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The prevalence and diagnostic/prognostic utility of sinus arrhythmia in the evaluation of congenital long QT syndrome

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Abstract

BACKGROUND—Congenital long QT syndrome (LQTS) affects 1 in 2,500 people and can cause syncope and sudden death. Sinus arrhythmia (SA) is nonpathologic baseline respiratory variation of the RR interval.

OBJECTIVE—This study sought to determine the frequency of SA and its clinical significance among patients with LQTS.

METHODS—We performed an institutional review board–approved retrospective review of all patients (N = 571) evaluated in our LQTS clinic from 7/2000 to 3/2008 diagnosed with LQTS (N = 281) or dismissed as otherwise normal (N = 290). Blinded to diagnosis, the first available electrocardiogram for each patient was examined to quantitate RR interval variability.

RESULTS—Overall, 151 of 281 patients (54%) with LQTS (159 female patients, average age 21.8 ± 16.5 years, average QTc 466 ± 43 ms) had SA with an average RR variability of $13\% \pm 8\%$ compared with 201 of 290 (69%) patients dismissed as normal (178 female patients, average age 21.7 ± 16 years, average QTc 424 ± 30 ms) who demonstrated SA with RR variability of $16\% \pm 10\%$ ($P < .0001$). These differences remained significant when patients on concurrent beta-blocker therapy were excluded ($P < .001$). SA was least common in LQT3 (23%) compared with LQT1 (61%, $P < .005$) and LQT2 (51%, $P = .055$). Patients presenting with torsades de pointes or aborted cardiac arrest had lower RR variability ($10\% \pm 7\%$, $P < .03$).

CONCLUSION—SA frequency and magnitude of RR variability was lower among patients with LQTS compared with those patients dismissed as otherwise normal. This attenuation in RR interval variability remained when patients on beta-blocker therapy were excluded. Although the presence/absence of sinus arrhythmia is of little diagnostic value due to cohort overlap, LQTS patients with negligible RR interval variation may be at higher risk.

Keywords

Long QT syndrome; Sinus arrhythmia; Prevalence; Sudden cardiac death; QT interval

Congenital long QT syndrome (LQTS) was first described clinically as Jervell and Lange-Nielsen syndrome and Romano-Ward syndrome in the late 1950s and early 1960s.^{1–3} Approximately 1 in 2,500 people is affected with LQTS.⁴ The trademark event for the symptomatic LQTS patient is the potentially lethal ventricular dysrhythmia known as torsades de pointes, which can precipitate syncope, cardiogenic seizures, or sudden death.^{5,6} LQTS stems from a group of genetically distinct arrhythmogenic disorders resulting from genetic mutations in cardiac potassium and sodium ion channels, termed cardiac channelopathies.^{7,8} Mutations in cell membrane proteins associated with ion channels can also cause LQTS.^{9,10} A total of 13 LQTS susceptibility genes have been discovered thus far.¹¹ Mutations in potassium channel genes *KCNQ1* (LQT1) and *KCNH2* (LQT2) and the sodium channel gene *SCN5A* (LQT3) account for approximately 75% of patients with clinically definite LQTS and encompass over 95% of genetically identifiable LQTS.^{11–14}

Sinus arrhythmia (SA) is the nonpathologic baseline respiratory variation of the RR interval, in which the RR interval is shortened during inspiration and prolonged during expiration.^{15,16} SA is an intrinsic physiologic mechanism in mammals that improves the efficacy of pulmonary gas exchange.^{17,18} SA is prominent in infants, but not always readily appreciated because of their relatively increased heart rates. The prominence of SA decreases with increasing age.¹⁹ Due to relatively young age but adult-level baseline heart rates, SA is noted frequently on the 12-lead electrocardiogram (ECG) in adolescent patients.^{15,19}

Prior reports have described methods of calculating the corrected QT interval (QTc) in patients with prominent SA.^{20,21} It is unclear, however, whether the presence of SA on a 12-lead ECG during an LQTS workup is of any diagnostic or prognostic value. Herein, we sought to determine the clinical significance of SA in the evaluation of LQTS.

Methods

In this institutional review board–approved study, the electronic medical record (EMR) was reviewed for all patients (N = 571) evaluated in our LQTS clinic between July 2000 and March 2008 who were either diagnosed with LQTS (N = 281) or dismissed as otherwise normal (N = 290). Diagnosis was made using known clinical criteria for LQTS along with genetic testing for the majority of cases (88%) of those ultimately dismissed with a diagnosis of LQTS. For the comparison group, this subset dismissed as otherwise normal underwent the same comprehensive clinical, electrocardiographic, and genetic evaluation for LQTS, and it was concluded that there was insufficient evidence to merit such a diagnosis.²²

Blinded to genotype and dismissal diagnosis, each patient's first available ECG was examined in a de-identified fashion by a single assessor (J.N.J.). Because of the retrospective nature of the study, the time performed and testing conditions of each ECG were not controlled. Instead, each ECG was performed per our usual outpatient protocols. However, the majority of patients (83%) had their first ECGs performed between 7 AM and 12 PM on the day of their visit to the LQTS clinic. The RR interval between each QRS complex was measured manually and recorded in a database. An ECG was considered to be positive for SA if there was >10% variability in the RR interval through the duration of the 10-second rhythm strip in the absence of changing P-wave morphology or axis (American College of Cardiology/American Heart Association/Heart Rhythm Society criteria). This was calculated by dividing the difference of the maximum and minimum RR intervals by the maximum RR interval in lead II.²³

Each patient's EMR was then abstracted for demographic variables, presence and type of symptoms, medication profile, LQTS clinic's dismissal diagnosis, history of genetic testing,

genotype if available, and resting QTc at time of initial diagnosis (Table 1). Patients were excluded if no ECG was available in the EMR, or if they had any form of extrinsic electronic pacing (atrial or ventricular), more than 1 premature atrial complex or single premature ventricular complex in a 10-second rhythm strip of a standard ECG, changing P-wave morphology or axis within the rhythm strip, or evidence of 2nd- or 3rd-degree AV block. In the presence of a premature atrial complex or single premature ventricular complex, aside from the ectopic beat's RR interval, the RR intervals both before and after the premature complex were excluded from the calculations.

Patients who underwent genetic testing did so after referral by a physician specializing in LQTS (M.J.A.). Genetic testing was performed using denaturing high-performance liquid chromatography and/or direct DNA sequencing and included comprehensive testing of at least the 3 canonical LQTS susceptibility genes responsible for LQT1 to LQT3. Genetic testing was performed in most patients after their first visit to the LQTS clinic; however, some had testing performed before their LQTS clinic visit because of a positive family genotype. Patients with a positive family genotype only underwent testing to confirm the presence or absence of their specific familial mutation. Of the 281 LQTS patients, there were 88 (31%) unrelated probands, with 197 patients being relatives of an already-diagnosed proband. The normal cohort had 150 of 291 unrelated patients, with the remainder being relatives of an already-misdiagnosed proband.

All continuous variables were reported as the mean $\pm$ SD. Proportions were analyzed and compared using a Z-test for proportions. Means were analyzed using the independent groups *t*-test for means. All QT and RR intervals were measured manually. QTc values were calculated using the standard Bazett formula.²⁴ A *P* value $<.05$ was considered to be statistically significant.

Results

Overall, patients with LQTS were less likely to show SA compared with those patients who had been dismissed as otherwise normal (Figure 1). A total of 151 of 281 patients (54%) with LQTS (159 female patients, average age 21.8 ± 16.5 years, average QTc 466 ± 43 ms) showed SA (again defined as $>10\%$ variability) compared with 201 of 290 (69%) patients dismissed as normal (178 female patients, average age 21.7 ± 16 years, average QTc 424 ± 30 ms, $P < .0001$) (Figure 2A). The average RR variability was $13.1\% \pm 8.4\%$ among LQTS patients compared with the significantly higher average variation in intervals RR of $16.4\% \pm 9.6\%$ ($P < .0001$) noted in the other cohort (Figure 2B). There were no differences between the 2 cohorts in terms of patient gender or age, nor was there any baseline gender-specific effect noted on RR variability ($P = .12$).

To ensure that the results were not affected by inaccuracies at high and low heart rates, the analysis was repeated excluding any patient with a heart rate <50 or >100 beats/min. Despite these exclusions, LQTS patients (130 of 227, 62%) continued to show SA less frequently than normal subjects (175 of 242, 76%, $P = .001$). Additionally, to ensure that a different definition of SA would not affect outcome, we used a different calculation method as described by Martin et al,²⁰ in which SA was designated when the maximum RR interval minus the minimum RR interval exceeded 80 ms in a 10-second rhythm strip. Here, 170 of 281 LQTS patients (61%) satisfied this definition of SA compared with 223 of 290 (77%) of normal subjects ($P < .0001$). Finally, when patients who were on concurrent beta-blocker therapy at the time of their ECG were excluded, the prevalence of SA among LQTS patients (87 of 165, 56%) remained statistically less than that of normal subjects (144 of 205, 75%, $P = .001$).

When subset analyses based on genotype were performed, SA was less common in patients with LQT3 (6 of 23, 23%) compared to patients with LQT1 (82 of 134, 61%, $P = .004$). LQT3 patients had less SA than patients with LQT2 (39 of 77, 51%), but this did not reach statistical significance ($P = .055$) (Figures 2A and 2B). Individually, both LQT2 and LQT3 as well as patients with only clinically diagnosed LQTS (i.e., negative or absent genetic test, 19 of 39, 49%) were all less likely to have SA compared with normal subjects ($P < .05$). LQT1 patients did not have a significantly different prevalence of SA compared with normal subjects ($P = \text{NS}$). There were 3 patients with mutations in 2 different LQTS genes, of which 1 patient had SA. There was no difference in SA prevalence between unrelated LQTS probands and non-probands (data not shown).

There was a wide spectrum of RR variability seen throughout this study (range 1% to 45%), with a significant overlap in variability values between the cohorts. The sensitivity and specificity of the presence of SA ($\geq 10\%$ RR variability cutoff) in diagnosing LQTS were thus only 54% and 31%, respectively. There were no LQTS patients with an RR variability $> 38.5\%$, although only 11 of 290 ($< 4\%$) normal patients showed this extreme degree of RR variability. The point of 95% sensitivity for ruling out LQTS was at $> 30\%$ variability, which represents substantial SA given its qualitative annotation at 10% variability.

The degree of SA as measured by RR variability was not significantly different between symptomatic ($N = 102, 13.1\% \pm 7.9\%$) and asymptomatic LQTS patients ($N = 179, 13.4\% \pm 9.2\%$, $P = \text{NS}$). Of the 102 symptomatic patients, 13 had initially presented with torsades de pointes or aborted cardiac arrest (average QTc 506 ± 77 ms). These patients had an RR variability of $9.6\% \pm 7.3\%$, significantly lower than the subset of patients dismissed as otherwise normal ($P < .03$). However, when compared with the other patients with LQTS, this low RR variability did not reach significance because of small sample size. When baseline QTc was plotted against RR variability for the whole cohort, we noted a significant relationship ($P < .0001$) (Figure 3). The r^2 coefficient for this relationship was relatively low at 0.03. Patients with a baseline QTc > 500 ms had a lower average RR variability of $11.7\% \pm 6.9\%$ compared to those with a QTc < 500 ms, who had an average RR variability of $15.1\% \pm 9.3\%$ ($P < .01$). In a logistic model of clinical criteria, QTc, and RR variability in our cohort, only QTc remained a significant indicator of significant cardiac events ($P < .0001$).

Discussion

In this study, patients with LQTS were shown to have less variability of their RR interval as compared with those subjects who had been evaluated and dismissed as otherwise normal.²² This attenuation remained significant even when excluding patients on beta-blocker therapy or those with extremes of heart rates.

SA has been shown in other cardiovascular disease states to be attenuated relative to normal subjects. For example, RR variability is decreased in patients with coronary artery disease, as well as after cardiopulmonary resuscitation in patients with malignant arrhythmias.^{25–27} In addition, the prognosis of a patient with coronary artery disease decreases in proportion to the degree of SA attenuation.^{15,28} These results assume that the heart remains innervated, because SA is largely negligible in patients after cardiac denervation (i.e., after cardiac transplant).²⁹

It is doubtful that the degree of RR variability could provide a low-cost LQTS diagnostic tool because of the poor sensitivity and specificity found in this study. Additionally, the extreme degree of overlap between LQTS and those subjects initially diagnosed elsewhere with possible LQTS but subsequently dismissed as otherwise normal obviates any diagnostic

value with respect to the simple presence or absence of SA, except that extreme SA (>40% RR variability) makes the diagnosis of LQTS unlikely.

The potential utility of RR variability for prognostic implications, particularly in predicting potential ventricular dysrhythmias, is unclear at this time. In our study, patients with a history of torsades de pointes or aborted cardiac arrest had the lowest degree of RR variability, independent of genotype. It is possible that this lower RR variability may be attributable to the history of ventricular arrhythmia and associated resuscitation.²⁶ Alternatively, it might indicate increased risk in the LQTS patient. However, SA is unlikely to be an independent risk factor because these patients also showed the longest QT intervals overall, and it was not ultimately significant in our clinical logistic model. It should be noted that there was a weak relationship between decreased RR variability and a higher baseline QTc ($P < .0001$, $r^2 = 0.03$), implying some individual effect of intrinsic autonomic tone. Other measures of RR and QT variability including QT dispersion remain under study at many institutions, but are of debatable value at this time, particularly in LQTS.^{30–34}

There are several confounders to the prevalence of sinus arrhythmia (SA) that need to be considered. Heart rate variability as assessed by degree of respiratory SA has been shown to occur more in female twins as compared with their male counterparts.³⁵ In this study, we did not find a gender-specific effect on RR variability. Further, heart rate variability as measured from continuous 2-hour recordings has been shown to have a heritable component.³⁶ This raises the possibility that certain familial cohorts may bias the data. In this study, however, we did not find any statistically significant difference between the unrelated LQTS probands and the LQTS cohort at large.

Schwartz et al³⁷ recently studied LQTS mutation carriers from a South African LQT1 founder population by determining their baroreflex sensitivity, defined as the quotient of RR interval change (ms) to the increase in blood pressure (mm Hg) after bolus injections of phenylephrine. Mutation carriers with lower resting heart rate and lower baroreflex sensitivity measurements (≤ 12 ms/mm Hg), i.e., those with blunted autonomic responses, were more commonly asymptomatic compared with the other cohorts. The investigators surmised that this finding provided an explanation of phenotypic heterogeneity in LQTS.³⁷ At first examination, our findings seem to contradict the study by Schwartz et al,³⁷ and are more consistent with reports in adult patients of decreased RR variability after myocardial infarction and cardiopulmonary arrest.^{25–28} It should be noted that our population was genetically heterogeneous across the entire genotypic spectrum of LQTS, whereas the study by Schwartz et al³⁷ focused on individuals with a single homogenous LQT1 genotype (KCNQ1-A341V).³⁷ Additionally, our patients with LQT1 did not have a markedly different RR variability than patients dismissed as otherwise normal.

In our cohort, LQT3 was associated with the lowest frequency of SA compared with other genotypes. LQT3 results from mutations in *SCN5A*, which encodes for the cardiac sodium channel,³⁸ unlike LQT1 and LQT2, which have causative mutations that affect cardiac potassium channels.^{37,38} It is unclear physiologically how accentuated late sodium current through LQT3-associated sodium channels could precipitate a detectable attenuation in RR variability. Perkiomaki et al³⁹ studied several measures of heart rate variability over a period of 10 minutes, and did not find a difference between 27 LQTS subjects and 34 nonaffected family member control subjects. They also did not find any genotype-specific differences. The method of assessment of heart rate variability and the overall cohort sizes are markedly different between their study and ours, making it difficult to speculate why there are differing results.

Considerable debate has transpired regarding the best method for measuring the corrected QT in the presence of SA. Our approach is to calculate an average QTc from analysis of the entire 12-lead ECG rhythm strip, ideally lead II or lead V5.²¹ Martin et al²⁰ have proposed previously a method in which the interpreter would apply the Bazett formula to the QT interval after the shortest available RR interval.²³ This is strongly discouraged because it will result in a marked inflation/overestimation of the QTc and lead to overdiagnosis. In contrast, using only the longest RR interval may underestimate the repolarization index.

Study limitations

This study is limited by the use of 10-second rhythm strips from ECGs for the measurements. Because the ECGs were obtained as part of clinical practice, we were not able to assess RR variability for longer periods of time or to control the respiratory rate. Consequently, there could be a tidal volume-dependent contribution to RR interval variability between the 2 cohorts.

Conclusion

The frequency of SA and magnitude of RR variability was lower throughout all 3 genotypes of LQTS, especially LQT3, compared with those patients dismissed as normal. This attenuation in the variability of the RR interval could not be attributed to beta-blocker therapy or extremes of heart rates. Although the presence or absence of SA is of negligible diagnostic value because of the degree of overlap, LQTS patients with minimal variation in their RR interval may be at higher clinical risk of an LQT-triggered cardiac event.

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ABBREVIATIONS

ECG	electrocardiogram
EMR	electronic medical record
LQTS	long QT syndrome
QTc	corrected QT interval
SA	sinus arrhythmia

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Figure 1.

Lead II of a 12-lead electrocardiogram from 3 distinct patients from our cohort, including (A) an 8-year-old female patient who was dismissed as normal, RR variability = 39%, (B) A 4-year-old male patient with LQT1, RR variability = 14%, and (C) a 24-year-old genotype-negative female patient with a history of aborted cardiac arrest, RR variability = 7%.

Figure 2.

Bar graph demonstrating (A) the frequency of sinus arrhythmia between patients dismissed as ostensibly healthy (normal subjects) and patients diagnosed with LQTS, and between the 3 most common LQTS genotypes, and (B) the RR variability (%) between the same groups. LQT = long QT syndrome; SA = sinus arrhythmia.

Figure 3. Scatter plot of baseline QTc compared with the RR variability of the entire cohort. Note the weak but significant relationship ($P < .0001$, $r = 0.03$).

Table 1

Demographic information of the patients ultimately dismissed as normal and the patients dismissed with a diagnosis of LQTS

Cohort	Normal subjects	LQTS patients
Number of patients	290	281
Sex (male/female)	112/178	122/159
	39%/61%	43%/57%
Age at diagnosis (yrs)	22 ± 16	22 ± 17
Range	0–75	0–73
Average QTc at diagnosis (ms)	424 ± 30	466 ± 43

All results are reported as mean ± 3 SD.