

Long QT syndrome with compound mutations is associated with a more severe phenotype: A Japanese multicenter study

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BACKGROUND: Long QT syndrome (LQTS) can be caused by mutations in the cardiac ion channels. Compound mutations occur at a frequency of 4% to 11% among genotyped LQTS cases.

OBJECTIVE: The purpose of this study was to determine the clinical characteristics and manner of onset of cardiac events in Japanese patients with LQTS and compound mutations.

METHODS: Six hundred three genotyped LQTS patients (310 probands and 293 family members) were divided into two groups: those with a single mutation ($n = 568$) and those with two mutations ($n = 35$). Clinical phenotypes were compared between the two groups.

RESULTS: Of 310 genotyped probands, 26 (8.4%) had two mutations in the same or different LQTS-related genes (compound mutations). Among the 603 LQTS patients, compound mutation carriers had significantly longer QTc interval (510 ± 56 ms vs

478 ± 53 ms, $P = .001$) and younger age at onset of cardiac events (10 ± 8 years vs 18 ± 16 years, $P = .043$) than did single mutation carriers. The incidence rate of cardiac events before age 40 years and use of beta-blocker therapy among compound mutation carriers also were different than in single mutation carriers. Subgroup analysis showed more cardiac events in LQTS type 1 (LQT1) and type 2 (LQT2) compound mutations compared to single LQT1 and LQT2 mutations.

CONCLUSION: Compound mutation carriers are associated with a more severe phenotype than single mutation carriers.

KEYWORDS Compound; Gene; Long QT syndrome; Mutation

ABBREVIATION QTS = long QT syndrome

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Introduction

Congenital long QT syndrome (LQTS) is a heterogeneous disease characterized by prolonged ventricular repolariza-

tion and episodes of syncope and/or life-threatening cardiac arrhythmias, particularly polymorphic ventricular tachycardia.¹ Several disease-causing genes have been identified, including genes encoding cardiac ion channel-composing proteins, namely, *KCNQ1* (LQT1), *KCNH2* (LQT2), *SCN5A* (LQT3), *KCNE1* (LQT5), *KCNE2* (LQT6), *KCNJ2* (LQT7), and *CACNA1C* (LQT8), and genes encoding a family of versatile membrane adapters, namely, *ANK2* (LQT4), *CAV3* (LQT9), *SCN4B* (LQT10), *AKAPs* (LQT11), and *SNTA1* (LQT12).^{2–5} Two modes of inheritance are involved in this syndrome, which exhibits both an autosomal dominant and an autosomal recessive pattern. The majority of LQTS cases are inherited in an autosomal dominant fashion. This pattern, which has been named as Romano-Ward syndrome,^{6,7} can result from a single mutation in one

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of the LQTS candidate genes. On the other hand, Jervell and Lange-Nielsen syndrome, which is inherited in an autosomal recessive fashion, is very rare,⁸ affecting less than 1% of LQTS cases. It is caused by homozygous or compound heterozygous mutations of *KCNQ1* or *KCNE1*.^{9,10}

Genetic analysis sometimes reveals two or more mutations in LQTS patients with clinical phenotypes of Romano-Ward syndrome. These compound mutations were shown to be associated with an increased arrhythmic risk.^{11,12} However, most previous studies were conducted in Caucasian patients, and few systematic studies have involved Asian cohorts. In the present study, we analyzed the clinical characteristics of LQTS patients who were registered in a Japanese multicenter study. Analysis of the more than 600 genotyped patients revealed that LQTS patients with compound mutations not only were common in Japan (8.4% among probands) but were associated with longer QTc and earlier onset of cardiac events. In patients who initially are diagnosed as LQT1 or LQT2, additional mutations may be present if patients have a more severe phenotype than expected; therefore, conducting a survey for major LQTS-related genes is critically important.

Methods

Patients and data collection

Major candidate genes were analyzed in 612 consecutive and unrelated probands with a suspected clinical diagnosis of congenital LQTS, who were referred to four centers in Japan (Shiga University of Medical Science, Otsu; Kyoto University Graduate School of Medicine, Kyoto; Kanazawa University Graduate School of Medical Science, Kanazawa; and National Cardiovascular Center, Suita) between June 1996 and January 2009. If gene mutations in LQTS-related genes were identified, further genetic analysis was conducted among family members as extensively as possible. All patients in the cohort were Japanese.

Genetic analysis

Informed consent was obtained from all individuals or their guardians according to standards established by the local institutional review boards. Genotypic and DNA sequence analyses of *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, and *KCNE2* were performed as described previously.¹³ In addition, *KCNJ2* (Andersen syndrome [LQT7]^{14,15}) was analyzed in patients who had not only QT prolongation but also the clinical phenotype of Andersen syndrome, for example, periodic paralysis or dysmorphic features. Other candidate genes (e.g., ankyrin-B [LQT4], *CACNA1C* [Timothy syndrome, LQT8]) were not analyzed because mutations in these genes are extremely rare. Denaturing high-performance liquid chromatography was performed as described previously.¹⁶ Abnormal conformers were amplified by polymerase chain reaction and sequenced using an ABI PRISM310 DNA sequencer (Perkin-Elmer Applied Biosystems, Wellesley, MA, USA). "Splicing error" mutations were defined as those that occurred within three bases of the splicing sites. When mutations were detected, 200 Japanese

control subjects were checked and single nucleotide polymorphisms were excluded from the study. If mutations of these genes were detected in the probands, their family members were also analyzed and genotype-phenotype correlations confirmed. Mutation-negative controls were defined as family members without mutations detected in each proband. Nonsynonymous as well as synonymous single nucleotide polymorphisms were excluded with the assistance of data from previous reports¹⁷⁻¹⁹ and from the National Center for Biotechnology Information database.

Clinical characterization

Baseline clinical data were recorded for each patient and included the following: age at diagnosis, age at first cardiac event, sex, cardiac events, family history of sudden cardiac death or LQTS members, ECG measurements, and therapeutic regimens administered. Schwartz scores also were calculated.^{20,21} In the analysis of triggers of arrhythmic events, triggers were divided into four categories: exercise/swimming, emotional stress/arousal stress, sleep/rest, and other conditions.

ECG parameters measured at baseline included RR, QT_{end}, QT_{peak}, and T_{peak-end} (QT_{end-peak}) intervals. The latter is thought to reflect transmural dispersion of ventricular repolarization.²² Measurements were the mean of at least three beats measured in lead V₅ from the 12-lead ECG during stable sinus rhythm and corrected by the Bazett formula.²³ QT_{end} 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 the maximal

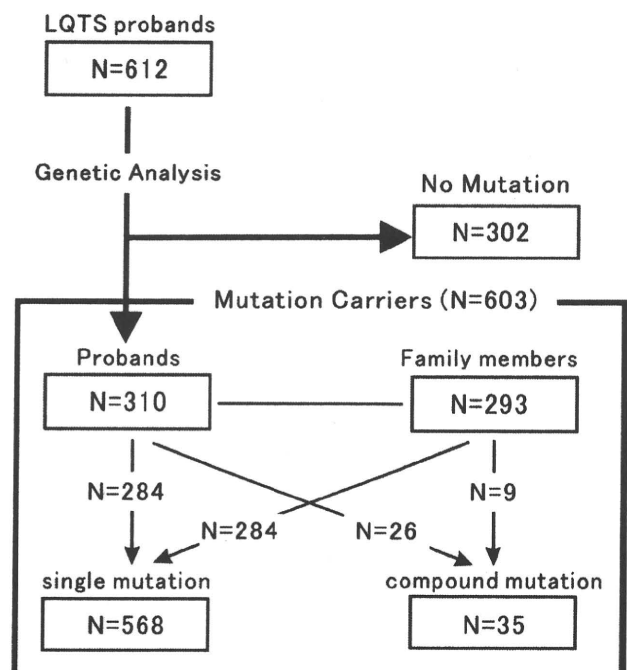


Figure 1 Schematic representation of the positive-mutation carriers in this study. LQTS = long QT syndrome.

Table 1 Overall data of patients with compound mutations

Research groups	Schwartz et al.	Westenkow et al.	Tester et al.	This study
Reported years	2003	2004	2005	2010
The corresponding number in the reference list	25	11	12	
Percentage of probands with compound mutations (probands with compound mutations/total probands) subtypes	4.6% (6/130)	5.2% (9/172*)	10.8% (29/269)	8.4% (26/310)
LQT1	7 (58%)	14 (35%)	30 (52%)	18 (35%)
LQT2	2 (17%)	10 (25%)	15 (26%)	17 (33%)
LQT3	3 (25%)	2 (5%)	13 (22%)	14 (27%)
LQT5-D85N	0 (0%)	10 (25%)	0 (0%)	0 (0%)
vs. single mutation carriers				
QTc interval	NA	prolonged	not significant	prolonged
Cardiac events	NA	frequent	not significant	not significant
Age of onset	NA	NA	younger onset	younger onset

*This table excluded probands with single nucleotide polymorphisms (SNP), NA = not available.

upslope of the negative T wave (QT_{end}). $QT_{end-peak}$ then was obtained by calculating as QT_{end} minus QT_{peak} .

Statistical analysis

All analyses were performed using the SPSS 16.0 statistical package (SPSS, Inc., Chicago, IL, USA). Data are expressed as mean \pm SD. $P < 0.05$ was considered significant. Univariate comparison of parameters between groups was performed by an unpaired t-test. Differences in incidence between groups were analyzed by Chi-square test or Fisher exact probability test. The cumulative probability of a first cardiac event (syncope, torsades de pointes, ventricular fibrillation, cardiac arrest, or sudden death) occurring before age 40 years and before beta-blocker therapy or after beta-blocker therapy was determined by means of the life-table method of Kaplan-Meier, and results were compared using log rank test.²⁴

Results

Genetic characteristics of mutations associated with single and compound mutations

Genetic analysis revealed gene mutations in 310 (51%) of 612 probands. The study enrolled 603 genotyped LQTS patients consisting of 310 genotyped probands and their 293 genotyped family members. A flowchart of the genetic diagnosis of the study population is shown in Figure 1.

Of the 310 genotyped probands, 26 (8.4%) had compound mutations. This rate is comparable to the rates in previous reports of Caucasian patients (Table 1). The 26 probands all had two mutations in the LQTS-related genes we examined. These 52 mutations in 26 probands consisted of 45 missense mutations, 4 frameshift mutations, 2 splice-site mutations, and 1 nonsense mutation (see Online Supplemental Data 1). The mutation types of the 284 single mutation carriers were 210 missense mutations, 34 frameshift mutations, 18 splice-site mutations, 12 deletions, 9 nonsense mutations, and 1 insertion mutation (see Online Supplemental Data 2). Therefore, the mutation types were similar between the two groups (Figure 2).

Among the 293 genotyped family members, there were 284 single mutation carriers and 9 compound mutation

carriers. In total, 568 patients with a single mutation (284 probands and 284 family members) consisted of 256 with LQT1, 248 with LQT2, 62 with LQT3, and 2 with LQT5. Thirty-five compound mutation carriers (26 probands and 9 family members) consisted of 9 with LQT2 and LQT3, 7 with LQT1 and LQT2, 6 with LQT1 and LQT3, 4 with double LQT1, 3 with double LQT2 mutations, 2 with LQT1 and LQT7, 2 with LQT2 and LQT7, 1 with double LQT3, and 1 with LQT1 and LQT6.

Families associated with compound mutations

In the analysis of family members associated with compound mutations, 28 single heterozygous mutation carriers and 4 obligate single mutation carriers were identified from 9 families, and single mutation carriers had milder clinical phenotypes than compound mutation carriers (Figure 3). Only 2 (6%) of the 32 single mutation carriers had syncope but no torsades de pointes, an incidence lower than that in compound mutation carriers (54% [19/35] patients, $P < .001$). For single heterozygous mutation carriers in compound mutation families, average QTc interval was 442 ± 30 ms, which was longer than that of the 15 mutation-negative controls (408 ± 28 ms, $P = .001$) but significantly shorter than that of compound mutation carriers (510 ± 56 ms, $P < .001$).

Early onset of cardiac events and more severe QT prolongation was observed in patients with compound mutations

Table 2 compares the clinical characteristics of 35 LQTS patients with compound mutation and 568 LQTS patients with a single mutation. The female-to-male ratio was similar between the two groups. However, the incidence of family members associated with double-hit patients was significantly smaller than that with a single mutation (26% vs 50%, $P = .005$). In the ECG analysis of 496 patients with available information, corrected QT interval was significantly longer in compound mutation carriers than in single mutation carriers (510 ± 56 ms vs 478 ± 53 ms, respectively, $P = .001$), whereas other ECG findings, R-R interval, corrected QT_{peak} , corrected $QT_{peak-end}$, and rates of

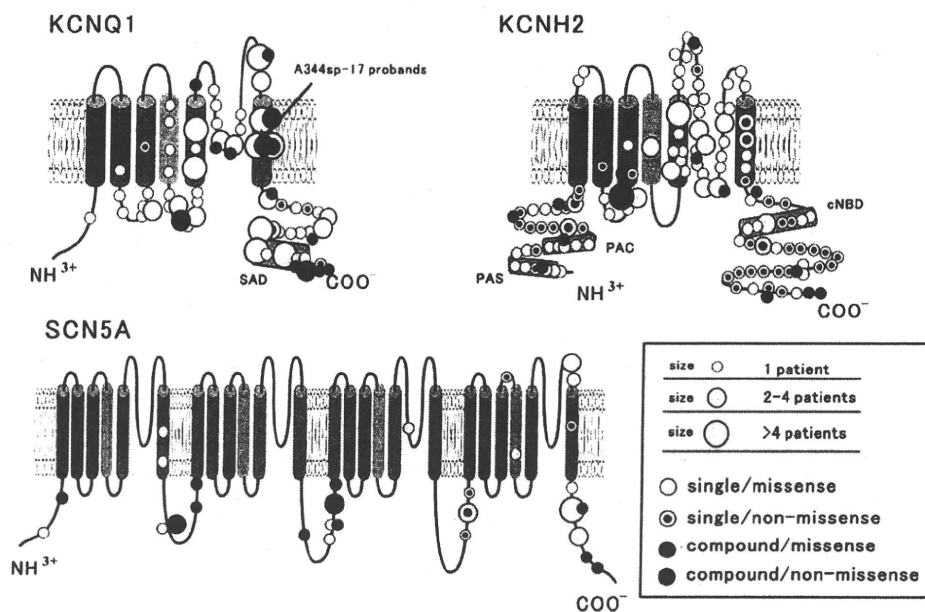


Figure 2 Conventional transmembrane topology of all mutations in the probands.

notched T wave and T-wave alternans were not different between the two groups. The frequency of patients with a normal QTc interval <440 ms was similar between the two groups, whereas the frequency of double-hit patients with QTc intervals >500 ms was significantly higher than in those with a single mutation (66% vs 26%, $P < .001$). Schwartz scores in the compound mutation group and the rate of patients with a score ≥ 4 were higher than those in the single mutation group (Schwartz score: 4.3 ± 2.1 vs 3.4 ± 1.9 points, $P = .017$; rates of Schwartz score ≥ 4 points: 70% vs 47%, $P = .026$). A significantly higher number of patients with compound mutations received beta-blocker therapy than did those with a single mutation (56% vs 33%, $P = .006$).

In the analysis of "all age groups," the frequency of cardiac events was similar between compound and single mutation groups, whereas age at first cardiac event was significantly lower in the compound mutation group (10 ± 8 years vs 18 ± 16 years, $P = .043$). For the occurrence of syncope or torsades de pointes before age 40 years, compound mutation carriers had significantly more events than did single mutation carriers (54% vs 37%, $P = .043$). The occurrence of cardiac arrest or ventricular fibrillation was similar between the two groups for patients before age 40 years. In 561 patients with available information on age at first cardiac events, Kaplan-Meier analysis showed that the cumulative rate of survival without a cardiac event before age 40 years and use of beta-blocker therapy differed significantly between compound and single mutation carriers ($P = .004$ by log rank test; Figure 4A) and between compound mutation carriers and each subgroup of single mutation carriers ($P = .004$ vs LQT1, $P = .018$ vs LQT2, $P = .001$ vs LQT3, by log rank test; Figure 4B). In the analysis of matched subtypes between single and compound mutation carriers, patients with additional mutations in an LQTS

subtype had a significantly poorer prognosis than LQT1 alone ($P = .001$; Figure 5) and LQT2 alone ($P = .035$) but not LQT3 alone ($P = .06$).

Discussion

In this multicenter study, the major findings were as follows. (1) LQTS-associated compound mutations in the Japanese population were as common as previously reported in studies of Caucasian patient cohorts. (2) Patients with compound mutations displayed longer QTc and earlier onset of cardiac events. (3) Patients with compound mutations had more cardiac events before age 40 years and more beta-blocker therapy. (4) Subgroup analysis showed more cardiac events in LQT1 and LQT2 compound mutations compared to single LQT1 and LQT2 mutations.

Twenty-six probands (8.4% of genotyped LQTS) were found to have two variants in genes encoding ion channels (*KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, or *KCNJ2*). This incidence rate is in general agreement with other studies that reported a prevalence of compound or multiple mutations of 5% to 11% of genotyped LQTS (Table 1).^{11,18,25}

Table 1 summarizes the genetic and clinical characteristics of patients enrolled in previous studies and compares them with the characteristics of patients enrolled in the present study. Sanguinetti and colleagues reported that patients with compound mutations not only had longer QT intervals than single mutation carriers but also had more frequent cardiac events.¹¹ However, Ackerman and colleagues demonstrated that, although compound mutation carriers were diagnosed at a younger age than single mutation carriers, they did not have significantly longer QT intervals.¹² The difference between these results might be explained by half of the 20 compound probands in the cohort of Sanguinetti et al possessing the common *KCNE1*-

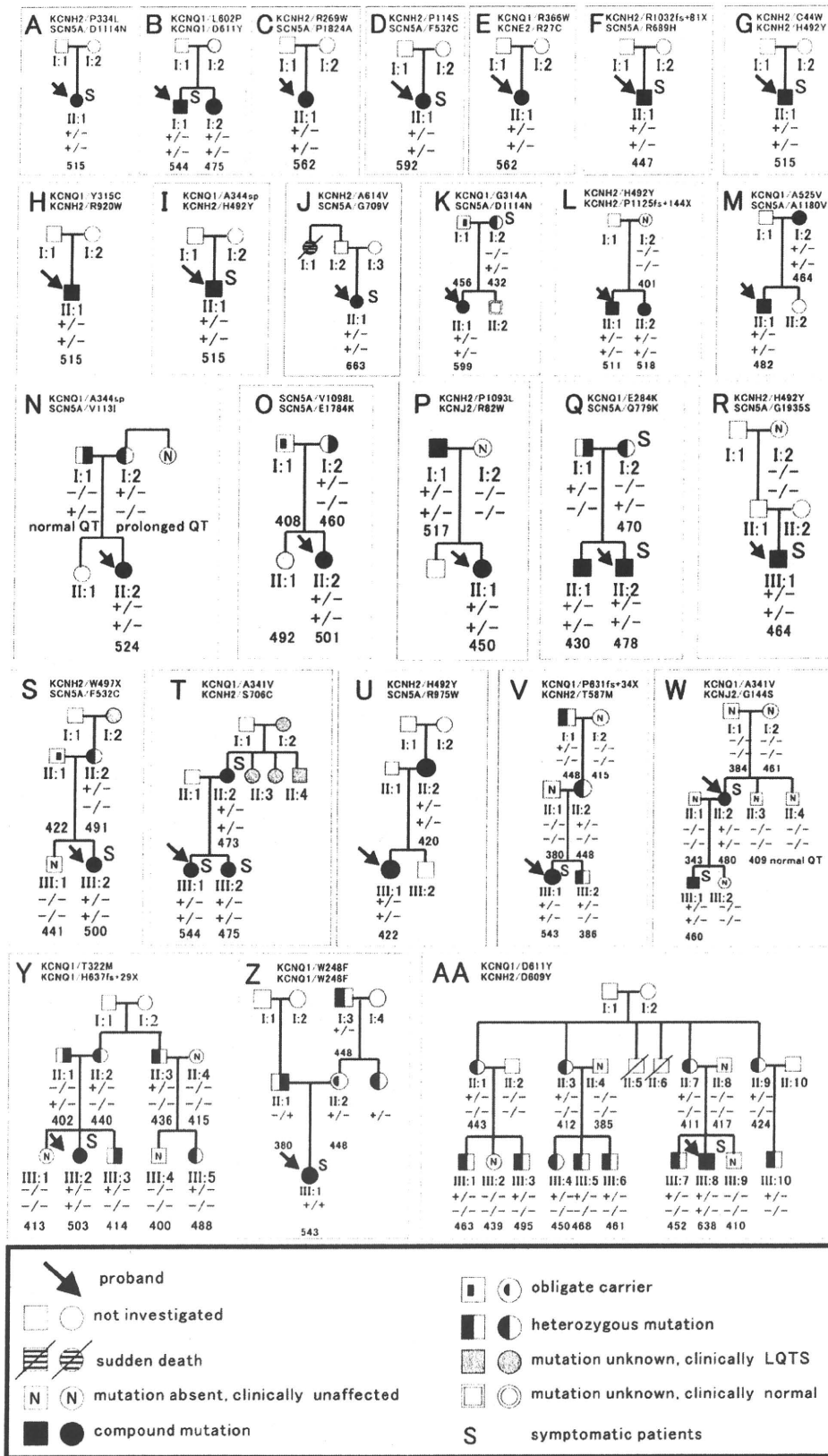


Figure 3 Pedigrees of the families associated with compound mutation probands.

Table 2 Clinical characteristics of LQTS patients with gene mutations

	Compound mutations (N=35)	Single mutations (N=568)	p value
Demographic			
Age at diagnosis (yrs)	19 ± 14 [15, 9-27]	28 ± 19 [22, 12-42]	0.001
Female gender	23 (66%)	330 (58%)	0.394
Proband	26 (74%)	284 (50%)	0.005
Family members	9 (26%)	284 (50%)	0.005
Cardiac events			
cardiac events in all age groups			
Age at first cardiac event (yrs)	10 ± 8 [11, 3.5-13.5]	18 ± 16 [12, 7-19]	0.043
syncope	19 (54%)	235 (41%)	0.161
TdP	10 (29%)	102 (18%)	0.136
cardiac arrest or VF	3 (9%)	44 (8%)	0.748
sudden death	0 (0%)	4 (1%)	1.000
cardiac events before 40 yrs			
syncope or TdP	19 (54%)	205 (37%)	0.043
cardiac arrest or VF	3 (9%)	37 (7%)	0.500
ECG measurements			
RR interval (ms)	866 ± 210	914 ± 174	0.252
corrected QT (ms)	510 ± 56	478 ± 53	0.001
corrected QT >500 ms (%)	23 (66%)	122 (26%)	<0.001
corrected QT <440 ms (%)	3 (9%)	91 (20%)	0.351
corrected QT peak (ms)	385 ± 70	384 ± 50	0.906
corrected QT peak-end (ms)	121 ± 73	95 ± 41	0.081
notched T wave	11 (31%)	200 (37%)	0.540
T-wave alternans	0 (0%)	30 (5%)	0.246
Diagnosis			
Schwartz score	4.2 ± 2.1	3.4 ± 1.9	0.017
Schwartz score ≥4	21 (70%)	219 (47%)	0.026
Therapy			
β-blocker	10 (56%)	175 (33%)	0.006
class Ib antiarrhythmic drugs	3 (9%)	53 (10%)	1.000
pacemaker	1 (3%)	15 (3%)	1.000
sympathectomy	1 (3%)	3 (1%)	0.218
defibrillator	1 (3%)	32 (6%)	0.712

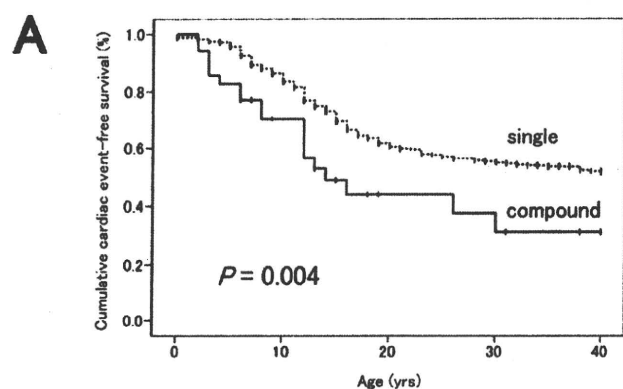
TdP = torsades de pointes, VF = ventricular fibrillation, NS = not significant, corrected QT = QT interval corrected for heart rate with Bazett formula [A, B], A = median, B-C = first interquartile range-third interquartile range.

D85N polymorphism as the “second hit” (Table 1).^{11,26} In all age groups of this study, the incidence of cardiac events, such as torsades de pointes or syncope, was similar between single and compound mutation carriers; however, the clinical phenotypes of those with compound mutations before 40 years of age were more serious than in those with a single mutation (Table 2). Thus, phenotypes with compound mutations appear to be more serious than single mutation carriers, regardless of race.

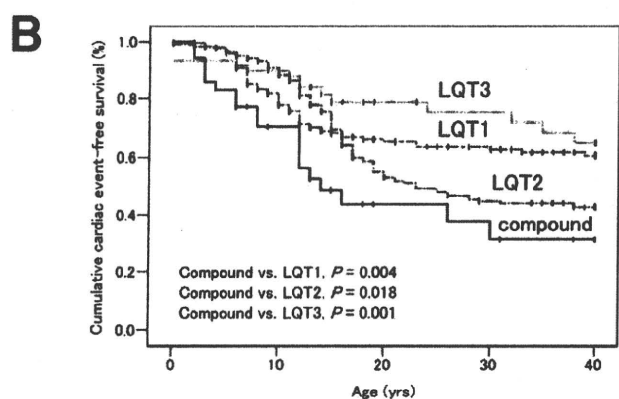
Beta-blocker therapy is first-line treatment for the prevention of cardiac events in LQTS. Beta-blockers have been shown to significantly reduce cardiac events in LQTS patients, especially LQT1 type.²⁷⁻²⁹ However, patients with LQT2 or LQT3 have been reported to be less responsive to beta-blocker therapy^{27,30} and may require additional therapy, such as pacemaker implantation for LQT2 or a Class Ib antiarrhythmic drug for LQT3. It may be recommended that patients with compound mutations receive additional individual therapy based on their LQTS subtype, for example, the combination of beta-blocker and Class Ib antiarrhythmic drugs for patients with LQT1 and LQT3. In patients who were first diagnosed as LQT1, Kobori et al³¹ reported that

additional mutations in different LQTS-related genes influenced phenotype severity and reduced beta-blocker effectiveness. Previous reports showed that approximately 20% of LQT1 patients were resistant to beta-blocker therapy. Additional or “latent” mutations may be present in these patients, and conducting a survey for major all LQTS-related genes, even after a possible mutation is identified, is critically important.

Family study analyses are of enormous importance because single mutation carriers in this study tended to have mild phenotypes. Most of the single mutation carriers in families of compound probands remained asymptomatic. However, double hits of these “latent” gene carriers could cause more serious phenotypes.^{32,33} Jervell and Lange-Nielsen syndrome is a well-documented LQTS phenotype with an autosomal recessive pattern. The loss of function of I_{Ks} on both alleles generally causes not only more severe clinical phenotypes but also deafness.^{9,10} In our study, two of three probands with double *KCNQ1* mutations had no deafness. We speculate that these mutations would functionally cause mild changes without complete loss of I_{Ks} . Westenskow et al¹¹ reported the molecular mechanism of



No. of Subjects					
single	526	396	195	161	124
compound	35	20	7	6	3



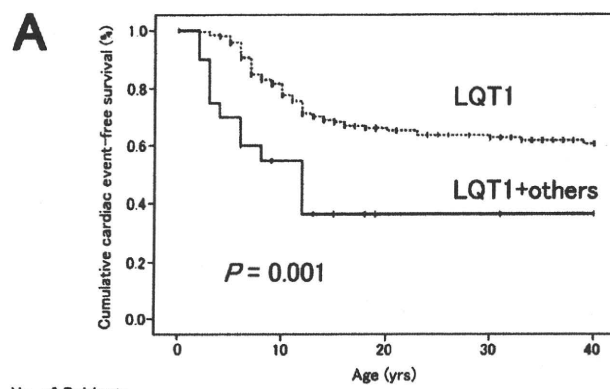
No. of Subjects					
LQT1	242	165	81	71	51
LQT2	224	182	89	68	55
LQT3	59	49	26	22	19
compound	35	20	7	6	3

Figure 4 Kaplan-Meier cumulative probability of cardiac event-free survival from birth to age 40 years and before therapy. **A:** Comparison between patients with a single mutation and compound mutations. **B:** Comparison among patients with long QT syndrome type 1 (LQT1), type 2 (LQT2), type 3 (LQT3), and compound mutations.

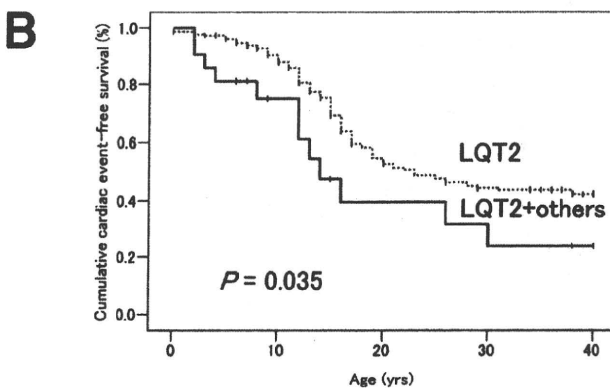
increased risk through compound mutations using heterologous expressions in *Xenopus* oocytes. When wild-type and variant subunits were coexpressed in appropriate ratios to mimic the genotype of the probands with mutations, the reduction in current density was equivalent to the additive effects of the single mutations. Coexpression of two mutant subunits caused a significant but incomplete reduction. Thus, either compound mutation seems to be associated with mild functional damage. It is necessary to have “double hits” of these mild mutations in order to produce symptoms.

Study limitations

This study has several limitations. First, six major LQTS candidate genes were examined, but not for minor genes encoding a family of versatile membrane adapters. However, excluding these minor genes from our investigations would not have affected the overall study results, largely because the incidence of these minor gene mutations reportedly is $\leq 1\%$. Second, analysis of single mutation carriers in compound mutation families is dominated by their presence



No. of Subjects					
LQT1	242	165	81	71	50
LQT1+others	20	9	2	2	1



No. of Subjects					
LQT2	224	181	88	67	54
LQT2+others	21	12	5	4	2

Figure 5 Kaplan-Meier cumulative probability of cardiac event-free survival from birth to 40 years of age and before therapy. **A:** Comparison between patients with long QT type 1 (LQT1_ subtype and compound mutation carriers with LQT1 plus other mutations. **B:** Comparison between patients with long QT syndrome type 2 (LQT2) and those with LQT2 plus other mutations.

in only 35% (9/26) of families. Therefore, there might be a statistical bias due to a mutation-specific effect. Third, Kapa et al¹⁹ reported the need for further studies on whether regions such as the interdomain linker of *SCN5A* could affect the clinical phenotypes of LQTS. In this study, we were able to distinguish mutations from these “genetic noises,” especially in the *SCN5A* gene.

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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.2010.06.013.

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Heart rate-dependent variability of cardiac events in type 2 congenital long-QT syndrome

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Aims

We aimed to examine the validity of heart rate (HR) at rest before β -blocker therapy as a risk factor influencing cardiac events (ventricular fibrillation, torsades de pointes, or syncope) in long QT type 2 (LQT2) patients.

Methods and results

In 110 genetically confirmed LQT2 patients (45 probands), we examined the significance of variables [HR at rest, corrected QT (QTc), female gender, age of the first cardiac event, mutation site] as a risk factor for cardiac events. We also evaluated frequency of cardiac events in four groups classified by the combination of basal HR and QTc with cutoff values of 60 b.p.m. and 500 ms to estimate if these two electrocardiographic parameters in combination could be a good predictor of outcome (mean follow-up period: 50 ± 39 months). Logistic regression analysis revealed three predictors: HR <60 b.p.m., QTc ≥ 500 ms, and female gender. When the study population was divided into four groups using the cutoff values of 60 b.p.m. for HR and 500 ms for QTc, the cumulative event-free survival by the Kaplan–Meier method was significantly higher in the group with HR ≥ 60 b.p.m. and QTc <500 ms than in the group with HR <60 b.p.m. and QTc <500 ms or that with HR <60 b.p.m. and QTc ≥ 500 m ($P < 0.05$). Irrespective of QTc interval, LQT2 patients with basal HR <60 b.p.m. were at significantly higher risk.

Conclusion

The basal HR of <60 b.p.m. is a notable risk factor for the prediction of life-threatening arrhythmias in LQT2 patients.

Keywords

Long QT syndrome • Arrhythmia • Genetics • Heart rate • Torsades de pointes

Introduction

Long QT syndrome (LQTS) is a primary electrical disease characterized by an abnormality in myocardial repolarization that leads to the prolongation of QT interval, morphological changes in T waves, and torsades de pointes (TdP) type of ventricular tachyarrhythmias on surface electrocardiogram (ECG).¹ Studies on genotype–phenotype correlation identified the clinical characteristics in each genetic subgroup, which made it possible to diagnose and introduce β -blocker therapy (BBT) appropriately in LQTS patients.^{2–4} In patients with LQTS type 1 (LQT1), β -blockers

are quite effective, whereas they are less effective in suppressing arrhythmic events in LQT2 and 3.²

Previous studies have demonstrated the importance of evaluating patients by clinical symptoms, gender, causative mutations, the type or biophysical function of mutations, and corrected QT (QTc) interval to stratify the arrhythmic risk in LQTS.^{3,5–14} Heart rate (HR) has been recognized since the establishment of LQTS as a clinical entity, and a low HR for age was included in the diagnostic criteria.¹⁵ A recent study by Schwartz *et al.*¹⁶ demonstrated that a lower resting HR and a relatively low baroreflex sensitivity in *KCNQ1* A341V carriers are protective factors,

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whereas HR at rest in other subtypes of LQTS has not been fully investigated. In clinical practice, we have noted that in some cases of LQT2 that TdP was triggered by HR of <60 b.p.m. and suppressed by pacing at 80 b.p.m., which made us evaluate the importance of HR in arrhythmic events of LQT2 patients. For these reasons, we aimed to analyse whether HR at rest before BBT could be a novel risk factor for cardiac events besides gender, genetic locus, and prolonged QT interval in LQT2. We also evaluated the relationship between HR at rest and arrhythmic events before and after BBT through the analysis of clinical data on patients with LQT2.

Methods

Study population

From September 1996 to July 2009, 587 probands with QT prolongation underwent genetic testing in three institutes in Japan, Shiga University of Medical Science, Kyoto University Graduate School of Medicine, and the National Cardiovascular Center. One hundred and fifty-two probands (26%) were genotyped as LQT2. We also screened mutations in *KCNQ1*, *SCN5A*, *KCNE1-3*, and *KCNJ2* using the standard genetic tests¹⁷⁻²⁰ and excluded 20 probands with compound mutations and/or modifier single-nucleotide polymorphisms known to affect the QT interval (*KCNH2* K897T and *KCNE1* D85N).^{21,22} The remaining 132 probands were found to have a single *KCNH2* mutation, and among them, we excluded from analyses patients under 15 years and those without detailed clinical information or with medication (except for β -blocker) which could influence baseline ECG measurements at the first medical contact and thereafter. Children <15 years old were not studied because they had relatively high basal HR. Family members of the 152 probands were recruited for the analysis if we could obtain necessary clinical information and if they were over 15 years old. As a result, the study population became 110 patients (45 probands and 65 family members) from 74 unrelated Japanese LQT2 families.

Both symptomatic and asymptomatic patients were included in the groups of probands and family members. Regardless of being probands or family members, patients were defined as symptomatic when they had a history of cardiac events (defined as ventricular fibrillation, TdP, or syncope due to ventricular arrhythmia) at the first medical contact or at the time of yearly follow-up. Patients with an apparent history of vasovagal syncope were not included in the study. The protocol for genetic analysis complied with the Declaration of Helsinki and was approved by the institutional ethics committees and performed under their guidelines. All individuals or their guardians gave written informed consent to genetic and clinical data analyses. Follow-up data were obtained from patients' regular hospitals working with the authors in case patients lived far from our institutions or hospitals and were not able to visit us.

Genetic analysis and characterization

Genomic DNA was isolated from venous blood lymphocytes using the QIAamp DNA blood midikit (Qiagen, Hilden, Germany). Established primer settings were used to amplify the entire coding regions of known LQTS genes from genomic DNA.¹⁷⁻²⁰ Denaturing high performance liquid chromatography (DHPLC) or direct sequencing techniques were employed as described elsewhere.¹¹ Polymerase chain reaction fragments presenting abnormal signals in DHPLC analysis were subsequently sequenced by the dideoxynucleotide chain

termination method with fluorescent dideoxynucleotides on an ABI 3113xl genetic analyzer (PE Applied Biosystems).

The pore region of the *KCNH2* channel was defined as the area extending from S5 to the mid-portion of S6 involving amino acid residues from 550 through 650 according to the previous report.¹⁰ The non-pore region included the N-terminus region, transmembrane domains apart from the pore region and the C-terminus region.

Clinical characterization

Routine demographic data and basal 12-lead ECGs were obtained from all subjects at the first medical contact as well as at yearly follow-up. In 104 patients, ECG parameters were measured before BBT was introduced. The remaining six patients, in whom BBT was started after the first cardiac event by an attending physician in other hospitals, visited a university hospital for further diagnostic confirmation of the symptoms. One of the six patients experienced aborted sudden cardiac death, four had documented TdP, and one had a syncopal attack. After obtaining informed consent, BBT was discontinued for more than five times the half life and examinations were performed, including a blood test, basal ECG, chest X ray, echocardiogram, and treadmill test for the diagnosis of congenital long QT syndrome.

Electrocardiograph parameters measured in the study were HR and QT interval. Rate-dependent QT intervals were corrected for HR using Bazett's method. QT interval was manually measured in lead V₅ using the tangent method⁴ with an average of 2 or 3 consecutive beats by three investigators who were completely unaware of the patients' clinical and genetic state. There were no significant differences in the measured data among three investigators. Bifid T waves, but not U waves, were included in the QT measurements. In the presence of bifid T waves, the end of the second T wave was defined as the end of the QT interval. If ECG recordings were obtained during a cardiac event, such as the appearance of frequent ventricular tachycardia, TdP, or cardiac arrest, they were requested to perform another examination after patient's general status had improved.

Data on patients who received BBT after the initial check-up were evaluated, including the dose of each drug, HR under medication, and recurrent arrhythmic episodes. Other treatments, such as implantable cardioverter-defibrillator (ICD) implantation and surgical left cardiac sympathetic denervation, were also evaluated. Follow-up data, including the occurrence of cardiac events and therapeutic changes, were collected retrospectively.

Statistical analysis

Student's *t*-test was employed to compare continuous data. Differences in frequencies were analysed by the χ^2 test or Fisher's exact test. Analysis of variance was used to test differences of variables among more than three groups. Stepwise regression analysis was performed to determine predictors of cardiac events. Variables with $P < 0.05$ on univariate analysis were included in a logistic regression model with cardiac events as dependent variables. To determine the connection of the selected clinical variables with the occurrence of cardiac events, odds ratios for unadjusted data and their 95% confidence intervals were calculated. The cumulative probability of the first cardiac event between 15 and 50 years old was estimated using the Kaplan-Meier method. The Cox proportional-hazards survivorship model was used to investigate whether there were any prognostic factors that could influence the occurrence of cardiac events. Data are reported as the mean \pm SD. Two-sided probability values <0.05 were considered significant. Statistical calculations were performed using SPSS software (version 18.0J).

Results

Clinical and genetic characteristics

The study population consisted of 110 consecutive patients from 74 unrelated Japanese LQT2 families (Table 1). The baseline ECG showed that the mean HR of probands tended to be lower than that of family members ($P = 0.06$).

All patients were genotyped to be a heterozygous carrier of 70 different *KCNH2* mutations (18 in the N-terminus, 15 in non-pore regions, 13 in pore regions, and 24 in the C-terminus). Forty-three mutations were missense mutations, 15 were deletion/insertions, 9 were frameshifts, and 3 were nonsense mutations.

Table 1 Basal characteristics of the study population

	All (n = 110)	Proband (n = 45)	Family member (n = 65)
Clinical characteristics			
Age (years)	40.8 ± 17.5 (15–87)	31.2 ± 15.6 (15–77)	47.4 ± 15.6 (16–87)**
Sex (male/female)	40/70	10/35	30/35*
Symptomatic patients [n (%)]	48 (44)	38 (84)	10 (15)**
Cardiac arrest (n)	7	4	3
Syncope (n)	46	38	8
Both (n)	5	4	1
ECG			
HR (b.p.m.)	62 ± 10	60 ± 9	63 ± 11
QTc (ms)	483 ± 58	508 ± 60	467 ± 50**

* $P < 0.05$ vs. proband.

** $P < 0.001$ vs. proband.

Factors determining cardiac events in LQT2 patients

We first evaluated whether HR and other variables (age at onset of cardiac events, female gender, site of mutation, missense mutation, and QTc) served as risk factors for cardiac events in LQT2 patients. Univariate analysis (Table 2) showed that HR of < 60 b.p.m. *per se* was a significant risk for cardiac events ($P < 0.01$). In addition, female gender, HR as a continuous variable, a QTc interval of ≥ 500 ms, and pore site mutation were associated with an increased risk for cardiac events ($P < 0.05$). Other variables such as age at onset of cardiac events, sites of mutation (non-pore transmembrane, N-terminal, and C-terminal), and missense mutation were not statistically significant.

Multivariate analysis (Table 2) was subsequently performed using female gender, HR of < 60 b.p.m., QTc of ≥ 500 ms, and pore site mutation. As for HR, we chose HR of < 60 b.p.m. for multivariate analysis because we aimed to clarify if low HR of < 60 b.p.m. was a significant risk factor for cardiac events. As shown in Table 2, female gender, HR < 60 b.p.m., and QTc ≥ 500 ms were revealed to be significant risk factors for cardiac events ($P < 0.05$).

Bradycardia as an arrhythmic risk factor in LQT2 patients

We employed two ECG parameters, HR and QTc, to scrutinize who were more prone to have cardiac events in our LQT2 cohort. Using cutoff values of 60 b.p.m. for HR without β -blockers and 500 ms for QTc, we classified 110 LQT2 patients into four groups (Figure 1). Closed and open circles in the figure indicate symptomatic and asymptomatic patients, respectively (including both probands and family members). There were only eight symptomatic patients (23%) in the quadrant area of HR ≥ 60 b.p.m. and QTc < 500 ms. In contrast, in the quadrant area defined as HR < 60 b.p.m. and QTc ≥ 500 ms, 12 subjects (86%) experienced cardiac events ($P < 0.05$, vs. HR ≥ 60 b.p.m. and QTc < 500 ms).

Table 2 Predictors of cardiac events (syncope, aborted cardiac arrest, or sudden cardiac death) in univariate and multivariate analyses

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Age at onset	1.08 (0.78–1.49)	0.639		
Female gender	3.56 (1.51–8.38)	0.004	4.54 (1.72–12.00)	0.002
HR < 60 b.p.m.	2.83 (1.30–6.16)	0.009	4.46 (1.77–11.24)	0.001
HR (continuous variable)	0.95 (0.91–0.99)	0.022		
QTc ≥ 500 ms	2.65 (1.18–6.00)	0.019	2.93 (1.13–7.59)	0.026
Mutation location				
Pore	2.45 (1.07–5.60)	0.034	1.77 (0.70–4.48)	0.230
Transmembrane, non-pore	0.91 (0.27–3.08)	0.914		
N-terminal	0.83 (0.33–2.04)	0.677		
C-terminal	0.57 (0.26–1.27)	0.169		
Missense mutation	2.10 (0.91–4.85)	0.081		

Table 3 summarizes the baseline characteristics of four groups divided by HR and QTc. The group of HR ≥ 60 b.p.m. and QTc < 500 ms was defined as Group A, the group of HR < 60 b.p.m. and QTc < 500 ms as Group B, HR ≥ 60 b.p.m. and QTc ≥ 500 ms as Group C, and HR < 60 b.p.m. and QTc ≥ 500 ms as Group D. There were no significant differences among four groups regarding age at baseline ECG recording, age at the first event, percentages of female gender, and BBT. In Group A, the

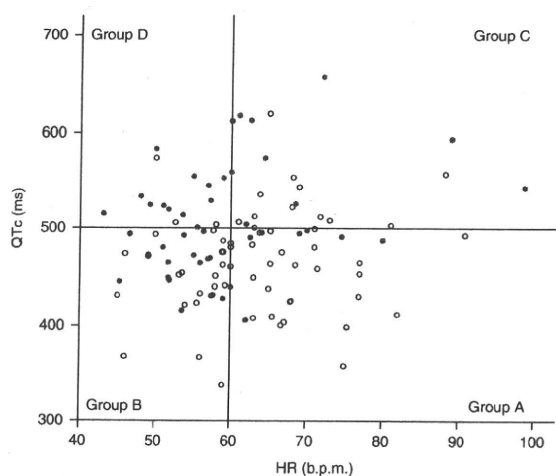


Figure 1 Distribution of KCNH2 mutation carriers according to the resting HR and QTc duration. Closed and open circles indicate symptomatic and asymptomatic patients, respectively. Two solid lines in the graph are drawn using the cutoff values of 60 b.p.m. and 500 ms. QTc was measured in lead V5. Groups A–D in the graph correspond to those in the text, Table 3 and Figure 2.

number of proband was significantly lower than that in Groups B and D. The incidence of syncope or aborted cardiac arrest in Group A was significantly lower than in the Groups B and C. In groups of HR < 60 b.p.m. (B and D), patients with QTc ≥ 500 ms (Group D) had more arrhythmic events than those with QTc < 500 ms (Group B).

We then estimated the cumulative probability of the first cardiac event between the age of 15 and 50 in four groups (Groups A–D, Figure 2). The Kaplan–Meier analysis of all subjects (Figure 2A) showed that cumulative event-free survival was significantly different ($P = 0.007$ by the log-rank test) and when adjusted for multiple comparisons, cumulative event-free survival was higher in Group A than in groups of HR < 60 b.p.m. ($P = 0.014$ vs. Group B, $P = 0.001$ vs. Group D). In contrast, the survival rate was not statistically different among Groups B–D.

In Figure 2B and C, we examined the clinical course of 45 probands and 65 family members separately. The Kaplan–Meier analysis revealed no statistical difference in probands (Figure 2B, $P = 0.206$ by the log-rank test), whereas in family members, cumulative event-free survival was significantly different among the subgroups (Figure 2C, $P = 0.017$ by the log-rank test, $P = 0.058$ for Group A vs. Group B, $P = 0.002$ for Group A vs. Group D in multiple comparisons). Thus, the statistical difference in overall subjects may result from the prognosis of family members in our study population.

Finally, in order to assess the significance and independence of HR and QTc for cardiac events, we evaluated the parameters with the Cox proportional-hazards survival model (Table 4). The values of HR and QTc were centred at 60 b.p.m. and 500 ms for ease of interpretation. Compared with patients in Group A, patients in groups of HR < 60 b.p.m. (Groups B and D) showed a higher risk for cardiac events by 2.6–4.4-fold. Although the hazard ratio in Group C was 2.16, there was no statistical difference between Groups A and C.

Table 3 Baseline clinical characteristics of four subgroups defined by QTc and basal HR

	QTc < 500 ms		QTc ≥ 500 ms	
	Group A: HR ≥ 60 b.p.m. (n = 35)	Group B: HR < 60 b.p.m. (n = 39)	Group C: HR ≥ 60 b.p.m. (n = 22)	Group D: HR < 60 b.p.m. (n = 14)
Age (years) at ECG (range)	43 \pm 18 (16–87)	39 \pm 17 (15–71)	42 \pm 18 (16–77)	39 \pm 17 (15–64)
Age (years) at first event (range, number of patients)	25 \pm 10 (13–42, n = 8)	27 \pm 15 (15–71, n = 19)	26 \pm 19 (15–77, n = 10)	26 \pm 15 (13–54, n = 10)
Female gender [n (%)]	23 (66)	22 (55)	16 (73)	9 (64)
Proband [n (%)]	8 (23)*	18 (46)	12 (55)	7 (50)
Pore site mutation [n (%)]	6 (17)**	11 (28)	10 (46)	7 (50)
Schwarz score	3.1 \pm 2.0 [§]	3.6 \pm 1.7 [§]	5.5 \pm 1.7	6.2 \pm 1.2
Syncope or aborted cardiac arrest [n (%)]	8 (23) [†]	19 (49) [†]	10 (46)	11 (79)
β -Blockers [n (%)]	7 (20)	13 (33)	9(41)	6 (43)

Values are given as the mean \pm SD where indicated. HR = heart rate.

* $P < 0.05$ vs. Groups B and C.

** $P < 0.05$ vs. QTc ≥ 500 ms (Groups C and D).

[§] $P < 0.001$ vs. QTc ≥ 500 ms (Groups C and D).

[†] $P < 0.05$ vs. Group D.

[‡] $P < 0.05$ vs. HR < 60 b.p.m. (Groups B and D).

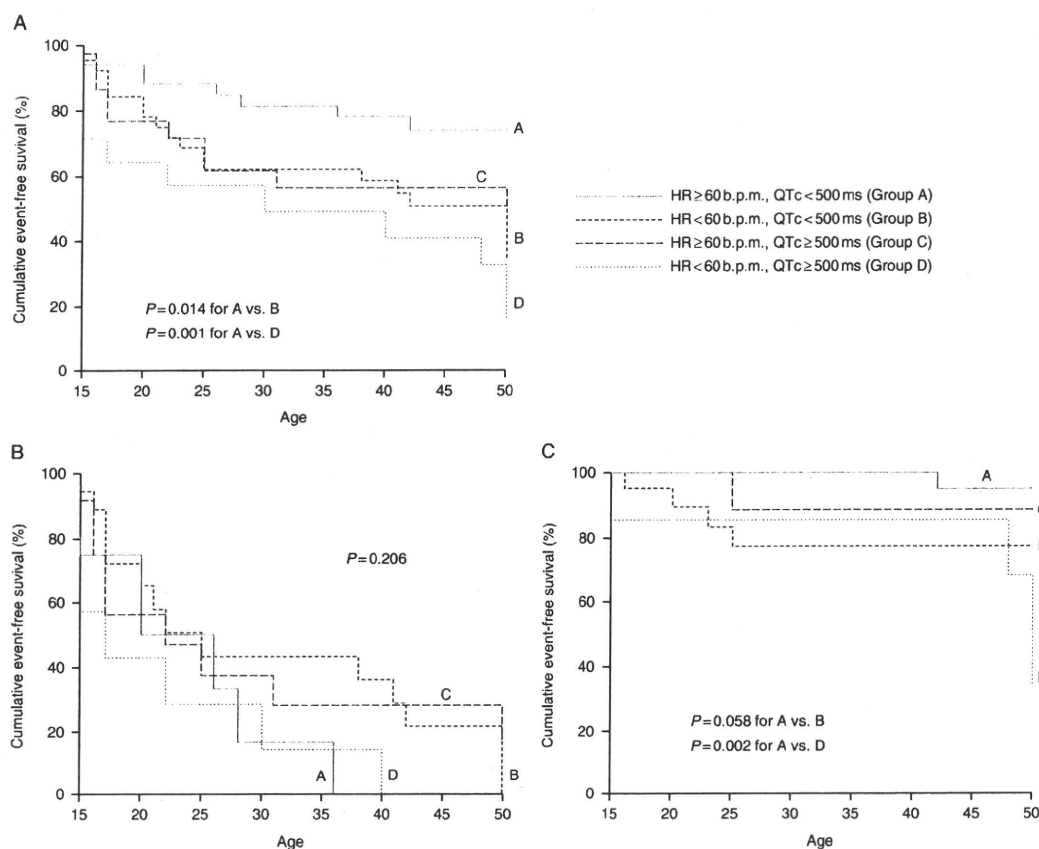


Figure 2 The Kaplan–Meier cumulative cardiac event-free survival curves from the age of 15–50 among each of four subgroups defined by cutoff values for HR of 60 b.p.m. and QTc of 500 ms. Panels A–C show the Kaplan–Meier curves of 110 patients, 45 probands and 65 family members, respectively. The group of HR ≥ 60 b.p.m. and QTc < 500 ms was defined as Group A, the group of HR < 60 b.p.m. and QTc < 500 ms as Group B, HR ≥ 60 b.p.m. and QTc ≥ 500 ms as Group C, and HR < 60 b.p.m. and QTc ≥ 500 ms as Group D.

Table 4 Contribution of QTc duration and HR to COX survival model

	Number of patients	Hazard ratio	95% CI	P-value
QTc < 500 ms				
HR ≥ 60 b.p.m. (Group A)	35	1	–	–
HR < 60 b.p.m. (Group B)	39	2.60	1.14–5.97	0.023
QTc ≥ 500 ms				
HR ≥ 60 b.p.m. (Group C)	22	2.16	0.85–5.47	0.105
HR < 60 b.p.m. (Group D)	14	4.39	1.76–10.92	0.001

Treatment

β-Blocker therapy was introduced in 35 patients (29 probands) after diagnosis of LQT2 was made. Mean HR on medication was 56 ± 8 b.p.m. Metoprolol was used in 3 patients (90 ± 52 mg, 30–120), carvedilol in 3 (15 ± 9 mg, 5–20), atenolol in 4 (50 ± 0 mg, 50), propranolol in 21 (42 ± 16 mg, 30–80), and bisoprolol in 4 (4 ± 1 mg, 2.5–5).

Implantable cardioverter-defibrillator was implanted in 12 patients (VF: five patients, syncope: seven patients) during the first hospitalization or follow-up. In seven patients with a history of cardiac arrest due to VF (Table 1), two patients were treated with an ICD, three with both ICD and β-blocker, one with a pacemaker, and one with β-blocker alone (because the patient rejected ICD implantation). In a patient with a pacemaker, TdP was

observed repeatedly whenever she fell asleep and sinus rhythm became <60 b.p.m. during her first admission to the hospital. After pacemaker implantation, atrial pacing at 80 b.p.m. completely suppressed TdP. None of the patients received surgical left cardiac sympathetic denervation in our study population.

Recurrence of arrhythmic events during follow-up

For the follow-up data, 36 patients (22 patients on BBT) followed more than 3 months were recruited and 86% of patients (31 patients: 18 patients on BBT, 8 patients with an ICD, 10 patients without treatment) completed the mean follow-up period of 50 ± 39 months (40 ± 35 months for 18 patients on BBT and 63 ± 42 months for 13 patients without BBT).

Eighteen subjects on BBT consisted of 14 symptomatic (due to syncope) and 4 asymptomatic patients. Arrhythmic events during follow-up were observed only in symptomatic patients (seven patients: VF was observed in one patient, syncope in six patients). Analysis of the relationship between HR of <60 b.p.m. and recurrent events was also performed. Cardiac events during follow-up were observed in three of nine patients who showed HR <60 b.p.m. before BBT and four of eight patients with HR <60 b.p.m. after BBT ($P = 0.60$ and 0.06 , respectively). Therefore, low HR of <60 b.p.m. at rest before or after β -blockers did not predispose ventricular arrhythmia, although the statistical insignificance could be due to a small number of patients for analysis. Details of treatment after recurrence in each individual were described below.

A 16-year-old male patient with a history of syncope experienced VF and was resuscitated. He underwent ICD implantation and dosage of bisoprolol was increased from 2.5 to 5 mg/day, which prevented any cardiac events for a follow-up period of 34.5 months. Recurrent syncope or documented TdP on BBT were observed in six patients: two patients who took metoprolol (one did not comply with the drug regimen and one with a syncopal episode on medication), one patient with atenolol (syncope twice and electrical storm due to TdP twice on medication), and three patients with propranolol (one did not comply with the drug regimen, two experienced a recurrent syncopal episode on medication). In those who did not comply with medication, syncope or TdP was suppressed by resuming BBT. Recurrent episodes of syncope in one patient on metoprolol (120 mg/day) have been suppressed by changing BBT to bisoprolol (2.5 mg/day) for 20 months. Implantable cardioverter-defibrillator implantation was also performed in this patient. Episodes of one patient on atenolol (50 mg/day) were not suppressed with additional prescription of mexiletine (400 mg/day), and ICD was implanted. He experienced an electrical storm after ICD implantation. While adjusting BBT, he was diagnosed with oesophageal cancer and died after 19.8 months follow-up. Syncope in one patient on propranolol (60 mg/day) was suppressed with combined medication of propranolol and diazepam. The other patient on propranolol (30 mg/day) was implanted with an ICD after recurrent episodes of syncope. Atrial pacing of 84 b.p.m. prevented arrhythmic events.

In 13 patients without BBT, 5 were symptomatic (1 VF and 4 syncope) at the first medical contact. In these patients, only one

patient with a history of VF experienced an appropriate ICD shock following recurrent VF. To note, pacing using ICD leads was introduced during the first hospitalization in three of five symptomatic patients in whom TdP was repeatedly observed under HR of 60 b.p.m. In these patients, pacing prevented recurrent cardiac events during follow-up.

Discussion

The present study demonstrated that basal HR of <60 b.p.m. was an apparent risk factor for cardiac events in LQT2 patients. Corrected QT ≥ 500 ms and female gender were also useful for risk stratification in LQT2. The Kaplan–Meier analysis in total study population revealed that cumulative event-free survival was significantly higher in the subgroup with HR ≥ 60 b.p.m. and QTc < 500 ms than in the two groups with HR < 60 b.p.m. ($P < 0.05$). The same trend was observed in the analysis of family members. On the other hand, there was no significant difference in basal HR irrespective of cardiac events in probands. Because, first, the number of probands ($n = 45$) was relatively smaller than that of family members ($n = 65$), and second, there was an entry bias: 84% of probands were referred for genetic testing as they were symptomatic, which influenced the evaluation of basal HR and cardiac events. Our examination of family members therefore suggested that *KCNH2* mutation carriers associated with more severe bradycardia may show a stronger penetrance.

Mutations in *KCNH2* are causative of LQT2, and *KCNH2* encodes for the rapid component of the delayed rectifier K-current (I_{Kr}). In electrophysiological studies, I_{Kr} was shown to be present in rabbit²³ and mouse²⁴ sinoatrial node cells. Pharmacological inhibition of I_{Kr} by E-4031 markedly suppressed the spontaneous activity of sinoatrial node cells, suggesting that I_{Kr} activation plays a key role in maintaining an adequate HR. In other experimental models,²⁵ I_{Kr} blockade has also been shown to cause bradycardia. In clinical studies, bradycardia is more frequently observed in LQT2.^{3,26} However, no previous studies have demonstrated the validity of bradycardia as a predictor of prognosis.

As for pore site mutations of *KCNH2*, known as a risk factor for cardiac events in LQT2, they were correlated with cardiac events in univariate but not multivariate analysis in our study cohort (Table 2). This contrasts with the previous report of Moss et al.¹⁰ and is probably due to the difference in the number of studied mutations as well as the exclusion of patients who had their first cardiac events before 15 years old.

β -Blockers are first line therapy for prevention of TdP in LQT2 because it suppresses early afterdepolarizations carried by L-type Ca^{2+} channels or Ca^{2+} channels.^{27–29} The result of our study, however, may cause concerns that BBT-induced HR-reduction could lead to recurrence of ventricular arrhythmias. To answer the question, we analysed the patient group on BBT during follow-up, but low HR of <60 b.p.m. at rest before or after β -blockers did not predict recurrence of cardiac events ($P = 0.60$ and 0.06 , respectively). Our study cohort may be too small to clarify this issue and therefore, further clinical evaluation with a large number of patients will be required to conclude the significance of low HR on/off β -blockers in LQT2. On the basis of our

findings, however, it is reasonable to hypothesize that pacing could be used as an adjunctive therapy in LQT2 patients showing HR <60 b.p.m. irrespective of QTc values. Our combined risk-evaluating scales (Figure 1) would help physicians estimate long-term therapy in asymptomatic *KCNH2* mutation carriers, both probands and family members.

Limitations

In some symptomatic patients, there was a long period between the average age at onset of symptoms and the average age at ECG recording. Regarding this issue, the risk evaluation should be carefully considered. In addition, it was difficult to gather ECG recordings of the first event, because many patients suffered syncope without a doctor witnessing the first event. However, among the four subgroups, there was no significant difference in age at ECG recording and age at the first event (Table 3). Therefore, we evaluated cardiac risk using the HR recorded by ECG at the first medical contact. As for the effect of BBT on HR as a risk factor for cardiac events, our cohort was too small to lead a relevant conclusion because follow-up of patients was insufficient. Hence, it awaits a further study with a larger number of genotyped LQT2 patients.

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Conflict of interest: none declared.

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Original Article

Prevalence and QT Interval of Early Repolarization in a Hospital-based Population

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Background: Early repolarization, which was regarded as benign, has recently been associated with malignant arrhythmia. Despite the newly emerged importance of early repolarization, little is known about prevalence and QT interval of early repolarization.

Methods: Early repolarization (defined as an elevation at the junction between QRS complex and ST segment ≥ 0.1 mV in at least 2 leads) was assessed in database containing 308,391 ECGs consisting of 102,065 patients (52,779 males and 49,286 females).

Results: A total of 1,775 patients (mean age, 49 ± 30 years) with early repolarization were chosen (1.7% of total population). The prevalence of early repolarization was about 11-times higher in male patients ($n = 1,623$) than in female patients ($n = 152$). The prevalence of early repolarization was 1.4% at the age of 0–9 years, peaked (5.0%) at the age of 10–19 years, and progressively decreased with advancing age from 20 to 79 years (3.3, 2.1, 1.6, 0.9, 0.5, and 0.3% at the age of 20–29, 30–39, 40–49, 50–59, 60–69, and 70–79 years, respectively). Bazett's QTc interval of patients with early repolarization did not significantly differ among groups of each decade and between genders.

Conclusion: The prevalence of early repolarization was both age- and gender-dependent in a hospital-based population. Yet, there was no association between QTc interval and age and between QTc interval and gender.

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Key words: Electrocardiography, QT interval, Repolarization, Age, Gender

Introduction

The term “early repolarization” which is characterized by a concave-shaped elevation of the ST-segment ending in a positive high amplitude of the T wave was introduced approximately half a century ago.^{1,2} Several reports acknowledged that ST-seg-

ment elevation was observed in apparently healthy individuals.^{3–5} This electrocardiographic pattern has been usually regarded as a normal variant with a benign prognosis.⁶ Recently, Haissaguerre et al.⁷ reported that an increased prevalence of early repolarization in idiopathic ventricular fibrillation was associated with occurrence and recurrence of

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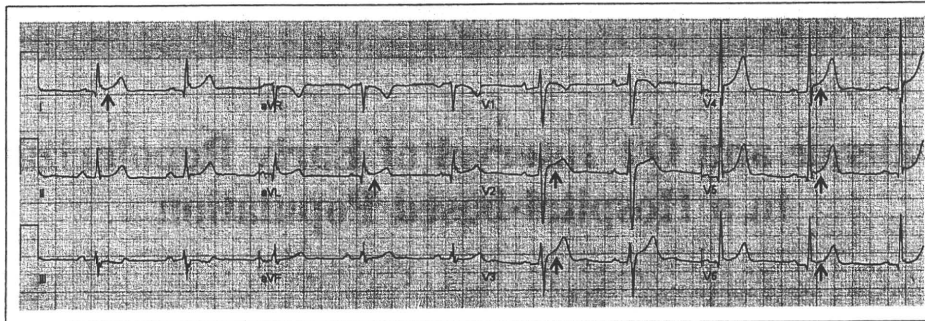


Figure 1 A typical ECG of a 58-year-old man. Arrows indicate elevation of ST segment corresponding to early repolarization.

malignant ventricular arrhythmia. In addition, they reported that the QTc interval in patients with early repolarization was shorter compared to those without.⁷⁾ The establishment of this new clinical entity motivated us to investigate details on the prevalence of early repolarization and the QT interval in patients with early repolarization in a large population. Furthermore, interest was aroused as to electrocardiographic abnormalities complicated with early repolarization. In this article, we reviewed 12-lead electrocardiographic recordings obtained from a hospital-based population.

Methods

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

Study Population

We analyzed resting 12-lead electrocardiograms (ECGs) recorded in our hospital related to Shiga University of Medical Science. The 102,065 consecutive patients (49,286 females and 52,779 males) who had undergone ECG recording between January 1983 and October 2008 were enrolled in the present study. A total number of 308,391 ECGs were obtained during this period. Twelve leads were simultaneously measured. The 12-lead ECG was recorded for 10 sec at a sweep speed of 25 mm/sec, calibrated to 1 mV/cm in the standard leads. The ECG signals were recorded with an interval of 2 ms (i.e., 500 Hz). Digital data were stored in a server computer with a 12-bit resolution.

Data Analysis

From the database, patients who displayed early repolarization were chosen using analysis software, MUSE7.1 (GE Marquette Medical Systems, Inc., Milwaukee, Wisconsin). A computer-processed algorithm defined early repolarization as an elevation at

the junction between the QRS complex and ST segment ≥ 1 mm from baseline level in at least 2 leads (Figure 1). ST-segment elevation must be present for at least 2 consecutive beats to identify early repolarization. First, we determined prevalence of early repolarization in our total population. Second, we determined QT interval of patients with early repolarization. Third, we determined the ECG abnormality complicated with early repolarization.

MUSE7.1 detected identical QRS waves with a template-matching technique. ECG variables including heart rate and QT interval were composed by measuring the averaged value during 10-sec of recording time. QT interval was measured from the earliest detection of depolarization in any lead (QRS onset) to the latest detection of repolarization where downsloping limb nearly joined the baseline in any lead (T offset), while U wave was excluded. T-wave offset was determined by the time when 98% of the integrated area of the T wave was over. This method allowed us to measure QT interval irrespective of T-wave morphology. QTc interval was calculated after correction for heart rate with Bazett's formula. Since all measurements of the 12-lead ECG were digitally performed using software, neither intra-observer nor inter-observer variability occurred in this study. We determined whether early repolarization coexisted with ECG abnormalities such as left ventricular hypertrophy (LVH), right ventricular hypertrophy (RVH), atrial fibrillation (AF), premature ventricular contraction (PVC), sinus bradycardia (≤ 50 beats/min), and sinus tachycardia (≥ 100 beats/min). The diagnosis of LVH and RVH was made by a point scoring technique provided by Marquette ECG Analysis Program.

Statistical Analysis

The data are presented as mean \pm standard deviation (SD). Statistical differences among more than 3 groups were tested with two-way ANOVA for

comparison. Differences among individual means were verified subsequently by Turkey-Kramer post hoc tests. All tests were two-tailed, and a value of $P < 0.05$ was considered statistically significant.

Results

Prevalence of Early Repolarization

A total of 1,775 patients (mean age; 49 ± 30 years) who exhibited early repolarization were chosen from our database. There was a male predominance of early repolarization: 1,623 male patients (3.1% of total male patients) vs. 152 female patients (0.3% of total female patients), $P < 0.001$. Overall prevalence of early repolarization was 1.7%. Clinical diagnosis of patients with early repolarization is shown in Table 1. There were 374 patients (28.4%) with cardiovascular disease in the total patients with early repolarization. Figure 2 shows the prevalence of early repolarization in the total population according to decades of age. The prevalence of early repolarization peaked at the age of 10–19 years and progressively decreased with advancing age at or above 20 years. Approximately half of patients with early repolarization were under the age of 20 years. Figure 3 shows the prevalence of early repolarization in female and male patients. In both genders, the prevalence of early repolarization was age-dependent with the peak at the age of 10–19 years, which was similar to the prevalence in the overall population.

Figure 4 shows heart rate, QT interval, and QTc interval in patients with early repolarization according to age. Heart rate was significantly ($P < 0.05$) faster and QT interval was significantly ($P < 0.05$) shorter at the age of 0–9 years as compared to other age groups. QTc interval did not significantly differ among all age groups studied and mean value of the QTc interval was within normal range. Figure 5 shows heart rate, QT interval, and QTc interval of female patients with early repolarization. Figure 6

shows the same ECG measurements of male patients with early repolarization as Figure 5. In both genders, heart rate was significantly ($P < 0.05$) faster, QT interval was significantly ($P < 0.05$) shorter at the age of 0–9 years as compared to other age groups, but QTc interval did not significantly differ among all age groups. There was no significant gender difference in heart rate, QT interval, and QTc interval in each decade.

ECG Manifestation of Early Repolarization

Table 2 shows ECG leads where early repolarization was present. Early repolarization most frequently occurred in anterior leads. In about 30% of patients, the ECG leads that manifested early repolarization were widely distributed (i.e., anterolateral, anteroinferior, and inferolateral leads). QTc interval was identical among ECG leads with early repolarization.

ECG abnormalities complicated with early repolarization are listed in Table 3. Early repolarization

Table 1 Clinical Diseases Associated with Early Repolarization

Clinical diagnosis	No. of patients
Angina pectoris	83 (4.7)
Myocardial infarction	11 (0.6)
Hypertension	132 (7.4)
Congenital heart disease or Valvular heart disease	75 (4.2)
Arrhythmia	133 (7.5)
Kawasaki disease	40 (2.3)
Surgery	501 (28.2)
Others	990 (55.7)

Values are expressed as N (%).

Surgery indicates patients who underwent ECG before surgical procedure. Others include patients who suffered various internal diseases or who were suspected to have cardiovascular disease.

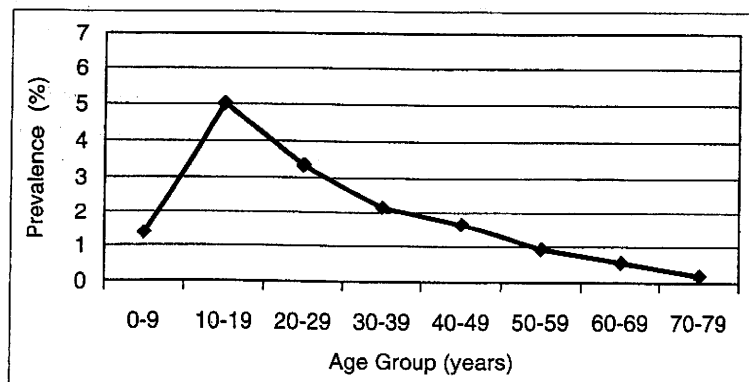


Figure 2 Age-specific prevalence of early repolarization in the total population.

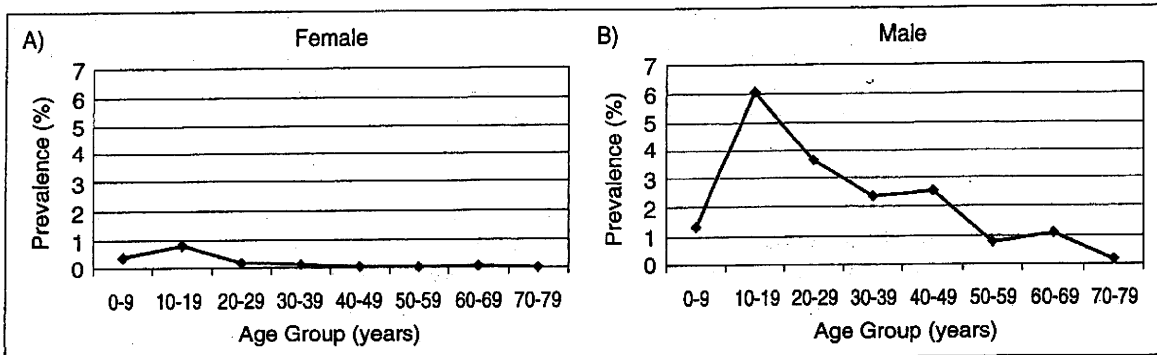


Figure 3 Age-specific prevalence of early repolarization of female patients (panel A) and male patients (panel B).

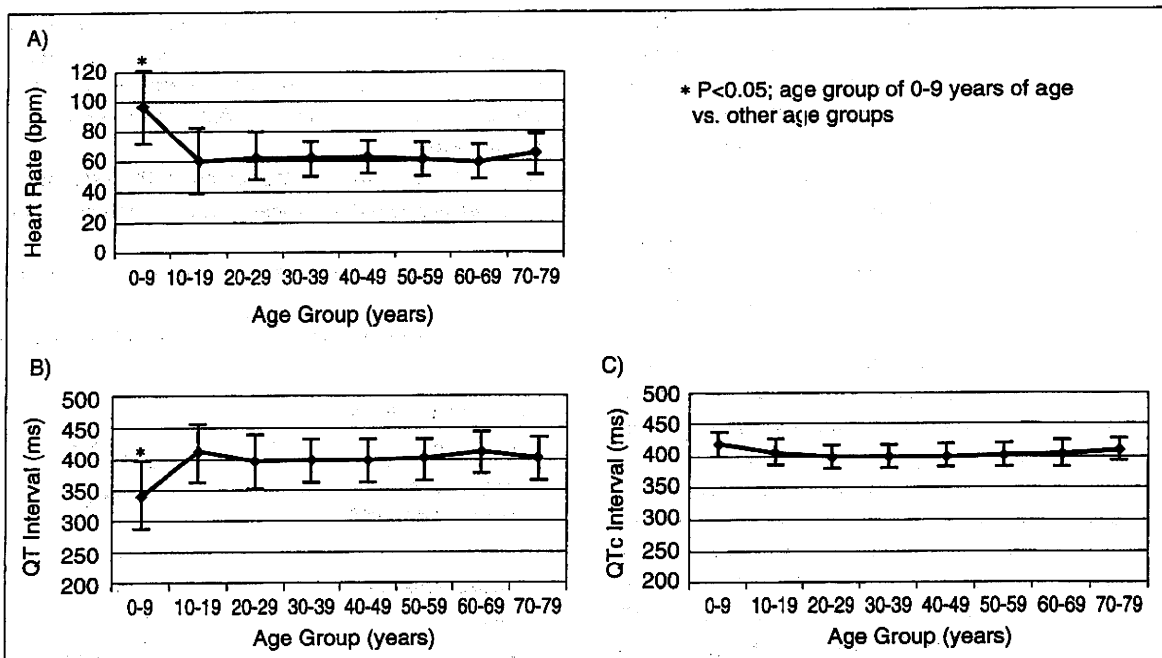


Figure 4 Age-specific heart rate (panel A), QT interval (panel B), and QTc interval (panel C) of patients with early repolarization in the total population.

coexisted with ECG abnormalities such as left ventricular hypertrophy, right ventricular hypertrophy, premature ventricular contraction, and atrial fibrillation. The complication rate of LVH was higher than that of RVH. AF was found in about 1% of patients with early repolarization, and the complication rate of PVC was also about 1%. Compared to AF and PVC, sinus bradycardia (≤ 50 beats/min) and sinus tachycardia (≥ 100 beats/min) were highly complicated in patients with early repolarization (i.e., 15.7% and 4.5%, respectively).

Discussion

Our results are consistent with previous reports in

the following points: 1) early repolarization is present in 1 to 5% of the general population, 2) early repolarization most frequently prevails in young individuals, and 3) a male preponderance is one of the characteristics of early repolarization.^{6,8)} The age-dependent distribution suggests that early repolarization might be an ECG phenotype during the development process. A male predominant presence of early repolarization strongly suggests that testosterone may be associated with occurrence of early repolarization. Presumably similar to Brugada syndrome, testosterone could increase outward transient current in the population of this study, leading to ST-segment elevation. This effect of testosterone strengthens the possible mechanism of juvenile male

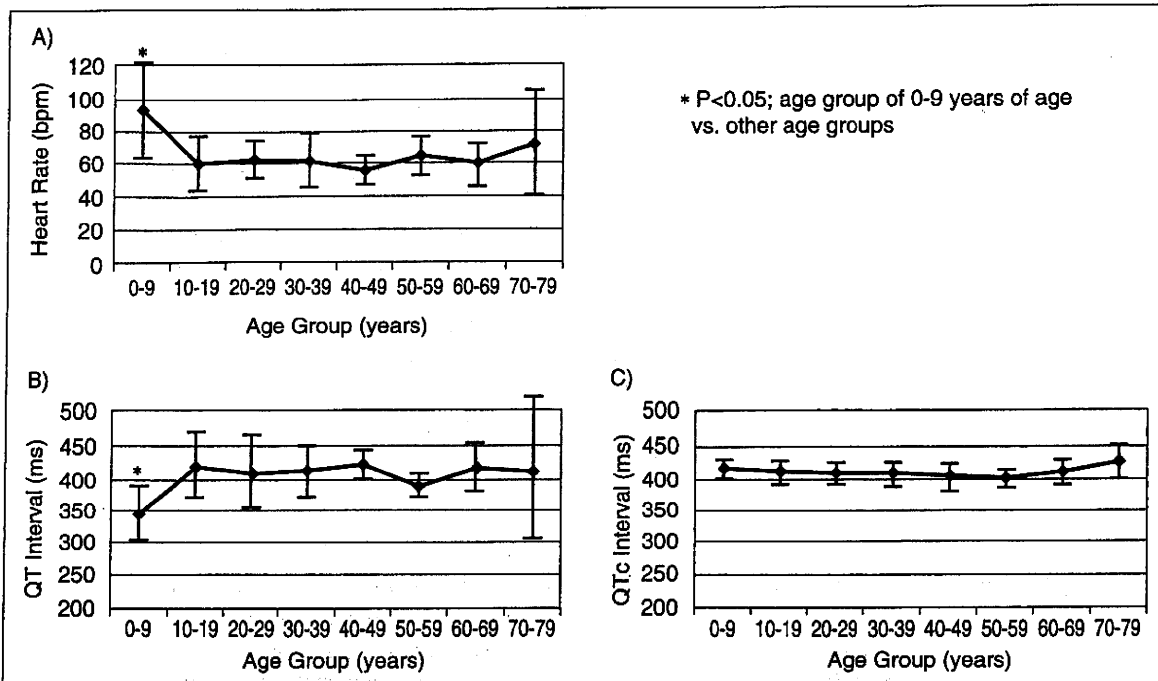


Figure 5 Age-specific heart rate (panel A), QT interval (panel B), and QTc interval (panel C) of female patients with early repolarization.

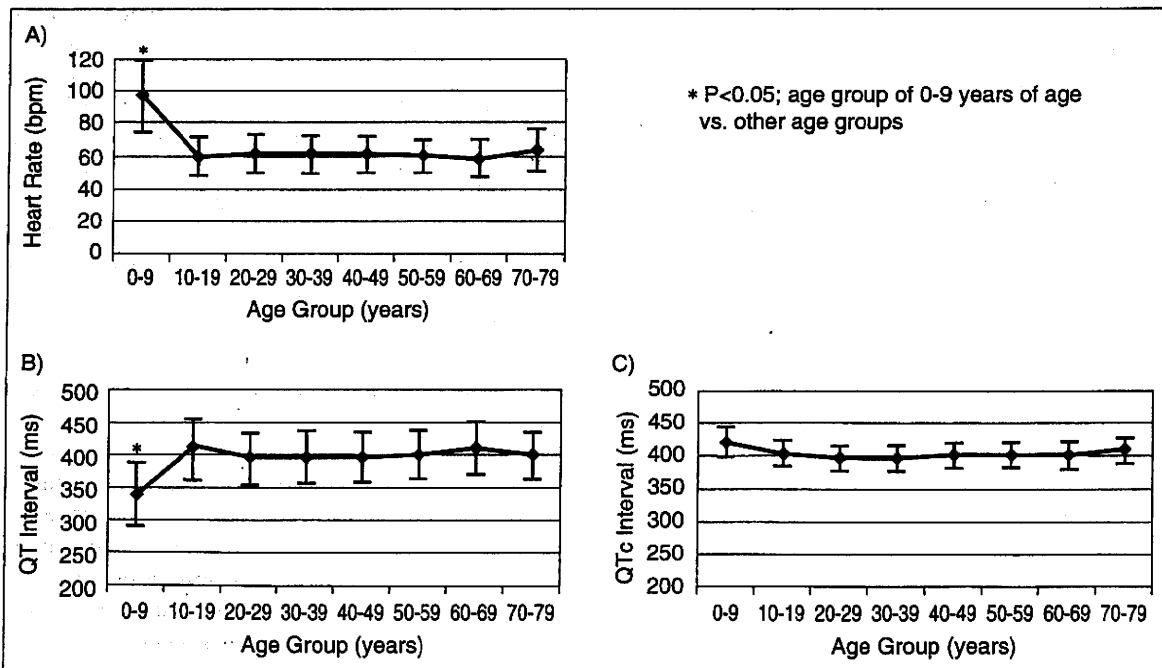


Figure 6 Age-specific heart rate (panel A), QT interval (panel B), and QTc interval (panel C) of male patients with early repolarization.

predominance of early repolarization. The peak of prevalence of early repolarization was, however, present at the age of 10–19 years not only in male patients but also in female patients, suggesting an

alternative possible mechanism such as growth hormone, for example. In this study, a mean value of QTc interval of patients with early repolarization was within normal range.^{9,10} Since the clinical