Changes in Ventricular Repolarization Duration During Typical Daily Emotion in Patients With Long QT Syndrome

RICHARD D. LANE, MD, PhD, WOJCIECH ZAREBA, MD, PhD, HARRY T. REIS, PhD, DERICK R. PETERSON, PhD, AND ARTHUR J. MOSS, MD

Objective: Intense emotions are known triggers of sudden cardiac death. However, the effect of typical daily emotion on repolarization has not been examined. We examined whether QT interval changes as a function of typical daily emotion in patients at risk for cardiac events in the context of emotion. **Methods:** We studied 161 patients ($n = 114$ females; mean age, 35 years) with the congenital form of the Long QT Syndrome during daily activities. Each day for 3 days, a 12-hour Holter recording was completed. Patients were paged ten times per day at random times and rated the intensity of 16 prespecified emotions during the preceding 5 minutes. Measurements of QT interval and interbeat intervals were synchronized with emotion ratings. **Results:** Low Arousal Positive Affect was associated with significant increases in QT interval corrected for heart rate (using Fridericia's QTc) ($p < .001$), whereas higher arousal Activated Positive Affect ($p < .001$) and Activated Negative Affect ($p < .01$) were associated with significant decreases in QTc. Changes in QTc as a function of daily emotion ranged from 5-ms increases to 11-ms decreases. High-frequency heart rate variability (vagal tone) was positively correlated with QTc ($p < .001$). The effects of each positive emotion variable on QTc were greater in LQT2 than LQT1 patients ($p < .001$). **Conclusion:** Ventricular repolarization duration (QTc) changes dynamically as a function of daily emotion. These changes are relatively small and do not constitute a risk in themselves. In the context of other risk factors, however, they may contribute to ventricular arrhythmias in vulnerable populations.
Key words: QT interval, Long QT Syndrome, heart rate, heart rate variability, ecological momentary assessments, emotion.

CLM = conditional linear models; **ECG** = electrocardiogram; **EMA** = ecological momentary assessments; **HF-HRV** = high-frequency heart rate variability; **ICD** = implanted cardioverter defibrillator; **LQTS** = Long QT Syndrome; **QTc** = Fridericia correction of QT interval for heart rate; **PDA** = personal digital assistant.

INTRODUCTION

Emotion is an evolutionarily designed system that has profound effects on the operation of nearly all systems in the human body. Consistent with this premise, Lane (1) argued that emotion and emotion regulation are the cornerstone of psychosomatic medicine. Yet, many important questions remain about how emotion contributes to disease and death. For example, sudden cardiac death is the leading cause of death in the western world, responsible for at least 300,000 individuals per year in the United States alone (2), and is therefore a leading problem in contemporary cardiology (3). This is the case despite decades of work focused on the myocardium and cardiac-specific mechanisms. Most existing research (4) on sudden cardiac death related to emotion focuses on instances of intense stress and strong emotions. Compelling evidence (5) indicates that intense stress and negative emotion are triggers of cardiac events in about 20% of cases. Relatively little research, however, has examined the physiological effects of everyday emotions—the more common, everyday affective states people experience on an ongoing basis. The current research examines the impact of everyday emotion on cardiac function in patients at risk for cardiac events in the context of emotion. By doing so, this research addresses the possibility that the influence of emotion on vulnerability to life-threatening arrhythmias is even broader than has been previously appreciated.

Long QT Syndrome (LQTS) has been called the Rosetta Stone for ventricular tachyarrhythmias (6). Because the myocardium, coronary arteries, and conduction system are normal, the genetically based repolarization abnormality that characterizes LQTS constitutes a simple but homogeneous abnormality that may make it possible to more easily detect the influence of factors that affect vulnerability to sudden cardiac death. Alternative clinical models, such as coronary artery disease, are more biologically heterogeneous and would likely require study of many more individuals. In this study, we examine patients with LQTS and evaluate how daily emotion influences changes in the QT interval.

Alterations in the QT interval, a marker of ventricular repolarization, may be due to inherited disorders, such as the long- or short-QT syndrome (7,8) or from acquired conditions, including drugs (9), cerebrovascular disorders (10), acute coronary disease (11), and autonomic factors involving the sympathetic and parasympathetic nervous systems (12). These QT-altering disorders and conditions have been associated with increased risk for ventricular tachyarrhythmias, syncope, and sudden cardiac death. A common genetic variant has been identified that influences the QT interval by a few milliseconds in normal subjects (13). It is generally appreciated that a concordance of several factors may come into play at any time to explain variation in the QT interval and the occurrence of life-threatening arrhythmias in vulnerable subjects. Although various emotional triggers have been associated with life-threatening cardiac events in the LQTS (14,15), including startling events such as the ringing of an alarm clock, no studies in either healthy volunteers or any clinical group have examined changes in QT interval in relation to emotion during routine daily activities.

Changes in QT interval in relation to emotion have been studied in the context of stress and depression. A study of

healthy physicians revealed that, in the context of heart rate increases associated with emergency phone calls while on call, QT interval was prolonged relative to the expected shortening associated with heart rate change (16). Another study (17) of healthy volunteers showed that performance of stressful mental arithmetic was associated with prolongation of QT interval corrected for heart rate. A third study (18) in patients with eating disorders revealed a positive correlation between QT interval corrected for heart rate and self-reported depression.

Previous studies (14,19) of emotional triggers of cardiac events have typically relied on recalled emotions. The biases inherent in retrospections about emotions and behavior are well established (e.g., retrospective reinterpretation, selection of events to describe, difficulties summarizing across diverse events, motivated forgetting) (20). "Event-sampling" techniques, such as ecological momentary assessments (EMA) (21), are a recent innovation that overcome many of these limitations. While in their natural social-ecological context, subjects are asked to rate the intensity of emotions experienced at a particular moment. By virtue of contemporaneity, the EMA procedure provides less biased emotion self-reports than has been typical in previous research relating emotions to the propensity for life-threatening arrhythmias. Moreover, unlike emotion ratings made shortly after a cardiac event (19), subjects have no knowledge of their momentary QT interval; thus, the latter cannot influence their ratings.

In a study involving 161 subjects with LQTS, we assessed the influence of emotions on the QT interval during usual daily activities. We hypothesized that alterations in emotional states during the day would have a definable influence on ventricular repolarization.

METHODS
Overview

Due to the rarity of LQTS and the small number of patients in any one location, home visits were made to LQTS patients throughout the United States. On each of 3 days, a Holter recorder was attached to the patient for a 12-hour recording. Patients engaged in their usual daily activities and were paged (on vibration mode) ten times per day at random times. Patients responded to the page by answering 59 questions, using a Palm personal digital assistant (PDA) pertaining to the 5 minutes preceding the page, including current activities (2 items), location (1 item), exertion intensity (1 item), social circumstances (24 items), and 22 emotion terms, and nine somatic symptoms rated on a 7-point intensity scale. Seventy-nine (1.7%) of the 3,967 pages occurred as subjects were exercising. The intensity of exertion varied evenly across a 7-point exertion intensity scale. These data indicate that exertion had a negligible influence on our results. The current study focused on the emotion ratings. Clocks in the pager, Holter, and PDA were synchronized.

Patients

Patients were recruited from the International Long QT Syndrome Registry located in Rochester, New York. Inclusion criteria limited enrollment to men and women ranging in age between 16 years and 50 years and who were genotype positive for LQT1 or LQT2, accounting for 90% of LQTS patients with genotypes (7). Exclusion criteria included diminished cognitive capacity interfering with informed consent or completion of the research procedures or lack of English fluency (needed for valid completion of self-report measures). Patients were not preselected for prior history of cardiac events, QTc duration, β blocker or implanted cardioverter defibrillator (ICD) treatment.

The study received approval from the appropriate Institutional Review Board/ethics committees, and all patients provided their informed consent. Data were collected between January 2003 and July 2006.

EMA

Participants were paged ten times per day for 3 days, using a modified random schedule. All signals were scheduled during a 12-hour window and during usual waking hours, typically between 8 AM and 10 PM (only one subject had pages after midnight [25% for that subject]). Signals were constrained so that no two signals could occur within 60 minutes of each other. Participants were instructed to turn on their PDA as soon as possible after the page, to begin responding immediately, and to complete the 59-item protocol without interruption.

Based on previous demonstrations of the influence of intense emotions on ventricular arrhythmias and sudden death (5,22), we were particularly interested in activated (high arousal) forms of positive and negative affect. To minimize participant burden, we selected a briefer subset of 22 items for the EMA protocol from the 33-item Positive and Negative Affect Scale (23), a widely used and validated instrument that shows excellent discriminant validity between the positive and negative affect scales. Based on past psychometric studies and clinical relevance to this sample, we preselected a subset of 16 items for the current analysis: 1) Activated Positive Affect: interested, attentive, excited (in a positive way), enthusiastic, and alert ($\alpha = 0.82$); 2) Activated Negative Affect: guilty, anxious, angry, hostile, jittery, and afraid ($\alpha = 0.70$); we also included low-arousal affect terms representing constructs that have been linked to cardiovascular activity in the literature; 3) Low Arousal Negative Affect: sad (24), lonely (25), depressed (26) ($\alpha = 0.73$); and 4) Low Arousal Positive Affect: calm, relaxed (27) ($\alpha = 0.81$). Thus, the present prespecified analysis included 16 of the 22 emotion terms rated. These four scales correspond to the four quadrants defined by two orthogonal dimensions of emotion self-reports, valence (positive-negative), and arousal (28) (Fig. 1).
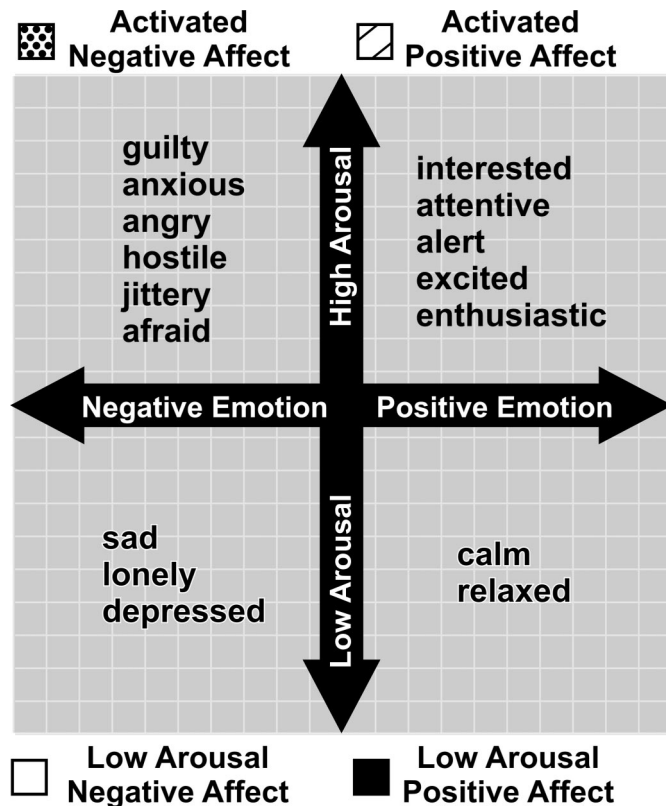

Figure 1. Location of emotion terms used for ecological momentary assessment ratings in relation to two fundamental dimensions of emotion, valence (positive-negative emotion) and arousal.
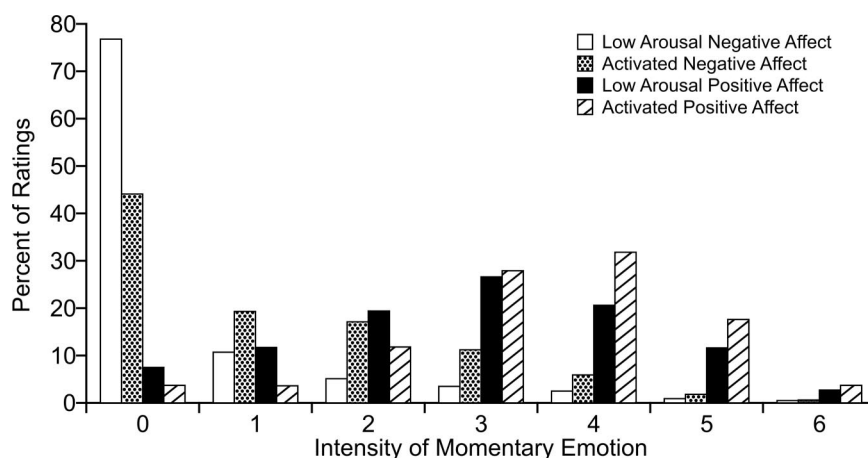
Figure 2. Percentage of emotion ratings at each intensity level. *Bars* depict the percentage of ratings at each intensity level for each of four scales of momentary emotion for 3,967 events. Each scale was rated for each event. See Figure 1 for the terms comprising each scale. The 7-point rating scale was: 0 = none; 1 = mild; 2 = somewhat; 3 = moderate; 4 = quite a bit; 5 = very much; 6 = extreme.

These adjectives were presented randomly with respect to the four affect scales but in the same order for all subjects in all trials. For each affect term, participants rated the extent to which they had experienced that emotion during the 5 minutes preceding the page, using a 0 ("not at all") to 6 ("extreme") scale (Fig. 2; note caption for anchoring terms). To maximize variance among the emotion variables and to maximize sensitivity to high intensity ratings, each of the four composite EMA variables was created by taking the maximum value among the individual items on that subscale for that particular page.

Compliance statistics for EMA ratings were computed by comparing the scheduled time of the page to the internal PDA record of when recording began. Subjects responded to 93.0% of the pages sent. Of these, 62.5%, 84.0%, 92.2%, 95.5%, and 96.9% were begun within 1, 5, 10, 15, and 20 minutes of the page, respectively. When we computed the percentage of reports begun within 15 minutes of the page for each participant, the median compliance rate was 98.3%. More than half the sample began all or all but one of their reports within 10 minutes, and only 19 participants began 4 or more reports more than 15 minutes after the page. On average, it took 2.35 ± 1.36 minutes to complete the EMA protocol.

These compliance statistics are very high for EMA research, based on comparable studies reported in the literature. To include as much data as possible, we decided to include all reports begun within 15 minutes of the page. This cutoff is well within the range typically recommended in the literature for EMA and similar protocols (20,29).

Electrocardiographic Measures

Holter electrocardiograms (ECGs) were obtained during 24 hours on the first day and during 12 daytime hours on days 2 and 3. Prespecified 5-minute segments from 1 to 6 minutes before each page were used to calculate mean values of Fridericia's correction of QT interval for heart rate (QTc) (30) and heart rate. The summary Fridericia QTc value in Table 1 (mean, 470 ms; standard deviation, 33) was calculated from the Holter-derived values of QT interval and heart rate taken from the 3,967 pages weighting each page equally. The Fridericia QTc correction for heart rate was chosen because this formula is preferred in studies evaluating changes in QTc over time (e.g., due to administration of drugs) in studied individuals (9,31). Although Bazett's formula is used most frequently clinically, this formula has several limitations by overestimating repolarization duration at fast heart rates and underestimating at low heart rates. Fridericia's correction is more reliable at low and high heart rates; therefore, its use is preferred when there is a need for evaluating dynamic behavior of repolarization (9,31). QT was measured from the beginning of the QRS complex to the end of the T wave determined by the intersection of the T wave and the isoelectric line or to the nadir between T and U waves. U waves were not incorporated in the measurement of QT interval. The high-frequency component of heart rate variability (HF-HRV)

TABLE 1. Demographic and Clinical Characteristics of the Study Sample

	$n = 161$
Female (%)	117 (73)
Age (years)	35 (10)
QTc (ms)	470 (33)
Heart rate (beats per minute)	74 (14)
HF-HRV (ms²)	39 (9)
Patients with previous arrhythmogenic cardiac event (%)	
Yes	80 (49.7)
No	80 (49.7)
Unknown	1 (0.6)
Patients taking β blockers	101 (63)
Patients with ICD	18 (11)
Genotype (%)	
LQT1	103 (67)
LQT2	58 (33)

QTc = Fridericia correction for heart rate; HF-HRV = high-frequency heart rate variability; ICD = implanted cardiac defibrillator.
Mean (standard deviation) reported for age, QTc, heart rate, and HF-HRV. The QTc mean and standard deviation values were derived from the 3,967 events in this study.

(0.15–0.40 Hz) was derived from a fast Fourier analysis of the RR interval spectrum over each 5-minute interval, reflecting mainly the influence of the parasympathetic system on the heart (32). ECG parameters were measured automatically, using the Mortara H-Scribe System and the Super ECG program (Mortara Instruments, Milwaukee, Wisconsin). All ECG analyses were interpreted in a central core laboratory in a blinded manner regarding subject and timing of pages.

Statistical Analysis

Descriptive statistics for time-independent participant-level variables were computed weighting each participant equally, whereas page-level time-dependent variables were summarized weighting each page equally. Each of the two 7-level positive affect measures were coarsened to three groups (0–1, 2–4, 5–6), yielding two parameters (2–4 versus 0–1 and 5–6 versus 0–1) to parsimoniously allow for potential nonlinearities. Negative affect measures were dichotomized as none (0) versus any (1–6 coded as 1), given the high frequency of zeroes and the paucity of extreme levels of negative affect (Fig. 2). With all of the resulting predictors thus being indicator variables, multiple

linear models are equivalent to multiway analysis of variance models, with no assumption of linearity for any given emotion.

We separately modeled each Holter outcome as a function of all measured emotions, using multivariable conditional linear models (CLM) (33). Thus, the Holter outcome variables (e.g., Fridericia QTc) corresponding to the emotion ratings (e.g., 2–4 versus 0–1) were compared. CLM conditions away the main effects of all participant-level time-independent variables (genotype, age, age^2, genotype × sex, etc.) via the implicitly unconstrained participant-level intercepts, and thus controls for clustering by participant more completely than a mixed model with a random intercept. Inference was based on a robust sandwich estimator for the covariance matrix, using residuals from a more flexible mean function allowing separate coefficients for all seven levels of each emotion, plus their interactions with genotype, as recommended with generalized estimating equations (34). Interactions with EMA variables were tested using robust 6 df F tests for interactions with all six EMA parameters of our main effects model. Within-subject common correlations between Holter measures were computed after conditioning away participant-specific intercepts using Verbeke's orthonormal contrast matrix, and p values were based on robust t tests for the univariate CLM. Analyses were performed using Splus 7.0.0.

RESULTS
Clinical Characteristics of Studied Patients

There were 161 (73% female) patients with a mean age of 35 years. The genotype distribution was 102 LQT1 (IKs), 58 LQT2 (IKr), and 1 LQT5 (the latter IKs mutation was grouped with LQT1 patients). As Table 1 indicates, 101 patients were taking β blockers and 60 were not, half had prior arrhythmogenic cardiac events, and 11% had ICDs.

EMA Analyses

A total of 3,967 pages, averaging 25 per patient, met inclusion criteria based on the presence and technical adequacy of both EMA and ECG data. The distribution of EMA ratings across the seven intensity levels of each of the four EMA variables is depicted in Figure 2. The modal rating for the two negative affect variables (Low Arousal Negative Affect and Activated Negative Affect) was 0, whereas the modal rating for Low Arousal Positive Affect was "moderate" (3 on the 0–6 scale) and for Activated Positive Affect was "quite a bit" (4 on a 0–6 scale).

Association Between EMA and ECG Parameters

Associations between EMA and ECG variables are shown in Table 2. The largest decreases in QTc occurred during Activated Positive Affect, with greater decreases in QTc when Activated Positive Affect was rated highest (5 = "very much" or 6 = "extreme") and smaller decreases when Activated Positive Affect was rated as moderately intense (2 = "somewhat," 3 = "moderate," or 4 = "quite a bit"), relative to when Activated Positive Affect was rated 1 "mild" or 0 "none." Activated Negative Affect when present (rated 1–6) was also associated with decreases in QTc relative to when Activated Negative Affect was rated 0, whereas when Low Arousal Negative Affect was present, no significant changes occurred in QTc. Low Arousal Positive Affect at high levels (calm and/or relaxed rated 5 "very much" or 6 "extreme") and moderate levels (calm and relaxed rated 2 "somewhat," 3 "moderate," or 4 "quite a bit") were associated with QTc increases. For QTc, β of −7.9 ms on Activated Positive Affect rated 2, 3, or 4 means that, compared with Activated Positive Affect values of 0 or 1, a value of 2, 3, or 4 is associated with a mean within-subject decrease of 7.9 ms in QTc. More generally, the QTc model states that as one emotion varies,

TABLE 2. Multivariable Conditional Linear Regression Coefficients (β) for All Emotions, Separately Modeling Each of Four Outcomes: 1) QTc Based on Our Genotype-Specific Correction for Heart Rate; 2) Fridericia's QTc; 3) Heart Rate; and 4) High Frequency Heart Rate Variability (HF-HRV)[a]

Emotion Predictor	QTc, Adjusted for Log (Heart Rate) and Its Interaction With Genotype			QTc (Fridericia)			Heart Rate			HF-HRV		
	β	(SE)	p	β	(SE)	p	β	(SE)	p	β	(SE)	p
Activated Positive Affect 2–4 (versus 0–1)	−5.1	(1.2)	<.001	−7.9	(1.5)	<.001	+4.8	(0.8)	<.001	−4.5	(0.7)	<.001
Activated Positive Affect 5–6 (versus 0–1)	−8.1	(1.5)	<.001	−11.1	(2.0)	<.001	+4.8	(1.0)	<.001	−4.6	(0.7)	<.001
Low Arousal Positive Affect 2–4 (versus 0–1)	+0.9	(1.0)	.35	+1.9	(1.0)	.06	−3.2	(0.6)	<.001	+1.5	(0.4)	<.001
Low Arousal Positive Affect 5–6 (versus 0–1)	+3.1	(1.4)	.03	+4.8	(1.4)	.001	−5.2	(0.8)	<.001	+3.8	(0.6)	<.001
Activated Negative Affect 1–6 (any versus none)	−2.1	(0.8)	.01	−2.2	(0.8)	.01	+0.8	(0.4)	.03	−0.9	(0.3)	.002
Low Arousal Negative Affect 1–6 (any versus none)	−1.0	(1.0)	.29	−1.1	(1.0)	.27	−0.4	(0.5)	.41	+0.3	(0.4)	.51
R^2 (%)	11.3			2.8			3.8			5.0		

For each emotion predictor, the regression coefficient (β), its robust standard error (SE), and robust p value are listed.

From left to right, the four multivariable model outcomes are: 1) Fridericia's QTc adjusted for the natural log of heart rate plus its interaction with genotype; 2) Fridericia's QTc with no further adjustment for heart rate; 3) heart rate; and 4) HF-HRV.

Regression coefficients for QTc are in ms and heart rate in beats per minute.

R^2 refers to the percentage of variance in the dependent variable explained by the entire model, including log (heart rate) and its highly significant interaction with genotype when included in 1), conditional on the participant-specific intercepts (whose contribution is thus not counted in either the numerator nor the denominator).

[a] All effects of emotions above are adjusted for each other emotion; however, the results were similar when each emotion was modeled separately, unadjusted for the other three emotion predictors.

while holding the subject and his/her other EMA variables constant, QTc changes on average by β.

Table 2 shows that the results were essentially the same, with slightly attenuated effect sizes, when additional variance due to heart rate was removed from QTc by further adjusting for log (heart rate) ($p < .001$) and its interaction with genotype ($p < .001$). Changes in HF-HRV and heart rate as a function of EMA variables showed similar patterns to those of QTc, except the signs of the significant effects were reversed for heart rate. The common within-subject correlations were: QTc and log (heart rate), -0.21; QTc and HF-HRV, 0.26; log (heart rate) and HF-HRV, -0.78; $p < .001$ for all.

Interactions With EMA Variables

Next, we determined whether the QTc findings in Table 2 differed as a function of interactions of emotions with age, sex, genotype, β blocker status, ICD treatment, or previous cardiac events. For the purposes of testing these interactions and for ease of interpretation, all potential modifiers were dichotomous, with age dichotomized at 35 years. There was insufficient evidence of interactions of EMA variables with age, sex, or ICD treatment ($p > .10$ for each), with or without adjusting QTc for heart rate and its interaction with genotype. There was borderline evidence of an interaction with β blocker status ($p = .04$), driven almost entirely by its interaction with Activated Negative Affect ($p = .04$), whereby the effect of Activated Negative Affect seemed to be solely among those who received β blockers ($\beta = -3.5$ ms, compared with -2.2 ms in the main effect model) and not those who did not receive β blockers ($\beta = 0.2$ ms, $p = .87$). There was significant evidence of interactions with genotype ($p < .001$), which was driven by interactions with the positive emotion variables but not Activated Negative Affect ($p = .15$) nor Low Arousal Negative Affect ($p = .97$). Table 3 shows that the effects of each positive emotion variable on QTc were in the same direction for each genotype but significantly more pronounced for LQT2 compared with LQT1 patients. However, when testing these same interactions in models for QTc further adjusted for heart rate and its interaction with genotype (as in column 1 of Table 2), there was insufficient evidence of

any such interactions, including those with genotype and β blockers. Thus, these interactions seem to be largely attributable to genotype-specific effects of heart rate on QTc that no global heart rate correction could eliminate. However, there was insufficient evidence of interactions of genotype with emotions when modeling heart rate ($p = .22$) or HF-HRV ($p = .24$) as the outcome; so, the effects of emotions on heart rate and HF-HRV do not seem to differ significantly by genotype.

DISCUSSION

The current study, to our knowledge, is the first of its kind in which people are paged at random times throughout the day and their momentary emotional experiences and ventricular repolarization values are simultaneously assessed. Our observation of statistically significant associations between emotion and QTc establishes for the first time that emotions during routine daily activities have a definable effect on ventricular repolarization duration in predisposed individuals.

The validity of the emotion ratings that we obtained were supported by the heart rate findings. Consistent with previous findings regarding the arousal dimension of emotion (35), heart rate increases were numerically greater during activated positive or negative emotion than during low arousal positive or negative emotion. Heart rate changes in relation to the valence (positive-negative) dimension were also consistent with previous findings showing greater effects for appetitive (positive) emotions (36), in that activated positive emotion was associated with greater heart increases than during activated negative emotion, and low arousal positive emotion was associated with greater heart rate decreases than low arousal negative emotion.

Previous research on dynamic changes in QT interval in relation to emotion has been limited. Prolonged QT intervals were observed in two previous studies (16,17) involving acute stress, a condition that involves a predominance of sympathetic over parasympathetic mechanisms (37). In the current study, the "activated" conditions, both positive and negative, were associated with QT interval decreases and the low arousal positive conditions were associated with QT interval

TABLE 3. Genotype-Specific Effects (β) of Emotions on Fridericia's QTc, Estimated via a Single Conditional Linear Model for QTc, Simultaneously Including All Emotions and Their Interactions With Genotype

Emotion Predictor	LQT1			LQT2			Interaction p Value
	β	(SE)	p	β	(SE)	p	
Activated Positive Affect: 2–4 versus 0–1	-4.7	(1.2)	$<.001$	-12.9	(3.4)	$<.001$	.02
Activated Positive Affect: 5–6 versus 0–1	-5.4	(1.3)	$<.001$	-20.6	(4.6)	$<.001$	.002
Low Arousal Positive Affect: 2–4 versus 0–1	$+0.3$	(1.1)	.75	$+4.6$	(2.0)	.02	.06
Low Arousal Positive Affect: 5–6 versus 0–1	$+1.5$	(1.4)	.26	$+10.7$	(3.0)	$<.001$	.005
Activated Negative Affect: >0 versus 0	-1.2	(0.8)	.16	-4.1	(1.8)	.03	.15
Low Arousal Negative Affect: >0 versus 0	-1.1	(0.9)	.22	-1.2	(2.4)	.61	.97
Overall 6 df robust F test of interaction							.001

Genotype-specific regression coefficients (β), standard error (SE), and p values in the second and third columns refer to that genotype group alone, whereas the interaction p values in the fourth column test equality of the genotype-specific effects for each emotion predictor (and overall, bottom row).
$R^2 = 4.1\%$ for this 12-parameter genotype interaction model, which does not include additional adjustments for heart rate and its interaction with genotype.

increases. These findings seem paradoxical based on predictions derived from stress research, but they make sense when considered from the perspective of routine daily activities. Under these circumstances, parasympathetic control of cardiovascular regulation predominates (38). Consistent with this thesis, activated positive and activated negative affect were associated with vagal tone decreases and low arousal positive affect was associated with vagal tone increases. Moreover, heart rate was strongly negatively correlated with vagal tone and QTc was significantly positively correlated with vagal tone. Together, these findings indicate that emotion influences repolarization even under routine circumstances. Given the strong association between daily emotions and vagal tone, however, the data may not be generalizable to emotional states accompanied by pronounced sympathetic nervous system activation.

In addition to the standard QTc (30), we also more stringently controlled QTc for residual variance due to heart rate to eliminate chronotropic effects from our measure of repolarization. These analyses revealed that Fridericia's QTc leaves significant residual variance due to heart rate embedded within it, at least for LQT2 subjects. However, removing this residual within-subject heart rate variance, as in this study, is not appropriate for routine clinical research that typically involves a comparison between individuals. For the latter purpose, Fridericia's QTc is preferable (9,31). A second reason for more stringently controlling QTc for heart rate was to examine the association between emotion variables and repolarization without confounding by emotion-heart rate relationships. Our analyses showing strong interrelationships between HF-HRV and both heart rate and QTc indicate that vagal tone influences the latter two parameters. It is well established that, under conditions of relative safety, as in routine daily activities, emotion and emotion regulation are predominantly regulated by vagal tone mediated by the phylogenetically newer myelinated vagus under the control of the nucleus ambiguus in the brain stem (relative to the phylogentically older unmyelinated vagus under the control of the dorsal motor nucleus) (38). As such, given the strong covariation of heart rate and HF-HRV, the elimination of additional variance due to heart rate from QTc also removes vagal tone variance that is intrinsic to the physiology of emotion under everyday circumstances. Thus, Fridericia's QTc provides the most accurate estimate of the magnitude of the association between daily emotion and ventricular repolarization duration, because if all variance due to heart rate (and vagal tone) is eliminated, the true association is underestimated.

Increased vagal tone is associated with increased QT interval duration, both in animal models with fixed heart rate (39,40) and in humans during fixed pacing and during sleep (41,42). The present observations, therefore, extend previous observations on the positive association between vagal tone and QT interval to the domain of emotion, which is important given the role of vagal tone in emotion and emotion regulation (38) and the role of emotion in sudden cardiac death (4,5).

Genotype proved to be an important explanatory variable, in that the effects of emotion on QTc were consistently stronger in LQT2 than LQT1 patients. These findings are consistent with a retrospective study of triggers of cardiac events in patients with LQTS, which showed that emotion was a more common trigger of cardiac events in LQT2 than LQT1 patients (14). The current findings raise the possibility that the vulnerability of LQT2 patients to emotions as electrically destabilizing influences may extend beyond sudden short-lived events, such as loud noises.

In a retrospective study of patients with LQTS, we (43) previously showed that lower levels of happiness during the prior day were a risk factor for arrhythmogenic cardiac events. We hypothesized that lower happiness might be associated with vagal withdrawal, which could increase the risk for cardiac events. That study did not attempt to disentangle high arousal from low arousal positive emotional states. In the current study, consistent with expectations based on arousal, as shown in Table 2, we observed that low arousal positive emotion (calm and relaxed) was associated with heighted vagal tone and that activated positive emotion was associated with reduced vagal tone and that low arousal positive emotion and activated positive emotion had opposite effects on QTc. Although longer QT intervals are associated with greater risk and shorter QT intervals are associated with lower risk in patients with LQTS (44), these associations are based on the entire QT interval derived from resting ECG data, not momentary changes in QT interval as a function of emotion. Whether momentary changes in QT interval due to emotion influence the timing of cardiac events has not been determined. Another fundamental reason why the data from the two studies may not be exactly comparable is that, under everyday circumstances, cardiac function and emotion are predominantly under vagal control (38), whereas emotional triggers of cardiac events typically involve negative states that are high arousal associated with sympathetic activation and/or vagal withdrawal (4,5). In this study, high levels of activated negative emotional states were very uncommon.

The emotional states that we examined were ongoing, typically low-level emotional states that are part of daily living. Evidence (45,46) shows that the majority of emotions experienced in life are of low intensity, and that low intensity emotions are more readily forgotten. Until the relatively recent advent of EMA and related experience sampling techniques, methods for reliably measuring such low intensity experiences did not exist. These considerations highlight the importance of our findings in the sense that they apply to the majority of one's waking experience and help to explain why such associations have not been previously observed.

As might be expected in the context of everyday emotion, the heart rate changes that we observed were of smaller magnitude than would typically be observed during exercise. Similarly, the changes observed in QT interval in this study were relatively small. The magnitude of the changes in QT interval, however, is comparable to those associated with certain specific gene variants (e.g., NOS1A associated with

2–5 ms changes) (13) and certain drugs (e.g., moxifloxacin causing a 4–7-ms increase in QT interval) (47). Their clinical significance is further supported when it is considered that sudden cardiac death is a multifactorial phenomenon (48). Many factors play a small role in affecting QTc, and when they coincide and act together, they provide our best current explanation as to why a cardiac event occurs at a given time and day of the week when it has not occurred on similar days and times in the past. The clinical importance of these findings is also evident when it is considered that our data reflect averages; thus, any given individual may have larger effects in certain emotional contexts, particularly as a function of genotype, β blocker status, or a combination thereof. These results may provide a new lead in identifying that subgroup of patients with LQTS who will experience life-threatening ventricular arrhythmias in the future. Conversely, the present data also suggest that a reduction in the QTc duration with certain daily emotions could be associated with a decreased risk for ventricular arrhythmias. Should this be demonstrated in future research, this association would have obvious clinical relevance.

Our study did not involve a healthy control group. It is, therefore, not known whether the observed changes in QT interval as a function of daily emotion are specific for patients with LQTS or whether similar effects are present in other clinical groups or in healthy subjects. However, previous stress research has shown similar QT prolongation in healthy individuals (16,17) and in LQTS patients (49), and no previous study has examined dynamic changes in QT interval as a function of daily emotion in healthy individuals. Second, our subjects reported emotions in a limited range of intensity, particularly negative emotions. The latter were often of very low intensity (0 was the modal response for Activated Negative Affect and Low Arousal Negative Affect), and thus extremely intense emotions that typically occur as precipitants of arrhythmias were generally not observed in this investigation. Future studies may benefit from studying the full range of positive and negative emotions. Third, we did not evaluate the effect of specific emotions, such as anger, depression, or happiness, because of our desire to examine broad dimensions of emotion.

In conclusion, we observed that typical daily emotions have a definable effect on cardiac repolarization. As such, the current findings highlight the dynamicity of the QT interval in daily living in patients with an inherited cardiac repolarization disorder. It is likely that these emotion-related repolarization changes are among the multiple factors that contribute to arrhythmic cardiac events in patients with LQTS.

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