ORIGINAL RESEARCH

QT Adaptation and Intrinsic QT Variability in Congenital Long QT Syndrome

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***Background*—**Increased variability of QT interval (QTV) has been linked to arrhythmias in animal experiments and multiple clinical situations. Congenital long QT syndrome (LQTS), a pure repolarization disease, may provide important information on the relationship between delayed repolarization and QTV.

***Methods and Results*—**Twenty-four-hour Holter monitor tracings from 78 genotyped congenital LQTS patients (52 females; 51 LQT1, 23 LQT2, 2 LQT5, 2 JLN, 27 symptomatic; age, 35.2±12.3 years) were evaluated with computer-assisted annotation of RR and QT intervals. Several models of RR-QT relationship were tested in all patients. A model assuming exponential decrease of past RR interval contributions to QT duration with 60-second time constant provided the best data fit. This model was used to calculate QTc and residual "intrinsic" QTV, which cannot be explained by heart rate change. The intrinsic QTV was higher in patients with long QTc (r=0.68; $P<10^{-4}$), and in LQT2 than in LQT1/5 patients (5.65±1.28 vs 4.46±0.82; P<0.0002). Both QTc and intrinsic QTV were similar in symptomatic and asymptomatic patients (467±52 vs 459±53 ms and 5.10±1.19 vs 4.74±1.09, respectively).

***Conclusions*—**In LQTS patients, QT interval adaptation to heart rate changes occurs with time constant ≈60 seconds, similar to results reported in control subjects. Intrinsic QTV correlates with the degree of repolarization delay and might reflect action potential instability observed in animal models of LQTS. **(*J Am Heart Assoc*. 2015;4:e002395 doi: 10.1161/JAHA.115.002395)**

Key Words: congenital long QT syndrome • QT adaptation • QT variability

Impaired ventricular repolarization is a feature of many cardiac diseases and noncardiac conditions. It is typically defined in terms of QT interval prolongation after correction for the effect of heart rate. However, impaired repolarization can be accompanied by other phenomena, such as increased spatial complexity of T-wave loop,[1] prolonged Tp-Te interval,[2–4] increased QT variability (QTV),[5,6] temporal T wave lability,[7] or spatial heterogeneity of ventricular contraction.[8]

Increased QTV has been associated with ventricular arrhythmias or sudden death in a wide range of situations, including coronary artery disease,[9–11] dilated cardiomyopathy,[12] and hypertrophic cardiomyopathy.[13] In congenital long-QT syndrome (LQTS), impaired repolarization occurs as the primary abnormality, without secondary changes related to structural heart disease. Surprisingly, the data available on QTV in congenital LQTS patients are somewhat limited. Some of the important articles describe QTV in carriers of a single mutation only. In general, increased QTV in congenital LQTS patients, as compared to control subjects, has been reported.[5,6,14]

We have previously found higher levels of QTV in LQTS patients compared to controls, and in LQT2/3 as compared to LQT1 patients.[14] We also noted that mean RR interval of the preceding 60 seconds predicts QT duration better than any function of instantaneous RR interval in both LQTS patients and control subjects.

An analysis of several models of QT-RR dependence from 2 independent control populations suggested that it may be best described by an exponential decay of past RR interval contribution to QT interval duration with 60-second time constant.[15] Additional support for this model has been

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Table 1. Detailed Data on the Study Subjects

Subject	Symptoms	Sex	Age (y) at Holter	BB Rx	QTc-wexp60 (ms)	QTV-wexp60	Protein	Gene	Reference	LQTS Type
1	1	F	18	Yes	490	7.652545693	G657C	c.1969G>T	NM_000238.3	2
2	1	F	22	Yes	429	4.86753445	Q530X	c.1588C>T	NM_000218.2	1
3	1	F	37	Yes	421	4.477336814	968AfsX151	c.2900_2901insC	NM_000238.3	2
4	0	F	44	No	491	6.519147288	E261D	c.783G>C	NM_000218.2	1
5	0	F	42	No	444	3.555348061	Q530X	c.1588C>T	NM_000218.2	1
6	1	M	18	Yes	421	4.912654886	E261D	c.783G>C	NM_000218.2	1
7	0	M	16	No	423	3.850147602	Q530X	c.1588C>T	NM_000218.2	1
8	0	F	41	No	418	3.496507561	V307WfsX47	c.919delG	NM_000218.2	1
9	0	M	37	No	443	3.713572067	Q530X	c.1588C>T	NM_000218.2	1
10	0	M	18	No	479	4.844187086	R534C	c.1600C>T	NM_000238.3	2
11	0	F	45	Yes	493	4.48863637	D896HfsX25	c.2681_2684dupGCAC	NM_000238.3	2
12	1	F	31	Yes	481	4.290459441	L342F	c.1016C>T	NM_000218.2	1
13	0	F	25	Yes	463	4.127134385	S546L	c.1637C>T	NM_000218.2	1
14	0	M	31	No	453	4.127134385	V307WfsX47	c.919delG	NM_000218.2	1
15	0	M	35	No	398	3.850147602	V307WfsX47	c.919delG	NM_000218.2	1
16	0	F	41	No	442	5.641907071	Q530X	c.1588C>T	NM_000218.2	1
17	1	M	41	No	449	5.293304825	P968AfsX151	c.2900_2901insC	NM_000238.3	2
18	1	F	40	Yes	473	5.159055299	L342F	c.1016C>T	NM_000218.2	1
19	1	F	42	No	465	3.63758616	V307WfsX47	c.919delG	NM_000218.2	1
20	0	F	44	No	460	4.624972813	Q530X	c.1588C>T	NM_000218.2	1
21	0	M	34	No	393	4.406719247	Q530X	c.1588C>T	NM_000218.2	1
22	0	F	44	No	419	4.025351691	Q530X	c.1588C>T	NM_000218.2	1
23	0	F	38	No	455	4.17438727	Q530X	c.1588C>T	NM_000218.2	1
24	0	F	22	Yes	427	4.043051268	R518X	c.1552C>T	NM_000218.2	1
25	1	F	21	Yes	484	4.700480366	D896HfsX25	c.2681_2684dupGCAC	NM_000238.3	1
26	0	F	28	No	436	4.317488114	R518X	c.1552C>T	NM_000218.2	1
27	1	F	34	Yes	463	4.060443011	R259L	c.776G>T	NM_000218.2	1
28	1	F	51	Yes	408	4.369447852	R32H	c.95G>A	NM_001127669.1	5
29	0	F	49	No	478	5.087596335	R259L	c.776G>T	NM_000218.2	1
30	0	F	40	No	485	5.170483995	T587M	c.1760C>T	NM_000218.2	1
31	0	F	56	No	458	4.204692619	W398R	c.1192T>C	NM_000238.3	1
32	0	M	23	No	436	4.234106505	Q530X	c.1588C>T	NM_000218.2	1
33	0	M	29	No	405	4.442651256	Q530X	c.1588C>T	NM_000218.2	1
34	0	M	41	No	429	3.496507561	G269S	c.805G>A	NM_000218.2	1
35	1	F	32	Yes	408	4.343805422	R32H	c.95G>A	NM_001127669.1	5
36	0	F	21	Yes	605	7.636269603	Q530X	c.1588C>T	NM_000218.2	1
37	1	F	17	Yes	439	4.219507705	L303P	c.908T>C	NM_000218.2	1
38	0	M	45	No	422	4.219507705	R259L	c.776G>T	NM_000218.2	1
39	0	M	45	No	439	5.332718793	L987RfsX70	c.2960delT	NM_000238.3	2
40	0	F	39	No	460	5.225746674	P968AfsX151	c.2900_2901insC	NM_000238.3	2

Continued

Table 1. Continued

Subject	Symptoms	Sex	Age (y) at Holter	BB Rx	QTc-wexp60 (ms)	QTV-wexp60	Protein	Gene	Reference	LQTS Type
41	1	F	58	Yes	445	4.343805422	R192CfsX91	c.572_576delTGCGC	NM_000218.2	1
42	0	M	49	Yes	430	4.804021045	L987RfsX70	c.2960delT	NM_000238.3	2
43	0	F	18	Yes	430	3.850147602	R518X	c.1552C>T	NM_000218.2	1
44	0	F	35	Yes	413	4.941642423	W398R	c.1198R	NM_000238.3	2
45	1	M	12	Yes	505	5.634789603	G314S	c.940G>A	NM_000218.2	1
46	1	F	36	Yes	605	5.659482216	E261D and Q530X	c.783G>C and c.1588C>T	NM_000218.2	JLNS
47	1	M	49	Yes	427	4.290459441	L987RfsX70	c.2960delT	NM_000238.3	2
48	1	M	17	Yes	422	4.96284463	L987RfsX70	c.2960delT	NM_000238.3	2
49	0	F	61	Yes	457	4.043051268	R192CfsX91	c.572_576delTGCGC	NM_000218.2	1
50	0	F	37	Yes	427	3.761200116	Splice site	c.1591-1G>A	NM_000218.2	1
51	0	F	42	Yes	434	5.220355825	L987RfsX70	c.2960delT	NM_000238.3	2
52	0	F	45	No	466	4.33073334	Q530X	c.1588C>T	NM_000218.2	1
53	0	M	58	No	412	4.418840608	V307WfsX47	c.919delG	NM_000218.2	1
54	0	M	20	Yes	505	5.214935758	G657C	c.1969G>T	NM_000238.3	2
55	0	F	30	Yes	529	6.606650186	W563X	c.1688G>A	NM_000238.3	2
56	0	M	47	Yes	480	4.8978398	L987RfsX70	c.2960delT	NM_000238.3	2
57	0	M	47	No	701	7.729735331	D896HfsX25	c.2681_2684dupGCAC	NM_000238.3	2
58	0	M	24	No	449	4.691347882	W563X	c.1688G>A	NM_000238.3	2
59	0	F	45	No	475	4.382026635	G572S	c.1714G>A	NM_000238.3	2
60	0	F	41	No	590	7.77569575	D896HfsX25	c.2681_2684dupGCAC	NM_000238.3	2
61	1	F	34	No	549	5.493061443	S649CfsX7	c.2145G>C	NM_000238.2	2
62	1	M	18	Yes	435	6.953684211	R259L	c.776G>T	NM_000218.2	1
63	1	F	48	No	573	6.814542897	R534C	c.1600C>T	NM_000238.3	2
64	1	F	38	Yes	468	4.727387819	E261D	c.783G>C	NM_000218.2	1
65	0	F	44	No	452	4.770684624	G269S	c.805G>A	NM_000218.2	1
66	1	F	16	No	441	4.077537444	G269S	c.805G>A	NM_000218.2	1
67	0	F	44	No	496	3.988984047	Q530X	c.1588C>T	NM_000218.2	1
68	1	M	17	Yes	517	6.860663671	Unknown	Unknown	NA	JLNS phenotype
69	1	F	31	No	436	3.970291914	E261D	c.783G>C	NM_000218.2	1
70	0	F	49	No	478	4.110873864	Q530X	c.1588C>T	NM_000218.2	1
71	0	F	57	Yes	470	4.605170186	Q530X	c.1588C>T	NM_000218.2	1
72	1	F	33	No	538	8.017966703	G657C	c.1969G>T	NM_000238.3	2
73	0	F	47	No	439	4.204692619	Q530X	c.1588C>T	NM_000218.2	1
74	0	M	17	Yes	426	3.737669618	Q530X	c.1588C>T	NM_000218.2	1
75	0	F	15	Yes	463	7.737616283	D896HfsX25	c.2681_2684dupGCAC	NM_000238.3	2
76	0	F	34	No	424	5.247024072	Q530X	c.1588C>T	NM_000218.2	1
77	0	M	21	No	412	3.891820298	Q530X	c.1588C>T	NM_000218.2	1
78	1	F	33	No	411	3.988984047	R518X	c.1552C>T	NM_000218.2	1

Presence of symptoms is coded as 0 (asymptomatic) or 1 (symptomatic). BB Rx indicate treatment with β-blockers at the time of Holter recording. Mutation status is listed for each patient on both protein and DNA level. LQTS indicates long QT syndrome; QTV, QT variability.

provided by measurement of QT interval change in response to sudden change in atrial pacing rate in otherwise healthy subjects undergoing radiofrequency ablation of supraventricular tachycardia.[16]

Increased QTV in LQTS patients could thus be explained by any of several different mechanisms, which are not mutually exclusive: increased slope of steady-state QT-RR relationship, faster response (ie, shorter time constant) of QT response to RR changes—resulting in less "smoothing" of QT response, or increased "intrinsic," heart-rate independent QTV, present even during constant heart rate. The last phenomenon has been described in animal experiments, where it is attributable to instability of action potential shape.[17,18] In optical mapping experiments, this instability is mechanistically linked to triggered activity and polymorphic ventricular tachycardia.[19,20]

It is possible that QTV might provide a more direct assessment of arrhythmic risk in congenital LQTS patients than QTc itself. We thus set out to analyze heart-rate–independent QTV in a population of genotyped LQTS patients in an attempt to answer this question.

Methods

Study Population

Genotyped LQTS subjects followed at Clinic of Cardiac Genetic Diseases at the Department of Cardiology, Oslo University Hospital, Rikshospitalet (Oslo, Norway), were studied with 24 Holter monitoring. Diagnosis of LQTS was made based on clinical presentation and QT interval prolongation along with the presence of disease-causing mutation in a LQTS-related gene. Patients with history of aborted cardiac arrest, documented ventricular tachycardia, or syncope were defined as symptomatic.

A total of 78 LQTS patients from 28 families were studied (52 females; age, 35.2±12.3 years). There were 51 LQT1, 23 LQT2, and 2 LQT5 patients. Two patients had Jervell and Lange-Nielsen syndrome (no mutation was found in 1 subject with clinical Jervell and Lange-Nielsen phenotype). A total of 35 patients were treated with a β-blocker at the time of the recording. Detailed information on the study subjects is provided in the Table 1.

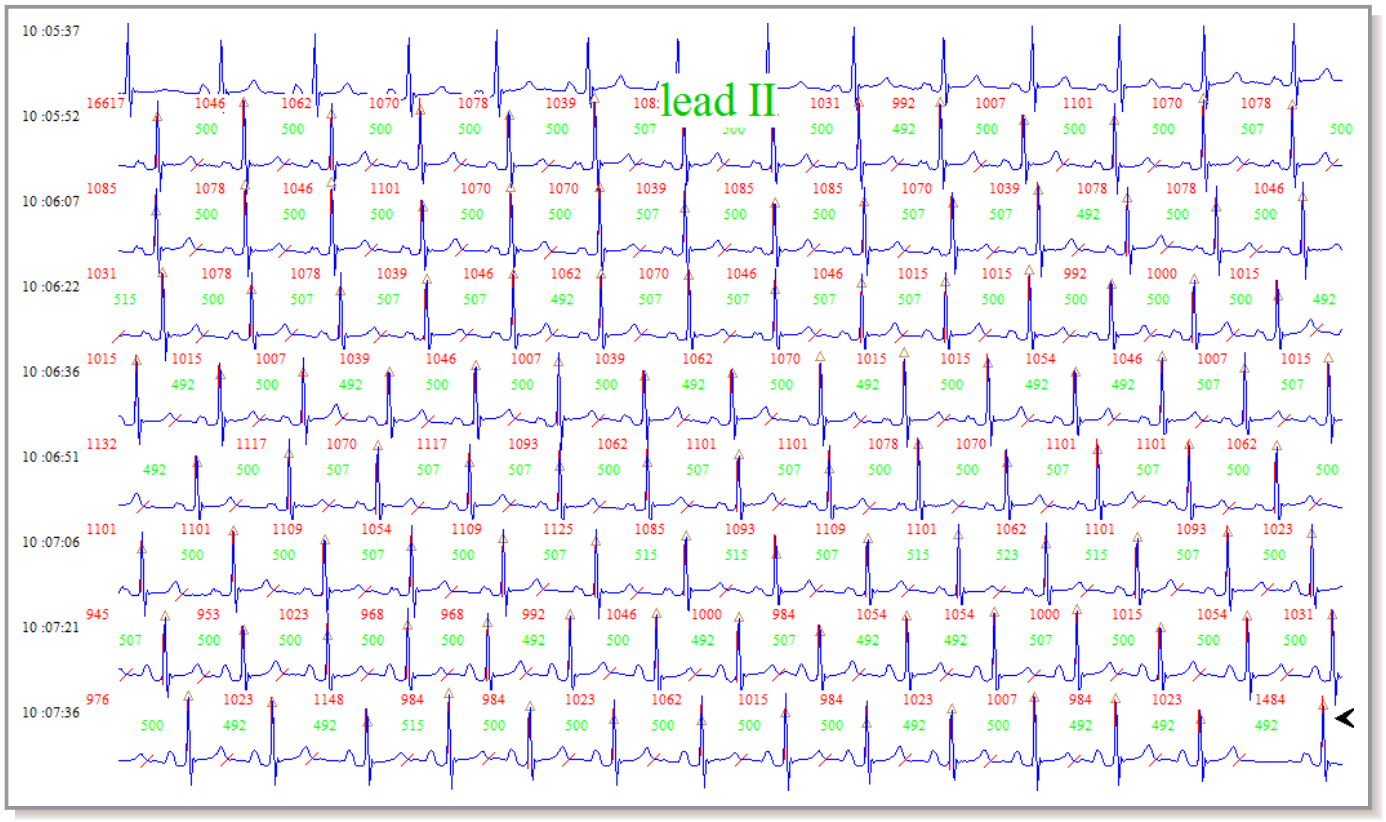

Figure 1. An example of a Holter recording with annotated R wave peaks (brown triangles) and T wave ends (diagonal red lines). The RR (red) and QT (green) intervals are displayed. Poor quality or mislabeled segments can be manually deleted, as seen at the top tracing, where the annotation markers are absent. The time from the beginning of the recording is indicated on the left in the hh:mm:ss format.

Genetic Analyses

Genetic testing was performed as part of the diagnostic workup in LQTS patients. Cascade genetic screening was performed in family members of mutation-positive index patients. DNA sequencing of the *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, and *KCNE2* genes was performed using version 3.1 of the BigDye-terminator cycle-sequencing kit and a Genetic Analyzer 3730 (Applied Biosystems, Foster City, CA). All participants signed written informed consent. The study was approved by the local ethics committee and complied with the Helsinki declaration.

Holter Recordings

Holter monitoring was performed for 24 hours with either Medilog or Darwin system (Schiller AG, Baar, Switzerland). A signal from 1 or 2 leads was available for analysis. Signal sampling frequency was 128 Hz. In 2 subjects, data were acquired at 250 Hz and undersampled for 125 Hz frequency before analysis. Semiautomatic annotation of the Holter data was performed as described before.[21] Briefly, Holter data were exported in a digital format. A custom software created in C++ (Microsoft Visual Studio, Microsoft Corp., Redmond, WA) by one of the investigators (J.N.) performed R wave detection, 20 Hz low-pass filtering (Bessel 3-pole digital filter), subtraction of smooth cubic spline passing through fiducial points in the isoelectric PR segment, and detection of Q wave onset and T wave end. An example of an annotated data segment is shown in Figure 1. The algorithm was previously validated against manual QT interval measurement in both healthy subjects and another population of LQTS patients.[21] All recordings were manually reviewed, and data segments incorrectly labeled by the software were deleted and excluded from further analysis. Editing consisted of deletion of incorrectly labeled segment only, that is, the software does not allow manual adjustment of incorrectly labeled T wave end. The investigators performing editing of the Holter tracings (S.S., P.S., and J.N.) were blinded to the clinical data and genetic information during editing.

Data Analysis

Several models of QT-RR dependence were evaluated in each patient as described before.[15] Briefly, for all QT intervals preceded by at least 180 seconds of uninterrupted data (ie, 180 seconds of data segments in which software annotation agreed with manual review and no manual data deletion was performed) in a given patient, linear regression between QT intervals and weighted averages of the RR intervals over the preceding 180 seconds were calculated. We tested exponential weight function with 60-, 30-, or 15-second time constants

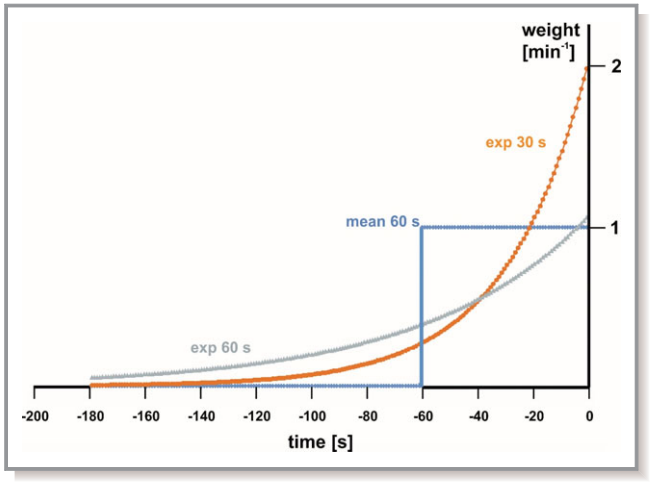

Figure 2. Three examples of weight functions used to model QT interval dependence on past RR intervals. QT intervals preceded by 180 seconds of manually verified signal annotation were used in the models. The QT interval was modeled as a linear function of mean RR interval over the preceding 60 seconds (blue), or of mean RR interval over the preceding 180 seconds weighted with an exponential function declining into the past with a time constant of 30 (orange) or 60 seconds (gray). Linear dependence on the instantaneous RR interval was also evaluated (not shown).

(LMwexp60, LMwexp30, and LMwexp15), as well as mean RR interval in the 60 seconds (LMm60) preceding the QT interval (Figure 2). Linear dependence of QT interval on the immediately preceding RR interval (LM0) was also evaluated. The precise formulation of the models is described in Data S1. Briefly, the models are linear regression models, with the measured QT interval as the dependent variable and the weighted RR interval as the independent variable. The models differ with respect to the weight function used for RR interval correction.

The fit of the models was compared based on the sum of the squared residuals, that is, the differences between the QT intervals predicted by the model and the actual QT values. For each model, the residual QTV (rQTV) was defined as natural logarithm of the root mean square of the residuals. The underlying assumption is that there are 3 independent sources of difference between the measured QT interval and the value predicted by the linear model for a given value of weighted RR interval:

1. Systematic difference between the QT interval predicted by the model and real QT interval behavior, that is, poor model performance;
2. Real QT variability independent of RR interval duration, that is, QT interval variability that would be present even during steady heart rate with perfect quality of the QT measurement; and
3. Errors of QT interval measurement, attributable to noise, limited sampling frequency, and so on.

In a given patient, the choice of the model would affect the first source of residual variability, but not the second and third.

Statistical Analysis

Data are presented as mean±SD. Data from each patient were fitted with all models; paired *t* test was for pair-wise comparison of the fit between 2 models. A model X was considered significantly better than model Y if rQTV values derived from model X were significantly lower than rQTV values derived from model Y in the population studied.

Nonpaired *t* test was used to compare values from symptomatic and asymptomatic patients, and from LQT1/5 and LQT2 patients (ie, for patients with LQT1 and LQT5 were analyzed as a single group, given that both genotypes correspond to a mutation of a single allele of a subunit of I_{Ks} current). The analysis was performed in the Microsoft Excel 2013 Data Analysis package (Microsoft Corp., Redmond, WA). All *P* values reported are 2-tailed. $P<0.05$ was considered statistically significant. No correction for multiple comparisons was performed.

Results

QT Interval Adaptation

The model assuming linear dependence of QT interval on mean RR interval over the preceding 60 seconds (LMm60)

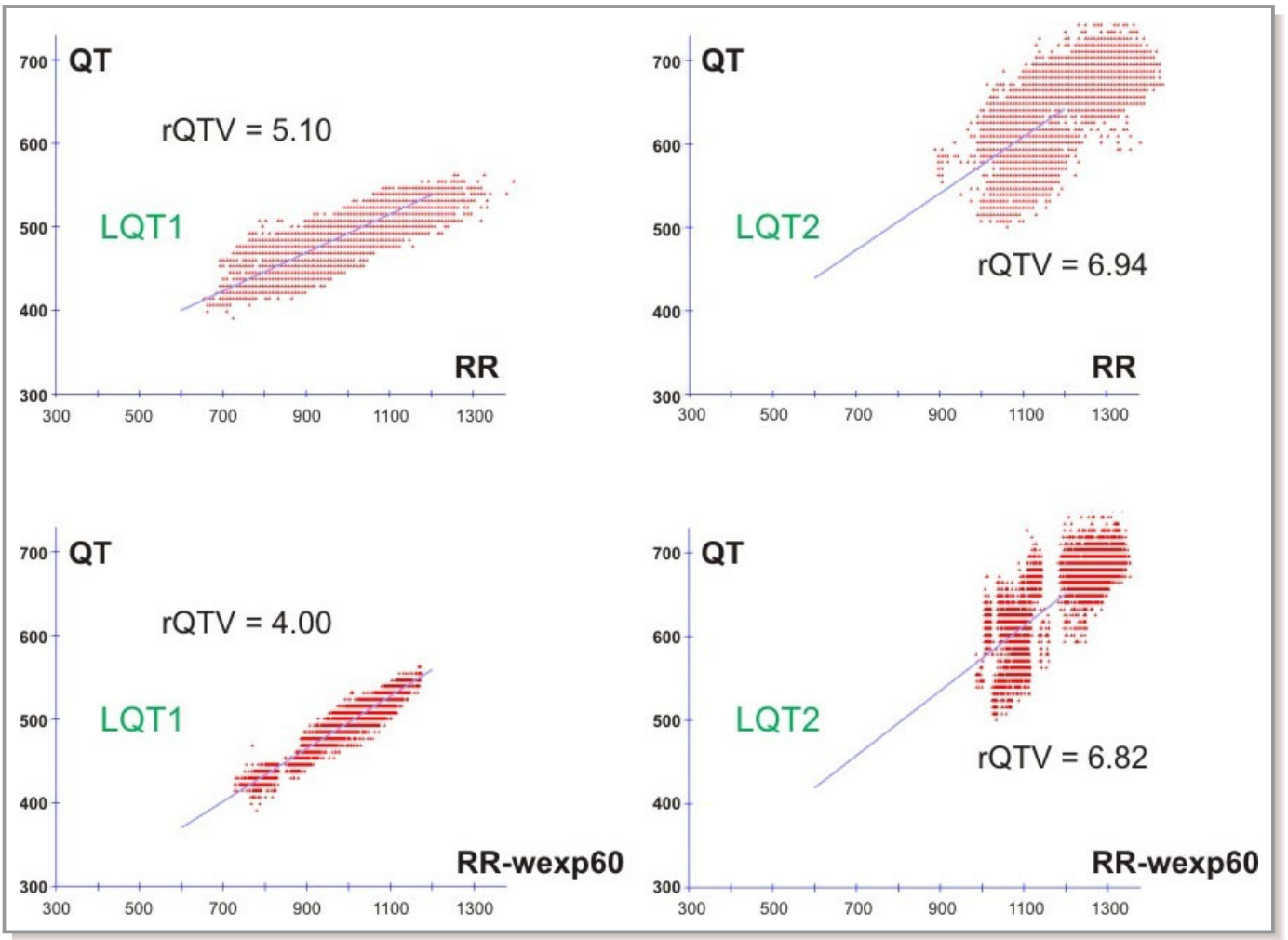

Figure 3. This figure provides an example of Holter data fit in 2 patients, 1 of them with LQT1 and another with LQT2. QT intervals are modeled as a linear function of immediately preceding RR interval, that is, LM0 (top panels), or as a linear function of mean RR interval over preceding 3 minutes, weighted with an exponential function with a 1-minute time constant, that is, LMwexp60 (bottom panels). The left panels show the data from the same LQT1 patient; the right panels correspond to an LQT2 patient. In both cases, the 1-minute exponential model provides the better fit, as indicated by the tighter clustering of data points along the regression lines in the bottom panels. The model fit is quantified by rQTV, calculated as the natural logarithm of the standard deviation of differences between the actual QT intervals and the QT values predicted by the regression line. The rQTV thus indicates QT interval variability which cannot be explained by heart rate changes. In this example, the value is substantially higher in the LQT2 than in the LQT1 patient. LQT indicates long QT; rQTV, residual QT variability.

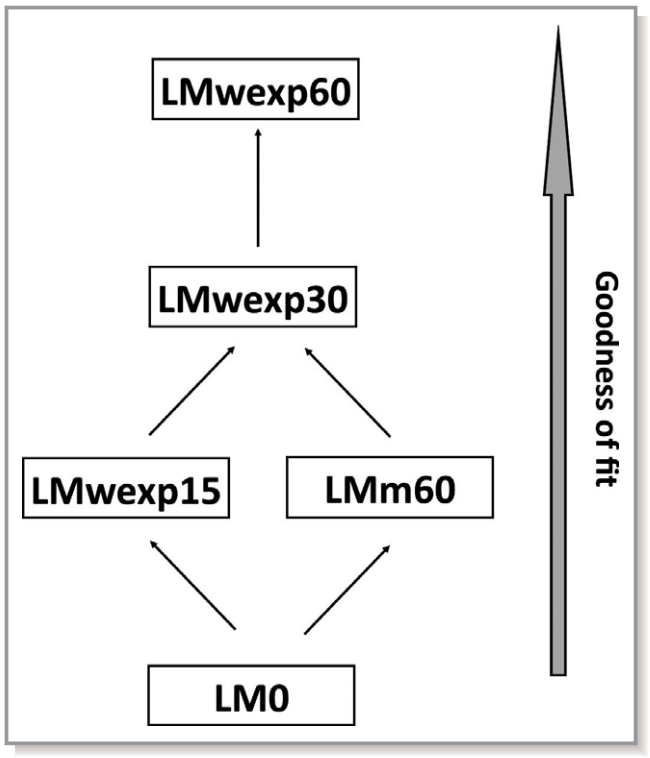

Figure 4. Hierarchy of RR-QT models studied in the LQTS population. A thin arrow linking 2 rectangles indicates a significantly better fit by the model in the upper rectangle. This figure is a nonquantitative graphical representation of the data in Table 2. LQTS indicates long QT syndrome.

was superior ($P<10^{-4}$) to a model assuming linear dependence on the instantaneous RR interval (LM0), as has been reported before in both control and LQTS patients.[14,15] The model with linear QT dependence on a weighted function of preceding RR intervals declining into the past with a time constant of 15 seconds (LMwexp15) was also superior to LM0 ($P<10^{-4}$) and comparable to LMm60. The model with an exponential weight function of a 30-second time constant (LMwexp30) provided a better data fit than both LMwexp15 and LMm60, but was inferior to the model with a time constant of 60 seconds (LMwexp60; $P<10^{-4}$ for all comparisons). Examples of data fit with LM0 and LMwexp60 in 2 patients are shown in Figure 3. *P* values for differences between models and details of the model hierarchy are shown in Figure 4 and Table 2.

The LMwexp60 model also provided a better fit than LMwexp30 in the LQT2 population (rQTV 5.69±1.28 vs 5.74±1.26; $P<0.001$) and was nonsignificantly better in the LQT1/5 population (4.46±0.82 vs 4.47±0.81; $P=0.09$).

We have used the model providing the best description of QT interval behavior (LMwexp60) to calculate QTc in each subject using the patient-specific regression line provided by the model (QTc-wexp60) and used the rQTV derived from the model (rQTV-wexp60) as an estimate of intrinsic QTV.

Residual QT Variability and QTc in LMwexp60

rQTV-wexp60 was significantly higher in LQT2 than in LQT1/5 patients (5.69±1.28 vs 4.46±0.82; $P<0.0002$; Figure 3) and correlated positively with QTc-wexp60 duration ($r=0.68$; $P<10^{-4}$; Figure 5). QTc-wexp60 was longer in LQT2 than in LQT1/5 patients (487±68 vs 447±35 ms; $P<0.05$). Correlation between rQTV-wexp60 and QTc-wexp60 was also significant when assessed separately in LQT1/5 and LQT2 subjects ($r=0.56$ and 0.67, respectively; $P<0.0005$ in both cases).

There was no difference in QTc or rQTV-wexp60 between symptomatic and asymptomatic subjects (467±52 vs 459±54 ms, 5.10±1.19 vs 4.74±1.10, respectively). There was no relationship between genotype and presence of symptoms. Symptoms were more frequent among patients treated with β-blockers than among those without β-blocker treatment; there was no significant difference in QTc or rQTV-wexp60 between patients treated and not treated with β-blockers (Table 3).

Table 2. Comparison of RR-QT Data Fit With Different Models

Model	LM0	LMm60	LMwexp15	LMwexp30	LMwexp60
rQTV	5.341±0.976	4.958±1.089	4.966±1.100	4.884±1.130	4.865±1.131
LM0	x	$P<0.0001$	$P<0.0001$	$P<0.0001$	$P<0.0001$
LMm60		x	$P>0.1$	$P<0.0001$	$P<0.0001$
LMwexp15			x	$P<0.0001$	$P<0.0001$
LMwexp30				x	$P<0.0005$
LMwexp60					x

The rQTV (not explained by the model) was calculated in each subject for each model; paired *t* test was used for comparisons of rQTV calculated by different models, with lower values indicating better data fit. The rQTV is lower for LMwexp60 than for all the other models, indicating that it provides the best description of QT dependence on RR intervals and that the rQTV provided by this model is the best estimate of "intrinsic" QTV. *P* values refer to significance of difference of fit (ie, difference in mean rQTV) between the column and row models. A graphic description of the model hierarchy is shown in Figure 4. rQTV indicates residual QT variability.

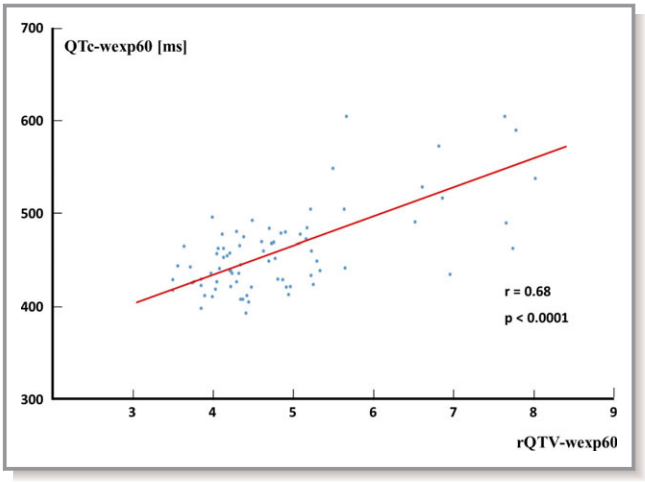

Figure 5. QTc is highly significantly correlated with rQTV in the LMwexp60 model. The regression line (QTc as function of rQTV) is shown in red. This relationship remains present when LQT1/5 and LQT2 subjects are analyzed separately. LQT indicates long QT; rQTV, residual QT variability.

Discussion

The results reported here provide detailed information on sources of QTV in a large and diverse population of congenital LQTS patients. We have previously reported, in a different population of congenital LQTS patients, that the average RR interval over the preceding minute (LMm60) provides a better explanation of QT behavior than the instantaneous RR interval.[14] Our data confirm this finding in an independent LQTS population and extend it by using more realistic models with exponential weight function, consistent with directly observed QT response to sudden heart rate change.[16]

The change of QT interval in response to changing heart rate is similar to that we previously reported in control subjects.[15] Specifically, the LMwexp60, which uses exponential weight function with a 1-minute time constant to describe the contribution of past RR intervals to current QT duration, provides the best description of RR-QT relationship among the models tested in both groups. The cellular mechanisms responsible for the slow component of QT adaptation are disputed and may involve accumulation of I_{Ks} conductance, increase in cytoplasmic Na^+ concentration, leading to stimulation of Na/K ATPase, or increase in Ca^{2+}-dependent I_{CaL} inactivation.[22–25] Our results suggest that during ambulatory electrocardiography (ECG) recording, these mechanisms may operate in a similar way in normal subjects and LQTS patients and are not likely to contribute to elevated QTV in LQTS.

Table 3. Comparison of ECG Parameters and Symptoms Between LQT1/5 and LQT2 Subjects

	QTc-wexp60 (ms)	rQTV-wexp60	Symptoms (%)	Sample Size
LQT1/5	447±35	4.46±0.82	17 (32)	53
LQT2	487±68*	5.69±1.28**	8‡ (35)	23
BB −	461±57	4.73±1.13	8 (19)	43
BB +	463±48‡	5.03±1.14‡	19† (54)	35

QTc and rQTV are both significantly higher in LQT2 than in LQT1/5 subjects. There is no difference between LQT1/5 and LQT2 with respect to proportion of symptomatic subjects. There were no significant differences between patients on β-blocker and without β-blocker therapy with respect to ECG parameters. Proportion of symptomatic subjects with significantly higher in the β-blocker-treated patients. LQT indicates long QT; rQTV, residual QT variability.
LQT1/5 vs LQT2, or β-blocker + vs β-blocker −: *P<0.05; **P<0.0005; †P<0.0001; ‡not significant.

Increased QTV in congenital LQTS has been reported before. We have described that both crude QTV and QT variability index (correcting for heart rate variability) were higher in 23 congenital LQTS patients followed at the Mayo Clinic than in control subjects.[14] This was a smaller population (only 7 LQT2 subjects) with a higher degree of QTc prolongation than the patients described here. Bilchik et al.[5] and Perkiomaki et al.[6] also found increased QTV in congenital LQTS patients (or a subset of that group). Satomi et al.[26] reported that epinephrine infusion increased QTV in LQT1, but not LQT2, patients.

On the cellular level, QTV reflects beat-to-beat changes in action potential (AP) duration and, in some cases, AP morphology. These have been reported in both canine[18,27] and rabbit[17,20] models of delayed repolarization even during constant rate—this might be labeled "intrinsic," or heart-rate–independent, QTV. Optical mapping experiments indicate that abnormal intracellular Ca^{2+} dynamics with systolic oscillations of cytoplasmic Ca^{2+} concentration results in lability of AP morphology and, eventually, early afterdepolarizations and polymorphic ventricular tachycardia.[20] The link between abnormal Ca^{2+} handling and long QT syndrome is supported by the echocardiographic data demonstrating regional dyssynchrony of LV contraction in this setting,[8] similar to spatial heterogeneity in Ca^{2+} transient observed in optical mapping experiments.[19]

The results of this study demonstrate a highly significant correlation between QTc—the measure of repolarization impairment—and rQTV-wexp60, an estimate of intrinsic QTV. It seems likely that rQTV reflects a degree of AP duration instability caused by repolarization delay.

Neither QTc nor rQTV, or any other ECG parameter, discriminated between symptomatic and asymptomatic subjects in our population. Although the degree of QTc prolongation has been associated with risk arrhythmia,[28–30] the relationship is relatively loose and our patient population may not have been large enough to observe it. T wave lability during adrenergic stimulation has been associated with symptoms in LQTS patients,[7] but it is more difficult to

measure with in Holter recordings, whose quality is affected by several sources of noise. Moreover, the degree of adrenergic stimulation present during the provocation test may rarely occur during Holter recordings, and if it does, it may be excluded from analysis because of motion artefact. Although it is possible that a correlation between symptomatic status and rQTV might be detectable if a substantially higher number of subjects were analyzed, it appears unlikely that rQTV derived from ambulatory ECGs will dramatically surpass QTc as a risk-stratification tool. In this sense, our data can be interpreted as a preliminary negative result, suggesting that a different, or at least modified, approach may be required for improved risk stratification of LQTS patients. Evaluating repolarization closer to the arrhythmia threshold, for example, during β-adrenergic stimulation in LQT1 patients, might be one way to improve risk stratification in LQTS subjects. It is also possible that integrating the rQTV or other repolarization indices with measures of heart rate variability reflecting autonomic regulation would improve risk stratification.[31]

We are unable to conclude whether rQTV might be useful for discrimination between LQTS patients and control subjects. We previously reported higher rQTV in LQTS patients, compared to normal subjects, using the LMm60 model (labeled "Lm" in the reference),[14] but we made no comparison to normal subjects in this study because we did not have access to a large population of normal subjects recorded with the same Holter system.

The higher proportion of symptomatic patients in the β-blocker-treated group likely reflects a higher propensity of the treating physician to initiate β-blocker treatment in the presence of symptoms.

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Disclosures

None.

References

1. Priori SG, Mortara DW, Napolitano C, Diehl L, Paganini V, Cantu F, Cantu G, Schwartz PJ. Evaluation of the spatial aspects of T-wave complexity in the long-QT syndrome. *Circulation*. 1997;96:3006–3012.
2. Castro Hevia J, Antzelevitch C, Tornes Barzaga F, Dorantes Sanchez M, Dorticos Balea F, Zayas Molina R, Quinones Perez MA, Fayad Rodriguez Y. Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. *J Am Coll Cardiol*. 2006;47:1828–1834.
3. Tanabe Y, Inagaki M, Kurita T, Nagaya N, Taguchi A, Suyama K, Aihara N, Kamakura S, Sunagawa K, Nakamura K, Ohe T, Towbin JA, Priori SG, Shimizu W. Sympathetic stimulation produces a greater increase in both transmural and spatial dispersion of repolarization in LQT1 than LQT2 forms of congenital long QT syndrome. *J Am Coll Cardiol*. 2001;37:911–919.
4. Viitasalo M, Oikarinen L, Swan H, Vaananen H, Glatter K, Laitinen PJ, Kontula K, Barron HV, Toivonen L, Scheinman MM. Ambulatory electrocardiographic evidence of transmural dispersion of repolarization in patients with long-QT syndrome type 1 and 2. *Circulation*. 2002;106:2473–2478.
5. Bilchick K, Viitasalo M, Oikarinen L, Fetics B, Tomaselli G, Swan H, Laitinen PJ, Vaananen H, Kontula K, Berger RD. Temporal repolarization lability differences among genotyped patients with the long QT syndrome. *Am J Cardiol*. 2004;94:1312–1316.
6. Perkiomaki JS, Zareba W, Nomura A, Andrews M, Kaufman ES, Moss AJ. Repolarization dynamics in patients with long QT syndrome. *J Cardiovasc Electrophysiol*. 2002;13:651–656.
7. Nemec J, Hejlik JB, Shen WK, Ackerman MJ. Catecholamine-induced T-wave lability in congenital long QT syndrome: a novel phenomenon associated with syncope and cardiac arrest. *Mayo Clin Proc*. 2003;78:40–50.
8. Haugaa KH, Amlie JP, Berge KE, Leren TP, Smiseth OA, Edvardsen T. Transmural differences in myocardial contraction in long-QT syndrome: mechanical consequences of ion channel dysfunction. *Circulation*. 2010;122:1355–1363.
9. Haigney MC, Zareba W, Gentlesk PJ, Goldstein RE, Illovsky M, McNitt S, Andrews ML, Moss AJ. QT interval variability and spontaneous ventricular tachycardia or fibrillation in the multicenter automatic defibrillator implantation trial (MADIT) II patients. *J Am Coll Cardiol*. 2004;44:1481–1487.
10. Segerson NM, Litwin SE, Daccarett M, Wall TS, Hamdan MH, Lux RL. Scatter in repolarization timing predicts clinical events in post-myocardial infarction patients. *Heart Rhythm*. 2008;5:208–214.
11. Oosterhoff P, Tereshchenko LG, van der Heyden MA, Ghanem RN, Fetics BJ, Berger RD, Vos MA. Short-term variability of repolarization predicts ventricular tachycardia and sudden cardiac death in patients with structural heart disease: a comparison with QT variability index. *Heart Rhythm*. 2011;8:1584–1590.
12. Berger RD, Kasper EK, Baughman KL, Marban E, Calkins H, Tomaselli GF. Beat-to-beat QT interval variability: novel evidence for repolarization lability in ischemic and nonischemic dilated cardiomyopathy. *Circulation*. 1997;96:1557–1565.
13. Atiga WL, Fananapazir L, McAreavey D, Calkins H, Berger RD. Temporal repolarization lability in hypertrophic cardiomyopathy caused by beta-myosin heavy-chain gene mutations. *Circulation*. 2000;101:1237–1242.
14. Nemec J, Buncova M, Shusterman V, Winter B, Shen WK, Ackerman MJ. Qt interval variability and adaptation to heart rate changes in patients with long QT syndrome. *Pacing Clin Electrophysiol*. 2009;32:72–81.
15. Razak E, Buncova M, Shusterman V, Winter B, Shen WK, Ackerman MJ, Donovan T, Lampert R, Nemec J. Slow QT interval adaptation to heart rate changes in normal ambulatory subjects. *Ann Noninvasive Electrocardiol*. 2011;16:148–155.
16. Seethala S, Shusterman V, Saba S, Mularski S, Nemec J. Effect of beta-adrenergic stimulation on QT interval accommodation. *Heart Rhythm*. 2011;8:263–270.
17. Hondeghem LM, Carlsson L, Duker G. Instability and triangulation of the action potential predict serious proarrhythmia, but action potential duration prolongation is antiarrhythmic. *Circulation*. 2001;103:2004–2013.
18. Thomsen MB, Volders PG, Beekman JD, Matz J, Vos MA. Beat-to-beat variability of repolarization determines proarrhythmic outcome in dogs susceptible to drug-induced torsades de pointes. *Circulation*. 2006;48:1268–1276.
19. Kim JJ, Nemec J, Li Q, Salama G. Synchronous systolic subcellular Ca^{2+}-elevations underlie ventricular arrhythmia in drug-induced long QT type 2. *Circ Arrhythm Electrophysiol*. 2015;8:703–712.
20. Nemec J, Kim JJ, Gabris B, Salama G. Calcium oscillations and T-wave lability precede ventricular arrhythmias in acquired long QT type 2. *Heart Rhythm*. 2010;7:1686–1694.
21. Nemec J, Buncova M, Bulkova V, Hejlik J, Winter B, Shen WK, Ackerman MJ. Heart rate dependence of the QT interval duration: differences among congenital long QT syndrome subtypes. *J Cardiovasc Electrophysiol*. 2004;15:550–556.
22. Viswanathan PC, Shaw RM, Rudy Y. Effects of IKr and IKs heterogeneity on action potential duration and its rate dependence: a simulation study. *Circulation*. 1999;99:2466–2474.
23. Eisner DA, Dibb KM, Trafford AW. The mechanism and significance of the slow changes of ventricular action potential duration following a change of heart rate. *Exp Physiol*. 2009;94:520–528.
24. Sanchez C, Corrias A, Bueno-Orovio A, Davies M, Swinton J, Jacobson I, Laguna P, Pueyo E, Rodriguez B. The Na+/K+ pump is an important modulator of

refractoriness and rotor dynamics in human atrial tissue. *Am J Physiol Heart Circ Physiol*. 2012;302:H1146–H1159.

25. Li GR, Yang B, Feng J, Bosch RF, Carrier M, Nattel S. Transmembrane ICa contributes to rate-dependent changes of action potentials in human ventricular myocytes. *Am J Physiol*. 1999;276:H98–H106.
26. Satomi K, Shimizu W, Takaki H, Suyama K, Kurita T, Aihara N, Kamakura S. Response of beat-by-beat QT variability to sympathetic stimulation in the LQT1 form of congenital long QT syndrome. *Heart Rhythm*. 2005;2:149–154.
27. Haigney MC, Wei S, Kaab S, Griffiths E, Berger R, Tunin R, Kass D, Fisher WG, Silver B, Silverman H. Loss of cardiac magnesium in experimental heart failure prolongs and destabilizes repolarization in dogs. *J Am Coll Cardiol*. 1998;31:701–706.
28. Goldenberg I, Moss AJ, Peterson DR, McNitt S, Zareba W, Andrews ML, Robinson JL, Locati EH, Ackerman MJ, Benhorin J, Kaufman ES, Napolitano C, Priori SG, Qi M, Schwartz PJ, Towbin JA, Vincent GM, Zhang L. Risk factors for aborted cardiac arrest and sudden cardiac death in children with the congenital long-QT syndrome. *Circulation*. 2008;117:2184–2191.
29. Moss AJ, Schwartz PJ, Crampton RS, Tzivoni D, Locati EH, MacCluer J, Hall WJ, Weitkamp L, Vincent GM, Garson A Jr, et al. The long QT syndrome. Prospective longitudinal study of 328 families. *Circulation*. 1991;84:1136–1144.
30. Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, Vicentini A, Spazzolini C, Nastoli J, Bottelli G, Folli R, Cappelletti D. Risk stratification in the long-QT syndrome. *N Engl J Med*. 2003;348:1866–1874.
31. Porta A, Girardengo G, Bari V, George AL Jr, Brink PA, Goosen A, Crotti L, Schwartz PJ. Autonomic control of heart rate and QT interval variability influences arrhythmic risk in long QT syndrome type 1. *J Am Coll Cardiol*. 2015;65:367–374.