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T-Wave Morphology Abnormalities In benign, potent and arrhythmogenic I_{kr} inhibition

Jean-Philippe Couderc, PhD^{1,2}, Xiajuan Xia, MS^{1,2}, Derick R. Peterson, PhD³, Scott McNitt, MS¹, Hongwei Zhao, PhD³, Slava Polonsky, MS¹, Arthur J. Moss, MD¹, and Wojciech Zareba, MD, PhD¹

¹Heart Research Follow-Up Program, Cardiology Department, University of Rochester Medical Center, Rochester, NY, USA

²Center for Quantitative Electrocardiography and Cardiac Safety, University of Rochester Medical Center, Rochester, NY, USA

³Department of Biostatistics and Computational Biology, University of Rochester, Rochester, NY, USA

Abstract

Background—There is a consensus on the limited value of QT/QTc prolongation as a surrogate marker of drug cardiotoxicity and as a risk stratifier in inherited LQTS patients.

Objective—We investigated the interest of repolarization morphology in the acquired and the inherited LQTS.

Methods—We analyzed two retrospective ECG datasets from healthy on/off moxifloxacin, and from genotyped KCNH2 patients. We measured QT, RR and T peak to T end intervals, early (ERD) and late repolarization duration, T-roundness, T-amplitude, left (α_L) and right slopes of T-waves. We designed multivariate logistic models to predict the presence of the KCNH2 mutation or moxifloxacin while adjusting for the level of QTc prolongation and the level of heart-rate in LQT2 patients. Independent learning and validation sets were used. A list of 4,874 ECGs from 411 healthy individuals, 293 ECGs from 143 LQT2 carriers and 150 non-carrier family members were analyzed.

Results—In the moxifloxacin model, ERD was associated with the presence of the drug (OR=1.15 per ms increase, CI:1.04-1.26, $p=0.0001$) after adjustment for QTc. The model for the LQT2 revealed that left slope was associated with the presence of the KCNH2 mutation (OR=0.38 per 1.5microV/ms decrease, CI:0.23-0.64, $p=0.0002$). Only T-roundness complemented QTc in the model investigating cardiac events in LQT2.

Conclusions—These observations demonstrate that the phenotypic expression of KCNH2 mutations and the effect of IKr-inhibitory drug on the surface ECG are specific. Future research

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Jean-Philippe Couderc, PhD, 601 Elmwood Ave, Box 653, Rochester, NY, USA, Phone: 585-275-1096, Fax: 585-273-5283, jean-philippe.couderc@thw-project.org.

Conflict of Interest: Drs. Couderc and Zareba have financial interest in a private company which licensed part of the technology described in this manuscript.

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should investigate if this phenomenon is linked to different level/form of loss functions of I_{Kr} channels, and if they could result in different arrhythmogenic mechanisms.

Keywords

Electrocardiogram; long QT syndrome; moxifloxacin; thorough QT studies; KCNH2

Introduction

In the acquired form of the LQTS, the arrhythmogenic effect of non-cardiac drugs is almost always associated with a decrease of the rapidly activating delayed rectifier potassium current (I_{Kr}), the channel formed by the human ether-a-go-go-related gene (HERG/KCNH2).¹ A similar mechanism is present in the congenital form of the LQTS in individuals who are carriers of the KCNH2 (LQT2) mutations.² If the effect of the drug on reducing ion currents is not enough to generate arrhythmias, it may contribute to increased risk for arrhythmias when additional predisposing risk factors are present such as electrolyte imbalance, hypothermia, clinically significant bradycardia, other drugs, or impaired hepatic or renal functions. Among the list of QT prolonging drugs, cisapride, terfenadine, astemizole, and mibefradil are drugs that received FDA approval and were subsequently associated with arrhythmic events. In order to reveal the QT-prolonging effect of new drug in human, the agency recommended to implement “thorough QT/QTc studies” (TQT). These studies include a positive arm to demonstrate that the QT measurement method employed in the study is sensitive enough to detect a drug-induced prolongation of 5 to 10 msec.³ Consequently, TQT studies provide a highly sensitive test for drug-induced QT prolongation. Unfortunately, the risk of drug-induced arrhythmias is not a linear function of the QT interval, nor of the extent of the QT-interval prolongation during drug therapy⁴ so there is a need for ECG markers that would complement QT/QTc prolongation in assessing the propensity of a new drug to trigger life-threatening arrhythmias.

In this proposal, we investigate the usefulness of several novel parameters to identify repolarization abnormalities in the acquired and congenital forms of LQTS (type 2): two disorders that primarily involve reduction in the I_{Kr} current, and we evaluate if these abnormalities are associated with cardiac events in patients with the LQT2 syndrome.

Methods

Study populations and ECG recordings

Moxifloxacin-induced I_{Kr} inhibition—A first dataset was shared by the FDA, it contained electrocardiograms (ECG) from seven TQT studies. Data included in the analyses are from the moxifloxacin and the placebo arms. The ECGs from the baseline and the placebo arms were recorded at the same time of the day than in the moxifloxacin arm. This database enabled us to evaluate the placebo-controlled moxifloxacin-induced QTc interval prolongation at expected peak concentration of the drug (2 hours post dosing). The information about age, gender, and study treatment were available. All these ECG signals were standard 12-lead resting recordings with a 500Hz sampling frequency stored in digital standard format (HL7 XML aECG).

KCNH2 mutation in LQTS patient—A second set of ECGs was from subjects with genetically tested KCNH2 mutations. This group encompasses 52 families from the International LQTS registry. Family members of genotyped LQTS probands were tested for proband identified mutation and were categorized as carriers or non-carriers. ECGs from subjects under 17 years of age were not included in the analysis because the T-wave morphology is age dependent and repolarization changes are frequently observed before

adulthood.⁵ The KCNH2 mutations were identified in each subject using standard genetic tests. The paper ECG tracings were extracted from the registry based on the following selection criteria: adult (age >17 yrs), individuals from LQT2 families (genotyped proband). Then, the tracings were scanned at 300 dpi. The images of ECGs were modified to be HIPAA compliant (physician and patient names were removed and a unique ECG identifier was associated with each ECG). The following rules were used to eliminate ECG tracings of too poor quality to be scanned: if the ECG has no grid (required for scaling ECG tracings), if the tracing is distorted (following photocopy), if the tracing is faded. Then, the accepted tracing were visually scanned for the presence of superimposed ECG signals with lead labels, superimposed ECG tracing with private health information, and superimposition between ECG tracing from different leads. The tracing including two of these patterns were ranked as low quality, average quality tracings had one of these patterns whereas high quality did not have any of the three patterns. ECG tracings were selected based on their quality rating. The measurement of a repolarization interval and of its preceding RR required two full cardiac beats (three QRS complexes) to be realized. Digitization of tracings was realized using the ECGScan software (AMPS llc, New-York, USA) with visual/manual adjustment if needed.⁶ All available leads were digitized but a minimum of 8 leads (I, II and V1 to V6) from the 12 lead was required to compute the repolarization parameters described below.

ECG Measurements

We quantified cardiac ventricular repolarization using several interval measurements: QT apex (QTa), QT, Tpeak to Tend (TpTe), the amplitude of the T-wave (Tamp), and the left and the right slopes of the T-wave (α_L , α_R). These measurements were applied to lead II (Figure 1, panel A). In addition, we generated the eigenleads by applying principal component analysis (PCA) to the scalar leads (ev1 and ev2 are shown in Figure 1, panel B). We applied the repolarization parameters described above to the first eigenlead (ev1). Then, we use ev1 and ev2 to analyze the T-loop by measuring the relative fatness of the loop (T roundness). Also, we implemented a set of measurements previously described as useful markers of subtle Ikr blockade: early repolarization duration (ERD) and late repolarization duration (LRD).⁷ The duration of these intervals are set by amplitude thresholds equal to 30% and 50% of the maximum vector amplitude of repolarization (see Figure 1, panel B). These measurements were realized using the COMPAS software technology (COMPrehensive Analysis of the repolarization Segment, Rochester, NY). The location of the end and the apex of the T-wave were visually checked in all recordings and manually adjusted if needed.

Statistical Analysis

We independently developed and validated models for the TQT data (“moxi models”) and for the LQTS data (“LQTS models”). In each analysis, independent subjects were randomly divided into two equal-sized groups (learning and validation), stratified by study (or carrier status, for the LQTS data) so that each study (or carrier group) contributed an equal number of subjects to learning and to validation. The design included three subset models called the clinical, the scalar and the vectorial models. The candidate variables for the clinical model included only RR and QTc from lead II, and gender and age (when needed). The scalar model enriched the candidate predictors for the clinical model with all scalar measurements in lead II (i.e. QTa, TpTe, left and right slope of the T-wave, T-wave amplitude). Finally, the vectorial model extended the clinical model by adding the candidate vectorial parameters: same interval measurements as the scalar model but based on the first eigenvector, ERDs, LRDs and T-roundness. We report the best moxi. and LQTS models amongst the overall set of investigated models and their validation.

The moxi. models—These analyses were based on conditional binary logistic regression. Each individual was used as his/her own reference, and drug status (moxi vs placebo) was modeled as a function of the baseline-adjusted changes in the medians of the ECG replicates, conditional on unconstrained subject-specific intercepts. For a given individual, we had 12 ECG tracings, 3 ECGs in each of the 4 arms –namely, baseline moxifloxacin, baseline placebo, treatment placebo and treatment moxifloxacin. One study did not have triplicate ECGs, so a single measurement was used for this study. The QT interval was forced into all models, but RR was not forced in since there was insufficient evidence that it contributed additional predictive information.

The LQTS models—The analysis for the LQTS families was based on unconditional binary logistic regression to predict carrier vs. non-carrier status as a function of the ECG measurements. The QT and RR intervals were forced into all models in order to demonstrate the ability of the novel ECG parameters to complement this information. Age and gender were tested as well. All novel ECG measures were tested via the following functional forms: raw ECG measure as linear in the logit, log-transformed as linear in the logit, and dichotomized at the 75th, 80th, 85th and 90th percentiles of the distribution among non-carrier LQTS in the learning set.

The identification of the best models of each size was based on best subset selection. In order to select the model size, a nominal p-value less than 0.05 was used as the threshold of statistical significance for retaining a parameter in a model. Meaningful interactions between predictors were tested (mostly gender and age interaction). The 95% confidence interval (CI) for odds and hazard ratios were reported.

Results

Study populations

The group of ECGs from the seven TQT studies included 411 healthy individuals. Each individual had triplicate ECGs in all studies but one. A set of 4874 digital ECGs were processed. The description of the study populations is provided in Table 1.

At the time of study, the total number of individuals in the International Registry in so-called LQT2 families was 622. LQT2 families have at least one individual with a KCNH2 mutation. From these individuals, the registry contained 1674 ECG tracings including 1145 from 301 LQT2 carriers patients and 529 tracings from 321 non-carriers. Digitization of tracings was not feasible in 40.3% of the tracings from LQT2 carriers and 49.3% of ECGs from non-carrier LQT2. We selected the oldest ECGs from each individual. The final numbers of ECGs were 204 and 189 for carrier and non-carrier LQT2, respectively.

The analysis of the ECG using the software COMPAS was feasible on 150 non-carrier LQT2 patients and 143 carrier LQT2 patients. Amongst the selected ECGs, 61% and 34% were baseline ECGs in the non-carriers and carrier groups, respectively (see Figure 2).

In LQT2 carriers, cardiac events (CE) were defined as cardiac arrest, syncope, or sudden cardiac death. We identified 69 LQT2 carrier patients with CE. Because of the small number of cases in this group, we did not use learning and validation dataset.

Profiling T-wave morphology in acquired and inherited LQT2

The RR values were similarly distributed between healthy individuals on and off moxifloxacin. They were significantly higher (976 ± 149 msec) in LQT2 carrier in comparison to their non-affected relatives (875 ± 145 msec, $p < 0.001$). The QTc intervals were not different between healthy and non-carrier individuals (411 ± 23 vs. 405 ± 29 msec) but ECGs

of individuals on moxifloxacin were associated with significant QTc prolongation of ~12 msec (422 ± 26 msec, $p < 0.001$) in comparison to these two groups. As expected, LQT2 carriers present ECGs with longer QTc interval duration (470 ± 47 msec, $p < 0.001$) in comparison to non-affected family members (405 ± 29 msec).

An increased TpTe interval (105 ± 35 vs. 75 ± 13 msec, $p < 0.001$), lower T-wave amplitude (0.18 ± 0.10 vs. 0.27 ± 0.12 mV, $p < 0.001$) and flatter right (2.4 ± 1.6 vs. 4.5 ± 2.2 μ V/msec, $p < 0.001$)ⁱ and left slopes (1.7 ± 1.1 vs. 3.3 ± 1.5 μ V/msec, $p < 0.001$) of T-wave characterize the T-wave of LQT2 patients. The vectorial parameters confirmed an increased T-loop roundness (0.43 ± 0.19 vs. 0.33 ± 0.17 , $p < 0.001$) in patients with a mutation. The ERDs and LRDs parameters were all increased in averaged by 45% in carrier LQT2 patients (in comparison to 16 % for the QTc interval), these differences were all significant with a p value inferior to 0.001.

From ECGs of healthy individuals on and off moxifloxacin, we observed a very subtle effect on the morphology of the T-wave. The QTc, QTac and TpTe interval were prolonged in average by 12, 7 and 4 msec respectively ($p < 0.001$). The T-wave right and left slopes very slightly decreased in absolute value of 0.5 and 0.2 μ V/msec ($p < 0.005$). However, the T-wave amplitude and T-roundness did not reveal any significant change. The ERDs and LRDs captured a small repolarization delay (<5msec) with statistical significance ($p < 0.001$): ERD30% was 40 ± 8 vs. 44 ± 9 msec, ERD50% was 66 ± 15 vs. 71 ± 16 msec, LRD30% was 28 ± 5 vs. 30 ± 6 msec and ERD50% was 41 ± 7 vs. 44 ± 8 msec.

Table 3 reports the values of the investigated ECG parameters between the groups of LQT2 carrier patients with (N=74) and without CE (N=69). Significant different values between LQT2 patients with and without events were observed: QTc (477 ± 44 vs. 462 ± 50 msec, $p = 0.026$), QTac (373 ± 42 vs. 354 ± 40 msec, $p = 0.013$), α L from ev1 (4.1 ± 2.8 vs. 5.0 ± 2.7 μ V/msec, $p = 0.008$), T amplitude (0.51 ± 0.30 vs. 0.62 ± 0.29 mV, $p = 0.003$) and T roundness (0.47 ± 0.19 vs. 0.39 ± 0.18 msec, $p = 0.006$).

Investigating complementarities between abnormal T-wave morphology and QT/QTc prolongation in acquired and inherited LQT2

In table 4, we report the best multivariate models and associated odds ratios when designed on the learning set and when applied to the validation datasets for the moxi. model (Table 4a) and for the LQTS model (Table 4b). In Table 4c, we provide the Cox models for CE in LQT2 carriers.

We used two different heart rate formula for QTc: Bazett's (QTcB) and Fridericia's (QTcF). The RR values did not contribute to the moxi model when QTcF was forced in; however RR did contribute if we forced QTcB instead of QTcF. These results confirmed that Fridericia's formula satisfactorily corrects QT for heart rate but Bazett's does not.⁸ In the LQTS model, Bazett's formula was found to correct better than Fridericia's confirming specific impairment of QT and RR profiles in LQT2.

We investigated if scalar T-wave morphological parameters (from lead II) would bring additional information to QT/QTc and RR intervals to detect the presence of Ikr blockade. In the moxi model, none of the scalar parameters contributed significantly to the models. While in the LQTS model the left tangent of the T-wave (from lead II) was associated with a significant odds ratio (0.38, 95% confidence interval [CI]: 0.23-0.64, $p = 0.0002$)

ⁱIn absolute values. The right slope coefficient is negative by definition for a positively oriented T-wave. We did not consider T-wave orientation in this analysis.

corresponding to a 62% increase probability of being carrier for each 1.5 $\mu\text{V/ms}$ decrease in the right slope of the T-wave.

T-wave morphology measured from eigenleads significantly contributed in both the moxi. and the LQTS models. In the moxi model, ERD30% was selected as the parameter contributing the most with 12% increase probability of being on moxifloxacin for each millisecond increases in ERD30% (OR:1.12, CI: 1.09-1.30, $p<0.0001$). The validation of this model on the independent set of data confirmed the importance of ERD30% with a 15% increase probability per same increment (OR=1.15, CI: 1.04-1.26, $p<0.0001$). For the LQT2 groups, as it was found in the scalar model the left slope (α_L) was selected but the measurement from lead *ev1* did performed better than from lead II. Results were similar between the learning and validation sets ~60% increased probability of carrying a KCNH2 mutation for each 1.5 $\mu\text{V/ms}$ decrease in slope (OR=0.46, CI: 0.28-0.75, $p=0.002$ in the learning set and OR=0.38, CI: 0.23-0.64, $p=0.0002$ in the validation set). Then, we evaluated the same model on all LQT2 carriers and non-carriers with QTc <500msec and QTc <470msec. In both subgroups, the same model remained valid. The OR for QTc decreased from 3.17 to 2.90 ($p<0.0001$) for the groups with QTc<500msec (N=263) and QTc <470msec (N=211), respectively (while OR values for α_L was similar 0.32 and 0.35, $p<0.0001$). In Figure 3, we plotted on the left panel the receiver operating characteristics (ROC) curves for discriminating between LQT2 carriers and non-carriers for all the study population, and on the right panel for the patients with normal QTc. The ROC curves emphasize the benefit associated with the morphological factors when investigating the most clinically challenging patients i.e. the LQTS patient carriers with normal QTc interval duration.

The CE model revealed that 1-msec increased in QTc duration was significantly associated with CE in LQT2 (HR=1.01, CI: 1.00-1.01, $p=0.045$), and increased T-roundness was associated with significant HR as well. A 15% increased probability of CE in LQTS patients for each 10% increase in roundness. After adjustment for presence of beta-blocker therapy, the results were not changed, HR for T-roundness was 1.15 (CI: 1.01-1.31, $p=0.036$). Figure 4 provides the Kaplan-Meier survival curves for T-roundness superior and inferior to its third quartile for all population (Figure 4A), for the subgroup of patients with QTc $\geq$ 500msec (N=25, Figure 4B), and for patients with QTc <500msec (N=115, Figure 4C). The survival curves show significantly higher probability for CE in patients with an increased T-roundness for the overall population and for a population including patients with QTc<500 msec only. T-roundness was not found useful in LQTS patients clinically identifiable i.e. with a QTc $\geq$ 500msec.

Discussion

The rationale for analyzing T-wave morphology comes from the need to reliably measure ventricular repolarization heterogeneity, a required component of arrhythmogenesis in both the clinical and drug safety contexts. Prior works have shown that the morphology of the T-wave from the surface ECG exhibits a large spectrum of shapes depending on drug concentration, drug timing, and the type of channelopathies⁹. In this work, we hypothesized that *I_{Kr}* impairment is associated with changes in morphology of the T-wave that are complementary to QTc prolongation. We investigated this hypothesis in individuals with subtle (moxifloxacin), potent (LQT2 carriers) and arrhythmogenic (CE in LQT2 patients) *I_{Kr}* inhibition. We describe methods to quantify T-wave morphology changes, and we confirm our preliminary reports about the interest of using T-morphology in drug studies⁷ and in the analysis of ECGs from LQT2 patients¹⁰ providing independent validations of the proposed models.

ERD30% parameter remained significantly associated with the presence of the drug after adjustment for QTc prolongation (Table 4a) in our learning and validation sets, so one would confidently state that ERD30% is a sensitive marker of subtle Ikr inhibition complementing the QTc interval prolongation. However, ERD30% values could not discriminate LQT2 patients with and without CE, its values were similarly high in the two groups (56 ± 18 and 54 ± 19 , $p=0.6$) in comparison to healthy subjects. In previous works, we measured ERD30% value in patients with profound heterogeneity, such as in patients with drug-induced torsades de pointes (43 ± 4 msec, unpublished data), in individuals exposed to sotalol including healthy subjects¹¹ (55 ± 15 msec) and cardiac patients with history of TdPs¹² (44 ± 13 msec). The ERD30% values never exceeded 60 msec. We believe the reason for ERDs lack of sensitivity in patients with CE resides in its definition. This parameter measures repolarization into a region of the repolarization signal close to the apex of the T-wave where the repolarization signal is stronger (larger voltage gradient in the ventricles due to larger of number of cells repolarizing, or/and amplitude-maximizing electrical state). Any subtle changes in the repolarization process, which is likely to be homogeneously distributed across the ventricle, are expected to be reflected inside this interval. When heterogeneity is more increased such as in patients with the LQTS, the changes in T-loop morphology are more profound and are likely to spread to the regions outside the ones covered by ERD and LRD parameters. Explaining why T-roundness which characterizes the overall shape of the T-loop (also referred as T-wave loop dispersion or PCA ratio) becomes more relevant.

For many years QT dispersion has been used as a maker of repolarization heterogeneity/dispersion, but it is now obsolete¹³, and the experts have increasingly used measurements of T roundness to quantify repolarization heterogeneity. Zabel et al.¹⁴ documented that automatically computed T wave loop dispersion successfully stratify post-infarction patients at risk of cardiac events; the same method was used by Porthan et al.¹⁵ in a large Finnish community-based cohort of elderly individuals in whom it was found that automatic T wave parameters are predictive for cardiac events in this low-risk cohort. Okin et al.¹⁶ demonstrated that abnormal T wave morphology quantified by the principal component analysis identifies patients with hypertension who are likely to develop cardiac events, and associate with cardiovascular mortality in the American Indian participants in the Strong Heart Study. The prognostic value of T-roundness for cardiac events (CE) is confirmed in our study for LQT2 patients with CE in comparison with those who did not experience such events (0.38 ± 0.17 vs. 0.47 ± 0.19 , $p=0.007$). Interestingly, T-roundness is not changed in healthy individuals exposed to moxifloxacin. T-roundness seems to be elevated in cardiac patients with underlying arrhythmogenic substrate but it does not have the ability to detect subtle changes as ERD parameters do. The clinical impact of this finding may be major since 13-15% of LQTS patients can present a near-normal QTc interval duration and in this set of patients the T roundness may become a surrogate marker of the presence of an increased risk for CE using a simple computerized surface ECG measurements. One would provocatively states that clinicians would benefit from having access to simple computerized measurements of T-loop morphology.

Limitation of the study

The main limitation of our study is a lack of validation sets for the model predicting cardiac events. Furthermore, our selection process for the ECGs from the registry led to a group of ECGs from baseline and from follow-up periods. Using only baseline ECGs may have led to different results since in our study the patients may have had their event before or after the ECG was recorded. Finally, it is noteworthy that the ECGs were recorded in different conditions between healthy subjects enrolled in TQT studies and LQTS patients. In TQT studies, the ECGs were recorded in a controlled condition after resting to avoid the

hysteresis effect of heart rate on the QT interval, while ECGs from LQTS patients were done in clinical settings or in the physician's office.

Conclusions

In conclusion, our work demonstrates that QTc prolongation is associated with specific changes in T-wave morphology in subtle, potent and arrhythmogenic levels of Ikr inhibition. Furthermore, QTc prolongation and morphological abnormalities were independently associated with the presence of Ikr inhibition while also being independent predictors of cardiac events in carrier LQT2 patients. Importantly, we observed specific repolarization morphological changes to phenotypic expression of KCNH2 mutations and to IKr-inhibitory drug. Future research should investigate whether they are linked to different level/form of loss functions of Ikr channels, and whether they could result in different arrhythmogenic mechanisms.

Acknowledgments

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A: Repolarization measurements for scalar lead (lead II) and eigenlead (ev1)

B: ERD30% and LRD30% measurements from the T-loop and reported to eigenlead 1 (ev1)

Figure 1.

Panel A illustrates the measurements on the T-waves from lead II and from first eigenlead (ev1). Panel B represents the T-loop i.e. T-wave signals plotted along ev1 and ev2 leads in the upper panel, and the eigenlead 1 (ev1) in the lower panel. ERD30% intervals originate from the time of maximum vector amplitude (Vmax) and ends at the time when Vmax has reached 30% decrease in amplitude (demarcated by the bold arc labeled “30% Vmax threshold”).

Figure 2.
Schematic description of the processes involved in the digitization of the paper ECG tracings from LQT2 families.

Figure 3.

Receiver operating characteristic curves for the discrimination of carriers from non-carrier LQT2 patients using 3 logistic models. The left panel shows the limited benefit of considering α L in addition to RR and QTc in LQT2 patients with prolong QTc. The right panel revealed that abnormal morphology is associated with major discriminative power when considering LQT2 patients with normal QTc interval.

Figure 4.

Kaplan-Meier curves describing the probability of cardiac events in LQT2 patients based on T roundness. Panel A: all population; panel B: LQT2 carriers with QTc ≥ 500 msec and panel C: LQT2 carriers with QTc < 500 msec

Table 1

Clinical Characteristics of the Study Populations

	Healthy	LQT2 non-carrier	LQT2 Carrier
N	411	150	143
Age	40±14	39±14	38±15
Female(%)	267 (65)	86 (57)	87 (61)
Symptoms			
Cardiac arrest(n)	-	1	11
Syncope(n)	-	19	77
SCD(n)	-	0	3
Therapy(at the time of the ECG)			
Beta-blockers	-	2	28
ICD	-	1	2

ICD: implantable cardio defibrillator

SCD: sudden cardiac death

Table 2

Absolute ECG measurements in healthy individuals, healthy individuals exposed to moxifloxacin, LQT2 non-carriers and LQT2 carriers

	Healthy (N=411)	Healthy on moxifloxacin (N=411)	Non-carrier LQT2 (N=150)	Carrier LQT2 (N=143)
RR(msec)	974±37	963±135	875±145	976±149*
Scalar Parameters (lead II)				
QTc(msec)	411±23	422±26*	405±29	470±47*
QTac(msec)	331±19	338±21*	326±24	363±42*
TpTe(msec)	79±11	82±12*	75±13	105±35*
T amplitude(mV)	0.33±0.15	0.32±0.14	0.27±0.12	0.18±0.10*
αL(μV/msec)	3.3±1.5	3.1±1.4 ^ψ	3.3±1.5	1.7±1.1*
αR(μV/msec)	5.4±2.6	4.9±2.5 ^ψ	4.5±2.2	2.4±1.6*
Vectorial Parameters (lead ev1)				
QTc(msec)	408±22	420±26*	410±27	466±46*
QTac(msec)	325±20	331±23*	325±23	355±42*
TpTe(msec)	79±11	82±12*	75±13	105±35*
T amplitude(mV)	1.05±0.45	1.02±0.44	0.88±0.40	0.57±0.30*
αL(μV/ms)	9.2±3.8	8.5±3.6 ^ψ	9.6±4.2	4.6±2.8*
αR(μV/ms)	16.6±7.7	15.2±7.2 ^ψ	13.0±6.7	5.7±4.5*
ERD30%(msec)	40±8	44±9*	38±7	55±19*
ERD50%(msec)	66±15	71±16*	57±10	84±26*
LRD30%(msec)	28±5	30±6*	29±5	42±17*
LRD50%(msec)	41±7	44±8*	42±7	59±23*
T roundness(n.u.)	0.20±0.10	0.21±0.10	0.33±0.17	0.43±0.19*

* p<0.001,

^ψ p<0.02 when comparing healthy on moxifloxacin vs. healthy off moxifloxacin, and carrier LQT2 vs. non-carrier LQT2

Table 3

ECG measurements in LQT2 patients with and without cardiac events

	No cardiac events (N=74)	Cardiac Events (N=69)	P value
Gender(%female)	39(53)	17(25)	<.001
RR(msec)	961±150	993±148	0.123
Scalar parameters (lead II)			
QTc(msec)	462±50	477±44	0.026
QTac(msec)	354±40	373±42	0.013
TpTe(msec)	106±38	103±31	0.626
T amplitude(mV)	0.19±0.09	0.18±0.11	0.184
α L(μ V/msec)	1.8±1.2	1.6±1.0	0.133
α R(μ V/msec)	2.5±1.5	2.3±1.7	0.206
Vectorial parameters (lead ev1)			
QTc(msec)	460±42	474±49	0.023
QTac(msec)	345±35	365±46	0.004
TpTe(msec)	113±40	107±34	0.396
T amplitude(mV)	0.62±0.29	0.51±0.30	0.003
α L(μ V/msec)	5.0±2.7	4.1±2.8	0.008
α R(μ V/msec)	6.0±4.4	5.4±4.5	0.190
ERD30%(msec)	56±18	54±19	0.613
ERD50%(msec)	84±25	83±28	0.668
LRD30%(msec)	43±18	41±16	0.574
LRD50%(msec)	60±24	58±22	0.581
T roundness(n.u.)	0.387±0.182	0.474±0.190	0.006

Table 4
a: Summary of the “moxifloxacin models” and associated odds ratios in the validation sets.

	Learning			Validation		
	OR	p	95% CI	OR	p	95% CI
RR(1 msec. inc.)	1.00	0.49	1.00-1.00	1.00	0.067	1.01-1.11
QTcF(lead ev1)(1 msec. inc.)	1.17	<0.0001	1.11-1.23	1.14	<0.0001	1.09-1.18
ERD30%(1 msec. inc.)	1.12	0.032	1.09-1.30	1.15	<0.0001	1.04-1.26

b: Summary of the “LQTS models” and associated odds ratios in the validation sets.

	Learning			Validation		
	OR	p	95% CI	OR	p	95% CI
RR(1 msec. inc.)	2.04	0.006	1.23-3.38	3.44	<0.0001	1.97-6.00
QTcB(lead ev1)(1 msec. inc.)	2.79	<0.0001	1.66-4.66	1.56	0.031	1.04-2.34
α L(lead ev1)(1.5 μ V/ms inc.)	0.46	0.002	0.28-0.75	0.38	0.0002	0.23-0.64

c: Summary of the Cox model for cardiac events in LQTS type 2.

	HR	p	95% CI
RR(1 msec. inc.)	1.00	0.097	1.000-1.011
QTcB(lead ev1)(1 msec. inc.)	1.01	0.045	1.000-1.011
T roundness(10% inc.)	1.15	0.036	1.009-1.310
Female(age $\leq$ 17)	1.15	0.74	0.486-2.735
Female(age >17)	4.24	0.0003	1.929-9.320

QTc are associated with different heart rate correction- F: Fridericia and B: Bazett Each parameter is associated with information about its associated lead.

** the parameters in the LQTS group were normalized using the standard deviation of the non-carrier population. Thus, each point estimate is associated with one increase of standard deviation of these values in non-carrier LQTS patients.