Comparing the Relationship between QT/RR Slope and Basal QTc in LQT1 Patients and Healthy Subjects

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Abstract

The dependency of the QT interval to the previous RR intervals has been widely studied, QT/RR slope and other modeling techniques revealed individual-specific relationship. In this work we studied the relationship between QT/RR slope and a basal QTc interval in 154 healthy subjects and in 97 patients with the inherited long QT syndrome type-1 (LQT1) to provide insights into the effect of the impairment of the outwardly directed delayed rectifier potassium current on the dynamic QT-RR coupling.

QT/RR slope values show strong relationship to basal QTc interval in healthy ($R=0.65$; $p<0.00001$) and in LQT1 patients ($R=0.56$; $p<0.00001$). The dependency of QT/RR slope on QTc is steeper in healthy ($a1=0.0016 \pm 0.0002$) than in LQT1 ($a1=0.0010 \pm 0.0002$), $p<0.0001$. The steeper dependency on QTc in healthy preserves proper shortening of QT intervals during increased heart rate in healthy while in LQT1 patients the QT intervals does not adapt to increased heart rate sufficiently (lack of QT adaptation to heart rate acceleration). This observation is consistent with current clinical mechanism associated with the triggering of life-threatening arrhythmias in the LQTS type-1 patients.

1. Introduction

Conventional QT-RR analysis has shown that the QT/RR slope, i.e. the relation between QT and RR changes, after correction for QT hysteresis, is steeper in LQTS patients than healthy subjects, leading to an increased propensity for life-threatening arrhythmias [1-3]. Yet, little attention has been given to the relationship between QT/RR slope and the basal heart-rate corrected QT interval (QTc: 60-bpm equivalent QT duration based on individual correction). In this work, we analyze the QT-RR coupling in LQT-1 patients and healthy controls. We hypothesize that LQT-1 patients have flatter relationship between QT/RR slope and basal QTc which would be consistent with the arrhythmogenic role of the lack of QT adaptation to increased heart rate in the LQT1 syndrome.

2. Methodology

Different algorithms and models are available to compute QTc and QT-RR coupling. Nonlinear static models of QT-RR coupling such as Bazett's or Fridericia's formulae are used in clinical and drug-safety studies, despite that only subject specific dynamic model of QT-RR coupling provides a "correct" heart rate correction for QTc because it deliver a subject-specific model of the QT-RR coupling [4-7].

We have developed a linear ARX(1,1) model of QT-RR coupling with three optimized parameters [7, 8]. Resulting QT parameters are:

i) QTc, i.e., a 60-bpm equivalent QT duration computed from the QT-RR model;

ii) The gain of QT-RR coupling for slow variability of RR ($Gain_S$), i.e., QT/RR slope, i.e. the parameter that describes QT memory;

iii) The gain of QT-RR coupling for fast variability of RR ($Gain_F$), i.e., the parameter that describes the sudden change of QT, i.e., QT restitution.

In addition the model computes a time constant of QT adaptation to RR changes and a random QT variability, i.e. QT variability not dependent on RR changes. These two last parameters were not studied in this work.

The parameters QTc and $Gain_S$ are not affected by hysteresis because the ARX model controls for it [7]. Hysteresis elimination is based on optimized dynamic parameters, where both dynamic QT properties (QT memory and QT restitution) were optimized.

We analysed the relationship between QTc and $Gain_S$ using correlation and linear regression with QTc as independent parameter:

$$Gain_S = a0 + a1 \times QTc$$

The coupling between QTc and $Gain_S$ defines different QT behavior between LQT1 subjects and controls during increased or decreased heart rate. The values of QT intervals during increased or decreased heart rate can be assessed from QTc and $Gain_S$:

$$QTx=QTc - (1000 – RRx) \times Gain_S$$

where QTx is the length of QT interval for heart rate defined by RRx. In addition, we analyzed the TQ interval (interval from end of T wave to the next Q wave, i.e. diastolic interval) and the QTx/TQx ratio.

$$TQx=RRx-QTx$$

where TQx is the length of TQ interval for heart rate defined by RRx.

3. Data

Two database from the Telemetric and Holter ECG Warehouse (THEW: www-thew-project.org) [9] hosted by the University of Rochester Medical Center (NY, USA) were used: Healthy Individuals (E-HOL-03-203-003) and the congenital LQTS (E-HOL-03-0480-013) databases. The QT parameters from the ARX model were computed from the recordings of 154 healthy and 97 LQT1 patients. The mean levels, standard deviations and statistical significance of differences between controls and LQT1 patients were already reported in [10].

4. Results

Scatter plot between QTc and $Gain_S$ for control subjects (red marks) and LQT1 patients (blue marks) and corresponding regression lines are reported in Fig. 1. Basic numerical results are in Tables 1 and 2.

Figure 2 provides a description of the TQ, QT/TQ values for LQT-1 patients and healthy subjects when considering either HR acceleration or HR deceleration. The figure emphasizes the primarily role of HR acceleration in exacerbating the increase of the QT/TQ ratio, while the deceleration shows small effect on QT/TQ.

Table 1. Mean levels ± standard deviations over groups for basic parameters. Significance of differences between controls and LQT1 patients for all parameters is $p<0.00001$.

	N	RR [ms]	QTc [ms]	$Gain_S$
Controls	154	826±118	384±26	0.18±0.06
LQT1	97	958±180	453±35	0.22±0.06

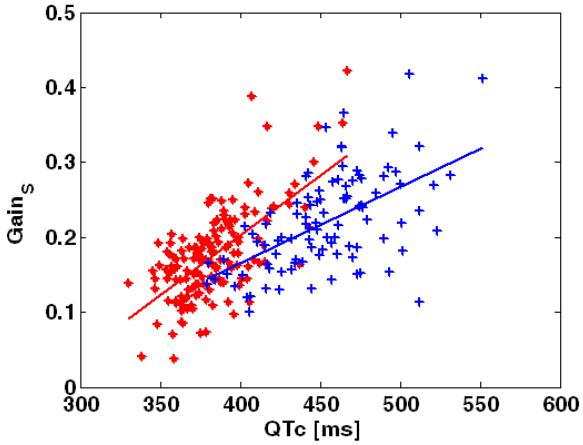

Figure 1. Scatter plot of $Gain_S$ and QTc values and associated linear fitting lines by study groups. Red stars are for controls, blue crosses are for LQT1 patients.

Table 2. Coupling between QTc and $Gain_S$ given by regression and correlation analyses. Significance of differences a0 (intercept), a1 (slope) between controls and LQT1 $p<0.0001$

	Regression		Correlation	
	a0	a1×1000	R	p-value
Controls	0.42±0.07	1.6±0.2	0.65	$<10^{-10}$
LQT1	0.24±0.06	1.0±0.2	0.56	$<10^{-8}$

5. Discussion

$Gain_S$ values show strong relationship to basal QTc interval in healthy ($R=0.65$; $p<0.00001$) and in LQT1 patients ($R=0.56$; $p<0.00001$). The dependency of $Gain_S$ on QTc is steeper in healthy a1=0.0016±0.0002 than in LQT1 a1=0.0010±0.0002. Such steeper dependency in healthy controls ensures the shortening of the QT intervals during increased heart rate while in LQT1 patients the flatter relationship reveals a lack of QT adaptation to increased heart rate [10]. With decreasing heart rate, the differences between LQT1 and controls in QT/RR ratio decreased (see Fig. 2).

The lost of QT adaptation to RR changes during exercise in LQT1 and LQT2 patients is mentioned by Paavonen [15] also, but up to now no analysis of the dependency between QTc and $Gain_S$ was reported. $Gain_S$ and QTc are dependent values and both values should be analyzed simultaneously. Only on the basis of both values may be predicted QT and TQ behaviour during increased or decreased heart rate (Fig. 2). The diagnosis based only on QTc or $Gain_S$ is insufficient, and improper conclusions may occur, as that increased $Gain_S$ is marker of prevalence to arrhythmias. Increased $Gain_S$ may preserve proper shortening of QT during exercise in the case of longer QTc and may compensate longer QTc.

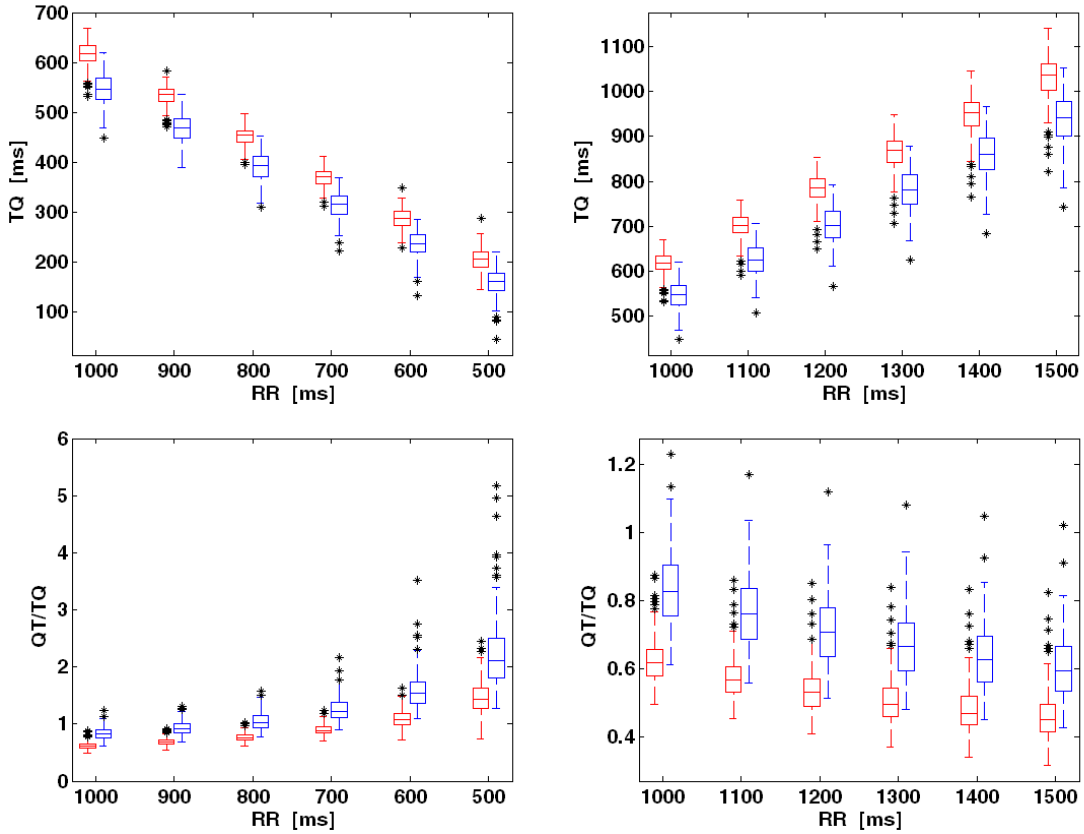

Figure 2: Distribution of TQ and QT/TQ values across heart rate in healthy subjects and LQT-1 patients. Red color – controls, blue color - LQT1.

It has been hypothesized that the primary defect in LQTS is an impaired adaptation of QT interval to abrupt changes in heart rate [11]. Our approach to characterize QT-RR coupling provides insights into this impairment of QT adaptation using continuous ECG monitoring. We believe the prevalence of arrhythmias could be evaluated using the length of TQ or the level of QT/TQ ratio as described by Fossa et al [12]. We did not present the statistical significance for TQ or QT/TQ between LQT1 and controls during increasing or decreasing of heart rate. Such significance is not important according to our opinion. Some physiological boundaries exist (minimal TQ interval, maximal QT/TQ ratio) and the values over these boundaries may lead to increased arrhythmia vulnerability. The effort to define these boundaries is given in [12], but the exact definition of these physiological boundaries requires more data to be appropriately defined.

Our model of QT-RR coupling is linear and the linearity of coupling is supposed in the assessment of TQ and QT/TQ values during varying heart rate. We believe that the linearity or at least quasi linearity of QT-RR coupling is a valid assumption in normal range of RR intervals, if the dynamic properties (hysteresis) of QT are eliminated. Some example of QT-RR linearity with eliminated QT hysteresis is presented in [13].

Different nonlinear models of QT-RR coupling are still tested [14]. But there is no generally valid nonlinear model of QT-RR coupling and the results [14] showed that a linear model frequently ensure optimum fit. The linearity of QT-RR coupling in "normal" area of RR intervals may be generally accepted and the mentioned nonlinearities may be given by improper elimination of hysteresis or/and by some QT irregularities. The reproducibility of QT nonlinearity was not tested. The attention should be directed toward the analysis of other QT important properties as: 1) the QT dynamic properties (only some models [5, 7, 8] suppose the true QT response – memory and restitution); 2) the definition of "normal" area of RR intervals where the linearity is valid; 3) the analysis of QT behaviour outside this area; and finally 4) the QT irregularities preceding RR changes [7].

Limitations: Holter recordings were analyzed without any knowledge about patient's activity. Parameters of QT-RR coupling are not only subject specific but also dependent on the type of stress associated with heart rate changes [15]. Therefore, QT/RR slope should evaluate if the type of stress (physical, mental, etc.) leads to different results [15].

6. Conclusion

Significant coupling exists between QT/RR slope and basal QTc, this coupling differs between controls and LQT-1. The differences in coupling explain the higher prevalence to arrhythmia in LQT-1 patients during increased heart rate. A steeper QT/RR slope relative to basal QTc preserves proper shortening of QT intervals during increased heart rate in healthy while in LQT1 patients the QT intervals does not adapt to increased heart rate sufficiently (lack of shortening).

Dynamic investigation of QT-RR coupling brings relevant information about the impairment of QT coupling to previous RR intervals. The use of mathematical models to characterize this coupling may help better assess the clinical risk of LQTS patients and bring complementary information to QT interval prolongation as the unique risk stratifies in LQTS patients.

Acknowledgements

This work was partially supported by grant No. P102/12/2034 of the Grant Agency of the Czech Republic and by European Regional Development Fund – Project FNUSA-ICRC No. CZ.1.05/1.1.00/02.0123.

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