Diagnostic performance of QT interval variables from 24-h electrocardiography in the long QT syndrome

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Aims The long QT syndrome is mainly defined by QT interval prolongation (QTc >0·44s). However, data obtained in genotyped patients showed that resting QTc measurement alone may be inaccurate for ascertaining the phenotype. The aim of this study was to evaluate the diagnostic performance of QT interval rate-dependence in untreated chromosome 11-linked patients.

Methods The study population consisted of 25 untreated long QT patients linked to chromosome 11 and 25 age- and gender-matched controls. QTc intervals were measured on 12-lead resting ECG recordings. From 24-h Holter recordings, the slope of the relationship between ventricular repolarization and heart rate was studied separately day and night to assess neural modulation. Mean heart rates and rate-dependences of QT and Q-maximum of T (QTm) intervals were compared between long QT patients and controls for both time periods.

Results In both groups, the rate-dependences were modulated by day–night influences. When compared to controls,

long QT patients showed a significant increase at night in QT/RR slopes (0·158 ± 0·05 vs 0·117 ± 0·03, $P=0·002$) and QTm/RR slopes (0·163 ± 0·05 vs 0·116 ± 0·04, $P=0·0006$). Multivariate analysis, adjusting QTc interval on age and gender, discriminated between long QT patients and controls with a 76% sensitivity and a 84% specificity. A 96% sensitivity and a 96% specificity were reached by taking into account the QTm/RR slope at night, the QTc interval and the mean heart rate during the day.

Conclusion QT interval variables obtained from 24-h ECG recordings improve long QT syndrome diagnosis by showing an increased nocturnal ventricular repolarization rate-dependence in genotyped chromosome 11-linked patients.
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Key Words: Long QT syndrome, ventricular repolarization, Holter monitoring, QT interval, LQT1.

Introduction

The Romano-Ward long QT syndrome (LQTS) is an autosomal dominant cardiac disease with a low prevalence but a high mortality of 5 to 20% per year in untreated symptomatic patients[1,2]. The three main genetic variants of LQTS, linked to chromosomes 11 (LQT1), 7 (LQT2), and 3 (LQT3), depend on specific mutations in potassium (KVLQT1 and HERG) and sodium (SCN5A) channel genes, respectively[3–5]. Severe forms are linked with major QT prolongation and torsade de pointes. However, ECG abnormalities are not always overt, and accurate diagnosis may be diffi-

cult. Despite QT interval measurement limitations, one of the main diagnostic criteria of LQTS remains the corrected QT interval (QTc by the Bazett formula >0·44s)[2]. However, genetic analysis has shown an overlap of QTc values (0·41s to 0·47s, representing a grey zone) between gene carriers and non-gene carriers in chromosome 11-linked families[6].

Since genetic testing still requires accurate clinical classification, a diagnostic score, including clinical symptoms and resting ECG data (QTc duration, gross T-wave alternans, notched T wave), has been proposed[2]. Other studies tried to better characterize the ECG phenotype and three ECG T-wave patterns have been associated with genetically distinct forms of LQTS[7]. Quantification of other resting ECG variables, such as QT dispersion, T-wave alternans and T-wave humps has also been proposed[8–10].

Table 1 **LQTS patients characteristics**

LQTS Patient	Age (years)	Gender	Symptoms	QTc (ms)	QTc disp (ms)	Score	RR8 (ms)	QTm/RR night slope	KVLQT1 mutations
1	7	F		436	43	1·5	705	0.225	Arg426Cys
2*	8	F		413	23	2	660	0·199	Arg426Cys
3	8	M		478	48	4·5	600	0·236	Arg426Cys
4	8	M		470	56	3·5	850	0·177	Arg426Cys
5	17	F	sudden death	490	60	7	695	0·194	Arg410Trp
6	20	M	sync	440	40	4	870	0·143	Arg410Trp
7*	21	M	sync	420	54	4	895	0·110	Arg410Trp
8	22	F		483	51	4·5	590	0·159	Arg426Cys
9*†	23	F		410	43	1·5	710	0·158	Arg426Cys
10	25	M		449	41	2·5	875	0·107	Arg426Cys
11	27	F	sync-tdp	456	52	6·5	1275	0·082	—
12	29	F	sync-tdp	480	21	6·5	845	0·164	—
13*	30	F		422	53	1	730	0·153	Arg426Cys
14	31	F	sync	472	37	5·5	695	0·100	Thr180Arg
15	31	F	sync	440	40	2·5	775	0·221	Arg426Cys
16	32	M		440	30	2	750	0·083	Arg426Cys
17	32	M		443	29	2	950	0·168	—
18	33	M	sync	459	42	5·5	860	0·092	Tyr186Ser
19	34	F		490	41	4·5	715	0·185	Arg426Cys
20	39	F		431	19	2	750	0·150	Arg426Cys
21	45	M		510	78	5	1040	0·228	Gly39Arg
22*	58	M		421	35	2	785	0·192	Arg426Cys
23	59	M		453	46	2	860	0·159	Arg426Cys
24*	62	M		414	18	2	945	0·145	Arg426Cys
25	70	M	sync	539	39	7	775	0·251	Tyr186Ser
mean	31	13M	9 sync	454	42	3·6	808	0·163	
± SD	± 17	12F		± 33	± 14	± 1·9	± 147	± 0·05	

LQTS=long QT syndrome; SD=standard deviation; sync=syncopal episode; tdp=torsade de pointes; disp=dispersion; score=Schwartz *et al.* score[2]; * and †=LQTS patients misdiagnosed by resting ECG and global models, respectively. Mutation positions are given according to the sequence published by Wang *et al.*[3].

Rate adaptation is another intrinsic property of ventricular repolarization[11,12]. In LQTS, the QT rate dependence has been investigated, by quantifying the relationship between QT and the preceding RR interval[13–15]. Some studies quantified the QT rate dependence by means of ECG Holter monitoring on a 24-h time basis[15]. However, low heart rate, stress-induced syncope and the beneficial effects of beta-blockers or of left stellectomy suggest that the autonomic nervous system has an important role in modulating ventricular repolarization electrophysiological abnormalities in the LQTS[16,17]. In this way, ventricular repolarization characteristics investigated during the day and at night could be more appropriate[18]. Other approaches utilized exercise-induced QT variations[14]. However, the subjects enrolled in all these studies included untreated patients and patients receiving beta-blockers. More critically, genotype was not determined, leading to an uncertainty regarding the disease gene involved, and thus the cardiac ionic channel involved.

The aim of this study was to investigate the diagnostic performance of the ventricular repolarization rate-dependence separately during the day and at night in untreated genotyped LQT1 patients.

Methods

Populations

Twenty five untreated LQTS patients matched in terms of age and gender to 25 control subjects form the basis of this study. All patients were part of a French molecular genetic study on the LQTS approved by the Ethical Committee of the Pitié-Salpêtrière Hospital (Paris, France). All patients provided written informed consent for the gene linkage studies and for 12-lead ECG and three-lead Holter monitoring.

The LQTS group (Table 1) consisted of 13 males and 12 females aged 7 to 70 years (mean age: 31 ± 17 years) belonging to 10 different families. QTc values were measured in lead II (n=24) or V_5 (n=1) on the resting ECG recorded closest to the Holter recording prior to any therapy. QTc dispersion was defined as the difference between the longest and shortest QT interval from any lead of the 12-lead ECG (manual measurement on 25 mm . s^{-1}, 10 mm . mV^{-1} paper print-outs). Nine patients had a history of syncope or documented ventricular tachyarrhythmias. The remaining 16 patients were asymptomatic. All patients were free of any other cardiac abnormality.

Family members have been genotyped, with several microsatellite markers corresponding to each LQTS locus for linkage analysis, as previously reported[19]. In these families, positive lod scores were in evidence for the disease and LQT1 markers and negative lod scores for the other LQTS loci. All LQTS patients included in the study were carriers of the chromosome 11 haplotypes linked to the disease. Available mutations in KVLQT1 are given in Table 1.

The control group consisted of 25 untreated healthy subjects free of any cardiac abnormality detectable by clinical examination, resting ECG, three-lead Holter recording, 2D echocardiography, and stress test for those over 40 years.

ECG ambulatory data acquisition

Each subject underwent a 24-h ECG recording (DelMar 459 recorder, DelMar Avionics, Irvine, CA, U.S.A.) with an XYZ pseudo-orthogonal electrode configuration, prior to any therapy. Tapes were played back through a Marquette Laser System (Marquette Electronics Inc., Milwaukee, WI, U.S.A.). The digitized ECG data (128 Hz sampling rate) were then transferred to a computer for specific analysis.

Definition of day and night periods

The diurnal period was defined as the 8 'awake' consecutive hours with the shortest mean RR interval (RR8) and the nocturnal period as the 4 sleeping consecutive hours with the longest mean RR interval (RR4).

The sympathovagal balance of each of these two periods was characterized by calculating the mean RR intervals and the three following parameters of heart rate variability: SDNN (standard deviation of all normal sinus cycles), rMSSD (root of the mean of the squared differences of adjacent sinus to sinus intervals), and the ratio of the low (LF) to the high (HF) frequency components of the power spectral density (LF: 0·04–0·15 Hz; HF: 0·15–0·40 Hz).

Beat-to-beat analysis

For each of the three XYZ digitized channels, the peaks of all R and T waves were estimated with a parabolic interpolation technique previously described[15]. The distance between the R-wave peak and the following T-wave peak (RTm interval) was associated to the preceding RR interval. The beat-to-beat RTm/RR relationship was evaluated during the whole 24-h period, during the day (RTmD/RR) and at night (RTmN/RR) separately.

Selective beat averaging

Ventricular repolarization rate-dependence was also analysed by calculating the QT/RR relationship, using a selective beat averaging method[20,21]. The main goal of this procedure was to average QRS-T complexes selected according to the preceding heart rate, thus obtaining low-noise templates related to a specific heart rate environment. Namely, the target QRS-T complexes to be averaged had to be preceded by a 1 min period of stable heart rate (including the immediately preceding RR intervals)[11,12]. A set of templates was obtained by stratifying the RR interval of the period of study in 25 ms intervals centered around the mean RR of the period.

Quantitative ECG analysis

ECG analysis was based on a three-dimensional algorithm that compared two spatial T-wave loops[21,22]. Briefly, the loops obtained from the templates were projected into a new orthogonal system, designed to free the signals from extracardiac variations, such as respiration and body position. The comparison aims at minimizing the mean quadratic deviation which represents the mean distance between the corresponding samples of the two loops (Fig. 1). This analysis is comparative, with a reference loop formed by averaging all the sinus complexes of the day (QT8) and night (QT4). We will report on the rate-dependences of the two following ventricular repolarization variables: QRS onset–end of T wave (QT) and QRS onset–maximum of T (QTm), examined separately.

Statistical analysis

Results are expressed as mean ± standard deviation. The effect of the RR interval on the ventricular repolarization duration was investigated with a linear regression model. The mean slopes of the QT/RR and QTm/RR relationships were compared between LQTS and controls by the non-parametric Wilcoxon signed-rank test. In order to discriminate between the two populations, a multiple logistic regression analysis was applied. Covariates were age and gender associated with either the QTc value alone (resting ECG model), or Holter ECG variables alone (Holter ECG model), or the combination of all ECG variables (global model). Holter ECG variables consisted of six slope values (two obtained from beat-beat analysis and four from selective beat averaging), RR8 and RR4. The regression equation based on either the resting ECG model or the global model was used to compute the predicted probability of belonging to the LQTS group. Sensitivity and specificity were calculated for each model as functions of the probability cut-off value. The Chi-square test was used to compare sensitivity and specificity values between each model.

Levels of significance were represented by *P* values derived from two-sided tests. A *P* value of 0.05 or less was considered to indicate statistical significance, except for multivariate analysis where a level of 0·1 was
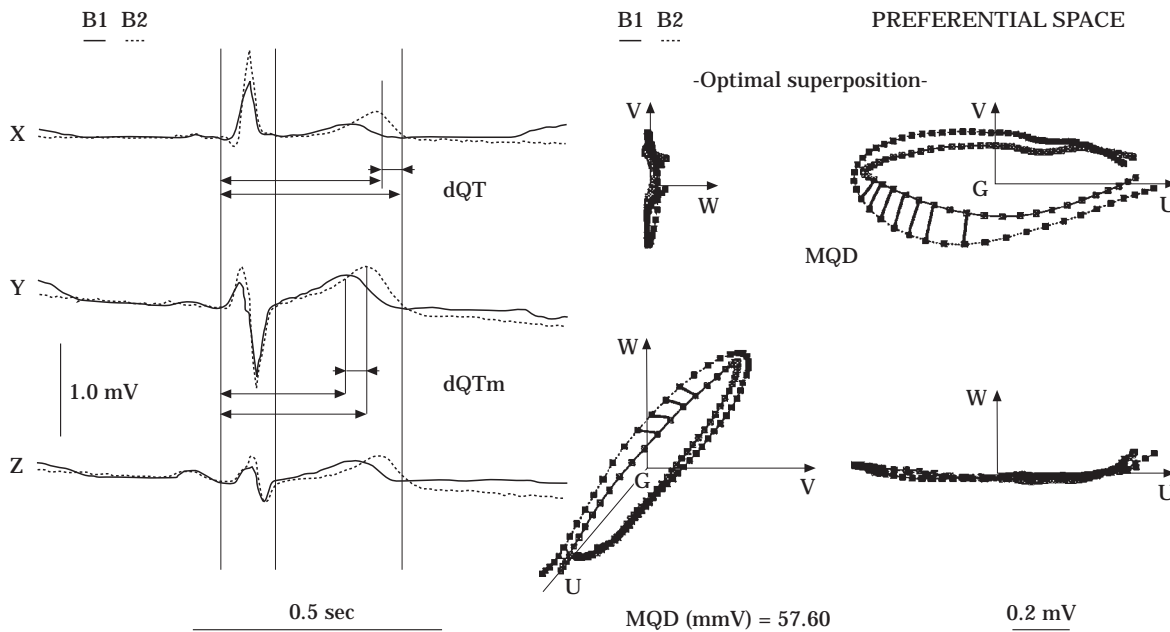
Figure 1 Three-dimensional quantitative analysis. The XYZ scalar representation of two beats to be compared (B1 and B2) is shown in the left part of the figure. The corresponding T-wave loops are projected in their preferential space and the mean quadratic deviation (MQD) between the two loops is computed. An iterative procedure then aims at minimizing the MQD and the time interval differences between B1 and B2 (dQT, dQTm) are computed from the newly defined fiducial points.

accepted. Statview (Abacus Concepts Inc. CA, U.S.A.) and SAS (Statistical Analysis System Inc., Carey, NC, U.S.A.) software packages were used.

Results

12-lead resting ECG data

LQTS patients had longer RR intervals when compared to controls (980 ± 179 ms vs 866 ± 208 ms, $P=0.02$), longer QTc intervals (454 ± 33 ms vs 396 ± 27 ms, $P=0.0001$) and a greater QTc dispersion (42 ± 14 ms vs 28 ± 11 ms, $P=0.002$). The mean LQTS score[2] of LQTS population was 3.6 ± 1.9 (Table 1).

24-hour Holter characteristics

The RR8 (mean diurnal RR interval) and RR4 (mean nocturnal RR interval) intervals were longer in LQTS patients than in controls (Table 2).

LQTS patients and controls did not show differences in all heart rate variability parameters regardless of the period considered (for the 24 h, SDNN: 168 ± 35 ms vs 160 ± 38 ms for LQTS patients and controls, respectively, $P=0.3$; rMSSD: 54 ± 27 ms vs 55 ± 31 ms, $P=0.8$; LF/HF: 3.2 ± 2 vs 3.9 ± 4.2, $P=0.7$). A covariance analysis was performed to take into

Table 2 Rate-dependences and heart rates in controls and LQTS patients

		Day	Night	*P*
QT/RR	Controls	$0.144_{\pm 0.04}$	$0.117_{\pm 0.03}$	*
	LQTS	$0.138_{\pm 0.06}$	$0.158_{\pm 0.05}$	ns
	P	ns	†	
QTm/RR	Controls	$0.174_{\pm 0.05}$	$0.116_{\pm 0.04}$	*
	LQTS	$0.149_{\pm 0.06}$	$0.163_{\pm 0.05}$	ns
	P	ns	*	
RTm/RR	Controls	$0.112_{\pm 0.04}$	$0.053_{\pm 0.02}$	*
	LQTS	$0.104_{\pm 0.05}$	$0.078_{\pm 0.03}$	*
	P	ns	†	
RR (Holter)	Controls	$703_{\pm 121}$	$965_{\pm 142}$	*
	LQTS	$808_{\pm 147}$	$1102_{\pm 143}$	*
	P	†	*	

*$P \leq 0.001$; †$P \leq 0.01$; ‡$P < 0.05$; LQTS=LQTS patients. Data are expressed as mean $\pm$ standard deviation.

account the different mean RR intervals in the two groups, and lack of any difference was still observed.

Beat-to-beat analysis

On the 24-h period, the mean value of the RTm/RR slope was not different between LQTS patients (0.136 ± 0.04) and controls (0.138 ± 0.03). In controls, diurnal slopes were clearly steeper than nocturnal slopes (Table 2). This day–night pattern was also found in the
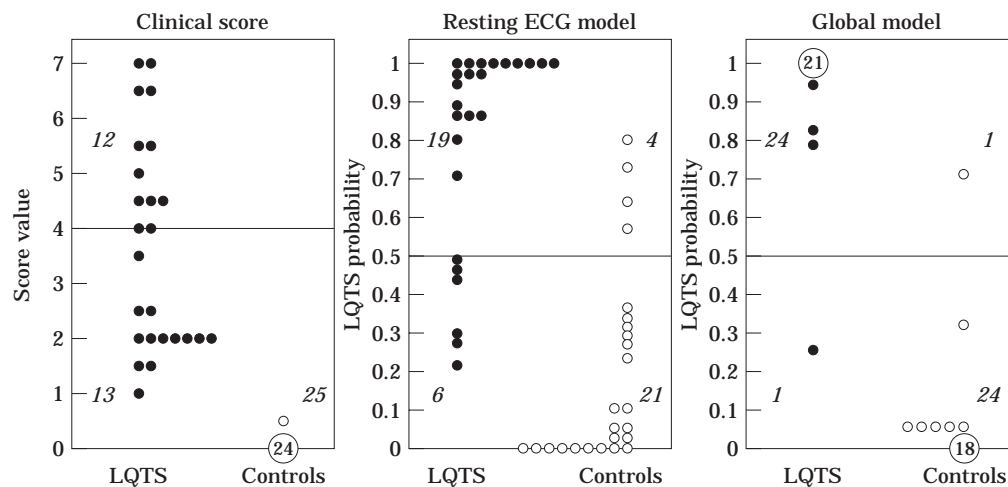
Figure 2   Diagnostic performance of resting and dynamic QT variables. Individual clinical scores (left panel) and LQTS probabilities calculated either by the resting ECG model (middle panel) or the global model (right panel) are displayed for both populations. A score value ≥ 4 or a LQTS probability above the cut-off value of 0·5 indicated LQTS patients. Italic characters indicate the number of subjects below or above the threshold of each diagnostic approach. Open circles indicate controls and filled circles correspond to LQTS patients.

LQTS group, but with a less marked difference. The diurnal slopes were not different between the two groups, whereas nocturnal slopes were significantly higher in LQTS patients.

Rate-dependence of ventricular repolarization at stable heart rate

In controls, separate analysis of day and night revealed significantly steeper diurnal QT/RR and QTm/RR slopes (Table 2). Conversely, in LQTS patients, no difference was found between night and day slopes. In fact, Table 2 presents evidence of two different phenomena. At night, the ventricular repolarization rate dependence was significantly increased in LQTS (0.158 ± 0.05) compared to controls (0.117 ± 0.03, $P=0.002$ for QT). During the day, slopes tended to be weaker in LQTS than in controls but the difference was not significant.

Univariate analysis selected four variables significantly associated with LQTS: the night QTm/RR slope ($P=0.003$), the night QT/RR slope ($P=0.004$), RR4 ($P=0.005$) and RR8 ($P=0.02$).

Diagnostic performance of QT variables

The respective diagnostic performances of the clinical score, resting ECG and Holter QT variables were quantified by the sensitivity and the specificity provided by each model. Figure 2 shows the score obtained for each subject and individual LQTS probabilities obtained in both populations, either from the resting ECG or the global model.

Table 3   *Multivariate relation of resting and dynamic ECG variables to LQTS risk*

Variable	Circadian period	Regression coefficient	P
Age	—	—	0·44
Gender	—	—	0·49
QTc	—	0·292	0·07
RR8	Day	0·062	0·08
RR4	Night	—	0·14
QT/RR	Day	—	0·28
QTm/RR	Day	—	0·61
QT/RR	Night	—	0·34
QTm/RR	Night	0·119	0·07
Constant	—	− 183·7	—

Thirteen LQTS patients and 25 controls had a score value <4 (Fig. 2). The scoring system was associated with a 48% sensitivity and a 100% specificity. The resting ECG model (QTc interval alone adjusted on age and gender) provided a 76% sensitivity and an 84% specificity. The Holter ECG model (six slope values, RR8 and RR4) selected two covariates: the night QTm/RR slope ($P=0.0007$) and the RR4 interval ($P=0.0007$). Both these variables had a positive estimated regression coefficient (the higher the value, the higher the LQTS probability). With this model, seven individuals out of 50 were misclassified (three patients and four controls), corresponding to an 88% sensitivity and a 96% specificity.

The global model (QTc interval and Holter variables adjusted on age and gender) selected three covariates: the night QTm/RR slope, the QTc interval and the RR8 interval (Table 3). All these covariates had a

positive coefficient. This model provided a 96% sensitivity and a 96% specificity, and only misclassified two individuals (one patient and one control). The LQT1 patient misclassified by this model was a 23-year-old asymptomatic female with a resting QTc value of 410 ms and a normal circadian pattern of QTm/RR rate dependences (diurnal slope greater than nocturnal one) (Table 1). The control misclassified was a 21-year-old male with a resting QTc value of 413 ms and a RR8 value of 787 ms.

Specificity was significantly different only when comparing the clinical score with the resting ECG model (100% vs 84% respectively, $P<0.05$). Sensitivity was significantly different between the global model and the resting ECG model (96% vs 76% respectively, $P<0.05$) and between the global model and the clinical score (96% vs 48% respectively, $P<0.001$). Even when considered alone, the Holter ECG model provided a higher sensitivity than the clinical score (88% vs 48% respectively, $P<0.01$).

Discussion

This is the first study to investigate the diagnostic performance of the dynamics of ventricular repolarization in a genetically homogeneous LQTS population. New information on the relationship between ventricular repolarization and heart rate in untreated LQTS patients linked to LQT1 has been provided. Separate analysis of day and night periods showed an increase in ventricular repolarization rate dependence only at night. This nocturnal increase, together with a lower mean diurnal heart rate, seems to be a major diagnostic criterion of LQTS.

Day–night influence on ventricular repolarization behaviour

The dynamic relationship between ventricular repolarization and the preceding single RR interval obtained from Holter recordings of LQTS patients has been analysed on a 24-h time basis by Merri *et al.*[15]. They were the first to report an increased RTm rate dependence in LQTS patients, when compared to controls. This previous approach was not effective to discriminate between our two populations. However, the patients enrolled in the Merri *et al.* study were not genotyped and included untreated patients and patients receiving beta-blockers. Certain drugs, such as mexiletine, affect the QT response to heart rate increase with a different behaviour according to the genotype[23]. Beta-blockers are likely to have such an effect on ventricular repolarization rate dependence. In our work, a clear difference between patients and controls was only obtained by analysing RTm rate-dependence during the day and at night separately. This approach demonstrated distinct environments of autonomic balance[18,20].

In addition, analysis of ventricular repolarization rate dependence by selective beat averaging following 1 min stable heart rate periods strengthened the differences between the two populations at night. Increased rate dependence at night seems to be a major diagnostic marker of LQTS, so far emphasized in only one study in the context of predominant parasympathetic balance during the recovery phase of an exercise test[14].

The increase in ventricular repolarization rate dependence observed only at night suggests an autonomic modulation of the LQTS electrophysiological substrate. This autonomic implication is also supported by the finding that electrical alternans, another ECG feature of LQTS, is abolished during left-sided sympathetic blockade[16,17]. However, cardiac sympathetic innervation assessed by myocardial scintigraphy gives conflicting results, suggesting either increased[24] or normal[25] sympathetic innervation in LQTS patients. Moreover, our heart rate variability data showed a slower heart rate, but did not support any abnormal autonomic balance at the atrial level. Nevertheless, normal innervation at the atrial level does not eliminate disturbance at the ventricular level.

Diagnostic performance of QT interval dynamics

The clinical score, as described by Schwartz *et al.*[2], includes clinical symptoms and resting ECG data, such as QTc duration, gross T-wave alternans and notched T-wave. In our population of LQT1 patients, there was a high proportion of patients below the score value of 4 (Table 1). However, this can be explained by the updated threshold values of QTc interval duration used in this score: 450 ms in males and 460 ms in females. The total number of our patients below these values is 14 out of 25. Moreover, gross T-wave alternans and notched T-wave were absent in all these LQT1 patients. Thus the score seems to better identify LQTS with major resting ECG abnormalities, which could correspond to a particular genotype.

The resting ECG model (QTc interval adjusted on age and gender) misclassified six out of the eight LQTS patients with QTc values <440 ms and the four controls with the longest QTc intervals (425 ms, 428 ms, 432 ms and 436 ms). The eight patients with a QTc value <440 ms belonged to the large families K1387 and K1822 and were carriers of the disease haplotype without recombination. When ventricular repolarization rate dependences and mean heart rate at day and night (Holter ECG model) were considered, only three patients and four controls were misdiagnosed. However, sensitivities and specificities provided by the Holter and resting ECG models were not significantly different. Combination of ventricular repolarization dynamics and mean heart rate data with the QTc interval (global model) led to a 96% sensitivity and a 96% specificity. Only one out of the six patients misdiagnosed by the

resting ECG model was still misclassified by the global model (Table 1). This misclassified LQT1 female patient had a QTc interval duration of 410 ms and was asymptomatic, but other members within the same family had much longer QTc intervals. It is highly probable that the expression of the genetic status is modulated by unknown additional factors. The control subject misclassified by the global model had unremarkable Holter and ECG variables. Thus, both static and dynamic QT variables seem to provide additional information on ventricular repolarization behaviour. However, the specificity and sensitivity are not optimal. Other features of ventricular repolarization could be added to such a model.

Possible cellular mechanisms

The finding that LQT1 and LQT2 genes, KVLQT1 and HERG, respectively, code for potassium channels[3,4], and that LQT3 gene (SCN5A) codes for the cardiac sodium channel[5] clearly demonstrates a cellular defect in the LQTS. More specifically, KVLQT1 has been recently demonstrated to underly the I_{Ks} cardiac potassium current when associated to minK. Mutations in KVLQT1 have dominant–negative effect, with a reduction of the outward potassium repolarizing current[26]. A dominant–negative effect was also described in the case of missense mutations in HERG, the gene encoding the potassium channel resulting in the I_{Kr} current[29]. Dofetilide, a class III antiarrhythmic agent, has been shown to be a specific I_{Kr} blocker and this block of HERG by dofetilide results in an increased ventricular rate dependence[30]. Our finding of increased nocturnal rate dependence in LQT1 patients could be related to the dominant–negative effect of KVLQT1 mutations.

Nevertheless, the pathophysiological mechanisms involved in this syndrome could also include abnormalities of sympathetic innervation, modulating the expression of intrinsic abnormalities of myocardial cells[16,17].

Conclusion

Analysis of QT interval from 24-h Holter recordings of untreated chromosome 11-linked patients allowed us to characterize the dynamics of repolarization in the LQT1 type syndrome and to improve the diagnosis. Since accurate clinical classification is still a prerequisite for genetic analysis, our findings might represent a significant step in the management of LQTS patients. Together with a lower mean heart rate during the day and a longer resting QTc interval, an increased nocturnal rate–dependence was identified as a valuable diagnostic marker. This phenomenon may be related to the modulation by the autonomic nervous system of the cellular defect that underlies repolarization abnormalities. These findings cannot be extrapolated to other

forms of LQTS (LQT2, LQT3) or to data obtained from patients receiving treatments such as beta-blockers which could modify ventricular repolarization dynamics. Our findings thus need to be confirmed on a larger LQTS population of genetically distinct forms.

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