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Effects of Epinephrine and Phenylephrine on QT Interval Dispersion in Congenital Long QT Syndrome

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Objectives. **Measurement of QT interval dispersion during pharmacologic adrenergic stimulation was used to assess the effect of alpha- and beta-adrenergic stimulation on arrhythmic vulnerability in familial long QT syndrome (LQTS).**

Background. **Nonhomogeneity in the ventricular action potential duration causes electrical instability leading to life-threatening ventricular arrhythmias and is markedly increased in LQTS. QT interval dispersion measured from the electrocardiogram (ECG) can be used as an index of nonhomogeneous ventricular repolarization.**

Methods. **Sixteen symptomatic patients with LQTS and nine healthy control subjects were examined at baseline and during epinephrine (mainly beta-adrenergic agonist, 0.05 μg/kg body weight per min) and phenylephrine infusions (alpha-adrenergic agonist, mean 1.4 μg/kg per min). QT interval dispersion was determined from a 12-lead ECG as interlead range and coefficient of variation measured to the end (QT_{end}) and apex (QT_{apex}) of the T wave.**

Results. **At baseline QT_{end} dispersion was greater in patients with LQTS compared with control subjects (mean [±SD] 68 ± 34 vs. 36 ± 7 ms, p = 0.001). QT_{end} dispersion was markedly increased in patients with LQTS by use of epinephrine (from 68 ± 34 to 90 ± 36 ms, p = 0.002), but remained unchanged in control subjects. Phenylephrine did not affect QT dispersion in either group (all p = NS). Atrial pacing to achieve comparable heart rates during baseline and epinephrine and phenylephrine infusions did not influence the magnitude of QT dispersion in either group. QT_{apex} dispersion analysis gave congruent results.**

Conclusions. **Epinephrine but not phenylephrine increased QT dispersion, suggesting that beta-adrenergic stimulation provokes arrhythmias in patients with LQTS by aggravating nonhomogeneity of ventricular repolarization, whereas alpha-adrenergic stimulation is less important for arrhythmic vulnerability. The results also suggest that rapid pacing may not reduce vulnerability to arrhythmias in congenital LQTS.**

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Nonuniform recovery of excitability is an important underlying mechanism of malignant ventricular arrhythmias (1–4). Familial long QT syndrome (LQTS) is a clinical disorder characterized by abnormal ventricular repolarization, ventricular arrhythmias triggered by sympathetic nervous activation and sudden death (5,6). Standard electrocardiography is a clinically available method to examine heterogeneity of ventricular repolarization, and interlead variability of the QT interval—QT dispersion—has been proposed as a marker of electrical instability of the heart (7,8). The shape and width of the T wave reflect local differences in recovery of excitability (9), a factor known to increase a patient's propensity to develop ventricular fibrillation. QT dispersion is markedly increased in patients with LQTS, which has been considered to indicate arrhythmia risk (8) in this disease. It has also been proposed that QT dispersion can predict therapeutic efficacy in LQTS, although its discriminating power may be insufficient to be a useful clinical tool (10,11).

Sympathetic nervous stimulation and catecholamines are known to produce QT prolongation and ventricular arrhythmias in familial LQTS (5,12). In the present study we examined the influence of alpha- and beta-adrenergic stimulation of QT dispersion in LQTS. Phenylephrine was used to produce alpha-adrenergic stimulation and epinephrine mainly beta-adrenergic stimulation. Because these pharmacologic interventions alter heart rate considerably, cardiac cycle length was controlled by atrial pacing. Also, the QT interval and ventricular monophasic action potential duration (MAPd) were examined.

Methods

Study subjects. Sixteen patients (12 women and 4 men, age range 6 to 66 years) with congenital LQTS were included in the study. All of these patients had a history of syncope, family members with diagnosed LQTS and a corrected QT interval (QTc) >440 ms (range 450 to 700). Nine other patients participating in a control electrophysiologic study after previous catheter ablation served as control subjects (4 women and 5 men, age range 19 to 59 years), and all had a structurally

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Abbreviations and Acronyms

ECG = electrocardiogram
LQTS = long QT syndrome
MAPd = monophasic action potential duration
QT_{apex} = dispersion of QT apex intervals
QTc = corrected QT interval
QT_{end} = dispersion of QT end intervals

normal heart and a normal QTc (<440 ms). All patients with LQTS and control subjects were examined without any antiarrhythmic medication, including beta-adrenergic antagonists. The study was approved by the Institutional Ethical Review Board, and each patient gave written informed consent.

Test procedure. Three quadripolar electrical catheters were placed in the right atrium, atrioventricular junction and right ventricle. MAP was recorded from the right ventricular septum using a silver/silver chloride MAP catheter and a 0.05- to 250-Hz bandpass filter. Blood pressure was measured from a femoral artery cannula. Standard 12-lead ECG, MAP and arterial pressure were recorded and stored digitally at a sample rate of 1 kHz (Cardiolab, Prucka Engineering).

The study data were obtained at baseline and under stabilized conditions during epinephrine and phenylephrine infusions. The target rate of epinephrine infusion was 0.05 μg/kg per min, which was reached stepwise while provocation of arrhythmias was carefully monitored. A phenylephrine dose of 1 to 2 μg/kg per min (average 1.4 μg/kg per min) was chosen to increase systolic arterial pressure by 30 mm Hg. Two patients with LQTS and two control subjects did not receive phenylephrine owing to high baseline arterial pressure or discomfort during the preceding epinephrine phase. None of the patients had frequent premature ventricular beats to prevent the analysis or any ventricular tachycardia during the test infusions.

Recordings were performed during sinus rhythm, and atrial pacing was maintained at least 30 s before measurement. The targeted pacing cycle intervals were 700, 600 and 500 ms. Data were not obtained at all cycle intervals because of a faster sinus rate or decreased atrioventricular node conductivity during pharmacologic interventions.

Measurements. QT and sinus cycle lengths (RR intervals) were measured from a computer display with 0.05 mV/mm amplification and 100 mm/s sweep speed using cursor-moved calipers with a discrimination accuracy of 1 ms (Cardiolab, Prucka Engineering). Omitted were leads with near isoelectric T waves and recordings where the paced atrial signal was superimposed on the peak or end of the T wave. To compensate for missing data at the 600-ms cycle interval, values from the 700-ms or 500-ms cycle interval were used in zero to two cases per group during drug infusions for analysis of QT dispersion (but not of QT interval duration).

The QT interval was measured from the onset of the QRS deflection to end of the T wave (QT_{end}), defined as the intersection of the isoelectric baseline and the tangent of the maximal downward T wave slope. The QT apex interval (QT_{apex}) was measured to the T wave apex, defined as the maximal amplitude of the dominant T wave component, whether positive or negative. The ventricular MAPd was determined at 90% of repolarization using cursor-moved calipers. The intervals and arterial pressure were determined from the same heart beats. All measurements were performed by one of the investigators.

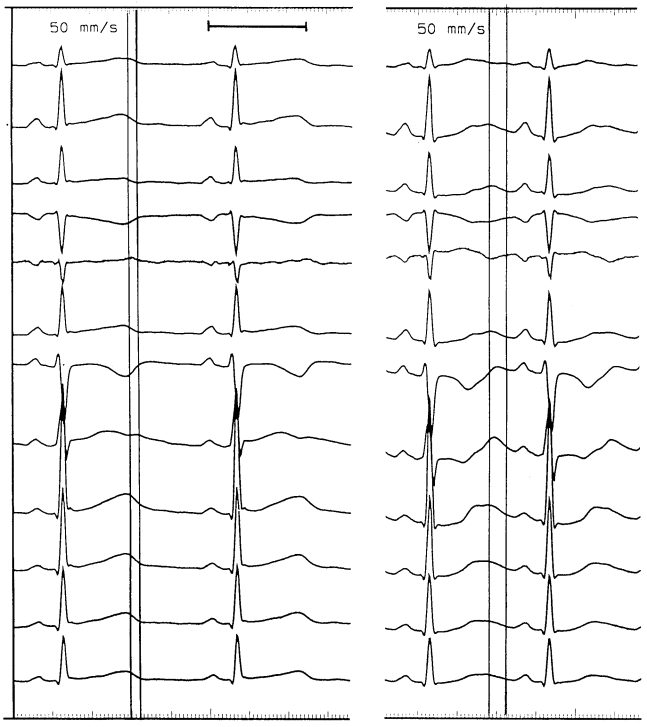


Figure 1. Measurement of QT_{end} interval dispersion of a 12-lead ECG (limb, auxiliary and chest leads in standard order) of a patient with LQTS. **Vertical lines** indicate earliest and latest T wave end in any lead at baseline **(left panel)** and during infusion of epinephrine **(right panel)**.

Data were accepted for dispersion analysis if at least nine ECG leads were analyzable. QT dispersion was examined using two indexes: interlead range as the longest minus shortest QT interval in any ECG lead and coefficient of variation of QT intervals. The latter index was obtained by dividing the standard deviation by the mean of the QT intervals, expressed as a percentage. This index attempted to avoid biases inherent in using two extreme values only and having groups with dissimilar QT interval durations. Dispersion was calculated for QT_{end} and QT_{apex} data. The QT_{end} interval was corrected to heart rate (QTc) by using Bazett's formula: $QTc = QT/\sqrt{RR}$. The given QT_{end}, QT_{apex} and QTc interval durations are means of all measured leads. Figure 1 illustrates the measurement of QT_{end} dispersion in a patient with LQTS.

Statistical analysis. Continuous variables are expressed as the mean value ± SD. Differences between patients with LQTS and control subjects were assessed using analysis of variance and the *t* test. The effects of the pharmacologic tests

Table 1. Characteristics of the Study Groups

	Patients With LQTS (n = 16)	Control Subjects (n = 9)	p Value
Age (yr)	32 ± 21	43 ± 11	NS
SBP (mm Hg)	143 ± 29	139 ± 18	NS
Sinus cycle interval (ms)	875 ± 203	859 ± 216	NS
QT_{end} interval (ms)	493 ± 74	381 ± 27	0.001
QT_{apex} interval (ms)	376 ± 41	300 ± 29	0.001
QTc interval (ms)	531 ± 52	417 ± 31	0.001
MAPd (ms)	400 ± 59	303 ± 19	0.001

Data presented are mean value ± SD. LQTS = long QT syndrome; MAPd = monophasic action potential duration; QT_{apex} = dispersion of QT apex intervals; QTc = corrected QT interval; QT_{end} = dispersion of QT end intervals; SBP = systolic blood pressure.

and atrial pacing were assessed by repeated measures analysis of variance. Relations were examined using least squares linear regression analysis. The chi-square test was used to examine incidences in the groups. A p value <0.05 was taken as statistically significant.

Results

The LQTS and control groups did not differ with regard to age, sinus cycle length or blood pressure. As anticipated by the patient selection, the QT and QTc intervals and MAPd were markedly longer in patients with LQTS than in control subjects (Table 1).

QT dispersion in baseline. QT_{end} dispersion was greater in patients with LQTS than in control subjects (Table 2). QT_{apex} dispersion tended to be greater in patients with LQTS than in control subjects during sinus rhythm and was clearly so during atrial pacing.

QT_{end} dispersion correlated with the QT_{end} interval (r = 0.66, p = 0.001) and MAPd (r = 0.65, p = 0.001), but not with the sinus cycle length in the LQTS group (r = 0.04, p = NS).

Physiologic effects of adrenergic interventions. Epinephrine shortened sinus cycle length equally in both groups (Table 3). Epinephrine did not change the QT_{end} interval in sinus rhythm, but increased the QTc and paced QT_{end} interval in the LQTS group. In the control group epinephrine had no effect on the QT_{end} interval during pacing (Table 3). No statistically significant effect on MAPd could be demonstrated during sinus rhythm or pacing in either group.

Phenylephrine increased the sinus cycle length equally in both groups (Table 3). Phenylephrine increased the QT_{end} interval in both groups but had no effect on the QTc or paced QT_{end} interval. Phenylephrine did not change MAPd during atrial pacing in either group.

Systolic blood pressure was not influenced by epinephrine, but phenylephrine increased it from 143 ± 29 to 167 ± 16 mm Hg (p = 0.001) in the LQTS group and from 139 ± 18 to 159 ± 12 mm Hg (p = 0.001) in the control group. The changes were comparable in both groups (p = NS).

Adrenergic effects on QT dispersion. Epinephrine increased QT dispersion markedly in the LQTS group (Fig. 2, Table 4). The effects on QT_{end} and QT_{apex} dispersions were comparable and both indexes—interval range and coefficient of variation—showed similar results (Fig. 3). No respective changes occurred in the control group (Table 4).

QT_{end} and QT_{apex} dispersions were not influenced by phenylephrine in either group, with neither of the indexes showing any statistically significant change (Table 4).

Pacing effect on QT dispersion. There were no statistically significant differences in QT dispersion between sinus rhythm and atrial pacing in either group at baseline (all comparisons p = NS) (Table 2). Atrial pacing did not attenuate the epinephrine-induced increase in QT dispersion in the LQTS group (Table 5, Fig. 4), nor did pacing have any effect on QT dispersion during phenylephrine.

Table 2. QT Dispersion in Patients With Long QT Syndrome and Control Subjects at Baseline

Dispersion Index*	Patients With LQTS	Control Subjects	p Value
During sinus rhythm	n = 16	n = 9	
QT_{end} (ms)	68 ± 34	36 ± 7	0.002
QT_{end} coeff (%)	4.2 ± 1.8	2.8 ± 0.6	0.010
QT_{apex} (ms)	62 ± 47	42 ± 11	NS
QT_{apex} coeff (%)	5.0 ± 3.8	4.2 ± 1.0	NS
During atrial pacing†	n = 14	n = 9	
QT_{end} (ms)	61 ± 32	37 ± 11	0.023
QT_{end} coeff (%)	4.1 ± 1.8	3.2 ± 1.2	0.050
QT_{apex} (ms)	69 ± 37	34 ± 13	0.012
QT_{apex} coeff (%)	7.0 ± 4.4	3.6 ± 1.5	0.033

*See Methods for explanation. †Atrial pacing was performed at a cycle length of 600 ms. Data presented are mean value ± SD. coeff = coefficient; other abbreviations as in Table 1.

Discussion

The present study of the effects of adrenergic stimulation on ventricular repolarization in patients with LQTS showed that epinephrine, mainly a beta-adrenergic agonist, increased QT interval dispersion markedly, whereas phenylephrine, an alpha-adrenergic agonist, had no influence on dispersion. Epinephrine prolonged the QT interval in LQTS at a controlled heart rate but did not influence MAPd in the right ventricle, suggesting that local and overall ventricular repolarization times became disparate.

Arrhythmias and autonomic nervous system in LQTS. The basic abnormality in congenital LQTS is a mutation in the genes coding a potassium channel in types 1 and 2 and a sodium channel in type 3 of the syndrome (13–15). Physical exertion and strong emotions are known to precipitate arrhythmic syncope and sudden death in LQTS (5). Exercise testing and isoproterenol infusion are reported to produce prolongation of the QT interval in LQTS (12,16). Protection against sudden death by use of beta-adrenergic antagonists (6) and left upper thoracic sympathectomy (17) confirms the importance of sympathetic stimulation as a trigger of arrhythmias. Thus, catecholamines play an important role in arrhythmogenesis in

Table 3. Effect of Pharmacologic Adrenergic Stimulation on Duration of Ventricular Repolarization During Sinus Rhythm and Atrial Pacing

	Baseline	Epinephrine	p Value*	Phenylephrine	p Value*
Patients with LQTS	n = 16	n = 16		n = 14	
Sinus cycle interval (ms)	875 ± 203	702 ± 104	0.001	992 ± 242	0.017
QT_{end} interval (ms)	493 ± 74	490 ± 70	NS	520 ± 78	0.001
QTc interval (ms)	531 ± 52	586 ± 68	0.001	527 ± 55	NS
MAPd (ms)	400 ± 59	378 ± 48	NS	414 ± 53	0.048
Atrial pacing	n = 14	n = 14		n = 13	
QT_{end} interval (ms)	427 ± 44	458 ± 49	0.013	445 ± 52	NS
MAPd (ms)	357 ± 40	359 ± 43	NS	348 ± 33	NS
Control subjects	n = 9	n = 9		n = 7	
Sinus cycle interval (ms)	859 ± 216	697 ± 172	0.005	957 ± 215	0.002
QT_{end} interval (ms)	381 ± 27	370 ± 30	NS	396 ± 32	0.005
QTc interval (ms)	417 ± 31	448 ± 25	0.004	409 ± 18	NS
MAPd (ms)	303 ± 19	300 ± 31	NS	326 ± 30	NS
Atrial pacing	n = 9	n = 8		n = 5	
QT_{end} interval (ms)	364 ± 31	365 ± 18	NS	358 ± 16	NS
MAPd (ms)	280 ± 10	290 ± 15	NS	291 ± 21	NS

*Statistical significance refers to comparison with baseline value. Data presented are mean value ± SD. Abbreviations as in Table 1.

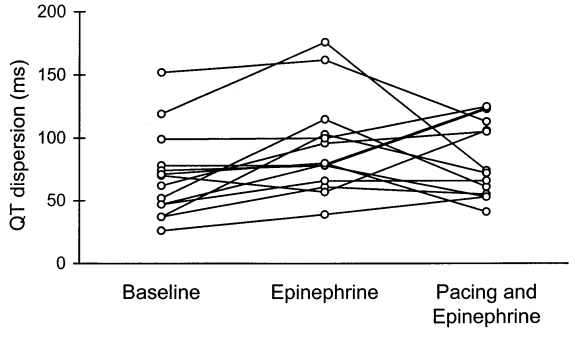
LQTS and could act by exaggerating the preexisting repolarization abnormalities.

Epinephrine stimulates myocardium mainly through $beta_1$ receptors and less through $beta_2$ receptors, whereas it induces only mild myocardial $alpha_1$ stimulation (18). The beta-adrenergic receptor stimulation shortens and the alpha-adrenergic receptor stimulation prolongs the action potential duration in experimental preparations (19–21). The beta-adrenergic stimulation produced in the present study was modest because the heart rate was only slightly increased.

Catecholamines and QT dispersion. QT dispersion is increased in familial LQTS (8,10,11). A sympathetic imbalance hypothesis (22) has been previously promoted in LQTS but has lost importance since the detection of ion channel defects as the basic anomaly. A normal distribution and density of cardiac sympathetic nerve terminals have been observed in LQTS (23), suggesting a more complex genesis of QT dispersion than mere differences in regional innervation.

In the present study, epinephrine increased QT dispersion markedly in patients with congenital LQTS. Thus, increasing the nonhomogeneity in ventricular repolarization is a possible mechanism by which the beta-adrenergic agonists provoke arrhythmias in LQTS. In addition, epinephrine prolonged the QT interval at a controlled heart rate. This should be considered arrhythmogenic because a greater length of the QT interval is associated with more malignant arrhythmias in LQTS (24). The present results cannot answer whether the increase in the dispersion or the duration of the QT interval is more important for arrhythmogenesis. Because QT dispersion was increased only by epinephrine and not by phenylephrine, this action is attributed to the beta-adrenergic component of the sympathetic system.

Figure 2. Dispersion of the QT_{end} interval at baseline and during infusion of epinephrine. Individual responses to epinephrine are indicated during sinus rhythm and atrial pacing.



A recent report by Hirao et al. (25) showed that epinephrine increases the difference in ventricular MAPd recorded from multiple intracardiac sites in patients with LQTS. Our results are consistent with their findings, assuming that QT dispersion on the surface ECG represents local differences in repolarization time, as has been suggested (9). In our study, at a controlled rate, epinephrine prolonged the QT interval duration but did not influence ventricular MAPd, which might represent different local responses (i.e., dispersion in ventricular repolarization) during beta-adrenergic stimulation.

An important observation was that phenylephrine did not increase QT dispersion in patients with LQTS. This suggests that alpha-adrenergic stimulation does not increase nonuniformity in ventricular repolarization, and because neither the QT interval nor MAPd was prolonged at a controlled heart rate, alpha-adrenergic stimulation would not be considered strongly arrhythmogenic. Vagal stimulation prolongs ventricular action potential duration largely by antagonizing the effect of beta-adrenergic stimulation (26). Acetylcholine has dissimilar effects on ventricular endocardium and epicardium (27), and thus could affect QT dispersion, although it is unknown

Table 4. Effect of Pharmacologic Adrenergic Stimulation on QT Dispersion

Dispersion Index*	Baseline	Epinephrine	p Value†	Phenylephrine	p Value†
Patients with LQTS	n = 16	n = 16		n = 14	
QT_{end} (ms)	68 ± 34	90 ± 36	0.003	71 ± 37	NS
QT_{end} coeff (%)	4.3 ± 1.8	5.8 ± 2.0	0.002	3.8 ± 1.5	NS
QT_{apex} (ms)	62 ± 47	102 ± 61	0.006	70 ± 47	NS
QT_{apex} coeff (%)	5.0 ± 3.8	9.7 ± 6	0.008	5.1 ± 3.3	NS
Control subjects	n = 9	n = 9		n = 9	
QT_{end} (ms)	36 ± 7	38 ± 13	NS	44 ± 16	NS
QT_{end} coeff (%)	2.8 ± 0.6	3.1 ± 1.2	NS	3.1 ± 1.1	NS
QT_{apex} (ms)	42 ± 11	40 ± 15	NS	39 ± 14	NS
QT_{apex} coeff (%)	4.2 ± 1.0	4.5 ± 1.9	NS	3.3 ± 0.9	NS

*See Methods for explanation. †Statistical significance refers to comparison with baseline value. Data, presented as mean value ± SD, were obtained in sinus rhythm at intervals indicated in Table 3. Abbreviations as in Tables 1 and 2.

whether vagal stimulation does so in humans. Therefore, baroreflex-mediated vagal stimulation during increased arterial pressure might have obscured a possible direct effect of phenylephrine on QT dispersion.

Effects of rate on QT dispersion. The noted absence of the effect of cardiac pacing on QT dispersion indicates that the opposite effects of alpha- and beta-adrenergic stimulations on heart rate cannot explain the results. It also suggests that pacing faster than the physiologic heart rate would not diminish QT dispersion in patients with LQTS in general. The experience on clinical benefit of pacing in LQTS is at variance. Some reports suggest that permanent pacing can reduce recurrent syncopal events in high risk patients with LQTS (28) and in patients with LQTS with conduction abnormalities (24). Our results favor the view that the benefit of cardiac pacing is due to prevention of severe bradycardia and cardiac pauses. An exception is probably type 3 LQTS with a sodium channel defect, where elevating the slow rest heart rate by pacing is considered protective (29). Thus, our conclusions would not be readily applicable to all LQTS subtypes.

Study limitations. Because of different individual physiology, comparison during pharmacologic stimulation could not always be performed at similar pacing cycle lengths. As noted in the present and previous studies (10), QT dispersion is not obviously dependent on heart rate, and therefore minor differences in compared cycle lengths would not have confounded the observations on QT dispersion.

Although care was taken to use consistent criteria to define the end of the T wave and to exclude U waves, the latter may have been unidentifiable across the leads and included in the QT interval when prominent. The uncertainty in defining the measurement points, owing to low T wave amplitude and overlapping atrial signal, resulted in omitting some leads. This would not diminish the comparability of our results, because the practice is common in QT dispersion studies.

The genotype was not known in all patients, but according to our previous analysis (30) of subtype distributions in the geographic area, the majority of the patients likely had a potassium channel abnormality of LQTS types 1 and 2. It is possible that a difference in genotype may affect the individual responses.

Conclusions. Modest beta-adrenergic stimulation increases QT dispersion markedly, suggesting that this component, as opposed to alpha-adrenergic stimulation, is most important for arrhythmic vulnerability in congenital LQTS. The results also suggest that pacing faster than the normal

Figure 3. Effect of epinephrine and phenylephrine on QT dispersion during sinus rhythm in patients with LQTS. **Solid columns** represent QT_{end} and **crosshatched columns** QT_{apex} dispersions (mean ± SEM). **p < 0.01 compared with baseline.

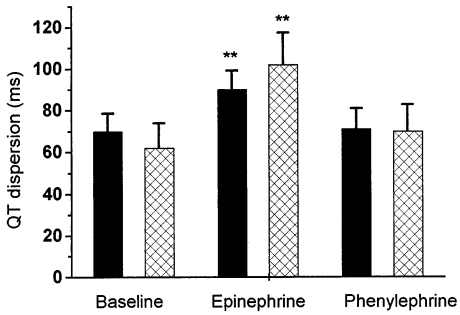


Table 5. Effect of Pacing on QT Dispersion in Patients With Long QT Syndrome*

Dispersion Index†	Sinus Rhythm‡	Atrial Pacing§
Baseline	n = 16	n = 14
QT_{end} (ms)	68 ± 34	61 ± 32
QT_{end} coeff (%)	4.3 ± 1.8	4.1 ± 1.8
QT_{apex} (ms)	61 ± 46	64 ± 26
Epinephrine	n = 16	n = 14
QT_{end} (ms)	90 ± 36	86 ± 31
QT_{end} coeff (%)	5.8 ± 2.0	5.4 ± 1.5
QT_{apex} (ms)	102 ± 61	98 ± 43
Phenylephrine	n = 14	n = 13
QT_{end} (ms)	71 ± 37	67 ± 31
QT_{end} coeff (%)	3.8 ± 1.5	4.6 ± 2.0
QT_{apex} (ms)	70 ± 41	57 ± 25

*p = NS for all comparisons. †See Methods for explanation. ‡Sinus cycle intervals are given in Table 3. §Atrial pacing cycle interval was 600 ms. Data presented are mean value ± SD. Abbreviations as in Tables 1 and 2.

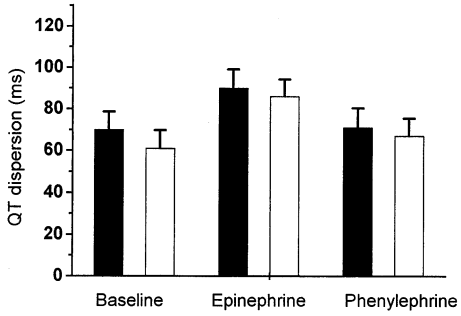


Figure 4. Effect of atrial pacing on QT_{end} dispersion in patients with LQTS during baseline and infusions of epinephrine and phenylephrine. **Solid columns** represent sinus rhythm and **open columns** atrial pacing (mean ± SEM). No differences (p = NS) existed between the sinus and paced rhythms during any study phase.

heart rate may not reduce the vulnerability of these patients to life-threatening arrhythmias.

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