A quantitative assessment of T-wave morphology in LQT1, LQT2, and healthy individuals based on Holter recording technology

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BACKGROUND The clinical course and the precipitating risk factors in the congenital long QT syndrome (LQTS) are genotype specific.

OBJECTIVES The goal of this study was to develop a computer algorithm allowing for electrocardiogram (ECG)-based identification and differentiation of LQT1 and LQT2 carriers.

METHODS Twelve-lead ECG Holter monitor recordings were acquired in 49 LQT1 carriers, 25 LQT2 carriers, and 38 healthy subjects as controls. The cardiac beats were clustered based on heart-rate bin method. Scalar and vectorial repolarization parameters were compared for similar heart rates among study groups. The Q to Tpeak (QTpeak), the Tpeak to Tend interval, T-wave magnitude and T-loop morphology were automatically quantified using custom-made algorithms.

RESULTS QTpeak from lead II and the right slope of the T-wave were the most discriminant parameters for differentiating the 3 groups using prespecified heart rate bin (75.0 to 77.5 beats/min). The predictive model utilizing these scalar parameters was validated using the entire spectrum of heart rates. Both scalar and vectorcardiographic models provided very effective identification of tested subjects in heart rates between 60 and 100 beats/min, whereas they had limited performance during tachycardia and slightly better discrimination in bradycardia. In the 60 to 100 beats/min heart rate range, the best 2-variable model identified correctly 89% of healthy subjects, 84% of LQT1 carriers, and 92% of LQT2 carriers. A model including 3 parameters based purely on scalar ECG parameters could correctly identify 90% of the population (89% of healthy subjects, 90% of LQT1 carriers, and 92% of LQT2 carriers).

CONCLUSION Automatic algorithm quantifying T-wave morphology discriminates LQT1 and LQT2 carriers and healthy subjects with high accuracy. Such computerized ECG methodology could assist physicians evaluating subjects suspected for LQTS.

KEYWORDS Electrocardiography; KvLQT1; KCNH2; Long QT syndrome; T-wave; Potassium channels; Discriminant analysis; RR-bin method

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Introduction

The long QT syndrome (LQTS) is an inherited arrhythmia disorder caused by genetically determined defects in ion channel structure and function. LQTS patients are at high risk of sudden cardiac death due to the development of ventricular tachycardia degenerating in ventricular fibrillation and cardiac arrest.[1–3] With increasing awareness of the LQTS among physicians and patients, there is a growing number of patients with borderline QTc who are suspected for the disorder. There is clinical need for developing electrocardiographic (ECG) methods assisting physicians in diagnosing LQTS patients and in providing indications regarding specific genotype. Although genetic testing remains the gold standard for verification of the underlying gene abnormality, it is frequently not accessible (patient refusal), too expensive, or the results could be delayed. The LQTS genotype is frequently associated with specific ECG phenotype; however, there is substantial variation and overlap in results of ECG phenotyping based on visual assessment of T wave morphology[4,5] as well as substantial variance in penetrance of causative genes.[6]

Consequently, it is important to assess whether computerized ECG might be helpful in clinical prescreening (prior to genotyping) of individuals suspected for LQTS. Discriminating gene-specific syndromes such as the LQT1 vs. LQT2 is of clinical importance because the prognosis and management might differ depending on findings.[1,3,7–12] In this case, the QT/QTc prolongation is not a useful marker because the QT interval is similarly prolonged in the 2 LQTS groups.

The analysis of the T-wave morphology from computerized ECG has been considered as a complementary alternative to QT prolongation.[13–22] The discrimination between the various forms of the congenital LQTS has been investigated in some of these studies emphasizing the presence of a phenotypic expression of LQTS mutation on the surface ECGs. Our recent work showed that T-wave morphology

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was useful for discriminating between LQT2 carriers and noncarriers with near-normal QT interval duration,[13] enhancing its role in LQTS diagnostics.

Most of the studies investigating the role of T-wave morphology as a phenotypic expression of specific mutation in congenital LQTS are limited to short standard 12-lead ECGs in which repolarization stability is difficult to assess. In this study, we designed an in-depth analysis of T-wave morphology in genotyped LQT1 and LQT2 carriers and healthy controls in whom digital 24-hour Holter ECGs have been acquired using the same recording technology. We adopted a method controlling for the effect of heart rate (HR) on the repolarization interval (the so-called RR bin method[23]), and we aimed to identify the most comprehensive set of quantitative parameters of the T-wave and T-loop morphology to document the presence of phenotypic expression of these 2 different mutations of the LQTS.

Methods

Study population

The study population consisted of 49 LQT1 and 25 LQT2 carriers from 26 LQT1 families and 19 LQT2 families in whom 12-lead digital ECG Holter ECGs were recorded. The KCNH2 and KvLQT1 mutations were identified using standard genetic tests.[3] Thirty-eight unrelated healthy subjects were included and used as a reference group.

ECG recordings

Twenty-four-hour 12-lead Holter ECGs were acquired using the H12 recorders from Mortara Instrument (Mortara Instrument, Milwaukee, Wisconsin). This equipment provides digital ECG signal at a sampling frequency of 180 Hz and with 12-bit amplitude resolution (6.25 μV). Eight true leads were recorded, and the remaining 4 leads (augmented limb leads aVR, aVL, aVF, and lead III) were computed.

Measurement technique

All measurements were based on representative median beats from 10 consecutive cardiac cycles throughout entire 24-hour Holter recording. Only beats with stable HR were taken into account. The HR stability assessment was based on the computation of the average HR within the 10 beats. This set of beats was accepted if all beats had HR between 90% and 110% of the average HR.

We investigated electrocardiographic and vectorcardiographic parameters to better define the abnormalities characterizing LQT1 and LQT2 carriers. To exclude circadian rhythm influence, we focused our analysis on the diurnal period.

Using our own developed software for Comprehensive Analysis of the Repolarization Signal (COMPAS),[13,24–26] we measured classical repolarization ECG measurements such as the QT interval, Q to Tpeak interval (QTpeak), Tpeak to Tend interval (TpTe), and the magnitude of the T-wave (Tmag) from lead II and lead V5. The end of the T-wave for the calculation of the QT interval is based on the maximum slope method, whereas the maximum of the T-wave, for the computation of T-wave magnitude and QTpeak, is defined as the apex of the parabola that best fits the T-wave.

The vectorcardiographic measurements were based on the principal components analysis (PCA) of the repolarization segment defined between the J point and the point located 220 ms before the next R peak to ensure that the analysis encompasses all components of the ventricular repolarization. More details about this method can be found elsewhere.[27,28] PCA, derived from 8 original leads, has been used previously for quantifying ventricular repolarization.[29–31] PCA measurements were obtained from the COMPAS PCA analysis package, which offers standard PCA parameters: complexity of repolarization (λ_2/λ_1),[29] T-loop planarity (λ_3),[32] and other T-wave morphology parameters such as the right (αR) and left (αL) slopes of the T-wave, computed on vectorcardiographic leads (VCG).

In addition, we investigated repolarization modeling technique recently described by Kanters et al.[14,18] for the discrimination between LQT1 and LQT2 and healthy subjects. This method is based on the modeling of the repolarization integral (RI) of the T-wave and the quantification of overall T-wave morphology. We implemented this technique to have a method of reference; however, we applied this method to the vectorcardiographic leads to compare the investigated techniques when based on the same initial signal.

HR-controlled analysis

The role of HR on the repolarization measurements is fundamental regardless of the type of measurements one can consider. In the discrimination between LQT1 and LQT2 carriers and noncarriers, the effect of HR cannot be neglected.[33] Because we had access to 24-hour Holter ECGs, we could compare QT interval values between the 2 populations at a similar HR. The technique called RR bin analysis[23,34] allows for controlling the effect of HR on repolarization measurements. It consists of a selective technique in which median cardiac beats are gathered when they are in a specified limited HR range; repolarization measurements are computed on these beats, and the results are averaged. We analyzed HR ranges from RR = 600 to 1,300 ms by steps of 25 ms. Initially, we focused on investigating the limited HR range in which the number of subjects was maximal for the 3 groups. This HR range was found to be between 75.0 and 77.5 beats/min, corresponding to an RR interval from 775 to 800 ms. On this limited HR range dataset, we designed a model for predicting genotype based on standard QT and RR, then adding scalar ECG parameters, and finally testing vectorcardiographic parameters. More detailed information is presented in the Statistical Analysis section.

Model validation in a wider HR range

Subsequently, we evaluated the diagnostic performance of our predictive models, developed on the limited HR range (75.0 to 77.5 beats/min), while using the full range of HR intervals recorded by Holter monitors to provide validation

Table 1 Clinical characteristics and standard electrocardiographic parameters in LQT1 and LQT2 patients and healthy individuals

	Healthy	LQT1	LQT2
N (female)	38 (29%)	49 (71%)*	25 (76%)*
Age (y)	27.5 ± 8.1	34.3 ± 10.2*	35.5 ± 9.4*
Beta-blockers (%)	0	63	44
RR (ms)	767 ± 74	849 ± 110*	837 ± 134
QT (ms)	360 ± 20	450 ± 38*	466 ± 70*
QTc F (ms)	394 ± 16	478 ± 29*	494 ± 49*
QTc B (ms)	413 ± 17	493 ± 29*	510 ± 41*

Average values and standard deviations for the overall diurnal period. Measurements are from lead V5.
QTc B = heart rate-corrected QT using the Bazett formula; QTc F = QTc corrected using the Fridericia formula.
*P <.05 in comparison to healthy controls.

of our models. We tested the developed models on data from 3 prespecified HR ranges: bradycardia defined as HR < 60 beats/min (RR > 1,000 ms), normal HR defined as 60 ≤ HR < 100 beats/min (600 < RR ≤ 1,000 ms), and tachycardia defined as HR ≥ 100 beats/min (RR ≤ 600 ms).

Statistical analysis

The ECG and VCG parameters were analyzed using multivariate analysis involving stepwise discriminant analysis (DA),[35] using SAS statistical software (SAS Institute Inc., Cary, North Carolina). We used the DA to design discriminant models and identify the most discriminating parameters in the subset of factors we have selected. We used the DA to discriminate among the 3 groups: LQT1 patients, LQT2 patients, and normal subjects. Averaged values of parameters were compared using a nonparametric test (Kruskal-Wallis). A P value <.05 was considered statistically significant. We used a statistical strategy in which a referential model based on classic ECG parameters (RR, QT, QTpeak, and TpTe intervals and Tmag from lead II and V5) was first implemented, and then it was compared with a second model including classic vectorcardiographic parameters (λ_2/λ_1, λ_3, αR, and αL) quantifying T-wave and T-loop morphology and parameters modeling the T-wave. The comparison between different discriminant models is based on the proportion of subjects correctly classified.

Results

Characteristics of the study population

The clinical characteristics of the study population and the values from the 12-lead ECG parameters from the overall diurnal period for the 3 groups are summarized in Table 1. The average ages were 34 ± 10 years for LQT1 carriers, 36 ± 9 years for LQT2 carriers, and 28 ± 8 years for healthy controls; healthy controls were younger than LQTS subjects. Average RR intervals were similar between LQT1 (849 ± 110 ms) and LQT2 (837 ± 134 ms, P = 0.9) carriers and significantly lower in the healthy controls (767 ± 74 ms, P = 0.02 and 0.06 between healthy and LQT1 carriers and between healthy and LQT2 carriers, respectively). Thirty-one LQT1 and 11 LQT2 carriers were on beta-blockers the day their Holter ECG was recorded.

Repolarization in LQT1 and LQT2 carriers: Univariate analysis

Table 2 provides the results from all repolarization measurements for the 3 study groups and for selected HR range from 75.0 to 77.5 beats/min. All T-wave morphology and repolarization duration parameters were significantly different between healthy subjects and LQTS patients. Almost all repolarization parameters (repolarization morphology in

Table 2 Computerized electrocardiographic parameters for specific heart rate range (75.0 to 77.5 beats/min)

	Healthy	LQT1	LQT2
N	37	48	23
RR (ms)	788 ± 2	788 ± 3	788 ± 3
QT (ms)	363 ± 16	442 ± 28*	451 ± 43
QTpeak (ms)	286 ± 15	357 ± 26*	342 ± 41*
TpTe (ms)	77 ± 8	84 ± 11*	109 ± 26*,†
Tmag (mV)	0.39 ± 0.15	0.33 ± 0.14	0.11 ± 0.15*†
λ_2/λ_1	0.15 ± 0.06	0.22 ± 0.10*	0.36 ± 0.17*†
λ_3 (mV)	0.040 ± 0.015	0.046 ± 0.020	0.082 ± 0.036*†
αL on VCG (μV/ms)	11.6 ± 3.9	8.0 ± 3.0*	3.6 ± 1.7*†
αR on VCG (μV/ms)	−17.6 ± 6.4	−12.7 ± 5.1*	−4.3 ± 2.6*†
Hill Vmax (mV s)	0.17 ± 0.05	0.16 ± 0.07	0.10 ± 0.05*†
Hill n	3.8 ± 0.7	5.3 ± 2.9*	4.6 ± 3.8†
Hill Km (s)	0.16 ± 0.02	0.24 ± 0.03*	0.24 ± 0.06*

Average values and standard deviations for a limited heart rate range. Kruskal-Wallis statistical nonparametric test.
*P <.05 between LQT1 or LQT2 and healthy controls.
†P <.05 between LQT1 and LQT2.

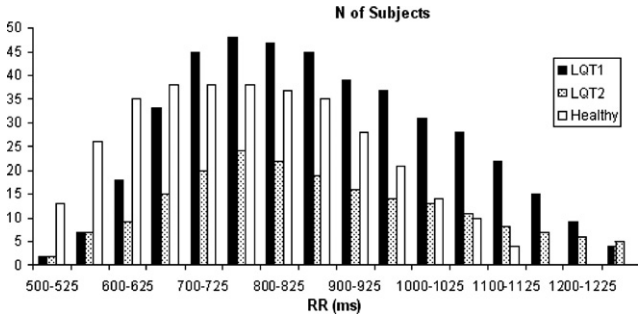

Figure 1 Distribution of number of individuals with at least 30 cardiac beats in a selected heart rate range.

particular) but QT intervals were significantly different between LQT1 and LQT2 carriers.

Figure 1 shows the distribution of the number of individuals by RR bins for the 3 groups (for clarity, every 100-ms bins are shown). The distribution of individuals for most studied HR ranges was similar among the groups. Only a low number of individual presented RR bins at low or very high HRs (RR $<$ 625 ms and RR $>$ 1100 ms).

In Figure 2, the absolute QT values (in lead V5) are presented across a wide spectrum of HR ranges for the 3 groups. For RR $<$ 1,000 ms (including fast HR), QT interval duration for the 2 LQTS groups was similar (443 $\pm$ 36 ms for LQT1 and 456 $\pm$ 60 ms for LQT2, $P = 0.40$), whereas for RR $\geq$ 1,025 ms, LQT2 carriers had longer QT interval durations than LQT1 patients (529 $\pm$ 63 ms vs. 492 $\pm$ 30 ms, respectively; $P = .05$), revealing a more pronounced QT prolongation during bradycardia in LQT2 carriers. As expected, QT measurements for healthy subjects were significantly shorter than LQTS carriers for all HR ranges ($P \leq .001$).

As previously described, LQT2 carriers usually present a low amplitude (magnitude) of T-waves,[2,36] lower in comparison to LQT1 carriers and healthy controls (Table 2). In our study, these results are further confirmed by the different values of T-wave slopes. Right and left slopes of T-wave were significantly lower in LQT2 than LQT1 patients: 8.0 $\pm$ 3.0 μV/ms vs. 3.6 $\pm$ 1.7 μV/ms for left slope ($P < .001$) and -12.7 ± 5.1 μV/ms vs. -4.3 ± 2.6 μV/ms for right slope ($P < .001$).

Based on discriminant analysis, the interval from Q to T peak was the best parameter for discriminating between LQT1, LQT2, and healthy subjects, with the overall proportion of correctly identified individuals of 73% (specifically, 97% for healthy, 71% for LQT1, and 40% for LQT2 subjects). The right slope of the T-wave was the best vectorcardiographic parameter, with an overall proportion of correctly identified individuals equal to 69% (specifically, 70% in healthy, 56% in LQT1, and 91% in LQT2 subjects). Other vectorial parameters, such as T-loop roundness (λ_1/λ_2) and T-loop planarity (λ_3), were significantly higher in LQT2 than in LQT1 subjects, revealing a profound difference in the repolarization process affecting the overall orientation and electrical activity within the myocardium between the 2 genetic forms of LQTS.

Results for the repolarization integral modeling using the Hill equation are presented in Table 2 for the selected HR range (75.0 to 77.5 beats/min). Both n and Vmax, parameters characterizing amplitude and morphology of the T-wave, were found to be significantly lower in LQT2 than in LQT1 carriers ($P = .001$, $P = .018$ for Hill n and Hill Vmax, respectively, in the 75.0 to 77.5 beats/min HR range), but none were found to be different among the 3 groups.

Gender characteristics of the 2 mutations

We investigated the role of gender in the 3 study populations. These results are summarized in Table 3. As expected, several repolarization parameters were significantly different between male and female subjects in the healthy group. QT interval and other repolarization parameters were not significantly different between male and female subjects in LQT1 and LQT2 carriers.

Discrimination between LQT1 and LQT2 carriers in multivariate analysis

To develop discrimination model for differentiating LQT1 and LQT2 carriers, we designed a model based on standard parameters (QT and RR), then we added all the scalar ECG parameters, and finally we introduced the vectorcardiographic parameters. These 3 models were designed based on the repolarization measurements within the select HR range: 75.0 to 77.5 beats/min.

Baseline model

This model was used as a reference. It described the level of discriminant power obtained when using only QT and RR intervals. As expected, this model performed poorly, with a proportion of correctly identified of 67%.

Scalar model

The parameters included in the model were RR, QTpeak, TpTe, T-wave magnitude, and QT from leads II and V5. Using the best subset modeling, a model selected 2 parameters: QT and TpTe from lead V5. The model provided a good separation of the 3 groups, the proportion of correctly identified was 86% (specifically, in healthy subjects 100%,

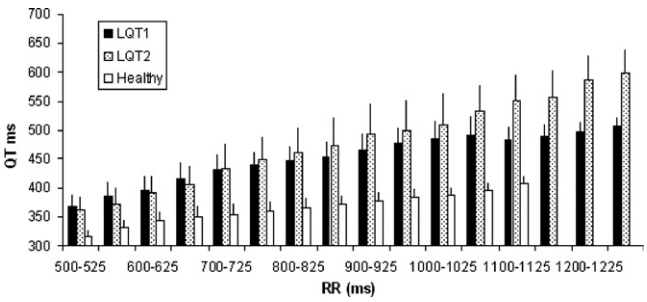

Figure 2 Average QT interval from lead V5 between LQT1 and LQT2 carriers and healthy individuals. Mean values and standard deviations among population are plotted for the whole spectrum of RR intervals.

Table 3 Computerized electrocardiogram parameters by genotype and gender for specific heart rate range (75.0 to 77.5 beats/min)

	Healthy (37)		LQT1 (48)		LQT2 (23)	
Gender	F (11)	M (26)	F (34)	M (14)	F (17)	M (6)
RR (ms)	788 ± 1	789 ± 1	787 ± 2	789 ± 3	787 ± 2	789 ± 2
QT (ms)	373 ± 15	358 ± 16*	443 ± 29	437 ± 28	456 ± 44	434 ± 41
QTpeak (ms)	295 ± 14	281 ± 13*	361 ± 28	349 ± 20	349 ± 35	322 ± 52
TpTe (ms)	78 ± 7	77 ± 9	82 ± 8	89 ± 15	108 ± 26	113 ± 28
T mag (mV)	0.39 ± 0.13	0.39 ± 0.17	0.31 ± 0.12	0.38 ± 0.18	0.12 ± 0.16	0.07 ± 0.13
αL on VCG (μV/ms)	9.5 ± 3.0	12.4 ± 3.9*	7.5 ± 2.4	9.3 ± 3.9	3.8 ± 1.8	3.1 ± 1.4
αR on VCG (μV/ms)	−14.1 ± 3.9	−19.1 ± 6.2*	−11.7 ± 4.2	−15.3 ± 6.2	−4.8 ± 2.8	−2.8 ± 1.3

Average values and standard deviations for a limited heart rate range.
*P <.05 between male and female patients.

in LQT1 subjects 85%, and in LQT2 subjects 65%). The addition of a third parameter, namely T-wave magnitude from lead V5, increased the discriminant power of the model to 92% (specifically, for healthy subjects 100%, for LQT1 subjects 90%, and for LQT2 subjects 83%).

Vectorial model

The design of the computerized model was based on the repolarization parameters from scalar model and λ_2/λ_1, λ_3, right and left slope of T-wave from vectorcardiographic leads and 3 parameters from T-wave modeling with the Hill equation. The best model relied on the following 2 variables: αR on vectorcardiographic leads and QTpeak from lead II, yielding overall discrimination equal to 90% (specifically proportion of correct identification was for healthy subjects 92%, for LQT1 subjects 88%, and for LQT2 subjects 91%).

Subsequent multivariate analysis showed that models containing only 2 variables, namely QT and TpTe from lead V5 or αR and QTpeak from lead II, could also discriminate the 3 populations with very high discriminant power (approximately 90%). Both scalar and vectorial models showed similar performances, although the latter contains only 2 variables.

Assessment of the effect of HR on the results of the predictive models

The results for the models in the 3 HR intervals are presented in Table 4. For high HR (HR ≥ 100 beats/min), all models have lower overall discriminant performance (45% to 53%) than for HRs < 100 beats/min (71% to 76%).

In Figure 3, we report the results for the 3 HR ranges for QTc and right slope of T-wave (αR) are presented. QTc (shown as a reference) is significantly different between the LQT1 and LQT2 carriers only during bradycardia (P = .004), whereas αR is significantly different among the 3 groups for all 3 HR ranges (P value for comparison between LQT1 and LQT2: <.01 for all comparisons).

Discussion

Our results showed that it is possible, with very good accuracy, to discriminate LQTS patients by genotype using automatic methods quantifying the morphology of the T-wave from both scalar ECG and vectorcardiographic signals. In particular, LQT2 patients are characterized by lower values of T-wave magnitude and different slopes of T waves. The TpTe interval was significantly longer in LQT2 than in LQT1 patients and healthy subjects.

Changes in T-wave morphology in patients with the LQTS have been observed and quantified in prior studies.[4,14,15,18,37,38] The first assessments of abnormal T-wave morphologies in congenital LQTS patients were reported in the mid 1990s. Malfatto et al.[15] hypothesized that morphologic analysis of the T-wave may contribute to the diagnosis of the congenital LQTS. In that study, the T-waves were coded from 1 to 5 using morphologic criteria: score 1 was given to ECGs with normal T-wave shapes, and scores 4 to 5 were given to abnormal ones (score 5 corresponded to

Table 4 Percentage of individuals correctly classified for the 3 developed models: Effect of heart rate ranges

		HR < 60 beats/min				60 ≤ HR < 100 beats/min				HR ≥ 100 beats/min			
Model type		All	H	LQT1	LQT2	All	H	LQT1	LQT2	All	H	LQT1	LQT2
N	Parameters	61	14	35	12	112	38	49	25	55	35	12	8
Scalar	QT, TpTe V5	71	50	86	75	82	89	86	60	45	86	17	38
Scalar	QT, TpTe, Tmag V5	71	36	91	83	90	89	90	92	53	86	17	75
Vectorial	αR on vect. lead + QTpeak LII	76	50	100	67	87	89	84	92	48	63	17	88

Values of percentage of subjects correctly identified (H, LQT1, LQT2 respectively) and overall (all) for 3 HR ranges. Number of individuals in each HR interval is also shown.
HR = heart rate; vect. = vectorcardiographic.

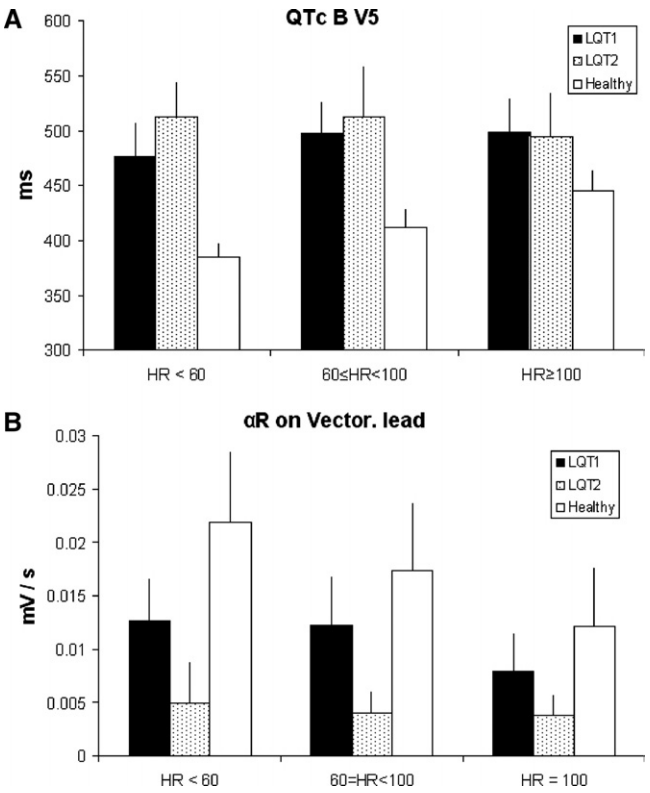

Figure 3 **A:** Average QTc interval, from lead V5 between LQT1 and LQT2 carriers and healthy subjects for 3 heart rate (HR) ranges. Bradycardia (HR $<$ 60 bpm), normal HR range (60 bpm $\leq$ HR $<$ 100 bpm), and tachycardia (HR $\geq$ 100 bpm). Based on nonparametric tests. QTc was significantly longer in both LQT1 and LQT2 when compared to healthy individuals for all HRs. For HR $<$ 60 bpm, QTc was longer in LQT2 than LQT1 patients. **B:** Comparison of αR average values measured from vectorcardiographic lead between LQT1 and LQT2 carriers and healthy subjects for 3 HR ranges. For all HRs, αR was larger in healthy individuals when compared to both LQT1 and LQT2 and it was significantly higher in LQT1 than LQT2.

notched T-waves). The findings revealed that symptomatic LQTS patients were presenting a significantly higher percentage of notched T-waves than asymptomatic patients (81% vs. 19%, respectively). The same year, Lehmann et al.[37] compared the prevalence of T-wave humps (double-peaked T-waves: T2) in 254 members of 13 (diagnosed) LQTS families to 2,900 healthy control subjects. He considered 3 groups: prolonged (QTc $>$ 470 ms), borderline (420 $\geq$ QTc $\geq$ 460 ms), and normal QTc (QTc $\leq$ 410 ms). Among the overall group, T2 waves were found in 27% of cases, 2% of spouses, and 1.5% of healthy controls. In the group of patients with a prolonged QT interval, T2 waves were present in 53% of individuals, but only in 16% of those with borderline QTc. In healthy volunteers, these numbers were $<$1%. Subsequently, Moss et al.[4] demonstrated the presence of phenotype–genotype correlations between 3 genetically defined LQTS patient groups and specific T-wave morphologies. These observations were shown using HR-corrected measurements of repolarization including QTc onset (beginning of QRS to beginning of T-wave), corrected T duration, and T-wave amplitude, among others. The HR-corrected QT onset was unusually prolonged in individuals with mutations involving the LQT3 mutation: 341 $\pm$ 42 ms, 290 $\pm$ 56 ms (LQT2), and 243 $\pm$ 73 ms (LQT1) (P $<$.001); T amplitude was generally small in LQT2: 0.36 $\pm$ 0.14 mV, 0.13 $\pm$ .07 mV (LQT2), and 0.37 $\pm$ 0.17 mV (LQT1) (P $<$.001); and T duration was particularly long in lead II of LQT1 patients: 187 $\pm$ 33 ms, 191 $\pm$ 51 ms (LQT2), and 262 $\pm$ 65 ms (LQT1) (P $<$.001). Thereafter, a more complex technique quantifying T-wave morphology was developed by Padrini et al.[17] The morphologic indices were based on mathematical functions decomposing the T-wave shape. Although the sample size was small, this method separated symptomatic (N = 7) from asymptomatic (N = 7) LQTS patients. It was also successful in discriminating symptomatic patients from age-matched healthy subjects (N = 14). In this study, the LQTS patients were not genotyped. The QTc interval and the QTc dispersion were also investigated, and both parameters failed to correctly separate the symptomatic from the asymptomatic patients.

The present study provided new insight into the independence between QT prolongation and abnormal repolarization morphologies. Most previous studies investigating T-wave morphologies in LQTS patients did not rely on genotyped data or were limited to small populations of genotyped individuals. However, these studies support the potential value of T-wave morphology in the identification of patients with congenital LQTS.

It is important to emphasize that in comparison with the majority of prior work on the genotype–phenotype relationship, we utilized an entirely computerized approach. We based our discrimination methods on computerized Holter technology that is more resource-demanding than the standard 12-lead recordings, but it provides a large set of beats in a large range of HRs. The access to numerous beats allows us to control the repolarization measurements for their HR dependency[23] and thus avoid using potentially misleading HR correction formulae.

Our results from the method based on the modeling of the T-wave shape using the Hill equation were different from the ones reported by Kanters et al.[14,18] In the univariate analysis, the coefficients of this model were significantly different between the 2 genotypes, but no parameter was significantly different for all 3 groups. In addition, they did not perform as well as scalar measurements when using multivariate analysis. The reason for these differences may be explained by methodological differences between our study and Kanters' work. We did not use 12-lead standard ECGs but Holter recordings, and we analyzed the vectorcardiographic lead instead of lead V2.

Our study showed that the use of simple measurements such as the amplitude of the T-wave, the length of specific intervals such as TpTe, and QT offset provide excellent discrimination among LQT1 and LQT2 carriers and non-carriers. It is interesting to note (Table 4) that the 2 best models, the one containing only scalar parameters and the

one containing the right slope of T-wave, have very similar discriminant power.

We believe that these differences between T-wave morphologies of these 2 LQTS groups are linked to abnormal kinetics of the delayed rectifier potassium currents of the myocardium cells. However, there is no demonstration of the relationship between the presence of inhibition of the potassium currents and morphologic changes on the surface ECGs. The complexity of such a relationship remains a challenge of modern electrocardiology; it relates fully to the classic unresolved inverse problem of electrocardiography. Nevertheless, one may hypothesize that these differences in the morphology of the action potential between the 2 types of mutation are reflected in the surface ECG by different signal characteristics. It is the efflux of potassium ions that produces the T-wave of the electrocardiogram. Agents that delay or prevent this movement of potassium will modify the appearance of the T-wave. Because I_{Kr} and I_{Ks} are currents moving potassium ions in the cardiac cells during the different phases of the action potential, one may expect to see changes on the surface ECG recordings in the different parts of the T-wave on the surface ECG.

Genotype prediction by ECG is useful for stratifying molecular genetic studies. With several disease genes and a few hundred LQTS mutations already identified, it is very costly and time consuming to screen all known genes and mutational sites, limiting the application of genetic studies. With a typical ECG pattern, the suspected gene can be the initial target for testing, with a higher likelihood of rapid identification of the mutation. Such a strategy will significantly reduce time and costs, allowing more families to be genotyped and enhancing genotype–phenotype correlation studies. Also, it might reveal the presence of an untested or novel mutation. Furthermore, if therapeutic interventions based on specific genotype are shown to be effective, phenotype identification by ECG could be helpful for monitoring effects of therapeutic measures.

The main limitation of the study resides in the lack of validation of the models on a distinct set of data. Such validation will depend on the availability of Holter recordings in a large population of patients with genotyped data.

There was a difference in the number of patients on beta-blockers between the 2 LQTS groups. We analyzed the influence of beta-blockers on the discrimination between LQT1 and LQT2 patients. We computed binary logistic regression using both scalar and vectorial models; the addition of the beta-blockers information did not change the discrimination models. Moreover, beta-blockers did not modify T-wave morphology differently in the 2 genotypes. These analyses revealed that the beta-blocker did not affect the performance of the predictive models.

Finally, the distribution of gender was different in the group of healthy individuals in comparison with the groups of patients with congenital LQTS. The role of gender is known to affect repolarization morphology.[39] We investigated the role of gender in the 3 study populations. As expected, several repolarization parameters were significantly different between genders in the healthy group. Such gender differences were not found in the ECG signals of LQTS carriers, indicating the profound influence of causative mutations overwhelming gender-specific differences in the repolarization process. Because of the small size of our study groups we could not developed a gender-based model, but we included gender in our multivariate models as potential confounding factor, and gender did not contribute significantly to any models and was not selected as one of the 3 best parameters in our DA models.

In conclusion, we showed that automatic algorithms quantifying T-wave morphology applied to digital Holter recordings are very effective in discriminating LQT1 and LQT2 carriers using simple parameters to discriminate these 2 types of mutations. T-wave morphology is much more informative than QT duration when discriminating the 2 LQTS genotypes.

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