Heart Rate Variability in Patients with Congenital Long QT Syndrome

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Background: The congenital long QT syndrome (LQTS) affecting myocardial repolarization is caused by mutations in different cardiac potassium or sodium channel genes. Adrenergic triggers are known to initiate life-threatening torsade de pointes ventricular tachycardias in LQTS patients, and anti-adrenergic therapy has been shown to be effective in many cases. Despite this well-documented adrenergic component, the data about autonomic modulation of the heart rate in LQTS, as described by heart rate variability (HRV) analysis, are very limited.

Methods: Conventional time- and frequency-domain and newer nonlinear measures of HRV were compared in resting conditions among 27 LQTS patients with gene mutations at the LQT1 (n = 8), LQT2 (n = 10) or LQT3 (n = 9) loci and 34 LQTS noncarrier family members.

Results: None of the conventional time- or frequency-domain or newer nonlinear measures of HRV differed significantly between the LQTS carriers and LQTS noncarriers or between the LQT1, LQT2, and LQT3 carriers.

Conclusions: These findings suggest that baseline cardiac autonomic modulation of the heart rate measured in resting conditions by traditional or newer nonlinear measures of HRV is not altered in LQTS patients. Furthermore, no differences are observed in HRV parameters between LQTS patients with potassium (KvLQT1, HERG), and sodium (SCN5A) ion channel gene mutations. HRV analysis in resting conditions does not improve phenotypic characterization of LQTS patients.

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Recently, the congenital long QT syndrome (LQTS) has been shown to be caused by different genetic mutations of cardiac ion channel genes[1-6] with mutations of four potassium channel genes and one sodium channel gene. It is well known that syncopal episodes in LQTS patients (usually due to torsade de pointes ventricular tachycardia) are characteristically triggered by sudden increase in sympathetic activity.[7] In addition, beta-adrenergic blocking agents and left cardiac sympathetic denervation are effective therapies in many patients with LQTS.[8-10] Previously, the observations of lower heart rate in LQTS patients raised interest in the sympathetic control of heart rate in this syndrome.[11] Nevertheless, the data on heart rate variability (HRV), an indirect measure of autonomic cardiac regulation, are very limited in these patients.

The present study was aimed to assess whether HRV analysis provides evidence for altered autonomic modulation of heart rate in LQTS. To study this question, conventional measures and nonlinear dynamics of HRV were compared among LQT1, LQT2, and LQT3 carriers and noncarriers.

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METHODS

Study Population

The study population consisted of 27 LQTS gene carriers and 34 noncarrier LQTS family members. There were 8 LQT1 gene carriers, 10 LQT2 gene carriers, and 9 LQT3 gene carriers. Electrocardiographic (ECG) recordings were performed without changing prescribed therapy, i.e., 20 LQTS carriers and 3 noncarriers were taking beta-blockers.

ECG Recordings

High resolution 1000 Hz ECG data were recorded for a 10-minute period using the Burdick Holter recorder (Spacelab-Burdick, Milton, WI) in resting supine conditions. The ECG data were transferred to a microcomputer for processing and analysis of HRV. Premature beats and noise were excluded both automatically and manually. Patients with segments with < 85% qualified beats were excluded from the analysis. HRV was analyzed by a software package with methodology described in detail previously.[12-15] Both conventional time-domain and frequency-domain and also newer nonlinear measures of HRV were analyzed.

Time- and Frequency-Domain Analysis of HRV

The standard deviation of all normal-to-normal R-R intervals (SDNN), the square root of the mean squared differences of successive normal-to-normal R-R intervals (RMSSD) and the proportion of interval differences of successive normal-to-normal R-R intervals greater than 50 ms (pNN50) were calculated as standard time-domain measures of HRV. Fast Fourier transformation spectral analysis of time-series was used to obtain low frequency power (LF, 0.04-0.15 Hz) and high frequency power (HF, 0.15-0.40 Hz) components in absolute values. The LF/HF ratio was also calculated.

Nonlinear Measures of HRV

Several new methods have recently been developed to describe the complexity of cardiac beat-to-beat behavior. There is a need for these kinds of methods as they may detect subtle abnormalities in R-R interval dynamics. We used two parameters: (1) a short-term scaling exponent based on the "detrended fluctuation analysis" of the tachogram providing an estimation of fractal correlations in R-R interval dynamics for short-term R-R interval data (< 11 beats, α_1);[16,17] and (2) approximate entropy, which measures the regularity and complexity of the tachogram.[12,18]

The parameter α_1 describes the self-similarity properties of the R-R interval time series. For totally uncorrelated data it has a value of 0.5 (corresponding to white noise) and has higher values when the tachogram shows correlation properties (fractal organization) of R-R changes. Hypothetically, a reduction of α_1 (converging towards 0.5) could be associated with a degradation of autonomic nervous system influences. Approximate entropy quantifies the likelihood that runs of patterns that are close remain close on next incremental comparisons and the larger the value of approximate entropy, the greater the unpredictability in the R-R interval time series. The approximate entropy input variable m determines the window length of compared runs of R-R interval data, and the variable r sets the tolerance for the comparison of these runs. The input variables m and r must be fixed to calculate approximate entropy, and m = 2 and r = 20% of the SD of the data sets were chosen as suitable values on the basis of previous findings of statistical validity.[18]

Measurement of QT Interval

The baseline QT interval was measured primarily from the limb lead II of the first available ECG. If the baseline QT interval was uninterpretable from the lead II, it was measured from the lead V_5 or V_2 in this order. Bazett's formula was used to obtain heart rate-corrected (c) values of QT intervals. The maximum QTc interval was determined as the longest QTc interval in the limb lead II among the ECGs available.

Statistical Analysis

The Mann-Whitney test was used to estimate the differences in age, QTc interval, R-R interval, and the HRV measures between the study groups, and the chi-square test to estimate the differences in gender, occurrence of cardiac events, and the usage of beta-blockers between the groups. The Kruskal-Wallis test was used to study the differences in the R-R interval and heart rate variability measures between LQT1, LQT2, and LQT3 carriers. The logistic regression analysis was used to test the independent power of different variables in discriminating between LQTS carriers and noncar-

Table 1. Clinical Characteristics and QTc Interval of the Study Subjects

	LQTS Noncarriers (n = 34)	LQTS Carriers (n = 27)	P Value
Age (years)	34 ± 17	35 ± 16	NS
Male/Female	20/14	16/11	NS
Cardiac events +/0/−	1/24/9	12/15/0	$P < 0.01$
Beta-blocker	3	20	$P < 0.001$
Baseline QTc interval (ms)	418 ± 25	498 ± 53	$P < 0.001$
Maximum QTc interval (ms)	423 ± 25	523 ± 65	$P < 0.001$

The data are presented as means ± SD or as the number of patients. The Mann-Whitney test was used to study the differences in age and QTc intervals, and the Chi-square test in gender, occurrence of cardiac events and the usage of blockers between the groups. NS = nonsignificant; cardiac events = a history of syncope, aborted cardiac arrest or cardiac death; + = present; 0 = absent; − = no information available.

riers. Pearson's correlation coefficients were calculated to determine the correlations between the HRV measures, QT, QTc interval, and age.

RESULTS

Clinical Characteristics of the Studied Patients

The clinical characteristics and the QTc intervals of the study subjects are presented in Table 1. Age and gender did not differ significantly between the study groups. The LQTS carriers had more frequent cardiac events and were more often on beta-blocking medication at the time of ECG recording compared to the noncarriers. The baseline and maximum QTc intervals were significantly longer in the LQTS carriers compared to the noncarriers.

Heart Rate Variability Parameters in LQTS Carriers and Noncarriers

The average R-R interval was significantly longer in the LQTS carriers as compared to the LQTS noncarriers and differed significantly between LQT1, LQT2, and LQT3 carriers, being the longest in LQT3 carriers and the shortest in LQT2 carriers (Tables 2 and 3). There were no significant differences in any of the measures of HRV between the

Table 2. Average R-R Interval and Heart Rate Variability in the Study Subjects

	LQTS Noncarriers (n = 34)	LQTS Carriers (n = 27)	P Value
Average R–R interval (ms)	863 ± 115	1014 ± 175	< 0.001
Time domain measures			
SDNN (ms)	50 ± 24	63 ± 32	NS
RMSSD (ms)	38 ± 24	50 ± 30	NS
pNN50	17 ± 20	24 ± 23	NS
Spectral components			
LF power (ms^2)	766 ± 848	970 ± 811	NS
HF power (ms^2)	755 ± 905	1114 ± 1106	NS
LF/HF ratio	1.7 ± 1.1	1.3 ± 0.9	NS
Nonlinear measures			
α_1	1.04 ± 0.23	1.01 ± 0.20	NS
ApEn	1.12 ± 0.22	1.05 ± 0.20	NS

α_1 = short-term scaling exponent obtained by using the detrended fluctuation analysis technique; ApEn = approximate entropy; HF = high frequency; LF = low frequency; NS = nonsignificant; pNN50 = the proportion of interval differences of successive normal-to-normal R-R intervals greater than 50 ms; RMSSD = the square root of the mean squared differences of successive normal-to-normal R-R intervals; SDNN = the standard deviation of all normal-to-normal R-R intervals. The data are presented as means ± SD. The Mann-Whitney test was used to study the differences in the R-R interval and heart rate variability measures between the study groups.

Table 3. Average R-R Interval and Measures of Heart Rate Variability in LQT1, LQT2, and LQT3 Carriers

	LQT1 Carriers (n = 8)	LQT2 Carriers (n = 10)	LQT3 Carriers (n = 9)	P Value
Average R-R interval (ms)	1070 ± 82	899 ± 145	1092 ± 209	< 0.05
Time domain measures				
SDNN (ms)	78 ± 36	50 ± 20	64 ± 37	NS
RMSSD (ms)	59 ± 28	41 ± 22	51 ± 39	NS
pNN50	28 ± 17	17 ± 17	28 ± 32	NS
Spectral components				
LF power (ms^2)	1448 ± 1094	741 ± 524	801 ± 673	NS
HF power (ms^2)	1359 ± 947	766 ± 831	1283 ± 1474	NS
LF/HF ratio	1.1 ± 0.3	1.3 ± 0.7	1.6 ± 1.3	NS
Nonlinear measures				
α_1	1.01 ± 0.11	1.02 ± 0.17	1.00 ± 0.30	NS
ApEn	1.00 ± 0.20	1.15 ± 0.14	0.98 ± 0.22	NS

Abbreviations are the same as in Table 2. The data are presented as means ± SD. The Kruskal-Wallis test was used to study the differences in the R-R interval and heart rate variability measures between LQT1, LQT2, and LQT3 carriers.

LQTS carriers and the LQTS noncarriers or between the LQT1, LQT2, and LQT3 carriers. LQT2 carriers had faster heart rates and as a consequence somewhat lower values of the conventional HRV parameters than LQT1 and LQT3 carriers. Since some of the studied subjects were on beta-blockers, we also compared HRV parameters in carriers and noncarriers off and on beta-blockers. The average R-R interval and all the HRV measures were very similar in LQTS noncarriers and LQTS carriers off beta-blockers (Table 4). The average R-R interval was significantly longer and approximate entropy smaller in the LQTS carriers who were on beta-blockers at the time of ECG recording, no other HRV measures differed significantly between the LQTS carriers who were on beta-blockers and the LQTS carriers who did not have beta-blocking medication (Table 5).

In logistic regression analysis including age, gender, the usage of beta-blocking medication, the baseline QTc interval, and the average R-R interval, only the baseline QTc interval was an independent discriminator between the LQTS carriers and noncarriers (OR = 1.6 for every 10 ms increment in QTc, P = 0.0043). None of the HRV parameters showed discriminating power, when tested one at a time in this model with the baseline QTc interval.

Table 4. Average R-R Interval and Heart Rate Variability in the Study Subjects off Beta-Blockers

	LQTS Noncarriers (n = 31)	LQTS Carriers (n = 7)	P Value
Average R-R interval (ms)	850 ± 111	858 ± 121	NS
Time domain measures			
SDNN (ms)	48 ± 22	51 ± 24	NS
RMSSD (ms)	36 ± 21	37 ± 17	NS
pNN50	15 ± 17	15 ± 17	NS
Spectral components			
LF power (ms^2)	639 ± 635	782 ± 662	NS
HF power (ms^2)	691 ± 865	678 ± 602	NS
LF/HF ratio	1.7 ± 1.2	1.3 ± 0.4	NS
Nonlinear measures			
α_1	1.04 ± 0.24	1.08 ± 0.09	NS
ApEn	1.13 ± 0.22	1.17 ± 0.11	NS

Abbreviations are the same as in Table 2. Data are means ± SD. The Mann-Whitney test was used to study the differences in HRV measures between the groups.

Table 5. Average R-R Interval and Measures of Heart Rate Variability among LQTS Carriers in Respect to Beta-blocking Medication at the Time of Electrocardiographic Recording

	No Beta-Blockers Used (n = 7)	Beta-Blockers Used (n = 20)	P Value
Average R-R interval (ms)	858 ± 121	1068 ± 159	< 0.01
Time domain measures			
SDNN (ms)	51 ± 24	67 ± 34	NS
RMSSD (ms)	37 ± 17	54 ± 33	NS
pNN50	15 ± 17	27 ± 24	NS
Spectral components			
LF power (ms^2)	782 ± 662	1036 ± 862	NS
HF power (ms^2)	678 ± 602	1267 ± 1211	NS
LF/HF ratio	1.3 ± 0.4	1.3 ± 1.0	NS
Nonlinear measures			
α_1	1.08 ± 0.09	0.99 ± 0.23	NS
ApEn	1.17 ± 0.11	1.00 ± 0.21	< 0.05

Abbreviations are the same as in Table 2. Data are means ± SD. The Mann-Whitney test was used to study the differences in HRV measures between the groups.

Association between Different HRV Measures, QT, QTc Interval, and Age (Table 6)

All the measures of HRV had a significant relation to R-R interval (heart rate). The time-domain measures of HRV, and HF power and LF/HF ratio of power spectrum were correlated with baseline QTc interval. However, absolute QT interval (unadjusted for heart rate) showed a weak correlation only with SDNN. All the conventional measures of HRV were dependent on age.

DISCUSSION

The present study shows that autonomic modulation of heart rate quantitated by traditional or newer nonlinear measures of HRV does not differ significantly between patients with genetically proven LQTS and their noncarrier family members, or between LQT1, LQT2, and LQT3 carriers. Previous data on different measures of HRV in LQTS patients have been very sparse. Spectral analysis of HRV from 24-hour ambulatory data in 13 LQTS patients without medications by Morita et al.[19] showed that the ratio of LF to HF (an index of sympathetic nervous activity) was lower and HF power (an index of parasympathetic nervous activity) was higher in LQTS patients than in controls. Furthermore, those patients with torsade de pointes ventricular tachycardia showed lower abnormal sympathetic nervous activity compared to those without torsade de pointes.[19] Data on chick embryos with experimentally induced long QT intervals have suggested that abnormal development of the sensory innervation of the heart may be important in the developmental LQTS expressed by these embryos.[20] Our findings do not support the presence of baseline autonomic imbalance in patients with LQTS.

Patients with mutations at the LQT1 or LQT2

Table 6. Association between Heart Rate Variability Measures, QTc Interval, QT Interval, and Age in Study Subjects

	SDNN	RMSSD	pNN50	LF	HF	LF/HF	α_1	ApEn
RR	.56*	.59*	.59*	.40*	.54*	−.29	−.31	−.30
QTc	.27	.31	.30	.11	.28	−.27	−.25	−.16
QT	.29	.24	.21	.11	.20	−.12	−.09	−.19
Age	−.52*	−.56*	−.54*	−.55*	−.53*	.36*	.19	−.05

QT = absolute QT interval (unadjusted for heart rate); QTc = baseline QTc interval; R-R = average R-R interval; other abbreviations as in Table 2. The values are Pearson's correlation coefficients. * = significant correlation at the 0.01 level.

locus have higher incidence of cardiac events compared to those with mutations at the LQT3 locus.[21] However, these events are more often lethal in LQT3 patients leading to similar cumulative mortality in these three patient groups. Furthermore, the length of QTc interval contributes independently of the genotype to the risk of cardiac events in these patients.[21] These differences in clinical course between LQT1, LQT2, and LQT3 patients could be caused by different propensity to arousal and nonarousal triggers.[22] LQT1 patients are likely to develop cardiac events during exercise or emotion, whereas they occur in LQT3 during sleep, and in LQT2 patients under either condition. Different mechanisms triggering cardiac events in LQT1, LQT2, and LQT3 patients may support different regulation of the heart by autonomic nervous system. The analysis of HRV performed in this study demonstrates that LQTS patients regardless of potassium or sodium channel gene mutation do not differ from each other in the resting autonomic modulation of the heart rate. During adrenergic triggers, there are sudden changes in the cardiac autonomic control, and in these settings the influence of autonomic nervous system on the homogeneity of repolarization may theoretically differ depending on the nature of the genetic ion channel defect. This cannot be excluded based on our analysis of resting ECG recordings. Moreover, the measures of HRV reflect mainly the autonomic nervous control at the sinus node level and may not reveal any possible differences at the ventricular level or in humorous regulation.

In congruence with the previous observations that time- and frequency-domain measures of HRV decrease with age in adults,[23] in the present study with mixed population of whom the majority were adults, the time-domain measures, LF and HF powers of HRV had a negative correlation with age. QTc interval, as mentioned, has value in the prediction of risk of cardiac events in LQTS patients.[21] In the present population the time-domain measures of HRV, and the HF component and LF/HF ratio of the power spectrum had a weak correlation with QTc interval, and even weaker with absolute QT interval duration. This further supports the lack of relationship between resting sympathovagal tone and repolarization duration.

Study Limitations

The gene carriers of LQTS were much more often on beta-blocking therapy at the time of ECG recording than noncarriers. Previous observations have suggested that beta-blockers may modify HRV, e.g., increase time-domain parameters.[24,25] However, we did not find significant differences in any conventional measures of HRV between LQTS carriers with and without beta-blocking medication at the time of ECG recording, possibly because the ECG recordings were done under stationary conditions while the study subjects were in supine position which may have minimized the influence of beta-blocking medication on HRV. We were not able to stop beta-blocking therapy in these patients since it is effective in preventing life-threatening arrhythmias in this syndrome. Separate subset analysis comparing HRV parameters in LQTS noncarriers and LQTS carriers off beta-blockers further demonstrated the absence of significant difference between LQTS carriers and noncarriers in autonomic modulation of the heart rate.

In the present study HRV was assessed from short-term recordings, which may not reveal possible disturbances in long-term regulation of heart rate or in autonomic cardiac control during adrenergic triggers. On the other hand, the recordings were made under stable conditions while the subjects were in supine position allowing the comparison of cardiac signal in standardized conditions. The number of genotype positive carriers was relatively small, and this may limit the power to detect small differences in HRV parameters.

CONCLUSION

In conclusion, the present data suggest that cardiac autonomic modulation of the sinus node as measured by conventional or newer nonlinear methods of HRV under resting conditions is not disturbed in patients with genetically proven LQTS. The analysis of HRV in resting conditions does not improve phenotypic description of LQTS patients.

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