When should a check for LQTS be considered?

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Key Words: Arrhythmia, Diagnosis, Long-QT syndrome, Genotype, Genes, Genotype, Molecular screening,

Phenotype, and Sympathetic stimulation.

ABSTRACT

Backgrounds The congenital form of long-QT syndrome (LQTS), especially LQT1 syndrome, is associated with high vulnerability to sympathetic stimulation and appears with incomplete penetrance.

Methods The 12-leads ECG parameters before and after epinephrine infusion were compared between 19 LQT1 mutation carriers with a baseline corrected QT (QTc) interval of ≥ 460ms (Group I), 15 LQT1 mutation carriers with a QTc of < 460 ms (Group II), 12 non-mutation carriers (Group III), and 15 controls (Group IV).

Results The mean QTc interval among 12-leads before epinephrine were significantly longer in Group I than in other 3 groups. Epinephrine (0.1 μg/kg bolus + 0.1 μg/kg/min) prolonged the QTc significantly in Groups I and II, but not in Groups III and IV, thus the QTc after epinephrine was longer in Groups I and II than in Groups III and IV. The sensitivity (penetrance) and specificity of the QTc measurements to identify mutation carriers were 59 % (20/34) and 100 % (27/27) respectively before epinephrine. The sensitivity was substantially improved to 91 % (31/34) without the expense of specificity (100 %, 27/27) after epinephrine. Our preliminary data suggest that the penetrance in LQT2 and LQT3 syndromes is relatively high; 90 % in LQT2 families and 85 % in LQT3 families, and that epinephrine test further improves the sensitivity of diagnosis in LQT2 syndrome.

Conclusions The present study and our preliminary data suggests that molecular screening (or epinephrine provocative test) could be applied to detect non-penetrant mutation carriers or increase the sensitivity of ECG diagnosis of LQTS, especially the LQT1 syndrome, thus reducing the risk of life threatening cardiac arrhythmias and managing the LQTS patients effectively.

INTRODUCTION

The congenital long QT syndrome (LQTS) is characterized by QT prolongation in the electrocardiogram (ECG) and polymorphic ventricular arrhythmia, Torsade de Pointes (TdP), and is caused by mutations in genes of the potassium and sodium channels or membrane adapter located on chromosomes 3, 4, 7, 11, 17 and 21.[1-5] 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,[6,7] 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.[8,9] Mutations in *SCN5A* result in an increase in the late sodium current (I_{Na}) responsible for the LQT3.[10] Mutations in *KCNJ2* decrease the inward rectifier potassium current (I_{K1}), and cause a prolonged QT interval and periodic paralysis, underlying the LQT7 syndrome.[4] 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.[5] Among the LQT1, LQT2 and LQT3 forms, which account for more than two thirds of genotyped patients, cardiac events are more often associated with sympathetic stimulation (physical or emotional stress) in LQT1 than in either LQT2 or LQT3 syndrome.[11-14] Concordant with the influence of sympathetic stimulation, β-blockers are the most effective in LQT1 syndrome.[11,15] Therefore, genotyping of LQTS is of major importance as it would enable us to manage and treat patients more effectively. Moreover, LQTS patients, especially LQT1, are frequently manifest with variable expressivity and incomplete penetrance.[16] Improvement of the sensitivity of ECG diagnosis would allow to implement prophylactic measures such as avoidance of strenuous physical activity and avoidance of QT prolonging drugs that may precipitate life threatening events in silent mutation carriers, especially the young population. Since molecular diagnosis is still unavailable to many clinical centers, clinical tools to improve the sensitivity of the ECG diagnosis of LQTS would be required. We recently performed a systematic evaluation of the sensitivity (penetrance) of LQT1 syndrome by the ECG diagnostic

criteria, and of the diagnostic value of epinephrine infusion in unmasking non-penetrant mutation carriers with LQT1 syndrome.[17] In this article, we present these data and our recent unpublished data, and discuss when we should consider a check for LQTS by clinical and/or molecular diagnosis.

METHODS (Figure 1)

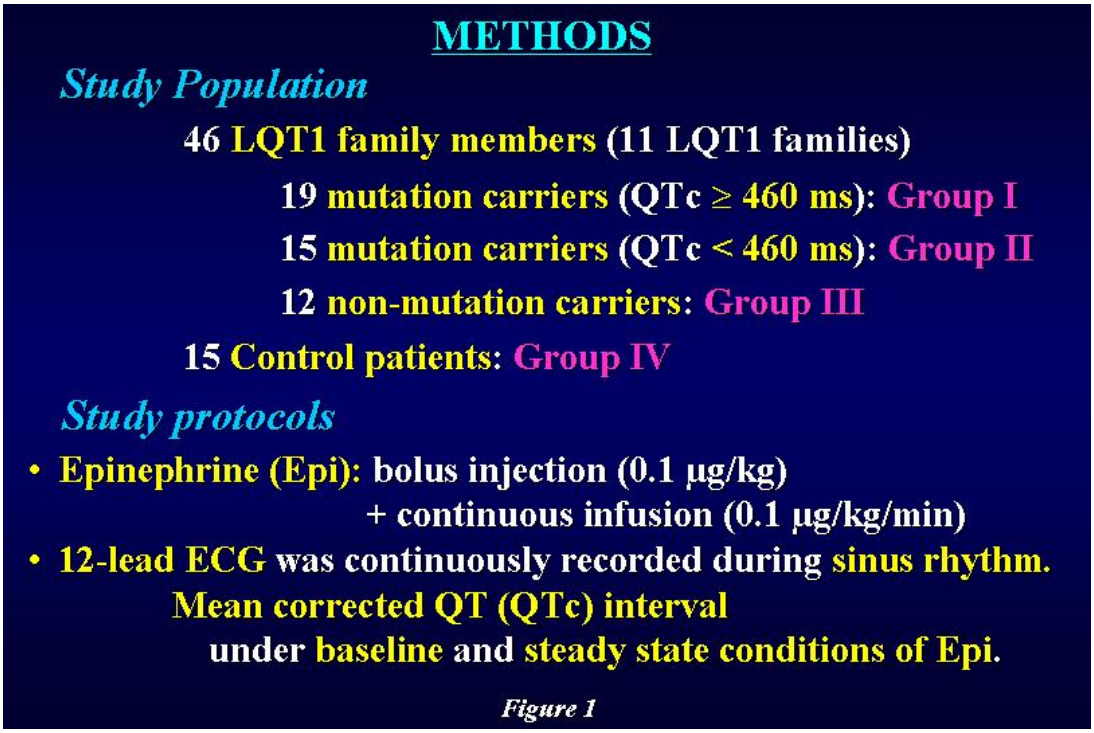

Figure 1. Methods of the present study.

Patient Population

Study population consisted of a total of 46 family members from 11 families affected with LQT1 syndrome. Eleven families included 19 LQT1 mutation carriers with a prolonged QTc interval of ≥ 460 ms (Group I), 15 LQT1 mutation carriers with a normal or borderline QTc of < 460 ms (Group II), and 12 non-mutation carriers (Group III) (Figure 1). As a control group (Group IV), fifteen healthy volunteers were enrolled (Figure 1). LQTS-

affected individuals were based on the ECG diagnostic criteria by Keating et al.,[18] including a QTc ≥ 470 ms in asymptomatic individuals and a QTc > 440 ms for males and > 460 ms for females associated with ≥ 1 of the following: (1) stress-related syncope, (2) documented Torsade de Pointes, or (3) family history of early sudden cardiac death. The LQTS score was also calculated using the diagnostic criteria by Schwartz et al..[19]

12-Leads ECG Recording and Measurement

All protocols were reviewed and approved by our Ethical Review Committee, and informed consent was obtained from all patients or their parents when the patients were less than 20 years of age. Standard 12-leads ECG was recorded with an FDX6521 (Fukuda Denshi Co., Tokyo, Japan) in the supine position without antiarrhythmic medications including β-blockers. These ECG data were digitized using analog-digital converters with a sampling rate of 1,000 samples/second/channel.

Measurement of the ECG parameters was performed in a blinded fashion as to genotype status against 5-averaged QRS complex by an off-line computer with the analysis program developed by our institution.[17]

The QT 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 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 (pathological U wave) appeared, it was included as part of the measurement of the QT interval, but a normal U wave, which was apparently separated from a T wave, was not included. The 5 QRS complexes were averaged first for each lead. Then, the QT interval was measured automatically from all 12-leads ECG, corrected by Bazett's method (QTc), and averaged among all 12-leads.

Epinephrine Administration

A bolus injection of epinephrine (0.1 μg/kg), an α+β-adrenergic agonist, was immediately followed by continuous infusion (0.1 μg/kg/min) (Figure 1). The 12-leads electrocardiogram was continuously recorded during sinus rhythm under baseline conditions and usually for 5 minutes under epinephrine infusion. The effect of

epinephrine on both RR and QT intervals reached steady state conditions usually 2-3 minutes after the start of epinephrine. Epinephrine infusion for more than 5 minutes was avoided, and ECG monitoring was continued for further 5 minutes after epinephrine infusion for possible occurrence of TdP. The ECG data were collected under baseline conditions and at steady state conditions of epinephrine (3-5 minutes after the start of epinephrine), and compared between the 4 groups (Figure 1). 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 values, except for those shown in the figures, which are expressed as mean ± SEM values. 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). Repeated-measures one-way analysis of variance followed by Scheffe`s test was 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 below 0.05 was considered to indicate significant.

RESULTS

Clinical and Molecular Diagnosis

Under baseline conditions, all 19 Group I patients could be diagnosed as having LQTS by the ECG diagnostic criteria; 18 patients had a score ≥ 4 (high probability of LQTS), and the average score of the 19 patients was 5.5±1.3 points. One Group II patient could be diagnosed as having LQTS; all 15 Group II patients had a score ≤ 2 and the average score of 0.7±0.7 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 (penetrance) and specificity for identifying mutation carriers among the family members and controls were 59 % (20/34) and 100 % (27/27), respectively, by using the ECG diagnostic criteria by Keating et

al..[18] They were 53 % (18/34) and 100 % (27/27) when an LQTS score ≥ 4 was used[19] (Table I). Among the 34 mutation carriers in the Groups I and II, 15 patients were symptomatic (Group I; 14/19, Group II; 1/15), and 19 patients were asymptomatic.

Diagnostic Accuracy of Clinical Parameters

	Baseline		Epinephrine	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
ECG criteria*	20/34 (59)	27/27 (100)	31/34 (91)	27/27 (100)
Score ≥ 4**	18/34 (53)	27/27 (100)	25/34 (74)	27/27 (100)
Δ QTc with Epi ≥ 30 ms			31/34 (91)	27/27 (100)

* A QTc > 470 ms in asymptomatic individuals and a QTc > 440 ms for males and > 460 ms for females associated with ≥ 1 of the following: (1) stress-related syncope, (2) documented TdP, or (3) family history of early sudden cardiac death.

** Diagnostic criteria by Schwartz et al.

Table 1

QTc Response to Epinephrine in the 4 Groups

Figure 2 illustrates marked QT prolongation and subsequent TdP induced by epinephrine infusion in a 14-year old boy who had been resuscitated from cardiac arrest during swimming and was referred to our hospital. His baseline 12-leads ECG showed borderline QTc interval (442 ms, Figure 2A), but epinephrine infusion prolonged the QTc remarkably (585 ms), leading to spontaneously terminating TdP (Figure 2B). 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.

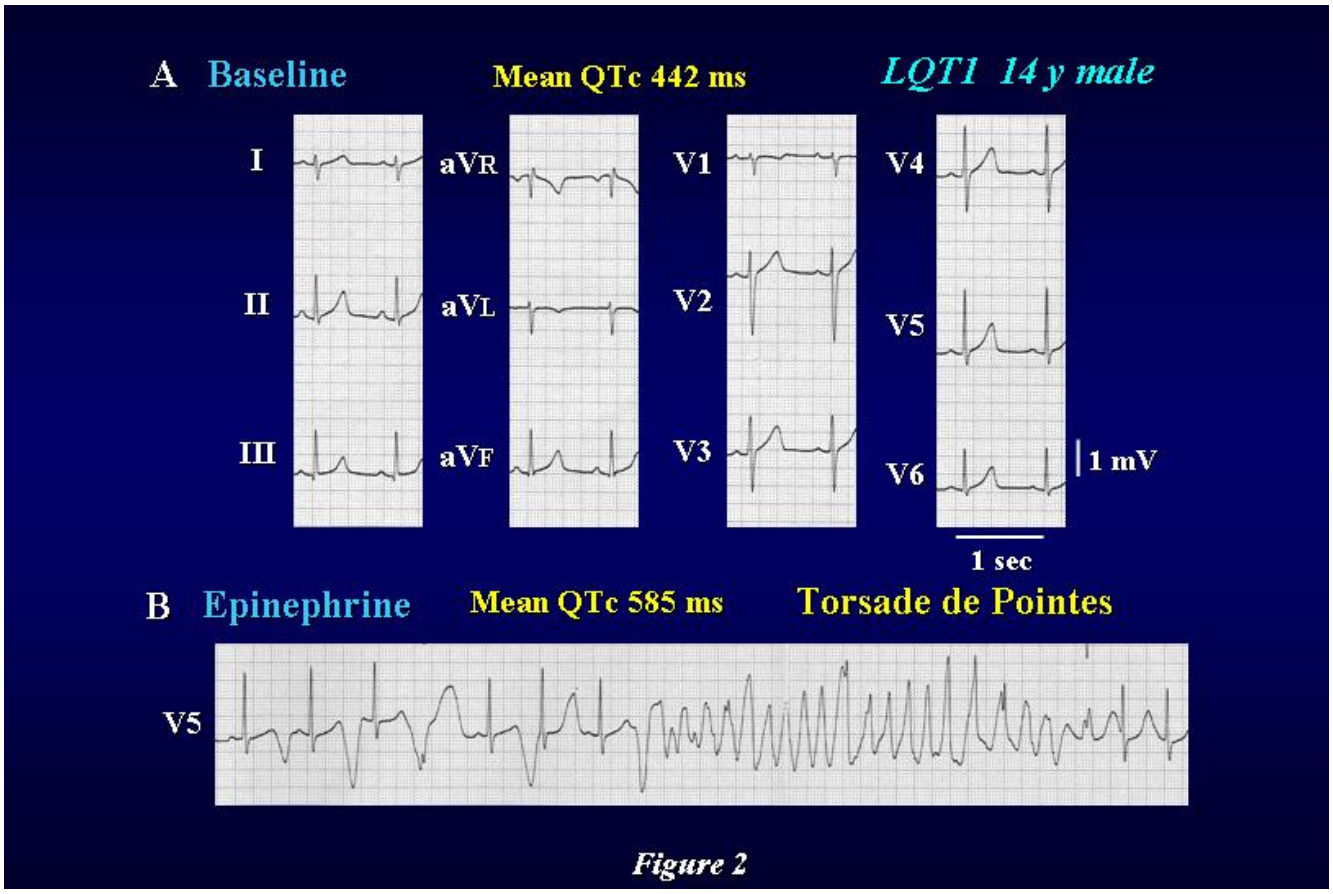

Figure 2. Twelve-leads ECGs under baseline condition (**A**) and a V5 lead ECG during epinephrine infusion (2 minutes after start of epinephrine) (**B**) in a 14 years boy affected with LQT1 syndrome. The mean corrected QT (QTc) interval was dramatically prolonged by epinephrine from 442 ms to 585 ms, resulting in T wave alternans and spontaneously terminating Torsade de Pointes.

Figure 3 illustrates 6-precordial lead ECGs under baseline conditions and during epinephrine infusion in the 4 group patients. In the Group I patient, the baseline QTc interval was prolonged (516 ms), and epinephrine produced a marked prolongation in the mean QTc (586 ms) (Figure 3A). Although the baseline QTc was normal in the Group II patient, it was prolonged from 435 ms to 516 ms (Figure 3B). The baseline QTc was also normal in the Group III and Group IV patients, and no significant changes were produced by epinephrine in both group III (from 402 ms to 349 ms) and IV (from 381 ms to 392 ms) patients (Figures 3C and 3D).

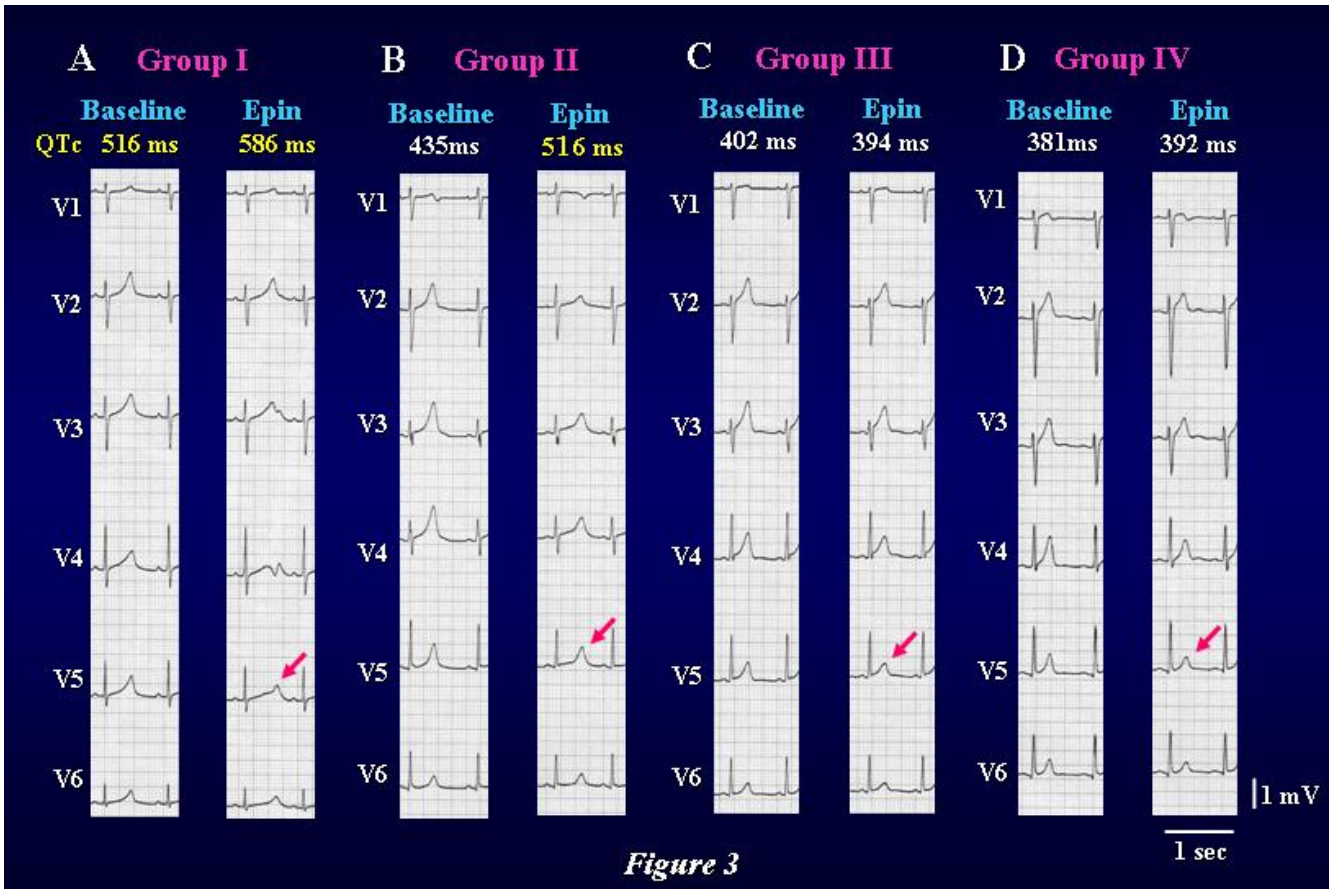

Figure 3. Six precordial-leads ECGs under baseline conditions and during epinephrine infusion (Epin) in Group I (**A**, mutation carrier ≥ 460 ms), Group II (**B**, mutation carrier < 460 ms), Group III (**C**, Non-mutation carrier), and Group IV (**D**, control) patients. Epinephrine markedly prolonged the mean corrected QT (QTc) interval in Group I (516 → 586ms) and Group II (435 → 516ms) patients, but not in Group III (402 → 394ms) and Group IV (381 → 392ms) patients.

Figure 4 shows composite data of the change of the QTc interval with epinephrine in the 4 groups. The mean QTc before epinephrine was significantly longer in Group I than in other 3 groups ($P<0.005$, Figures 4A). Epinephrine prolonged the QTc significantly in Groups I and II ($P<0.005$), but did not in Groups III and IV. Therefore, the QTc

after epinephrine was significantly longer in Groups I and II (Mutation carriers) than those in Groups III (Non-mutation carriers) and IV (Controls) (P<0.005, Figures 4A).

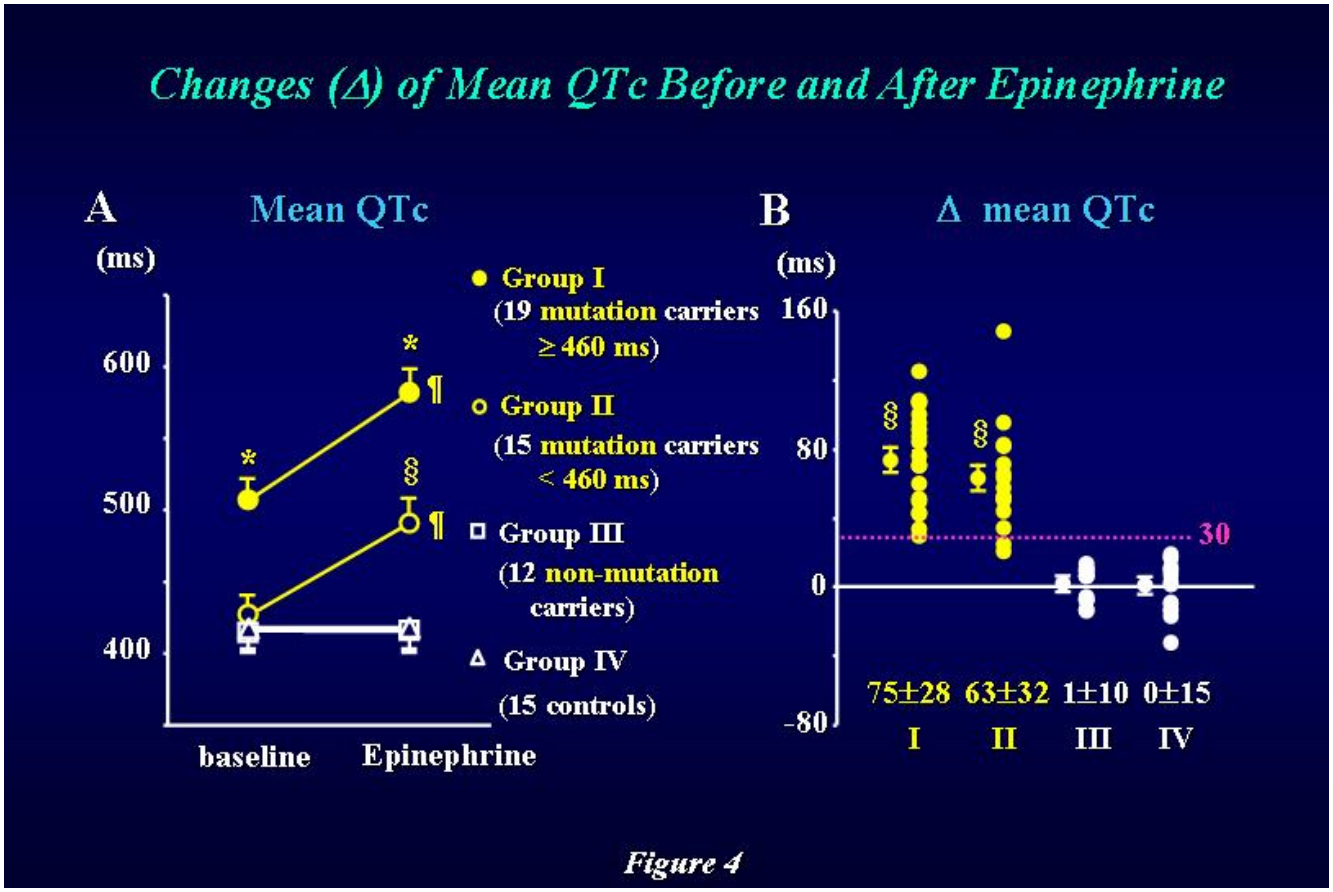

Figure 4. Composite data of the change (Δ) of the mean corrected QT (QTc) interval with epinephrine in Groups I (closed circle), II (open circle), III (open square), and IV (open triangle).

*P<0.005 vs. Groups II, III and IV, ¶P<0.005 vs. Groups III and IV, §P<0.005 vs. before.

The changes (Δ) in the mean QTc with epinephrine was not different between Groups I and II, but they were significantly larger than those in Groups III and IV (P<0.005, Figures 4B). The sensitivity for differentiating mutation carriers from non-mutation carriers and controls was substantially improved by epinephrine test without the expense of specificity (100 %, 27/27); 91 % (31/34) by using the ECG diagnostic criteria, and 74 % (25/34)

when the LQTS score ≥ 4 was used. The Δ QTc with epinephrine ≥ 30ms also improved the sensitivity to 91 % (31/34) without the expense of the specificity (Table I, Figure 4B). Even if we excluded the Group I patients who had a clear diagnosis of LQTS before epinephrine and analyzed the sensitivity in only Group II patients, the sensitivity was improved with epinephrine test; from 7 % (1/15) to 80 % (12/15) by using the ECG diagnostic criteria, from 0 % (0/15) to 40 % (6/15) when an LQTS score ≥ 4 was used, and to 87 % (13/15) when the Δ QTc was used. The heart rate before and after epinephrine and the increases of heart rate were not different between the 4 groups.

QTc Response to Epinephrine Between Symptomatic and Asymptomatic Mutation Carriers

The QTc interval before and after epinephrine were compared between 15 symptomatic patients and 19 asymptomatic mutation carriers in Groups I and II. The mean QTc before and after epinephrine were significantly longer in the 15 symptomatic patients than in the 19 asymptomatic mutation carriers ($P<0.005$). Epinephrine prolonged significantly the QTc in both symptomatic and asymptomatic mutation carriers ($P<0.005$). The prolongation (Δ) of the QTc with epinephrine was significantly greater in the 15 symptomatic patients than in the 19 asymptomatic mutation carriers (81±34 vs. 61±24 ms; $P<0.005$).

Torsade de Pointes and Premature Ventricular Contractions

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

DISCUSSION

It has long been suggested that the ECG-based diagnosis could miss some genetically-affected LQTS patients.[20] Vincent et al. first reported that 5 (6 %) of 82 mutation carriers from 3 large LQT1 families had a normal QT interval.[21] Priori and co-workers reported a very low penetrance (38 %) in 9 families with only 1 clinically

affected individual of LQTS.[16] Similarly, the average penetrance is relatively low (59 %) among 11 LQT1 families in the present study. In contrast, our preliminary data suggest that the penetrance in LQT2 and LQT3 syndromes is relatively high; 90 % in LQT2 families and 85 % in LQT3 families. The present study also demonstrates that epinephrine provocative test significantly improves the sensitivity of ECG diagnosis in LQT1 syndrome. Our preliminary data also suggest that epinephrine test further improves the sensitivity of diagnosis in LQT2 syndrome, although the baseline penetrance is relatively high in this genotype. In contrast, the sensitivity of LQTS diagnosis is not changed with epinephrine in LQT3 syndrome. Because the LQT1 and LQT2 syndromes are the two most common forms of congenital LQTS, molecular screening or epinephrine provocative challenge could be applied to all family members in genotyped LQT1 or LQT2 families, especially in LQT1 families. Based on current data, probands of congenital LQTS who had cardiac events during exercise and emotion and particularly during swimming have a high probability of being affected with LQT1 syndrome. Accordingly, all their family members become likely candidates for molecular screening or epinephrine provocative challenge. The identification of affected individuals with normal ECG phenotype is of major importance as it would enable to limit exposure of these individuals to potentially dangerous conditions such as participation into competitive sport and use of drugs known to prolong repolarization, thus reducing the risk of life threatening cardiac arrhythmias. Considering that genotyping of LQTS enables us to manage and treat the patients more effectively, and that first cardiac event may lead to sudden cardiac death in children, molecular screening for LQTS should be recommended in all probands regardless of age. Molecular screening or epinephrine test could be applied to all family members if the family was genotyped especially as LQT1 syndrome.

CONCLUSIONS

The present study and our preliminary data suggest that molecular screening (or epinephrine provocative test) could be applied to detect non-penetrant mutation carriers or increase the sensitivity of ECG diagnosis of LQTS, especially the LQT1 syndrome, thus reducing the risk of life threatening cardiac arrhythmias and managing the LQTS patients effectively.

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