

# Impaired T-Amplitude Adaptation to Heart Rate Characterizes $I_{Kr}$ Inhibition in the Congenital and Acquired Forms of the Long QT Syndrome

JEAN-PHILIPPE COUDERC, PH.D., M.B.A.,\* MARTINO VAGLIO, M.S.,\* XIAJUAN XIA, M.S.,\* SCOTT MCNITT, M.S.,\* PIERRE WICKER, M.D.,† NENAD SARAPA, M.D.,‡ ARTHUR J. MOSS, M.D.,\* and WOJCIECH ZAREBA, M.D., PH.D.\*

From the \* Heart Research Follow-Up Program, Cardiology Department, University of Rochester Medical Center, Rochester, New York, USA; †Pfizer Inc., Global Research and Development, Groton, Connecticut, USA; and ‡Daiichi Sankyo Pharma Development, Edison, New Jersey, USA

**Adaptation of Repolarization Magnitude to Heart Rate.** *Introduction:* The QTc interval prolongation is not a perfect surrogate marker of the presence of an increased risk for arrhythmic events. In the search for alternative markers, we investigated the T-amplitude and QT interval adaptation to heart rate (HR) in patients with the congenital long QT syndrome (LQTS) and individuals with sotalol-induced QT prolongation.

*Methods and Results:* Our investigation is based on the analysis of continuous 12-lead digital Holter recordings in: 49 LQT1 carriers, 25 LQT2 carriers, 37 healthy individuals off drugs and on 160 mg of sotalol, and 21 of them also on 320 mg of sotalol. The Holter recordings were used to investigate repolarization parameters and their HR dependency. A loss of HR dependency of the T-amplitude was found as a common feature in individuals with impaired  $I_{Kr}$  kinetics: LQT2 carriers and subjects on sotalol. The T-amplitude/RR slope was significantly ( $P < 0.05$ ) flatter in LQT2 ( $0.31 \pm 0.27 \mu\text{V}/\text{ms}$ ) than in both LQT1 ( $0.62 \pm 0.40 \mu\text{V}/\text{ms}$ ) and healthy individuals ( $0.55 \pm 0.29 \mu\text{V}/\text{ms}$ ). A dose-dependent reduction of the T-amplitude/RR slope was also observed in subjects on sotalol (160 mg dose:  $0.26 \pm 0.19 \mu\text{V}/\text{ms}$ ; 320 mg dose:  $0.21 \pm 0.14 \mu\text{V}/\text{ms}$ ). The QT/RR slope was less effective than T-amplitude/RR slope in differentiating between congenital and drug-induced repolarization delay.

*Conclusions:* Impaired adaptation of T-amplitude to changing HR is a common electrocardiographic feature associated with KCNH2 mutation and  $I_{Kr}$  blockade by sotalol. This ECG marker may play an important role in the future of the assessment of the penetrance of KCNH2 mutation and the identification of a drug effect on the  $I_{Kr}$  kinetics. (*J Cardiovasc Electrophysiol*, Vol. pp. 1-7)

*QT, T-wave amplitude, heart rate, electrocardiography, long QT syndrome*

## Introduction

In the acquired long QT syndrome (LQTS), an inhibition of the rapidly activating delayed rectifier potassium current ( $I_{Kr}$ ) is the main mechanism associated with drug-induced repolarization delay and risk of cardiac arrhythmia known as torsades de pointes (Tdps).<sup>1</sup> The molecules of these QT-prolonging drugs bind to various sites of the KCNH2 (HERG) channels of the myocardial cells and disturb their functional properties.<sup>2</sup> The underlying torsadogenic mechanism observed in drug-induced LQTS is similar to the one

reported in patients with the LQT2 syndrome. In this congenital form of the syndrome, the genetic KCNH2 mutation leads to structural ion channel defects<sup>3</sup> and/or intracellular “trafficking” abnormalities,<sup>4</sup> causing a reduction in the number of operational  $I_{Kr}$ -specific ion channels, thus prolonging the ventricular repolarization process and increasing heterogeneity of repolarization within the ventricles.<sup>5</sup>

It is well accepted that a QTc interval beyond 500 ms is a clear predisposing factor for the occurrence of TdPs in both congenital and acquired form of LQTS, but the presence of a prolonged QT interval duration below 500 ms is associated with a less clear-cut risk. A majority of patients with acquired or congenital LQTS show QTc < 500 ms, a value with equivocal diagnostic and prognostic significance.<sup>6</sup> The development of new biomarkers complementing the QT interval measurements for the identification of a predisposition to ventricular arrhythmias in congenital LQTS and for the assessment of the  $I_{Kr}$ -inhibitory effect of drugs is of major interest.

Repolarization is a dynamic phenomenon largely influenced by the heart rate. Investigations of the QT/RR relationship and QT hysteresis phenomenon indicated that QT/RR slope could be considered as a marker of sudden cardiac death after myocardial infarction,<sup>7,8</sup> and demonstrated that QT hysteresis is strongly modified by  $I_{Kr}$ -blocking drugs.<sup>9</sup>

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A provisional patent from the University of Rochester, NY, has been filed for the use of T-amplitude/RR impairment as an ECG biomarker.

Address for correspondence: Jean-Philippe Couderc, Ph.D., M.B.A., Box 653, Heart Research Follow-Up Program, Cardiology, University of Rochester Medical Center, Rochester, NY 14642 USA. Fax: 585-275-5283; E-mail: jean-philippe.couderc@heart.rochester.edu

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In this study, we aimed to investigate the dynamic aspects of the repolarization morphology, namely T-wave amplitude adaptation to changing heart rate during various conditions attributed to abnormal  $I_{Kr}$  kinetics due to congenital or acquired forms of LQTS.

## Methods

### Study Populations

The study populations consisted of 49 LQT1 carriers, 25 LQT2 carriers, and 37 healthy individuals who participated in a study focused on the effect of sotalol on ECG parameters of repolarization. The group of LQTS patients included individuals with genetically identified KCNH2 (HERG) and KCNQ1 mutations. We investigated these two types of mutations since they are associated with two different ion-kinetic dysfunctions of potassium currents: the KCNH2 is linked to a reduction of the rapidly activating repolarizing potassium current ( $I_{Kr}$ )<sup>10</sup> and the KCNQ1 to the slowly activating repolarizing potassium current ( $I_{Ks}$ ).<sup>11</sup> We analyzed the patients in whom 24-hour digital 12-lead Holter recordings were available in order to be able to investigate heart rate dependency of their repolarization morphology. The healthy individuals were enrolled in the sequential treatment study described elsewhere,<sup>12</sup> which included 3 days of Holter recordings: at baseline, on single 160 mg dose of sotalol, and a single 320 mg dose of sotalol. The dosing was done at 8:00 AM during the two exposure days under fasting conditions.

### ECG Recordings and Processing

All the Holter ECGs were recorded for 24 hour using the same type of equipment: digital 12-lead Holter recorder H12 (H-12 recorder, Mortara Instrument, Milwaukee, WI, USA), providing digital ECG signal at a sampling frequency of 180 Hz and with 12-bit amplitude resolution. The eight original leads are recorded and the remaining four leads (augmented limb leads aVR, aVL, aVF, and lead III) are calculated. Beat classification was performed using the H-Scribe scanning software (H-Scribe, Mortara Instrument) and manually reviewed and adjusted when necessary. The information about cardiac beat annotation was exported in XML format and integrated into the COMPAS software (Comprehensive Analysis of the Repolarization Segment Software, University of Rochester Medical Center, Rochester, NY, USA) for the QT and T-amplitude measurements.

### Ensuring Repolarization Stability: Steady State

To ensure stability of repolarization and increase signal-to-noise ratio, we adopted the following strategy: the Holter recordings were divided in sections of 10 continuous sinus beats. A representative beat (median beat) was computed from the consecutive 10 beats only if the section was preceded by stable heart rate within the previous 5 minutes. Heart rate stability required having less than 300 ms changes between continuous RR values within these preceding 5 minutes. Then, the 10-beat section was defined stable if the variation of the nine RR intervals remained into the range of values defined by  $\pm 10\%$  of the average RR interval. The QT interval and T-amplitude measurements were based on the "stable representative beats" from lead II.

### Measuring QT Interval and T-Wave Amplitude

Based on a technique ensuring an appropriate stability of the modeling of the relationship between repolarization measurements and the RR intervals,<sup>13</sup> we investigated two electrocardiographic measurements: the QT interval, the amplitude of the T-wave, and their relationship with RR intervals.

The end of T-wave was identified based on the tangent method, with the crossing point between the tangent and the isoelectric line identifying the end of the T-wave (least-squares technique).<sup>14</sup> The amplitude of the T-wave was measured at the maximum value of the T-wave signal in absolute value. For negative T-waves, the sign of the amplitude was conserved. For biphasic T-waves, we measured the highest portion of the signal in absolute value. No manual adjustments of measurements were performed. The diurnal periods were analyzed (from 9:00 AM until 7:00 PM).

### RR Bin Analysis of the T-Wave Amplitude (Tamp) and the QT Interval

The RR bin method is inspired from the work of Badilini *et al.*<sup>15</sup> We developed a slightly different algorithm in which averaged values of QT interval duration and T-wave amplitude are measured from a set of representative beats rather than a unique one for a given RR bin (limited RR-interval range). This ensures that repolarization measurements are based on valid representative beats in case of rapid drug-induced changes in T-wave morphology, such as the ones we observed in individuals on sotalol. The representative beats (10-beat based) are selected according to their heart rate. We investigated the repolarization values for heart rate between 86 bpm and 53 bpm using 17 bins (RR varying from 700 to 1,125 ms by steps of 25 ms). For each bin, we computed the average values of QT duration and T-wave amplitude and the standard deviation of these measures (see Figs. 1 and 2).

### Statistical Analysis

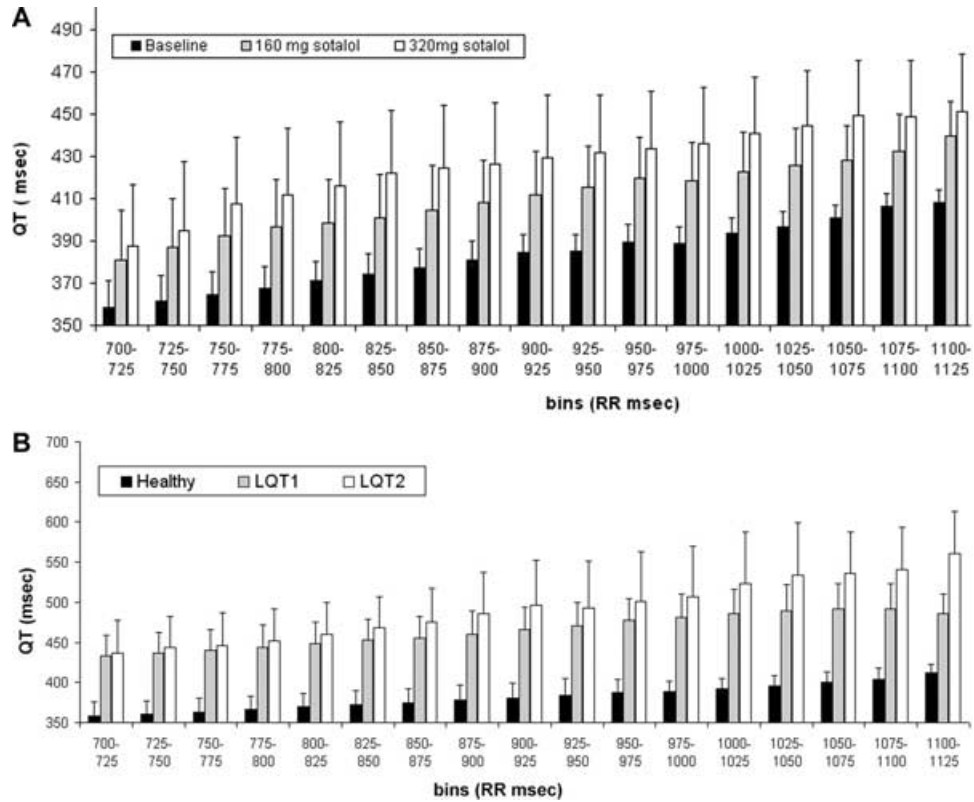
Based on *t*-tests or nonparametric Kruskal-Wallis tests, we compared means and median values between groups. A *P* value  $< 0.05$  was considered significant. All analyses including the linear regression analysis for QT/RR and Tamp/RR models were computed using the SAS software (SAS Institute Inc., Cary, NC, USA). We visually reviewed each scatterplots describing the QT/RR and Tamp/RR in order to evidence outlying values that might have biased the modeling of the linear relationship.

Because the sotalol study had a cross-over design (time-dependent measures in the same individuals), we opted for generalized linear mixed models, used to fit logistic regression with random intercepts,<sup>16</sup> to investigate the role of various ECG parameters in predicting the presence of sotalol. Binary logistic regression models were used to predict the type of mutations when analyzing the data from the patients with the congenital long QT syndrome.

## Results

### Population Characteristics

The study groups consisted of 25 LQT2 carriers (age:  $35.5 \pm 9.4$  years), 49 LQT1 carriers (age:  $34.3 \pm 10.2$  years), and 37 healthy individuals (age:  $27.5 \pm 8.1$  years). The



**Figure 1.** Description of the distribution of the QT interval durations across heart rate in healthy individuals on and off sotalol (panel A) and in patients with the congenital LQTS (panel B). In A: baseline vs 320 mg:  $P < 0.05$  for all RR bins; baseline vs 160 mg:  $P < 0.05$  for all RR bins; 160 mg vs 320 mg:  $P = 0.05$  for  $RR \geq 750$  ms. In B: Healthy vs LQT1/2:  $P < 0.05$  for all RR bins; LQT2 vs LQT1:  $P < 0.05$  for all  $RR \geq 1,075$  ms.

demographic characteristics and summary statistics for ECG intervals in these groups are provided in Table 1. There were more females in LQT2 and LQT1 groups than in the cohort of healthy subjects. Thirty-one LQT1 (63%) and 11 LQT2 carriers (44%) were on beta-blockers at the time of the recording of the Holter ECG. Mean QTc at baseline was significantly longer in LQTS subjects in comparison to healthy controls. There was a trend toward a longer baseline QTc in LQT2 than LQT1 subjects. Mean T-wave amplitude at baseline was significantly lower in LQT2 carriers in comparison with LQT1 carriers and healthy subjects.

The size of the group of healthy subjects was reduced from 37 to 21 in the 320 mg sotalol dose arm. All 10 females were excluded because of the large QT prolongation measured at a 160 mg dose. As shown in Table 1, QTc was prolonged by sotalol in a dose-dependent manner. Mean levels of T-wave amplitude were not significantly different when comparing values off and on sotalol.

### RR Bin Analysis: QT Interval and T-Wave Amplitude Across Heart Rate

The RR bin analyses of the QT interval duration are summarized in Figure 1. They demonstrate the presence of significant QT interval prolongation in patients with the LQT1 and LQT2 as well as in individuals on sotalol in comparison to baseline recordings in healthy individuals.

In the congenital LQTS (Fig. 1B), we found a significant difference of QT interval duration ( $540 \pm 53$  vs  $492 \pm 31$  ms,  $P < 0.05$ ) between LQT1 and LQT2 patients only

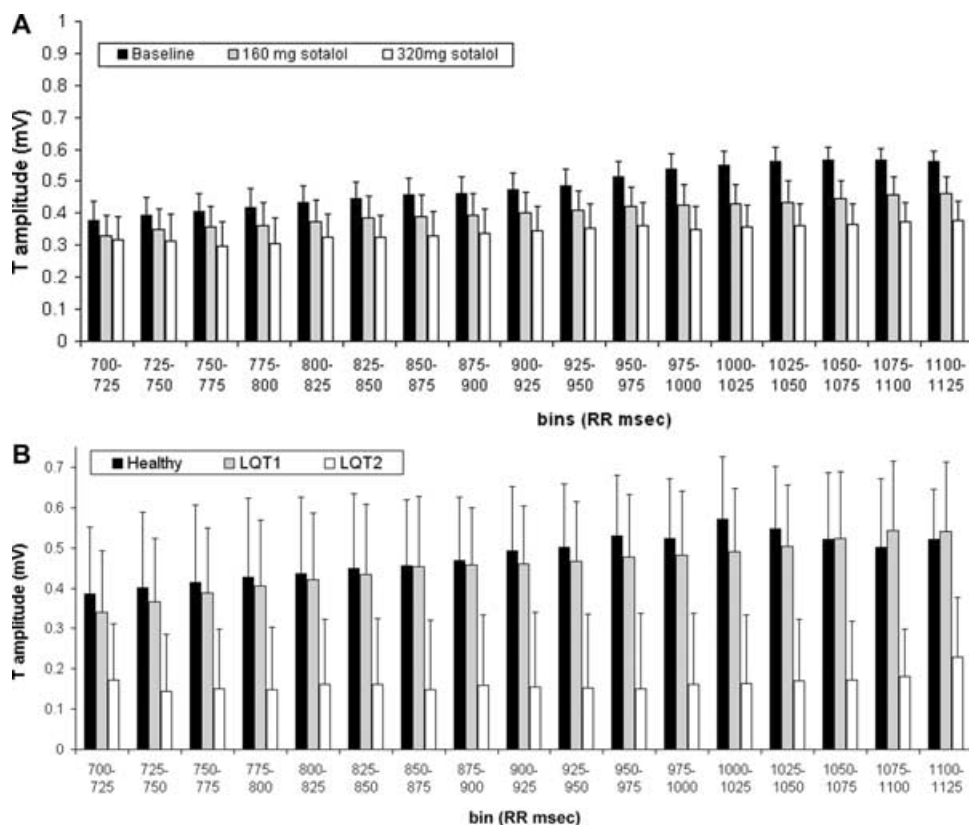
at low heart rate (for  $RR > 1,075$  ms). The dose-dependent effect of sotalol on QT interval duration also occurred at low heart rate, but this trend did not reach significance.

In Figure 2A and B, the values of T-wave amplitude are shown across the RR bins. In the congenital LQTS patients, no difference was found between LQT1 and healthy individuals, whereas LQT2 patients showed strong significant decrease ( $P < 0.05$ ) of T-wave amplitude, leading to a loss of the relationship between T-amplitude and RR bin. The effect of sotalol on T-wave amplitude shows very similar pattern with a clear dose-dependent effect of the drug on T-wave amplitude exacerbated at low heart rate. The example of the effect of heart rate and sotalol on the surface ECG is illustrated in Figure 3.

### Repolarization and HR Dependency

#### QT/RR relationship

The analysis of QT/RR relationship at baseline in healthy subjects (Table 2) showed a linear slope equal to  $0.12 \pm 0.04$  in healthy subjects and a significantly higher slope in LQT1 and LQT2 carriers (QT slope  $> 0.17$ ). The effect of sotalol on the QT/RR relationship in healthy subjects was much less pronounced with values equal to  $0.15 \pm 0.05$  and  $0.14 \pm 0.06$  for 160 mg and 320 mg dose, respectively. It is noteworthy that the sotalol-induced QT/RR slope changes were not dose-dependent. The upper panel of Figure 4 provides a schematic presentation of the QT/RR relationship for all groups.



**Figure 2.** Description of the distribution of the T-wave amplitude across heart rate in healthy individuals on and off sotalol (panel A) and in patients with the congenital LQTS (panel B). In A: Baseline vs 320 mg:  $P < 0.05$  for all RR bins; Baseline vs 160 mg:  $P < 0.05$  for  $RR \geq 975$  ms; 160 mg vs 320 mg:  $P = 0.05$  for  $RR \geq 1000$  ms. In B: Healthy vs LQT1: not significant for all RR bins; LQT2 vs LQT1:  $P < 0.05$  for all RR bins.

#### T-amplitude/RR relationship

The value of the slope characterizing the relationship between the amplitude of the T-wave and the RR intervals was  $0.55 \pm 0.29 \mu\text{V/ms}$  in healthy individuals. In Holter recordings of patients with the KCNQ1 mutation, no difference of T-amplitude/RR slope was observed, compared with the healthy group ( $0.62 \pm 0.40 \mu\text{V/ms}$ ). However, a significantly decreased slope was found in patients carrying a KCNH2 mutation ( $0.31 \pm 0.27 \mu\text{V/ms}$ ) in comparison to healthy individuals ( $P < 0.05$ ). Also, we found a dose-dependent effect on the slope of the T-wave amplitude/RR relationship

in the ECGs of healthy subjects on sotalol. The slope on the 160 mg and 320 mg doses was  $0.26 \pm 0.19 \mu\text{V/ms}$  and  $0.21 \pm 0.14 \mu\text{V/ms}$ , respectively ( $P < 0.05$ ). The T-amplitude/RR relationship for all investigated groups is provided in the lower panel of Figure 4.

#### Role of Age, Gender, and Beta-Blockers: A Multivariate Investigation

We implemented two multivariate models: the first one for predicting the presence of LQT2 mutation among the

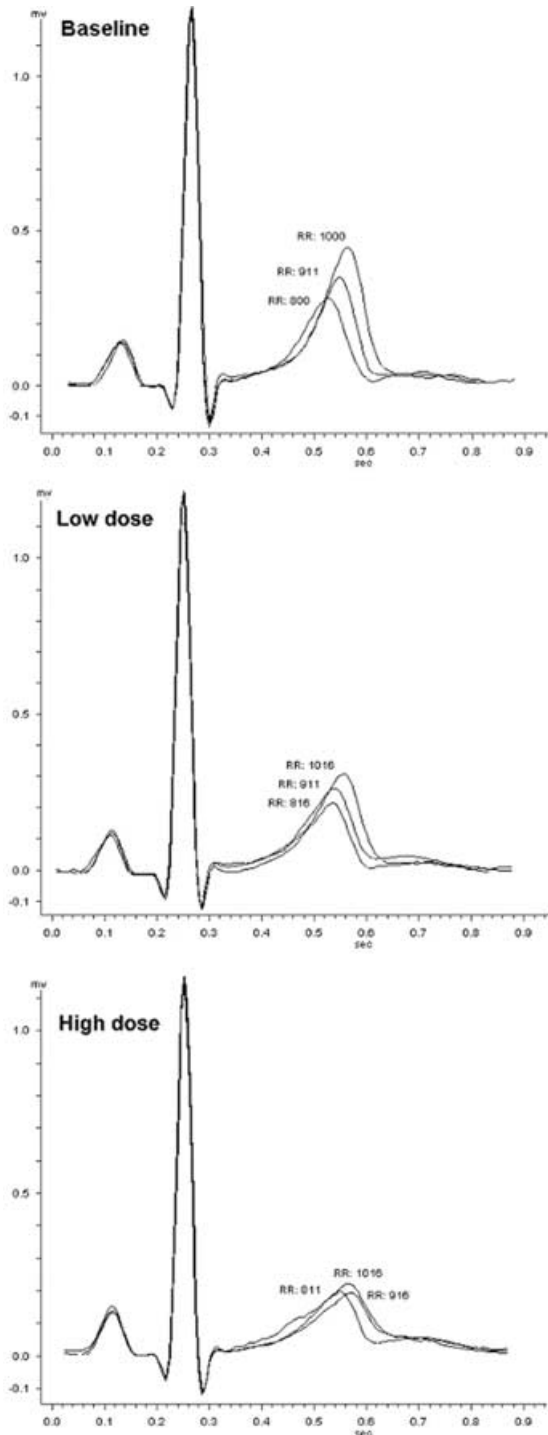
TABLE 1

Characteristics of the Study Populations

	Healthy (n = 37)	LQT1 (n = 49)	LQT2 (n = 25)	Healthy after 160 mg (n = 37)	Healthy after 320 mg (n = 21)
Females	29%	71% <sup>†</sup>	76% <sup>†</sup>	29%	0%**
Age (yrs)	27.5 ± 8.1	34.3 ± 10.2 <sup>†</sup>	35.5 ± 9.4 <sup>†</sup>	-	-
Beta-blockers (%)	0	63	44	-	-
RR (ms)	784 ± 72	841 ± 114 <sup>†</sup>	837 ± 153	893 ± 63 <sup>‡</sup>	947 ± 70 <sup>‡**</sup>
T amplitude (mV)	0.41 ± 0.15	0.42 ± 0.16	0.16 ± 0.17 <sup>†*</sup>	0.41 ± 0.15	0.36 ± 0.12
QT (ms)	367 ± 19	451 ± 37 <sup>†</sup>	470 ± 69 <sup>†</sup>	405 ± 23 <sup>‡</sup>	427 ± 24 <sup>‡**</sup>
QTc F (ms)	399 ± 16	479 ± 28 <sup>†</sup>	499 ± 48 <sup>†</sup>	422 ± 22 <sup>‡</sup>	437 ± 20 <sup>‡**</sup>
QTc B (ms)	417 ± 18	495 ± 28 <sup>†</sup>	515 ± 40 <sup>†</sup>	431 ± 24 <sup>‡</sup>	441 ± 20 <sup>‡</sup>

Average values and standard deviations for the overall diurnal period.

Measurements are from lead II. QTc B: heart rate corrected QT using Bazett's formula; QTc F: QTc corrected using Fridericia formula. <sup>†</sup> $P < 0.02$  in comparison with healthy group. \* $P < 0.05$  in reference to LQT1. <sup>‡</sup> $P < 0.01$  in comparison with healthy group. \*\* $P < 0.05$  in reference to low dose group.



**Figure 3.** The ECG tracings from lead II for the same individual at similar heart rate during baseline, and on 160 mg (low dose) and 220 mg (high dose) dose of sotalol. The figure illustrates the morphological changes of the T-wave induced by sotalol as well as the impairment of T-amplitude dependency to heart rate (RR interval) in msec.

patients with the congenital LQTS, and a second model for predicting the presence of sotalol. The objectives in both models were to assess the independent predictive values of QTc, QT/RR, Tamp/RR, age, gender, and beta-blockers for identifying LQT2 mutation or the presence of sotalol.

First, a binary logistic model was used to compute the odds ratio (OR) for each factor associated with the prediction of LQT2. Only Tamp/RR slope was associated with a statistically significant predictive value ( $P = 0.002$ ,  $OR = 0.67$ ) after adjustment for QTc, QT/RR slope, age, gender, and presence of beta-blockers. For each decrease of  $0.10 \mu\text{V}/\text{ms}$  of the Tamp/RR slope, there was a 33% increase probability of being a LQT2 patient. When predicting the presence of sotalol, QTc and Tamp/RR slope were two significant independent predictors. Each 1 ms increment in QTc interval duration was associated with 5% increased probability of being on sotalol ( $P = 0.004$ ), and each  $0.10 \mu\text{V}/\text{ms}$  decrease in Tamp/RR slope was associated with 46% increased probability of being on sotalol ( $P = 0.005$ ), the model was adjusted for age and gender.

## Discussion

This study investigates parameters of repolarization dynamics in conditions reflecting congenital and acquired abnormality of  $I_{K_r}$  function and in drug-free baseline recordings in healthy subjects. The analysis confirmed the greater steepness of the QT/RR slope in individuals with the LQT1 and LQT2 compared to the baseline in healthy subjects, as well as the increase from baseline in the QT/RR slope in healthy subjects on sotalol.<sup>17</sup> In LQT2 patients, the QT interval was longer at slower heart rate leading to a steeper QT/RR slope than in LQT1 and healthy subjects. These results confirm previous observations on the heart rate dependency of QT interval in subtypes of the congenital LQTS<sup>18,19</sup> and the prominent role of  $I_{K_r}$  current at slow heart rate.<sup>20</sup> The Tamp/RR relationship was found to be significantly reduced in patients with the LQT2 syndrome and on sotalol in comparison to healthy individuals and LQT1 patients. This observation related to abnormal dynamics of the amplitude of the T-wave in individuals with  $I_{K_r}$ -related abnormalities is novel. Following our preliminary observations, this factor may be useful for improving the diagnosis of congenital LQTS because of its phenotype/genotype correlation and also for the assessment of early drug cardiotoxicity specific to  $I_{K_r}$  blockade.

### T-Amplitude and Heart Rate Dependency

It is noteworthy that most studies looking at the relationship between T-amplitude and RR interval have focused on postexercise period in healthy individuals and demonstrate a relationship between the amplitude of the T-wave and RR interval that is inversely proportional.<sup>21,22</sup> In our investigation, the T-wave signals are analyzed during repolarization steady state ensured by selecting cardiac beats with stable RR intervals. Interestingly, the relationship of T-amplitude and RR interval is inverted in comparison to nonsteady state with increased amplitude during slower heart rate (RR increased). This confirms previous observations from Lehman and Yang.<sup>23</sup> The mechanisms behind the inverted relationships of T amplitude and RR interval between repolarization steady-state and recovery periods are unknown. Further investigations will be needed to demonstrate the mechanisms involved in this profound change on the repolarization process.

TABLE 2  
Repolarization Parameters and Heart Rate Dependency in Studied Groups

	Healthy (n = 37)	LQT1 (n = 49)	LQT2 (n = 25)	Healthy after 160 mg (n = 37)	Healthy after 320 mg (n = 21)
Q1 RR (ms)	700 ± 64	764 ± 94	771 ± 129	810 ± 64	864 ± 66
IQR RR (ms)	165 ± 42	151 ± 76	123 ± 53	162 ± 48	162 ± 30
Nb beats	5393 ± 459	3000 ± 910	2584 ± 955	4790 ± 410	4526 ± 320
QT/RR slope	0.12 ± 0.04	0.17 ± 0.10*	0.22 ± 0.16*	0.15 ± 0.05*	0.14 ± 0.06
Tamp/RR ( $\mu$ V/ms) slope	0.55 ± 0.29	0.62 ± 0.40	0.31 ± 0.27*‡	0.26 ± 0.19*‡	0.21 ± 0.14*‡

P < 0.05 in reference to healthy, †P < 0.05 in reference to LQT1.

Q1 = first quartile and IQR = interquartile range.

Nb beats: average number of representative beats for the calculation of the regression slopes.

### *I<sub>Kr</sub>* Blockade and T-Wave Amplitude

The clinical observation described in this work on the effect of *I<sub>Kr</sub>*-blocking compound on the amplitude of T-wave is not consistent with current work on the modeling of ionic currents and the genesis of the electrocardiographic waveforms.<sup>24</sup> Gima *et al.* report increased T-wave amplitude following a blockade of the *I<sub>Kr</sub>* ion currents when modeling the surface ECG in simulated LQT2 mutation. The explanation for this inconsistency is unclear. It may reside in the cycle-dependency of *I<sub>Kr</sub>* kinetic in human cardiac cells, which remains to be fully understood.

The changes in the T-amplitude/RR slope are more pronounced than the changes of QT/RR slope. The largest changes in QT/RR slope were found in LQT2 patients with a 1.8-fold increase in steepness compared to the baseline recordings from healthy subjects. For the T-amplitude/RR slope, all groups of individuals with abnormal *I<sub>Kr</sub>* kinetics

have at least a 2-fold decrease in slope. We conclude that the lack of changes in T-amplitude/RR slope in comparison to healthy individuals is a common feature found in individuals with *I<sub>Kr</sub>* inhibition. This conclusion requires further demonstration to be fully acceptable, but it is consistent with current studies that have investigated the effect of *I<sub>Kr</sub>*-blocking compounds or *I<sub>Kr</sub>*-related channelopathies. For instance, the work from Houltz *et al.* investigated the predictive value of ECG parameters for almokalant-induced conversion of chronic atrial tachyarrhythmias.<sup>25</sup> They reported a significant decrease of T-wave amplitude in individuals on almokalant, but the heart rate dependency of this amplitude decrease was not studied. In other reports, *I<sub>Kr</sub>*-inhibitory drugs have been associated with a reduction of the T-wave,<sup>26,27</sup> but again, these studies have not investigated the effect of this ion-current inhibition on the T-amplitude/RR relationship or consider correcting the T-amplitude measurements for heart rate.

### Limitations of the Study

This is an observational study involving patients with the congenital LQTS and healthy individuals with sotalol-induced QT prolongation. The limited size of our study population did not provide enough power for a meaningful investigation of the role of gender in the T-amplitude impairment to heart rate. As shown in Table 1, the number of females is significantly higher in the LQTS groups than in the healthy population. To address this problem, we forced gender as a covariate in our multivariate models in order to adjust for it when looking for the predictive values of Tamp/RR slope for identifying the presence of *I<sub>Kr</sub>* blockade. Gender was never significantly contributing to the model. The T-wave amplitude can be affected by the body position, body weight, and the selected lead.<sup>28</sup> In this study, we did not consider these factors. Also, we analyzed surface ECGs in healthy subjects; our observations may not reflect what happened in patients treated by sotalol over a long period of time. Finally, an independent dataset is required for validating our predictive models.

### Conclusion

This work confirms the presence of a positive relationship between the T-wave amplitude and the RR interval at steady state. This relationship is inverted in comparison with the relationship described during exercise. An impaired adaptation of T-wave amplitude has been observed as a common electrocardiographic feature associated with KCNH2

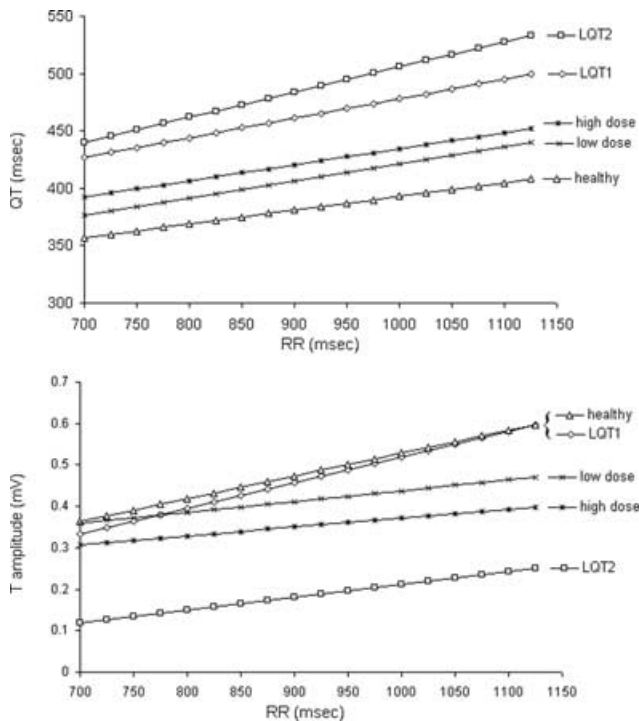


Figure 4. Summary of the QT/RR and T-amplitude/RR relationship in healthy individuals, and in individuals with sotalol-induced QT prolongation and the congenital form of the LQTS.

mutation and the acquired repolarization delay by the  $I_{Kr}$ -blocking drug sotalol. This ECG marker may play an important role in the future of the assessment of the penetrance of KCNH2 mutation and the identification of the presence of drug effect on the  $I_{Kr}$  ion kinetics.

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