

"QT clock" to improve detection of QT prolongation in long QT syndrome patients



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BACKGROUND The QT interval is a risk marker for cardiac events such as torsades de pointes. However, QT measurements obtained from a 12-lead ECG during clinic hours may not capture the full extent of a patient's daily QT range.

OBJECTIVE The purpose of this study was to evaluate the utility of 24-hour Holter ECG recording in patients with long QT syndrome (LQTS) to identify dynamic changes in the heart rate-corrected QT interval and to investigate methods of visualizing the resulting datasets.

METHODS Beat-to-beat QTc (Bazett) intervals were automatically measured across 24-hour Holter recordings from 202 LQTS type 1, 89 type 2, and 14 type 3 genotyped patients and a reference group of 200 healthy individuals. We measured the percentage of beats with QTc greater than the gender-specific threshold (QTc ≥ 470 ms in women and QTc ≥ 450 ms in men). The percentage of beats with QTc prolongation was determined across the 24-hour recordings.

RESULTS Based on the median percentage of heartbeats per patient with QTc prolongation, LQTS type 1 patients showed more frequent QTc prolongation during the day (~ 3 PM) than they did at night (~ 3 AM): 97% vs 48%, $P \sim 10^{-4}$ for men, and 68% vs 30%,

$P \sim 10^{-5}$ for women. LQTS type 2 patients showed less frequent QTc prolongation during the day compared to nighttime: 87% vs 100%, $P \sim 10^{-4}$ for men, and 62% vs 100%, $P \sim 10^{-3}$ for women.

CONCLUSION In patients with genotype-positive LQTS, significant differences exist in the degree of daytime and nocturnal QTc prolongation. Holter monitoring using the "QT clock" concept may provide an easy, fast, and accurate method for assessing the true personalized burden of QTc prolongation.

KEYWORDS Long QT syndrome; Electrocardiography; Diagnostic; Cardiac monitoring

ABBREVIATIONS C-loop = cytoplasmic loop; I_{Kr} = rapid component of the late repolarizing potassium current; I_{Ks} = slow component of the late repolarizing potassium current; **LQT1** = long QT syndrome type 1; **LQT2** = long QT syndrome type 2; **LQT3** = long QT syndrome type 3; **LQTS** = long QT syndrome; **QTcB** = heart rate-corrected QT based on Bazett formula

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Introduction

The congenital long QT syndrome (LQTS) is an inherited channelopathy that is associated with a prolonged duration of ventricular repolarization, predisposing patients to life-threatening ventricular tachyarrhythmias such as torsades de pointes and sudden cardiac death.^{1,2} Hundreds of mutations have been identified in LQTS; however, mutations in the *KCNQ1* and *KCNH2* genes are the most common forms of the disease—LQTS type 1 (LQT1) and LQTS type 2 (LQT2), respectively. LQT1 is associated with a reduction of the slow component of the late repolarizing potassium

current I_{Ks} , whereas LQT2 is associated with a reduction of the rapid component I_{Kr} .³ Heart rate-corrected QT prolongation (QTc), type of mutation, gender, history of syncope, and age are recognized modulating risk factors associated with LQTS.⁴

In standard clinical practices, the LQTS diagnosis is confirmed by the presence of known LQTS mutation(s), but detection of the disease is suspected primarily by a history of syncope or cardiac events in the patient or family and the presence of QTc prolongation measured from the standard ECG at rest. Despite the recognized clinical value of QTc prolongation as a surrogate marker of the presence of the syndrome, Goldenberg et al⁵ reported that approximately 25% of genotyped-confirmed patients have a concealed form of the disease, wherein genotype-positive patients have an ECG tracing that exhibits normal range QTc intervals (QTc ≤ 440 ms). To address this issue, experts have proposed strategies to unmask the repolarization impairment in LQTS patients to reveal the presence of the syndrome using

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protocols that include drug (epinephrine) and exercise-based challenges.^{5,6}

In this work, we investigated the role of 24-hour Holter recordings in LQTS patients to determine the dynamic nature of QTc prolongation. We hypothesize that beat-to-beat analysis of QT intervals from Holter ECG recordings of patients with LQTS may help identify the periods of the day when QTc interval prolongation is exacerbated. We propose a unique and comprehensive solution to quickly assess the presence of QTc prolongation and monitor changes in the QT interval over time.

Methods

Study population

Holter tracings used to conduct this study were obtained from the Telemetric and Holter ECG Warehouse (THEW),^{7,8} an initiative hosting a warehouse of continuous and fully de-identified digital Holter ECGs open to the scientific community for the development of ECG technologies. From this database, we accessed 200 Holter recordings from 200 healthy subjects, 294 Holter recordings from 202 genotyped LQT1 patients, 145 Holter recordings from 89 genotyped LQT2 patients, and 35 Holter recordings from 14 genotyped LQT3 patients. All Holter recordings were 24-hour recordings (2- or 3-lead configuration) from different clinical devices. The LQTS data were donated to the THEW⁸ by the Hospital Lariboisière (Paris, France).^{9,10} The recordings from healthy subjects were recorded during the Intercity Digital Electrocardiology Alliance project (IDEAL).⁸ In addition to genetic testing, demographic data and cardiac events (ie, syncope, documented torsades de pointes, sudden cardiac death, and treatment, specifically beta-blocker treatment) were available. We did not know whether the Holter recordings were acquired before or after the patient's cardiac events. We report the gender-specific distribution of QTc intervals using the Bazett correction formula because this is the most often clinically used QT correction formula. Finally, we considered subgroups of the LQT1 and LQT2 population by characterizing patients using the specific locations of missense mutations (while ignoring other mutation types, eg, frameshift). We extracted the Holter recordings of LQT1 and LQT2 patients on and off beta-blockers. Mutations in the cytoplasmic loop (C-loop) in LQT1 patients were defined as those in the region between the S2 and S3 transmembrane domains and between S4 and S5, involving amino acid residues 171–195 (S2–S3) and 242–262 (S4–S5) of the KCNQ1 subunit. In LQT2 subjects, the pore region of the hERG channel was defined as the domain extending from the fifth transmembrane region (S5) to the end of S6 from residues 548 to 659.

Beat-to-beat QTc measurements

ECG measurements were computed using the open source program developed by Chesnokov et al.¹¹ The software was modified to read the International Society for Holter and

Non-invasive Electrocardiology (ISHNE) file format and applied to Holter ECG signals to all available leads delivering measurement of R peak locations, QRS onset, and T-wave offset on a beat-to-beat basis. Then, the QT intervals were measured as the time between earliest QRS onset and latest T-wave offset among all available leads. For RR interval measurements, we used the median value across all leads.

QT interval measurements were computed in all beats. Nonsinus beats and annotation errors were removed using the following filtering techniques:

1. RR, QT, and therefore QTc were not calculated in the neighborhood of ventricular ectopic beats.
2. Values outside expected ranges were discarded, such as values $40 \text{ bpm} > \text{HR} > 160 \text{ bpm}$, and/or $210 \text{ ms} > \text{QT} > 700 \text{ ms}$.
3. Beat-to-beat QTc datasets were filtered using a 10-minute moving median to remove any remaining noise or outliers.

The corrected values of QT interval for heart rate (QTc) were computed using the Bazett formula.

“QT clock”

We developed a novel graphical concept designed to facilitate the review of a large set of QTc measurements and to provide an infographic understanding of 24-hour QTc dynamics. The QT clock is a circular plot representing a 24-hour clock (00:00 to 24:00), with midnight at the top of the clock. The radius of the clock represents the QTc interval values varying from 300 to 600 ms from the center to the perimeter. The clock is used to present information for 2 different purposes:

1. Viewing the expected QTc range for a *population* (ie, their typical QTc values across the day).
2. Monitoring changes in QTc for an *individual patient*. QTc values extracted from a single Holter recording may provide insight about personal daily variation and period of maximum QTc prolongation.

Statistical analysis

Statistical analysis was performed using the SciPy stats module. The Mann-Whitney *U* test was used when assessing statistical differences between different populations, and the Wilcoxon signed-rank test was used when comparing results within the same population. A χ^2 test was used in the case of binary variables. In all cases, $P \leq .05$ were considered significant.

Results

Study population

A description of the study population is given in [Table 1](#). There was no statistical difference in age between the LQT1

Table 1 Demographics of the study population

	Healthy (n = 200)	Long QT syndrome type 1 (n = 202)	Long QT syndrome type 2 (n = 89)	Long QT syndrome type 3 (n = 14)
Gender (male/female)	101/99 (51%)	88/114 (44%)	42/47 (47%)	8/6 (57%)
Age (years)	38 ± 16	26 ± 18	24 ± 18	17 ± 15
Beta-blockers (%)	0	43%	55%	57%
Symptoms	0	48%	47%	50%

Some individuals were monitored several times under different circumstances (eg, at different ages), so age, beta-blocker use, and symptoms are reported as a percentage of recordings rather than a percentage of patients.

and LQT2 populations. However, the LQT3 cohort had a younger average age than the other groups, and the healthy cohort had a higher average age than any of the LQTS cohorts. Differences in gender distribution, symptoms, and beta-blocker use were statistically insignificant among the 3 types of LQTS, although the LQT1 group was slightly skewed toward more female subjects compared to the healthy cohort ($P = .05$). Among patients with LQT1, we identified 36 patients with missense mutations in the cytoplasmic loop regions (C-loop) and 42 patients with missense mutation outside the loop region (non-C-loop). In the LQT2 group, 31 patients had missense mutation in the pore region, whereas 36 had their mutation outside the pore regions.

The gender-specific average values and standard deviations of heart rate (HR), QT and QRS intervals, and heart rate-corrected QT values based on the Bazett formula for each of the groups are given in Table 2.

QTc prolongation and concealment in patients with LQTS

We measured the beat-to-beat RR and QT intervals in 24-hour Holter recordings for healthy patients (n = 200) and genotype-positive LQTS patients (n = 305). The number of QTc intervals measured was approximately 10 million in each healthy group (male and female), 12 million in each LQT1 group, and 6 million in each LQT2 group. Figure 1 highlights gender-specific QTc distributions for healthy patients compared with LQT1 and LQT2. There is a difference in the distribution of QTc intervals in men vs women. In men, LQT2 is associated with longer median QTc intervals

compared to those with LQT1 (471ms vs 455ms, $P = .03$), but this difference is weaker in females (479 ms vs 470 ms, $P = .04$). The QTc distribution plot in LQT1 males shows the largest common area with the distribution of QTc in healthy males, indicating that this group of LQTS patients may have the least QTc prolongation.

Gender-specific QTc prolongation in Holter ECGs from LQTS patients

Population- and gender-specific distributions of QTc for our study cohorts are plotted on the QT clock in Figure 2. The lower and higher boundaries of these patterns correspond to the 16th and 84th percentile (ie, inner 68% of patients), with 1-minute resolution. This percentile range was chosen to highlight the equivalent of ± 1 SD during each 1-minute epoch, without assuming a normal distribution. Such presentations reveal that there is a very stable, circular, “healthy” range of QTc across 24-hour variations (defined by our healthy cohort, dark green areas in Figure 2). We superimposed on these plots the 24-hour variation of QTc for LQT1 in the upper panels, LQT2 in the middle panels, and LQT3 in the lower panels. Figure 2 reveals different configurations of 24-hour QTc dynamics according to LQTS types. The most striking one is the change in symmetry of the pattern in LQT2 and LQT3 groups revealing the exacerbation of QTc interval prolongation during the night period. This phenomenon is stronger in LQT3 male patients but is not present in LQT1 patients. Note that the “healthy” and “LQTS” regions rarely overlap, in contrast to what we see in Figure 1. This is mainly because the clocks only show the inner 68% of each group—the tails of their respective

Table 2 Gender-based description of the baseline ECG measurements for healthy and LQTS cohorts using 24-hour averages

	Healthy		LQT1		LQT2		LQT3	
	Men (N = 101)	Women (N = 99)	Men (N = 88)	Women (N = 114)	Men (N = 42)	Women (N = 47)	Men (N = 8)	Women (N = 6)
HR (bpm)	77 ± 9	81 ± 10*	72 ± 11	77 ± 14*	77 ± 17	76 ± 15	72 ± 15	77 ± 7
QT (ms)	358 ± 21	365 ± 20*	430 ± 48	435 ± 48	433 ± 59	450 ± 54	463 ± 58	453 ± 65
QRS (ms)	93 ± 5	90 ± 4*	95 ± 10	92 ± 8*	94 ± 9	92 ± 8	97 ± 11	94 ± 6
QTc (ms)	400 ± 16	416 ± 16*	466 ± 53	482 ± 36*	476 ± 42	491 ± 40*	490 ± 35	497 ± 57

Values were computed using the process described in the section on Beat-to-Beat QTc Measurements, with the addition of J-point annotation to compute QRS.

LQTS = long QT syndrome; LQT1 = long QT syndrome type 1; LQT2 = long QT syndrome type 2; LQT3 = long QT syndrome type 3.

* $P < .05$ vs men of same genotype.

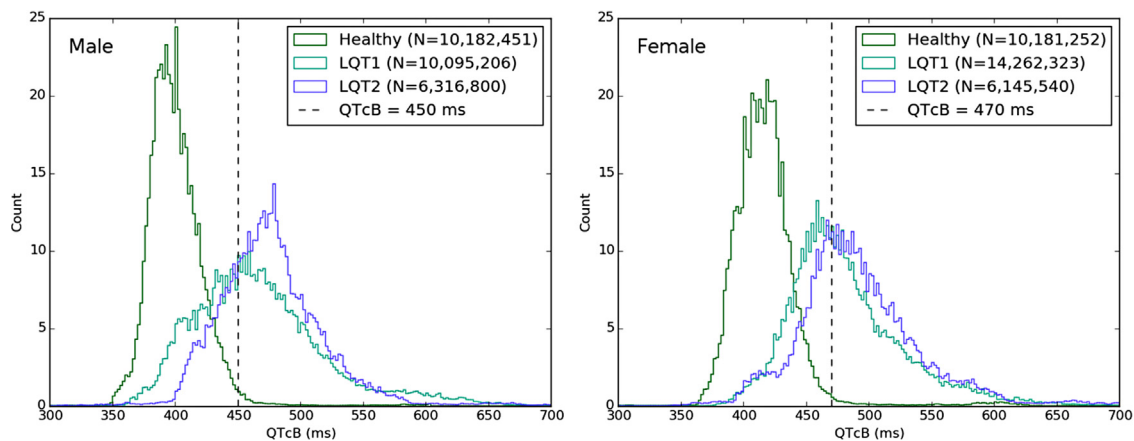


Figure 1 Distribution of beat-to-beat QTc intervals (corrected using Bazett formula) in healthy individuals and in long QT syndrome type 1 (LQT1) and long QT syndrome type 2 (LQT2) patients. Distributions were normalized (same area), so “Count” is a normalized count of cardiac beats. The cohort with long QT syndrome type 3 was not plotted because of its small size. Note the overlap of LQT1 and LQT2 groups with the healthy population indicating the level of concealment in these populations.

histograms are omitted. A version of this figure with an expanded percentile range is available as an Online [Supplementary Download](#) (Fig. 2).

Rather than comparing *QTc value* distributions at different times of day, it can be instructive to compare *QTc prolongation percentages* (ie, the chance of QTc exceeding the clinical prolongation thresholds). [Table 3](#) lists the percentage of heartbeats that showed QTc prolongation in the 3 LQTS cohorts for the same time periods: one nocturnal (3 AM–4 AM) and one diurnal (3 PM–4 PM). In the LQT1 and LQT2 cohorts, we observed a significant variation in median QTc prolongation (13%–49%) between these 2 periods ($P < .01$, or $P < 10^{-5}$ if gender is ignored). Specifically, in the LQT1 cohort, prolongation was significantly *higher*, regardless of gender, during the afternoon than late at night, whereas in LQT2 the afternoon hours showed significantly *lower* prolongation than at night. In LQT3, there were no statistically significant differences in prolongation when comparing these 2 time ranges, most likely because of the small size of our cohort.

Hourly median prolongation percentages are plotted in [Figure 3](#). LQT1 and LQT2 patients appear to have very similar patterns of QTc prolongation during clinic hours (“day”) but are quite distinct during sleeping hours (“night”). At night, QTc prolongation becomes much more prevalent in LQT2 subjects and less common in LQT1. For readability, we did not plot separate lines for each gender in this figure. However, when the plot is separated by gender, it reveals a slightly higher QTc prolongation percentage in men than women, about 12% higher on average. This agrees with our expectations from inspecting [Figure 1](#), in which the threshold for males (450 ms) appears to offer higher sensitivity than the threshold for females (470 ms). Finally, we identified the 2 periods of the day with the most significant differences in median percentage of QTc prolongation within each LQTS family. In LQT1, the most significant difference in percentage of beats with QTc prolongation is found when comparing 05:30 (early morning) to 15:30 (afternoon) (39% vs 83%,

$P \sim 10^{-9}$), whereas in LQT2 the most significantly different periods of the day are around 00:30 (night) and 18:30 (evening) (100% vs 74%, $P \sim 10^{-6}$).

Mutation location and QT clock profile in LQT1 and LQT2

[Figure 4](#) shows the gender-specific QT clocks for the groups of LQT1 patients with C-loop vs non-C-loop mutations, and LQT2 patients with pore vs non-pore mutations. In male LQT1 patients, we observed no clear differences in the QTc clock profiles between patients with mutations inside or outside the C-loop regions, although the C-loop region appears slightly worse overall (ie, more QTc prolongation). In women with LQT1, QTc values remained >450 ms throughout the day, and nearly overlapping QTc clock profiles were observed in those with C-loop and non-C-loop mutations. However, among male patients with LQT2, those with a pore region mutation consistently had more QTc prolongation compared to those with non-pore mutations. This observation is consistent with a prior report in LQT2 patients, which revealed that male LQT2 patients with non-pore mutations were associated with lower risk for events.¹² Finally, in female LQT2 patients, the trend for increased QTc prolongation in those with pore mutations also appears to be present but has more overlap with the non-pore subjects than we see in the male cohort.

The percentage of patients taking beta-blockers was not significantly different in LQT1 patients with C-loop mutations vs those with non-C-loop mutations (33% vs 24%, $P = .15$) or in LQT2 patients with mutations in pore vs non-pore regions (47% vs 42%, $P = .47$).

Discussion

The severity of the functional defects and the phenotypic penetrance in the LQTS are modulated by numerous factors, among which age, gender, and type and location of LQTS mutation play crucial roles.¹³ However, this also means that

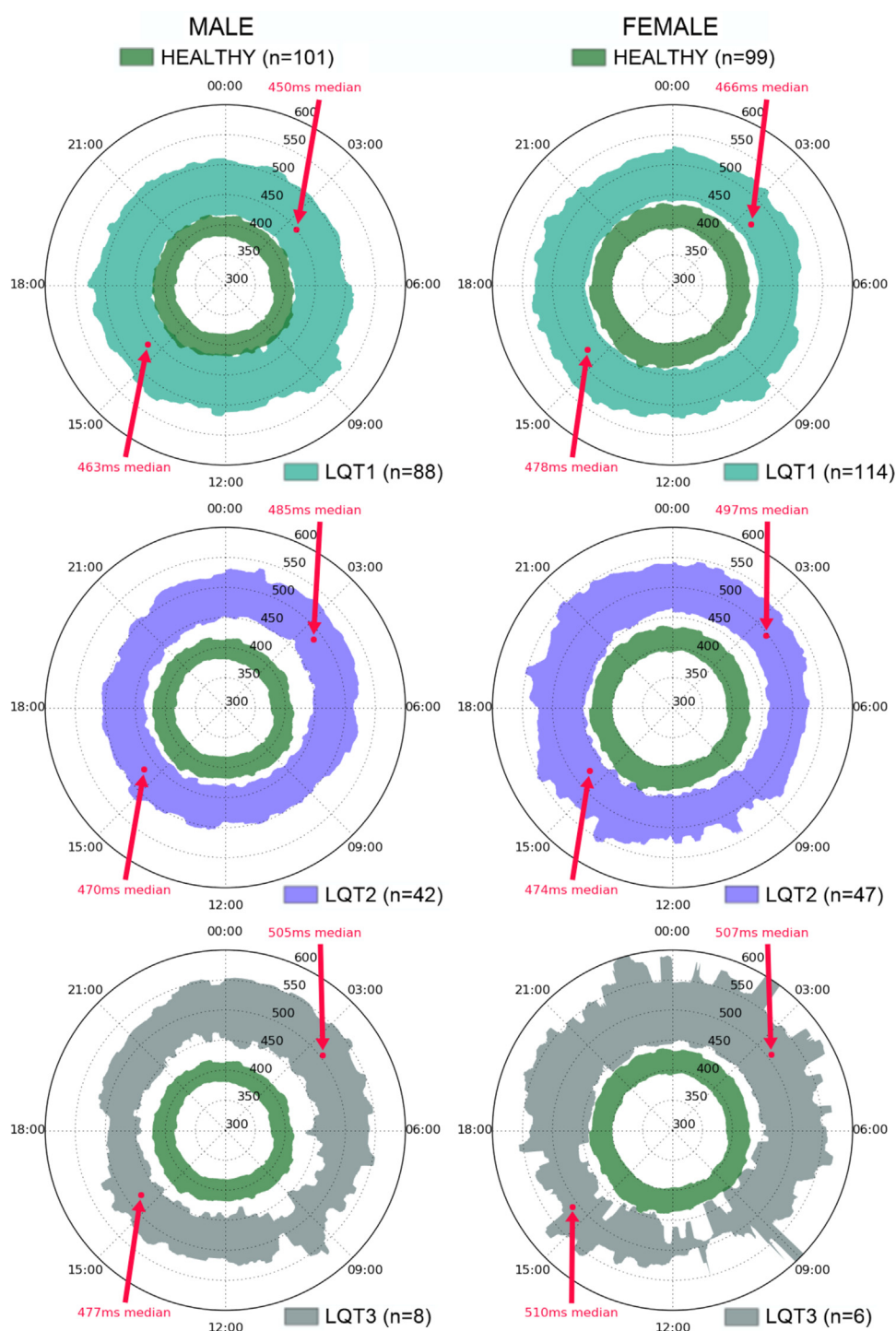


Figure 2 “QTc clock” plots for long QT syndrome type 1 (LQT1) males and females (**top left and right panels**, respectively), long QT syndrome type 2 (LQT2) males and females (**middle left and right panels**, respectively), and long QT syndrome type 3 (LQT3) males and females cohorts (**bottom left and right panels**, respectively). Each area is defined by the middle 68th percentile of QTc values, that is, same percentage as ± 1 SD, measured across all Holter recordings, for each 1-minute slice. Dark green area represents expected range of QTc variations in our healthy cohort. The figure highlights the changes in QT prolongation in LQT2 and LQT3 cohorts during the night. This phenomenon is expressed as graph asymmetry in which the area corresponding to LQT2/3 cohort stretches away from the normal value during the nighttime (22:00 to 08:00). Arrows indicate median QTc at the time periods reported in Table 3. Note that the LQT3 ranges are computed from only 6 female and 8 male patients.

genetic tests do not fully capture individual risk. Furthermore, although the standard 12-lead ECG is an important diagnostic tool used in the investigation, evaluation, and monitoring of patients with LQTS, its utility in predicting

risk may be limited by the fact that QT concealment may give the false impression of low risk in certain subsets of patients. The presence of QTc concealment in LQTS has been studied previously using standard 10-second ECG

tracings. The limitation of such an approach is that these ECGs are usually acquired during clinical hours, and they may not provide the most accurate assessment of risk but rather should be considered a *snapshot* measurement of risk.

The cardiac events in LQTS have been shown to be strongly associated with triggers linked to inappropriate QT adaptation to changes in heart rate. Therefore, challenging the ventricular repolarization process in these patients using protocols to exacerbate QT prolongation have been proposed, such as brisk standing,¹⁴ exercise, and epinephrine challenge.^{6,14,15} Such protocols exploit the fact that beta-adrenergically enhanced potassium currents (I_{Kr} and I_{Ks}) are required to counterbalance the larger inward depolarizing current of the L-type Ca^{2+} current (also enhanced by beta-adrenergic stimulation).¹⁶ Abnormal regulation of these potassium currents under condition of adrenergic tone places LQT1 and LQT2 patients at risk for life-threatening ventricular arrhythmias. The cellular and environmental factors that affect repolarization are, of course dynamic, and therefore a static assessment of QTc may be limited in conveying the true extent of abnormal repolarization for any given patient.

In contrast to the methods described earlier, we use Holter data to identify dynamic changes in repolarization during a 24-hour time period. Although modern Holter systems may provide basic reporting on the QTc interval (eg, maximum QTc and percentage of time that it is prolonged), the QT clock can present the time, duration, and magnitude of all prolongation events in a simple picture. The QT clock was used to display results for populations of patients and to compare the dynamic QT changes of individuals to larger populations of interest. Our findings show that there are significant differences in the patterns and degrees of QT prolongation in patients with LQT1 and LQT2. We demonstrate that Holter monitoring of LQTS patients (coupled with computerized beat-to-beat QT interval measurement) provides an opportunity to better characterize the extent and

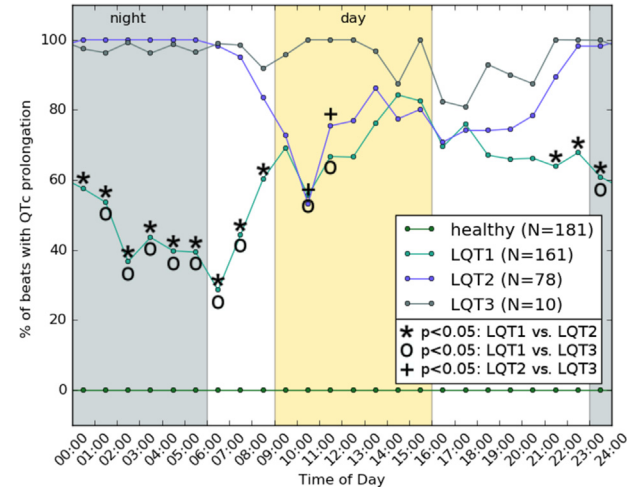


Figure 3 Median levels of QTc prolongation across 24 hours for the healthy, long QT syndrome type 1 (LQT1), long QT syndrome type 2 (LQT2), and long QT syndrome type 3 (LQT3) cohorts. This plot can be thought of as the *chance to detect prolonged QTc* (although, because this is the median, 100% indicates that *most*, not all, beats show QTc prolongation at a given hour). Prolongation in all LQTS cohorts is significantly higher than in healthy subjects ($P < 10^{-6}$ at all times). Availability of Holter data varied from hour to hour, for example, as patients may have been recorded for 22–23 hours rather than the full 24 hours. Therefore, we report N values as the minimum across all datapoints.

duration of QT prolongation and provides insights as to when maximum and minimum QT prolongation present in the subpopulations of patients with LQTS. Note that the QT clock could also use 12-lead ECG data as input. However, the utility of these clocks in understanding beat-to-beat variations in QTc and whether they can be used to predict adverse clinical events remain to be proven.

Interestingly, in our study we identified a signature pattern of QT prolongation in patients with LQT1 and LQT2 during a 24-hour period. Patients with LQT1 typically have adverse cardiac events during high sympathetic tone. When looking at the degree of QT prolongation, our results reveal that LQT1 patients are more likely to have diagnostic QTc prolongation during the daytime hours. During the night, when sympathetic withdrawal occurs, a much lower degree of QTc prolongation can be observed. On the other hand, LQT2 patients show QT prolongation during the nighttime hours compared to the daytime hours. These findings raise the question as to whether these signature patterns of QTc prolongation can be used to identify and separate out subgroups of LQTS. The number of patients with LQT3 in our study were too few to conclude any differences in QT prolongation over time.

Future applications of the QT clock

We have proposed a visualization tool to quickly review long-term QTc monitoring data and visually assess the presence of abnormal QTc interval prolongation throughout the day. The QT clock concept can be used to display measurements from a single ECG recording for a given patient. Examples are given in Figure 5, in which we plot the

Table 3 Percentage of QTc prolongation (median values) in LQTS subjects between 2 periods of the day: 3–4 AM and 3–4 PM

Percentage of cardiac beats with QTc prolongation	LQT1		LQT2		LQT3	
	Men	Women	Men	Women	Men	Women
N	82	108	40	47	8	5
Period: 3AM–4 AM	48%	30%	100%	100%	100%	81%
Period: 3 PM–4 PM	97%	68%	87%	62%	100%	95%
P value	.0002	.00001	.0002	.002	.2	1

Prolongation percentage is defined as the percentage of heartbeats with QTc above the gender-specific threshold during the given hours. Periods starting at 3 AM and 3 PM were chosen as representative times to illustrate changes in QTc prolongation between sleeping and waking hours. Median QTc values at these times are identified in Figure 2, and prolongation percentage for the full 24 hours is shown in Figure 3. N is reported as the number of patients with Holter recordings containing data during the required hours.

LQTS = long QT syndrome; LQT1 = long QT syndrome type 1; LQT2 = long QT syndrome type 2; LQT3 = long QT syndrome type 3.

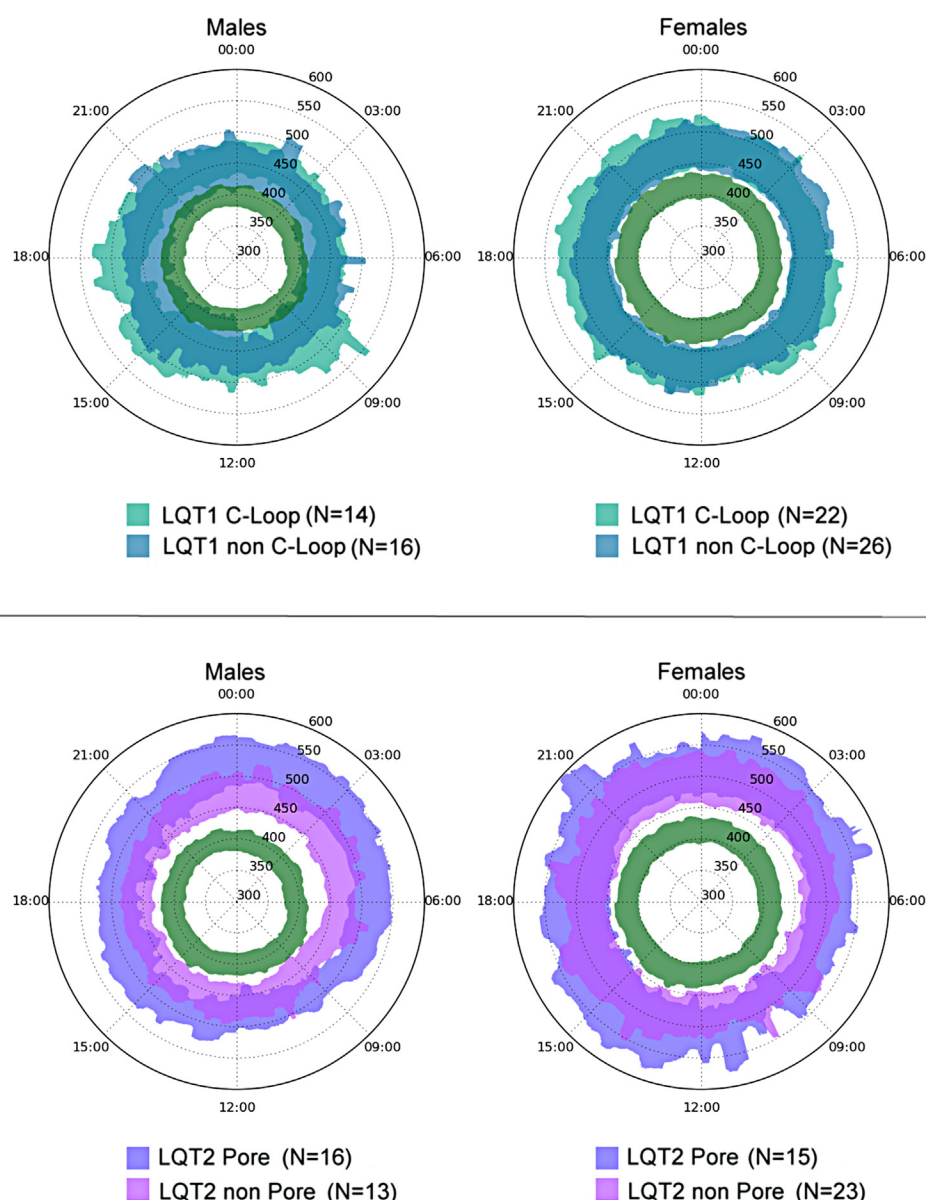


Figure 4 Gender-specific heart rate–corrected QT based on Bazett formula (QTcB) clocks for long QT syndrome type 1 (LQT1) and long QT syndrome type 2 (LQT2) patients with missense mutations. The clocks show the 16th–84th percentile of QTc for LQT1 patients with mutations inside or outside the cytoplasmic loop (C-loop) and for LQT2 patients with mutations in pore and non-pore regions. *Green area* is the healthy region defined in [Figure 2](#). Plots reveal the more pronounced QTc prolongation in males with missense mutations in the C-loop and pore regions for LQT1 and LQT2, respectively. In females, these differences are less pronounced.

QTc interval across whole recordings of a healthy individual (left panel), a patient with LQT1 (middle panel), and a patient with LQT2 (right panel). The blue line is a 10-minute moving median. The light green area is the 16th to 84th percentile range for healthy individuals of the same gender as the subject. This percentile range is used to remain consistency with the other figures; however, for diagnostic purposes, it may be desirable to expand this area (eg, to 5%–95%) or to show several percentile tiers/contours in different shades of green. This representation helps to easily pinpoint periods of the day associated with QTc prolongation and therefore counsel patients about their daily periods/activities associated with risk. It is worth noting that the

QT clock may be used to monitor patients receiving known QT-prolonging drugs, specifically during inpatient dofetilide initiation when the dose-dependent effect of the drug needs to be assessed over a couple of days. The QT clock may also be used during the ambulatory outpatient period to assess the long-term safety and efficacy of a QT-prolonging drug.

Study limitations

Our analysis is based on Holter recordings acquired using 2- or 3-lead configurations. These leads were not systematically reported, but they were V₁-, aVF-, or V₅-like leads.

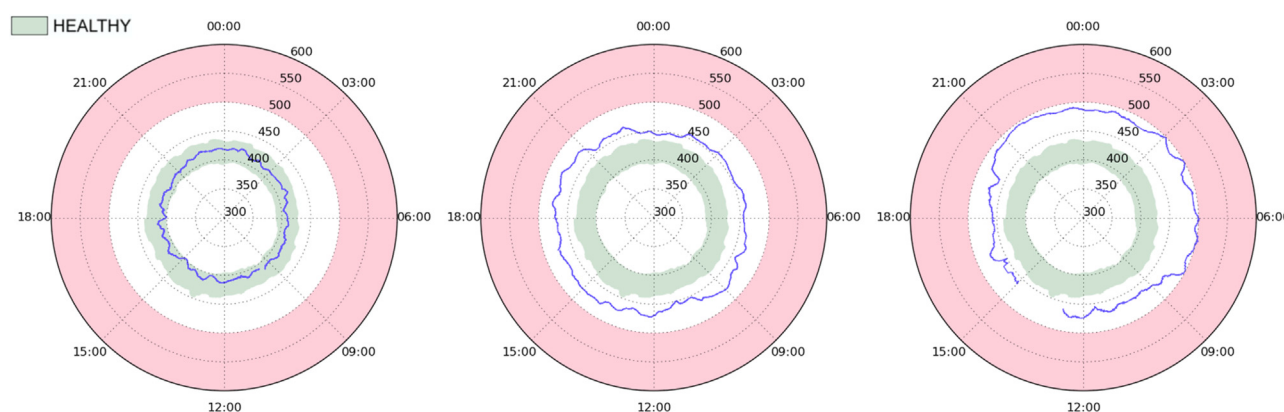


Figure 5 Example QT clock plots of individual patients (blue line) in reference to the healthy QTc range (green area defined in Figure 2) for 3 different subjects: healthy 27-year-old (left), 64-year-old long QT syndrome type 1 patient with non-C-loop mutation (middle), and 1-year-old long QT syndrome type 2 (LQT2) patient with pore missense mutation (right). All subjects are female, and none were taking beta-blockers. Red area marks QTc > 500 ms zone. Individual plottings are median-filtered beat-to-beat QTc values. Plots emphasize how the proposed “QTc clock” enables the physician to quickly identify periods of prolonged QTc, for example, nighttime for the LQT2 patient.

Therefore, in this analysis we do not deliver a lead-based comparison in terms of identifying prolongation, but we are limited to assessing the presence of prolongation using the longest QT interval measured from nonstandard leads in all beats. How lead selection may affect our analysis and the accuracy compared to standard 12-lead ECGs remain to be elucidated. We were limited by the low number of recordings available for the LQT3 cohort, making it difficult to draw conclusions from that group. Additionally, in the “population average” QT clocks (Figures 2 and 4) and the QTc histogram (Figure 1), every heartbeat is given equal weight. Consequently, patients with different numbers of heartbeats on file (due to length/number of Holter recordings, or different average heart rates) will contribute disproportionately to these plots.

Finally, we did not report the comparison of QT clocks between asymptomatic and symptomatic LQTS patients because we did not have information about the timing of events in relation to when the Holter recordings were acquired. We also opted not to report the QT clocks comparing groups of patients with and those without beta-blocker therapies because the prescription of beta-blocker therapy is dependent on the level of QTc prolongation, hence biasing the data. Although we do have Holter recordings from a few patients before and after initiation of beta-blocker therapy, the number of these patients is too small to draw any conclusions. The QT clocks for the LQTS cohorts (1) with and without beta-blockers and (2) with and without symptoms have been made available as Online Supplementary Figures (Figs. 1 and 3, respectively).

Conclusion

In genotype-positive LQTS patients, dynamic changes in QTc can be uncovered using Holter monitoring. The QT clock is a useful illustration of QT dynamics and can be used to plot QTc measurements for a population or for an individual patient. There are unique patterns of QT

prolongation during a 24-hour period in patients with LQT1 and LQT2. Future research is needed to determine whether Holter monitoring and QT prolongation patterns can aid in identifying the different subsets of LQTS patients.

Appendix Supplementary data

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.hrthm.2015.08.037>.

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CLINICAL PERSPECTIVES

Cardiac repolarization, recorded on the surface ECG using the QT interval, is a dynamic parameter and can be influenced by a variety of cellular and environmental factors. In this study, we used Holter monitoring and the concept of a QT clock to display changes in QTc in genotype-positive long QT syndrome (LQTS) patients. A computer algorithm that measures QTc in a beat-to-beat manner was developed. Periods of maximum and minimum QTc prolongation over 24 hours were determined for each of the subgroups of LQTS. Unique patterns of QTc prolongation were observed for patients with LQTS types 1 and 2. We believe this study will encourage clinicians to make use of standard Holter recordings and the newly developed QT clock concept to better understand an individual patient's burden of QT prolongation and the potential risk associated with it. Furthermore, the QT clock may prove beneficial as an application to closely and continuously monitor the QTc interval in patients exposed to QT-prolonging drugs, such as for monitoring patients with atrial fibrillation treated with dofetilide.