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Gene-specific paradoxical QT responses during rapid eye movement sleep in women with congenital long QT syndrome

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Abstract

BACKGROUND—Patients with congenital long QT syndrome (LQTS) type 2 (LQT2) may develop arrhythmias during emotional stress, acoustic stimuli, or sleep. Women with LQT2 are more susceptible to fatal arrhythmias than are men.

OBJECTIVE—The purpose of this study was to examine the effects of sleep on RR and QT intervals in patients with LQT1, in those with LQT2, and in controls and to test the hypothesis that there is a gene-specific effect of sleep on the QT interval in LQT2 that may be especially evident in women with LQT2.

METHODS—Thirty-four subjects with genotyped LQTS and 18 healthy controls were studied. Among the 34 subjects with LQTS, 16 (10 women, age 32 ± 3 years) had LQT1 and 18 (11 women, age 38 ± 3 years) had LQT2. Subjects underwent standard polysomnography including ECG recordings. RR, QT, and QTc (Bazett and Fridericia formulas) were measured over recordings obtained during stable conditions during wakefulness, during stage 2 and stages 3–4 of non-rapid eye movement (NREM), and during rapid eye movement (REM) sleep.

RESULTS—LQT2 women showed a marked RR decrease and marked QT and QTc increase from NREM to REM sleep, changes that were not observed in either women or men with LQT1 or in men with LQT2.

CONCLUSION—Pronounced cardiac activation during REM and substantial QTc prolongation is noted in a sex- and gene-specific fashion among women with LQT2. REM-related changes in cardiac activation and ventricular repolarization may be implicated in sleep-related malignant arrhythmias in women with the LQT2 genotype.

Keywords

Autonomic nervous system; Heart rate; Long QT syndrome; QT interval; Sex; Sleep

Introduction

The congenital long QT syndrome (LQTS) is a genetically heterogeneous disease characterized by abnormal ventricular repolarization with prolonged QT interval and malignant arrhythmias leading to syncope, cardiac arrest, and sudden death.^{1–3} Hundreds of LQTS susceptibility mutations have been identified in the genes encoding for ion channels involved in the control of cardiac repolarization.⁴ The most frequent mutations occur in the gene *KCNQ1* (*KVLQT1*) of chromosome 11^{5,6} and in the gene *KCNH2* (*HERG*) on chromosome 7.^{7,8} *KCNQ1* mutations yield LQTS type 1 (LQT1) stemming from a functionally perturbed slow component of the delayed rectifier potassium current I_{Ks} , whereas *KCNH2* (*HERG*) mutations affect the rapidly activating component of the delayed rectifier potassium currents I_{Kr} and are responsible for LQTS type 2 (LQT2). Although both LQT1 and LQT2 are characterized by diminished repolarizing outward K^+ currents, the time and voltage characteristics of the function of these ion channels are associated with different phenotypes, features on ECG,⁹ mechanisms^{4,10} and triggers underlying arrhythmia,^{11,12} and prognosis.^{11,13} The heart-rate corrected QT interval (QTc) has been identified as an ECG marker of cardiac events in patients with LQTS.¹³ However, among patients with LQT2 but not LQT1, women have a worse prognosis than men,¹³ suggesting that interactions between genotype and gender have a significant effect on the clinical manifestations of LQTS.

Data from the International Registry of LQTS show that the trigger for arrhythmic episodes is genotype specific.¹¹ Although the most frequent trigger of major cardiac events in patients with LQT1 is exercise, in patients with LQT2 the most frequent triggers are emotional stress and sudden acoustic stimuli causing arousal from rest or sleep.¹¹ Importantly, almost 30% of all events and 49% of fatal events in LQT2 patients are related to sleep or rest in the presumed absence of any arousal.¹¹ Sleep may be associated with autonomic responses that may contribute to arrhythmogenesis.¹⁴

Sleep is a dynamic highly organized process generated in the brain. It modulates the physiology of most body organs and systems, including heart and vessels.¹⁵ Based on several polysomnographic features, sleep is conventionally divided into non-rapid eye movement (NREM) and rapid eye movement sleep (REM), which differ on various levels, including brain electrical activity, muscle tone, and respiratory and cardiovascular control. NREM, the restorative sleep, is defined by a synchronized electroencephalogram and is further subdivided into four stages that parallel the depth of sleep, with arousal threshold highest in stages 3 to 4. REM sleep, the state in which dreams are most likely to occur, is defined by electroencephalographic activation (resembling wakefulness), muscle atonia, and bursts of rapid eye movements. NREM sleep and REM are also characterized by unique autonomic influences on cardiac and circulatory physiology. NREM is marked by relative autonomic stability with a stable low heart rate and low blood pressure,¹⁶ whereas REM sleep, a state of autonomic instability, is dominated by remarkable fluctuations in cardiovascular autonomic tone with abrupt blood pressure and heart rate surges. The “autonomic instability” typical of REM sleep may facilitate the occurrence of arrhythmias in the presence of cardiac pathology.¹⁶ Sleep can also affect ventricular repolarization¹⁷ and

influence the QT/RR relationship in a gender-specific manner in healthy normal subjects.¹⁸ In men, the QT interval adapts to changes in RR that occur during both non-REM (NREM) and REM. In contrast, in women the capacity of the QT to adapt to changes in RR, preserved during NREM, is attenuated during REM, when a reduction of RR is accompanied by a paradoxical increase in QT, leading to QTc prolongation.¹⁹

In the present study, we examined the effects of sleep on RR and QT intervals in normal subjects and in patients with LQT1 or LQT2. We sought to test the hypothesis that there are gene-specific effects of REM sleep on the QT interval in LQT2, which may be especially evident in women with LQT2.

Methods

Study population

The study population consisted of 34 subjects with genotyped LQTS and 18 controls. Subjects were free from other significant medical and psychiatric comorbidities. Sixteen subjects (10 women and 6 men; age 32 ± 3 years [mean $\pm$ SEM]) had LQT1; 18 subjects (11 women and 7 men, age 38 ± 3 years) had LQT2. All LQTS subjects hosted single mutations in either *KCNQ1* (LQT1) or *KCNH2* (LQT2). The 16 subjects with LQT1 subjects belonged to 11 unrelated families. The 18 LQT2 subjects belonged to 10 unrelated families. Five (31%) LQT1 subjects (4 women and 1 man) and 6 (33%) LQT2 subjects (4 women and 2 men) were taking beta-blockers. Other than beta-blockers, none of the subjects was taking any medications. Five subjects (3 LQT1, 2 LQT2) had an implantable cardioverter-defibrillator secondary to a previous cardiac arrest. Eighteen healthy subjects (11 women and 7 men; age 35 ± 3 years) were studied as controls.

Study protocol

Subjects presented to the Mayo Clinic GCRC Sleep Laboratory at 7 PM. They had been asked to avoid caffeine for 24 hours prior to the study. After a brief assessment that included personal and family medical histories, physical examination, and 12-lead ECG, the subjects underwent a sleep study using full polysomnography with simultaneous continuous recording of ECG and respiration, according to our standard laboratory procedure.¹⁹ The study was approved by the Mayo Foundation Institutional Review Board. All subjects signed the consent form.

Data collection

Monitored polysomnography was performed according to a standard clinical protocol,¹⁹ with recording of EEG (C3-A2, Fz-Cz, Cz-Oz), submental and anterior tibialis electromyography, electrooculography, electrocardiography, and oronasal airflow (thermocouples). Thoracic activity and abdominal respiratory activity were monitored by inductive plethysmography (Respirtrace, Ambulatory Monitoring, Ardsley, NY, USA), upper airway sounds by microphone, and oxyhemoglobin saturation by finger probe oximeter (Nellcor pulse oximeter). Simultaneous ECG, beat-by-beat blood pressure (Colin Pilot 9200-Tonometric Blood Pressure, Colin Corp. San Antonio, TX), and respiration (Respirtrace [NIMS], Miami Beach, FL) were recorded, digitized, and stored for subsequent analysis.

Data analysis

Sleep studies were scored according to standard methods.²⁰ Polysomnographic data acquired included sleep efficiency (total sleep time divided by total time in bed), percentage of each stage of sleep, arousal index (number of arousals per hour of sleep), periodic leg movements index (number of periodic limb movements per hour of sleep), apnea hypopnea

index (number of apneas and hypopneas per hour of sleep), and mean oxygen saturation (mean SaO₂).

ECG data (PowerLab 16 SP, ADInstruments, Inc, Colorado Springs CO) were used for computation of RR and QT intervals. One-minute segment recording of cardiovascular and respiratory signals was selected in each subject for inactive wakefulness (eyes closed and lights out, at the beginning of the study), stage 2, slow-wave sleep, and REM according to the following criteria:

1. Segments were selected, when possible, between 11 PM and 2 AM in order to reduce any possible bias due to time of inactivity on RR and QT intervals.^{20,21}
2. Segments were selected 1 minute after the beginning of each stage and at least 1 minute away from arousals in order to minimize any effects of possible transient abrupt changes in autonomic tone associated with cortical and subcortical activation.
3. Only segments with a stable breathing pattern were selected in order to avoid any QT changes associated with respiratory changes.
4. Only segments with stable blood pressure and RR interval were selected in order to limit any effect of hemodynamic changes on QT.

According to these criteria, the longest duration consistently available for all stages in all subjects was approximately 1 minute.

Data were analyzed blind to genotype and date of study. Data selected were processed by ScopeWin (Annalab, St Anne Hospital, Brno, Czech Republic), which allows automatic detection of R-wave peak, QRS onset, and end of T wave. All recordings were automatically analyzed, manually edited and corrected, and then recomputed to obtain QT values. A bifid or secondary T wave (simulating a pathologic U wave merging from the descendent branch of the T wave) was included as part of the measurements of the QT interval; a normal U wave, which was clearly separated from a T wave, was not included.⁶ The absolute QT was corrected for heart rate RR by applying the Bazett formula ($QT_{cB} = QT/RR^{0.5}$)²² and the Fridericia formula ($QT_{cF} = QT/RR^{0.33}$).²³ Average RR, absolute QT, QT_{cB} , and QT_{cF} intervals were considered.

Statistical analysis

Statistical analysis was performed using Statistica 6.1 (Stat-Soft, Inc., Tulsa, Oklahoma, USA). Differences in demographic and sleep characteristics between groups were assessed by one-way analysis of variance (ANOVA). Post hoc analysis by Tukey Honestly Significant Differences (HSD) was performed in the presence of significance. Sleep-related changes in ECG measures were examined by two-way ANOVA with group as the independent factor [(1) all subjects with LQT1, LQT2, and controls; (2) only females with LQT1, LQT2, and controls; (3) males and females with LQT1; (4) males and females with LQT2] and with state (wakefulness and sleep stages) as a repeated measure. $P \leq .05$ (adjusted) was considered significant. Planned comparisons were performed in the presence of significant interaction, followed by post hoc analyses (Tukey A).

Results

Demographic and sleep parameters

Demographic and sleep characteristics of the three groups are listed in Table 1. Age, body mass index, and sex distribution were similar among the three groups. Beta-blocker use was similar between LQT1 and LQT2 subjects.

ECG changes through sleep in all subjects

None of the subjects presented complex ventricular arrhythmias during sleep recordings. Only one LQT1 female showed repetitive premature ventricular contractions during REM sleep.

Changes in RR and QT intervals from wakefulness through sleep in the three groups of subjects are listed in Table 2. In all groups, RR interval was longer during NREM sleep compared to wakefulness and REM, when values were similar to wakefulness (state effect: $F = 9.06$, $P < .0001$; group by state interaction: $P = \text{NS}$; post hoc analyses in Table 2). QT interval, which was always more prolonged in LQTS subjects than in controls, was more prolonged during stage 2, stages 3–4, and REM compared to wakefulness in all groups (group effect: $F = 10.9$, $P < .001$; state effect: $F = 7.5$, $P < .001$; group by state interaction: $P = \text{NS}$). QT_{CB} and QT_{CF} , which were both consistently more prolonged in LQTS subjects than in controls, remained overall stable from wakefulness through NREM and slightly increased during REM compared to wakefulness and NREM sleep (state effect: $F = 6.8$, $P < .01$; post hoc analysis: $P < .05$ REM vs wakefulness and NREM; group by state interaction: $P = \text{NS}$).

Women with LQT1, LQT2, and controls

Figure 1 shows the comparison of ECG variables in women with LQTS and controls. Overall, RR interval changed from wakefulness through sleep (state effect: $F = 13.4$, $P < .0001$) and increased slightly during stage 2 NREM compared to wakefulness ($P < .05$) and REM sleep ($P < .05$). However, in women with LQT2 compared to controls and those with LQT1, RR interval did not increase during stage 2 and stages 3–4 of NREM sleep compared to wakefulness, and decreased more markedly during REM compared to wakefulness and NREM (interaction: $F = 2.13$, $P < .05$; planned comparison: controls: $F = 7.3$, $P < .001$, LQT1, $P = \text{NS}$; LQT2: $F = 9.9$, $P < .0001$).

QT interval, which always was higher in females with LQTS than in controls (group effect: $F = 4.5$, $P = .02$), was overall slightly increased during NREM as well as during REM (state effect: $F = 4.3$, $P = .03$; post hoc analysis: all sleep stages vs wakefulness $P < .05$). No groups by state interaction was observed, although in LQT2 the QT tended to be longer during REM compared to the other groups.

A group by state interaction was observed for both QT_{CB} and QT_{CF} , which increased significantly only in LQT2 women during REM versus NREM and REM versus wakefulness (interaction: $F = 3.1$ and 3.6 , $P < .01$ for both variables; planned comparison $P < .00001$ in LQT2 only, post-hoc analyses: $P < .01$ during REM versus wakefulness and REM versus NREM).

In a woman with LQT2, slight shortening in RR interval during REM was accompanied by beat-to-beat changes in the T-U waves, which were absent during wakefulness and stage 2 NREM (Figure 2).

Women and men with LQTS

Figures 3 and 4 show the comparison of the ECG changes in women and men with LQT1 and LQT2 respectively. No group by state interaction was observed for RR, QT, QT_{CB} and QT_{CF} among LQT1 subjects (Figure 3). In LQT2 subjects, a more marked NREM-to-REM RR shortening was observed in women (~100 ms) compared to men (~10 ms) (state effect $F = 5.2$, $P < .01$; group by state interaction $F = 2.3$, $P = 0.09$) (Figure 4). QT tended to increase during REM in women (Interaction $F = 1.8$, $P = 0.16$). QT_{CB} and QT_{CF} were more prolonged during REM sleep compared to wakefulness and NREM only in women, and did not change

in men (Interaction for QT_{CB}: $F = 3.56$, $P < 0.05$; QT_{CF}: $F = 3.4$, $P < 0.05$; planned comparison: $P < 0.001$ in women only, for both variables; post-hoc: QT_{CF} REM versus NREM and wakefulness < 0.05).

LQT2 women with and without beta-blockers

Figure 5 shows the results of the comparison between LQT2 women with and without beta-blockers. In both groups with and without beta-blockers the RR shortened significantly (State effect $F = 9.9$, $P < 0.001$), and the QTc significantly increased ($F = 4.3$, $P < 0.01$) during REM compared to wakefulness and NREM (for all, $P < 0.01$). No group by state interaction was observed to affect any of the ECG variables examined.

Discussion

In the current study, we examined sleep-related changes in RR and QT intervals in subjects with LQT1 and LQT2 and healthy controls. We found that the modulations of RR and QT intervals during sleep are altered in women with LQT2 but are preserved in men with either LQT1 or LQT2 and in women with LQT1. More specifically, (1) LQT2 women did not show the expected increase in RR during non-REM sleep; (2) LQT2 women, but not LQT1 women (Figure 1), had striking increases in heart rates during REM, which appear to be an exaggeration of a pattern previously observed in their healthy counterparts¹⁹ such that heart rates during REM were faster even than during wakefulness; and (3) RR shortening during REM in LQT2 women was associated with a marked increase in rate-corrected QTc, using either the Bazett or Fridericia formula for heart rate correction. Such RR and QT changes during REM observed in LQT2 women appear to be sex specific as they were not observed in LQT2 men (Figure 4).

About one third of major cardiac events in LQT2 patients occur during sleep or at rest, in the absence of any known arousal.¹¹ The underlying mechanisms are not known. Women with LQT2 have been reported to have a worse prognosis than LQT2 men.¹³ An association between sex and the type of trigger of events (e.g., sleep or arousal) has not yet been reported. What is known is that female gender and QTc ≥ 500 ms are associated with increased risk of life-threatening cardiac events.⁴ In our study, QTc in REM in women with LQT2 increased to 532 ± 23 ms compared to only 481 ± 18 ms in women with LQT1.

This is the first study evaluating sleep stage-specific changes in QT and RR modulation in patients with congenital LQTS. A previous study using 24-hour Holter monitoring did not find any significant change in QTc during the nighttime compared to the daytime in subjects with LQT2.²⁴ However, actual sleep, sleep stages, breathing changes, and any effects of sex on RR intervals and the QT/RR relationship were not taken into consideration.

In the present study using complete overnight polysomnography, we showed that REM sleep has distinct effects on modulation of the RR and the QT/RR relationship in women with LQT2 compared to women with LQT1 and in men with either LQT1 or LQT2. Importantly, such effects were mitigated when considering LQTS groups without distinguishing by sex (Table 2). Thus, our results suggest that REM sleep may induce significant cardiac activation and affect ventricular repolarization only in women but not men with the LQT2 genotype, suggesting a potential mechanism for generation of sleep-related life-threatening arrhythmias in these subjects.

As mentioned, the LQT2 women in our study showed an exaggeration of the physiologic response to REM sleep previously observed in normal women.^{19,25} Normal women, regardless of their age and hormonal status, have a more marked cardiorespiratory activation in response to REM sleep compared to their male counterparts.^{19,26} These gender

differences also appear to be associated with significant prolongation of QT and QTc interval during REM in women¹⁹ that persists after menopause.²⁶ Whether male hormonal mechanisms or nonhormonal gender-related central mechanisms are implicated in this difference requires further investigation.

One third of our LQTS patients were receiving beta-blocker therapy (atenolol, nadolol, or propranolol), which could not be discontinued for ethical reasons. In LQT2 women, significant QT prolongation during REM was evident whether or not subjects were taking beta-blockers. Nevertheless, beta-blocker use could have affected the ECG responses through sleep in LQTS women. Indeed, LQT1 women showed a blunted heart rate increase in response to REM compared to controls, conceivably an effect of beta-blocker treatment. LQT2 women, despite beta-blocker therapy and slower heart rate during presleep wakefulness, manifested a significant heart rate *increase* in REM (faster even than wakefulness; Figure 5) and greater than the REM-related heart rate increase in controls (Figure 1) and in LQT2 men (Figure 4), indicating the magnitude of REM-related cardiac activation among the LQT2 women. Therefore, in patients with LQT2 the neurophysiologic events occurring during REM and the associated surges in sympathetic activity^{27,28} appear to overcome the cardiac slowing action of beta-blockers.

Our findings suggest an explanation that can reconcile the apparent discrepancy between the variety of triggers for events in LQT2 patients, which include sleep and acoustic arousal. A proposed mechanism underlying the occurrence of arrhythmias during sudden intense arousal is abrupt neurally mediated release of catecholamines occurring while the heart rate is relatively slow and “without allowance of time for QT adaptation to faster heart rates.”¹¹ During exercise in LQT2 patients, QT adequately shortens with progressive increase of heart rate.²⁹ In contrast, a bolus injection of epinephrine induces a transient marked prolongation of QTc that is followed by “normalization” to baseline values during steady infusion.^{30,31} Experimental *in vitro* cellular models mimicking the genetic defect of LQT2 describe prolongation of action potential duration and development of early afterdepolarization during early phases of isoproterenol infusion that normalized at steady state.³² Another experimental setting using wedge canine preparations of LQT2 reported that isoproterenol transiently increases transmembrane action potentials and induces torsades de pointes in association with transmural dispersion of repolarization.³³ These data support the potential for sudden increases of sympathetic tone to induce transitory abnormal repolarization and ventricular arrhythmias in LQT2 patients. During REM sleep, phasic events such as bursts of rapid eye movements are accompanied by abrupt changes in autonomic tone with sudden increases in cardiac and peripheral sympathetic drive.¹⁶ These could reproduce the neurohumoral pattern evoked by an intense arousal, with an abrupt increase of heart rate and transient electrophysiologic changes translating into prolongation of QTc and increased arrhythmic vulnerability.

Precedence exists for supposing that the response to REM sleep has features in common with the responses to acoustic stimuli. Typical neurophysiologic features of REM sleep occurring with periods of phasically enhanced excitability and rapid eye movements (pontogeniculo-occipital spikes)³⁴ have been shown in animals to be elicited during wakefulness by intense auditory stimuli that evoke the startle and orienting response.³⁵ Therefore, REM sleep and acoustic stimuli seem to activate common central pathways, which conceivably may be implicated in the genesis of arrhythmias in patients with LQT2, particularly women.

REM is the stage during which the most vivid and emotionally intense dreams occur.³⁶ Fear and anger are common emotions during dreaming.³⁷ Verrier et al³⁸ related emotional stress such as anger to the occurrence of delayed myocardial ischemia and proposed that a strong emotional content of dreams may be able to precipitate life-threatening arrhythmias,¹⁴

possibly by acting through distinct pathways within the central nervous system and involving the sympathetic nervous system.³⁹ Therefore, intense emotional states achieved during dreams could be implicated in the genesis of cardiac events during REM in some patients with LQT2, especially women.

Study limitations

Limitations of the study include the potentially confounding presence of beta-blocker therapy, which could not be discontinued, in one third of our LQTS subjects. Nevertheless, we were able to make some potentially important observations. The ineffectiveness of beta-blockers in moderating the sinus node response and ventricular repolarization during REM was a specific feature of LQT2 women, providing possible insight into the relatively lower efficacy of beta-blockers in preventing events in patients with LQT2.⁴⁰ Second, because of the very low prevalence of patients with LQT3, LQT4, LQT5, LQT6, and other LQT genotypes, these patients were not included in this study. Thus, the study observations are limited to the two most common LQTS genotypes.

Conclusions

Modulation of RR and QT intervals during REM sleep is strikingly different in women with LQT2 than in men with either LQT1 or LQT2 and in women with LQT1. Women with LQT2 experience a significant increase in heart rate (RR shortening) during REM, despite therapy with beta-blockers. This cardiac chronotropic activation in LQT2 women is associated with an abnormal prolongation of QTc suggesting that REM-related changes in cardiac rate and ventricular repolarization may provide the substrate for sleep-related malignant arrhythmias in women with LQT2.

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ABBREVIATIONS

LQT1	long QT syndrome type 1
LQT2	long QT syndrome type 2
NREM	non-rapid eye movement
REM	rapid eye movement

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Figure 1. RR, QT, QTc_F, and QTc_B intervals during wakefulness and sleep in women with LQT1, LQT2, and controls. LQT2 women differed from controls and women with LQT1 with regard to RR (interaction group by state effect: $F = 2.13$, $P = .018$) and QTc (interaction group by state effect: $F = 3.3$, $P = .02$). Specifically, in LQT2 the RR interval did not increase during stage 2 and stages 3–4 non-rapid eye movement (NREM) sleep compared to wakefulness and decreased markedly during rapid eye movement (REM) compared to NREM and wakefulness. QTc in LQT2 was significantly greater during REM compared to NREM sleep and wakefulness.

Wakefulness **Stage 2 N-REM** **REM**

↑ **6 seconds** ↑

Figure 2.

ECG recording during wakefulness, stage 2 non-rapid eye movement (NREM), and rapid eye movement (REM) sleep in a woman with LQT2. During REM, slight shortening of the RR interval was associated with marked prolongation of the QT and QTc intervals and with the appearance of bifid-notched T waves.

Figure 3. RR, QT, QT_{cF}, and QT_{cB} intervals during wakefulness and sleep in men with LQT1 and women with LQT1. RR, QT, QT_{cB}, and QT_{cF} were similar across sleep among LQT1 women and men. REM = rapid eye movement.

Figure 4.

RR, QT, QT_{cF} and QT_{cB} intervals during wakefulness and sleep in men with QT2 and women with LQT2. RR interval during REM shortened slightly in men and more markedly in women (group by state interaction: $F = 2.3$, $P = .09$). A group by state interaction affected both QT_{cF} ($F = 3.4$, $P = .03$) and QT_{cB} ($F = 3.5$, $P = .02$) due to significantly prolonged QT_{cF} and QT_{cB} during rapid eye movement (REM) observed in women but not in men.

Figure 5.

RR, QT, QTc_B, and QTc_F intervals during wakefulness and sleep in LQT2 women with and without beta-blockers. In both groups, RR was significantly decreased (state effect: $F = 9.9$, $P < .001$) and QTc_F significantly increased ($F = 4.3$, $P < .01$) during rapid eye movement (REM) compared to wakefulness and non-rapid eye movement ($P < .01$ for all). No group by state interaction was observed for these variables.

Table 1

Demographic, clinical, and sleep characteristics in subjects with long QT syndrome and controls

	LQT1 (N = 16)	LQT2 (N = 18)	Controls (N = 18)
Female/male	10/6	11/7	11/7
Age (years)	32 ± 3	38 ± 3	35 ± 3
Body mass index (kg/m ²)	26.6 ± 1.2	28.0 ± 1.6	26.7 ± 1.2
Beta-blocker use	6/16*	6/18*	0/18
Sleep latency	20 ± 6	20 ± 5	19 ± 5
TST/TIB (%)	76 ± 3	75 ± 3	78 ± 3
MA index (n/hr)	25 ± 4	28 ± 4	18 ± 4
PLMS index (n/hr)	5.8 ± 2.6	6.6 ± 2.5	4.5 ± 2.6
AHI (n/hr)	4.4 ± 1.6	2.6 ± 1.5	0.8 ± 1.5

All values are given as number or mean ± SE.

AHI = apnea-hypopnea index; LQT1 = long QT syndrome type 1; LQT2 = long QT syndrome type 2; MA = microarousal; PLMS = periodic leg movements during sleep; TST/TIB = total sleep time/Time in bed.

* $P < .0001$ LQT1 and LQT2 vs controls.

Table 2

RR and QT measurements during sleep in subjects with long QT syndrome and controls (adjusted univariate test for repeated measures)

	Wakefulness	Stage 2	Stages 3–4	REM	P value (ANOVA)	Post hoc
RR						
Controls	948 ± 37	1,010 ± 38	1,019 ± 39	949 ± 41	Group = NS	
LQT1	989 ± 39	1,024 ± 39	1,029 ± 41	977 ± 42	State <.0001	<i>a, b, d, e</i>
LQT2	1,048 ± 37	1061 ± 40	1,058 ± 41	989 ± 43	Interaction = NS	
QT						
Controls	413 ± 13	427 ± 12	427 ± 13	423 ± 14	Group <.001	
LQT1	469 ± 12	482 ± 13	478 ± 13	472 ± 14	State <.001	<i>a, b, c</i>
LQT2	487 ± 12	500 ± 13	501 ± 13	507 ± 15	Interaction = NS	
QTc_B						
Controls	430 ± 10	432 ± 9	432 ± 10	441 ± 14	Group <.001	
LQT1	472 ± 10	476 ± 10	475 ± 10	479 ± 13	State <.005	<i>c, d, e</i>
LQT2	479 ± 10	486 ± 9	488 ± 10	512 ± 13	Interaction = NS	
QTc_F						
Controls	420 ± 9	427 ± 9	426 ± 9	432 ± 13	Group <.0001	
LQT1	471 ± 9	479 ± 10	474 ± 10	476 ± 12	State <.005	<i>c, d, e</i>
LQT2	480 ± 9	489 ± 9	491 ± 10	509 ± 14	Interaction = NS	

ANOVA = analysis of variance; LQT1 = long QT syndrome type 1; LQT2 = long QT syndrome type 2; REM = rapid eye movement.

^a Wakefulness vs stage 2;

^b wakefulness vs stages 3–4;

^c wakefulness vs REM;

^d stage 2 vs REM;

^e stage 3–4 vs REM.