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Epinephrine Unmasks Latent Mutation Carriers With LQT1 Form of Congenital Long-QT Syndrome

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OBJECTIVES This study was designed to test the hypothesis that epinephrine infusion may be a provocative test able to unmask nonpenetrant *KCNQ1* mutation carriers.

BACKGROUND The LQT1 form of congenital long QT syndrome is associated with high vulnerability to sympathetic stimulation and appears with incomplete penetrance.

METHODS The 12-lead electrocardiographic parameters before and after epinephrine infusion were compared among 19 mutation carriers with a baseline corrected QT interval (QTc) of ≥460 ms (Group I), 15 mutation carriers with a QTc of <460 ms (Group II), 12 nonmutation carriers (Group III), and 15 controls (Group IV).

RESULTS The mean corrected Q-Tend (QTce), Q-Tpeak (QTcp), and Tpeak-end (Tcp-e) intervals among 12-leads before epinephrine were significantly larger in Group I than in the other three groups. Epinephrine (0.1 μg/kg/min) increased significantly the mean QTce, QTcp, Tcp-e, and the dispersion of QTcp in Groups I and II, but not in Groups III and IV. The sensitivity and specificity of QTce measurements to identify mutation carriers were 59% (20/34) and 100% (27/27), respectively, before epinephrine, and the sensitivity was substantially improved to 91% (31/34) without the expense of specificity (100%, 27/27) after epinephrine. The mean QTce, QTcp, and Tcp-e before and after epinephrine were significantly larger in 15 symptomatic than in 19 asymptomatic mutation carriers in Groups I and II, and the prolongation of the mean QTce with epinephrine was significantly larger in symptomatic patients.

CONCLUSIONS Epinephrine challenge is a powerful test to establish electrocardiographic diagnosis in silent LQT1 mutation carriers, thus allowing implementation of prophylactic measures aimed at reducing sudden cardiac death. (J Am Coll Cardiol 2003;41:633–42) © 2003 by the American College of Cardiology Foundation

Recent evidence has suggested that cardiac events associated with sympathetic stimulation are more common among the LQT1 form than the LQT2 or LQT3 forms of congenital long QT syndrome (LQTS) (1–4). LQT1 is one of the two most common genetic form of LQTS so far identified, and is frequently manifest with variable expressivity and incomplete penetrance (5). Because molecular diagnosis is still unavailable to many clinical centers, and it requires high costs and a long time to be performed, there is a strong need to devise clinical tools to improve the sensitivity of clinical tests to establish the diagnosis of LQTS. Infusion of catecholamines, such as epinephrine or isoproterenol, has been used to unmask patients with suspected LQTS (6). Recent clinical data from our group and others have demonstrated the differential response of dynamic QT interval to epinephrine infusion in LQT1, LQT2, and LQT3 syndrome and the paradoxical QT prolongation in LQT1 syndrome (7,8). The present study was prompted by the successful management of a 14-year-old boy who had been resuscitated from cardiac arrest during swimming and was referred to our hospital. His baseline 12-lead electrocardiogram (ECG) showed borderline corrected QT interval (QTc) (442 ms) (Fig. 1A), but epinephrine infusion prolonged the QTc remarkably (585 ms), leading to spontaneously terminating torsade de pointes (TdP) (Fig. 1B). The QTc interval was within normal range in his family members examined (parents and two sisters). Molecular screening for LQTS mutation was performed later, confirming the diagnosis of LQT1 syndrome. We designed a study to perform a systematic evaluation of the diagnostic value of epinephrine infusion in unmasking nonpenetrant mutation carriers with LQT1 syndrome.

METHODS

Study population. Eleven families affected with LQT1 syndrome were entered into the present study (six *KCNQ1* missense mutations, one splice mutation, and one deletion

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Abbreviations and Acronyms

APD = action potential duration
ECG = electrocardiogram
I_{Ks} = slow component of the delayed rectifier potassium current
I_{Na} = sodium current
$I_{Na\text{-}Ca}$ = Na^+/Ca^{2+} exchange current
LQTS = long QT syndrome
QTc = corrected QT interval
QTce = corrected Q-Tend interval
QTcp = corrected Q-Tpeak interval
Tcp-e = corrected interval between Tpeak and Tend
TdP = torsade de pointes

mutation). Among the eight mutations, five were in the core domain (six families) and three in the C-terminal domains (five families). Eleven families included 19 mutation carriers (seven families) with a prolonged QTc interval of ≥460 ms (Group I), 15 mutation carriers (seven families) with a normal or borderline QTc of <460 ms (Group II), and 12 nonmutation carriers (eight families) (Group III). Fifteen healthy volunteers were selected from doctors and nurses in our hospital and entered as controls (Group IV). LQTS-affected individuals were noted on the basis of electrocardiographic diagnostic criteria by Keating et al. (9), including a QTc ≥470 ms in asymptomatic individuals and a QTc >440 ms for men and >460 ms for women associated with one or more of the following: 1) stress-related syncope, 2) documented TdP, or 3) family history of early sudden cardiac death. The score of the LQTS was also calculated using the diagnostic criteria by Schwartz et al. (10).

Recording of standard 12-lead ECGs. Genotyping of LQTS was reviewed and approved by our Ethical Review Committee, and written informed consent was obtained from all patients, or their parents when the patients were <20 years of age. The epinephrine test was conducted as part of clinical evaluation of the LQTS. Standard 12-lead ECG was recorded with an FDX6521 (Fukuda Denshi Co., Tokyo, Japan) in the supine position without antiarrhythmic medications including beta-blockers. These electrocardiographic data were digitized using analog-digital converters with a sampling rate of 1,000 samples/s/channel.

Measurement. Measurement of the electrocardiographic parameters was performed in a blinded fashion as to genotype status against five-averaged QRS complex by an offline computer using the analysis program developed by our institution. The Q-Tend interval was defined as the interval between the QRS onset and the point at which the isoelectric line intersected a tangential line drawn at the minimum first derivative (dV/dt) point of the positive T-wave or at the maximum dV/dt point of the negative T-wave. When a bifurcated or secondary T-wave (pathologic U-wave) appeared, it was included as part of the measurement of the Q-Tend interval, but a normal U-wave, which was apparently separated from a T-wave, was not included (11). The Q-Tpeak interval was defined as the interval between the QRS onset and the peak of the positive T-wave or the nadir of the negative T-wave. When the T-wave had a biphasic or a notched configuration, peak of the T-wave was defined as that of the dominant T deflection. The five QRS complexes were averaged first for each lead. Then, the Q-Tend, Q-Tpeak and Tpeak-end (Q-Tend minus Q-Tpeak) intervals, as an index of transmural dispersion of repolarization, were measured automatically from all 12-lead ECGs, corrected by Bazett's method (corrected Q-Tend [QTce], corrected Q-Tpeak [QTcp], corrected Tpeak-end [Tcp-e]), and averaged among all 12-leads. As an index of spatial dispersion of repolarization, dispersion of the QTce and the QTcp was defined as the interval between the maximum and the minimum of the QTce and the QTcp among 12-leads, respectively.

Epinephrine administration. A bolus injection of epinephrine (0.1 μg/kg), an alpha + beta-adrenergic agonist, was immediately followed by continuous infusion (0.1 μg/kg/min). The 12-lead ECG was continuously recorded during sinus rhythm under baseline conditions and usually for 5 min under epinephrine infusion. The effect of epinephrine on both RR and QT intervals usually reached steady-state conditions 2 to 3 min after the start of epinephrine. Epinephrine infusion for more than 5 min was avoided, and electrocardiographic monitoring was continued for a further 5 min after epinephrine infusion for possible occurrence of TdP. The electrocardiographic data were collected under baseline conditions and at steady-state conditions of epinephrine (3 to 5 min after the start of epinephrine), and compared among the four groups. The epinephrine test was performed in a blinded fashion as to genotype status in 31 of 46 family members, because the 31 members were not genotyped at the epinephrine test.

Statistical analysis. Data are expressed as mean ± SD, except for those shown in the figures, which are expressed as mean ± SEM. Repeated-measures two-way analysis of variance followed by Scheffe's test was used to compare measurements made before and after epinephrine, and to compare differences between the groups (STATISTICA, 98 edition, StatSoft Inc., Tulsa, Oklahoma). Repeated-measures one-way analysis of variance followed by Scheffe's test were used to compare changes (Δ) of the measurements with epinephrine between the groups. Differences in frequencies were analyzed by the chi-square test. A two-sided p value <0.05 was considered significant.

RESULTS

Clinical and molecular diagnosis. Clinical characteristics of the four groups are shown in Table 1. All 19 Group I patients could be diagnosed as having LQTS by electrocardiographic diagnostic criteria; 18 patients had a score ≥4 (high probability of LQTS), and an average score of the 19 patients was 5.5 ± 1.3 points (range 3 to 7.5 points). One Group II patient could be diagnosed as having LQTS; all 15 Group II patients had a score ≤2 and an average score of 0.7

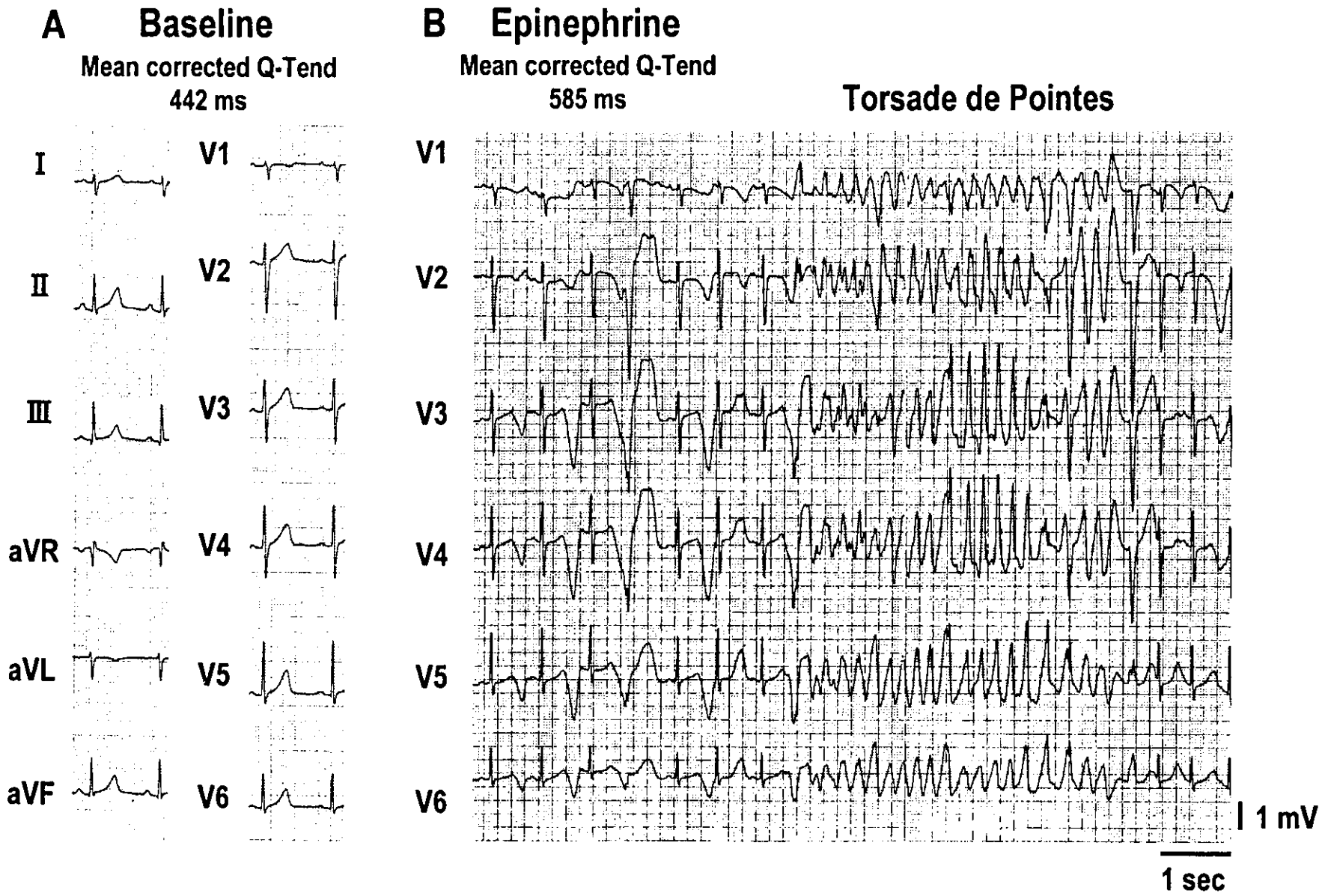

Figure 1. Twelve-lead electrocardiograms under baseline condition **(A)** and precordial electrocardiograms during epinephrine infusion (2 min after start of epinephrine) **(B)** in an LQT1 mutation carrier. The mean corrected Q-Tend interval was dramatically prolonged by epinephrine, leading to spontaneously terminating torsade de pointes.

Table 1. Clinical Characteristics of Groups I, II, III, and IV

	Group I (n = 19)	Group II (n = 15)	Group III (n = 12)	Group IV (n = 15)
Age, yrs	27 ± 18	22 ± 17	31 ± 18	28 ± 16
Age < 15 yrs (%)	7/19 (37%)	9/15 (60%)	3/12 (25%)	4/15 (27%)
Female gender (%)	14/19 (74%)	7/15 (47%)	8/12 (67%)	9/15 (60%)
Heart rate, beats/min	68 ± 9	70 ± 10	69 ± 11	67 ± 10
QTc, ms	507 ± 31*	427 ± 21	414 ± 18	417 ± 20
Syncope or aborted cardiac arrest (%)	14/19 (74%)*	1/15 (7%)	(0%)	(0%)
Beta-blockers (%)	(0%)	(0%)	(0%)	(0%)
Core domain mutation (%)	12/19 (63%)	6/15 (40%)	NA	NA

Values are mean ± SD where indicated. *$p < 0.005$ vs. Groups II, III and IV.
NA = not applicable; QTc = corrected QT interval.

± 0.7 points (range 0 to 2 points). All 12 Group III patients could not be diagnosed as having LQTS, and had a score ≤1 (0.7 ± 0.5 points). All 15 Group IV controls had a QTc of <440 ms and no symptoms. Therefore, the sensitivity and specificity for identifying mutation carriers among the family members and controls were 59% (20/34) and 100% (27/27), respectively, by using the electrocardiographic diagnostic criteria of Keating et al. (9). They were 53% (18/34) and 100% (27/27) when an LQTS score ≥4 was used (10), and 59% (20/34) and 100% (27/27) when a score ≥2 was used (Table 2). Average penetrance in the 11 LQT1 families was 59% (20/34). Among the 34 mutation carriers in Groups I and II, 15 patients were symptomatic (Group I, 14/19; Group II, 1/15) and 19 patients were asymptomatic.

Comparative influence of epinephrine in the four groups. Figure 2 illustrates 12-lead ECGs under baseline conditions and during epinephrine infusion in Group I and Group II patients. In the Group I patients, both the mean QTce and QTcp were prolonged (516 ms, 431 ms) and the mean Tcp-e was increased (85 ms) under baseline conditions (Fig. 2A). Epinephrine produced a marked prolongation in the mean QTce (586 ms), but a mild prolongation in the mean QTcp (459 ms), resulting in a further increase in the mean Tcp-e (127 ms) (Fig. 2B). Although the baseline electrocardiographic parameters were normal in the Group II patients (Fig. 2C), epinephrine prolonged both the mean QTce (435→516 ms) and QTcp (362→420 ms), and increased the mean Tcp-e (73→96 ms) (Fig. 2D). Figure 3 illustrates 12-lead ECGs under baseline conditions and during epinephrine infusion in Group III and Group IV patients. The Group III patient is an older brother of the Group II patient shown in Figures 2C and 2D. The baseline electrocardiographic parameters were normal (Figs. 3A and 3C), and no significant changes were produced by epinephrine in both group patients (Figs. 3B and 3D). Figures 4A through 4E show composite data of the electrocardiographic parameters before and after epinephrine in the four groups. The mean QTce, QTcp, and Tcp-e before epinephrine were significantly larger in Group I than in the other three groups (Scheffe's test value, $p < 0.005$, Figs. 4A to 4C). Epinephrine significantly increased all the electrocardiographic parameters except the dispersion of the QTce in Groups I and II (Scheffe's test value, $p < 0.05$), but did not increase parameters in Groups III and IV. Therefore, all electrocardiographic parameters after epinephrine were significantly larger in Groups I and II (mutation carriers) than those in Groups III (nonmutation carriers) and IV (controls) (Scheffe's test value, $p < 0.05$, Figs. 4A to 4E). The changes (Δ) in the mean QTce, QTcp, and Tcp-e with epinephrine were not different between Groups I and II, but they were significantly larger than those in Groups III and IV (Scheffe's test value, $p < 0.005$, Figs. 5A to 5C). The changes in the dispersion of the QTce and the QTcp with epinephrine were not different among the four groups, except for the change in the dispersion of the QTcp between Groups I and III (Scheffe's test value, $p < 0.05$, Figs. 5D and 5E). The sensitivity for differentiating mutation carriers from nonmutation carriers and controls was substantially

Table 2. Diagnostic Accuracy of Clinical Parameters Before and After Epinephrine

	Baseline		Epinephrine	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
ECG criteria (8)	20/34 (59%) (1/15 [7%])	27/27 (100%)	31/34 (91%) (12/15 [80%])	27/27 (100%)
Score ≥ 4 (9)	18/34 (53%) (0/15 [0%])	27/27 (100%)	25/34 (74%) (6/15 [40%])	27/27 (100%)
Score ≥ 2 (9)	20/34 (59%) (2/15 [13%])	27/27 (100%)	31/34 (91%) (12/15 [80%])	27/27 (100%)
ΔQTc ≥ 30ms	NA NA	NA	31/34 (91%) (13/15 [87%])	27/27 (100%)

Number in parenthesis indicates the sensitivity in only 15 Group II patients.
ECG = electrocardiographic; NA = not applicable; ΔQTc = an increase of mean corrected Q-Tend with epinephrine.

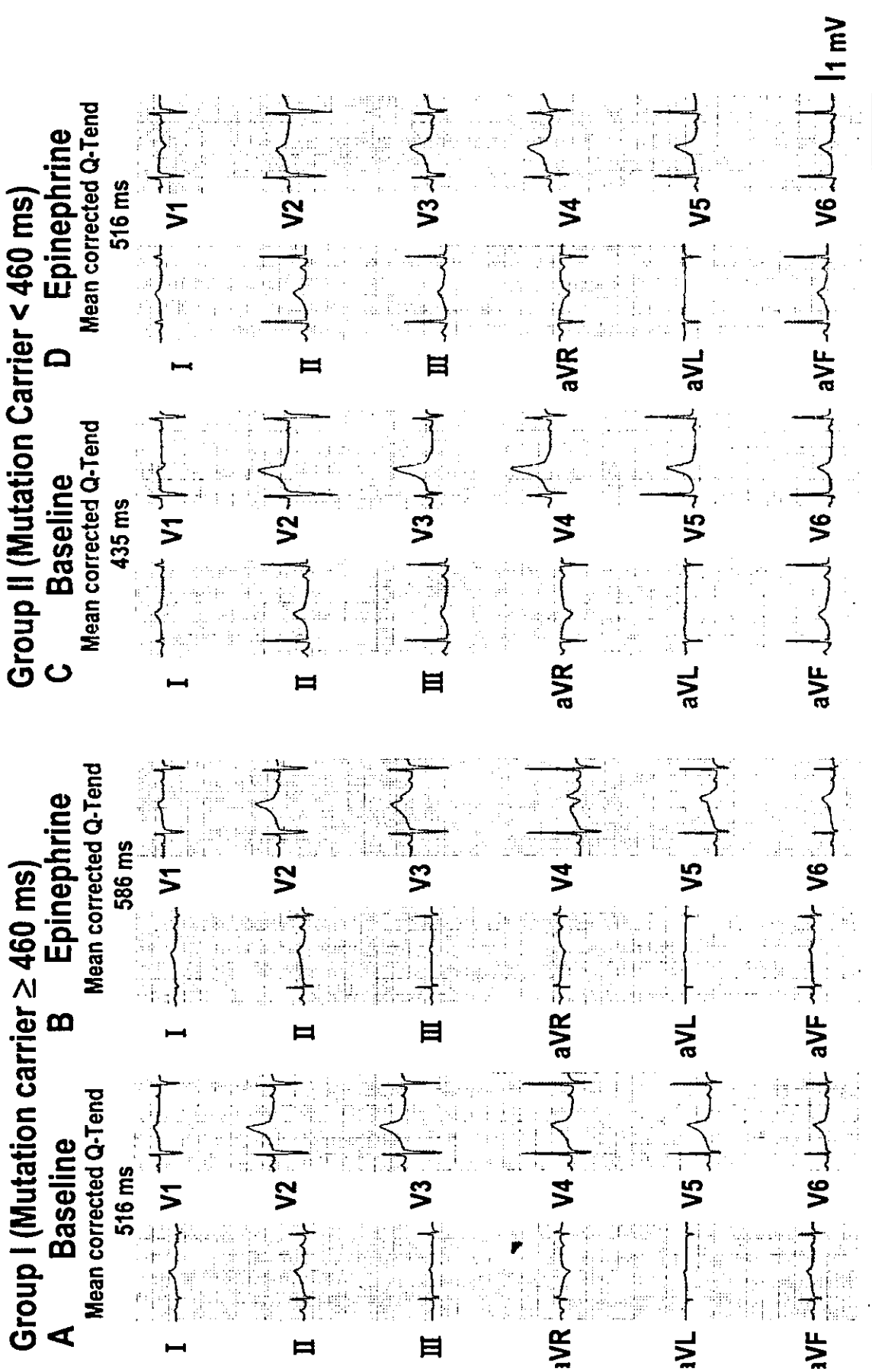

Figure 2. Twelve-lead electrocardiograms under baseline conditions and during epinephrine infusion in Group I (**A and B**) and Group II (**C and D**) patients. Epinephrine markedly prolonged the mean corrected Q-Tend in both Group I (516→586 ms) and Group II (435→516 ms) patients.

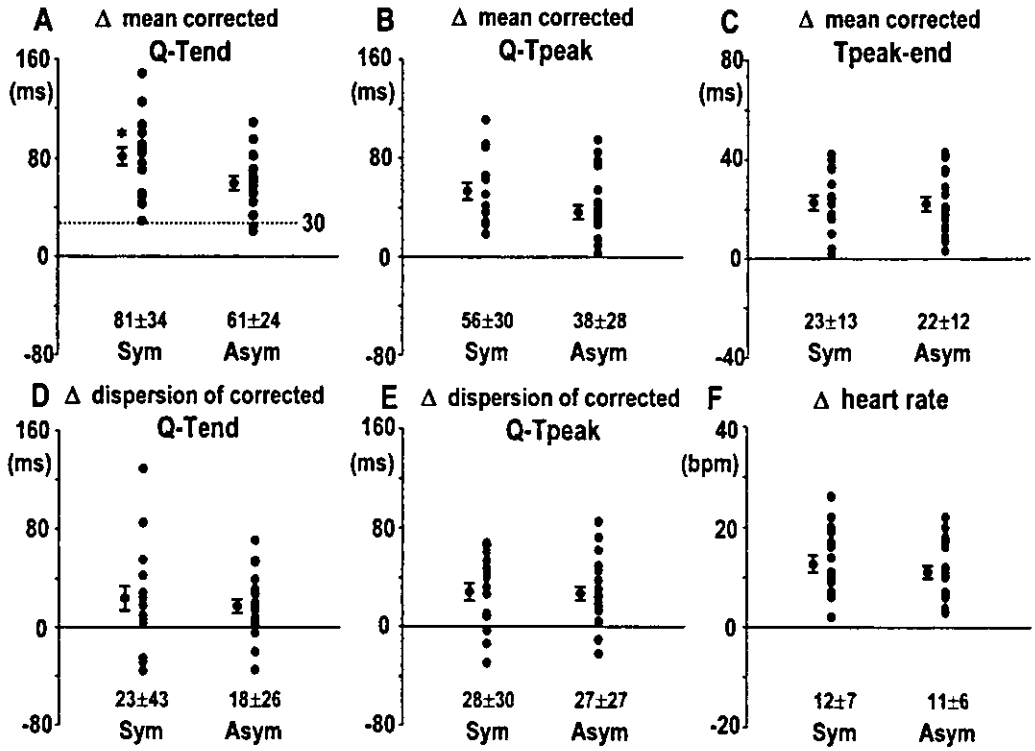

Figure 6. Composite data of the changes (Δ) of the electrocardiographic parameters **(A to E)** and heart rate **(F)** with epinephrine in 15 symptomatic patients (Sym) and 19 asymptomatic mutation carriers (Asym) in Groups I and II. *p < 0.05 vs. Asym.

improved by epinephrine test without the expense of specificity (100%, 27/27): 91% (31/34) by using the electrocardiographic diagnostic criteria or when an LQTS score ≥2 was used, and 74% (25/34) when a score ≥4 was used. An increase of mean QTce with epinephrine ≥30 ms also improved the sensitivity to 91% (31/34) without the expense of the specificity (Table 2, Fig. 5A). Even if we excluded the Group I patients who had a clear diagnosis of LQTS before epinephrine and analyzed the sensitivity only in Group II patients, the sensitivity was improved with the epinephrine test: from 7% (1/15) to 80% (12/15) by using the electrocardiographic diagnostic criteria, from 0% (0/15) to 40% (6/15) when an LQTS score ≥4 was used, from 13% (2/15) to 80% (12/15) when a score ≥2 was used, and to 87% (13/15) when an increase of mean QTce with epinephrine ≥30 ms was used (parenthesis in Table 2). The heart rate before and after epinephrine and the increases of heart rate were not different among the four groups (Figs. 4F and 5F).

Influence of epinephrine between symptomatic and asymptomatic mutation carriers. The electrocardiographic parameters and the heart rate before and after epinephrine were compared between 15 symptomatic patients and 19 asymptomatic mutation carriers in Groups I and II. The mean QTce, QTcp, and Tcp-e both before and after epinephrine were significantly greater in the 15 symptomatic patients than in the 19 asymptomatic mutation carriers (Scheffe's test value, $p < 0.05$), whereas neither dispersion of the QTce nor dispersion of the QTcp were different between the two groups. Epinephrine significantly increased all the electrocardiographic parameters except the dispersion of the QTce in both symptomatic and asymptomatic mutation carriers (Scheffe's test value, $p < 0.05$). Figure 6 illustrates composite data of the changes (Δ) of the electrocardiographic parameters and the heart rate with epinephrine in the 15 symptomatic patients and the 19 asymptomatic mutation carriers. The prolongation of the mean QTce with epinephrine was significantly greater in the 15 symptomatic patients than in the 19 asymptomatic mutation carriers (Scheffe's test value, $p < 0.05$), whereas the changes in the other parameters were not different between the two groups.

Complications. Spontaneously terminating TdP was induced by epinephrine infusion (2 min after the start of epinephrine) in one Group II patient (Fig. 1), and spontaneous premature ventricular contractions were induced in one Group I patient.

DISCUSSION

The present study demonstrates that epinephrine infusion is a provocative test that greatly increases the sensitivity of electrocardiographic diagnosis of LQT1 syndrome, one of the two most common variants of LQTS, thus providing clinicians with a powerful tool for improving appropriate diagnosis and management of LQTS.

Low penetrance in the LQT1 syndrome. The hypothesis that electrocardiographic diagnosis could miss patients affected by LQTS had already been proposed before the

genetic bases of the disease were known (12). These initial observations were based on the evidence that syncopal events could occur among family members with a "normal" QT interval. Several years later, Vincent et al. (13) reported that five (6%) of 82 mutation carriers from three LQT1 families had a normal QT interval. More recently, Priori et al. (5) have demonstrated a very low penetrance (38%, 9/24) in nine families with only one individual clinically affected with LQTS. In the present study, the average penetrance was 59% (20/34) among 11 LQT1 families. The sensitivity and specificity for identifying mutation carriers were 59% and 100% by using the electrocardiographic diagnostic criteria or when an LQTS score ≥2 was used, and they were 53% and 100% when a score ≥4 was used. Our data are in agreement with other reports demonstrating a 100% specificity and 53% sensitivity for diagnosis of high probability of LQTS (14). Overall, these findings strongly point to the need of novel tools to unveil nonpenetrant mutation carriers of LQTS.

Usefulness of epinephrine infusion in unmasking LQT1 mutation carriers. Provocative tests using catecholamine or exercise testing have long been considered to unmask some forms of congenital LQTS (6). Recent preliminary data by Ackerman et al. (8) have suggested the usefulness of an epinephrine test to unveil concealed LQT1 syndrome. This study provides systematic evaluation of the efficacy of epinephrine provocative challenge to unmask silent forms of LQTS in a group of genetically characterized individuals. Our data demonstrate that intravenous administration of epinephrine significantly improves the sensitivity of electrocardiographic diagnosis of LQTS in carriers of *KCNQ1* defects. Because *KCNQ1* is one of the two most common forms of congenital LQTS, this provocative challenge could be applied to a large number of individuals suspected to be affected by this variant of the disease. On the basis of current data, probands of congenital LQTS who had cardiac events during exercise and emotion (4), and particularly during swimming (2,3), have a high probability of being affected by *KCNQ1* genetic defects. Accordingly, all their family members become likely candidates for epinephrine provocative challenge. The identification of affected individuals with normal electrocardiographic phenotype is of major importance, as it would enable limiting exposure of these individuals to potentially dangerous conditions such as participation in competitive sports and use of drugs known to prolong repolarization, thus reducing the risk of life-threatening cardiac arrhythmias (15). However, it goes without saying that an epinephrine provocative test should only be done by cardiologists under enough preparation of intravenous beta-blockers as well as a direct cardioverter for unintentionally induced ventricular fibrillation. Darbar et al. (16) reported that the QTc was increased in lead II (but not in lead V_3) by epinephrine infusion even in normal controls, and suggested that this was due to increasing calcium current as well as hypokalemia induced by epinephrine. In this study, the QTce was not prolonged by epinephrine in Group III (nonmutation carrier) and Group IV (controls), probably as a result of the measurement of averaged QTce among all 12-leads as well as too-short epinephrine infusion (<5 min) to induce hypokalemia (17).

Mechanism of influence of epinephrine in LQT1 mutation carriers. Both experimental and clinical studies have suggested a differential response of action potential duration (APD) and QT interval to sympathetic stimulation among LQT1, LQT2, and LQT3 (7,8,18). Persistent and paradoxical prolongation of APD and QT interval at steady-state conditions of catecholamines was reported in LQT1 syndrome. Under normal conditions, beta-adrenergic stimulation is expected to increase net outward repolarizing current, owing to larger increase of outward currents, including Ca^{2+}-activated slow component of the delayed rectifier potassium current (I_{Ks}) and Ca^{2+}-activated chloride current, than that of an inward current, Na^+/Ca^{2+} exchange current ($I_{Na\text{-}Ca}$), resulting in an abbreviation of APD and QT interval. A defect in I_{Ks} in the LQT1 syndrome could account for failure of beta-adrenergic stimulation to abbreviate APD and QT interval, resulting in a persistent and paradoxical QT prolongation under sympathetic stimulation (18). In LQT2 syndrome, catecholamines are reported to initially prolong but then abbreviate APD and QT interval, probably because of an initial augmentation of $I_{Na\text{-}Ca}$ and a subsequent stimulation of I_{Ks}. In contrast to the LQT1 and LQT2 syndromes, catecholamines are reported to constantly abbreviate APD and QT interval as a result of a stimulation of I_{Ks} in the LQT3 syndrome, because an inward late sodium current (I_{Na}) was augmented in this genotype. Taken together with the data in the present study, the epinephrine test may be applied not only for unmasking silent mutation carriers with LQT1 syndrome but also for predicting genotype.

Symptomatic versus asymptomatic mutation carriers. In this study, the mean QTce, QTcp, and Tcp-e under the baseline conditions were significantly greater in the 15 symptomatic patients than in the 19 asymptomatic mutation carriers, consistent with previous large family studies without molecular diagnosis (12,19). Moreover, the epinephrine-induced prolongation of the mean QTce was significantly larger in the 15 symptomatic patients. This indicates a higher vulnerability of ventricular repolarization to sympathetic stimulation in symptomatic patients, although unknown factors may influence this phenomenon. The data also suggest that the epinephrine test may detect high-risk mutation carriers by the degree of QTc prolongation. In reverse, epinephrine-induced QTc prolongation was smaller in asymptomatic mutation carriers, indicating that the epinephrine test does not exert as great an effect to unveil mutation carriers in asymptomatic family members. However, epinephrine-induced prolongation of the mean QTce was >30 ms in all but two asymptomatic mutation carriers, and was clearly greater than those in either nonmutation carriers or normal controls. Prospective study using 30-ms cutoff with epinephrine challenge will be

needed in order to conclude the diagnostic value of the epinephrine test.

Dispersion of repolarization. The mean QTce was the most sensitive parameter to epinephrine; however, the mean Tcp-e was also increased by epinephrine only in the mutation carriers, suggesting that sympathetic stimulation increases transmural dispersion of repolarization (20), leading to arrhythmogenesis in the LQTS with *KCNQ1* defects. In contrast, the dispersion of the QTce, as an index of spatial dispersion of repolarization, was not significantly increased by epinephrine in Groups I and II (mutation carriers), and the changes in the dispersion of the QTce with epinephrine were not different among the four groups. These data may be explained by a recent elegant study using computer simulation conducted by Burnes et al. (21), in which they suggested that regional heterogeneity of repolarization was not reflected in QT dispersion recorded from the body surface ECG.

Study limitations. First, the numbers of families and of individuals in the present study are relatively small, and all patients are the same ethnic origin (Japanese). Because the issue of ethnicity as a modulator of genetically determined disease is receiving increasing attention, our data may or may not be applicable to other ethnicities.

Second, although peak of the T-wave was defined as that of the dominant T deflection when the T-wave had a biphasic or a notched configuration, it is still unclear which peak of the biphasic or notched T-wave reflects the repolarization of epicardial action potential. Further basic studies will be needed to conclude the cellular basis for complex T-waves.

Third, we used Bazett's formula for correction of heart rate. Bazett's formula is derived from normal individuals, and its use at higher heart rate is likely to lead to an overestimation of the QTc, thus contributing to the increase in sensitivity, which should be taken into account to interpret data in this kind of study.

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Genotype-specific clinical manifestation in long QT syndrome

Wataru Shimizu

The congenital form of long QT syndrome (LQTS) is characterized by QT prolongation in the electrocardiogram (ECG) and a polymorphic ventricular tachycardia, Torsade de Pointes (TdP) mainly as a result of an increased sympathetic tone during exercise or mental stress. Recent genetic studies have so far identified seven forms of congenital LQTS caused by mutations in genes of the potassium and sodium channels or membrane adapter located on chromosomes 3, 4, 7, 11, 17 and 21. It is of particular importance to examine the genotype-phenotype correlation, especially in the LQT1, LQT2 and LQT3 forms of LQTS, which make up more than 90% of genotyped patients with LQTS, because it would enable us to manage and treat genotyped patients more effectively.

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The congenital form of long QT syndrome (LQTS) is an hereditary disorder characterized by a prolonged QT interval in the electrocardiogram (ECG) and is often associated with a polymorphic ventricular tachycardia known as Torsade de Pointes (TdP), leading to severe symptoms such as syncope and sudden cardiac death (FIGURE 1) [1–5]. Genetic studies have shown that congenital LQTS is a primary electrical disease and have so far identified seven forms of congenital LQTS caused by mutations in genes of the potassium and sodium channels or membrane adapter located on chromosomes 3, 4, 7, 11, 17 and 21 [6–8]. Mutations in *KCNQ1* and *KCNE1* are responsible for defects in the slowly activating component of the delayed rectifier potassium current (I_{Ks}) underlying the LQT1 and LQT5 forms of LQTS [9,10], while mutations in *KCNH2* and *KCNE2* cause defects in the rapidly activating component of the delayed rectifier potassium current (I_{Kr}) responsible for the LQT2 and LQT6 [11,12]. Mutations in *SCN5A* result in an increase in the late sodium current (I_{Na}) responsible for the LQT3 [13]. Mutations in *KCNJ2* decrease the inward rectifier potassium current (I_{K1}) and cause a prolonged QT interval and periodic paralysis, underlying the LQT7 syndrome [7]. More recently, a mutation in *Ankyrin-B*, a member of a family of versatile membrane adapters, is reported to lead to altered Ca^{2+} signaling, underlying the LQT4 syndrome [8]. Among the seven forms of LQTS, the LQT1 and LQT2 syndromes are the two most common genetic variants and each accounts for 40–50% of genotyped patients [6]. The LQT3 syndrome accounts for approximately 10% of genotyped patients [6]. Therefore, the LQT1, LQT2 and LQT3 forms constitute more than 90% of genotyped patients with LQTS [6], although there are still 40–50% of patients clinically affected with LQTS in whom no responsible mutations can be identified. Evaluation of the genotype–phenotype correlation, especially in LQT1, LQT2 and LQT3 patients, is of major importance as it would enable us to manage and treat genotyped patients more effectively.

Genotype-specific T wave morphology

Experimental studies in the late 1990s using an arterially perfused canine ventricular wedge preparation, which was developed in Antzelevitch's laboratory, have greatly advanced our knowledge on the inscription of the T wave in the ECG [14–17]. In the arterially perfused wedge preparations, transmembrane

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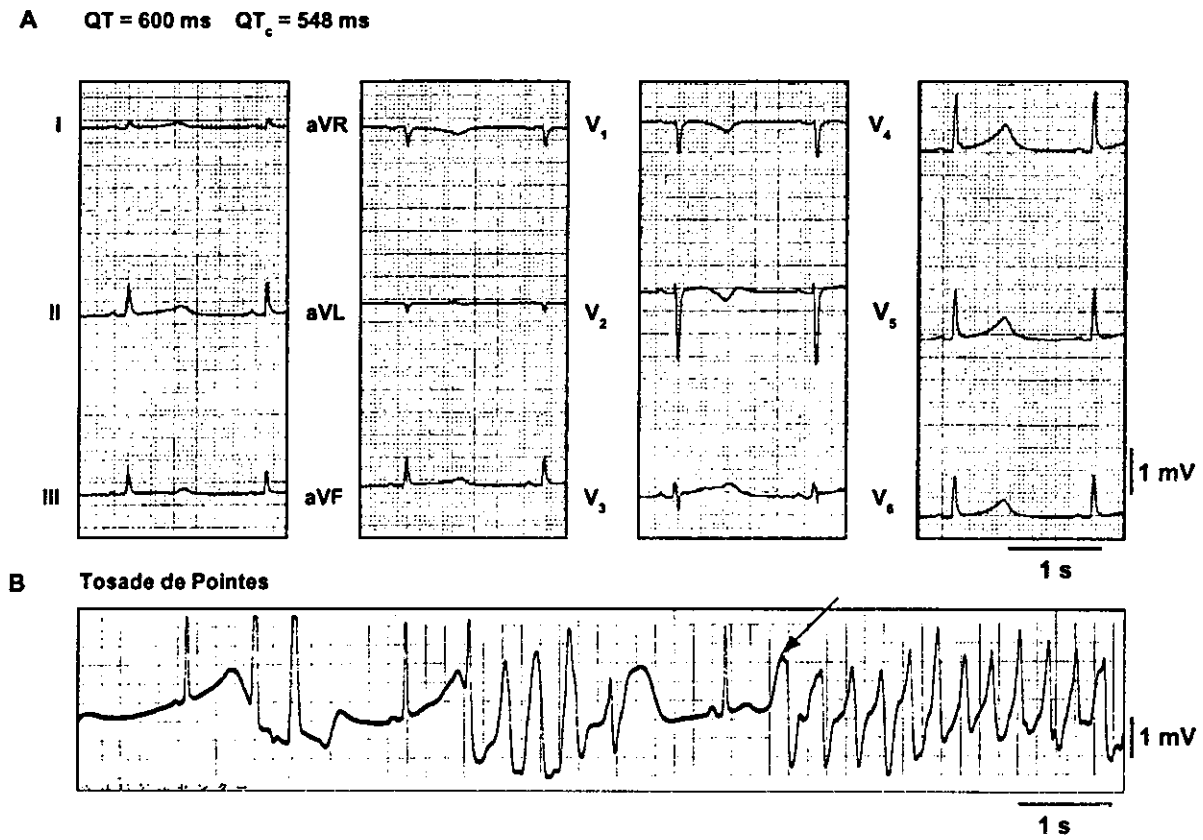

Figure 1. 12-lead electrocardiogram and TdP in a patient with LQT2 syndrome. (A) Remarkable QT prolongation (QT_c interval = 548 ms) and a low amplitude T wave with a notched configuration are seen. **(B)** TdP was induced following typical short-long-short initiating sequence.
QT_c: Corrected QT interval; TdP: Torsade de Pointes

action potentials from epicardial, mid-myocardial (M), endocardial and Purkinje cells are simultaneously recorded together with a pseudo-ECG along the same axis, permitting a correlation between transmembrane and ECG activity. The data from the wedges showed that currents flowing down voltage gradients on either side of the M region underlie the T wave in the ECG, at least in unipolar left precordial leads (V_4–V_6), reflecting the potentials of the left ventricular free wall. The interplay between these opposing currents determines the morphology, height and width of the T wave as well as its duration. In the normal T wave, repolarization of the epicardial action potential is earliest and coincides with the peak of the T wave in the ECG, whereas that of the longest M cell action potential is the last and coincides with the end of the T wave. The repolarization of the endocardial cells is usually between those of the epicardial and the M cells.

The action potential duration (APD) and the morphology of the action potential plateau are modulated differently in each cell type by a defect in the ion channel function caused by mutations in each genotype of the LQTS. Therefore, a variety of T wave morphologies and different QT intervals are expected in each genotype. Moss and colleagues initially suggested the genotype-specific T wave morphology in LQT1, LQT2 and LQT3 patients of the International Long-QT Syndrome Registry (FIGURE 2) [18]. LQT1 patients often show broad-based prolonged T waves, while low-amplitude T waves with a notched or bifurcated configuration are more commonly observed in LQT2 patients. Late-appearing T waves with a long isoelectric ST-segment are characteristic in LQT3 patients. However, the T wave morphology and QT interval are dynamic, waxing and waning from day to day, and are modulated by a variety of factors, such as heart rate, electrolytes and autonomic tone. Takenaka and colleagues recently reported that exercise testing further elicits broad-based T waves in LQT1 patients and notched T waves in LQT2 patients, even though the characteristic T wave patterns are not observed in the resting ECG [19]. The more rare LQTS forms (LQT5 and LQT6), for which mutations in the β-subunits are responsible, appear to have a less expressive manifestation in the ECG. The TU abnormalities including biphasic T waves after preceding long pauses have been reported in LQT4 and LQT7 [7,8].

The cellular basis for the characteristic T wave patterns in the LQT1, LQT2 and LQT3 syndromes has been demonstrated by pharmacological LQTS models employing arterially perfused wedge preparations [14,20–26]. The data suggested that differences in the time course of repolarization of the epicardial,

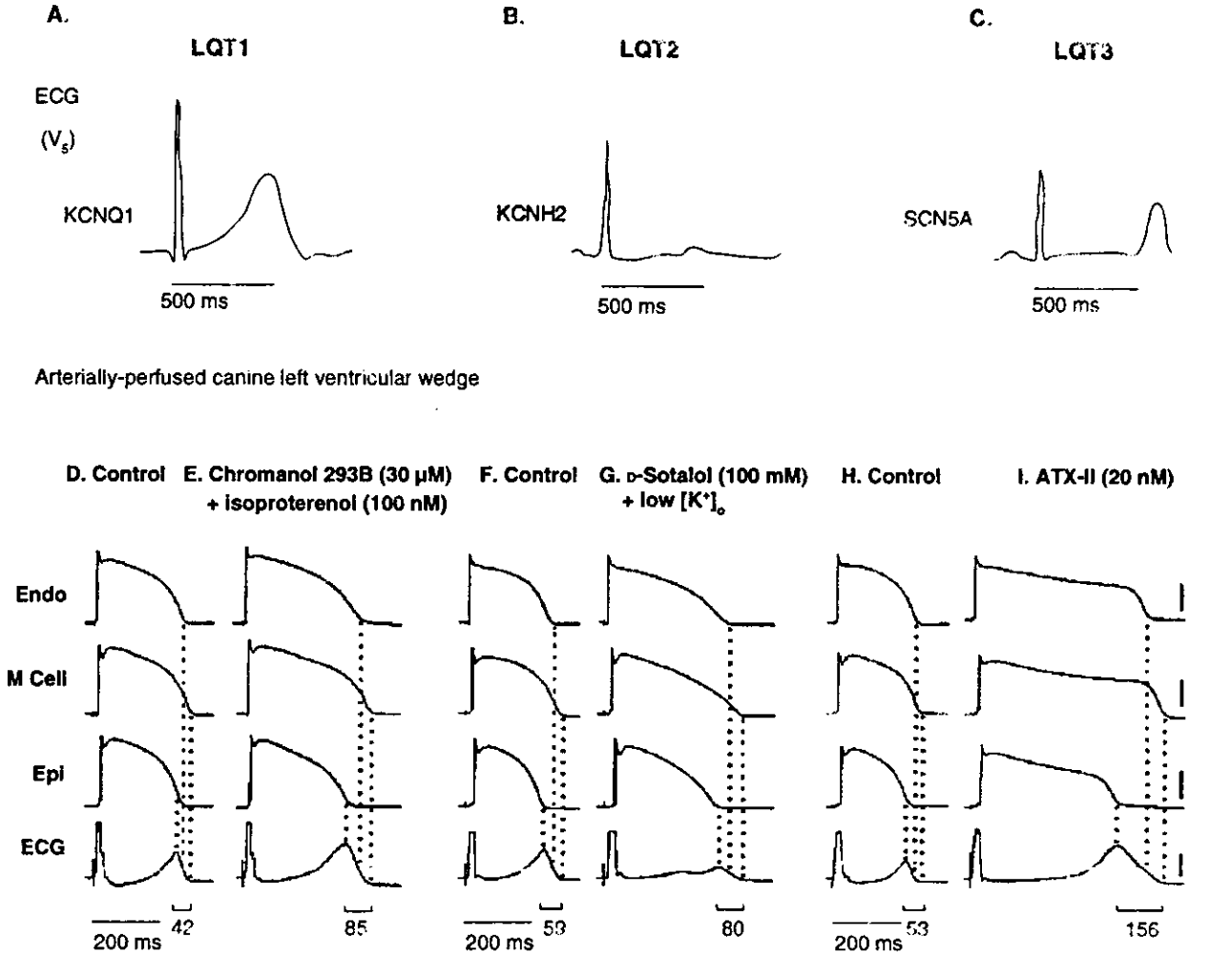

Figure 2. Cellular basis of abnormal T wave patterns in LQT1, LQT2 and LQT3 syndrome. Panels A–C illustrate electrocardiographic lead V_5 recorded in patients with LQT1, LQT2 and LQT3 syndrome. **Panels D – I** illustrate transmembrane action potentials recorded simultaneously from endocardial (Endo), M and epicardial (Epi) cells together with a transmural ECG at a BCL of 2000 ms in the three models of the arterially-perfused canine wedge preparations. Pharmacologic models mimic the phenotypic appearance of the abnormal T waves in all three models. Modified from [20,21] with permission.
BCL: Basic cycle length; ECG: Electrocardiogram; Endo: Endocardial; Epi: Epicardial; M: Mid-myocardial.

M cells and endocardial cells give rise to voltage gradients responsible for the abnormal T wave patterns in all three genotypes of LQTS (FIGURE 2). Chromanol 293B, a specific I_{Ks} blocker, is used to mimic the LQT1 syndrome and isoproterenol, a β-adrenergic agonist, is used to assess the influence of the β-adrenergic system [21,25,26]. I_{Ks} block alone produces a homogeneous prolongation of repolarization in the three cell types. The addition of isoproterenol abbreviates the APD in the epicardial and endocardial cells but not in the M cells, resulting in a dramatic augmentation of transmural dispersion of repolarization (TDR) and a broad-based T wave (FIGURES 2A & 2E). D-sotalol, an I_{Kr} blocker, in the presence of hypokalemia is used to mimic the LQT2 syndrome [20,25,26]. I_{Kr} block produces a more preferential APD prolongation in the M cells than that in the epicardial or endocardial cells and a slowing of Phase 3 of the action potential in all three cell types, resulting in a large TDR and a low-amplitude T wave with a notched or bifurcated appearance (FIGURES 2B & 2G). ATX-II, which augments late I_{Na}, is used to mimic the LQT3 syndrome [20,23,25,26] ATX-II produces a greater prolongation of the APD in the M cells than that in the other cell types, thus causing a sharp rise in the TDR. ATX-II also produces a relatively large effect on the APD in the epicardial and endocardial cells, resulting in a marked delay in the onset of the T wave consistent with the late-appearing T wave pattern (FIGURE 2C & 2I).

Genotype-specific triggers for cardiac events

Recent evidence has suggested genotype-specific triggers for cardiac events in the LQT1, LQT2 and LQT3 syndromes [27–30]. Schwartz and coworkers have reported that most (62%) cardiac events occur during exercise in LQT1 patients and that very few events (3%) occur during sleep/rest [30]. Swimming is reported to be a specific trigger in the LQT1 syndrome [29]. In sharp contrast with the pattern shown in LQT1 patients, the majority

(39%) of cardiac events occur during sleep/rest, and exercise-related cardiac events are rare (13%) in LQT3 patients [30]. LQT2 patients show an intermediate pattern, with cardiac events occurring similarly during exercise (13%) and during sleep/rest (15%) [30]. A sudden startle in the form of an auditory stimulus (e.g., telephone ring, alarm clock and ambulance siren) is a specific trigger of cardiac events in LQT2 patients [28]. The basis of the genotype-specific triggers can be explained by the genotype-specific response of repolarization to sympathetic stimulation in the LQT1, LQT2 and LQT3 syndromes.

Differential sensitivity to sympathetic stimulation between genotypes

Data from the LQTS models using arterially perfused wedges suggested a differential cellular effect of sympathetic stimulation on repolarization in the three genotypes of LQTS [17,21,25]. In the LQT1 model with I_{Ks} block, β-adrenergic stimulation with isoproterenol prolongs the QT interval and the APD of the M cells but abbreviates those of the epicardial and endocardial cells, resulting in a persistent increase in the QT interval and the TDR [25]. The persistent increase in the QT interval and the TDR during β-adrenergic stimulation is consistent with the greater sensitivity of LQT1 patients to sympathetic stimulation. In the LQT2 model with I_{Kr} block, isoproterenol initially prolongs and then abbreviates the QT interval and the APD of the M cells to the control level, whereas the APD of the epicardial and endocardial cells is always abbreviated, leading to a transient increase in the QT interval and the TDR [25]. The transient increase in the QT interval and the TDR following an increase in sympathetic activity may explain why cardiac events in LQT2 patients generally occur following a startle, especially in a state of sleep. In the LQT3 model with an augmentation of late I_{Na}, isoproterenol produces a persistent abbreviation of the QT interval and the APD of the three cell types, resulting in a persistent decrease in the QT interval and the TDR [25]. The protective effects of β-adrenergic stimulation on repolarization are concordant with the observation that cardiac events occur more often during sleep/rest, when sympathetic tone is expected to be low in LQT3 patients.

Clinically, our group and others have demonstrated the differential response of the QT interval to sympathetic stimulation with adrenaline infusion or exercise testing [31,32]. Noda and coworkers recently reported that dynamic response of the corrected QT (QT_c) interval to intravenous adrenaline (0.1 μg/kg bolus + 0.1 μg/kg/min) was apparently different between LQT1, LQT2 and LQT3 patients (FIGURE 3) [31]. In LQT1 patients, the QT_c interval is dramatically prolonged at the peak adrenaline effect when the heart rate is maximally increased and the QT_c remains prolonged at the steady-state adrenaline effect (FIGURE 3A). Adrenaline also prolongs the QT_c interval markedly at the peak adrenaline effect in LQT2 patients but shortens it close to the baseline levels at the steady-state adrenaline effect (FIGURE 3B). In LQT3 patients, the QT_c prolongation at the peak adrenaline effect is much less pronounced than that in LQT1 and LQT2 patients and the QT_c is shortened below the baseline levels at the steady-state adrenaline effect (FIGURE 3C). Ackerman and colleagues also used low-dose adrenaline infusion and demonstrated paradoxical QT prolongation during adrenaline infusion in LQT1 patients but not in LQT2 or LQT3 patients [32]. Tanabe, Shimizu and colleagues recorded an 87-lead body surface ECG and suggested that adrenaline infusion produces a greater increase in both the corrected $T_{peak-end}$ interval reflecting TDR and the dispersion of QT_c reflecting spatial dispersion of repolarization (SDR) in LQT1 patients than in LQT2 patients, further explaining why LQT1 patients are more sensitive to sympathetic stimulation [33,34]. Takenaka and colleagues reported that sympathetic stimulation with treadmill exercise testing produces a significant increase in the QT_c interval and the corrected $T_{peak-end}$ interval in LQT1 patients but not in LQT2 patients [19]. Viitasalo and coworkers analyzed the $T_{peak-end}$ interval by Holter recording in LQT1 and LQT2 patients and demonstrated abrupt increases in the $T_{peak-end}$ at elevated heart rates when sympathetic tone seems to be increased in only LQT1 patients [35]. Overall, these clinical data may explain why the triggers for cardiac events are genotype-specific in the LQT1, LQT2 and LQT3 syndromes.

Role of provocative test in the LQTS

It has long been known that the clinical ECG diagnosis could overlook some patients genetically affected with LQTS. In other words, some genetically affected LQTS patients may have a normal or borderline QT interval but harbor a lethal arrhythmogenic substrate, especially in the LQT1 syndrome. This finding strongly points to the need of new diagnostic tools to unveil nonpenetrant mutation carriers of LQTS (concealed LQTS). Provocative tests using catecholamine or exercise testing have long been considered to unmask such concealed LQTS patients. We recently reported that an adrenaline test significantly improves the sensitivity of ECG diagnosis in concealed LQT1 patients with a normal or borderline QT interval [36]. The identification of individuals with concealed LQT1 is of major importance as it would enable us to limit exposure of these individuals to potentially dangerous conditions, such as participation in competitive sport and use of drugs known to prolong repolarization, thus reducing the risk of life-threatening cardiac arrhythmias.

Our preliminary data also suggested that the adrenaline test may have a diagnostic value in predicting the genotype of the LQT1 and LQT2 syndromes, the two most frequent genetic variants, as well as in improving clinical diagnosis of concealed LQT1 and LQT2 patients [37]. Since molecular diagnosis is still unavailable to many institutes and requires costly and time-consuming procedures, genotype prediction of the LQT1 and LQT2 syndrome by the adrenaline test would facilitate molecular screening by targeting suspected genes at the initial study.

Genotype-specific therapy

β-blocker therapy and limiting exercise were long believed to be the first line of therapy in most patients with congenital LQTS until genetic linkage analysis became available [4]. A direct link

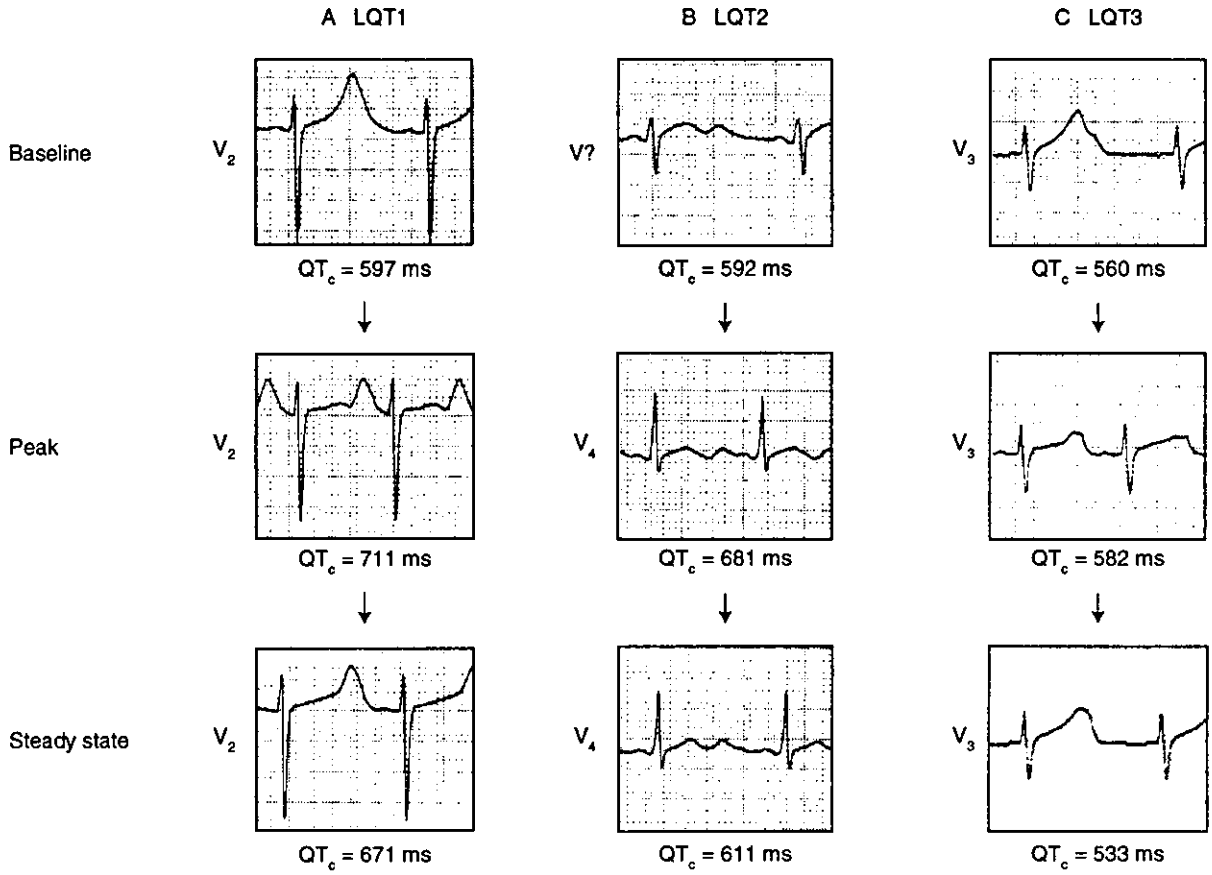

Figure 3. Differential response of the QTc interval to sympathetic stimulation with adrenaline infusion in patients with LQT1, LQT2 and LQT3 syndromes. (A) The QT_c interval is remarkably prolonged at the peak adrenaline effect (597–711 ms) and remains prolonged at the steady-state adrenaline effect (671 ms) in LQT1 patient. **(B)** The QT_c interval is also prominently prolonged at the peak adrenaline effect (592–681 ms) in LQT2 patient but is shortened close to the baseline level at the steady-state adrenaline effect (611 ms). **(C)** The QT_c interval is slightly prolonged at the peak adrenaline effect (560–582 ms) but much less than those in LQT1 and LQT2 patients and is shortened below the baseline level at the steady-state adrenaline effect (533 ms) in LQT3 patient.
QT_c: Corrected QT interval.

between mutations in the ion channel genes and each genotype has made possible the advent of genotype-specific therapies for congenital forms of LQTS. Schwartz and coworkers have shown that sodium channel block with mexiletine or rapid heart rate is much more effective in abbreviating the QT interval in LQT3 patients than in LQT2 patients [38]. Exogenously administered potassium has been reported to correct repolarization abnormalities in LQT2 patients with I_{Kr} defect and acquired form of LQTS patients [39]. Intravenous administration of a potassium channel opener, nicorandil, has been shown to improve repolarization abnormalities recorded on monophasic action potential (MAP) in LQT1 patients with I_{Ks} defect [40]. Although these clinical studies examined the effects of antiarrhythmic agents and rapid pacing on the QT interval and MAP duration, they did not assess the actions of these treatments on TDR or on the relative risk for development of TdP. In other words, abbreviation of the QT interval and the MAP duration by these interventions is not necessarily consistent with their efficacy in decreasing arrhythmic risk or sudden cardiac death. The LQTS models involving the arterially perfused wedge preparations enable us to quantify these parameters. The available data are presented in (TABLE 1).

β-blocker therapy

β-blockers are widely reported to reduce the incidence of syncope and sudden cardiac death in patients with congenital LQTS [4]. Patients with the LQT1 genotype are reported to be most responsive (80%) to β-blockers [30]. Moderate effectiveness is reported in LQT2 patients, while the effectiveness of β-blockers in LQT3 patients is unknown, largely because LQT3 patients are very rare. In the LQT1 model involving the wedges, a β-blocker, propranolol, completely inhibits the influence of isoproterenol to increase TDR and to produce spontaneous as well as stimulation-induced TdP, suggesting

Table 1. Genotype-specific therapy in LQT1, LQT2 and LQT3 syndromes.

	LQT1 (LQT5) 293B + isoproterenol	LQT2 (LQT6) D-sotalol	LQT3 ATX-II
Sensitivity to sympathetic stimulation	+++++ (Sustained ↑ in TDR)	+++ (Transient ↑ in TDR)	- (↓ in TDR)
Torsade de pointes (clinic)	Exercise-related (swimming)	Startle (alarm clock)	Sleep/rest
Effectiveness of β-blockers	+++++	+++	-
Effectiveness of late Na^+ channel blockers	+++	++++	+++++
Effectiveness of K^+ channel openers	++	++	-
Effectiveness of Ca^{2+} channel blockers	+++	+++	++?
Pacemaker therapy	++	++	+++++

TDR: Transmural dispersion.

the dramatic effectiveness of β-blockers in this genotype [21,25]. In the LQT2 model, propranolol completely suppresses the influence of isoproterenol to transiently increase the TDR and the incidence of TdP, indicating that β-blockers may be protective in LQT2 patients [25]. In contrast, propranolol shows no protective effects in the LQT3 model, consistent with the observation that LQT3 patients are most likely to develop TdP during sleep/rest [25]. However, systematic clinical evaluation of the actions of β-blockers in LQT3 patients is needed to define whether β-blockers are effective or arrhythmogenic in this rare genotype.

Late sodium channel blockers

Late sodium channel blockers, such as mexiletine or lidocaine, a class IB agent, display rapid dissociation kinetics from the sodium channel and are known to abbreviate the QT interval much more in LQT3 patients than in LQT1 or LQT2 patients [38]. However, the extent to which sodium channel blockers may be effective in preventing sudden death in any of the LQTS genotypes is not known. The LQTS models using the wedges have shown that mexiletine is more effective in abbreviating the QT interval in the LQT3 model than in either the LQT1 or LQT2 model [20,21], concordant with the clinical findings. More importantly, mexiletine reduces TDR and prevents the development of TdP in the LQT1 and LQT2 models as well as in the LQT3 model [20,21]. These experimental findings suggest that while late sodium channel blockers are a first line of treatment in LQT3 patients, they may warrant further consideration as a conjunctive therapeutic approach in LQT1 and LQT2 patients.

Potassium channel openers

Nicorandil, a potassium channel opener, has been shown to suppress early afterdepolarizations (EADs) and to abbreviate MAP duration and QT interval in LQT1 patients, suggesting that it may be of therapeutic value in congenital LQT1 patients [40]. The data from the wedge preparations have suggested that intravenous nicorandil is capable of abbreviating the QT interval, reducing TDR and preventing TdP when LQTS is secondary to reduced I_{Ks} (LQT1) or I_{Kr} (LQT2) but not when it is due to augmented late I_{Na} (LQT3), although relatively high concentrations of nicorandil are required [26].

Calcium channel blockers

Several clinical studies using standard 12-lead ECG and MAP recording suggested that verapamil, a calcium channel blocker, may be of therapeutic value in congenital LQTS syndrome [41]. More recently, our preliminary data from the wedge preparations have indicated that verapamil is effective in decreasing the QT interval and the TDR and in suppressing EADs and subsequent TdP in a model of LQTS [42].

Pacemaker therapy

Schwartz and colleagues initially reported that increases in heart rate abbreviate the QT interval in LQT3 patients much more than that in LQT2 patients [38]. Experimental data employing wedges have shown that the APD-, QT- and TDR-rate relations are generally much steeper in the LQT3 model than in either the LQT1 or LQT2 model, possibly due to slow kinetics of reactivation of late I_{Na} [20,21]. The APD rate relations in the LQT1, LQT2 and LQT3 models, however, are all steeper than in the controls. These results suggest that, although pacemaker therapy is likely to be most effective in LQT3 patients, its usefulness in LQT1 and LQT2 patients should not be discounted.

Conclusions & expert opinion

Seven forms of congenital LQTS caused by mutations in genes of ion channels or membrane adapters have been identified to date. The genotype–phenotype correlation, especially in LQT1, LQT2 and LQT3 forms, enables us to manage and treat genotyped patients more effectively. The differential response of the QT interval to sympathetic stimulation with adrenaline infusion or exercise testing has been demonstrated between

LQT1, LQT2 and LQT3 patients. Therefore, the provocative test using adrenaline or exercise testing may have a diagnostic value to predict the genotype of LQT1, LQT2 and LQT3 syndromes. Moreover, the provocative test may also improve the clinical diagnosis of concealed LQTS patients, especially LQT1 patients, who have normal or borderline QT interval in the resting ECG. A direct link between mutations in the ion channel genes and each genotype has made possible the advent of genotype-specific therapies for congenital LQTS. LQT1 patients are the most responsive to β-blockers. Moderate effectiveness of β-blockers is reported in LQT2 patients, while β-blockers are not effective or may be arrhythmogenic in LQT3 patients. Late sodium channel blockers, such as mexiletine, are a first line of treatment in LQT3 patients and may warrant further consideration as a conjunctive therapeutic approach in LQT1 and LQT2 patients. Intravenous nicorandil, a potassium channel opener, is a choice of treatment for preventing TdP in LQT1 and LQT2 but not in LQT3 patients, although relatively high concentrations of nicorandil are required. Our preliminary data also suggest that verapamil, a calcium channel blocker, may be of therapeutic value in LQTS patients.

Five-year view

Evaluation of the genotype–phenotype correlation in both experimental and clinical studies during the past several years has made possible the advent of genotype-specific management and therapies for patients with congenital forms of LQTS. More recently, mutation site-specific differences in arrhythmic risk have been examined in each genotype and the mutation site-specific management and therapies may be considered in the near future. On the other hand, no responsible mutations can be identified in 40–50% of patients who are clinically affected with congenital LQTS. Therefore, determining the molecular mechanism for the other unknown genetic determinants of the unsolved LQTS will be of great importance.

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Key issues

- Genetic studies have so far identified seven forms of congenital long QT syndrome (LQTS) caused by mutations in genes of the potassium and sodium channels or membrane adapter located on chromosomes 3, 4, 7, 11, 17 and 21.
- Evaluation of the genotype-phenotype correlation, especially in LQT1, LQT2 and LQT3 patients, is of major importance as it would enable us to manage and treat genotyped patients more effectively.
- The differences in the time course of repolarization of the epicardial, mid-myocardial and endocardial cells across the ventricular wall give rise to voltage gradients responsible for the genotype-specific T wave patterns in LQT1, LQT2 and LQT3 syndromes.
- The basis of the genotype-specific triggers for cardiac events can be explained by the differential response of repolarization to sympathetic stimulation between LQT1, LQT2 and LQT3 syndromes.
- The provocative test using adrenaline or exercise testing may have a diagnostic value to predict the genotype of LQT1, LQT2 and LQT3 syndromes as well as to improve clinical diagnosis of concealed LQTS patients, especially LQT1 patients.
- The genotype-specific therapy has just been applied in the genotyped patients according to the data of experimental and preliminary clinical studies.

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Exercise Stress Test Amplifies Genotype-Phenotype Correlation in the LQT1 and LQT2 Forms of the Long-QT Syndrome

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Background—Experimental studies suggest that the interval between peak and end of T wave (Tpe) in transmural ECGs reflects transmural dispersion of repolarization (TDR), which is amplified by β-adrenergic stimulation in the LQT1 model. In 82 patients with genetically identified long-QT syndrome (LQTS) and 33 control subjects, we examined T-wave morphology and various parameters for repolarization in 12-lead ECGs including corrected QT (QTc; $QT/R\text{-}R^{1/2}$) and corrected Tpe (Tpec; $Tpe/R\text{-}R^{1/2}$) before and during exercise stress tests.

Methods and Results—Under baseline conditions, LQT1 (n=51) showed 3 cardinal T-wave patterns (broad-based, normal-appearing, late-onset) and LQT2 (n=31) 3 patterns (broad-based, bifid with a small or large notch). The QTc and Tpec were 510±68 ms and 143±53 ms in LQT1 and 520±61 ms and 195±69 ms in LQT2, respectively, which were both significantly larger than those in control subjects (402±36 ms and 99±36 ms). Both QTc and Tpec were significantly prolonged during exercise in LQT1 (599±54 ms and 215±46 ms) with morphological change into a broad-based T-wave pattern. In contrast, exercise produced a prominent notch on the descending limb of the T wave, with no significant changes in the QTc and Tpec (502±82 ms and 163±86 ms: n=19) in LQT2.

Conclusions—Tpe interval increases during exercise in LQT1 but not in LQT2, which may partially account for the finding that fatal cardiac events in LQT1 are more often associated with exercise. **(*Circulation*. 2003;107:838-844.)**

Key Words: electrocardiography ■ genetics ■ ion channels ■ long-QT syndrome ■ exercise

Congenital long-QT syndrome (LQTS) is a fatal disease entity caused by various mutations in at least five genes coding cardiac ion channels.[1-2] Mutations in *KCNQ1* and *KCNH2* are most commonly identified and cause LQT1 and LQT2 forms of LQTS. Those mutations induce functional defects in either slow (I_{Ks}: LQT1) or rapid (I_{Kr}: LQT2) component of the delayed rectifier potassium current. In association with inhomogeneous functional modulation of LQTS-related ion channels, distinct phenotypic patterns of T waves have been noted in a respective genotype.[3,4] Moreover, recent studies have suggested differences in the sensitivity of the genotypes to β-adrenergic stimulation.[5,6] In LQT1, cardiac events (arrhythmias and sudden cardiac death) are more frequently associated with enhanced adrenergic factors (physical or emotional stress) than in other forms of LQTS.[7] In this accordance, β-blockers have been reported to be most preventive against cardiac events in LQT1.[7]

Electrophysiological studies with single mammalian ventricular cells demonstrated that β-adrenoceptor stimulation enhances I_{Ks} and L-type Ca current ($I_{Ca,L}$) but not I_{Kr}.[8-11] In LQT1 (reduction in basal I_{Ks}), β-adrenergic stimulation produces a larger prolongation of the QT interval because $I_{Ca,L}$, which is a counterpart of I_{Ks} and carries inward currents, remains intact and increases. In LQT2 (reduction in basal I_{Kr}), phenotypic ECG change may be more prominent at slower heart rate because of its rapid activation properties.[10-14] Exercise stress tests were therefore used to study β-adrenergic modulation on ECG parameters in patients with LQTS who had been identified as either LQT1 or LQT2 and compared with healthy control subjects. In both baseline and exercise conditions, we measured T-wave morphology and repolarization characteristics: QT and Tpeak-end (Tpe).

Methods

Patient Population

The study population consisted of three groups: (1) LQT1 (n=51 from 29 unrelated families), (2) LQT2 (n=31 from 19 unrelated families), and (3) healthy volunteers (n=33) as a control group. We

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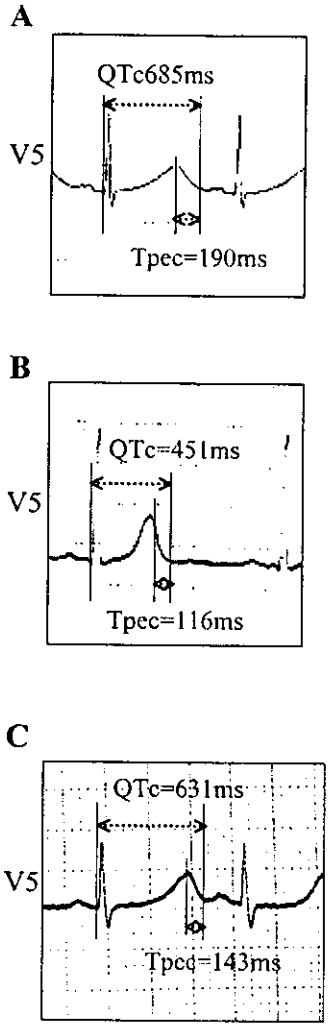

Figure 1. Three typical T-wave patterns in baseline lead V_5 ECGs of LQT1. A, Broad-based T-wave pattern. Both of the QTc and Tpec were prolonged. B, Normal-appearing T-wave pattern. C, Late-onset T-wave pattern. Flat ST segment was especially prolonged.

excluded patients taking any medications that affect the repolarization, including β−blockers, during the study.

DNA Isolation and Mutation Analysis

One hundred eighty-three patients were included for genotyping under the diagnosis of LQTS (135 probands and 48 family members). Genomic DNA was isolated from leukocyte nuclei by conventional methods. The protocol for gene analysis was approved by the institutional ethics committee, and all patients gave informed consent according to the committee's guideline. Screening for mutations of *KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2* was performed with the use of polymerase chain reaction (PCR)/single-strand conformation polymorphism analyses. Briefly, PCR products were heat-denatured with formamide, applied to a 12% polyacrylamide gel, and stained with SYBR Green II (Molecular Probe). For aberrant PCR products, DNA sequencing was conducted with a DNA sequencer (ABI PRISM 320, PE Applied Biosystems). Twenty-two *KCNQ1* and 19 *KCNH2* mutations were identified in 29 unrelated LQT1 and 19 LQT2 probands, respectively. In those LQT1 and LQT2 subtypes, no other LQTS-associated mutations were found.

Identification of T-Wave Pattern

ST-T morphology was evaluated in all 12 ECG leads, and a representative pattern was determined in each case. When different patterns were present in different leads, the most prevalent (present in at least 4 leads including lead V_5 and V_6) was chosen as the representative ECG pattern.

ECG Measurements

Forty-nine patients (30 patients with LQT1 and 19 with LQT2) and 22 healthy control patients were included for the analysis with exercise stress tests.

All subjects were in sinus rhythm, and none had atrioventricular or bundle branch block. Exercise stress tests were performed according to the standard Bruce protocol.[15] Twelve-lead ECGs were recorded at several specific heart rates from the resting state to the maximal stress state by step of ≈10 beats/min. The QT was manually measured as the time interval between QRS onset (Q) and the point at which the isoelectric line intersected a tangential line drawn at the maximal downslope of the positive T wave or at the maximal upslope of the negative T wave (Tend). V_5 and V_6 were used for measurement because they are unipolar leads that reflect the potential from the free wall of the left ventricle.[16,17] The Q-Tpeak (QTp) was defined as the time interval between QRS onset and the point at the peak of the positive T wave or the nadir of the negative T wave. Tpe was then obtained by calculating as QT minus QTp (Figure 1). When the T wave had a biphasic or bifid configuration, the peak of the T wave was defined as the former peak. The latter peak of the positive T wave was designated as a notch (Figure 2). Measurements were performed as the mean of 3 beats in lead V_5. They were corrected to heart rate according to Bazett's method[18]: corrected QT (QTc; $QT/R\text{-}R^{1/2}$) and corrected Tpe (Tpec; $Tpe/R\text{-}R^{1/2}$). During exercise tests, the QT and Tpe were measured at 6 to 12 sampling points and plotted against the corresponding the R-R interval. The QT/R-R and Tpe/R-R were calculated in each exercise test by fitting raw data to the simple linear regression analysis with a commercially available program (Sigma Plot 2001 ver7, SPSS Inc). Measurements were carried out by two investigators who were unaware of subject's

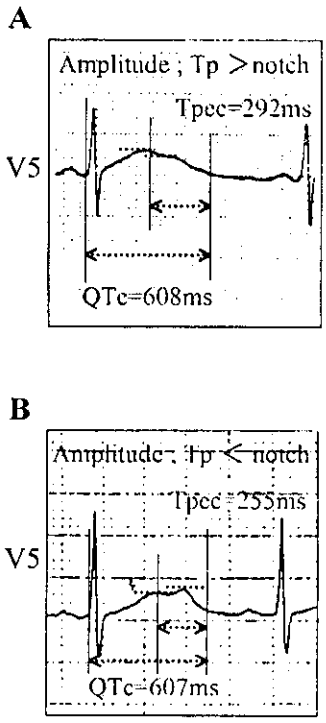

Figure 2. Two typical T-wave patterns identified in baseline lead V_5 ECGs of LQT2. A, Bifid T wave with notch S, which indicates a notch lower than Tpeak. B, Bifid T wave with notch L, which is higher than Tpeak. In bifid T wave, Tpeak (Tp) was defined as the former apex and a notch as the latter apex.

TABLE 1. Comparison of Clinical Characteristics

	LQT1 29 Families			LQT2 19 Families			Control 33 Families		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
No.	15	36	51	12	19	31	17	16	33
Age, y	12±21	31±18	28±20	28±22	33±17	31±18	34±19	30±15	32±17
Symptomatic patients	7	23	30	7	10	17	0	0	0
Onset age, y	8±3*	25±20	21±19	12±12	17±8	15±10	...	...	...
Triggers of syncope	Exercise 13 (Swimming 6) Hypokalemia 3			Sleep 6 Auditory stimuli 5 Bradycardia 1			...	...	...

*P=0.048 between men and women with LQT1.

genetic status. There were no significant differences in measured data between the two (data not shown).

Statistical Analysis

Data are presented as mean±SD. Two-way repeated-measures ANOVA followed by Scheffé's test were used to compare each parameter among 3 groups and a 2-tailed Student's t test to compare measurements at rest and during exercise. A probability value <0.05 was considered significant.

Results

Comparison of Clinical Characteristics

Thirty patients with LQT1 (59%) were symptomatic. Among them, all of the men had the first syncope attack before 16 years of age. In contrast, half of the women had the first syncope at age >16 years. The onset-age of men with LQT1 (8±3 years of age) was significantly lower than that of women (P=0.048).[7] Typical triggers of cardiac events were exercise, especially swimming, and emotional stress in patients with LQT1. Seventeen patients with LQT2 (55%) were symptomatic, triggered by sleep, auditory stimuli, and bradycardia. The onset age did not significantly differ between the two sexes (Table 1).

Baseline ECGs Show Different T-Wave Patterns and Repolarization Parameters

The ECG data in the 3 study groups are summarized in Table 2. There was no significant difference in R-R intervals among the 3 groups, although patients with LQT2 showed a bradycardiac tendency. Baseline QTc and Tpec values in the 2 LQTS groups were significantly longer than those in control patients. At variance with a previous report,[17] the Tpec in LQT2 was significantly longer than that in the LQT1 group.

TABLE 2. Baseline Conditions: ECG Data in LQT1, LQT2, and Control

Genotype (No.)	LQT1 (n=51)	LQT2 (n=31)	Control (n=33)	P
R-R, ms	907±192	976±188	870±80	NS*†
QT, ms	484±82	511±60	358±91	NS*/P<0.001†
QTc, ms	510±68	520±61	402±36	NS*/P<0.001†
Tpe, ms	132±52	191±67	86±20	P<0.001*†
Tpec, ms	143±53	195±69	99±36	P<0.001*†

QTc indicates $QT/RR^{1/2}$; and Tpec, $Tpe/R\text{-}R^{1/2}$.

*Between LQT1 and LQT2, †LQT1 and LQT2 compared with control, respectively.

LQT1

Three cardinal T-wave patterns were identified: broad-based T (Figure 1A), normal-appearing T (Figure 1B), and late-onset T (Figure 1C). The broad-based T-wave pattern represented a single and smooth T wave and was seen in 43% of patients with LQT1. The normal-appearing T-wave pattern with small but significant prolongation of QT was seen in 28%. The late-onset T wave characterized by a prolonged ST segment was seen in 25%.

LQT2

Most of patients with LQT2 showed two types of bifid T-wave patterns: bifid T wave with a small notch (designated as notch S, Figure 2A) and the one with a large notch (designated as notch L, Figure 2B). The former pattern was observed in 33% and the latter seen in 25% of patients with LQT2. However, the broad-based T wave was also seen in 34% at rest.

Exercise Produces Differential Response in T-Wave Morphology and Repolarization Parameters

Forty-nine patients (30 patients with LQT1 and 19 with LQT2) and 22 healthy control patients were included for the analysis with exercise stress tests. Table 3 summarizes R-R, QTc, and Tpec values in the three groups at rest and maximal stress point. All baseline R-R, QTc and Tpec showed values similar to those evaluated in total study patients (Table 2), indicating that these subsets of patients are representative of each group. Mean ages of study patients were not significantly different between LQT1 and LQT2 subgroups (23.6±16.5 versus 25.2±13.1 years, NS).

T-Wave Morphology

In exercise, the patients with LQT1 with a broad-based T wave revealed a prominent prolongation in both QTc and Tpec without changing the T-wave morphology (Figure 3A). On the contrary, half of the late-onset T and most of the normal-appearing T patterns were changed to the broad-based pattern, resulting that 23 of 30 patients with LQT1 showed the broad-based pattern during exercise (Figure 4A). The positive predictive value (PPV) of a broad-based T wave at