complexes were computed (up to 1440 ECG waveforms over 24 hours). Averaged digital QRS-T complexes were considered suitable for quantitative ECG measurement if (1) they included a minimum of 20 individual QRS-T complexes of sinus origin and (2) if the level of residual noise was less than 3 μ V. The QT interval duration was automatically measured by the WinAtrec algorithm with further manual adjudication (blinded for treatment and genotype) using on-screen moving cursors (Fig. 1).

All QT intervals in a given patient were used to compute individual log/log QT/RR relationships ($\log(\text{QT}) = \alpha * \log(\text{RR}) + \beta$), separately off drug and under beta-blocker therapy.^{16,17} From the individual log/log QT/RR relationship the QT interval duration at prespecified RR intervals (from 600 to 1100 ms with 100 ms increments) was calculated according to the formula:

$$\text{QT}_x = x^{\alpha} * 10^{\beta}$$

where x = RR interval in ms and α and β are the coefficients of the individual log/log QT/RR relationship.

In addition, the first three (triplicate) 1-minute waveforms at the beginning of each Holter recording were selected to calculate a rate corrected QT interval. At this time (morning period), all patients were sitting in resting conditions while getting diary instructions. The rate correcting coefficients were Bazett ($\alpha_{\text{Bazett}} = 1/2$), Fridericia ($\alpha_{\text{Fridericia}} = 1/3$) and the subject and treatment-specific α coefficient derived from the log/log QT/RR scatterplots (Heart rate QT correction using Bazett's coefficient (1/2) (QTcB), rate QT correction using Fridericia's coefficient (1/3) (QTcF) and Heart rate QT correction using subject- and treatment-specific coefficient (QTci), respectively).

Statistical Analysis

Data are presented as mean $\pm$ SD. Comparisons between groups were performed using paired or unpaired Student's tests as appropriate. The effect of beta-blocker according to LQTS type

Figure 1. The time binning method. The figure displays the 1439 consecutive 1-minute RR and QT interval over the 24-hour Holter recording in 1 patient. For each suitable 1-minute averaged QRS-T complex (>20 individual QRS-T complexes and residual noise $<3 \mu\text{V}$) QT interval duration was automatically measured with further manual adjudication using on-screen moving cursors.

was evaluated using paired 2-way ANOVA. The ANOVA model included a gene factor (LQT1, LQT2), a treatment factor (off drug and under beta-blocker), and a gene-treatment interaction. A P value <0.05 was considered as significant. Statistical analysis was performed using Statview 5.0 (SAS Institute Inc, Cary, NC, USA).

RESULTS

Baseline LQT1 and LQT2 Data

At the time of Holter recording in off drug conditions, the mean age was 21 ± 17 years for the 30 LQT1 patients (8 males) and 19 ± 15 years for the 16 LQT2 patients (8 males).

The median time between the 2 Holter recordings (i.e., before and after beta-blocker initiation) was 1 year (minimum 7 days, maximum 7 years). Beta-blocker was nadolol in 39 patients (85%),

bisoprolol in 6 patients (13%) and propranolol in one (2%) (no significant difference between type 1 and type 2 LQTS).

Before treatment (Table 1 and Figure 2), the mean 24-hour RR intervals were similar between LQT1 and LQT2 patients. LQT2 patients had higher individual α coefficients when compared to LQT1 patients (0.531 ± 0.102 vs. 0.400 ± 0.109 , $P < 0.001$). At predefined RR intervals, LQT1 patients consistently had shorter QT intervals in comparison with LQT2 patients, and this trend reached statistical significance at RR intervals of 1000 and 1100 ms (481 ± 39 ms vs. 521 ± 38 ms, $P < 0.05$ at 1000 ms RR intervals).

The triplicate ECGs in resting conditions at the beginning of Holters showed the same trends, (shorter QTc in LQT1 patients) regardless of the rate correction formula used (Bazett, Fridericia, or individual) without statistical significance ($P = 0.07$ for QTci, Table 2).

Figure 2. Baseline data. Left-hand panel: baseline individual α coefficients in LQT1 (white circles) and LQT2 patients (grey circles). Right-hand panel: baseline QT duration at specified RR intervals in LQT1 (white bars) and LQT2 (grey bars) patients.

Beta-Blocker Therapy

Beta-blockers significantly prolonged the mean RR interval (827 ± 161 ms before treatment vs 939 ± 197 ms on beta-blocker, $P < 0.0001$). The magnitude of the drug-induced heart rate decrease was not significantly different in LQT1 and LQT2 patients. The α coefficients were not significantly affected by beta-blocker therapy in both LQTS genetic groups (Table 1).

ANOVA showed that beta-blocker therapy was associated with a significant gene and treatment interaction (Table 1 and Figure 3) with a consistent lengthening of the QT interval in LQT1 patients in contrast with a QT interval shortening in LQT2 patients. For instance, at 60 beats per minute (1000 ms RR intervals) the QT duration increased from 481 ± 39 to 498 ± 43 ms in LQT1 patients but decreased from 521 ± 38 to 503 ± 32 ms in LQT2 patients ($P < 0.001$). This differential response was observed in patients on nadolol as well as in patients on other beta-blocker agent.

Individual data plotted in Figure 4 demonstrated that the gene and treatment interaction was consistent across patients. Beta-blocker therapy prolonged the QT interval (at RR intervals of 1000 ms) in 24 out of the 30 LQT1 patients and

Figure 3. Beta-blocker effects on QT duration. Upper panel: in LQT1 patients, beta-blockade was associated with a consistent QT prolongation at all RR intervals. Lower panel: in LQT2 patients, beta-blockade was associated with a consistent QT shortening at all RR intervals.

oppositely decreased the QT interval in 14 out of the 16 LQT2 patients (80% and 88%, respectively, $P < 0.0001$). Figure 4 also evidences that the drug related changes in QT interval are not dependent on the amplitude of the drug related heart rate change.

Table 1. 24-Hour ECG Data

Parameter	LQT1		LQT2		P Value for Effect of		Gene*
	Off-Treatment	On Beta-Blocker	Off-Treatment	On Beta-Blocker	Treatment	Gene	
Mean RR (ms) (min; max)	835 ± 150 477 ± 86; 1137 ± 201	960 ± 195 567 ± 90; 1251 ± 230	812 ± 183 453 ± 112; 1107 ± 254	900 ± 202 540 ± 95; 1187 ± 263	<0.001	NS	NS
α coefficient	0.400 ± 0.109	0.413 ± 0.087	0.531 ± 0.102	0.517 ± 0.124	NS	<0.001	NS
Range	0.223; 0.853	0.244; 0.650	0.287; 0.713	0.327; 0.711	NS	<0.001	NS
β coefficient	35.9 ± 19.5	33.8 ± 20.8	16.7 ± 14.6	18.8 ± 14.0	NS	<0.001	NS
QT600 (ms)	392 ± 24	403 ± 41	397 ± 19	386 ± 16	NS	NS	<0.05
QT700 (ms)	417 ± 26	430 ± 41	431 ± 23	418 ± 17	NS	NS	<0.01
QT800 (ms)	440 ± 29	454 ± 41	463 ± 27	448 ± 20	NS	NS	<0.001
QT900 (ms)	461 ± 34	477 ± 42	493 ± 33	476 ± 25	NS	NS	<0.001
QT1000 (ms)	481 ± 39	498 ± 43	521 ± 38	503 ± 32	NS	<0.05	<0.001
QT1100 (ms)	500 ± 45	518 ± 44	549 ± 44	529 ± 38	NS	<0.05	<0.001

NS: not significant.

Figure 4. Individual effect of beta-blockade on QT1000 duration. LQT1 patients are represented as white circles, LQT2 as grey circles. The upper right insert shows ECGs before and after beta-blocker initiation in the patient with an “extreme” QT prolongation at 60 beat per minute (> 100 ms) after beta-blockade.

Resting ECG Data and the Role of Different Rate Correction Coefficients

In LQT1 patients, the mean individual α coefficients were 0.400 ± 0.109 and 0.413 ± 0.087 at baseline and under beta-blocker, respectively. The QTc duration was overestimated with the Bazett coefficient ($\alpha = 1/2$) but underestimated with the Fridericia formula ($\alpha = 1/3$) when compared to the QTci values (Table 2).

In LQT2 patients, the mean α coefficients were higher than in LQT1 patients, 0.531 ± 0.102 and 0.517 ± 0.124 at baseline and under treatment, respectively, which is pretty close to the universal Bazett α coefficient of 0.50. In this LQT2 population, therefore, the QTcB and the QTci values were nearly similar, whereas Fridericia corrected QTc intervals were shorter (Table 2).

The impact of the rate correcting coefficient when evaluating the effects of a pharmacologic beta-adrenergic blockade on the QT interval is shown in Table 2 and in Figure 5.

In LQT1 patients, a drug induced QTc prolongation was found using both the individual and the Fridericia coefficients, whereas this was blurred using Bazett formula

Conversely, in LQT2 patients, a QTc shortening induced by beta-blocker treatment was observed when using the Bazett formula but it was reduced when using the Fridericia formula (Table 2). Figure 5 shows two representative individual examples

Figure 5. Impact of the rate correction coefficient when evaluating the effects of a pharmacologic beta-adrenergic blockade on the QT interval. The left-hand panel shows a single LQT1 patient and the right-hand panel a single LQT2 patient. Using different rate correction coefficients (individual, Bazett or Fridericia) is associated with different in QTc durations at baseline and after beta-blocker treatment initiation. These differences can lead to contradictory evaluation of the qualitative effect of drug intervention.

illustrating the impact of the rate correction coefficients on resting ECG data. The drug induced QTc changes are similar between the QTci and either the Bazett (LQT2) or the Fridericia (LQT1) corrections, but they diverge in the opposite direction when the coefficient is far from the individual ones.

DISCUSSION
Main Findings

At baseline, before treatment initiation, LQT2 patients had longer QT interval duration and steeper QT rate-dependency when compared to LQT1 patients. The effect of adrenergic blockade on QT duration was gene-specific. Beta-blocker treatment was associated with a significant prolongation of the QT interval in LQT1 patients whereas it shortened the ventricular repolarization duration in LQT2 patients. Within the two genotype groups, the QT rate dependency was not significantly modulated by beta-blockers.

Optimal QT Rate Correction in LQTS

Ventricular repolarization is rate dependent and it has long been demonstrated that the QT/RR relation is individual.¹⁷⁻¹⁹ Consequently, the use of a so-called “universal” formula in the LQTS

Table 2. Resting ECG data

Parameter	LQT1		LQT1		LQT2		P Value for Effect of		
	Off-Treatment	On Beta-Blocker	On Beta-Blocker	Off-Treatment	On Beta-Blocker	Treatment	Gene	Gene*Treatment	
RR triplicate	754 ± 159	871 ± 136	835 ± 174	738 ± 207	835 ± 174	<0.001	NS	NS	
QT triplicate	424 ± 56	460 ± 62	444 ± 44	431 ± 57	444 ± 44	<0.01	NS	NS	
QTcB triplicate	491 ± 35	494 ± 50	490 ± 29	506 ± 34	490 ± 29	NS	NS	0.06	
QTcF triplicate	467 ± 39	482 ± 52	474 ± 27	479 ± 36	474 ± 27	NS	NS	<0.05	
QTci triplicate	476 ± 43	489 ± 50	494 ± 34	517 ± 38	494 ± 34	NS	0.07	<0.01	

NS: not significant.

as in other patient populations is associated with potential mathematical bias. Patients presenting with cardiac channelopathy are young and in this population the heart rates are fast. Currently, Guidelines recommend the use of individual rate correction in clinical trials and Bazett formula is no longer required by Regulatory Agencies.²⁰ Individual QT rate correction so far has not been implemented in studies dealing with LQTS population. In the present report we used 24-hour ECG data to calculate for each patient an individual coefficient, separately at baseline (off drug) and under beta-blockers.¹⁶ The use of 24-hour ECG data offers important advantages such as the large number of QT/RR pairs (up to 1440) and a broad range of RR intervals, both factors being important for fitting an accurate QT/RR model.²¹ Signal averaging over 1 minute of ECG data also improves the signal to noise ratio thus facilitating manual adjudication of ECG intervals.¹²

In our study, the mean QT/RR coefficients in LQT2 patients were 0.53 and 0.52 (off drug vs. under drug, respectively) which is close to the Bazett's factor. Oppositely, the mean coefficients in LQT1 patients were around 0.40, higher than Fridericia's but lower than Bazett's coefficients. Our findings are supported by the experimental data reported by Brunner and coauthors in transgenic awake rabbits. Using an ECG methodology similar to our approach (24 hour ECG telemetry and individual QT/RR relation) they showed that the slope of the regression was steeper in LQT2 animals than in LQT1 (0.50 vs. 0.32).²² In patients, Barsheshet et al. also reported that QT correction coefficients are different in LQT1 and LQT2 patients.²³ They found a higher coefficient in LQT1 patients than in LQT2 (0.8 vs. 0.2) in contrast with our study and the data from Brunner et al. However, the assessment of a new gene-specific QTc formula in the Barsheshet's report was based on pooling resting ECGs across all patients (a single QT and a single RR from each patient), whereas we fitted an individual model from multiple QT/RR pairs in a given patient. Table 1 and Figure 2 show that the range of individual QT correction coefficients within each genotype is large, from 0.223 up to 0.853 in LQT1 and from 0.287 up to 0.713 in LQT2, at baseline.

There is an important clinical implication from our study. The use of a population specific (LQT1 and LQT2) coefficients as suggested by Barsheshet and coauthors²³ might not be sufficient

to provide a reliable rate corrected QT interval, and consequently to perform risk assessment for life threatening events in LQT1 and LQT2 patients. In addition, the use of a genotype specific formula should be useful only when the genotype is known but not in nongenotyped LQTS patients.

QTc Duration According to Genotype and the Effects of Beta-Blockers

In our study, LQT2 patients showed in off-drug conditions longer QTc duration than LQT1 patients. Such a difference has been previously reported in some studies but not in others. Wong et al.²⁴ found that the QTc tended to be 20 ms longer in LQT2 when compared to LQT1 patients, free of beta-blockers, but this difference did not reach statistical significance. In the study of Wong and coauthors, the QT interval was corrected using the Bazett's formula but heart rates were identical in both groups. Lanfranchi et al. also reported a 10 ms QTc difference between genotypes, LQT2 being more prolonged (both Bazett and Fridericia corrected). Of note LQT1 patients had faster resting heart rates than LQT2.²⁵ Another study found no difference in resting QTc (Bazett) between LQT1 or LQT2 patients but around 50% of patients where on beta-blocker.²⁶

Our data based on individual QT correction support the data from Wong and Lanfranchi that LQT2 patients have longer QTc intervals at baseline. Despite the small size of our population, the difference was statistically significant. Nonetheless, we believe that there is not enough evidence to rule in a genotype specific QTc duration and further studies are warranted to validate this finding.

Using optimal QT rate correction is of paramount importance to evaluate the effects of a drug on the ventricular repolarization when there are concomitant drug related heart rate changes.¹⁴ The genotype specific effect of beta-blockers on QTc duration observed in our study, with a significant QTc prolongation in LQT1 patients but a QTc shortening in LQT2 patients has not been demonstrated so far, to the best of our knowledge. Yet, a similar trend was observed by Wong et al.²⁴ with a different methodology. Interestingly, Viitasalo et al.,²⁷ from 24-hour Holter recordings in LQT1 patients, and comparison at identical heart rates before and after beta-blockade, found a consistent QT prolongation under beta-blocker

(4 ms at 60 beats per minute) that did not reach statistical significance. However, in this study, Viitasalo also evaluated the effects of therapy on the largest QT duration at predefined heart rates. The prolongation of the largest QT duration by beta-blockers was statistically significant.²⁷

In our study, these gene-specific effects consistent among our patients, were not dependent on drug related heart rate changes (Fig. 4) or on pretreatment QT duration (data not shown).

If further confirmed on a larger dataset, there would be important clinical implications from our findings. Ventricular repolarization duration changes after beta-blocker therapy initiation could not be a good surrogate of their clinical efficacy. Indeed, it is well established that the rate corrected QT interval is a major risk factor and that beta-blockers are more efficient in preventing arrhythmic events in LQT1 than in LQT2 patients.^{2,6} Our data suggesting that beta-blockers prolong QTc duration in LQT1 patients are therefore conflicting. However, there are cardiac events among LQT1 patients treated with beta-blocker therapy and some subgroups of patients might be less protected. Conversely, in a transgenic model, the arrhythmic substrate has been shown to be different in LQT1 and LQT2 rabbits.²² One can speculate that beta-blockade has different effects on the trigger (autonomic modulation) and on the substrate (ventricular repolarization) or on their interaction according to the genotype. It is noteworthy that the LQT1 patient (49 years old female symptomatic patient with a SER277TRP mutation) showing the largest QTc prolongation under beta-blocker (>100 ms, Figure 4) has remained totally free of symptoms with a 7-year follow up. The two Holters recorded in this patient in 2005, and the ECG patterns extracted from the two Holters shown in Figure 4 (a large QTc prolongation under treatment) are a repeated observation at each follow up visit until recently. This individual case report illustrates the point that the role of the QTc duration as a surrogate for therapy efficacy is questionable.

Recent data show that in LQT1 patients the position of the mutation could impact the effect of beta-adrenergic stimulation.²⁸ In our study LQT1 patients with mutations in the C-loop part of the channel (7 out of 30) showed a similar QT1000 prolongation after beta-blocker initiation when compared to non-C-loop mutation patients (data not shown). However, we cannot rule out a

mutation-specific QTc duration response to beta-adrenergic receptor blockade.

Possible Pathophysiological Explanations

Type 1 LQTS (LQT1) is defined by a loss of function in KCNQ1 encoded channel resulting in a decrease in IKs current. IKs is activated by fast heart rates but also directly by catecholamines²⁹ and in these conditions shortens ventricular repolarization duration. As a consequence, IKs is a major determinant of the adaptation of ventricular repolarization duration to rate. The mechanism by which blockade of adrenergic receptors could induce a QT prolongation in LQT1 patients is not obvious.

Chromanol 293B is a specific IKs blocker used as a LQT1 model on the transmural ECG recorded from an arterially perfused wedge of canine left ventricle. In this wedge LQT1 model, propranolol actually was rather associated with a small shortening of QT interval.^{8,30} But, in another canine model of IKs blockade using HMR1556, beta-blockade by nadolol induced a reverse use-dependence that was not evidenced in absence of nadolol.³¹ This effect could account for the larger QT prolongation on beta-blocker therapy observed at slow heart rates than at faster heart rate in our LQT1 patients (Table 1).

Finally, in the transgenic LQTS rabbits, Brunner showed that the elimination of one repolarizing current (IKs or IKr) was actually associated with a down regulation of the reciprocal repolarizing current.²² This interaction is one facet of the complex consequences of a single cardiac ion channel malfunction.

It is fair to admit that further experimental studies are needed to better understand the complex interaction between autonomic manipulation and impaired repolarizing currents.

Limitations

Because of the small sample size of our study, our results need to be reproduced in a larger population of LQT1 and LQT2 patients. In addition the demographic tables available in this study did not allow us to review in depth the therapy such as drugs daily dosages. Ongoing demographic tables are more targeted to provide such important therapeutic options data.

Assessment of the individual QT/RR relationship over a 24-hour period does not take into account its circadian modulation.¹⁹ We have, thus redone the analysis with a diurnal and a nocturnal individual QT/RR relationship and we still found the same gene-specific response of beta-blocker effect on QTc duration (data not shown).

Editing on screen up to 1440 one minute ECG templates is labor intensive and cannot be recommended as a realistic option to be considered daily at bedside. Improvements should be implemented to decrease the workload, in particular automated QT measurements. However, the T-wave morphology in LQTS patients is not equivalent to the ECG patterns observed in healthy volunteers, and the ECG algorithms have mainly been validated in phase 1 clinical trials.

CONCLUSION

Our study shows that, in LQTS patients, beta-blockade has different effects on QTc interval between LQT1 and LQT2 patients. The diagnosis as well as the prognosis based on QT/QTc duration might need to be reevaluated using individualized QT/RR relation. The QTc prolongation following beta-blocker administration in LQT1 population observed in our study definitely needs to be confirmed by both larger clinical sample sizes and with new experimental data.

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