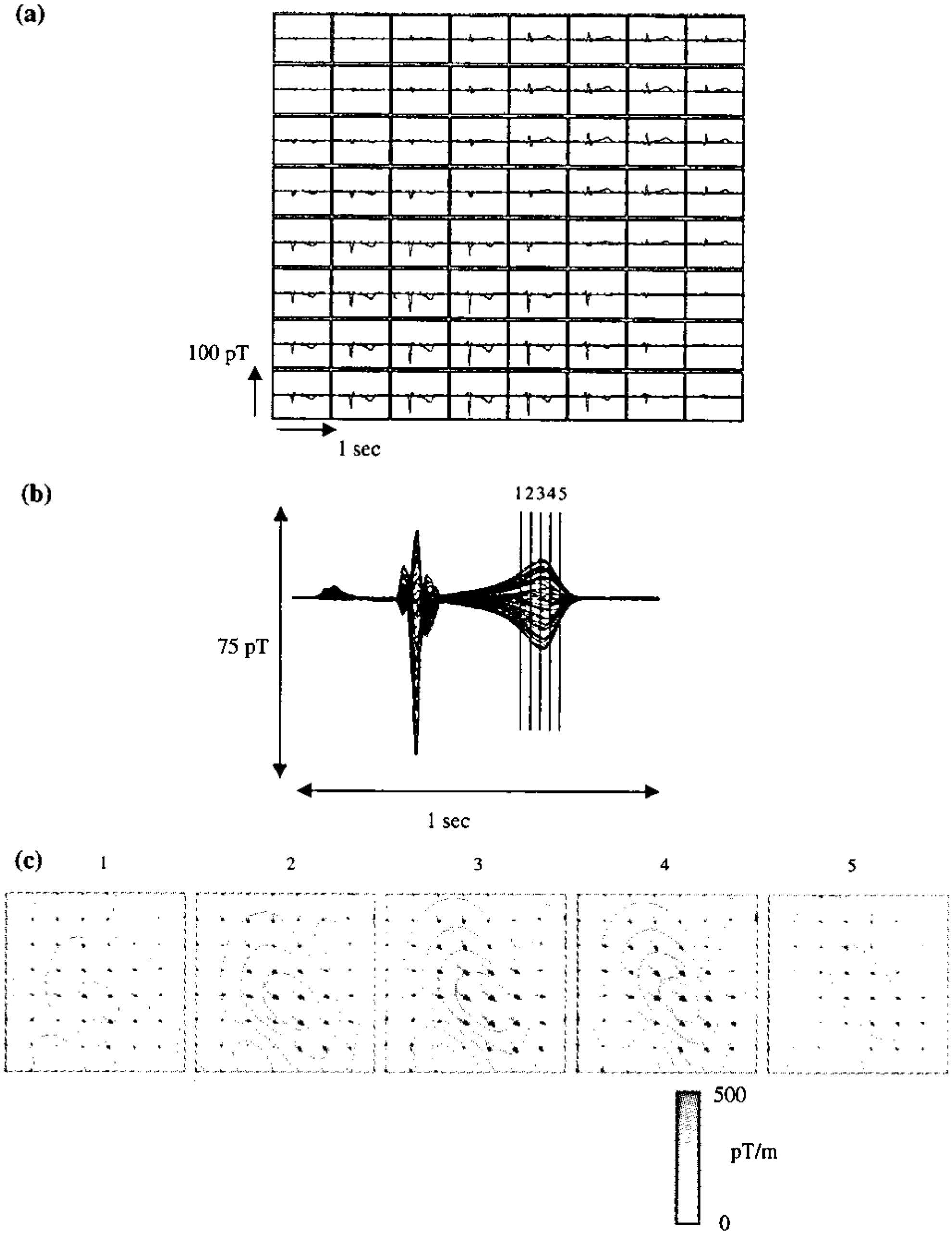

Figure 2. MCG analysis of typical normal control: (a) 64 waveforms of MCG signals, (b) overlapped 64 waveforms and (c) CAMs at five lines in T-wave of (b).

figure 2(c) were taken (CAMs). In figure 2(c), the change of the current distribution, which appears in the T-wave, has a simple pattern. In short, the distribution does not change dramatically, and the direction of the main distribution is towards the lower right. The MCGs and CAMs of all 33 normal subjects showed these characteristics.

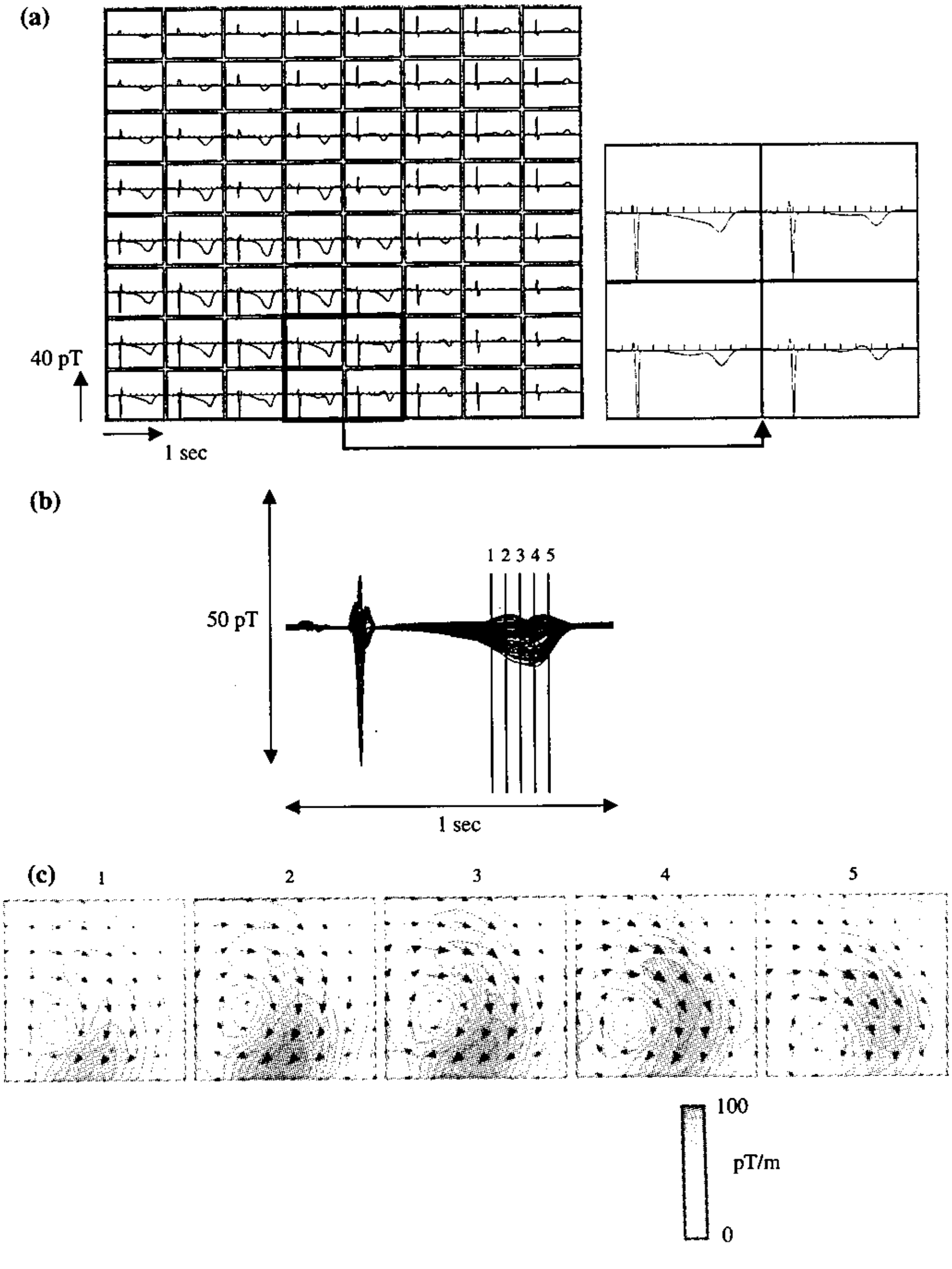

Figure 3. MCG analysis of typical abnormal patient with LQT1 (patient 1 in table 1): (a) 64 waveforms of MCG signals, (b) overlapped 64 waveforms and (c) CAMs at five lines in T-wave of (b).

3.2. CAM pattern of LQT1 patients

Sixty-four abnormal waveforms of an LQT1-syndrome patient (patient 1 in table 1) are shown in figure 3(a). It is clear that the T waveforms in the lower part of the figure have an

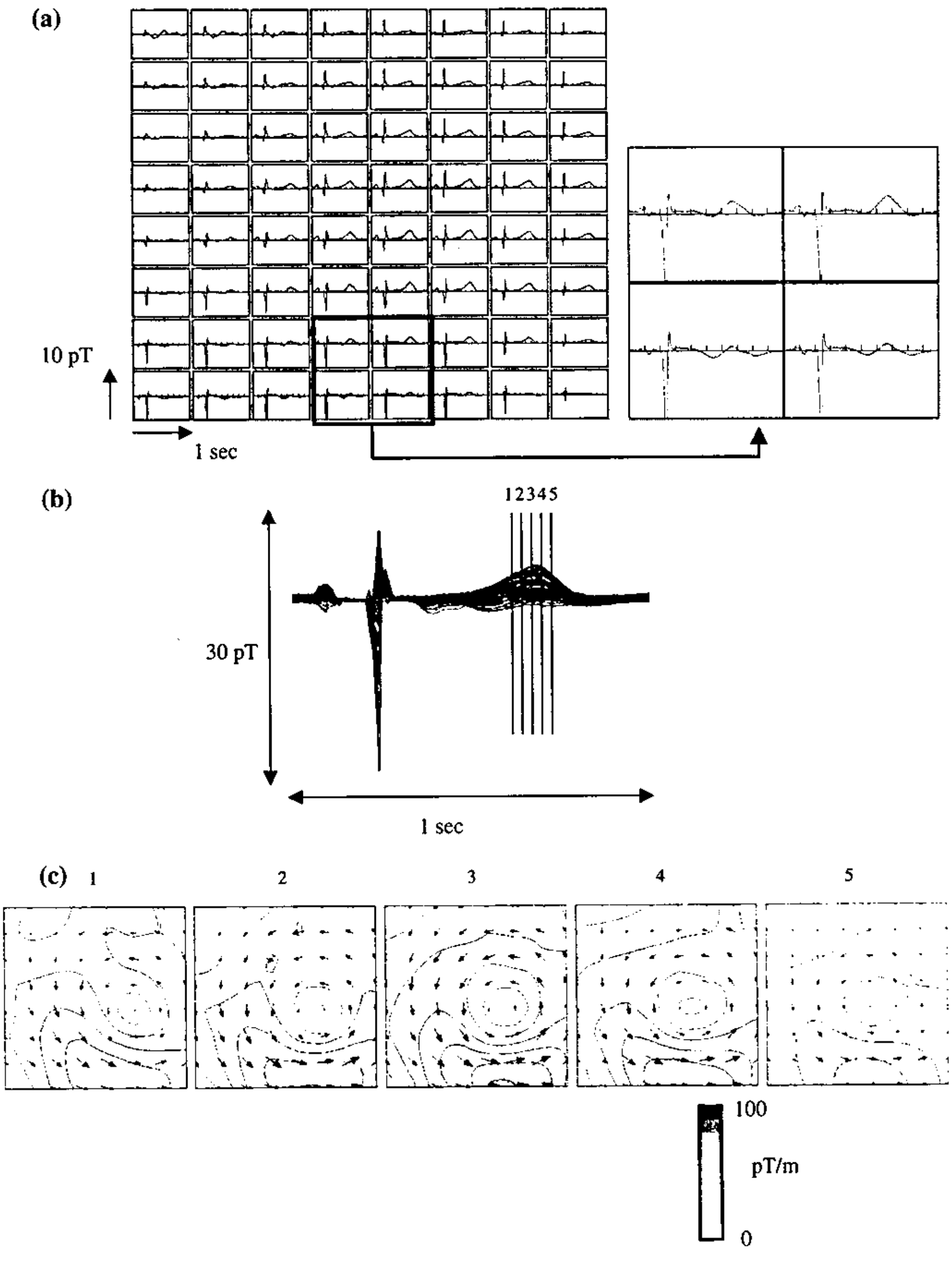

Figure 4. MCG analysis of typical abnormal patient with LQT2 (patient 8 in table 1): (a) 64 waveforms of MCG signals, (b) overlapped 64 waveforms and (c) CAMs at five lines in T-wave of (b).

abnormal shape, like a two-phase T-wave (enlarged figures to the right). In the overlapped waveforms shown in figure 3(b), five vertical lines are drawn on the T-wave to indicate the times corresponding to figure 3(c) (CAMs). In figure 3(b), two peaks appear in the T-wave.

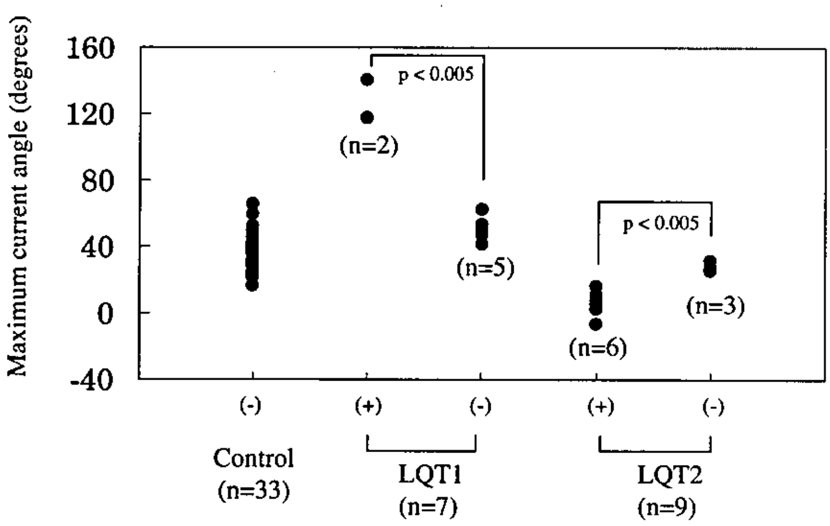

Figure 5. Relationship of maximum current-arrow angle among control, LQT1 patients and LQT2 patients. Regarding LQT1 and LQT2, there is a significant difference between the positive patient and the negative patient.

The CAMs shown in figure 3(c), with respect to the first peak (lines 1, 2 and 3), indicate an abnormal current-arrow pattern, in which the current arrows point towards the lower left direction, near the lower part of the left ventricular muscle. The current-arrow patterns corresponding to lines 4 and 5 show a recovery phase. This abnormal pattern appeared in two patients (patients 1 and 3, indicated by positive marks (+) in table 1).

3.3. CAM pattern of LQT2 patients

Sixty-four typical abnormal waveforms of an LQT2-syndrome patient (patient 8 in table 1) are shown in figure 4(a). T waveforms with a low amplitude and a notched pattern can be seen in the lower part of the figure (enlarged figures on the right). In the 64 overlapped waveforms shown in figure 4(b), T-waves have a low amplitude and broad shape. The CAMs corresponding to the five lines (figure 4(b)) are shown in figure 4(c) in order to investigate the abnormality of current orientation. In figure 4(c), abnormal current arrows appear in the lower part in the map for line 3 near the lower side of the right ventricular muscle. Six patients showed the same abnormal current-arrow pattern (patients 8, 9, 12, 13, 14 and 16, indicated by positive marks (+) in table 1).

3.4. Quantitative evaluation of abnormal current direction

The directions of the abnormal maximum-current arrows in the abnormal group (+) are compared with those in the negative group (−) (each LQTS type) in figure 5. The directions of those in the control group ($n = 33$) are also plotted to indicate the normal range. The normal direction was $36.1° \pm 10.5°$ ($n = 33$). Two LQT1 patients in the positive abnormal group show current angles larger than 110°. The current angles of five LQT1 patients in the negative abnormal group are $50.6° \pm 7.8°$, which fit in the normal range. In the plots of the angles, there is a significant difference between the positive and negative abnormal groups of LQT1 patients. On the other hand, the maximum current of the positive abnormal group of

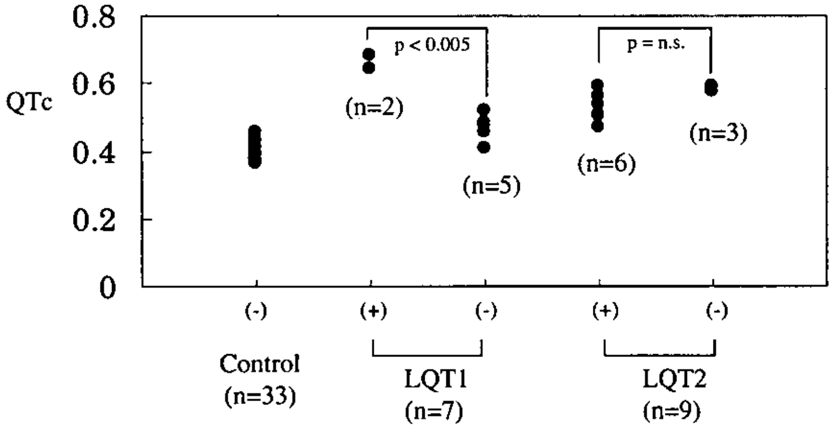

Figure 6. Relationship between QTc of control group, LQT1 patients and LQT2 patients. Regarding LQT1, there is a significant difference between the positive patient and the negative patient. But the difference in LQT2 patients is not significant.

LQT2 patients has angles lower than 20° (5.7° ± 7.9°). The current angles of the negative abnormal group of LQT2 patients are in the normal range (31.0° ± 3.1°). The plots of the angles show that there is a significant difference between the positive and negative abnormal groups of LQT2 patients.

3.5. Relationship between appearance of abnormal current and QTc

The relation between QTc and the presence or absence of abnormal current is plotted in figure 6. QTc of the normal control is 411 ± 24 ms ($n = 33$). Two LQT1 patients in the positive abnormal group have QTc values greater than 600 ms. The average QTc of five LQT1 patients in the negative abnormal group is 468 ± 41 ms. There is a significant difference between QTc values of the LQT1 patients in positive and negative abnormal groups. On the other hand, both positive and negative abnormal groups of LQT2 patients have longer QTc (529 ± 43 ms and 586 ± 8 ms) than that of the control group. However, there is no significant difference between QTc of the LQT2 patients in positive and negative abnormal groups.

4. Discussion

4.1. Repolarization abnormality of LQT1 patients

Abnormal current arrows appeared above the inferior part of the heart in two LQT1 patients with long QTc (>0.6), and the current direction was from left to right in the ventricular muscle. The angle (>110°) indicates that the left ventricular potential is higher than the right potential on the heart muscle. This higher potential may be caused by prolonged left-vernacular APD. Experimental LQTS studies using dogs (Vos *et al* 2000) have demonstrated that long QTc just preceding TdP was associated with longer APD of the LV than that of the right ventricle (RV). Clinical observations using MAPs also suggest that genesis of TdP was induced by an EAD trigger in the case of long QTc (Ohe *et al* 1990, Shimizu *et al* 1991, 1995, Kurita *et al* 1997). Therefore, in the case of LQT1 syndrome, our findings concerning LV abnormality (abnormal direction (> 110°) and large QTc) may indicate the predominance of a repolarization abnormality in the LV.

4.2. Repolarization abnormality of LQT2 patients

In six out of the nine LQT2 patients, abnormal current arrows (with angles below 20°) were observed on the right inferior part of the heart or on the lower septum. The current direction was from the right to the left ventricular muscle, indicating that the APD of the RV or lower septum is stronger than that of the LV. Despite the high detection rate (6/9) of the abnormal current arrows, the abnormalities appeared when QTc values were relatively low. This may suggest that the correlation between the abnormalities and QTc at rest is low, because a sudden shock in the form of an auditory stimulus (e.g., an alarm clock) is the predominant trigger of cardiac events in patients with LQT2 (Wilde *et al* 1999).

4.3. Advantage of CAM method

Magnetocardiographic turbulence (spatial beat-to-beat variability) of only two patients with LQT has been analysed by estimating an equivalent current dipole (ECD) (Schmitz *et al* 1998). They analysed changes of one ECD in the case of a T-wave peak for 100 s. However, as shown in figures 3 and 4, the abnormal current and normal repolarization current appeared simultaneously. Therefore, the two-dimensional current distribution is important in order to obtain more information about repolarization abnormality. Furthermore, ECD estimation often produces errors because of non-linear analysis. We have thus developed a total-current-vector (TCV) method (Kandori *et al* 2001a, 2001c), which is the summation of all current vectors of a CAM, to estimate the ECD orientation as one dipole. TCV, which indicates the direction of an ECD, is very useful for analysing low-amplitude MCG signals such as an ST segment or a foetal T-wave. However, multi-focal activation (combining normal and abnormal activation) should be directly analysed by CAM. Apart from the CAM method, the field-gradient magnetic-field method has been used to study patients with single-vessel coronary artery disease (Hänninen *et al* 2000, Takala *et al* 2001). However, this method cannot directly determine the orientation of the current distribution because it cannot convert magnetic-field orientation to a current orientation.

An evaluation method based on the orientation of abnormal current plotted on a CAM is a good quantitative diagnostic tool for severe LQTS patients, and the CAM method can provide visual information on the spatial current dispersion. The combination of the orientation and the QTc (or QT) intervals can predict TdP occurrence; this prediction may evaluate the efficacy of drug medication as a quantitative value. Furthermore, a CAM may have the possibility of visualizing a re-entry circuit of TdP, because a re-entry circuit of atrial flutter can be observed as a circular current-arrow pattern (Yamada *et al* 2001, Kandori *et al* 2002).

4.4. Study limitation

There are several limitations in the present study. First, MCG signals of many LQTS patients, which are defined by genotype, are needed in order to evaluate the specificity of each LQT type. Second, CAM has the limitation that it does not express a real current distribution on the ventricular muscle. To overcome these problems, a combination of a large number of statistical CAMs, animal examination and cellular-based examination may be needed. While the present study is methodologically simple and the results are preliminary because of the above limitations, our findings are important in understanding the mechanism of LQTS.

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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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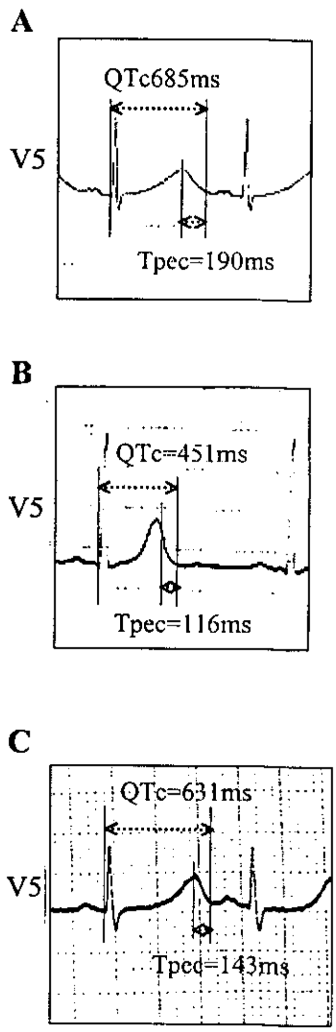

Figure 1. Three typical T-wave patterns in baseline lead V_5 ECGs of LQT1. A, Broad-based T-wave pattern. Both of the QTc and Tpec were prolonged. B, Normal-appearing T-wave pattern. C, Late-onset T-wave pattern. Flat ST segment was especially prolonged.

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-R$^{1/2}$) and corrected Tpe (Tpec; Tpe/R-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

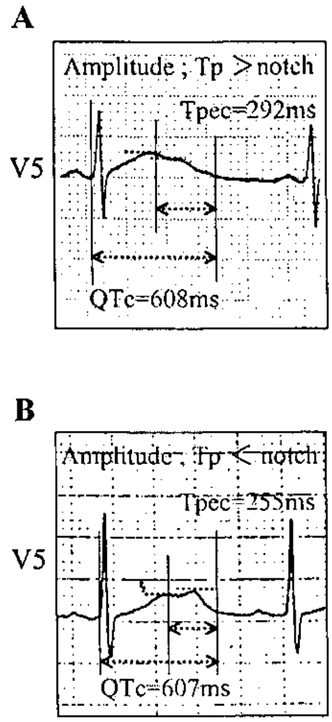

Figure 2. Two typical T-wave patterns identified in baseline lead V_5 ECGs of LQT2. A, Bifid T wave with notch S, which indicates a notch lower than Tpeak. B, Bifid T wave with notch L, which is higher than Tpeak. In bifid T wave, Tpeak (Tp) was defined as the former apex and a notch as the latter apex.

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

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-R$^{1/2}$.

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

patients. At variance with a previous report,[17] the Tpec in LQT2 was significantly longer than that in the LQT1 group.

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

TABLE 3. ECG Data Before and During Exercise in LQT1, LQT2, and Control

	Baseline	Peak Exercise	*P*
R-R, ms			
LQT1	888±155	461±146	*P*<0.001‡
LQT2	1020±184	514±134	*P*<0.001‡
Control	816±188	475±64	*P*<0.001‡
P	NS*†	NS*†	
QTc, ms			
LQT1	511±64	599±54	*P*<0.001‡
LQT2	513±55	502±82	NS‡
Control	402±36	418±17	NS‡
P	NS*/*P*<0.001†	NS*/*P*<0.001†	
Tpec, ms			
LQT1	142±46	215±46	*P*<0.001‡
LQT2	197±70	163±86	NS‡
Control	127±59	98±21	NS‡
P	*P*<0.001*†	NS*/*P*<0.001†	

*Between LQT1 and LQT2, †LQT1 and LQT2 group compared with control, respectively, ‡between baseline condition and peak exercise.

peak exercise was 96%, and its negative predictive value (NPV) was 72%.

In the LQT2 subset, a notch on the descending T-wave limb became prominent during exercise (Figure 3B). Under the baseline condition, the bifid T-wave pattern with notch L was seen in 6 of 19 patients with LQT2, the one with notch S in 5, and the broad-based T in 6 patients(Figure 4B). In exercise, the broad-based T-wave pattern was changed into bifid T type, eventually the bifid or biphasic T-wave pattern was observed in 17 of 19 patients with LQT2 (Figure 4B). The PPV of the bifid with a notch at peak exercise was 80%, and its NPV was 90%.

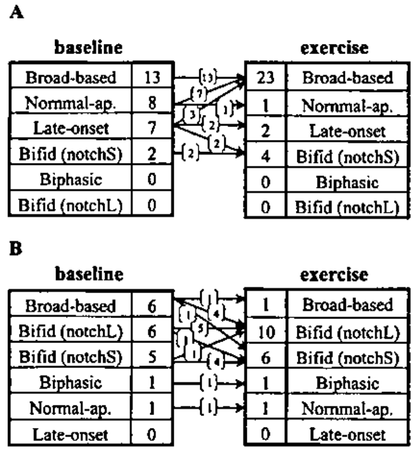

Figure 4. Changes in T-wave pattern during exercise in LQT1 (A) and LQT2 (B) subgroups. Numbers in tables indicate absolute numbers of patients in each subgroup (30 patients with LQT1 and 19 with LQT2). Numbers in parentheses indicate numbers of patients that showed the change in T-wave pattern by exercise.

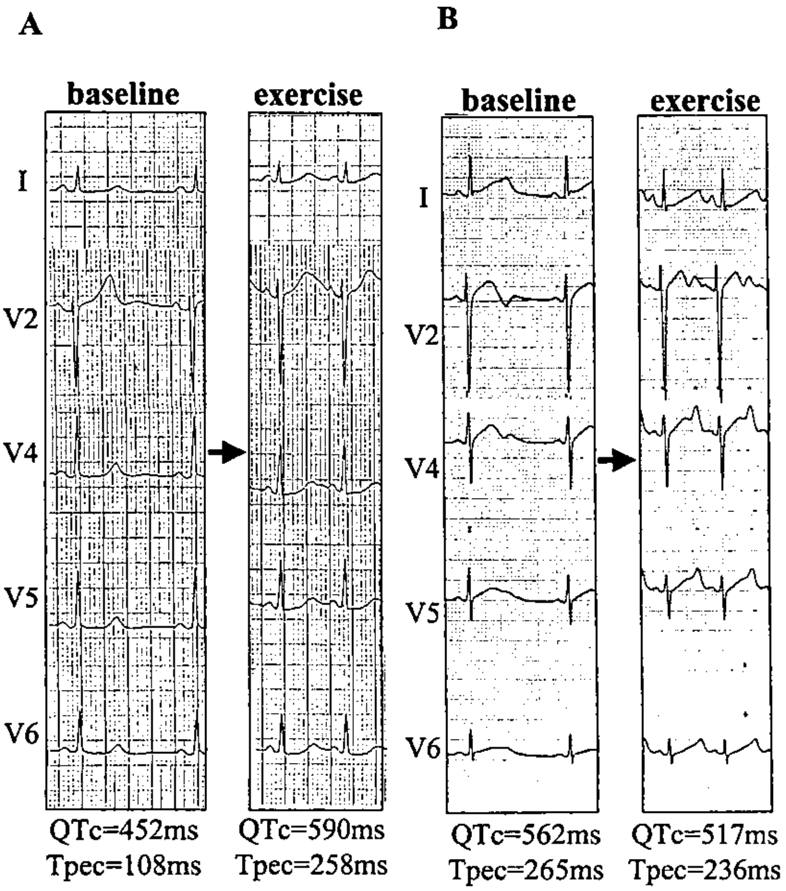

Figure 3. Representative morphologic changes in the 5 leads of ECGs during exercise in patients with LQT1 (A) and LQT2 (B). Measured values for QTc and corrected Tpe (Tpec; Tpe/R-R$^{1/2}$) are shown at the bottom of each column.

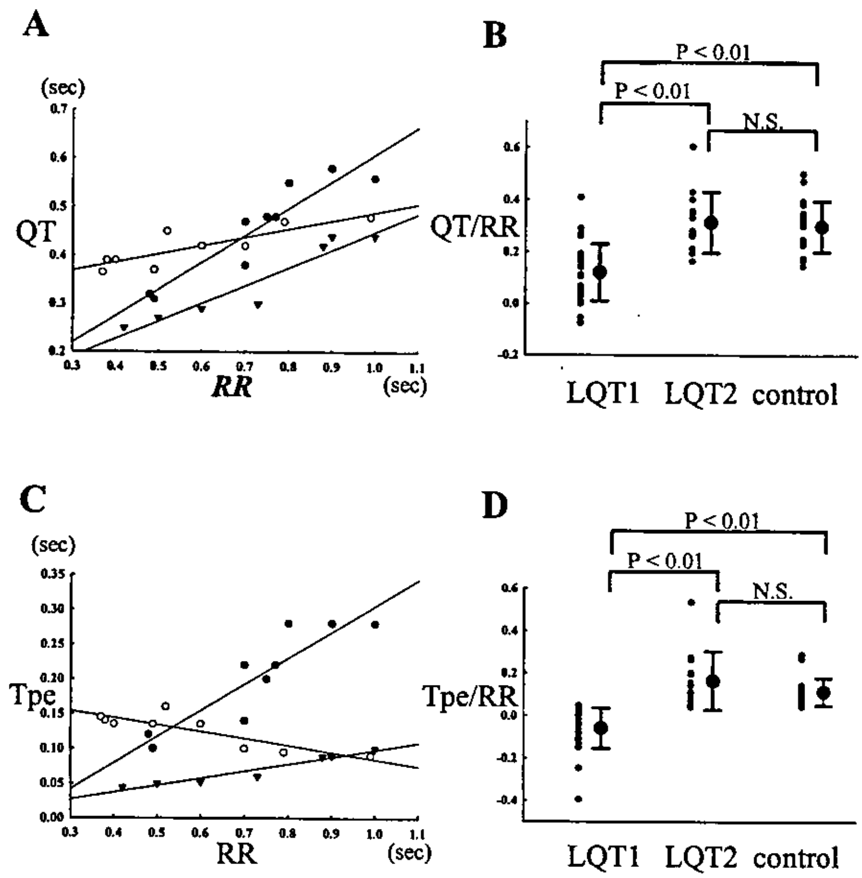

Figure 5. Responses of two parameters of cardiac repolarization to R-R intervals during exercise in 3 groups. A, Relations of QT to R-R intervals during exercise: ○, LQT1; ●, LQT2; and ▲, control. Solid lines are best fit by least-squares method. Slope of each line (QT/R-R) was 0.13, 0.56, and 0.42, respectively. B, QT/R-R slopes in 3 groups are summarized: Each symbol indicates slope value from one individual. C, Relations of Tpe to R-R intervals during exercise: ○, LQT1; ●, LQT2; and ▲, control. Solid lines are best fit by least-squares method. Slope of each line (Tpe/R-R) was −0.10, 0.37, and 0.10, respectively. D, Tpe/R-R slopes in 3 groups are summarized: Each symbol indicates slope value from one individual.

Rate-Dependent Adaptation of QT Intervals

In the LQT1 group, the QTc interval significantly prolonged in response to the shortening of the R-R by exercise. In contrast, the QTc remained unchanged by exercise in both the LQT2 and control groups (Table 3). As was shown in the previous data on QT/R-R slopes and their genotype-dependent differences,[19] our data also suggested that the QT/R-R relation has genotype-related differences. In Figure 5A, QT values are plotted against R-R intervals in 3 representative patients. Open circles indicate data points from a LQT1 patient, closed circles those from a LQT2 patient, and closed triangles from a control patient. Three solid lines are best fit by a least-squares method. All QT/R-R values thus calculated are summarized in Figure 5B. The QT/R-R slope was significantly less steep in LQT1 than those in the other two groups.

Patients With LQT1 and LQT2 Show Different Responses in Tpe to Exercise

Exercise increased the Tpec significantly only in LQT1 (Table 3). The rate-dependent adaptation of Tpe was evaluated by plotting raw data against the R-R, as depicted in Figure 5C. In the LQT2 patient (closed circles) and the control (closed triangles), the Tpe was reduced in response to the shortening of R-R, thereby producing a positive Tpe/R-R slope. In contrast, the Tpe significantly prolonged when R-R shortened in patients with LQT1 (open circles), resulting in a negative Tpe/R-R slope.

The Tpe/R-R slopes in the 3 groups are illustrated in Figure 5D. None of the patients with LQT2 or the control patients had a negative Tpe/R-R slope. In contrast, 80% of patients with LQT1 showed a negative Tpe/R-R slope (PPV 100%, NPV 75%). Therefore, the exercise-induced QT prolongation in the LQT1 group was due mainly to the augmentation of Tpe intervals.

Discussion

The present study demonstrates that exercise amplifies the phenotypic appearance of T wave in both LQT1 and LQT2. The data also suggested that exercise produces a significant increase in both QT interval and Tpe, reflecting transmural dispersion of repolarization (TDR) only in LQT1. Since mutations in different genes are identified in LQTS, resting ECGs have been noted to differ considerably among the genotypes.[3,4,20] Indeed, bifid T waves with a notch, which are characteristic to LQT2,[4,20,21] were also found in about two thirds of our patients with LQT2. At variance with previous reports,[3,4,20] the remaining one third of patients with LQT2 showed a broad-based T-wave pattern, which is thought to be typical in LQT1. Therefore, baseline T-wave morphology does not efficiently serve as a diagnostic criterion for LQTS genotyping.

On the other hand, exercise stress testing could produce distinct responses in T-wave morphology between the two groups. The broad-based T-wave pattern observed at rest in the LQT1 group remained unchanged during exercise. More interestingly, other types of T waves were changed into the broad-based pattern during exercise, which was associated with a significant increase in the QTc and the Tpec. In contrast, the T-wave morphology was altered to the bifid pattern during exercise in most cases of LQT2.[21]

Arterially perfused wedge preparations[6] have been used to develop pharmacological models of LQT1, LQT2, and LQT3, in which the phenotypic appearance of T wave depended on currents flowing down voltage gradients among three different cell types across the ventricular wall; epicardial, midmyocardial (M), and endocardial cells. In all 3 models, the Tpe in the transmural ECG appeared to provide an index of TDR defined usually as the time lag for repolarization between epicardial and M cells,[14,16] and an amplified TDR was linked to ventricular arrhythmias such as torsade de pointes.[6,14,16] In three distinct layers, epicardial and endocardial cells have intrinsically stronger net repolarizing currents (as the result of strong I_{Ks} and weak late I_{Na}) than M cells (weak I_{Ks} and strong late I_{Na}).[22,23] Therefore, a large augmentation of residual I_{Ks} by β-adrenergic stimulation would result in epicardial or endocardial cells but not in M cells, especially in the LQT1 model (in scarce I_{Ks} state).[6,24,25] This may lead to an increased TDR and a broad-based T wave, which is consistent with the phenotypic appearance of ECGs during exercise in our patients with LQT1, and thereby explains the higher incidence of cardiac events with exercise in this special subset.

The cellular basis for low-amplitude T-waves with a notched configuration often seen in LQT2 has also been demonstrated by experimental studies with wedge preparations[14,16]: A notch on the descending limb of the T wave indicates the timing when the voltage gradient between endocardial and the M cells changes abruptly after the full repolarization of epicardial cells. A notch on the ascending limb of the T wave occurs when a gradient develops between endocardium and M region, which is capable of generating a current sufficient to change the direction of net current flow across the wall. Both types of notches were often observed in the wedge preparations perfused with I_{Kr} blockers. However, in the LQT2 model, the influence of β-adrenergic stimulation has not been yet examined on the repolarization gradient.

Study Limitations

In the present study, men with LQT1 were significantly younger than those in other groups. This may reflect the finding that the onset age of men with LQT1 was younger, as reported in previous study,[7] and may affect the analysis. In regard to the study patients with exercise tolerance testing, however, this influence of a widely scattered age range could be ruled out because there was no difference in the proportion of children under 16 years of age (numbers of the children were 9 in 30 with LQT1 and 6 in 19 with LQT2). Mean ages of study patients were not significantly different. There was also no significant difference in maximum heart rate attained by exercise, excluding the age-dependent influence on ECG parameters.

At variance with a previous report,[17] the Tpec in LQT2 was significantly longer than that in the LQT1 group. It may be due to the difference in definition of Tpe. Because T peak was defined as the former peak of the bifid T-wave pattern in our analyses, the Tpe interval became longer in the bifid T wave, which was the main pattern of LQT2.

In summary, the present study demonstrated that exercise-induced genotype-specific changes in the T wave and exaggerated prolongation of the QT interval in LQT1[5] were due principally to increase in Tpe, reflecting TDR. Exercise testing is useful to facilitate genotyping of most common variants of the LQTS, although prospective study will be needed to conclude its diagnostic value.

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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.

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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-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

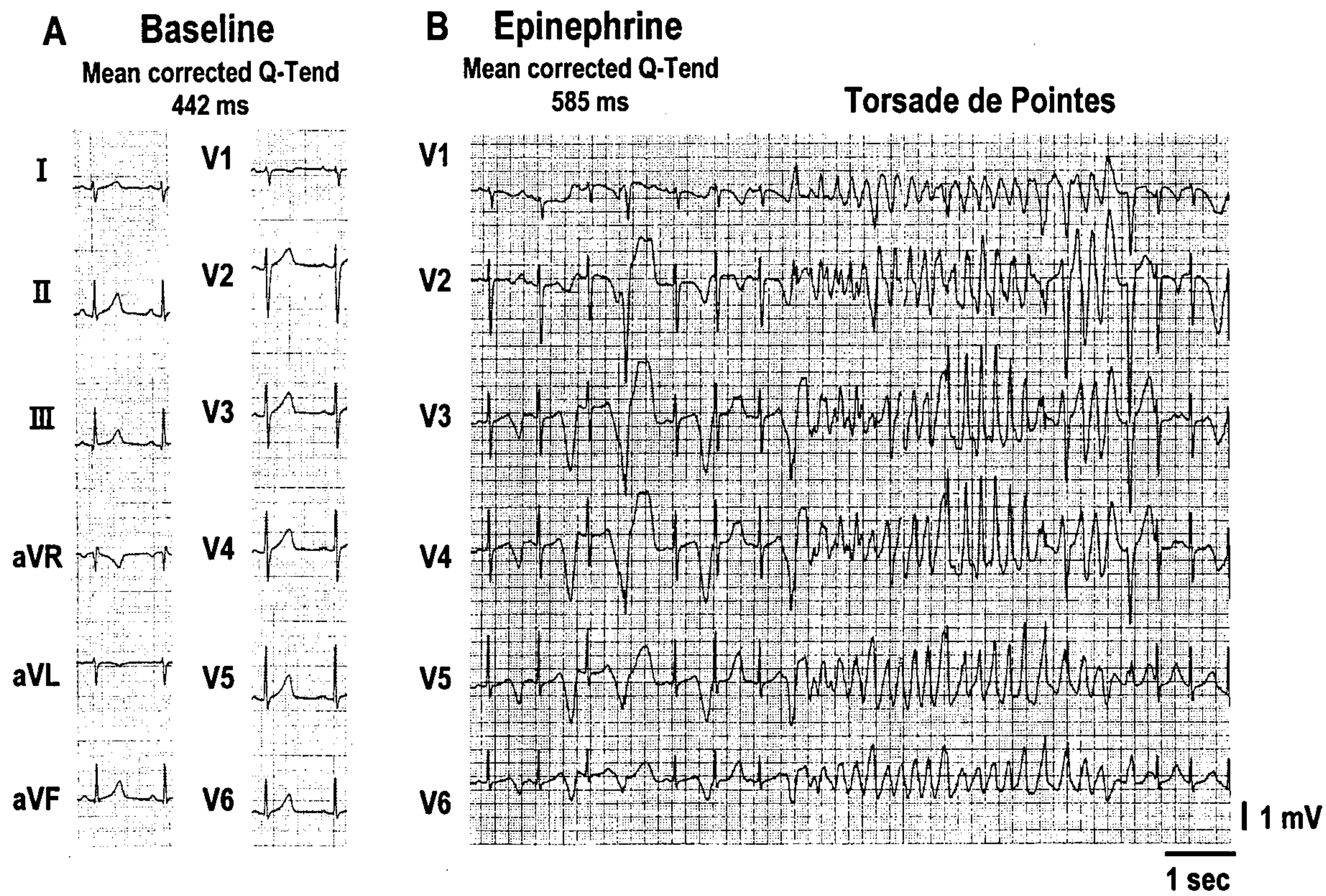

Figure 1. Twelve-lead electrocardiograms under baseline condition (A) and precordial electrocardiograms during epinephrine infusion (2 min after start of epinephrine) (B) in an LQT1 mutation carrier. The mean corrected Q-Tend interval was dramatically prolonged by epinephrine, leading to spontaneously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

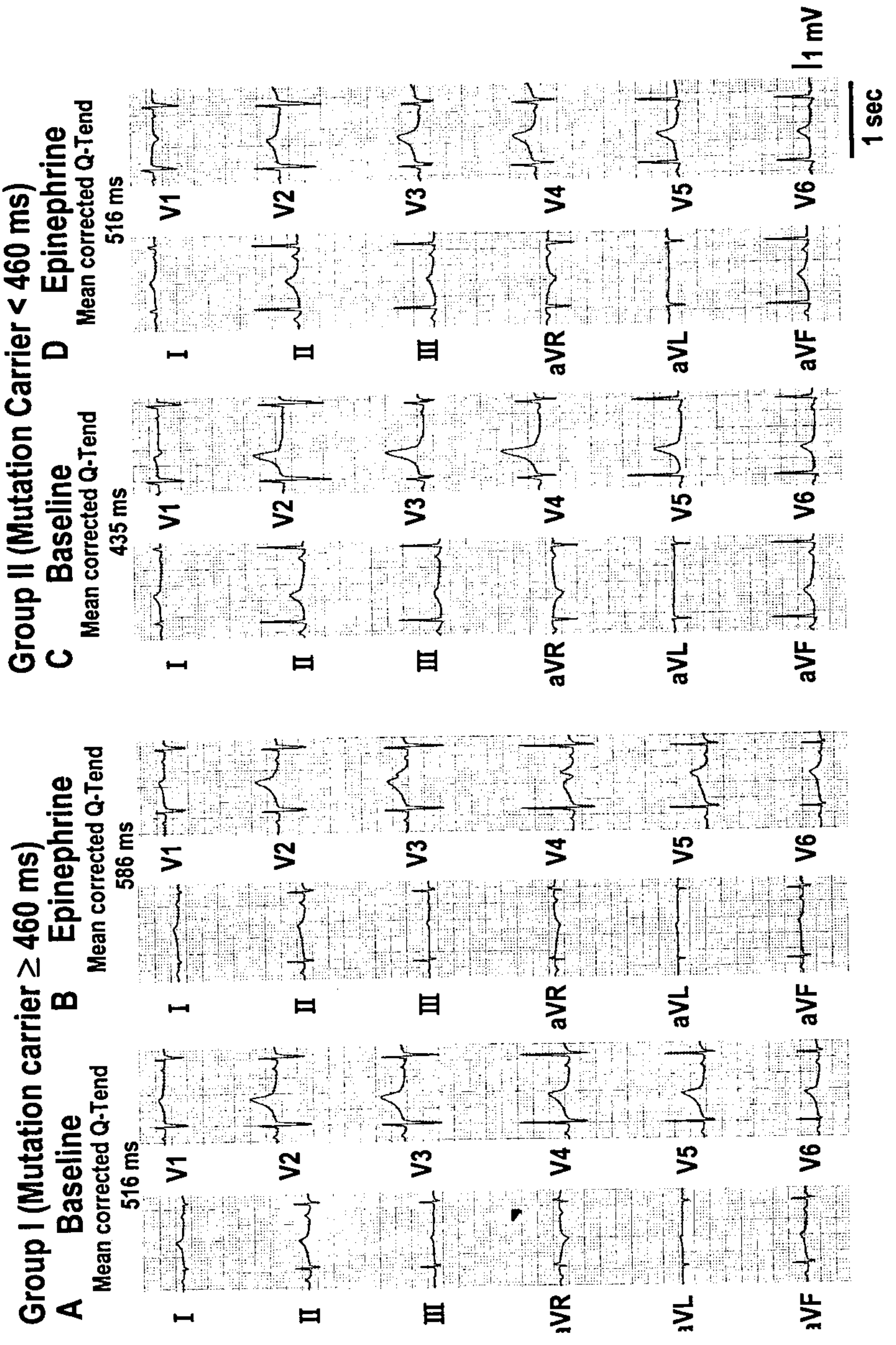

Figure 2. Twelve-lead electrocardiograms under baseline conditions and during epinephrine infusion in Group I (A and B) and Group II (C and D) patients. Epinephrine markedly prolonged the mean corrected Q-Tend in both Group I (516→586 ms) and Group II (435→516 ms) patients.