Discrimination of HERG Carrier from Non-Carrier Adult Patients with Borderline Prolonged QTc Interval

JP Couderc, W Zareba, AJ Moss

University of Rochester Medical Center, University of Rochester, NY, USA

Abstract

Ten to fifteen percent of individual with the hereditary long-QT syndrome (LQTS) involving the human ether-a-go-go related gene (HERG) do not have an abnormal QT prolongation but are at risk of lethal arrhythmic event. We investigated the phenotypic T-wave morphology for the identification of patients with HERG mutations. The standard 12-lead ECGs from carrier and non-carrier LQT2 patients were digitized and the RR intervals and T-waves were quantified using QT/QTc, QT apex, T-wave amplitude, ascending (α_L) and its descending slopes (α_R). A logistic regression model selected 3 parameters for the classification of the groups: QT, RR and α_L. The model provided 92.7% sensitivity and 90.0 % specificity The information within the T-wave morphology is complementary to the information of repolarization duration. Abnormal T-wave morphology is a phenotypic expression of the HERG mutation in adult LQTS patient.

1. Introduction

The long QT syndrome (LQTS) is an inherited disorder associated with 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. The QTc prolongation is not a perfect clinical surrogate marker for identifying patients affected by the LQTS because of substantial number of LQTS patients do not have QTc prolongation.

Various techniques have been used to replace the QT prolongation risk factor, they were based on static and dynamic aspects of repolarization: prolongation of the T-peak to T-end (TpTe) and QT dispersion,(2) abnormal T-wave morphology,(3-5) RT hysteresis from exercise testing (6), microvolt-level T-wave alternans,(7;8) and repolarization variability.(9;10) In our study, we investigated a large cohort of genotyped LQT2 carriers and non-carriers from the International Registry for the LQTS (11) in order to determine the role of the T-wave morphology in the identification of LQT2 patients.

2. Methods

The study population consisted of subjects with genetically tested HERG mutation. 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.

The total list of LQT2 paper tracings available in the International Registry was 1583. We defined a group consisting of 69 patients who carried the LQT2 mutation and 90 non-carriers from LQT2 family members.

Based on the distribution of the QTc values on the study population (Fig. 1), we focused our analysis on a range of QTc between 390 and 470 msec representing the overlapping portion of the distribution of QTc intervals between the carrier and non-carrier groups. In this subgroup, the clinical diagnosis of the presence of the LQTS is challenging. Ninety-five patients were included in this group: 46 carriers and 49 non-carrier LQT2 patients.

Before processing the ECG tracings for digitalization, they were visually reviewed in order to eliminate the ones: 1) without grid (grid is required for the digitalization process), 2) strongly faded and 3) with signal distortion that can occur when the tracing has been photocopied multiple times. These three requirements defined the scanning criteria. The acceptable tracings were scanned using a 600dpi resolution scanner (Epson Expression® 1680 Professional, EPSON Inc., Long Beach , CA) into bitmap files. The resulting digital images were converted to digital ECG signals using the commercial software ECGScan© (ECGScan, Amps LLC, NY, USA).(12) Lead II had the largest T-wave amplitude and this lead was selected for digitization and measurement in this study. The digitalization process provided a signal with a 500 Hz sampling frequency and 16-bit resolution.

ECG measurements

The COMPAS© software (University of Rochester Medical Center, NY, USA). (13) was utilized for repolarization measurements. The software provides a set of classic and morphological measurements of the repolarization intervals:

1/ RR intervals, QT intervals are based on the maximum slope method (QT) and Bazett's corrected QT interval (QTc).

2/ QT apex intervals are measured based on a technique fitting a parabola to the T-wave.

3/ Maximum ascending slope (α_L) and maximum descending slopes ($|\alpha_R|$) of the T-wave are measured and expressed in µV/2.msec. They represent the maximum velocity of the ascending and descending limbs of the T-wave.

4/ Symmetry of the T-wave is computed as the absolute value of the ratio of T-wave slopes ($|\alpha_L/\alpha_R|$).

5/ The T apex to T end interval (TpTe) defined as QT offset minus QT apex interval durations.

6/ T-wave symmetry defined by the ratio between T-wave slopes ($\alpha_L/|\alpha_R|$).

7/ Amplitude of the T-wave in mV.

No U-wave was included in the study. If a bifid T-wave was present, the first and last slopes were measured. Bazett's formula was used to correct the QT intervals for heart rate (QTc).
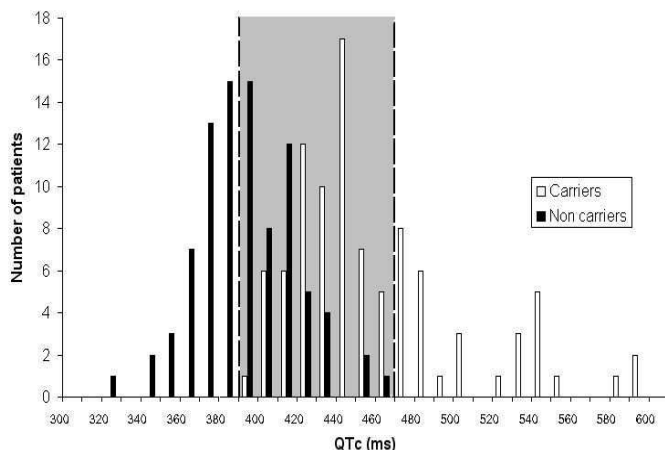

Figure 1: Distribution of QTc values within the study population. The grey area marks the interval of near-normal QT c interval duration.

A Stepwise Logistic Regression Model (LRM) for detecting variables that discriminate between LQT2 carriers and non-carriers was used.

3. Results

Comparison of clinical characteristics of carrier and non-carrier patients revealed a significantly higher number of rate of cardiac events and a significant lower heart rate in carriers of the LQT2 mutation (Table 1).

ECG quantifiers in LQT2 patients

Table 2 describes the average values of ECG quantifiers and their standard deviations among the two groups with near-normal QT interval duration. In the two considered groups, all quantifiers were significantly different between carrier and non-carrier patients ($p<0.01$) except T-wave symmetry

	Groups			
	No β-blockers		No β-blockers 390≤QTc≤470	
	NC	C	NC	C
N	90	69	46	49
Female (%)	61.1	58.0	78.3	59.2*
Age (yrs)	33±14	38±17	32±14	37±17
Prior CE	5.6	31.9*	6.5	26.5*
HR (bpm)	72±14	67±13*	76±13	67±13[†]

Table 1: CE: Cardiac Event rate. * p≤0.05 and [†] *p≤0.01* when comparing carrier (C) to non-carrier (NC) group.

	No β-blockers therapy 390≤QTc≤470	
	Non-carrier	**carrier**
N	46	49
T magnitude (mV)	0.24±0.12	0.16±0.07*
QT apex (msec)	293.9±24.5	336.2±33.6*
QT (msec)	368.9±28.4	428.1±35.5*
QTc (msec)	412.6±17.7	435.4±18.6*
RR (msec)	807.1±136.2	972.7±149.1*
α_R (µV/2*msec)	-17±9	-10±5*
α_L (µV/2*msec)	13±6	6±3*
TpTe (msec)	74.7±9.9	93.0±25.8*
T symmetry	0.80±0.36	0.76±0.38

Table 2: Bazett's correction was used, QT were semi-automatically measured in lead II or V5 if lead II was not available.* p<0.01.

Significantly reduced T-wave magnitude and slope values ($|\alpha_R|$ and α_L) were observed in LQT2 carrier patients in comparison to non-carrier patients in the two study groups.

Significantly increased QT apex, QT offset, QTc, TpTe intervals ($p=0.0001$), were present in those with versus without the LQT2 mutation.

Discriminant power of repolarization indexes in LQT2 carrier patients

The parameters entered in the logistic 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 in the model. The best model was Log(pr/(1-pr))=-44.0+0.083QTc-0.013RR-0.383α_L (Where pr is the event probability for a

patient to be carrier) providing a sensitivity and specificity equal to 89.8% and 86.9%, respectively. Also, 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. Adding RR and α_L to the model improved the classification by 15% in specificity and 6.5% in sensitivity in comparison to the clinical model that includes QTc.

When considering QT instead of QTc: QT, RR and α_L, in the model. The sensitivity and specificity were equal to 92% and 81.4 %. The same model applied to the overall group led to a ROC area of 0.97 (sensitivity 92.7%, specificity 90.0%). The coefficients of the binary logistic regression were: $Log(pr/(1-pr))=-27.7+0.095QT-0.008RR-0.304\alpha_L$

The correlations of α_L and α_R with RR values were group dependent. Parameter α_L was not significantly correlated with RR in non-carrier subjects, but it 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 non-carrier individuals: in carrier $r^2=10.2\%$, p=0.01 vs. $r^2=4.3\%$ (negative r), p=0.05 in non-carrier subjects, a finding suggesting a disturbed repolarization process associated with the HERG mutation.

4. Discussion and conclusions

Among the LQTS subjects affected by the HERG mutation, a meaningful proportion does not present an abnormal prolongation of the QT interval. In this study, we showed that the morphology of the T-wave may be useful for the identification of LQTS patients with borderline QT prolongation. Based on the analysis of only one lead (lead II), a LRM based on 3 ECG parameters (RR, QT and α_L) permitted correct classification in 97% of the 209 individuals in our study population. The optimal model relies on QT heart rate and the ascending limb slope of the T-wave demonstrating that the morphology of the T-wave contributes to an improved discrimination between carriers and non carriers. The relevance of morphological parameters was conserved when analyzing only the patients with near normal QT interval values. Our results support the hypothesis that there is a phenotypic expression of the HERG mutation on the surface ECG that is useful in the risk stratification of subjects with congenital form of the LQTS.

Phenotypic characterization of the surface ECG in LQT2 patients

Abnormalities of T-wave morphology have been investigated over the past 10 years. Most of this research emphasized interest in the information contained in the morphology of the T-wave. Studies have shown that T-wave notches (TWN) are an accepted marker of electrical instability and their presence has been included in diagnostic criteria for the HERG mutation(14). Our study reveals another type of subtle abnormality involving the morphology of the T-wave. A flattened T-wave shape with significant reduction of the slope of the ascending limb of the T-wave (α_L) provided greater discrimination of carrier versus non-carrier LQT2 individuals than the TpTe interval or the slope of the descending limb of the T-wave (α_R).

Moss et al. found a broad-based low-amplitude T-waves in LQT2, and our study confirms this observation and provides a quantitative description of these morphological abnormalities. The HERG 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 the morphology of the T-wave remain to be elucidated. The I_{kr} ion current is mainly involved at the end of phase 2 and beginning of phase 3 of the action potential of the cardiac cells. Thus, finding a more pronounced phenotypic expression of the HERG mutation before than rather after the peak of the T-wave is consistent with the known physiology that the reduction of the I_{kr} current is present to a greater degree in the earlier than at the later phase of the repolarization processThe morphological changes we observed in our study were also linked to QT/QTc prolongation, with the QT/QTc duration the most relevant parameter even in a subject with near-normal QT duration.

Restier et al.(15) used 3D-digital techniques to show an electrocardiographic 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 morphological features from all leads (either independently or through mathematical combination). Our study was limited to the analysis of lead II, and a multi-lead analysis may be even more discriminative.

The morphology of the T-wave when quantified from lead II in scalar ECGs brings complementary information to QT prolongation in LQT2 patients. Our study showed significant alteration in T-wave morphology in patients carrying the HERG mutation even when the QT interval of these patients was in near-normal range.

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Address for correspondence

Jean-Philippe Couderc, PhD, MBA
University of Rochester Medical Center
601 Elmwood Av. , box 653
Rochester, NY 14642, USA
Jean-philippe.couderc@heart.rochester.edu