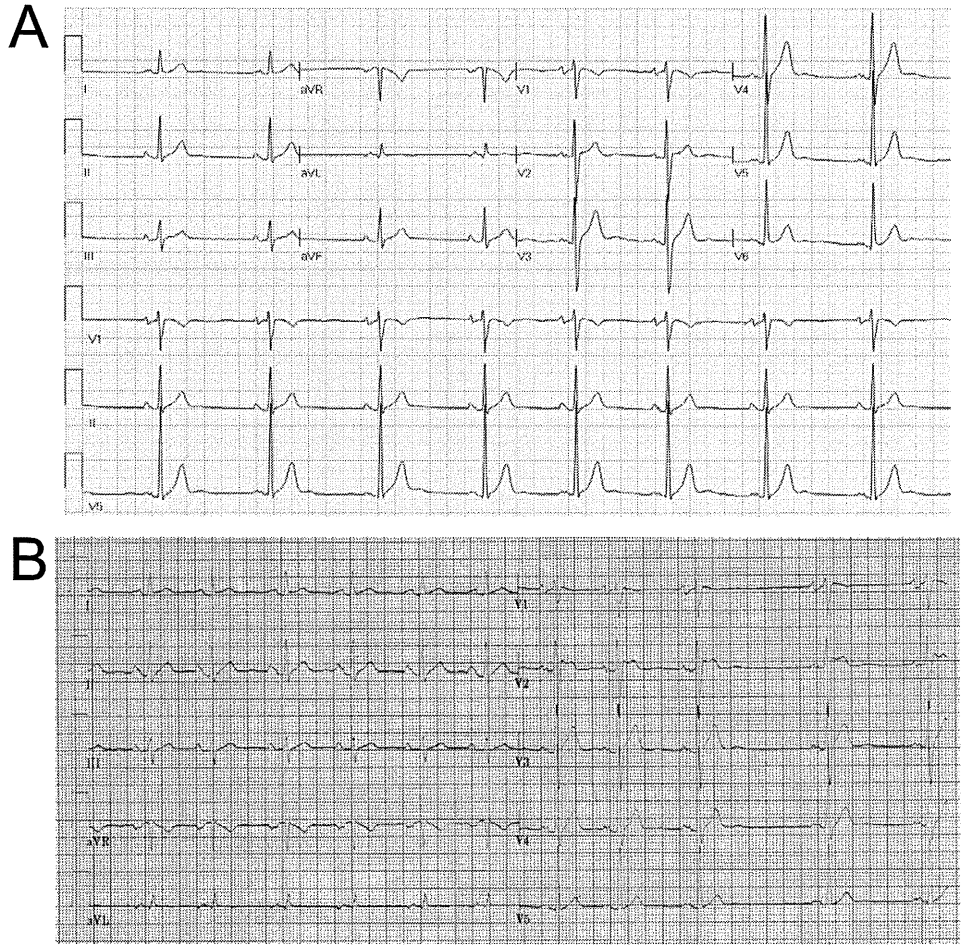

Figure 4 **A:** Twelve-lead ECG of a 54-year-old male patient who developed syncope repeatedly. Mean heart rate is 51 beats/min; mean QT interval, 386 ms; and mean QTc interval, 355 ms. Early repolarization is absent. **B:** ST-segment elevation in right precordial leads by intravenous administration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

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

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.

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	

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, $P<0.001$ 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. χ^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.

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 PM/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, PM/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 PM/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.

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

SD, by triple extrastimuli to group T, and noninducible patients to group N. We also evaluated the significance of the site of induction (the RVA or the RVOT) and the coupling interval of extrastimuli at the time of VA induction (<200 ms or ≥200 ms) on the prognosis of the patients.

Follow-up

An ICD implantation was proposed for all the patients with a previous VF and for those in whom VF or PVT was induced during the electrophysiological study. All patients were followed up in the outpatient clinic. Patients with and without ICD were followed up at every 3 and 6 months, respectively. Primary clinical outcome was determined as an occurrence of VF, sustained ventricular tachycardia, or sudden death.

Statistical analysis

Data were analyzed with JMP 8.0 software package (SAS Institute, Inc, Cary, NC). Numeric values were expressed as mean ± standard deviation. χ^2test, Student's t test, or 1-way analysis of variance was performed when appropriate to test for statistical differences. $P<.05$ was considered statistically significant. Event rate curves were plotted according to the Kaplan–Meier method and were analyzed with the log-rank test. Univariate and multivariate Cox regression were performed to assess predictive values of factors for subsequent cardiac events.

Results

Electrophysiological study

VA was induced in 81 patients (VF in 71 and PVT in 10): in 4 by single extrastimulus, in 41 by double extrastimuli, and in 36 by triple extrastimuli. There were 45 patients in group SD, 36 in group T, and 27 in group N.

Patients' characteristics are presented in Table 2. There were no significant differences among the 3 groups in gender, age, history of VF or syncope, family history of BrS or sudden death under 45 years of age, and age at the first cardiac event. There were also no significant differences in ECG parameters of the RR interval, PQ interval, QRS duration, corrected QT interval, and incidence of *SCN5A* mutation. Spontaneous coved-type ST segment was the only factor with significantly higher incidence in group SD than in group T and group N. LAS40 tended to be longer and RMS40 tended to be smaller in group SD and group T than in group N.

Table 2 Clinical, electrocardiographic, genetic, and electrophysiological characteristics

Characteristics	Group SD (n = 45)	Group T (n = 36)	Group N (n = 27)	*P* value
Clinical				
Male	44 (98%)	34 (94%)	26 (96%)	.73
Age (y)	48 ± 11	45 ± 13	44 ± 14	.31
Hx of VF	11 (24%)	9 (25%)	6 (22%)	.97
Hx of syncope	17 (38%)	13 (36%)	10 (37%)	.99
Asymptomatic	17 (38%)	14 (39%)	11 (41%)	.97
Family Hx of BrS	3 (7%)	0 (0%)	3 (11%)	.15
Family Hx of sudden death under age 45 y	10 (22%)	6 (17%)	6 (22%)	.80
Age at first CE (y)	44 ± 16	43 ± 14	41 ± 13	.86
Electrocardiographic				
RR interval (ms)	978 ± 125	990 ± 112	936 ± 108	.18
PQ interval (ms)	173 ± 27	178 ± 23	181 ± 39	.54
QRS duration (ms)	95 ± 15	99 ± 16	96 ± 19	.63
Corrected QT interval (ms)	404 ± 31	405 ± 26	406 ± 30	.97
Spontaneous coved-type ST segment	32 (71%)	19 (53%)	11 (41%)	.033
Total filtered QRS duration	122 ± 19	119 ± 16	114 ± 14	.17
LAS40	49 ± 16	49 ± 19	41 ± 13	.13
RMS40	14 ± 10	17 ± 10	20 ± 13	.051
Late potential*	32/44 (73%)	25/35 (71%)	13/24 (54%)	.25
Genetic				
SCN5A mutation	6 (13%)	3 (8%)	3 (11%)	.78
Electrophysiological				
AA interval	921 ± 153	903 ± 174	905 ± 143	.86
AH interval	106 ± 31	101 ± 21	108 ± 33	.65
HV interval	45 ± 12	44 ± 8	42 ± 9	.58
Induction of ventricular arrhythmia				
Ventricular fibrillation	40 (89%)	31 (86%)		NA
PVT >15 successive beats	5 (11%)	5 (14%)		NA
Site of induction				
Right ventricular apex	11 (24%)	13 (36%)		NA
Right ventricular outflow tract	34 (76%)	23 (64%)		NA

AH = atrio–His; BrS = Brugada syndrome; CE = cardiac event; HV = His–ventricular; Hx = history; NA = not available; PVT = polymorphic ventricular tachycardia; VF = ventricular fibrillation.

*Late potential was considered present when the 2 criteria (LAS40 > 38 ms and RMS40 < 18 μV) were fulfilled.

As for electrophysiological characteristics, AA, atrio–His, and His–ventricular intervals showed no significant differences among the 3 groups. VA was more frequently induced from the RVOT than from the RVA (57 [70%] vs 24 [30%], respectively).

Subsequent cardiac events during follow-up

We recommended all patients with prior VF episode, group SD patients, and group T patients with prior syncope to undergo an ICD implantation. For asymptomatic group T patients, and group N patients without prior VF, ICD implantation was performed only for those who wanted it after informed consent. Forty-one of the 45 group SD patients (91%), 25 of the 36 group T patients (69%), and 13 of the 27 group N patients (48%) underwent an ICD implantation.

There were no deaths during 82 ± 48 months of follow-up; 24 patients had VF events. All these 24 patients had undergone ICD implantation, and VF was documented on the recordings of the ICD. No patients without ICD experienced any syncope. There were no significant differences in the follow-up period among the 3 groups (group SD 83 ± 50 months, group T 81 ± 44, and group N 80 ± 49; P = .96). Significantly more VF episodes occurred in group SD (16 of 45 [36%]) than in group T (3 of 36 [8%]) and in group N (5 of 27 [19%]) (P = .012).

Figure 1 shows the results of the Kaplan–Meier analysis of subsequent cardiac events. As previously reported, induction of VA was not associated with subsequent cardiac events (Figure 1A, log-rank, P = .78). When we focused on the numbers of extrastimuli, group SD had a significantly higher risk of subsequent cardiac events than did group T (log-rank, P = .004), but there were no significant differences in the subsequent cardiac event rate between group SD and group N and between group T and group N (Figure 1B). Among 82 patients without prior VF episode, VA induction with up to 2 extrastimuli was a significant risk factor of subsequent cardiac events (Figure 1C, log-rank, P = .003).

In 81 patients with induced VA, the site of induction (the RVA or the RVOT) and the coupling interval of extrastimuli at the time of VA induction (<200 ms or ≥200 ms) were not associated with subsequent cardiac events (Figures 2A and 2B, log-rank, P = .57 and .52, respectively). The cardiac event rate was associated with the number of extrastimuli, not with the site of induction and the coupling interval (Figures 3A and 3B).

As for 42 asymptomatic patients, 2 of the 17 patients in group SD experienced subsequent VF episodes, whereas none of the 14 patients in group T and 11 in group N experienced subsequent cardiac events. Although the number of patients was small, group SD showed a significantly higher cardiac event rate than did group T and group N (log-rank, P = .046).

Predictors of long-term prognosis

The results of Cox regression analysis are shown in Table 3. In univariate Cox regression, history of VF, VA induced with up to 2 extrastimuli, incidence of spontaneous coved-type ST segment, and Late potential were significant predictors of subsequent cardiac events. Multivariate Cox re-

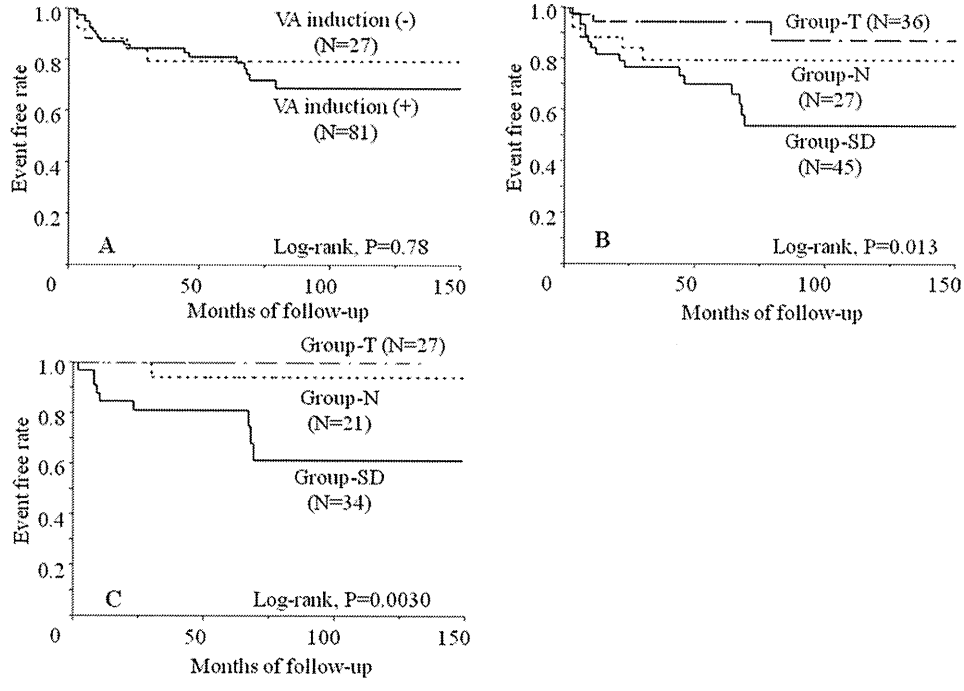

Figure 1 Kaplan–Meier curves of subsequent cardiac events during follow-up. Kaplan–Meier curves of cardiac events (**A**) depending on the overall inducibility of ventricular arrhythmias (VFs and polymorphic ventricular tachycardia >15 successive beats) by up to triple extrastimuli, (**B**) in the 3 groups, and (**C**) in the population of patients without history of VF depending on the 3 groups. Although the overall inducibility was not associated with subsequent cardiac events, inducibility by up to 2 extrastimuli had significant predictive values for the occurrence of subsequent cardiac events. Group SD had a significantly higher cardiac event rate than did group T. In the population of patients without previous VF, inducibility by up to 2 extrastimuli was strongly associated with subsequent cardiac events.

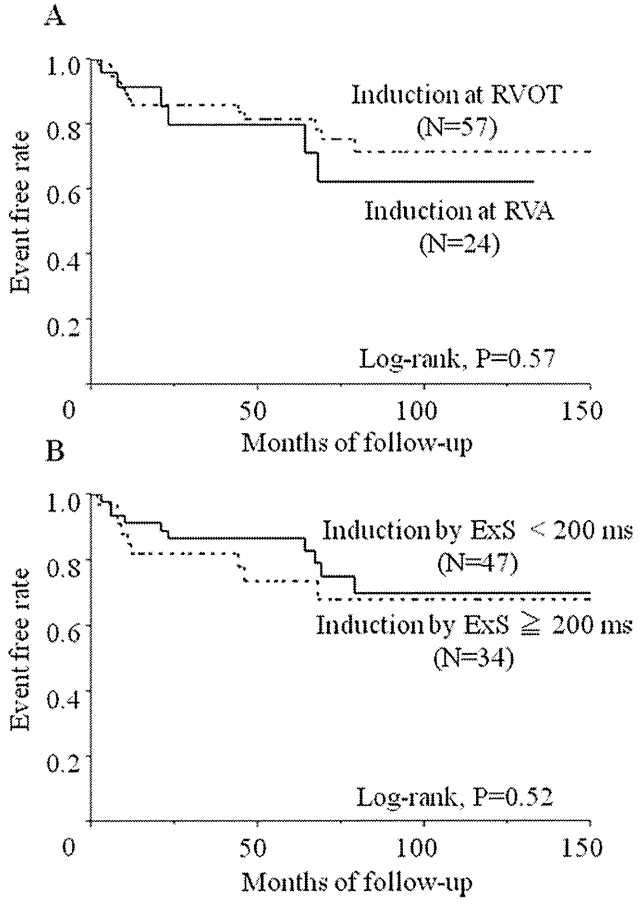

Figure 2 Kaplan–Meier curves of subsequent cardiac events during follow-up. Kaplan–Meier curves of cardiac events (**A**) depending on the induction site and (**B**) the minimum coupling interval of extrastimuli at the time of induction. Neither the site of induction, the right ventricular outflow tract or the right ventricular apex, nor the minimum coupling interval, longer or shorter than 200 ms, was associated with subsequent cardiac events.

gression demonstrated that the only predictive index was VA induction with up to 2 extrastimuli except for history of VF. Neither VA induction from the RVA nor the coupling interval of extrastimuli <200 ms at the time of VA induction was a predictor of subsequent cardiac events.

Discussion

The major findings of the present study were the following: (1) induction of VA by triple extrastimuli was not associated with a higher incidence of subsequent VF, (2) patients with VA induced by up to 2 extrastimuli had significantly more frequent VF episodes during 7 years of follow-up, (3) neither the site of VA induction (the RVA or the RVOT) nor the coupling interval of VA induction (<200 ms or ≥200 ms) was associated with the incidence of subsequent cardiac events.

We evaluated the prognostic role of VA induction by PES and found that the number of extrastimuli that induced VA was prognostic for patients with Brugada type 1 ECG.

Clinical significance of PES in patients with BrS

Conflicting data have been reported from several registries as to the prognostic value of PES in patients with BrS.[4,6,7] Brugada et al reported that PES was a good predictor of arrhythmic events. Meanwhile, Priori et al and Probst et al argued that it was not a useful index. Meta-analysis data indicated that PES was not useful for predicting subsequent cardiac events, and the published ACC/AHA/ESC guidelines referred to PES as a class IIb indication in asymptomatic patients with BrS for risk stratification.[11–13] However, there were several limitations for each registry such as the different PES protocols.[14] Moreover, these conflicting data may be related to the specific inclusion criteria of each registry. Recently, Giustetto et al[9] reported that PES protocol up to 2 extrastimuli with ventricular effective refractory period was useful in risk stratification in patients with BrS. This Italian study agrees with our result that VA induction with up to 2 extrastimuli could help predict subsequent cardiac events if a consistent PES protocol is used. The present study also demonstrated that a PES protocol with up to 3 extrastimuli was not useful for risk stratification in patients with BrS. We presume that this result in part explains why several registries reported conflicting data.

Patients without VA induction, especially patients with history of VF, had subsequent arrhythmic events in the present study (5 of 27 [19%]). In this respect, the present study differs from the Italian study. We can cite 2 contributing factors. First, our follow-up period was nearly 7 years, which was much longer than that of the Italian study. Second, we adopted only 1 basic cycle length, whereas Giustetto et al adopted 2 basic cycle lengths; hence, it is possible that we could not induce VA in some patients.

Underlying mechanism

Arrhythmogenicity in patients with BrS is possibly associated with both repolarization and depolarization abnormal-

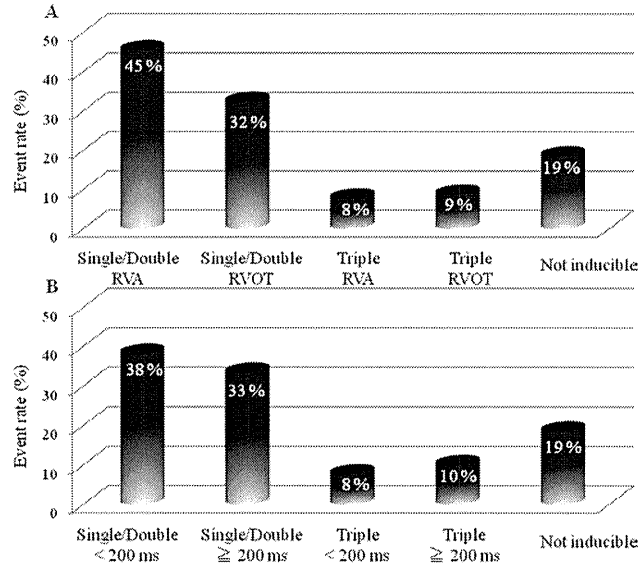

Figure 3 Incidence of subsequent cardiac events according to the number of extrastimuli, the site of induction, and the minimum coupling interval at the time of induction. Incidence of cardiac events (**A**) according to the number of extrastimuli and the site of induction and (**B**) the number of extrastimuli and the minimum coupling interval. The patients whose ventricular arrhythmias were induced by up to 2 extrastimuli had a higher incidence of cardiac events in both categories.

Table 3 Predictive factors of subsequent cardiac events

	Univariate analysis		Multivariate analysis	
	Hazard ratio	*P* value	Hazard ratio	*P* value
Hx of VF	4.59 (2.05–10.7)	<.001	3.47 (1.50–8.27)	.004
VA induced with double extrastimuli	3.21 (1.41–7.92)	.005	3.03 (1.26–8.00)	.013
Spontaneous coved-type ST segment	3.20 (1.28–9.65)	.011	1.77 (0.67–5.56)	.26
Late potential	2.72 (1.02–9.40)	.046	1.77 (0.60–5.98)	.34
SCN5A mutation	2.92 (0.96–7.33)	.057	1.66 (0.47–4.63)	.40
VA induction at the RVA	1.29 (0.47–3.07)	.60		
VA induced with CI < 200 ms	0.86 (0.37–1.91)	.71		
VA induced by PES	1.21 (0.48–3.64)	.71		
Family Hx of sudden death under age 45	1.18 (0.39–2.95)	.74		

CI = coupling interval; Hx = history; PES = programmed electrical stimulation; RVA = right ventricular apex; VA = ventricular arrhythmia; VF = ventricular fibrillation. Parentheses represent 95% confidence interval.

ities. In the present study, patients with induced VA had longer LAS40 (49±17 vs 41±13; $P = .042$) and smaller RMS40 (15±10 vs 20±13; $P = 0.034$) than did noninduced patients, which may reflect depolarization abnormality and is concordant with our previous report.[15]

There have been several reports regarding depolarization abnormalities in BrS such as *SCN5A* mutation or fragmented QRS.[16–18] By using an experimental model, Aiba et al[19] showed that depolarization abnormalities played a significant role in VF maintenance. Thus, if PES results reflect depolarization abnormality, we could evaluate how easily VF continues through PES. The initiation of VF is thought to be due to phase 2 reentry-induced premature beats (repolarization abnormality).[19,20] It could be difficult to evaluate repolarization abnormality through PES, and this is why PES in BrS cannot completely predict subsequent cardiac events.

Clinical implication

According to the ACC/AHA/ESC guidelines, patients with BrS with spontaneous ST-segment elevation and syncope are a class IIa indication for ICD implantation.[13] However, some patients with BrS experience neurally mediated syncope, as previously reported, which should be distinguished from syncope of unknown origin.[21] Therefore, only the history of syncope could lead to unnecessary use of ICD. We showed that PES of up to 2 extrastimuli can predict subsequent events of patients with prior syncope, demonstrating the possibility that PES could help reduce the unnecessary use of ICD in those patients (Figure 1C).

Meta-analysis studies of patients with BrS could not identify a significant role of PES for predicting subsequent arrhythmic events.[11,12] However, many registries included in their meta-analysis adopted PES protocol of up to 3 extrastimuli. Triple extrastimuli could induce VA even in normal individuals and exaggerate nonspecific depolarization abnormality leading to induction of nonspecific VA. This suggests that VA induction by triple extrastimuli may be highly unnatural, resulting in false-positive VA induction.

ACC/AHA/ESC guidelines have not yet delineated an appropriate PES protocol in detail, such as the number of extrastimuli. We showed that single extrastimulus or double extrastimuli are adequate for PES for patients with BrS. Although the number of patients was small, VA induction with up to 2 extrastimuli was associated with subsequent arrhythmic events even in asymptomatic patients. Positive and negative predictive values according to PES protocols are shown in Table 4. Based on our criteria that VA induction was considered positive when VF or PVT with more than 15 successive beats was elicited, a protocol of up to 2 extrastimuli showed that the positive predictive value (PPV) was 36% and the negative predictive value (NPV) was 87%. On the other hand, a protocol of up to 3 extrastimuli showed that PPV was 23% and NPV was 81%. Even when we consider only VF as an induction criterion, both PPV and NPV were higher with up to 2 extrastimuli (Table 4). Based on our data, protocols up to 2 extrastimuli were sufficient for PES in patients with BrS. In the subgroup of 82 patients without prior VF or aborted cardiac arrest, VF occurred in 9 of the 34 patients with VA induced by up to 2 extrastimuli. No VF occurred in 27 patients with VA induced by triple extrastimuli, and only 1 of the 21 noninducible patients experienced VF. The PPV of PES protocol up to 2 extrastimuli was 26%, but the NPV was high at 98%. However, a low PPV of PES can cause unnecessary use of ICD implantation, especially for asymptomatic patients. We still need to make a decision based on several indices combined, as Delise et al[22] have recently reported.

Table 4 Positive and negative predictive values according to protocols of PES

Protocols	PPV	NPV
VF and NSPVT >15 successive beats		
PES with up to 2 ExS	16/45 (36%)	55/63 (87%)
PES with up to 3 ExS	19/81 (23%)	22/27 (81%)
Only VF		
PES with up to 2 ExS	13/40 (33%)	57/68 (84%)
PES with up to 3 ExS	16/71 (23%)	29/37 (78%)

ExS = extrastimuli; NPV = negative predictive value; NSPVT = nonsustained polymorphic ventricular tachycardia; PES = programmed electrical stimulation; PPV = positive predictive value; VF = ventricular fibrillation.

Study limitations

This study has several limitations. First, this was a retrospective study. However, we believe that our data have validity because this was not an interventional study but an observational study, and moreover, the follow-up periods of the 3 groups were not significantly different. Second, this study consisted of a small population of 108 patients, insufficient to fully evaluate the prognosis of patients with BrS. Further study with a larger number of patients with BrS and with consistent protocol of PES will be required to draw a firm conclusion on the importance of the number of extrastimuli. If each registry does not have a large enough number of patients, a meta-analysis that can compare the numbers of extrastimuli could validate the significance of PES. Third, we could have underestimated the cardiac event rate because the end point of the patients without ICD was based on symptoms (syncope); thus, asymptomatic cardiac events during sleep could be missed. Fourth, we adopted only 500 ms as a basic cycle length, and so VA could not be induced in some patients in the present study because this was shorter than in other studies that employed more than 2 basic cycle lengths. However, VA was induced in 75% and VF was induced in 68% of the patients. This induction rate was comparable to that in other registries; this suggests that a single basic cycle length of 500 ms is enough to induce VA. We did not deliver extrastimuli coupled with intervals shorter than 180 ms. Therefore, we could not assess the significance of delivering extrastimuli with intervals shorter than 180 ms. However, extra stimulus with shorter intervals may exaggerate nonspecific depolarization abnormality, leading to induction of nonspecific VA. This issue needs to be addressed. Fifth, the incidence of *SCN5A* mutation was relatively low at 11%, even though we searched the entire coding sequence of *SCN5A*. As previously pointed out, the incidence of *SCN5A* in Japan is lower than in Western countries, and so this study agrees with previous data.[23,24] Finally, there were 46 patients (7 with prior VF, 21 with prior syncope, and 18 asymptomatic) with drug-induced type 1 ECG, which can be misdiagnosed as BrS because of its false-positive ECG morphology. However, the percentage of these patients was lower than that in the FINGER study, and we confirmed the obvious coved ST elevation induced by sodium-channel–blocker test in patients with type 2 and type 3 ECG.

Conclusion

The number of extrastimuli in PES that induced ventricular arrhythmias served as a prognostic indicator for patients with type 1 Brugada ECG. The site of induction and the coupling interval of extrastimuli at the time of VF induction were not prognostic indicators of patients with BrS. Our data suggest that PES in patients with type 1 Brugada ECG should employ up to 2 extrastimuli, rather than 3.

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Effect of sodium-channel blockade on early repolarization in inferior/lateral leads in patients with idiopathic ventricular fibrillation and Brugada syndrome

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BACKGROUND A high incidence of early repolarization (ER) pattern in the inferolateral leads has been reported in patients with idiopathic ventricular fibrillation (IVF). Brugada syndrome (BS) is characterized by J-point or ST-segment elevation in the right precordial leads and ventricular fibrillation, and some patients with BS also have ER in the inferolateral leads.

OBJECTIVE To compare the clinical characteristics and effects of sodium-channel blockade on ER between IVF patients with ER (early repolarization syndrome [ERS]) and BS patients with or without ER.

METHODS Fourteen patients with ERS and 21 patients with BS were included in this study. ER was defined as an elevation of at least 0.1 mV from baseline in the QRS–T junction in the inferoro-lateral leads. Provocative tests with sodium-channel blockers were conducted in all patients with ERS to distinguish ERS from BS.

RESULTS In the ERS group, all patients were male and most patients experienced ventricular fibrillation during sleep or low activity (79%). ER was attenuated by sodium-channel blockers in most patients with ERS (13/14, 93%) and BS (5/5, 100%), whereas ST-segment elevation was augmented in the right precordial leads in the BS group. The rates of positive late potentials were significantly higher in the BS group (60%) than in the ERS group (7%) ($P < .01$).

CONCLUSIONS Some similarities were observed between ERS and BS, including gender, arrhythmia triggers, and response of ER to sodium-channel blockers. Unlike the ST segment in the right precordial leads in BS, ER was attenuated in patients with both ERS and BS, suggesting a differential mechanism between ER in the inferolateral leads and ST elevation in the right precordial leads.

KEYWORDS Early repolarization; J wave; Idiopathic ventricular fibrillation; Brugada syndrome; Sudden death; Sodium-channel blocker

ABBREVIATIONS **BS** = Brugada syndrome; **ECG** = electrocardiogram; **ER** = early repolarization; **ERS** = early repolarization syndrome; **IVF** = idiopathic ventricular fibrillation; **LPs** = late potentials; **QTc** = corrected QT interval; **SAECG** = signal-averaged electrocardiogram; **SCD** = sudden cardiac death; **VF** = ventricular fibrillation; **VT** = ventricular tachycardia

Introduction

Early repolarization (ER) pattern is often found in the general population and has been considered a benign electrocardiographic finding. Its prevalence has been estimated to be between 1% and 5% of healthy adults.[1–4] Idiopathic ventricular fibrillation (IVF) presenting prominent ST-segment elevation in the inferior leads has been considered as a variant of Brugada syndrome (BS).[5,6] BS[7] is characterized by ST-segment elevation in the right precordial leads V1 to V3 and is considered to have a high propensity toward sudden cardiac death (SCD).[8,9] Recently, several reports have suggested the association of IVF with ER in the inferior and/or lateral lead in the electrocardiogram (ECG).[3,10–14] ER is reported to be found more frequently among patients with IVF than among healthy control subjects.[10,15] However, little is known about the clinical and electrocardiographic characteristics and the pharmacological response of ER in patients with IVF and BS associated with ER and their different re-

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sponse from that of ST elevation in the right precordial leads in patients with BS. The present study aimed to investigate the similarities and differences between IVF with ER (early repolarization syndrome [ERS]) and BS with or without ER.

Methods

Patient characteristics

Among 38 patients with IVF, admitted to the National Cerebral and Cardiovascular Center between 1994 and 2009, ER in the inferior and/or lateral ECG leads was recorded in 14 patients (37%). These 14 patients were included in this study as an ERS group (all males, aged 27–64 years, mean age 44.7 ± 13.6 years). Twenty-one patients with BS with a history of ventricular fibrillation (VF) or aborted SCD were also included in this study. According to the published guidelines,[16,17] patients were diagnosed as suffering from IVF if they had no structural heart disease confirmed by noninvasive studies (physical examination, ECG, exercise stress test, echocardiogram, and cardiac magnetic resonance imaging or computed tomography) and invasive studies (coronary angiography and left ventricular cineangiography). Long QT syndrome (corrected QT [QTc] interval ≥440 millisecond), short QT syndrome (QTc interval <340 millisecond), and BS were also excluded to diagnose a patient as suffering from IVF. To exclude BS, all subjects in the ERS group were proven to be negative with a pharmacological challenge with pilsicainide.[8,18]

The BS group consisted of 21 patients (19 males, aged 20–64 years, mean age 39.7 ± 12.6 years) with an episode of documented VF or aborted SCD. Eleven had a spontaneous type 1 ECG, and in the remaining, it was induced by a sodium-channel blocker. Ethical approval of the present study was obtained from the Institutional Review Committee of the National Cerebral and Cardiovascular Center.

Electrocardiography

All available conventional ECGs (25 mm/s, 10 mm/mV) were investigated in the search for ER. ER was defined as an elevation of at least 1 mm (0.1 mV) in the J point (QRS–ST junction) in at least 2 leads (Figure 1), either as QRS slurring (smooth transition from QRS to the ST segment) or as notching (a positive J deflection inscribed on the S wave).[10] The inferior (II, III, and aVF) and lateral (I, aVL, and V4–V6) leads were evaluated. To exclude BS, no J-point elevation must exist in the right precordial leads (V1–V3).

All ECGs were interpreted blindly by 2 independent cardiologists (H.K., W.S.). The following parameters were assessed in lead II, which include P-wave duration and PQ and RR intervals. QRS duration and QT interval were assessed in leads II and V5. The QTc interval was calculated using Bazett's method. The amplitude of ER was assessed in the inferior leads (II, III, and aVF), the lateral leads (I, aVL, and V4–V6), or both, and the maximum ER amplitude was measured. We selected leads II and V5 as representative of inferior and lateral leads for the analysis of ER amplitude.

BS was diagnosed when a type 1 coved-type ST-segment elevation (≥0.2 mV at J point) was observed in >1 of the right precordial leads (V1–V3) in the presence or absence of

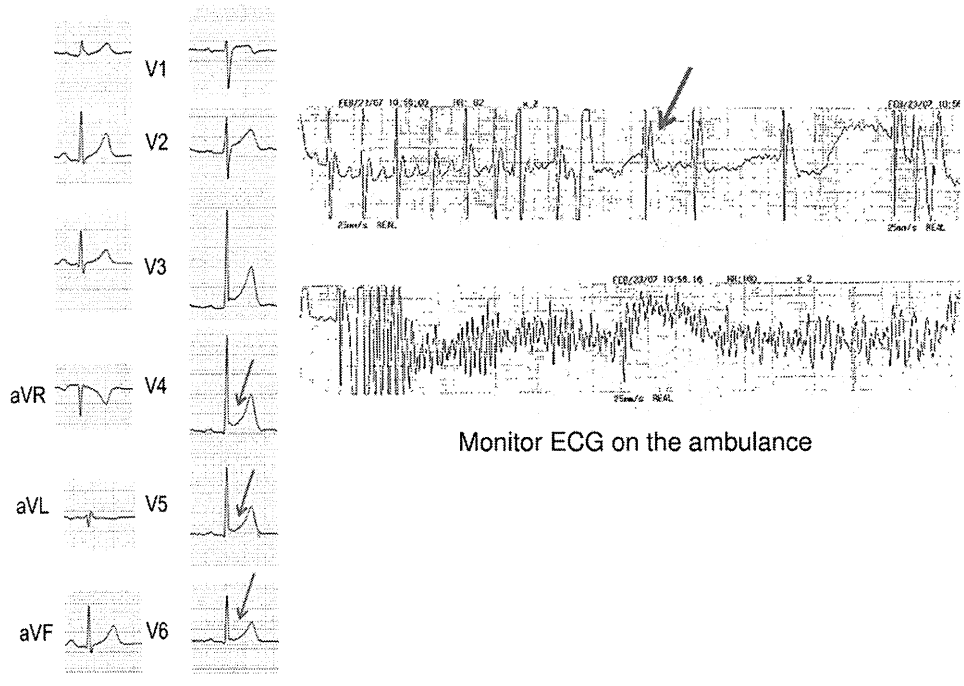

Figure 1 **A:** Twelve-lead ECG in a patient with early repolarization syndrome. ER (arrow) was seen in the lateral leads (V4–V6) under baseline conditions. **B:** Monitor ECG recorded during the arrhythmic periods in the same patient showed a consistent increase in the amplitude of ER, followed by initiation of ventricular fibrillation. ECG, electrocardiogram; ER, early repolarization.