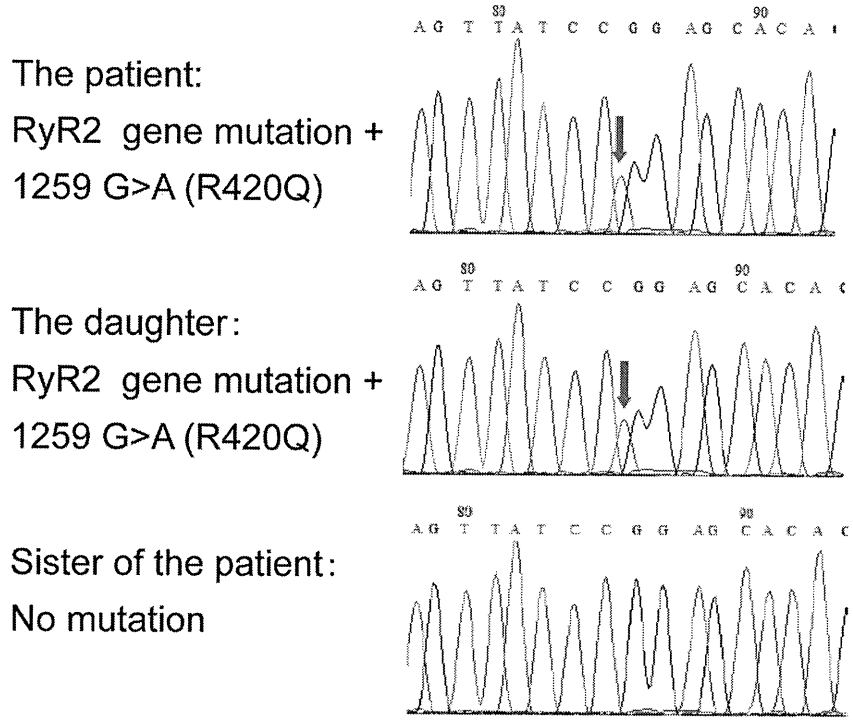


**Figure 5.** Results of genetic analysis. A mutation in the ryanodine receptor gene (*RyR2*) was detected in both the patient and her daughter. The mutation was not detected in the patient's sister.

therapies in patients with CPVT. To clarify the effectiveness and safety of this procedure, more cases and longer-term observation are mandatory.

## Disclosures

None.

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KEY WORDS: catecholaminergic polymorphic ventricular tachycardia ■ catheter ablation ■ arrhythmia



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# Clinical and electrocardiographic characteristics of patients with short QT interval in a large hospital-based population

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**BACKGROUND** Short QT syndrome is one of the underlying disorders associated with ventricular fibrillation. However, the precise prognostic implication of a short QT interval remains unclear.

**OBJECTIVE** The purpose of this study was to investigate the prevalence and long-term prognosis in patients with a shorter-than-normal QT interval in a large hospital-based population.

**METHODS** We chose patients with a short Bazett QTc interval from a database consisting of 114,334 patients to determine the clinical characteristics and prognostic value of a short QT interval.

**RESULTS** A total of 427 patients (mean age 43.4 ± 22.4 years) had a short QT interval with about a 1.2 times higher male predominance (234 men). The QTc interval was significantly longer in female than in male patients (363.8 ± 6.1 ms vs 357.1 ± 5.8 ms, $P < .0001$). The age-specific prevalence of patients with short QT interval was biphasic, peaking at young and old age. Atrial fibrillation and early repolarization were complicated with short QT interval in 39 (9.1%) and 26 (6.1%) patients, respectively. The prognosis of 327 patients (182 men; mean age, 46.4 ± 27.3 years) with a short QT interval could be assessed (mean follow-up period, 54.0 ± 62.0 months). During the follow-up, 2 patients, 1 of whom had early repolarization, developed life-threatening events, in contrast to 6 patients who died of noncardiac causes and did not have early repolarization.

**CONCLUSION** The prevalence of a short QT interval showed a slight male preponderance and biphasic age-dependent distribution in both genders. The complication rate of atrial fibrillation was higher in those with a short QT interval than in general populations. The long-term outcome suggested that early repolarization in a short QT interval might be associated with potential risk of lethal arrhythmia.

**KEYWORDS** Electrocardiography; QT interval; Prevalence; Prognosis; Repolarization

**ABBREVIATIONS** **AF** = atrial fibrillation; **CI** = confidence interval; **ECG** = electrocardiogram

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## Introduction

The QT interval is an invaluable prognostic marker for evaluating whether ventricular arrhythmia occurs.[1–3] Long QT syndrome is characterized by ventricular cells that fail to repolarize sufficiently quickly. On the other hand, short QT syndrome manifests an extremely abbreviated QT interval.[4,5] Genetic mutations underlie both syndromes, in which sudden cardiac death occurs.[6,7] It was reported that short QT syndrome complicated other electrocardiogram (ECG) abnormalities, such as atrial fibrillation (AF)[4] and early repolarization.[8] Although close attention must be paid to short QT interval, there may be overlap between normal QT interval and abnormally short QT interval.[9] In addition, the prognostic value of short QT syndrome in relation to AF or early repolarization is yet to be determined.

In our university hospital, more than 350,000 ECGs obtained from more than 110,000 patients are available for digital analysis. Using this large hospital-based population, we aimed: (1) to determine the distribution of the QT interval in the entire population, (2) to determine the clinical and ECG characteristics in individuals with short QT interval, and (3) to investigate the prognostic value of short QT interval.

## Methods

The research protocol was approved by the Ethical Committee of Shiga University of Medical Science.

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## Database

We analyzed resting 12-lead ECGs recorded in the university hospital of Shiga University of Medical Science. The 114,334 consecutive patients (55,091 female and 59,243 male patients) who had undergone ECG recordings between January 1983 and July 2010 were enrolled in the present study. A total number of 359,737 ECG recordings were obtained during this period. The 12-lead ECG was recorded for 10 seconds at a sweep speed of 25 mm/s, calibrated to 1 mV/cm in the standard leads. Twelve leads were simultaneously acquired. The ECG signals were recorded with a temporal sampling interval of 2 ms (i.e., 500 Hz). Digital data were stored in a server computer with 12-bit resolution.

## Digital analysis of ECG

MUSE7.1 (GE Marquette Medical Systems, Inc., Milwaukee, Wisconsin) detected an identical P wave and QRS complex with a template matching technique. When AF (defined as irregular RR intervals with fibrillatory waves) was present, only QRS complex was identified by template-matching technique. ECG variables measured were composed by the averaged value during a 10-second recording time. QT interval was measured from the earliest detection of depolarization in any lead (QRS onset) to the latest detection of repolarization in any lead (T wave offset). T wave offset was determined by the time when 98% of the integrated area of T wave was over, which corresponded to a point where the T wave downsloping limb nearly joined the baseline. U wave was excluded. The QTc interval was calculated after correction for heart rate with the Bazett formula. Early repolarization was defined as an elevation at the junction between QRS complex and ST-segment $\geq$0.1 mV from baseline level in at least 2 leads. ST-segment elevation should be present in at least 2 consecutive beats to identify early repolarization. ECG recordings of a mean heart rate <50 or >100 beats/min were excluded from the analysis in the first analysis, and then the prevalence of short QT interval in patients with sinus bradycardia <50 beats/min was additionally investigated. ECGs with ventricular pacing were also excluded. Because all measurements of 12-lead ECG were digitally performed by virtue of software, neither intraobserver nor interobserver variability occurred in this study. To determine whether the automatic measure of QT interval correlates with the manual measure of QT interval, 1,000 ECGs were randomly selected, and then we compared the automatic and manual measure of the QT interval. The manual measure of the QT interval was performed by a standard tangential method in lead V5. The manual QT interval measurement was obtained by averaging the QT interval of 3 consecutive beats.

## Data analysis

First, we constructed histograms according to QTc interval. QTc interval divided by 5 ms and the number of ECGs or patients used for frequency density were shown on the abscissa and the ordinate, respectively. Second, the prevalence of patients with a short QTc interval in association with age and gender was determined. Third, clinical and ECG characteristics of patients with a short QTc interval were determined. The prevalence of AF and early repolarization complicated by short QT interval was determined. Fourth, the prognostic value of a short QTc interval was assessed. Long-term outcome was determined by assessing whether sudden cardiac death, life-threatening ventricular arrhythmia, or any cause of death occurred. Patients were considered to have died suddenly if death was observed and had occurred within 1 hour after new or more serious complaints of probable cardiovascular cause. Life-threatening ventricular arrhythmia was determined by documented ECG. We reviewed the medical records of patients with short QT interval to evaluate their physical health status. In patients whose medical records were not available to determine prognosis, we gathered information on health status by a postal questionnaire. We performed gene analysis (see Supplementary Materials) in patients who developed life-threatening events with short QT interval.

## Statistical analysis

The data are presented as mean $\pm$ SD. A comparison between 2 groups was performed with the Student $t$ test or the nonparametric Mann-Whitney $U$ test, as appropriate. Categorical variables were compared with $\chi^2$ test. Kolmogorov-Smirnov test was performed to determine whether QTc interval distribution fit to a normal distribution. All tests were 2-tailed, and a value of $P$ <.05 was considered statistically significant.

## Results

In the database, there were 11,416 and 21,450 ECGs with heart rate of <50 and >100 beats/min, respectively. We excluded these ECGs from this study, thus 301,345 ECGs derived from 105,824 patients (56.0% men; mean age, 52.6 $\pm$ 20.7 years) were included for the analysis of this study. The autonomic QT interval measure was a little but significantly longer than the manual QT interval measure (421.8 $\pm$ 23.2 ms vs 418.0 $\pm$ 24.5 ms, $P$ <.0001).

The mean difference between the manual and automatic QT interval measure was 3.8 ms (median 3.7 ms), and there was a significant linear correlation (r = 0.95, $P$ <.00001) between the manual and autonomic measure of QT interval (Supplementary Figure 1), indicating the accuracy of the computer-assessed measure of QT interval.

## Prevalence of QT interval

Figure 1 shows the distribution of the QTc intervals of total, male, and female patients. The histograms that were constructed as a function of the number of ECGs are shown in the upper row of Figure 1. The mean QTc interval was 421.4 $\pm$ 25.7 ms (95% confidence interval [CI] 382 to 482 ms, range 329 to 693 ms) in total patients; 418.9 $\pm$ 25.7 ms (95% CI 380 to 480 ms, range 331 to 693 ms) in male patients; and 424.7 $\pm$ 25.3 ms (95% CI 387 to 483 ms, range 329 to 687 ms) in female patients. The QTc interval was significantly ($P$ <.0001) longer in female patients than

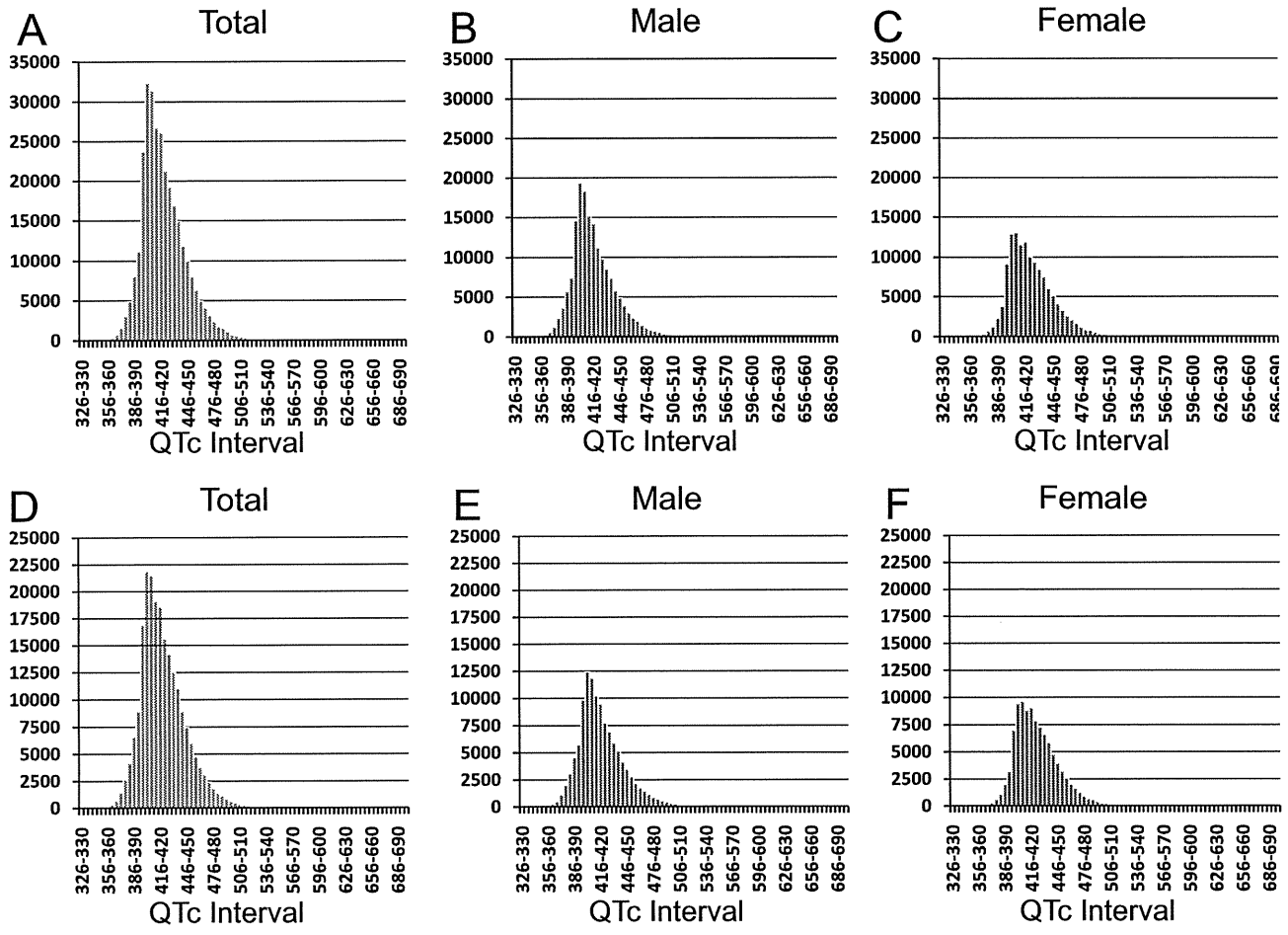


**Figure 1** Distribution of Bazett QTc interval according to the number of patients (upper row) and the number of ECGs (lower row). Histograms of total, male, and female patients in this study population are displayed in panels A and D, B and E, and C and F, respectively.

in male patients. The QTc interval distributions did not fit a normal distribution curve ($P < .01$ for each) because the distributions were asymmetrical and right skewed. The histograms of QTc interval that were generated as a function of the number of patients are shown in the lower row of Figure 1. Similarly, the histograms of the QTc interval were right-skewed, which failed to fit to a normal distribution ($P < .01$ for each). The mode of QTc interval was 401 to 405 ms (range 329 to 693 ms), 401 to 405 ms (range 331 to 693 ms), and 406 to 410 ms (range 329 to 687 ms) in total, male, and female patients, respectively. Table 1 shows the lowest percentiles of QTc interval. The QTc interval at the lowest 2.5 percentile was longer than the lower limit of normal QTc interval previously reported.[9] The QTc interval[10,11] at the lowest 0.15 percentile was similar to the lower border of QTc interval. We therefore adopted a definition of short QT on the basis of previous studies, the cutoff value matching the 0.15 percentile of our whole population (234 male patients with QTc interval ≤362 ms, 193 female patients with QTc interval ≤369 ms). Furthermore, we divided the short QT population into percentiles and selected the 2.5 percentile of the short QT population as the very short QT (Table 2).

## Clinical characteristics of short QT interval

Four hundred twenty-seven patients with short QT interval were chosen for the analysis according to the abovementioned rationale. The prevalence of patients with a short QT interval was about 1.2 times higher in male patients (N = 234) than in female patients (N = 193). The mean age was not different between male and female patients (41.9 ± 21.5 years vs 45.2 ± 23.4 years). Table 3 shows clinical characteristics of the patients with short and very short QTc intervals. The mean age was not different between short and

**Table 1** The lowest percentiles of Bazett QTc interval for this study population

| | Bazett QTc interval (ms) | |
|---|---|---|
| Percentile | Male | Female |
| 2.5 | 380.0 | 387.0 |
| 2.0 | 378.0 | 386.0 |
| 1.0 | 373.0 | 381.0 |
| 0.5 | 369.0 | 376.0 |
| 0.15 | 362.0 | 369.0 |
| 0.1 | 361.0 | 367.0 |
| 0.0 | 331.0 | 329.0 |

**Table 2** The percentiles for patients with short QT interval

| Percentile | Bazett QTc interval (ms) | |
|---|---|---|
| | Male | Female |
| 100 | 362.0 | 369.0 |
| 99.5 | 362.0 | 369.0 |
| 97.5 | 362.0 | 369.0 |
| 90 | 362.0 | 369.0 |
| 75 | 361.0 | 368.0 |
| 50 | 359.0 | 366.0 |
| 25 | 355.0 | 362.0 |
| 10 | 349.0 | 355.4 |
| 2.5 | 340.6 | 345.9 |
| 0.5 | 331.2 | 329.0 |
| 0.0 | 331.0 | 329.0 |

very short QT intervals in both genders. There was a 1.8-fold male predominance in patients with very short QT interval. There are various underlying diseases, in which rate did not differ between short and very short QTc intervals in both genders. Figure 2 shows the age-specific prevalence of total, male, and female patients with short QT interval. The histograms generated according to the number of patients are shown in the upper row of Figure 2. The prevalence was biphasic in each group, with a higher prevalence in young and old adults and with a lower prevalence in middle-aged individuals. The prevalence showed comparable distribution when histograms were generated according to a ratio of patients with short QT interval to total patients in each decade (the lower row in Figure 2).

## ECG characteristics of short QT interval

Table 4 lists ECG characteristics. There was no significant difference in various ECG variables between patients with short and very short QT intervals. AF was present in 23 of 234 (9.8%) male and 16 of 193 (8.3%) female patients ($P$ = NS). The prevalence of AF did not differ significantly between patients with short and very short QT intervals in both genders. The prevalence of early repolarization was significantly ($P$ = .0001) higher in 23 of 234 (9.8%) male than in 3 of 193 (1.6%) female patients, but was not significantly different between patients with short and very short QT intervals in both genders. In these patients, 11 (42.3%) exhibited early repolarization in anterior leads (V1-4); 9 (34.6%) patients in inferolateral leads (II, III, aVF, V5, 6); and 5 (19.2%) patients in anteroinferior leads (V1-4, II, III, aVF).

## Long-term outcome

Long-term prognosis was assessed in 327 of 427 (77%) patients (182 men; mean age, 46.4 ± 22.3 years) with short QT interval. The mean follow-up period was 54.0 ± 62.0 months (range 1.1 to 299.8 months). In patients whose prognosis was evaluated, QT interval was 360.3 ± 24.8 ms and QTc interval was 359.8 ± 7.1 ms. During the follow-up period, 2 male patients developed life-threatening events. One patient was a 22-year-old man who exhibited early repolarization. This patient was admitted to our hospital because he suffered from syncope when drinking in 1989. There was nephritic syndrome in his past medical history, but no family history of cardiac disorders or sudden unexplained death. On admission, 12-lead ECG exhibited early repolarization in ECG leads corresponding to the inferolateral wall of the left ventricle (Figure 3). This patient revealed no evidence of abnormality of cardiac function and morphology by transthoracic echocardiography. Coronary angiography failed to find morphological abnormality, and coronary spasm was not induced by ergonovine injection. However, ventricular fibrillation occurred when the ECG recording was taken after hyperventilation. Because sinus bradycardia preceded the occurrence of ventricular fibrillation, orciprenaline sulfate (30 mg/day) was administered. Seven years later, the patient experienced a storm of ven-

**Table 3** Clinical characteristics in patients with short and very short QT intervals

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | Very short (≤355 ms, N = 65) | Short (356 to 362 ms, N = 169) | $P$ value | Very short (≤360 ms, N = 36) | Short (361 to 369 ms, N = 157) | $P$ value |
| Age (yrs) | 43.6 ± 23.4 | 41.2 ± 20.8 | .46 | 46.3 ± 24.9 | 45.0 ± 23.1 | .77 |
| Hypertension (N, %) | 13, 20.0 | 31, 23.9 | .54 | 10, 27.8 | 27, 26.7 | .90 |
| Angina (N, %) | 6, 9.2 | 15, 11.5 | .62 | 1, 2.8 | 12, 11.9 | .08 |
| Myocardial infarction (N, %) | 4, 6.2 | 3, 2.3 | .19 | 2, 5.6 | 1, 1.0 | .14 |
| Valvular disease (N, %) | 2, 3.1 | 8, 6.2 | .34 | 3, 8.3 | 7, 6.9 | .78 |
| Heart failure (N, %) | 12, 18.5 | 22, 16.9 | .79 | 6, 16.7 | 18, 17.8 | .88 |
| Arrhythmia (N, %) | 19, 29.2 | 25, 19.2 | .12 | 7, 19.4 | 15, 14.9 | .53 |
| Diabetes (N, %) | 8, 12.3 | 23, 17.7 | .32 | 4, 11.1 | 15, 14.9 | .57 |
| Dyslipidemia (N, %) | 7, 10.8 | 22, 16.9 | .24 | 6, 16.7 | 18, 17.8 | .88 |
| Follow-up (months) | 42.1 ± 47.3 | 54.0 ± 64.6 | .20 | 49.3 ± 65.7 | 49.7 ± 62.7 | .98 |
| Death (N, %) | 3, 4.6 | 3, 1.8 | .24 | 0, 0 | 0, 0 | — |
| Ventricular fibrillation (N, %) | 1, 4.2 | 0, 0 | — | 0, 0 | 0, 0 | — |

Arrhythmia involves patients with various types of rhythm disorders, except for patients who exhibited AF when the ECG was taken. Surgery indicates patients who underwent ECG recording before surgical procedure. Others includes patients who suffered various internal diseases or who were suspected to have a cardiovascular disease.

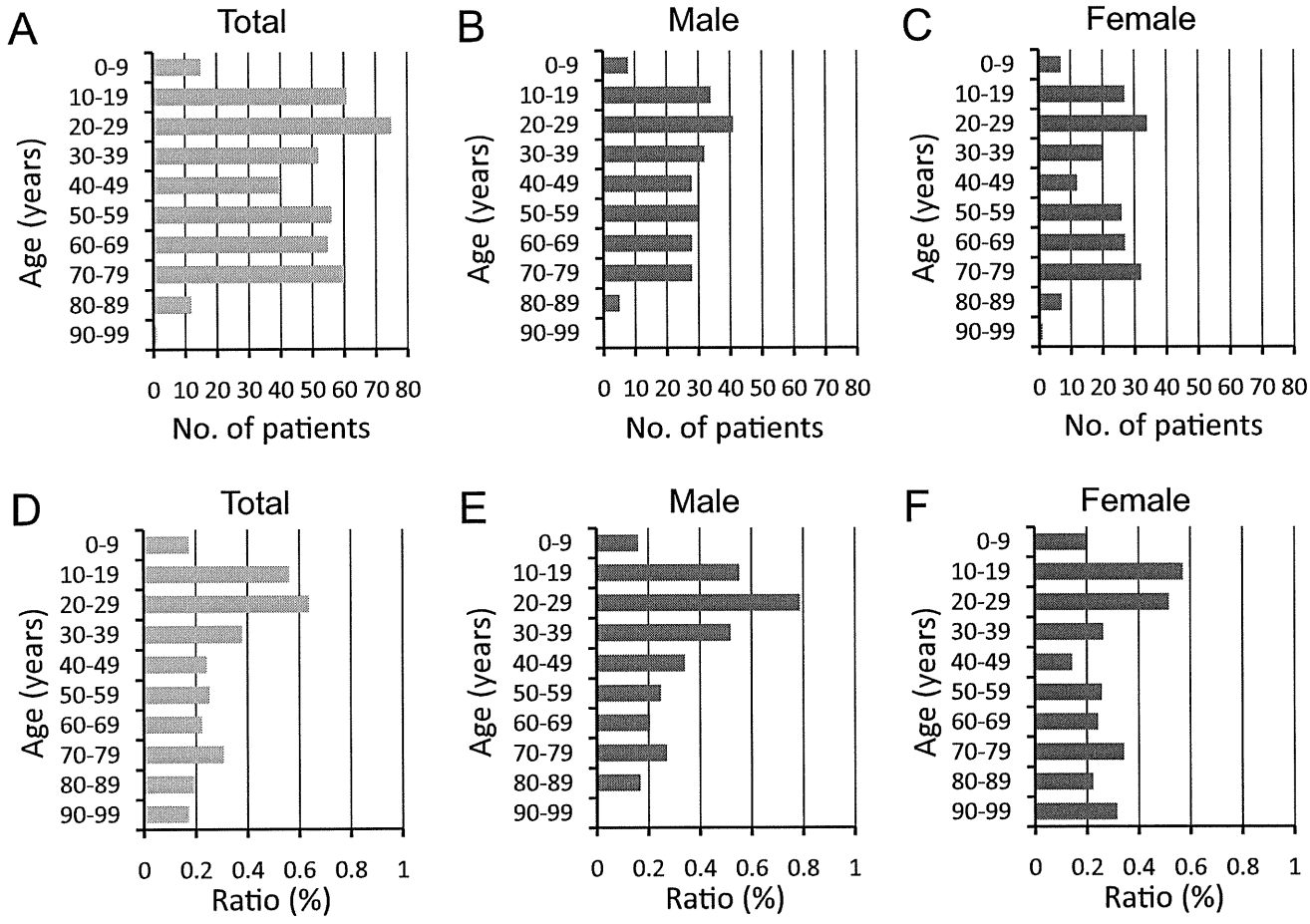


**Figure 2** Age-specific prevalence of patients with short QT interval in decades according to the number of patients (upper row) and a ratio of patients to the total population of this study (lower row). Histograms of total, male, and female patients are displayed in panels A and D, B and E, and C and F, respectively.

tricular fibrillation (5 repetitive attacks per day) that occurred when bradycardia occurred (Figure 3B). A ventricular pacing lead was emergently introduced into the right ventricle to maintain rapid heart rate. Subsequently, a permanent pacemaker was implanted (DDDR mode, 80 beats/min). Six years after the storm, ventricular fibrillation recurred during a routine pacemaker check. Ventricular fibrillation repeatedly initiated after bradycardia because of threshold margin check. The patient received an implantable cardioverter-defibrillator with atrioventricular sequential pacing applied at a rate of 85 beats/min. Another 54-year-old man developed repetitive syncopal episodes with urinary incontinence in 2001 when sleeping. This patient did not exhibit early repolarization (Figure 4). He did not have a family history of cardiac disorders or sudden unexplained death. This patient revealed no evidence of abnor-

**Table 4** ECG characteristics in patients with short and very short QT intervals

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | Very short (≤355 ms, N = 65) | Short (356 to 362 ms, N = 169) | *P* value | Very short (≤360 ms, N = 36) | Short (361 to 369 ms, N = 157) | *P* value |
| Heart rate (beats/min) | 58.7 ± 8.3 | 60.3 ± 8.5 | .20 | 60.6 ± 8.5 | 63.3 ± 9.8 | .13 |
| P wave axis (degree) | 49.2 ± 37.5 | 47.8 ± 25.3 | .77 | 47.7 ± 29.4 | 38.8 ± 28.5 | .12 |
| PQ interval (ms) | 165.4 ± 37.2 | 163.4 ± 36.9 | .75 | 161.7 ± 46.6 | 156.3 ± 39.0 | .50 |
| QRS complex duration (ms) | 92.6 ± 8.4 | 92.3 ± 10.0 | .82 | 87.5 ± 7.9 | 85.9 ± 8.4 | .30 |
| R wave axis (degree) | 49.3 ± 32.8 | 57.3 ± 27.1 | .060 | 50.6 ± 31.7 | 53.4 ± 26.4 | .58 |
| QT interval (ms) | 357.4 ± 23.7 | 362.6 ± 22.9 | .12 | 355.4 ± 25.0 | 360.2 ± 25.8 | .31 |
| T wave axis (degree) | 46.8 ± 48.5 | 48.0 ± 34.9 | .83 | 43.2 ± 45.4 | 48.0 ± 56.7 | .64 |
| Atrial fibrillation (N, %) | 10, 15.4 | 13, 7.7 | .089 | 1, 2.8 | 15, 9.6 | .14 |
| Early repolarization (N, %) | 3, 4.6 | 20, 11.8 | .076 | 1, 2.8 | 2, 1.3 | .54 |

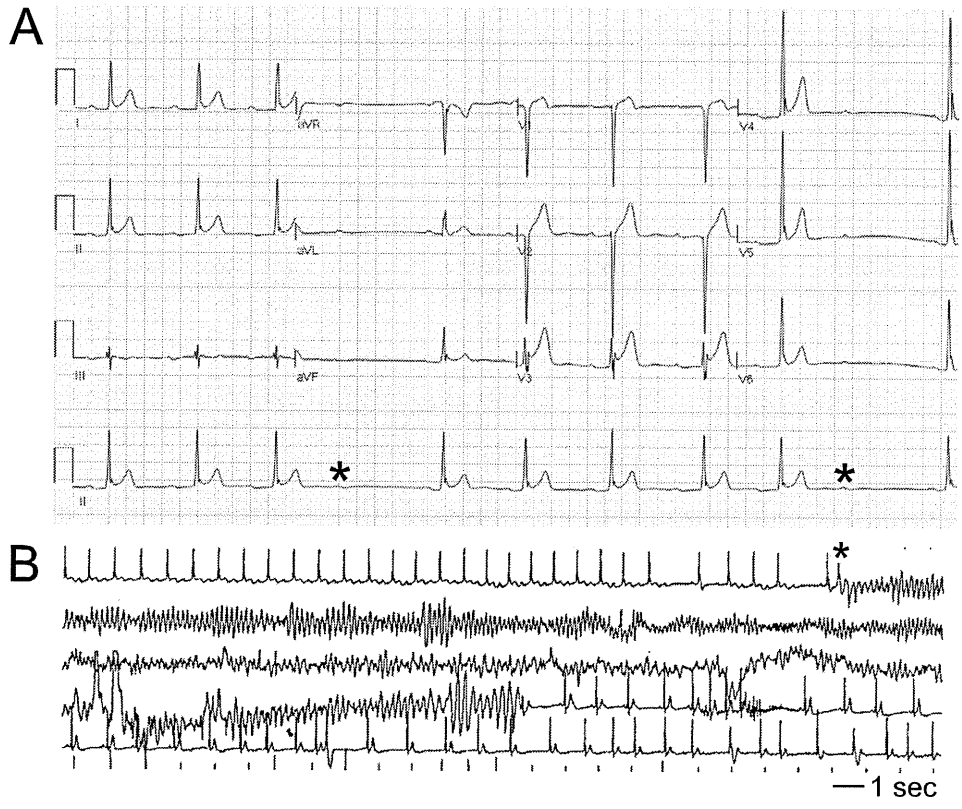


**Figure 3** **A:** Twelve-lead ECG of a 22-year-old male patient who developed ventricular fibrillation. Mean heart rate is 50 beats/min; mean QT interval, 364 ms; and mean QTc interval, 332 ms. Early repolarization is present in leads I, II, aVF, and V3-6. *Nonconducting P wave due to Wenckebach atrioventricular block. **B:** Monitored ECG showing occurrence of ventricular fibrillation. *A short-coupled ventricular premature contraction initiated ventricular fibrillation that lasted for >1 minute and then self-terminated.

mality of cardiac function and morphology by transthoracic echocardiography and coronary angiography. His ECG showed Brugada-type ECG after intravenous administration of pilsicainide (Figure 4B). The ST-segment elevation in right precordial leads was accepted as sign of Brugada syndrome in the context of a clinical history, suggesting malignant syncope in this patient. To secure this patient from sudden death, an implantable cardioverter-defibrillator was implanted. These 2 patients did not have gene abnormalities, including *KCNQ1*, *KCNH2*, and *SCN5A*. In addition, we confirmed 6 deceased patients: 2 patients died of pneumonia at 70 and 72 years of age; 1 patient, congestive heart failure at 74 years of age; 1 patient, pancreatic cancer at 70 years of age; 1 patient, colon cancer at 74 years of age; and 1 patient, an unknown cause at 79 years of age. These 6 patients did not have early repolarization. AF was present in 1 patient who died of pneumonia.

## Discussion

In the present study, we demonstrated detailed characteristics of patients with short[10–12] QT interval in a large hospital-based population. Consistent with previous reports, patients with short QT interval were rare and had a male preponderance. The age-specific prevalence of patients with short QT interval showed a biphasic distribution with a relatively low prevalence in middle-aged patients. Long-term prognostic assessment revealed that 2 male patients with short QT interval suffered from life-threatening events in this study population.

## Characteristics of short QT interval

The present study disclosed distinct characteristics regarding patients with short QT interval. The gender difference in the prevalence of short QT interval that was manifested in this study is presumably due to sex-specific biology, including hormone, membrane ion channel availability, and intracellular signal transduction. A male predominance of patients with short QT interval shown in this study is similar to the fact that QT interval is generally longer in female[13–15] than in male patients. Of interest, the pattern of prevalence of patients with short QT interval exhibited inhomogeneous distribution with 2 peaks at young and old ages in both genders. Although we do not know the mechanism by which this age-dependent distribution had 2 peculiar peaks in patients with short QT interval, one can speculate that the underlying mechanism of short QT interval may be different between young and aged patients because health condition is apparently diverse between them. Further investigations will be needed to explore the mechanism underlying the gender difference and age-specific distribution. Contrary to a previous report,[11] the prevalence of short QT interval in patients with heart rate of <50 beats/min (male, 2.4%;

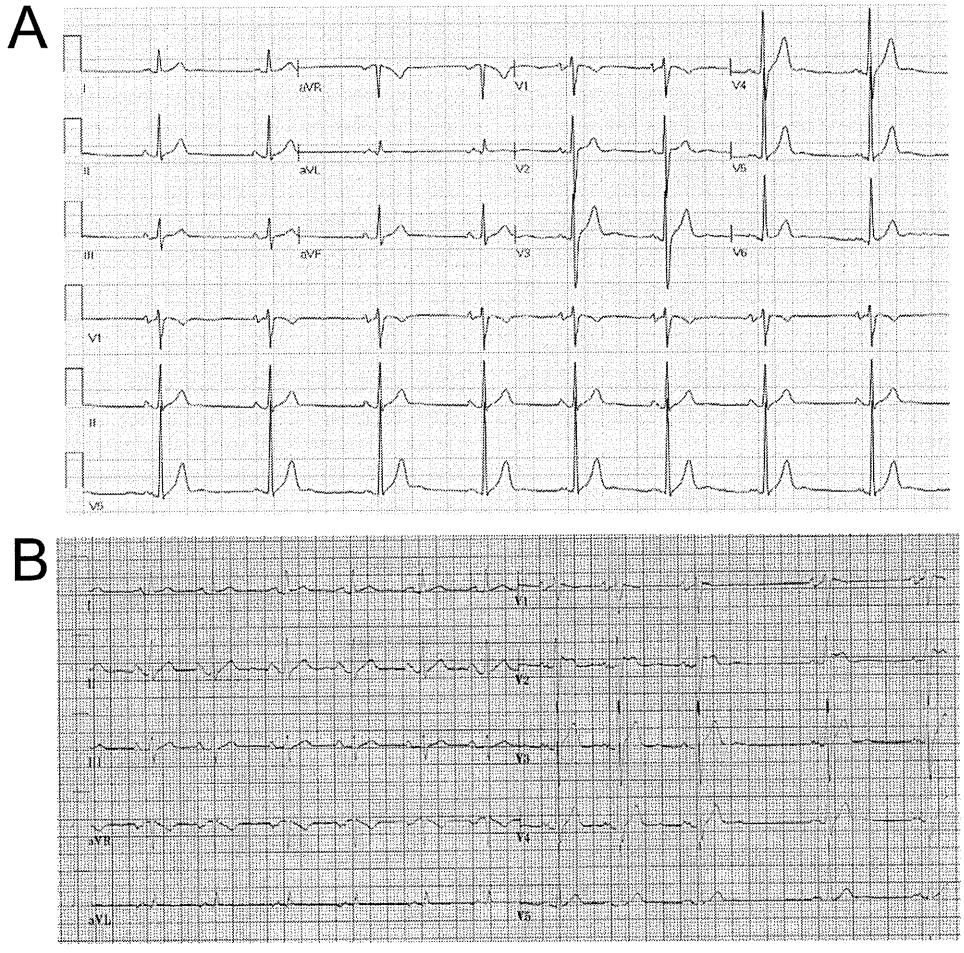


**Figure 4** **A:** Twelve-lead ECG of a 54-year-old male patient who developed syncope repeatedly. Mean heart rate is 51 beats/min; mean QT interval, 386 ms; and mean QTc interval, 355 ms. Early repolarization is absent. **B:** ST-segment elevation in right precordial leads by intravenous administration of pilsicainide.

female, 1.6%) was comparable to that in total patients in this study. This is probably due to differential study populations; specifically, the present study population includes only hospital-based patients, and it is therefore possible that many of the patients with slow heart rate were receiving medications that prolonged their QT interval. In contrast, Kobza et al[11] reported on healthy army recruits. We investigated 2 ECG complications of short QT interval: AF and early[4,5,16,17] repolarization. It was reported that AF occurred in patients with short QT syndrome. In this study, the complication rate of AF was much higher compared with the prevalence of AF in the general population of Japan[18] and in total patients in this study (male, 4.1%; female, 1.9%), suggesting atrial involvement of abbreviated action potential with sharing the same mechanism as is present in the ventricle. Early repolarization was usually present in 1% to 5%[19,20] of general populations, which was regarded as benign. The prevalence of early[19,20] repolarization of this study was a little higher than that of those studies and that of the total population of this study (3.9%), but was lower than that of short QT syndrome.[8] To date, Haissaguerre et al[21] reported malignant early repolarization syndrome. In addition, Kamakura et al[22] found that early repolarization was associated with poor outcome in patients with Brugada-type ECG. In these reports, early repolarization was present in inferolateral leads. In contrast, our patient had early repolarization most frequently in anterior leads. Thus, the location of early repolarization may matter in terms of occurrence of life-threatening events.

## Short QT interval and short QT syndrome

There may be overlap between the QTc intervals of patients with and without inherited short QT syndrome.[9] The syndrome characterized by extremely abbreviated QT[23,24] interval causes sudden cardiac death. Gene mutation that causes a gain of function in the $K^+$ channel is attributed to this shortening in this syndrome, suggesting that a specific family[5,16,25] member is affected with this disorder. In general, the QTc interval was <300 ms[4,5,26,27] in subjects with short QT syndrome. In contrast, Antzelevitch et al reported Brugada-type ST-segment elevation in probands whose QT interval was approximately 360 ms. In their cases, gene mutation encoding L-type calcium channel was detected, and those subjects died suddenly. Recently, a mutation of

*KCNJ8* was identified in patients with idiopathic ventricular fibrillation and early repolarization, which might be attributed to sudden death.[28] A new mutation in calcium channel regarding congenital short QT syndrome type 6 was reported.[29] A proband of this mutation had a short QT interval of 329 ms; however, a genotype-positive grandmother had a normal QT interval of 432 ms, although she had myocardial infarction. This study suggests that a phenotypical QT interval might be modified by myocardial necrosis in this syndrome, giving rise to normalization. Thus, one has to consider lack of genotype-phenotype correlation in short QT syndrome. However, genetic mutation was not detected in 2 patients who experienced life-threatening events in this study. Therefore, further investigations of gene analysis are needed in these patients.

## Arrhythmogenesis in short QT interval

Gallagher et al[12] reported that a QTc interval of ≤330 ms was extremely rare in healthy subjects and did not bear a significant risk of sudden death. However, in our hospital-based population, 2 patients with short QTc interval developed life-threatening events. An experimental study that dealt with an association of early repolarization with ventricular fibrillation showed that modulating factors amplified transmural electrical heterogeneity that caused early repolarization to generate reentry.[26] In this study, 1 patient who experienced bradycardia-dependent occurrence of ventricular fibrillation presented J wave. This finding suggests manifestation of transmural electrical gradient during slow heart rate,[30–32] which is consistent with previous reports. Another patient who exhibited Brugada-type ECG after the administration of sodium channel blocker suggests that a mechanism underlying life-threatening events in short QT syndrome may be similar to a mechanism accounting for ventricular fibrillation in Brugada syndrome. In clinical practice, it is difficult to diagnose short QT syndrome unless a subject is symptomatic. Indeed, 2 patients who had developed life-threatening events in this study were found to have a short QT interval afterward. This finding indicates incidental discovery of short QT syndrome.

## Study limitations

First, patients enrolled in this study were derived from a hospital-based population, indicating that our data do not properly apply to a general population. Because our data were based on the hospital population, patients who had organic heart diseases or took drugs with QT-prolonging effects were involved. We could not search medication uses thoroughly, as Ramirez et al[33] did. In addition, patients with bundle branch block or pre-excitation syndrome were not excluded from the analysis. The QT interval was longer when computer-assisted measure was performed as compared with manual measure of QT interval in lead V5. These underlie the right-skewed distributions of QTc interval. The fact that we included patients with medications probably had a limited effect on the number of patients with very short QT because medications (and conditions such as bundle branch block) tend to prolong the QT, not to shorten it. Second, we could assess the prognosis of 327 patients (77%) with short QT interval. However, the long-term outcome was not thoroughly investigated and the follow-up period was not long enough. Further assessment is necessary to clarify the prognosis of patients with short QT interval. Third, it must be considered how to correct QT interval. Correlation of QT interval by the Bazett formula has a tendency to overestimate or underestimate QT interval when heart rate is particularly fast or slow, respectively. We first set the heart rate to ranging from 50 to 100 beats/min not to include overestimation and underestimation of QT interval by the Bazett formula. Even in an additional analysis in patients with heart rate <50 beats/min, the prevalence of short QT interval was similar to that in the first analysis. This might be attributed to our hospital-based population.

## Conclusion

Until now, there have been mounting reports of short QT syndrome. Nevertheless, ECG features of prognostic significance are still lacking. This study proposed that early repolarization concomitant with short QT interval indicates a potential for sudden cardiac death. The complication rate of AF and early repolarization was higher in patients with short QT interval than in a general population and total patients of this study. Although our database contains a huge number of ECGs, we could assess a rather small group of patients with short QT interval. This implies that multicenter clinical research will be required to further determine the prognostic value of short QT interval. Despite the small number of patients enrolled in this study, the findings could shed light on the prognostic value of early repolarization in patients with short QT interval.

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## Appendix

### Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.hrthm.2011.08.016.

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# Clinical Characteristics and Genetic Background of Congenital Long-QT Syndrome Diagnosed in Fetal, Neonatal, and Infantile Life
## A Nationwide Questionnaire Survey in Japan

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***Background***—Data on the clinical presentation and genotype-phenotype correlation of patients with congenital long-QT syndrome (LQTS) diagnosed at perinatal through infantile period are limited. A nationwide survey was conducted to characterize how LQTS detected during those periods is different from that in childhood or adolescence.

***Methods and Results***—Using questionnaires, 58 cases were registered from 33 institutions. Diagnosis (or suspicion) of LQTS was made during fetal life (n=18), the neonatal period (n=31, 18 of them at 0 to 2 days of life), and beyond the neonatal period (n=9). Clinical presentation of LQTS included sinus bradycardia (n=37), ventricular tachycardia/torsades de pointes (n=27), atrioventricular block (n=23), family history of LQTS (n=21), sudden cardiac death/aborted cardiac arrest (n=14), convulsion (n=5), syncope (n=5), and others. Genetic testing was available in 41 (71%) cases, and the genotype was confirmed in 29 (71%) cases, consisting of LQT1 (n=11), LQT2 (n=11), LQT3 (n=6), and LQT8 (n=1). Ventricular tachycardia/torsades de pointes and atrioventricular block were almost exclusively observed in patients with LQT2, LQT3, and LQT8, as well as in those with no known mutation. In LQT1 patients, clues to diagnosis were mostly sinus bradycardia or family history of LQTS. Sudden cardiac death/aborted cardiac arrest (n=14) was noted in 4 cases with no known mutations as well as in 4 genotyped cases, although the remaining 6 did not undergo genotyping. Their subsequent clinical course after aborted cardiac arrest was favorable with administration of β-blockers and mexiletine and with pacemaker implantation/implantable cardioverter-defibrillator.

***Conclusions***—Patients with LQTS who showed life-threatening arrhythmias at perinatal periods were mostly those with LQT2, LQT3, or no known mutations. Independent of the genotype, aggressive intervention resulted in effective suppression of arrhythmias, with only 7 deaths recorded. (***Circ Arrhythm Electrophysiol.* 2010;3:10-17.)**

**Key Words:** arrhythmia ■ long-QT syndrome ■ genes ■ death (sudden)

Congenital long-QT syndrome (LQTS) is an inherited disorder characterized by polymorphic ventricular tachycardia (VT), or torsades de pointes (TdP), syncope, and sudden cardiac death.[1] LQTS is often diagnosed in children from school age to young adulthood[2] and sometimes during fetal, neonatal, and infantile life.[3–5] Previous case reports

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**Table 1. Questionnaire Items**

1. Patient: Serial No. in each institution, initials, birth year, and month, sex
2. Age at diagnosis or suspicion (including gestational age for a fetus)
3. Clinical symptoms: Fetal arrhythmias, fetal heart failure, syncope, convulsion, heart failure, aborted cardiac arrest, others
4. ECG findings and arrhythmias (heart rate, QTc on ECG at presentation, sinus bradycardia, VT/TdP, atrioventricular block, other arrhythmias)
5. Family history of LQTS or other arrhythmias or sudden cardiac death (which member, and their outcome?)
6. Genotype
7. Treatment (acute therapy and maintenance therapy)
   pharmacotherapy (which drug, dose, age at initiation, and duration)
   device therapy (pacemaker implantation/implantable cardioverter-defibrillator) and age at application
8. Duration of follow-up
9. Outcome (alive or death, and neurological sequels of cardiac arrest)

suggest that the latter cases are at higher risk of development of life-threatening arrhythmias necessitating emergency treatment[3–5] and show higher mortality rates than the former age groups.[3,5–11] For example, recent progress in molecular biology has clarified that LQTS partly contributes to sudden infant death syndrome (SIDS).[12,13] Unfortunately, prenatal diagnosis of LQTS has been extremely difficult to confirm except for a limited number of cases for which prenatal gene screening[14] or fetal magnetocardiography (fMCG)[15–17] was applied.

**Clinical Perspective on p 17**

Thus, the clinical presentation, the genotype-phenotype correlation, and the outcome of patients with fetal, neonatal, or infantile presentation of LQTS remain to be elucidated. The purposes of this study were first, to report the findings of a nationwide survey conducted to define the clinical characteristics and the genotype-phenotype correlation, and second, to report the outcome of patients with LQTS diagnosed before birth and in the first year of life.

## Methods

### Population

The study population included fetuses, neonates, and infants (<1 year of age) diagnosed with LQTS based on ECG findings including prolonged QTc >0.46 seconds (using Bazett formula), with or without VT/TdP, who had no structural heart disease, family history of LQTS, or had undergone genetic testing. Those with normal QTc duration and no gene mutation known to cause LQTS were excluded. Patient data were collected using questionnaires. The form was sent to those councilors of the Japanese Society of Pediatric Cardiology and Cardiac Surgery who responded to a preliminary survey that they had 1 or more cases of LQTS diagnosed during fetal, neonatal, and infantile life. The items obtained from the responders are presented in Table 1.

The study protocol was approved by the Ethics Committee of the University Hospital of Tsukuba, and informed consent was obtained from each patient (or parents, if the patient was younger than 15 years of age) by a coordinator in charge in each institution before the patient's data were registered.

### Genetic Analysis and Genotype-Phenotype Correlation

Genetic analyses were performed in 4 established laboratories in Japan. DNA was isolated from blood samples in each patient. Screening for mutations of at least 3 major genes causing LQTS (*KCNQ1, KCNH2, SCN5A*) was performed using polymerase chain reaction (PCR)/single-strand conformation polymorphism or denatured high-performance liquid chromatography analysis. For aberrant PCR products, DNA sequencing was conducted with a DNA sequencer (ABI 3700 and ABI 3130xl, Applied Biosystems, Foster City, Calif). For those subjects in whom genotype was confirmed and those who underwent genetic analysis but found to have no mutation, genotype-phenotype correlations (or mutation-negative phenotype correlations) with the aforementioned items (Table 1) were investigated.

### Statistical Analysis

All statistical calculations were conducted using the R software. Quantitative variables (heart rate [HR] and QTc) are presented as mean±SD and categorized variables (presence of FH, sinus bradycardia, VT/TdP, and atrioventricular block [AVB]) as proportions (percentages). One-way ANOVA was applied for comparisons of continuous variables, followed by pairwise comparisons with Bonferroni adjustment of probability values among 4 groups (LQT1, LQT2, LQT3, and mutation-negative groups). The equality of proportions for categorical variables among the 4 groups was examined by the $\chi^2$ test (global test). When there was a significant difference in proportions, we performed pairwise comparisons between pairs of proportions with correction for multiple testing using Bonferroni inequality of probability values. Tests were 2-sided, and a probability value <0.05 was considered significant.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

## Results

### Population

A total of 58 cases (all Japanese; males 30, females 28) were registered from 33 institutions. Forty-one were born during the last 10 years (between 1999 and 2008), 14 between 1989 and 1998, 1 in 1986, and 2 in 1984. LQTS was diagnosed or suspected during fetal life at 18 to 40 weeks of gestation in 18 individuals, during neonatal life at 0 to 28 days in 31, and in infancy (<1 year) at 1 to 9 months in 9.

### Clinical Features

For 18 fetuses with LQTS, clinical presentation (or clues to diagnosis or suspicion of LQTS) included bradycardia (15 cases), AVB (8 cases), VT/TdP (7 cases), and family history of LQTS (6 cases), including 1 family with a previous intrauterine death (items overlapped in some cases). Two fetuses were confirmed to be LQTS by fMCG, with QTc values of 570 and 680 on fMCG, and 590 and 700 on ECG soon after birth, respectively (these 2 cases have been reported previously).[16,17] No fetal death was noted in this group.

For 31 neonates with LQTS, the most frequent feature was sinus bradycardia (17 cases), followed by VT/TdP (15 cases), positive family history of LQTS (15 cases), including 1 with previous intrauterine death and 1 with infantile death, AVB (10 cases), syncope (5 cases), convulsion (5 cases), and others (items overlapped in some cases). Among the 31 neonatal cases, 18 (70%) were diagnosed within 2 days of life, and 8 of them had some significant fetal presentation (4 bradycardia or bradyarrhythmias, 4 tachyarrhythmias, and 1 hydrops), retrospectively.

As described above, the number of patients with LQTS diagnosed during infancy beyond the neonatal period was only 9. The clinical presentation of these patients included sinus bradycardia (5 cases), sudden cardiac death (SCD)/


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aborted cardiac arrest (ACA) (5 cases), AVB (5 cases), VT/TdP (5 cases), and other miscellaneous abnormalities.

The ECG on diagnosis, or immediately after birth for fetal cases, showed that the HR and QTc interval (corrected using Bazett formula) ranged from 50 to 160 (102±28) bpm, and from 360 to 774 (563±70) ms, respectively.

## Genotype-Phenotype Correlation

Among 41 patients who underwent genetic testing, mutations were identified in 29 (71%) cases; including *KCNQ1* gene mutations (LQT1) in 11, *KCNH2* mutations (LQT2) in 11, *SCN5A* mutations (LQT3) in 6, and *CACNA1C* (LQT8) in 1. Twelve patients also underwent genotyping, but no mutation was found. Table 2 lists the demographic and clinical features of these subjects (references 16, 17, and 23 reported the same cases 2, 12, and 27 in Table 2) and of those with no known mutations.

The remaining 17 subjects (6 fetuses, 8 neonates, 3 infants) did not undergo genetic analysis due to lack of such analysis at that time, death soon after birth, or refusal by parents. Five had SCD/ACA (Table 3), including a 1-day-old neonate who had AVB and died at 57 days of age in 1984. This case was later assumed to be LQT8, based on characteristic phenotypes such as syndactyly. AVB and VT/TdP were observed in 7 and 5 cases, respectively, in this group.

Although HR and QTc values were not different among LQT1, LQT2, LQT3, and mutation-negative groups, the incidence of VT/TdP was higher in LQT2 and LQT3 compared with LQT1 (Table 4). The incidence of AVB tended to be higher in LQT3 compared with LQT1 but statistically insignificant. On the other hand, the presence of family history of LQTS was more frequent in LQT1 than the mutation-negative group. The incidence of sinus bradycardia was comparable among the 4 groups (Table 4).

Table 3 lists cases with SCD/ACA; only 4 genetically confirmed cases were included, and 4 were mutation-negative, although the remaining 6 cases did not undergo genotyping. These individuals showed bradycardia (97±31 bpm; 10/14 showed HR <110 bpm) and markedly prolonged QTc (617±81 ms).

## Treatment

With regard to the treatment of fetal VT/TdP, antiarrhythmic agents were administered transplacentally in 4 of 18 fetal cases (propranolol in 3 cases, lidocaine in 1, mexiletine in 1, flecainide in 1, and magnesium in 1), using the method described in detail in our previous report.[17] None of the 4 cases was genetically confirmed prenatally. When 2 or 3 of the following findings of sinus bradycardia, VT, and AVB were observed in a structurally normal heart, LQTS was strongly suggested, and β-blockers, sodium channel blockers (lidocaine, mexiletine), and magnesium (Mg) were selected as typical antiarrhythmic agents, instead of amiodarone or sotalol, which may prolong the QT interval. These drugs were used in combination until VT/TdP was controlled and proved effective in all 4 cases. However, preterm delivery was conducted in 2 cases both at 33 weeks of gestation due to recurrent VT/TdP and depression of fetal physical activity in one and to fetal hydrops and distress in the other. In the remaining 14 cases, pharmacotherapy was initiated after confirmation of the type of arrhythmias after birth. However, no fetal death was noted.

For 15 neonatal cases who presented with VT/TdP (including those who did not undergo genotyping), acute pharmacotherapy consisted of 2 or more of the following drugs: β-blockers, mexiletine, lidocaine, Mg, phenytoin, and others, except for 2 cases who were treated with phenytoin alone and 1 with mexiletine alone. Most of these cases were judged to respond the combination therapy. In 5 neonates in whom LQT3 was strongly suggested based on a typical ECG finding called late-appearing T wave, mexiletine was first administered but proved insufficient, and β-blockers were also added in all 5.

For those with LQTS presenting in infancy, 6 cases received acute pharmacotherapy (2 or all of propranolol, mexiletine, and Mg). No additional agent was administered. Thus, in all age groups, the acute therapy for VT/TdP consisted of a single drug to which 1 or more drugs was then added until the arrhythmia was controlled, independent of the genotype. Actually, the genotype was not identified during the acute phase in most cases. Furthermore, genotyping was not conducted in those 17 cases who presented before 1999.

Maintenance therapy consisted mainly of β-blockers (or no therapy) for LQT1 and mostly of mexiletine/β-blockers for LQT2 and LQT3 (Table 2). β-Blockers were added in 8 LQT2 cases after confirmation of the genotype. In all 6 LQT3 cases, mexiletine was maintained (combined with β-blockers) from acute through chronic phase after determination of the genotype.

Nine patients underwent pacemaker implantation (PMI), 5 with ventricular pacing mode (VVI) and 1 with atrial pacing mode (AAI), from age 1 day to 8 years due to severe bradycardia caused by AVB, inducing VT/TdP. In 6 cases, VT was completely suppressed after PMI. Only 2 patients had an implantable cardioverter-defibrillator (ICD) at ages 4 (LQT3) and 25 months (mutation negative), respectively, due to recurrent VT/TdP with satisfactory results.

## Outcome

During the follow-up period of 8 days to 23.5 years (median, 4.25 years), 7 SCD and 7 ACA were registered (age at SCD or ACA range, 8 days to 10 years; median, 10.5 months); 6 did not have genetic testing, whereas 4 showed no mutation. Only 4 were genetically confirmed (Table 3). One case was later suspected to be LQT8, based on the phenotype including syndactyly. Among the 14 SCD/ACA cases, 12 had been under pharmacotherapy, 5 with both β-blockers and sodium channel blockers, and 2 had had PM or ICD. Four cases developed significant neurological deficits after cardiorespiratory resuscitation.

# Discussion

The noteworthy finding of the present study was that 49 of 58 cases (84%) were diagnosed at the fetal or neonatal period, although this survey covered the entire infantile period. Remarkably, two thirds of the neonatal cases were diagnosed within 2 days of life; this period should be recognized as the most vulnerable period. The number of cases diagnosed after the neonatal period was only 9. Considering that the average age at appearance of symptoms in LQT2 and LQT3 is after


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**Table 2. Clinicogenetic Details**

| Case | LQT Type | Mutation | Age at Diagnosis/Sex | Clinical Presentation | FH | HR, bpm | QTc, ms |
|---|---|---|---|---|---|---|---|
| 1 | LQT1 | Thr587Met | Fetus/M | FH, brady | + | 109 | 561 |
| 2 | LQT1 | Ala341Val | Fetus/M | Brady | + | 110 | 590 |
| 3 | LQT1 | Ala341Val | Neonate/M | FH | + | 110 | 520 |
| 4 | LQT1 | Ile313Lys | Neonate/M | FH | + | 102 | 589 |
| 5 | LQT1 | Ile313Lys | Neonate/M | FH | + | 115 | 554 |
| 6 | LQT1 | 276delSer | Neonate/M | Prolonged QT | + | 115 | 570 |
| 7 | LQT1 | Asp611Tyr | Neonate/M | Brady | + | 80 | 550 |
| 8 | LQT1 | Asp611Tyr | Neonate/F | FH | + | ND | ND |
| 9 | LQT1 | Thr458Met | Neonate/M | FH | + | 126 | 530 |
| 10 | LQT1 | Gly643Ser | Infant/M | ACA | − | 109 | 554 |
| 11 | LQT1 | Gly269Ser | Infant/F | Cyanosis | − | 113 | 586 |
| | | | | | 82% | 109±12 | 560±24 |
| 12 | LQT2 | Gly628Ser | Fetus/M | VT/TdP, AVB | − | 50 | 631 |
| 13 | LQT2 | del(7)(q32qter) | Fetus/F | TdP | − | 111 | 492 |
| 14 | LQT2 | Ser243+112X | Fetus/F | FH | + | 160 | 360 |
| 15 | LQT2 | Gly628Ala | Fetus/F | Syncope, VT/TdP, AVB | + | 78 | 570 |
| 16 | LQT2 | Thr613Met | Fetus/M | VT/TdP, AVB | − | 60 | 578 |
| 17 | LQT2 | Ala561Val | Neonate/M | Cyanosis, VT/TdP | − | 86 | 520 |
| 18 | LQT2 | Gly628Ser | Neonate/M | TdP, brady | − | 111 | 550 |
| 19 | LQT2 | Thr613Met | Neonate/M | convulsion, VT | − | 140 | 599 |
| 20 | LQT2 | Gly572Ser | Neonate/F | TdP, AVB | − | 91 | 520 |
| 21 | LQT2 | Ala614Val | Neonate/F | Syncope, VT | + | 98 | 500 |
| 22 | LQT2 | Asn633Ser | Infant/F | VT/TdP, AVB | − | 60 | 600 |
| | | | | | 27% | 95±34 | 538±74 |
| 23 | LQT3 | Ala1186Thr | Fetus/M | AVB | + | 78 | 679 |
| 24 | LQT3 | Asn1774Asp | Fetus/M | convulsion, VT/TdP, AVB | − | 115 | 670 |
| 25 | LQT3 | Val176Met | Neonate/F | TdP, AVB | + | 63 | 600 |
| 26 | LQT3 | Asn406Lys | Neonate/M | Syncope, TdP | + | 129 | 598 |
| 27 | LQT3 | Arg1623Gln | Neonate/F | Heart failure | − | 79 | 483 |
| 28 | LQT3 | Leu1772Val | Infant/M | ACA | − | 138 | 520 |
| | | | | | 50% | 100±31 | 592±79 |
| 29 | LQT8 | Gly406Arg | Neonate/M | AVB | − | 141 | 581 |
| 30 | Unidentified | − | Fetus/F | Brady | + | 80 | 554 |
| 31 | Unidentified | − | Fetus/M | Brady | − | 100 | 510 |
| 32 | Unidentified | − | Fetus/M | VT | − | 85 | 590 |
| 33 | Unidentified | − | Fetus/M | AVB | − | 80 | 600 |
| 34 | Unidentified | − | Neonate/F | Syncope | − | 100 | 647 |
| 35 | Unidentified | − | Neonate/F | Arrhythmia | − | 126 | 586 |
| 36 | Unidentified | − | Neonate/F | ACA | − | 111 | 638 |
| 37 | Unidentified | − | Neonate/M | Brady | − | 93 | 550 |
| 38 | Unidentified | − | Neonate/F | FH | + | 120 | 520 |
| 39 | Unidentified | − | Infant/F | ACA | − | 160 | 470 |
| 40 | Unidentified | − | Infant/F | ACA | − | 100 | 774 |
| 41 | Unidentified | − | Infant/F | PAC with block | − | 60 | 460 |
| | | | | | 17% | 104±32 | 575±86 |

(Continued)

Cases 2, 12, and 27 are reported in references 16, 17, and 23, respectively. ACA indicates aborted cardiac arrest; AVB, atrioventricular block; BB, β-blocker; brady, bradycardia; FH, family history; HR, heart rate; ICD, implantable cardioverter-defibrillator; Isp, isoproterenol; Lido, lidocaine; Mexil, mexiletine; Mg, magnesium; Nifed, nifedipine; PAC, premature atrial contraction; Pheny, phenytoin; PM, pacemaker; SCD, sudden cardiac death.



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**Table 2. Continued**

| Sinus Brady | VT/TdP | AVB | Acute Therapy | Maintenance Therapy | PMI/ICD | Follow-Up | Outcome |
|---|---|---|---|---|---|---|---|
| + | − | + | − | − | − | 0 mo | Alive |
| + | − | − | − | BB | − | 9 y | Alive |
| + | − | − | − | BB | − | 4 y, 1 mo | Alive |
| + | − | − | − | BB | − | 11 y, 10 mo | Alive |
| + | − | − | − | BB | − | 10 mo | Alive |
| + | − | − | − | − | − | 11 mo | Alive |
| + | − | − | − | − | − | 7 y, 3 mo | Alive |
| + | − | − | − | − | − | 5 y, 8 mo | Alive |
| − | − | − | − | − | − | 4 y, 5 mo | Alive |
| + | − | − | Lido, Mexil | Mexil | − | 9 y, 1 mo | Alive |
| + | − | − | − | − | − | 7 y, 8 mo | Alive |
| 73% | 0% | 9% | | | | Median 68 mo | |
| + | + | + | Lido, Mg, BB, Mexil, Pacing | BB, Mexil | PM | 3 y | Alive |
| + | + | − | − | BB | − | 1 y | Alive |
| − | − | − | − | BB | − | 2 y, 2 mo | Alive |
| + | + | + | Lido, Mg, BB, Mexil, pacing | BB, Mexil | PM | 8 y, 1 mo | Alive |
| + | + | + | Mg, Mexil | BB, Mexil | − | 8 mo | Alive |
| + | + | − | Lido, Mg, Mexil | BB, Mexil | − | 11 y, 4 mo | Alive |
| + | + | + | Mexil | BB, Mexil | − | 7 mo | Alive |
| − | + | − | Mg, BB | BB | − | 8 y | Alive |
| + | + | + | Pheny | BB, Mexil | − | 18 y, 5 mo | Alive |
| + | + | − | Pheny, DC | Pheny, BB | − | 23 y, 6 mo | Alive |
| + | + | + | − | BB, Mexil | PM | 15 y, 4 mo | Alive |
| 82% | 91% | 55% | | | | Median 96 mo | |
| + | + | + | Mexil | Mexil | PM ICD | 3 y, 4 mo | Alive |
| + | + | + | BB, Mexil, Mg | BB, Mexil, Flecainide | PM | 11 y, 4 mo | Alive |
| + | + | + | Lido, Mg, BB, Mexil | BB, Mexil | − | 1 y, 3 mo | Alive |
| + | + | − | Lido, BB | BB, Mexil | − | 11 mo | Alive |
| + | + | + | BB, Mexil, Lido | BB, Mexil | PM | 8 y | Alive |
| − | + | + | Mg, BB, Mexil | BB, Mexil | − | 3 y, 2 mo | Alive |
| 83% | 100% | 83% | | | | Median 39 mo | |
| − | + | + | BB, Mexil, Nifed | BB, Mexil, Nifed | − | 3 y, 2 mo | Alive |
| + | − | + | − | BB, Mexil | − | 2 y, 5 mo | Alive |
| + | − | − | − | BB | − | 6 y, 5 mo | Alive |
| + | + | − | Lido, Mg | Mexil | − | 5 y, 5 mo | Alive |
| + | − | + | BB, Mexil, Mg | BB, Mexil | − | 4 mo | Alive |
| + | − | − | Lido, Mg, Isp | Mexil | − | 4 y, 3 mo | Died |
| + | + | − | BB, Mg | BB | − | 9 y, 5 m | Alive |
| − | + | − | Lido, BB, pheny, Mexil | Mexil | − | 11 y, 9 mo | Alive |
| + | − | − | − | − | − | 9 y, 6 mo | Alive |
| − | − | − | − | − | − | 6 mo | Alive |
| − | + | − | BB, Mexil | BB, Mexil | ICD | 7 y, 2 mo | Alive |
| + | + | + | Mexil | Mexil | − | 4 y3 mo | Alive |
| + | − | − | BB, Mexil | BB, Mexil | − | 7 y, 5 mo | Alive |
| 75% | 42% | 25% | | | | Median 71 mo | |


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**Table 3. Clinicogenetic Details of Cases With Sudden Cardiac Death or Aborted Cardiac Arrest**

| Case | Case No. in Table 2 | Genotyping | Age at Diagnosis | Age at SCD or ACA | HR, bpm | QTc, ms | Maintenance Therapy Until SCD/ACA | Acute Therapy for SCD/ACA Event |
|---|---|---|---|---|---|---|---|---|
| 1 | 23 | LQT3 (Ala1186Thr) | Fetus (28 wk) | 1 y, 10 mo (aborted) | 78 | 679 | Mexil | Mexil, DC |
| 2 | ... | No gene test | Fetus (31 wk) | 8 d | 60 | 570 | ... | Lido, Isp, Pacing, DC |
| 3 | ... | No gene test | Fetus (36 wk) | 57 d | 90 | 600 | BB, Mexil | DC |
| 4 | 29 | LQT8 (Gly406Arg) | Neonate (0 d) | 1 y, 5 mo (aborted) | 141 | 581 | BB, Nifed | Mexil, Mg |
| 5 | ... | Negative result | Neonate (0 d) | 4 y | 100 | 647 | Mexil | DC |
| 6 | ... | Negative result | Neonate (0 d) | <1 mo (aborted) | 111 | 638 | Mexil | Lido, Mexil, BB, Pheny |
| 7 | 17 | LQT2 (Ala561Val) | Neonate (1 d) | 10 y (aborted) | 86 | 520 | BB, Mexil | Lido, Mexil, Mg, DC |
| 8 | ... | No gene test (possible LQT8)* | Neonate (1 d) | 57 d | 70 | 640 | BB | ... |
| 9 | ... | No gene test | Neonate (4 d) | 5 y, 4 mo | 60 | 590 | ... (refused) | ... |
| 10 | ... | No gene test | Infant (1 mo) | 2 y | 130 | 640 | BB, Mexil | Lido, Mg |
| 11 | ... | No gene test | Infant (1 mo) | 1 y, 10 mo | 60 | 740 | BB, Mexil, PM | Lido, Mexil, BB, Mg, Pacing |
| 12 | 10 | LQT1 (Gly643Ser) | Infant (1 mo) | 1 mo (aborted) | 109 | 554 | Mexil | Lido |
| 13 | 39 | Negative result | Infant (2 mo) | 4 mo (aborted) | 160 | 470 | BB, Mexil, ICD | (aborted by ICD) |
| 14 | 40 | Negative result | Infant (2 mo) | 2 mo (aborted) | 100 | 774 | Mexil | Mexil |
| | | | | median 10.5 mo | 97±31 | 617±81 | | |

ACA indicates aborted cardiac arrest; BB, β-blocker; ICD, implantable cardioverter-defibrillator; Isp, isoproterenol; Lido, lidocaine; Mexil, mexiletine; Mg, magnesium; Nifed, nifedipine; Pheny, phenytoin; SCD, sudden cardiac death.

*LQT8 was retrospectively possible because phenotype included syndactyly.

school age,[2] we speculate a considerable number of patients are considered to go through infancy uneventfully.

Garson et al[4] reported 287 patients with LQTS age <21 years; their mean±SD age at presentation was 6.8±5.6; and 9% presented with cardiac arrest, 26% with syncope, and 10% with seizures. Although 20% of their subjects were <1 month of age, they did not investigate that age group separately. In the present study, confined to the subjects age <1, clinical features were largely different; that is, the incidence of malignant arrhythmias and bradycardia was high[6,7] whereas that of syncope and seizures was low.

Regarding genotype-phenotype correlations, Zareba et al[18] investigated child and adult LQTS and reported that LQT1 was associated with the highest risk of first cardiac event among the 3 most typical genotypes (LQT1–3). By the age of 15, syncope, ACA, or SCD was noted in 53% of their patients with LQT1 compared with 29% of LQT2 and 6% of LQT3, although cardiac events occurred in LQT3 were more lethal compared with those in LQT1 or LQT2. In contrast, the present study demonstrated that patients complicated by VT/TdP or AVB were almost exclusively those with LQT2 or LQT3 (and LQT8). LQT3 patients in the present study showed the most severe clinical course, similar to those in later-presenting LQT3. Further, patients with LQT1 mostly showed an uneventful clinical course apart from sinus bradycardia,[6] and the reason for diagnosis was bradycardia or prolonged QT interval itself on ECG identified on family screening. Another remarkable feature in our young age group was that a considerable number of patients with malignant arrhythmias were mutation-negative as far as LQT1–3 genes were typically examined. This suggests that this age group includes individuals with rare known mutations that were not examined in the present study as well as those with currently unidentifiable mutations.

**Table 4. Comparison of Parameters Among the Groups**

| Parameter | LQT1 (n=11) | LQT2 (n=11) | LQT3 (n=6) | Negative (n=12) | Global Test | Pairwise Comparison |
|---|---|---|---|---|---|---|
| HR, bpm | 109±12 (n=10*) | 95±34 | 100±31 | 104±32 | NS | |
| QTc, ms | 560±24 (n=10*) | 538±74 | 592±79 | 575±86 | NS | |
| Proportion with family history, % | 82 | 27 | 50 | 17 | $P<0.05$ | LQT1–Negative, $P<0.05$ |
| Proportion with sinus bradycardia, % | 73 | 82 | 83 | 75 | NS | |
| Proportion with VT/TdP, % | 0 | 91 | 100 | 42 | $P<0.05$ | LQT1–LQT2, $P<0.001$<br>LQT1–LQT3, $P<0.005$ |
| Proportion with AVB, % | 9 | 55 | 83 | 25 | $P<0.05$ | (LQT1–LQT3, $P=0.068$) |

Data are mean±SD or %. One-way ANOVA was used to compare mean values of HR and QTc. $\chi^2$ test was used to test differences in proportions of subjects with family history, sinus bradycardia, VT/TdP, and AVB among the 4 groups. Pairwise comparisons were conducted using Bonferroni adjustment and Bonferroni inequality of $P$ value. NS indicates not significant; Negative, gene mutation-negative group.

*No. of cases is 10 because data were not available in 1 case.



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Notably, many patients in the present study showed sinus bradycardia, although HR was not significantly different among LQT1, LQT2, and LQT3. Sinus bradycardia has been considered a significant presentation of LQTS, especially in the fetal-neonatal period,[3,19,20] and is often a clue to the diagnosis of LQTS. The present study verified that sinus bradycardia is common among all types of LQTS in this age group, especially in fetal-neonatal periods.

Another remarkable feature of the present study was the high incidence of AVB (55% in LQT2, 83% in LQT3), compared with 5% or less in child or adult LQTS.[4,20] It is intriguing that mutations in our LQT2 patients were almost exclusively located at the pore region of HERG gene (amino acid residues 550 through 650),[21] as mutations in that region are related to high risk for cardiac events.[21,22] Lupoglazoff et al[6] reported similar phenotype tendency for neonates with LQTS, that AVB is associated with LQT2 and sinus bradycardia with LQT1. Most of their LQT2 cases also had a mutation in the pore region of the HERG gene, although this was not mentioned in their report. AVB in neonates with an SCN5A mutation have also been reported in single case reports.[8,11,23,24] Considering the implication of sodium channel dysfunction in many other hereditary arrhythmias,[25] the association between LQT3 and AVB is an important finding.

SCD/ACA was seen in 14 cases (24% of all subjects) (7 SCD, 7 ACA), even though 12 of them were under treatment with β-blockers, mexiletine, or both when the events occurred (Table 3). The direct trigger of SCD/ACA remains to be determined, but the mean QTc interval of those patients was apparently prolonged (617±81 ms), and patients with no gene test (6 cases) were included as well, possibly making the selection of drugs inappropriate, such that only β-blockers were given to a possible LQT3 patient. Furthermore, 4 other cases had no known mutation on genotyping. It is possible that the cryptogenic mutations unidentifiable in the current era could be resistant to many drugs.

### Therapy

Because individuals with LQT3 showed serious clinical disorders, they were treated aggressively with multiple antiarrhythmic drugs including mexiletine, β-blockers, lidocaine, Mg, and PM/ICD, and only 1 definite LQT3 patient showed ACA. For LQT2, malignant arrhythmias were a little more controllable with the same kind of pharmacotherapy than for LQT3. Again, only 1 definite LQT2 patient showed ACA. Thus, no death was ultimately observed in LQT2 and LQT3. This favorable clinical course might be derived from implicit strategy prevalent among pediatric cardiologists in our country that early-onset LQTS should be treated with the combination of β-blockers and mexiletine at the start of therapy because the genotype is not easy to confirm immediately. In other words, treatment strategies in Japan have been driven more by the clinical symptoms than by the genotype. Nevertheless, the response to the multiple antiarrhythmic pharmacotherapy and the long-term outcome presented in this study are encouraging.

It should be noted that the number of patients who underwent PMI/ICD was small in the present cohort compared with other reports.[5,6] It is known that TdP tends to follow a prolonged R-R interval in LQT2 and LQT3, in which conduction disturbances or sinus node dysfunction are common features.[25,26] Thus, PMI/ICD should be considered without delay even when the patient who shows drug-resistant, bradycardia-induced VT/TdP is a small baby.[27]

### Study Limitations

Because of the retrospective nature of the present survey using questionnaires, the extent of clinical data that could be obtained varied among cases. Although approximate tendency in genotype-phenotype correlations for infants with LQT1, LQT2, and LQT3 was determined, most cases registered in the present study did not undergo genetic analysis for genes other than the 3 typical types. One case with LQT8 was registered in addition to LQT1–3, but no cases with the other types (LQT4–7) were found. Also, decision of treatment strategy depended on the in-charge physician in each case without the use of a uniform protocol for VT/TdP and/or AVB, making it difficult to evaluate the effects of pharmacotherapy and to determine the event rate beyond infancy for each genotype other than the last outcome, alive or death. Therefore, we should wait for accumulation of more cases for establishment of the genotype-specific strategy.

## Conclusion

Our nationwide survey indicates that early-onset malignant LQTS are mostly those with LQT2 and LQT3 among the 3 major genes, and the most vulnerable age to life-threatening arrhythmias is from 0 to 2 days of age. A combination pharmacotherapy with a β-blocker and mexiletine sometimes combined with Mg and PMI/ICD is recommended as the initial therapy. Prospective study of a large number of patients with LQTS diagnosed from fetal to infantile periods and further application of gene testing are needed to establish the most appropriate treatment strategies for those patients.

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## Disclosures

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## CLINICAL PERSPECTIVE

The congenital long-QT syndrome (LQTS) diagnosed at perinatal life and through infancy is associated with high morbidity and mortality rates. However, data on the clinical presentation and genotype-phenotype correlation of this youngest age group of LQTS are limited. A nationwide survey was conducted in Japan, and 58 cases (18 fetuses, 31 neonates and 9 infants) were registered. Among them, the peak age at diagnosis was 0 to 2 days, and the 3 most frequent clinical presentations included sinus bradycardia, ventricular tachycardia/torsades de pointes, and atrioventricular block. The genotype was confirmed in 29 (71%) of 41 patients who underwent genotyping; the incidence resembled that of child LQTS. Patients who presented with early-onset ventricular tachycardia/torsades de pointes and atrioventricular block were almost exclusively those with LQT2 and LQT3 among the 3 major genes, but a considerable number of genetically unidentified ones were included. Sudden cardiac death/aborted cardiac arrest were prevalent in the latter. LQT1 patients tended to show only sinus bradycardia or positive family history of LQTS. These results mean that many life-threatening episodes observed in early-onset LQTS should be treated immediately and aggressively even without knowledge of the genotype. On the other hand, the present study was encouraging in that the outcome of patients was favorable with multiple pharmaceutical agents, typically with β-blockers, mexiletine, and magnesium and with pacemaker implantation/implantable cardioverter-defibrillator, independent of the genotype. Further application of gene testing is needed to establish the most appropriate genotype-specific strategy for these patients.


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# Clinical impact of the number of extrastimuli in programmed electrical stimulation in patients with Brugada type 1 electrocardiogram

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**BACKGROUND** Use of programmed electrical stimulation (PES) for risk stratification of Brugada syndrome (BrS) is controversial.

**OBJECTIVE** To elucidate the role of the number of extrastimuli during PES in patients with BrS.

**METHODS** Consecutive 108 patients with type 1 electrocardiogram (104 men, mean age 46 ± 12 years; 26 with ventricular fibrillation [VF], 40 with syncope, and 42 asymptomatic) underwent PES with a maximum of 3 extrastimuli from the right ventricular apex and the right ventricular outflow tract. Ventricular arrhythmia (VA) was defined as VF or nonsustained polymorphic ventricular tachycardia >15 beats. Patients with VA induced by a single extrastimulus or double extrastimuli were assigned to group SD (Single/Double), by triple extrastimuli to group T (Triple), and the remaining patients to group N.

**RESULTS** VA was induced in 81 patients (VF in 71 and polymorphic ventricular tachycardia in 10), in 4 by a single extrastimulus, in 41 by double extrastimuli, and in 36 by triple extrastimuli. During 79 ± 48 months of follow-up, 24 patients had VF events. Although the overall inducibility of VA was not associated with an increased risk of VF (log-rank $P = .78$), group SD had worse prognosis than did group T ($P = .004$). Kaplan–Meier analysis in patients without prior VF also showed that group SD had poorer outcome than did group T and group N ($P = .001$). Positive and negative predictive values of VA induction with up to 2 extrastimuli were, respectively, 36% and 87%, better than those with up to 3 (23% and 81%, respectively).

**CONCLUSIONS** The number of extrastimuli that induced VA served as a prognostic indicator for patients with Brugada type 1 electrocardiogram. Single extrastimulus or double extrastimuli were adequate for PES of patients with BrS.

**KEYWORDS** Brugada syndrome; Programmed electrical stimulation; Number of extrastimuli; Risk stratification; Sudden death

**ABBREVIATIONS** **BrS** = Brugada syndrome; **ECG** = electrocardiogram; **ICD** = implantable cardioverter-defibrillator; **LAS40** = duration of low-amplitude signals <40 μV of the filtered QRS complexes; **NPV** = negative predictive value; **PES** = programmed electrical stimulation; **PPV** = positive predictive value; **PVT** = polymorphic ventricular tachycardia; **RVA** = right ventricular apex; **RVOT** = right ventricular outflow tract; **RMS40** = root mean square voltage of the terminal 40 ms of the filtered QRS complexes; **VA** = ventricular arrhythmia; **VF** = ventricular fibrillation

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## Introduction

Brugada syndrome (BrS) is a channelopathy that can cause sudden death due to ventricular fibrillation (VF) in apparently healthy individuals in their prime. Since Brugada et al reported it first in 1992, several indices have been reported as reliable prognostic factors.[1–6] However, there remains much room for debate in prognostic indices except for history of VF.[7] Although induction of lethal ventricular

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arrhythmia (VA) by programmed electrical stimulation (PES) is still widely adopted for deciding the indication of an implantable cardioverter-defibrillator (ICD), controversial data have been reported regarding its prognostic value.[2,4,7–9] Brugada et al reported that VF inducibility by PES can be a strong predictor of subsequent cardiac events in patients with BrS.[8] However, other studies could not confirm these findings.[2,4,7] Because protocols of PES and backgrounds of patients were different in each study, direct comparison of the results was not possible. Moreover, clinical significance of the number of extrastimuli, the site of induction, and the coupling interval of extrastimuli at the time of VF induction by consistent protocol have not been fully elucidated.

The aim of the present study was to test the hypothesis that subsequent cardiac events occur more frequently in patients with BrS with induction of VAs by fewer extrastimuli during PES. Thus, we examined the relationships of several parameters of PES, especially the number of extrastimuli, the site of induction, and the coupling interval of extrastimuli at the time of VF induction, with subsequent cardiac events.

## Methods

### Study population

The study population consisted of consecutive 108 Japanese patients with Brugada type 1 electrocardiogram (ECG) in the absence or presence of sodium-channel–blocking agent (104 men, mean age 46 ± 12 years) who underwent electrophysiological study at National Cerebral and Cardiovascular Center, Suita, Japan, between 1993 and 2009. Twenty-six patients had a history of VF, 40 had a history of syncope, and 42 were asymptomatic at the time of the electrophysiological study. Patients' characteristics are shown in Table 1. Two patients with nocturnal agonal respiration were included in VF patients.

**Table 1** Overall clinical and electrocardiographic characteristics of 108 patients

| Characteristics | N (%) |
|---|---|
| Clinical | |
| Male | 104 (96%) |
| Age (y) | 46 ± 12 |
| Hx of VF | 26 (24%) |
| Hx of syncope | 40 (37%) |
| Asymptomatic | 42 (39%) |
| Family Hx of BrS | 6 (6%) |
| Family Hx of SD under age 45 y | 22 (20%) |
| Age at first CE (y) | 43 ± 14 |
| Electrocardiographic | |
| RR interval (ms) | 971 ± 118 |
| PQ interval (ms) | 176 ± 29 |
| QRS duration (ms) | 96 ± 16 |
| Corrected QT interval (ms) | 405 ± 29 |
| Spontaneous coved-type ST segment | 62 (57%) |
| Total filtered QRS duration | 119 ± 17 |
| LAS40 | 47 ± 16 |
| RMS40 | 16 ± 11 |

BrS = Brugada syndrome; CE = cardiac event; Hx = history; SD = sudden death; VF = ventricular fibrillation.

Brugada type 1 ECG was diagnosed when a coved ST-segment elevation (≥0.2 mV at J point) was observed in more than one of the right precordial leads (V1–V3) in the presence or absence of a sodium-channel–blocking agent. Sixty-two patients exhibited spontaneous type 1 ECG, and the rest of the patients showed type 2 or 3 ECG at baseline and type 1 ECG after administration of 1 mg/kg of pilsicainide. Obvious type 1 ECG (>2 mm J-point elevation followed by >3 mm ST elevation in precordial leads) was confirmed after pilsicainide administration in all patients with drug-induced type 1 ECG. Patients were diagnosed as suffering from BrS according to the report of the second consensus conference.[10]

### Clinical information

History taking, physical examinations, chest roentgenogram, and ECG were conducted. All participants underwent echocardiography to exclude structural heart disease. Clinical information including age, sex, family history, and age of first cardiac event was collected. Twelve-lead ECG was recorded in all 108 patients, and the RR interval, PR interval (lead II), QRS duration (lead V5), and corrected QT interval (lead V2) were measured. Signal-averaged ECG was recorded and analyzed in 91 patients by using a signal-averaged ECG system (Arrhythmia Research Technology 1200EPX, Milwaukee, WI). Three parameters were assessed by using a computer algorithm: (1) total filtered QRS duration, (2) root mean square voltage of the terminal 40 ms of the filtered QRS complexes (RMS40), and (3) duration of low-amplitude signals <40 μV of the filtered QRS complexes (LAS40). Late potential was considered positive when the 2 criteria (RMS40 < 18 μV and LAS40 > 38 ms) were fulfilled. Genetic test for the presence of an *SCN5A* mutation was also performed by direct sequencing, and the entire coding sequence of the *SCN5A* gene was thoroughly searched.

### Electrophysiological study

An electrophysiological study was conducted in fasting and nonsedated state after written informed consent. None of the patients received antiarrhythmic drugs before the electrophysiological study. The atrio–His and His–ventricular intervals were measured during sinus rhythm. We defined the induction of VA as an induction of VF or nonsustained polymorphic ventricular tachycardia (PVT) of more than 15 consecutive beats. A maximum of 3 programmed ventricular extrastimuli were delivered from the right ventricular apex (RVA) and the right ventricular outflow tract (RVOT), unless VA was induced. First, single extrastimulus and double extrastimuli were delivered from the RVA followed by the RVOT. Next, triple extrastimuli was delivered from the RVA followed by the RVOT. The basic cycle length was 500 ms. The coupling interval was reduced in decrements of 10 ms until ventricular refractoriness, coupling interval reached 180 ms, or VF was induced.

We divided the study subjects into 3 groups according to the results of the PES. Patients with VA induced by a single extrastimulus or double extrastimuli were assigned to group