

Repolarization morphology in adult LQT2 carriers with borderline prolonged QTc interval

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BACKGROUND At least 50% of LQT2 carriers have borderline QTc (0.42–0.47 s), and they present a diagnostic difficulty to clinicians evaluating patients suspected of having long QT syndrome (LQTS).

OBJECTIVES Because QTc in this borderline range is nondiagnostic, the purpose of this study was to investigate whether analysis of phenotypic features of T-wave morphology could help identify LQT2 carriers with normal or near-normal QTc-interval duration.

METHODS Standard 12-lead ECGs recorded without beta-blockers from LQT2 carriers ($n = 90$, 33 ± 14 years, 61% female) and noncarriers ($n = 69$, 38 ± 17 years, 58% female) were digitized. The following parameters were automatically measured: RR interval, QT/QTc, QT apex, T-wave amplitude, ascending (α_L) and descending slopes (α_R) of the T wave, and T-wave symmetry. We used a linear logistic regression model to identify the most relevant parameters for separating LQT2 carriers from noncarriers, within

the overall population and among patients without overt QTc prolongation ($390 \leq \text{QTc} \leq 470$).

RESULTS Logistic regression selected three parameters: QT, RR interval, and α_L in all models. In the overall population, the model provided 92.7% sensitivity and 90.0% specificity. In the group of patients without beta-blockers and near-normal QTc interval, 92.0% sensitivity ($n = 46$) and 81.4% specificity ($n = 49$) were achieved by the model including α_L .

CONCLUSION Abnormal T-wave morphology is a phenotypic expression of LQT2, and its quantification could be used to identify patients with suspected LQTS who do not have overt QTc prolongation ($\text{QTc} > 470$).

KEYWORDS Long QT syndrome; KCNH2 mutation; T-wave morphology; QT interval

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Introduction

The long QT syndrome (LQTS) is an inherited disorder associated with prolonged ventricular repolarization and a propensity to torsades de pointes, syncope, and sudden arrhythmic death.¹ Early diagnosis of LQTS is critical because various prophylactic therapies can effectively reduce the risk for life-threatening arrhythmias; such therapies include surgical denervation,² beta-blocker medications,^{3,4} cardiac pacemakers,⁵ and implantable cardioverter-defibrillators.⁶ Diagnostic methods rely on the patient's cardiac history, heart rate, and prolongation of the heart-rate corrected QT interval (QTc).⁷ Nevertheless, QTc prolongation is not a perfect surrogate marker for identifying patients affected by LQTS. A substantial number of LQTS patients do not have QTc prolongation. For these patients, genotyping can differentiate between carriers and noncarriers of the mutant gene, but the test is expensive and results may not be available for a considerable time.

Among patients who have long QT syndrome with KCNH2 mutation (LQT2), 11% have normal QTc (≤ 0.44 s)

and at least half have $\text{QTc} \leq 0.47$ s.^{8,9} Therefore, ECG diagnostic techniques better than QT prolongation measurements are needed to identify subjects suspected of having LQTS. Several methods have been used to replace or complement the hereditary or acquired QT prolongation risk factor with other noninvasive markers. These techniques were based on static and dynamic aspects of repolarization: prolongation of the T-peak to T-end interval (TpTe) and QT dispersion,¹⁰ abnormal T-wave morphology,^{11–13} RT hysteresis from exercise testing,¹⁴ microvolt-level T-wave alternans,^{15,16} and repolarization variability.^{17,18} In this study, we investigated a large cohort of genotyped LQT2 carriers and noncarriers from the International LQTS Registry⁷ to determine the role of T-wave morphology in identifying LQT2 patients.

We hypothesized that a phenotypic expression of the KCNH2 mutation on the surface ECG provides complementary information to QT-interval prolongation and may help identify LQT2 patients. ECG analysis of additional readily available parameters might assist physicians in bedside clinical diagnosis when LQTS is suspected.

Methods

Study population

The study population consisted of subjects with genetically tested KCNH2 mutation. This group encompasses 52 families from the International LQTS Registry. Family members of genotyped LQTS probands were tested for proband

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identified mutation and categorized as carriers or noncarriers. Subjects younger than 17 years were not included in the analysis because T-wave morphology is age dependent, and repolarization changes are frequently observed before adulthood.¹⁹ KCNH2 mutations were identified in each subject using standard genetic tests. All subjects provided informed consent for the genetic and clinical studies.

A total of 1,583 LQT2 paper tracings were available from the International LQTS Registry. Of this total, 712 were of sufficiently high quality to be scanned and digitized (46%). Of the 712 tracings, repolarization measurements were possible for 335 tracings (based on signal quality and lead availability). We arbitrarily selected the first (oldest) tracing from each individual of the LQT2 families (209 tracings), including 104 tracings from genotyped carriers and 105 ECGs from genotyped noncarriers of the KCNH2 mutation. Because β -blockers affect heart rate, slightly prolong the QTc interval (~ 10 ms),²⁰ and may change the T-wave morphology, patients who were taking β -blockers were excluded from the study. We defined a group (excluding those taking beta-blockers) consisting of 69 patients who carried the LQT2 mutation and 90 noncarriers from LQT2 family members.

Based on the distribution of QTc values in the study population (Figure 1), we focused our analysis on a range of QTc between 390 and 470 ms, which represented the overlapping portion of the distribution of QTc intervals between carrier and noncarrier groups. From this subgroup, 95 patients (46 carriers and 49 noncarrier LQT2 patients) were included.

ECG processing

Standard 12-lead ECGs were acquired during 34-year period between May 1968 and September 2002.

Before ECG tracings were processed for digitalization, they were visually reviewed in order to eliminate traces that (1) did not have a grid, which is required for the digitalization process; (2) were strongly faded; and (3) had signal

distortion, which can occur when tracings have been photocopied multiple times. These three requirements defined the scanning criteria.

Acceptable tracings were scanned using a scanner with 600 DPI resolution (Epson Expression 1680 Professional, Epson Inc., Long Beach, CA, USA) into bitmap files. The resulting digital images were converted to digital ECG signals using the commercial software ECGScan (ECGScan, AMPS LLC, New York, NY, USA).²¹ Lead II generally had the largest T-wave amplitude and was selected for digitization and measurement. The digitalization process provided a signal with 500-Hz sampling frequency and 16-bit resolution.

ECG measurements

The commercial software COMPAS (University of Rochester Medical Center, Rochester, NY, USA) was used for repolarization measurements.²² The software provides a set of classic and morphologic measurements of repolarization intervals (Figure 2):

- RR intervals and QT intervals are based on the maximum slope method (QT) and Bazett-corrected QT interval (QTc).
- QT apex intervals are measured based on a technique fitting a parabola to the T wave.
- Maximum ascending slope (α_L) and maximum descending slope (α_{Rl}) of the T wave are measured and expressed in $\mu V/2 \cdot ms$. They represent the maximum velocity of the ascending and descending limbs of the T wave.
- Symmetry of the T wave is computed as the absolute value of the ratio of T-wave slopes ($|\alpha_L/\alpha_{Rl}|$).
- T-peak to T-end interval (TpTe) is defined as QT offset minus QT apex interval durations.
- Amplitude of the T wave in mV.

No U wave was included in the study. If a bifid T wave was present, the first ascending and last descending slopes

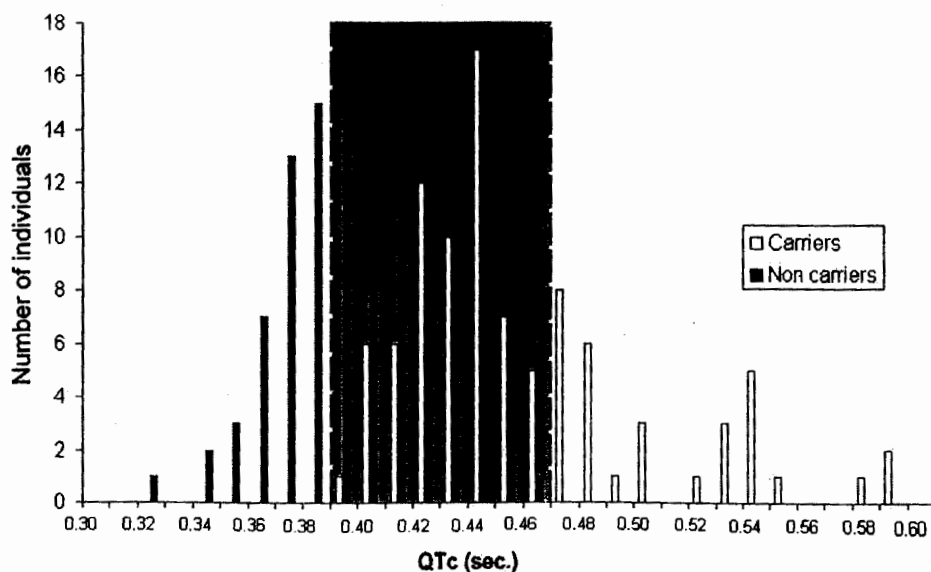


Figure 1 Distribution of QTc values measured from lead II in 90 LQT2 carriers and 69 noncarriers. Gray area marks the QTc interval defining the subpopulation of individuals with near-normal QTc-interval duration.

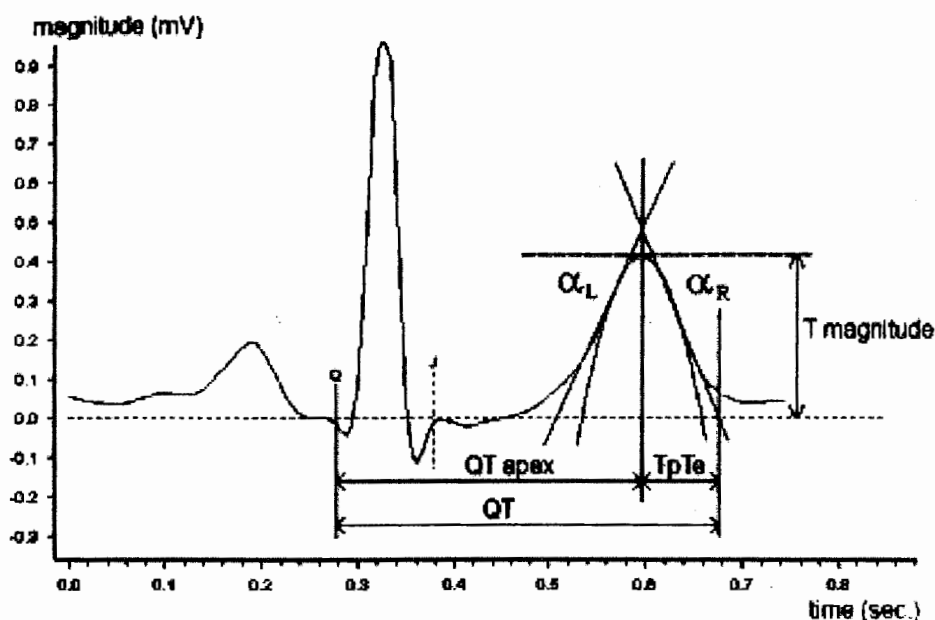


Figure 2 The six parameters used for quantification of T-wave morphology in lead II. α_L , α_R , amplitude of T wave, and QT apex, QT offset, and TpTe intervals were measured for two to three beats, and average values are reported for each individual.

were measured. The Bazett formula was used to correct the QT intervals for heart rate (QTc).

All automatic measurements were visually reviewed and manually corrected if needed.

Statistical analysis

ECG quantifiers were analyzed in multivariate fashion. Multivariate analysis involved a stepwise logistic regression models for detecting variables that discriminate between LQT2 carriers and noncarriers. Sensitivity and specificity were used to assess the efficacy of the classification techniques. In addition, the areas under the receiver operating characteristic (ROC) curves were used to compare the various techniques for discriminating carrier and noncarrier patients. Correlation analysis was based on the Pearson product moment correlation.

Results

Population characteristics

Comparison of clinical characteristics of LQT2 carriers and noncarriers revealed that carriers of the LQT2 mutation had

a significantly higher number of cardiac events and a significant lower heart rate (Table 1). None of the patients in our study population had an implantable cardioverter-defibrillator, pacemaker, or sympathectomy at the time of ECG recordings.

In the subjects not receiving beta-blocker therapy, the percentage of females in the carrier and noncarrier groups was similar (61.1% vs 58.0%, respectively). Among individuals with QTc duration between 390 and 470 ms, females predominated in the noncarrier group.

In the overall population of LQT2 carrier and noncarrier individuals, information about mutation location was not available for 17 individuals. In patients carrying the KCNH2 mutation, 27 had a mutation located in the C-terminus of the HERG, 14 in the N-terminus, 5 in the pore region, 3 in the S1-S6 region, 9 in the cyclic nucleotide binding domain, and 1 inside the nucleotide binding domain.

ECG quantifiers in LQT2 patients

Table 2 shows comparisons of ECG parameters between LQT2 carriers and noncarriers for the entire group studied

Table 1 Clinical characteristics of the study populations

	Group			
	No β -blocker therapy		No β -blocker therapy (390 \leq QTc \leq 470)	
	Noncarrier	Carrier	Noncarrier	Carrier
N	90	69	46	49
Female (%)	61.1	58.0	78.3	59.2*
Age (yr)	32.9 \pm 14.4	37.8 \pm 17.0	32.4 \pm 13.8	36.7 \pm 16.6
Prior cardiac events	5.6	31.9*	6.5	26.5*
Heart rate (bpm)	71.7 \pm 13.8	67.0 \pm 12.6*	76.2 \pm 13.1	66.7 \pm 12.6†

* $P \leq .05$ and † $P \leq .01$ when comparing carrier group to noncarrier group.

Table 2 Descriptive statistics for ECG quantifiers

	Group			
	No β -blocker therapy		No β -blocker therapy (390 \leq QTc \leq 470)	
	Noncarrier	Carrier	Noncarrier	Carrier
N	90	69	46	49
T magnitude (mV)	0.25 \pm 0.13	0.14 \pm 0.08*	0.24 \pm 0.12	0.16 \pm 0.07*
QT apex (ms)	289.9 \pm 25.9	346.9 \pm 38.9*	293.9 \pm 24.5	336.2 \pm 33.6*
QT (ms)	364.6 \pm 29.7	445.8 \pm 50.2*	368.9 \pm 28.4	428.1 \pm 35.5*
QTc (ms)	394.6 \pm 27.4	455.6 \pm 39.5*	412.6 \pm 17.7	435.4 \pm 18.6*
RR (ms)	867.4 \pm 166.7	964.5 \pm 151.8*	807.1 \pm 136.2	972.7 \pm 149.1*
α_R (μ V/2 \cdot ms)	-19 \pm 10	-8 \pm 6*	-17 \pm 9	-10 \pm 5*
α_L (μ V/2 \cdot ms)	13 \pm 6	6 \pm 3*	13 \pm 6	6 \pm 3*
TpTe (ms)	74.5 \pm 10.5	100.0 \pm 32.5*	74.7 \pm 9.9	93.0 \pm 25.8*
T symmetry	0.78 \pm 0.33	0.88 \pm 0.81	0.80 \pm 0.36	0.76 \pm 0.38

Bazett correction was used. QT was semi-automatically measured in lead II or in V₆ if lead II was not available. *P <0.01.

and for subjects with normal/borderline QTc. All parameters were significantly different between carriers and non-carriers (P <0.01), except for T-wave symmetry. In particular, significantly reduced T-wave magnitude and slope values (α_R and α_L) were observed in LQT2 carriers in comparison to noncarriers. These results are illustrated in Figure 3, which shows three ECG tracings from a noncarrier individual and two carrier patients. Figure 3 shows that T-wave morphology may be quite variable even when the QT-interval duration remains in the normal range (two lower tracings).

Significantly increased QT apex, QT offset, QTc, and TpTe intervals (P <.01) were present in those with vs those

without the LQT2 mutation. The QT interval is 22% longer in carrier individuals than in noncarriers, whereas TpTe interval is 33% longer in carrier individuals than in noncarriers. This observation reveals that TpTe is more prolonged than QTc apex in genotyped LQT2 patients relative to the values found in noncarrier individuals.

Discriminant power of repolarization indexes in LQT2 carrier patients

ROC curves were computed to obtain an assessment of individual discriminant power of each repolarization parameter. Table 3 lists the optimal values of sensitivity and specificity from classifying individuals in the group without

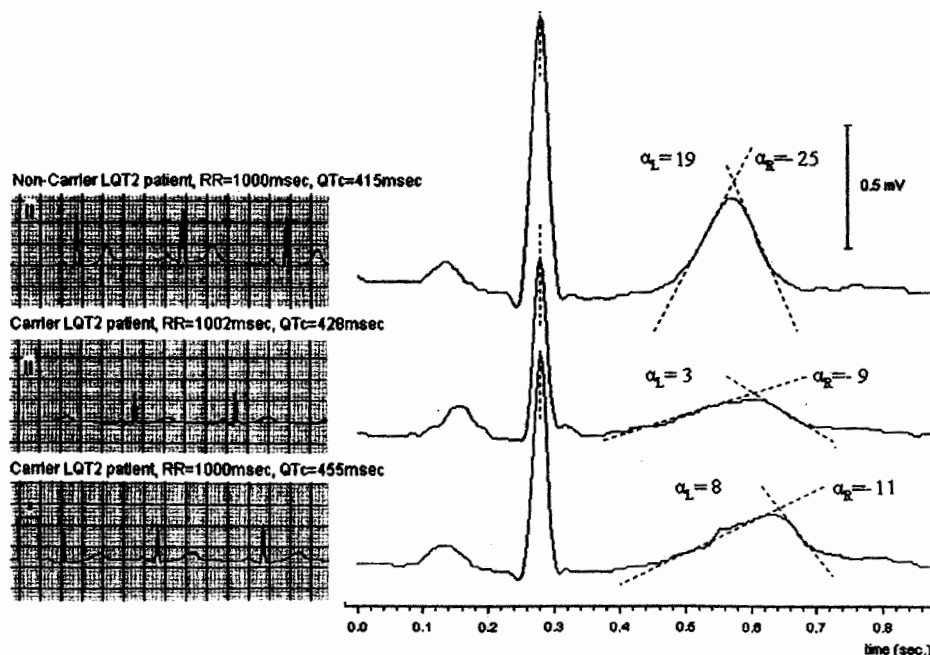


Figure 3 Examples of ECG tracings from a noncarrier (upper tracing) and two patients carrying the KCNH2 mutation (lower tracings). Heart rates were similar, and QTc was slightly increased in the second tracing (QTc = 428 ms) and more prolonged in the third tracing (QTc = 455 ms). Changes in the ascending slope of the right limb of the T waves are present in LQT2 carriers.

beta-blockers, with corresponding threshold values and ROC areas. In this near-normal QTc-interval duration group, uncorrected QT intervals (QT and QT apex) remain the most discriminant parameters. Heart rate, α_L , and TpTe intervals have similar estimated discriminant power, with an ROC area close to 0.80. T magnitude and α_R have the poorest performance.

Repolarization morphology is different between genders, with the instantaneous slope of the ST-T segment lower (flatter slope) in females than in males.²³ In our study population, a larger number of females was present in the noncarrier group (78.3% vs 59.2%, $P < 0.01$) than in the carrier group, which may create a bias in our analysis. Consequently, we included gender in all our logistic models, but it never contributed significantly to the models.

The parameters entered in the models were T-wave amplitude, α_L , α_R , T symmetry, RR, QT apex, and QTc. When using a forward selection model, QTc, α_L , and RR were systematically selected. The best model was $\log[\text{pr}/(1 - \text{pr})] = -44.0 + 0.083\text{QTc} - 0.013\text{RR} - 0.383\alpha_L$, where pr = event probability for a patient to be carrier, providing sensitivity of 89.8% and specificity of 86.9%. In addition, we investigated two "clinical models" based on parameters readily available from a standard 12-lead ECG, one including QTc only and a second relying on QTc and RR. Figure 4 shows the ROC curves for the three models. Adding RR and α_L to the model improved the classification specificity by 15% and sensitivity by 6.5% compared with the clinical model that included QTc.

When considering QT instead of QTc, QT, RR, and α_L were selected in the model, leading to sensitivity of 92% and specificity of 81.4%. The same model applied to the overall group led to an ROC area of 0.97 (sensitivity 92.7%, specificity 90.0%). The coefficients of the binary logistic regression were $\log(\text{pr}/[1 - \text{pr}]) = -27.7 + 0.095\text{QT} - 0.008\text{RR} - 0.304\alpha_L$.

QT/QTc prolongation and abnormal T-wave morphology

Correlations of α_L and α_R with RR values were group dependent. The parameter α_L was not significantly corre-

Table 3 Univariate discriminant power of ECG quantifiers for separating carrier from noncarrier individuals of LQT2 mutations with near-normal QT-interval duration

	Threshold*	Sensitivity (%)	Specificity (%)	ROC area
RR (ms)	>876	76	76	0.80
QTc (ms)	>421	78	76	0.82
T magnitude (mV)	<0.17	61	65	0.70
QT (ms)	>396	84	83	0.90
QT apex (ms)	>316	78	78	0.86
α_L ($\mu\text{V}/2 \cdot \text{ms}$)	<8	71	72	0.80
α_R ($\mu\text{V}/2 \cdot \text{ms}$)	<12	63	65	0.74
TpTe (ms)	>80	76	70	0.79

*Threshold is based on the optimal separation point based on the receiver operating characteristic (ROC) curve of the considered parameter.

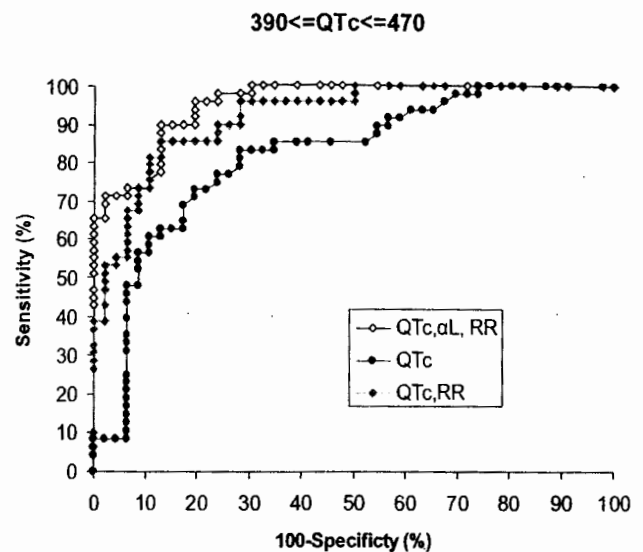


Figure 4 Receiver operating characteristic curves showing the efficacy of the statistical models developed for classification of genotyped carriers and noncarrier individuals when considering the group with near-normal QT-interval duration. Adding RR and α_L to the model improves the discriminate power of the model.

lated with RR in noncarrier subjects but was negatively correlated with previous RR in the carrier group ($r^2 = 5.6\%$, $P = 0.05$). The α_R correlation with RR was inverted between carrier and noncarrier individuals: $r^2 = 10.2\%$ ($P = 0.01$) in carriers vs $r^2 = 4.3\%$ (negative r ; $P = 0.05$) in noncarriers, a finding suggesting a disturbed repolarization process associated with the KCNH2 mutation.

Discussion

Among LQTS subjects with the KCNH2 mutation, a meaningful proportion do not have abnormal prolongation of the QT interval. In this study, we showed that the morphology of the T wave may be useful for identifying LQTS patients with borderline QT prolongation. Based on the analysis of only one lead (lead II), a logistic regression model based on three ECG parameters (RR, QT, and α_L) permitted correct classification in 88% of the 95 individuals in our study population with near-normal QT-interval duration ($390 \leq \text{QTc} \leq 470$ ms). The optimal model relies on QT, heart rate, and slope of the ascending arm of the T wave demonstrating that T-wave morphology contributes to improved discrimination between carriers and noncarriers. The relevance of morphologic parameters was conserved when only patients with near-normal QT-interval values were analyzed. Our results support the hypothesis of a phenotypic expression of the KCNH2 mutation on surface ECG that is useful for risk stratification of subjects with the congenital form of LQTS and may be useful as an ECG marker for patients with the acquired form of LQTS.

Phenotypic characterization of the surface ECG in LQT2 patients

Abnormalities of T-wave morphology have been qualitatively¹³ and quantitatively^{10,24,25} investigated over the past

decade. Most of this research emphasized the information contained in T-wave morphology. Studies have shown that T-wave notches are considered a marker of electrical instability, and their presence has been included in diagnostic criteria for the KCNH2 mutation.²⁴ Our study reveals another type of subtle abnormality involving T-wave morphology. A flattened T-wave shape with significant reduction of the slope of the ascending arm of the T wave (α_T) provided greater discrimination of carrier vs noncarrier LQT2 individuals than did the T-wave amplitude, TpTe interval, or slope of the descending arm of the T wave (α_R).

Moss et al¹³ found low-amplitude T waves in LQT2. Our study confirms their observation and provides a quantitative description of these morphologic abnormalities. The KCNH2 mutation has been associated with a reduction of the rapidly activating delayed rectifier potassium current I_{Kr} , but the associated underlying mechanisms leading to changes in T-wave morphology remain to be elucidated. The I_{Kr} ion current is mainly involved at the end of phase 2 and at the beginning of phase 3 of the action potential of the cardiac cells. Thus, finding a more pronounced phenotypic expression of the KCNH2 mutation before, rather than after, the peak of the T wave is consistent with the known physiology that reduction of the I_{Kr} current is present to a greater degree in the earlier than in the later phase of the repolarization process.

Yan and Antzelevitch²⁶ studied the effect of hypokalemia plus sotalol on transmural dispersion of repolarization and on T-wave morphology. They reported a prolonged low-amplitude T wave and interruption of the T-wave ascending limb when recorded in a wedge preparation.²⁶ The similarity of their findings with our results using standard ECG parameters from genotyped-positive LQT2 patients is noteworthy.

A more recent study investigated the occurrence of T-wave notches in a large cohort of LQT1, LQT2, and LQT3 patients.²⁷ That study found a higher incidence of T-wave notches in LQT2 families but no relevance for risk stratification in genotyped individuals. The prevalence of T-wave notches was higher for patients with QTc ≥ 500 ms than in patients with QTc < 500 ms, revealing an association between repolarization prolongation and the occurrence of T-wave notches. The morphologic changes we observed in our study were also associated with QT/QTc prolongation. QT/QTc duration remained the most significant parameter differentiating carriers from noncarriers, although its clinical usefulness was very limited in a subgroup of subjects with borderline QTc.

Restier et al²⁸ used three-dimensional digital techniques to show an ECG phenotype of LQT2 mutation combining repolarization amplitude and orientation differences between repolarization and depolarization phases. The method successfully separated genotyped LQT2 from normal subjects with a diagnostic accuracy of 96%. The high performance (without considering QTc interval) of this method encourages the use of morphologic features from all leads (either independently or through mathematical combina-

tion). Our study was limited to analysis of lead II, and a multilead analysis may be even more discriminatory.

Time location of repolarization abnormalities in LQT2

The repolarization abnormality identified in LQTS patients carrying the KCNH2 mutation corresponds to a delay of the ascending slope of the T wave. Neither the TpTe interval nor the QT apex interval was selected by the statistical model for increasing the ability of the model to discriminate carriers from noncarriers. Based on this observation, one might further hypothesize on the role of this specific portion of the T wave as a marker of the presence of I_{Kr} ion dysfunctions (delay of early phase 2 repolarization) and perhaps an increased vulnerability to cardiac arrhythmias. The number of patients in our study population with cardiac events was too small to provide reliable correlation between decreased α_R and a history of cardiac events. Nevertheless, one may note that it is during this very same short time interval of the T wave on surface ECG that an external chest wall blow triggers arrhythmic events (commotio cordis) as shown by Link.²⁹ Link reported the importance of timing in commotio cordis and revealed that the shocks occurring during an interval located between 10 and 30 ms before T peak were associated with the occurrence of ventricular tachycardia or fibrillation in an animal experiment.²⁹ In congenital LQTS, a recognized trigger of torsades de pointes is the occurrence of an R-on-T extrasystole or phase 2 early afterdepolarization. This triggering mechanism, documented by Yan et al in two animal models, has been shown using I_{Kr} inhibitory compounds (dl-sotalol and azimilide). In the acquired form of LQTS, some drugs (e.g., amiodarone) are associated with QT prolongation but very few cardiac events, whereas other drugs (e.g., terfenadine) slightly prolong the QT interval but has torsadogenic properties.²⁶ Consequently, one may speculate that a delay of the repolarization process that occurs specifically before the apex of the T wave could be a more powerful predictor of increased vulnerability to cardiac arrhythmias than QT prolongation itself. If the underlying arrhythmogenic mechanism remains to be elucidated, one may further speculate that increased transmural dispersion of repolarization might be reflected on the 12-lead ECG during this specific interval (prior to T apex) rather than during the TpTe interval.

Age-modulating factor

Adults with the LQT2 mutation who survive prepuberty have a higher risk for cardiac events than earlier in their life.³⁰ This age modulation of LQTS clinical outcome in LQT2 patients is noteworthy. Our method is limited to individuals older than 17 years, so the ECG abnormalities observed in our study may not be present in younger individuals. This clarification will be needed to enhance any future risk stratification method based on the ECG abnormalities observed in this study.

Study limitations

The limitations of the study are the lack of validation of the classification model and the potential bias selection that could have occurred when paper ECGs were selected for digitization. Our study population was too small to implement a validation of the models, so one can speculate that our classification model is over-designed and may result in a higher error rate in a different population.

Conclusion

T-wave morphology provides information complementary to QT prolongation for differentiating LQT2 carriers from noncarriers with borderline QTc. Our study showed significant alteration in T-wave morphology in patients carrying the KCNH2 mutation even when the QT interval of these patients was in the near-normal range.

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