Instantaneous Response of the QT Interval to Heart Rate Change in Patients with Type-1 Long QT Syndrome

Jean-Philippe Couderc, Xiaojuan Xia, Wojciech Zareba

University of Rochester Medical Center, Rochester, New York, USA

Abstract

Genotyping is considered the most reliable tool to identify the presence of the long QT syndrome (LQTS) but genetic testing captures only 75% of phenotypically affected LQTS individuals, and negative test in a phenotype-positive patient does not rule out the presence of the syndrome. Also, these tests do not fully capture an individual risk to life-threatening arrhythmias that is modulated by exogenous factors. The surface electrocardiogram (ECG) is an investigational tool that could provide insights into the integrated functional defects associated with LQTS mutations. We designed a method to visualize and quantify the dynamic features of the QT interval that is known to play a crucial role in the triggering of arrhythmias in these patients. The method is applied to a set of 24-hour Holter recordings acquired in 195 healthy individuals and 68 genotyped LQTS patients from the Telemetric and Holter ECG Warehouse (THEW) project. The technique provides a three dimensional representation of the instantaneous adaptation of the QT interval across heart rate and across the spectrum of autonomic states recorded during the ambulatory Holter ECG. Our results provide a description of the "normal" range of values of instantaneous response of QT to HR changes and confirm the presence of abnormal regulation of the QT interval in LQT-1 patients which revealed to be specific to the location of their mutation in the KCNQ1 channel.

1. Introduction

The inherited long QT syndrome (LQTS) is recognized as a common cause of sudden cardiac death in children and young adults. Its frequency was estimated between one and 20 carriers out of 5,000 individuals within the general population in the United States where it is thought to be responsible for as many as 3,000 deaths each year. The mutations in the KCNH2 (LQT-2, cytogenetic location 7q36.1) and the KCNQ1 (LQT-1, cytogenetic location 11p15.5) genes represent almost 90 % of the clinical cases [1]. In LQT-1 patients, a reduction of the slow delayed rectifier potassium current (I_{Ks}) leads to less effective shortening of the QT intervals during tachycardia. Therefore, exercise is the primary stimulus for cardiac event in these patients, and the adrenergic stimulation plays a critical role in the arrhythmogenesis processes associated with the LQTS. Importantly, genotype-phenotype investigations of LQT-1 patients have evidenced that mutation location plays a significant role in patient propensity to cardiac events with higher risk for patients with a mutation located in the cytoplasmic loops regions of the KCNQ1 channel (S2-S3 and S4–S5 region of the α subunit of the I_{ks} channel).[2]

Currently, patient genotyping represents the most accurate and reliable approach to identify individuals carrying known LQTS mutation but it does not fully capture an individual's risk because the functional defects associated with one or multiple LQTS mutations remain poorly understood (impaired trafficking, voltage dependency, ion selectivity, and tetramerization). The most recognized markers of risk in the LQTS is the level of QTc prolongation, yet most recent clinical studies revealed that QTc prolongation, measured from resting standard ECG is an imperfect marker: 25% to 32% of the at-risk LQTS patients have concealed form of the syndrome.

Therefore, scientists have strived to develop tests leveraging adrenergic stimulation to exacerbate repolarization impairment. More precisely, the measurement of the response of the QT interval to brisk standing, exercise or to epinephrine challenge has been helpful to identify the patients with concealed-form of the syndrome. However, these tests must be conducted using heavy clinical support including appropriate resuscitation equipment and the presence of an interventionist team.

In this work, we propose a technique leveraging the information acquired during ambulatory 24-hour Holter recordings to measure the spectrum of response of the QT interval to heart rate changes. Our working hypothesis is that LQTS patients have genotype-specific spontaneous response of QT previous to RR interval changes that can be measured form Holter ECGs and used as both clinical diagnostic and prognostic tools. We will evaluate this approach in LQT-1 patients considering mutation location and cardiac events as independent outcomes.

2. Method

2.1. Study population and ECG recordings

The ECG files analyzed in this study are from the Telemetric and Holter ECG warehouse (THEW)[3]. This project hosts multiple sets of ECG waveforms from various studies and clinical trials to be shared with the scientific community for the advancement of technologies related to digital electrocardiography. We will use two databases from this repository: the congenital LQTS (E-HOL-03-0480-0013) and the database of ECGs acquired in healthy subjects (E-HOL-03-0202-003). We limited our study populations to adults and teenagers (age>13 yrs). LQTS patients on beta-blocker therapy at the time of their ECG were excluded. From the E-HOL-03-0480-0013 database, we identified the LQT-1 patients with missense mutations located either in the cytoplasmic regions (CLQT-1) or outside of the C-loop regions (NCLQT-1). Patients with mutation in the N-terminal region were excluded.

Our technique requires the Holter ECG waveforms to be annotated and manually adjudicated prior to run the automatic QT measurement algorithm. This annotation process included two steps: 1) an automatic annotation based on commercial scanning software, and 2) a manual adjudication of the automatic ECG waveform annotation. This process was consistently applied to the 263 24-hour Holter recordings used in this study.

2.2 Beat-to-beat QT interval measurements

The ECG waveforms are processed in order to extract the duration of QT intervals from all available sinus cardiac beats. Non-sinus beats and noisy beats are excluded from the analysis. The sinus beats preceding ventricular ectopic beats were removed as well. This ensures the exclusion of waveform in which the repolarization interval is polluted by the ectopic beat.

The QT interval measurements rely on both an accurate identification of the onset of the QRS complex and of the end of the T-wave. The detection of the QRS was based on the algorithm described by Zong et al.[4]

The offset of QT interval relied on a method inspired from the so-called tangent method which fits a line through the terminal downslope phase of the T-wave (upslope if negative T-wave). The crossing point between this slope and the isoelectric line of the ECG waveform marks the offset of the T-wave and the end of the QT interval.

2.1. Instantaneous QT response to RR interval

We designed a method providing a visual and quantitative assessment of the instantaneous QT response to acceleration and deceleration of heart rate across the spectrum of autonomic regulation found in ambulatory condition. The method computes three values for each selected sinus beats n such as: 1) dQTn=QTn-QTn-1, 2) the immediately preceding RR changes dRRn=RRn-RRn-1, and 3) the average RR values computed from the 3 minutes preceding the beat n (aRRn). Then, we form dRR and aRR bins: 70 bins including aRR values from 500 ms to 1200 ms by step of 10 ms, and 40 dRR bins which range from -100 to +100 ms by step of 5 ms. The 40 dRR bins define the X axis and the 70 aRR bins the Y axis. The map consists of 40*70=2800 d-aRR cells of 5-ms width and 10-ms height. We regroup each dQTn value associated with the same d-aRR cell (based on their respective aRRn and dRRn values). For instance, any QTn value preceded by a dRRn included in the range 50 to 55 ms and with an aRRn value between 800 and 810 ms will be associated with the same d-aRR cell. Once each dQTn has been processed, we compute the median value from all dQTn intervals associated with the same d-aRR cell, the so-called dQTad [ms] value. If the cell contains less than 20 dQTn values, dQTad is not reported. Finally, we plot a 3-D map in which the dimensions are dRR bins (X), aRR bins (Y) and dQT (Z).

We computed population-based maps in order to capture a representative profile of the instantaneous QT response to HR for a given study population. Only the a-dRR cells containing at least 30 values from different recordings are plotted in order to eliminate dQT values that have poor representation.

Quantifying the QT response from the dQT maps is done based on a set of parameters measuring the distribution of QT changes in the acceleration and deceleration areas. We visually defined two sectors: the iQTacc and iQTdec sectors. The values associated with these sectors are the percentage of a-dRR cells containing an instantaneous QT change coherent with the previous RR change i.e. QT shortening (negative values) following heart rate acceleration and QT prolongation (positive values) when heart rate decreases. These two sectors are symmetrically located on the map as follows: both iQTacc and iQTdec areas are delimited by 900>aRRn>1100ms; iQTdec sector includes 0<dQTad<50, while iQTacc sector encompasses -50<dQTad<0. The ratio of iQTdec to iQTacc is called iQTbal.

We included time-domain estimators of heart rate variability (SDNN and RMSSD) in order to gain insights into autonomic innervation of our study groups and adjust for their potential confounding effects in our analysis.

3. Results

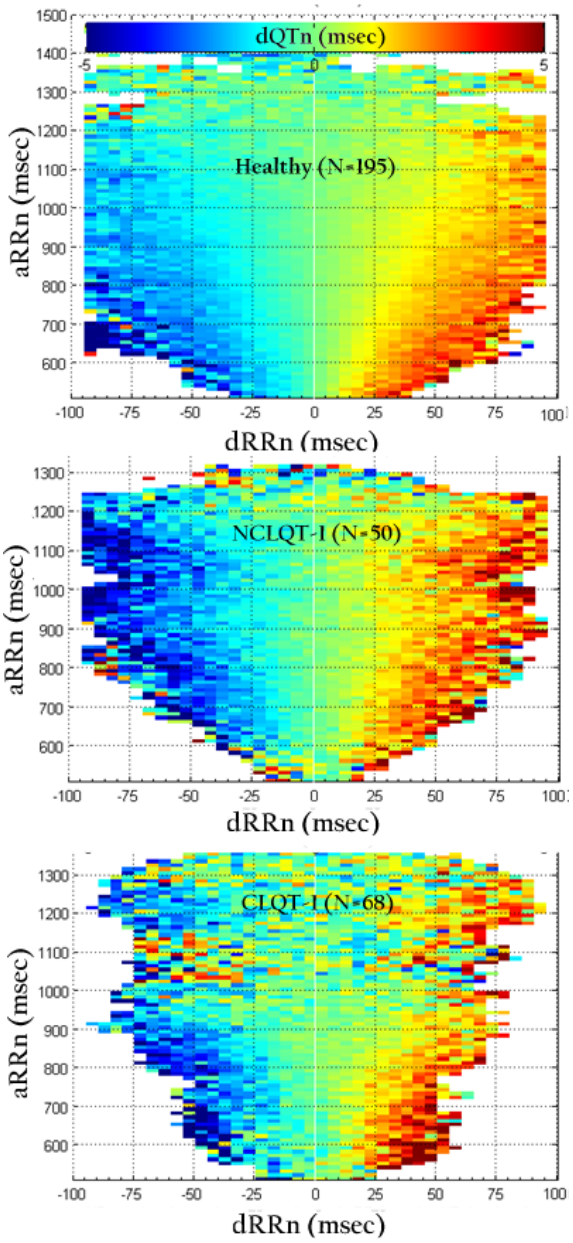

Figure 1. Average instantaneous dQT maps for healthy subject (n=195), NCLQT-1 (n=50), and CLQT-1 (n=68) populations presented in the top, middle and bottom panels, respectively.

3.1. Study population

Seven ECGs from the 202 files available in the THEW E-HOL-03-0202-003 were excluded from the analysis. Three were excluded because the subjects were younger than 13-yrs old. Four recordings had low-quality signal in which beat-to-beat QT measurements could not be done. The files from the remaining 195 subjects included 50% women with age 38±16 yrs. In the group of LQT-1 patients, 68 recordings were processed including 50 NCLQT-1 (32±19 yrs, 60% women) and 18 CLQT-1 patients (34±20 yrs, 61 % women).

3.2. Instantaneous QT-RR profiles and mutation location in LQT-1

The QT-RR maps computed from the healthy, NCLQT-1 and CLQT-1 groups are presented in Figure 1 in the top, middle and bottom panels respectively. Z axis is presented using a colour scale with cold colours for QT shortening (left side of the map) and hot colours for QT prolongation (right side of the map). The map reveals an adaptation of QT interval to both heart rate acceleration and deceleration that is profoundly visually different in CLQT-1 patients than in healthy and NCLQT-1 groups. The QT does not shorten properly following heart rate acceleration around aRRn values of 1000-1100 ms (presence of hot-color cells in left side of the map).

The Table 1 provides the RR, QTc, SDNN, RMSSD, iQTacc, iQTdec and iQTbal values for the three study and groups. The CLQT-1 group has a significantly longer QTc interval, decreased SDNN values and lower iQT values than NCLQT-1 patients revealing a significantly stronger impairment of their instantaneous QT response to RR changes than NCLQT-1 patients (and healthy controls). We implemented logistic models to study the association between the ECG parameters considering the LQT-1 groups as outcomes.

Table 1. ECG measurements form the three study groups .

	Controls	NCLQT-1	CLQT-1
N	195	50	18
RR (ms)	803±100	851±98*	841±127
QTc (ms)	431±22	486±23*	491±25*
SDNN (ms)	150±50	151±52	121±40 ψ
RMSSD (ms)	47±24	51±38	36±11
iQTacc (%)	74±16	69±20	54±23*ψ
iQTdec (%)	73±14	66±17*	51±24* ψ
iQTbal (n.u.)	1.01±0.24	0.95±0.17	0.95±0.20

*P<0.05 significantly different than controls, ψ significantly different than NCLQT-1.

Only iQTacc was significantly associated with the presence of a NCLQT-1 mutation: OR=1.42, 95% CI:0.41-2.43, p=0.04. Each 10% decrease of iQTacc value was associated with 42% increased probability to carry a CLQT-1 mutation after adjusting for all parameters described in Table 1.

3.3. Instantaneous QT-RR profiles and cardiac events in LQT1

In order to gain insight into the proposed method as a prognostic tool, we defined two new groups of LQT-1 patients, those with (n=15) and without events (n=40) and a QTc <500 ms (to focus on patients who are clinically difficult to identify). It is noteworthy that the events may have occurred before or after the ECG recording was acquired because the time of the event is not available in this database, thus time-dependent analysis was not feasible. In table 2, only iQT values are statistically different (p=0.008) between LQT-1 patients with and without life-threatening events. A multivariate binary logistic model confirmed this association after adjustment for QTc, RMSSD, SDNN age, and gender. Each 10% increment of iQTbal value were associated with 37% increased probability to have events (OR=1.37, 95%CI: 1.00-1.85, p=0.04).

Table 2. ECG measurements and cardiac event in LQT-1 patients.

	LQT1 No event	**LQT-1 events**	**p**
N	40	15	
RR (ms)	828±98	868±127	0.35
QTc (ms)	471±27	479±19	0.15
iQTacc (%)	72±22	64±28	0.22
iQTdec (%)	69±14	72±20	0.23
iQTbal (n.u.)	0.92±0.20	1.12±0.33	0.008

4. Discussion and conclusion

The relationship between QT interval duration and the immediately preceding RR interval has been shown to be influenced by many factors such as the presence of drugs, ambient heart rate and, importantly, the autonomic regulation of the heart. We used Holter recordings to investigate the instantaneous response of QT to preceding RR values. We speculate that the instantaneous QT profile provides a method to assess abnormal dynamic features of the ventricular repolarization process representing new insights complementary to QT/QTc prolongation. Our study reveals that the iQT map can be used to identify mutation-specific abnormalities of repolarization in LQT-1. Furthermore, the results show preliminary encouraging results on their ability to identify information associated with life-threatening events.

One could speculate that an increased value of iQTbal represent an imbalanced instantaneous response of QT interval to heart rate acceleration and deceleration. All current model of QT-RR relationship merges the QT response to heart rate acceleration and deceleration. Yet, differentiating between response of QT interval to heart rate acceleration from deceleration seems crucial because cardiac potassium currents forming the repolarization reserve show complex regulation schemes in which the KCNQ1 channel is up-regulated at fast heart rate through phosphorylation [5] and it is characterized by slow deactivation leading to current accumulation.[6] These fast and slow deactivations are consistent with the presence of at least two independent time constants characterizing the response of QT to heart rate acceleration and deceleration.

To conclude, we present a preliminary Holter-based technique to assess the level of severity of repolarization impairment complementary to QTc prolongation in LQT-1 patients.

Acknowledgements

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Address for correspondence.

J.P. Couderc.
University of Rochester Medical Center
Room No.4322
265 Crittenden Blvd., CU 420653
Rochester, NY 14642-0653
Jean-Philippe.couderc@thew-project.org.