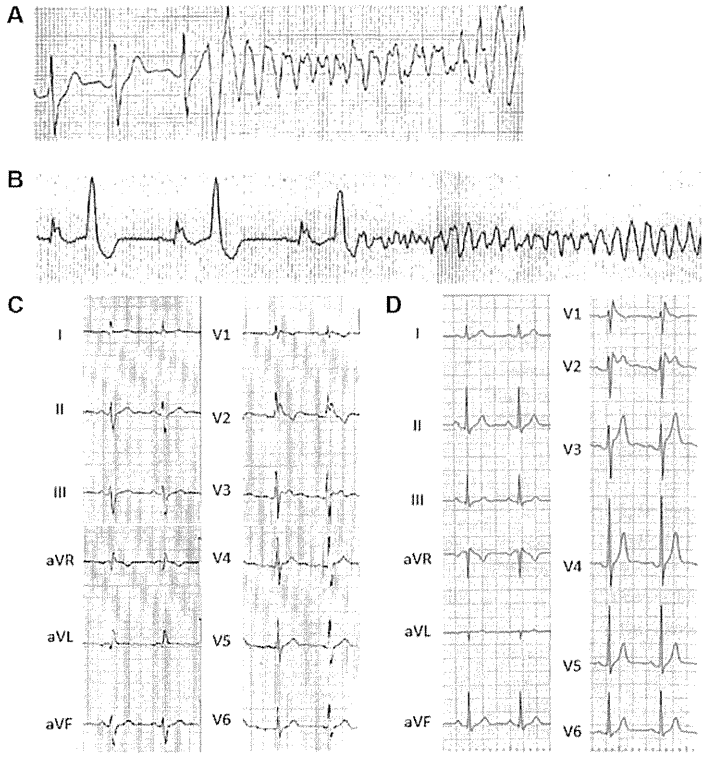

Figure 1. Onset of ventricular fibrillation (VF). **A**, VF developing during undisturbed sinus rhythm (*patient no 3*). **B**, VF following a short-long-short sequence with frequent premature ventricular complexes (patient no 10). **C** and **D**, J waves were absent during sinus rhythm on the 12-lead ECG of each patient.

drugs. However, 6 patients treated with bepridil, 100 to 200 mg daily, 2 patients treated with quinidine, 300 to 600 mg daily, and 1 patient treated with amiodarone, 100 mg daily, remained free from VF recurrences. One patient treated with disopyramide 300 mg daily experienced a single recurrence of VF. During follow-up, the J wave disappeared in 1, decreased in amplitude in 2 (Figure 3), and remained unchanged in 7 of 10 patients whose ECG were available during long-term follow-up.

ICD were implanted in 21 control patients, including 17 patients with histories of VF and 4 with histories of syncope. Quinidine was used for secondary prevention of VF in 1 patient. A single patient (5%) untreated with an antiarrhythmic drug experienced a recurrence of VF.

By Kaplan-Meier analysis of the cumulative incidence of recurrent arrhythmic events, the prognosis of patients with ES was significantly worse than that of patients without ES (Figure 4).

Discussion

The main finding of our study was a high prevalence of ER in patients presenting with BrS with versus without ES. Intravenous isoproterenol seemed effective in the short-term

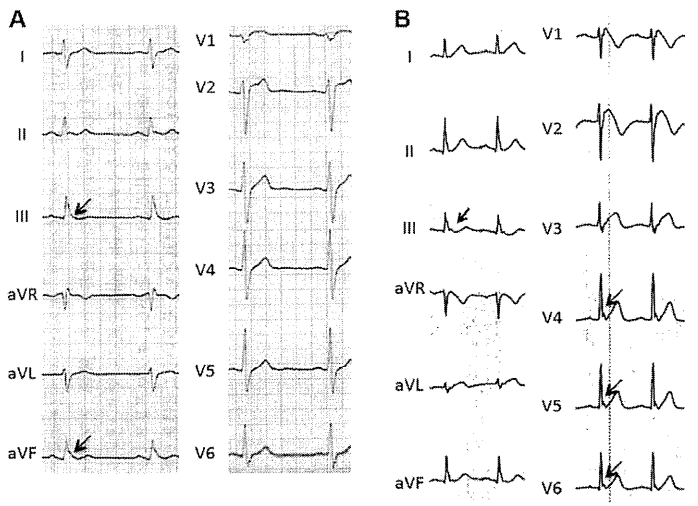

Figure 2. Twelve-lead ECG with J waves during sinus rhythm. **A**, J waves followed by horizontal/descending ST elevation are present in the inferior leads (arrows; patient no 14). **B**, J waves followed by rapidly ascending/upsloping ST elevation are visible in the inferolateral leads (patient no 7).

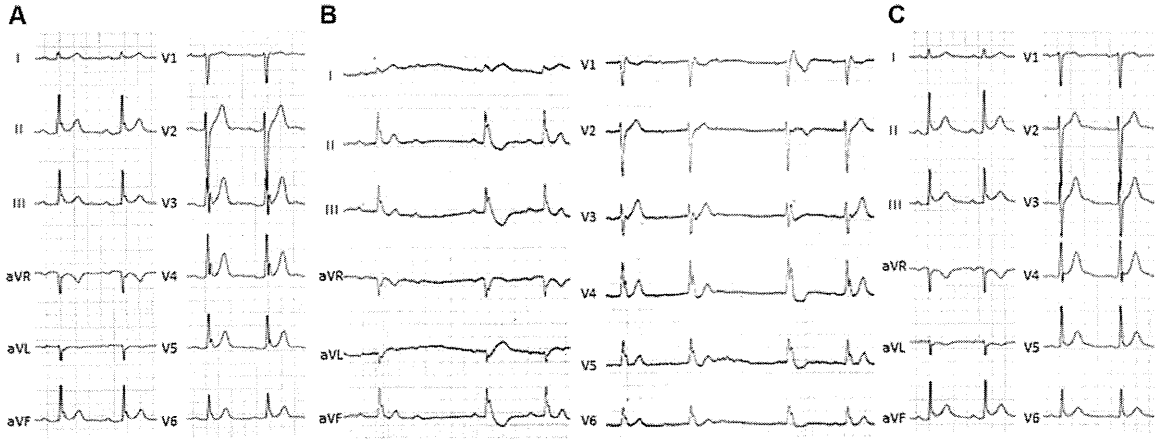

Figure 3. Accentuation of the J wave during electrical storm in patient no 13. **A**, 12-lead ECG recorded on admission before electrical storm (ES). J waves with a maximum amplitude of 0.5 mV were observed in leads I, II, III, aVF, and V3-V6. **B**, 12-lead ECG recorded before the second episode of VF on the same day. The J waves are more prominent than in (**A**). The pause-dependent augmentation is evident when the RR interval is lengthened by atrioventricular block. **C**, VF was well controlled by the infusion of isoproterenol. The amplitude of the J wave decreased in all leads. VF indicates ventricular fibrillation. Reprinted from Kaneko et al[7] with permission of the publisher. Copyright © 2012, Wiley Periodicals, Inc.

suppression of ES, while oral bepridil and quinidine effectively prevented long-term recurrences of VF. Patients with BrS and ER were at higher risk of ES and VF recurrences than patients without ER.

Regarding the ECG characteristics, patients with BrS and ES in this study had a higher prevalence of type 1 ECG pattern and J waves than the controls (Table 2). The prevalence of ER was also higher than reported in general Western populations[4,8,16,17] and in this country.[9,18] Therefore, the prevalence of J waves in patients with BrS and ES is higher than in (1) patients with BrS without ES,[12] and (2) the general population. Several studies have suggested that the presence of inferolateral J waves in BrS is associated with a higher risk of recurrent VF.[6,11–13] However, a relationship with ES in particular has not been described previously.

Studies in animals have suggested a common mechanism underlying (1) the ECG phenotype of BrS and (2) ER (the J wave) in idiopathic VF, both explained by a voltage gradient in the early phase of repolarization.[19] In BrS, the presence of a J wave in V1 to V3 is explained by a notched phase 1 of the right ventricular outflow tract myocardial action potential, which, when augmented, may be followed by a secondary dome resulting in a coved ST-T segment.[19,20] However, the pathophysiological mechanism(s) behind the ST-T changes observed in patients presenting with BrS remain(s) vigorously debated, and hypotheses have been formulated in favor of abnormalities of both depolarization and repolarization to explain the ECG phenotype of BrS.[21]

Table 2. Characteristics of 22 Men With BrS and ES vs 110 Men With BrS and No ES

	With ES	Without ES	*P*
Age, y	39 (23)	44 (18)	0.04
Family history of sudden death/BrS	3/0	12/3	0.47/0.58
Electrocardiographic intervals, ms			
RR	785 (212)	909 (213)	0.0005
PR	180 (26)	162 (24)	0.048
QRS	100 (29)	104 (16)	0.21
QT	340 (40)	396 (41)	<0.0001
QTc	390 (51)	394 (33)	0.02
Spontaneous type 1 ECG	17 (77)	31(28)	<0.0001
J wave >0.1 mV	8 (36)	10 (9)	0.003
J-wave amplitude, mV	0.3 (0.1)	0.2 (0.01)	0.03

Values are median (interquartile range) or numbers (%) of observations. BrS indicates Brugada syndrome; and ES, electrical storm.

In patients with idiopathic VF, J waves are more prevalent in the inferior and lateral precordial leads and may be explained by a mechanism similar to that of the J waves observed in BrS.[19,20] They are augmented by an increased repolarization inhomogeneity from undetermined causes, along with the development of phase 2 reentry and subsequent VF. Although the ECG phenotype and response of VF to pharmaceuticals in BrS and J wave–associated idiopathic VF are similar, the J wave is only enhanced by class I antiarrhythmic drugs in BrS and not in J wave–associated idiopathic VF.[14] The presence of ER in BrS increases the risk of ES and recurrent VF[6,11–13] although the significance of the association between BrS and ER remains to be clarified.

A dissimilar mode of onset of VF has been reported in BrS–associated versus in J wave–associated idiopathic VF. In the study by Nam et al,[4] VF was triggered by a premature ventricular complex with a short-long-short sequence in 42 of 58 patients with ER (72.4%) versus 13 of 86 patients (15.1%) with BrS ($P<0.01$). Furthermore, the mean coupling interval of the VF-triggering premature ventricular complexes was significantly shorter in the group of patients presenting with idiopathic VF and ER than in patients presenting with BrS ($P<0.01$). In the present study, the mode of VF onset was known in 19 patients and developed during regular sinus rhythm in 14 patients (74%), after a short-long-short sequence in 4 (21%),

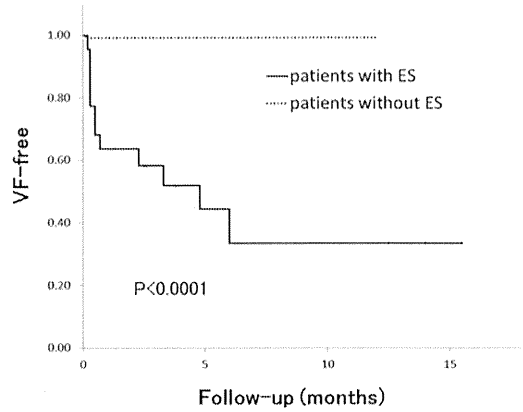

Figure 4. Kaplan-Meier estimates of ventricular fibrillation (VF) recurrence after electrical storms.

and in both circumstances in 1 patient (5%). Although the presence of ER did not influence the mode of onset of VF in the patients experiencing BrS complicated by ES, the role of ER in the development of VF is in need of further studies.

An association between (1) horizontal/descending ST elevation followed by ER and (2) an increased arrhythmic risk was recently observed in the general population[16] and in patients with histories of idiopathic VF.[17,22,23] Although we did not find a significantly higher prevalence of horizontal/descending ST elevation combined with ER in patients presenting with BrS and ES, a larger observational study is needed to clarify this point.

Intravenous isoproterenol or oral quinidine are the drugs of choice for the short-term management of ES in both BrS- and ER-associated idiopathic VF.[2–4] We found these drugs to be particularly effective in BrS with ER, presumably by augmenting the inward calcium currents, restoring the dome of the action potential, and mitigating the inhomogeneity of repolarization. Besides quinidine, bepridil, a class IV antiarrhythmic drug with Ito blocking properties, prevented VF in a small number of patients with BrS, although its long-term safety and efficacy was limited, especially in a severe form of BrS.[24–27] It is noteworthy that bepridil was effective in preventing VF storms on the long-term in the report of the largest number of patients presenting with BrS.[24–27]

Limitations of Our Study

The sample size of our study is small, although is the largest collected thus far. Furthermore, a genetic screen in search of a mutation could have contributed to (1) the identification of an arrhythmogenic cause and mechanism, and (2) providing insights into the therapy of this complication of BrS, although was not systematically performed.

Conclusions

In a subgroup of patients experiencing BrS with ER, a spontaneous type 1 ECG pattern was more prevalent than in similar patients without ER and seemed to incur a risk of ES and recurrent VF. Intravenous isoproterenol seemed effective in the short-term management of ES, while oral bepridil and quinidine prevented long-term recurrences of VF.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Electrical storms (ESs) in patients with Brugada syndrome (BrS), although rare, are potentially lethal. We compared the ECG characteristics of 22 men with BrS and ES, defined as ≥3 episodes/d of ventricular fibrillation, recruited at 8 Japanese medical centers, with those of 110 age-matched, control men with BrS without ES. We found a high prevalence of J waves in the group of patients with BrS complicated by ES. Specifically, a spontaneous type I ECG pattern and J waves and horizontal/descending ST elevation were present in 77%, 36%, and 88% of patients with ES, respectively, versus 28% ($P<0.0001$), 9% ($P=0.003$), and 60% ($P=0.06$) of controls, respectively. ES were suppressed by isoproterenol or quinidine. All patients with ES received an implantable cardioverter defibrillator and, over a follow-up of 6.6±5.3 years, the prognosis of patients with ES was significantly worse than that of patients without ES. Ventricular fibrillation was prevented on the long-term in 6 of 6 patients treated with bepridil. This is, to our knowledge, the largest study of patient presenting with BrS and ES. It underscores the significant association between the presence of J wave and ES in patients with BrS, and a high effectiveness of bepridil in the long-term prevention of ventricular fibrillation in the highest-risk patients with BrS.

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Electrocardiographic Parameters and Fatal Arrhythmic Events in Patients With Brugada Syndrome

Combination of Depolarization and Repolarization Abnormalities

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Objectives This study aimed to determine the usefulness of the combination of several electrocardiographic markers on risk assessment of ventricular fibrillation (VF) in patients with Brugada syndrome (BrS).

Background Detection of high-/low-risk BrS patients using a noninvasive method is an important issue in the clinical setting. Several electrocardiographic markers related to depolarization and repolarization abnormalities have been reported, but the relationship and usefulness of these parameters in VF events are unclear.

Methods Baseline characteristics of 246 consecutive patients (236 men; mean age, 47.6 ± 13.6 years) with a Brugada-type electrocardiogram, including 13 patients with a history of VF and 40 patients with a history of syncope episodes, were retrospectively analyzed. During the mean follow-up period of 45.1 months, VF in 23 patients and sudden cardiac death (SCD) in 1 patient were observed. Clinical/genetic and electrocardiographic parameters were compared with VF/SCD events.

Results On univariate analysis, a history of VF and syncope episodes, paroxysmal atrial fibrillation, spontaneous type 1 pattern in the precordial leads, and electrocardiographic markers of depolarization abnormalities (QRS duration ≥120 ms, and fragmented QRS [f-QRS]) and those of repolarization abnormalities (inferolateral early repolarization [ER] pattern and QT prolongation) were associated with later cardiac events. On multivariable analysis, a history of VF and syncope episodes, inferolateral ER pattern, and f-QRS were independent predictors of documented VF and SCD (odds ratios: 19.61, 28.57, 2.87, and 5.21, respectively; $p < 0.05$). Kaplan-Meier curves showed that the presence/absence of inferolateral ER and f-QRS predicted a worse/better prognosis (log-rank test, $p < 0.01$).

Conclusions The combination of depolarization and repolarization abnormalities in BrS is associated with later VF events. The combination of these abnormalities is useful for detecting high- and low-risk BrS patients. (J Am Coll Cardiol 2014;63:2131–8) © 2014 by the American College of Cardiology Foundation

Brugada syndrome (BrS) is a distinct form of idiopathic ventricular fibrillation (VF). BrS is characterized by a unique electrocardiographic pattern consisting of a right bundle branch blocklike morphology and ST-segment elevation in precordial leads. Results of many studies (1–10) have suggested that patients with syncope, particularly patients with a spontaneous type 1 electrocardiographic pattern, have a significant risk of sudden cardiac death (SCD) or VF.

See page 2139

In the remaining population of asymptomatic subjects, the risk is lower, but not negligible (1,5). Therefore, assessment of the risk of SCD and VF in patients with a Brugada-type electrocardiogram (ECG) is clinically important, especially when sporadic cases are detected during routine medical checkups.

Many markers for the development of VF in BrS have been reported, including clinical markers of a family history

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Abbreviations and Acronyms

BrS = Brugada syndrome
CI = confidence interval
ECG = electrocardiogram
EP = electrophysiological
ER = early repolarization
f-QRS = fragmented QRS
HR = hazard ratio
ICD = implantable cardioverter-defibrillator
PAF = paroxysmal atrial fibrillation
SCD = sudden cardiac death
VF = ventricular fibrillation

of SCD (11), syncope with nonprodromal episodes (12), episodes of paroxysmal atrial fibrillation (PAF) (13), electrocardiographic markers of a spontaneous type 1 electrocardiographic pattern, existence of late potential (14), fragmented QRS (f-QRS) (15), T-wave alternans after sodium channel blocker injection (16), an inferolateral early repolarization (ER) pattern (17,18), a genetic marker of *SCN5A*, a gene encoding the cardiac sodium channel (19), electrophysiological markers of VF inducibility by programmed electrical stimulation, abnormal restitution properties, and ventricular effective refractory period <200 ms (20). However, the relationship of these markers and the usefulness of their combination have not been sufficiently examined.

In this study, we examined risk markers, with a focus on noninvasive surface electrocardiographic markers categorized by depolarization and repolarization abnormalities, and attempted to improve the accuracy of predicting and classifying high- and low-risk BrS patients.

Methods

Patient population and clinical data collection. We retrospectively analyzed data from 246 consecutive patients (236 men; mean age, 47.6 ± 13.6 years) with a Brugada-type ECG in Okayama University Hospital. All patients showed a typical electrocardiographic Brugada pattern with or without a sodium channel blocker (pilsicainide), which was defined previously (11). Informed consent was obtained from all patients, and clinical data, including data on age, sex, family history of SCD (younger than 45 years of age), history of syncope episodes, history of VF episodes, and VF induction during an electrophysiological (EP) study were obtained from patient records. Follow-up data defined the start of follow-up as the first visit and the end of follow-up as death, arrhythmic events, or the last visit.

Electrocardiographic measurements. Standard 12-lead ECGs were recorded in the same way and were evaluated for the R-R interval, PQ interval, QRS width, QT interval, ST-segment level at the J point, and number of positive spikes within the QRS complex in leads V_1 through V_3. A spontaneous type 1 pattern was defined as documentation by an ECG of a type 1 pattern in the absence of class I antiarrhythmic drugs. The presence of a late potential was evaluated by a signal-averaged ECG (ART 1200 EPX [Arrhythmia Research Technology, Inc., Fitchburg, Massachusetts], noise level <0.3 μV, and high-pass filtering of 40 Hz with a bidirectional 4-pole Butterworth). A late potential was considered positive when the following 2 criteria were met: root mean square voltage of the terminal 40 ms in the filtered QRS complex of <20 μV and a duration of low-amplitude signals <40 μV in the terminal filtered QRS complex of >38 ms (21).

The presence of f-QRS was defined as an abnormal fragmentation within the QRS complex as ≥4 spikes in 1 or ≥8 spikes in leads V_1, V_2, and V_3, as described previously (15) (Fig. 1A).

An inferolateral ER pattern was defined as an elevation of the J-point in at least 2 consecutive leads. The amplitude of the J-wave or J-point elevation had to be at least 1 mm above the baseline level, either as QRS slurring or notching in the inferior lead (II, III, and aVF), lateral lead (I, aVL, and V_4 to V_6), or both, as described previously (17,18,22–25) (Fig. 1B).

We divided the patients into the depolarization abnormality (PQ interval >200 ms, QRS width ≥120 ms, positive late potential, and f-QRS) group and the repolarization abnormality (QT prolongation and inferolateral ER pattern) group.

EP study. After obtaining written informed consent from patients, an EP study was performed as described previously (1,26) in all patients. The criterion for the induction of ventricular arrhythmia was induction of sustained polymorphic ventricular tachycardia or VF by programmed

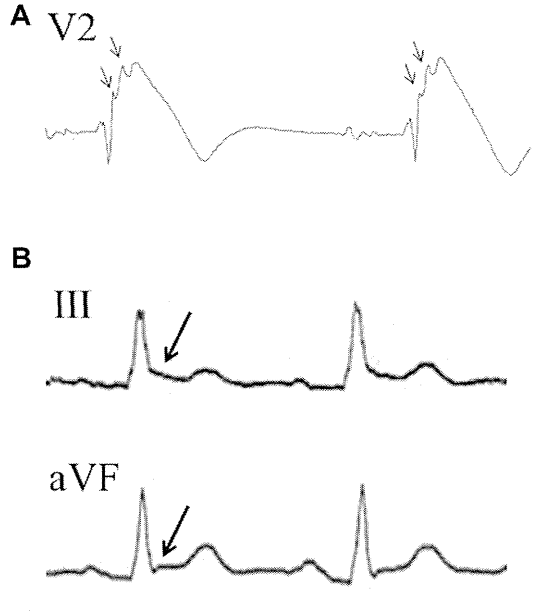

Figure 1 Representative Electrocardiograms of f-QRS and ER

(A) Fragmented QRS (f-QRS) was observed in lead V_2. Note that there are 4 spikes (**arrows**) in this lead. **(B)** Early repolarization (ER) pattern in the inferior leads. Note that J-point elevation above the baseline (>1 mm) can be seen in leads III and aVF.

electrical stimulation from the right ventricular apex, right ventricular outflow tract, or left ventricle with a maximum of 3 extrastimuli at 2 cycle lengths.

Gene mutation analysis of *SCN5A*. This study was performed in compliance with guidelines for human genome studies of the Ethics Committee of Okayama University, as described previously (13). In brief, all exons of *SCN5A* were amplified by polymerase chain reaction from DNA isolated from peripheral leukocytes of the patients. Genomic DNA was extracted from peripheral blood leukocytes using a DNA extraction kit (Gentra, Minneapolis, Minnesota) and was stored at −30°C until use. Twenty-seven exons of the *SCN5A* gene were amplified with previously reported intronic primers (13).

Statistical analysis. Statistical analysis was performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, Illinois). Data are expressed as mean ± SD or median (interquartile range). A Student *t* test was performed to test for statistical differences between 2 unpaired mean values, and categorical data and percentage frequencies were analyzed by the chi-square test. On univariate analysis, 9 predictors were significantly associated with arrhythmic events. Multivariate analysis using Cox proportional hazards regression analysis estimated those 9 predictors and was performed in search of independent risk factors for arrhythmic events. This analysis was based on a stepwise algorithm, with the p value set at 0.05 for entering and 0.1 for exclusion. The effects of ER and f-QRS on arrhythmic events during the follow-up period were evaluated using the log-rank test and were described using a Kaplan-Meier curve. A p value < 0.05 was considered statistically significant.

Results

Patient characteristics. Baseline patient characteristics are summarized in Table 1. Sixty-nine patients (28.0%) had a family history of SCD, 40 (16.3%) had history of syncope episodes, and 13 (5.3%) had history of VF episodes. Gene analysis showed that an *SCN5A* gene mutation was present in 17 patients (13.8%). A spontaneous type 1 ECG pattern was observed in 156 patients (63.4%). In the EP study, VF was induced in 71 patients (45.8%), and 63 of them (25.6%) had received an implantable cardioverter-defibrillator (ICD). During the follow-up period of 45.1 ± 44.3 months, fatal arrhythmic events occurred in 24 patients (23 appropriate ICD shocks caused by VF and 1 cardiac arrest during sleep).

Clinical/genetic/electrocardiographic parameters and cardiac events. Clinical and genetic parameters were compared in BrS patients with and without cardiac events during the follow-up period (Table 2). PAF episodes (9 of 24, 37.5% vs. 35 of 222, 15.8%, p = 0.013), a history of VF (9 of 24, 37.5% vs. 4 of 222, 1.8%; p < 0.001), a history of syncope episodes (13 of 24, 54.2% vs. 27of 222, 12.2%; p < 0.001), VF inducibility during the EP study (17 of 24, 70.8% vs. 54 of 131, 41.2%; p = 0.007), and spontaneous type 1 ECG pattern (22 of 24, 91.7% vs. 134 of 222, 60.4%; p = 0.002) were observed more often in VF/SCD patients than in those without VF/SCD, but other parameters such as age, sex, family history of SCD, and *SCN5A* gene mutation were not different.

Table 1 Patient Characteristics

Male/female	236/10
Age, yrs,	47.6 ± 13.6
Mean follow-up period, mo	45.1 ± 44.3
History of syncope episodes	40 (16.3)
History of VF episodes	13 (5.3)
Family history of SCD	69 (28.0)
PAF	44 (17.9)
Spontaneous type 1 ECG	156 (63.4)
ER pattern	25 (10.2)
f-QRS	78 (31.7)
Positive LP	166/235 (70.6)
SCN5A gene mutation	17/123 (13.8)
VF induction during EP study	71/155 (45.8)
ICD implantation	63 (25.6)
VF or SCD event during follow-up	24 (9.8)

Values are n, mean ± SD, n (%), or n/N (%).
ECG = electrocardiogram; EP = electrophysiological; ER = early repolarization; f-QRS = fragmented QRS; ICD = implantable cardioverter-defibrillator; LP = late potential; PAF = paroxysmal atrial fibrillation; SCD = sudden cardiac death; VF = ventricular fibrillation.

Among the electrocardiographic parameters of depolarization abnormalities, QRS width ≥120 ms (8 of 24, 33.3% vs. 29 of 222, 13.1%; p = 0.015), and f-QRS (20 of 24, 83.3% vs. 58 of 222, 26.1%; p < 0.001) were observed more often in patients with VF/SCD than in those without VF/SCD. Among the ECG parameters of repolarization abnormalities, a prolonged QTc interval >440 ms (7 of 24, 29.2% vs. 28 of 222, 12.6%; p = 0.036), and inferolateral ER pattern (8 of 24, 33.3% vs. 17 of 222, 7.7%; p < 0.001) were observed more often in patients with VF/SCD than in those without VF/SCD.

Multivariate analysis showed that the following 4 parameters were independent risk factors for arrhythmic events: f-QRS (hazard ratio [HR]: 5.21; 95% confidence interval [CI]: 1.69 to 16.13; p = 0.004), inferolateral ER pattern (HR: 2.87; 95% CI: 1.16 to 7.14; p = 0.023), a history of VF episodes (HR: 19.61; 95% CI: 4.12 to 90.91; p < 0.001), and a history of syncope episodes (HR: 28.57; 95% CI: 6.14 to 142.86; p < 0.001) (Table 2).

Patient characteristics with f-QRS. On multivariate analysis, depolarization abnormalities of f-QRS were an independent risk factor for arrhythmic events. Therefore, clinical, genetic, and electrocardiographic data for patients with and without f-QRS were analyzed again (Table 3). There were no significant differences in age, family history of SCD, and incidence of the *SCN5A* gene mutation between patients with and without f-QRS. However, a history of syncope episodes, a history of VF episodes, and VF inducibility during EP study were more frequently observed in patients with f-QRS than in those without f-QRS (p = 0.002, p = 0.005, and p = 0.002, respectively). PQ

Table 2 Characteristics of Patients With and Without VF/SCD During Follow-Up

			Univariate Analysis			Multivariate Analysis		
	VF/SCD +	VF/SCD −	OR	95% CI	p Value	HR	95% CI	p Value
Clinical/genetic parameters								
Male/female	23/1	213/9	1.029	0.125–8.490	0.649			
Age (yrs), median (IQR)	47 (15)	48 (21)			0.835			
History of syncope episodes	13 (54.2)	27 (12.2)	8.535	3.477–20.955	<0.001	28.571	6.135–142.857	<0.001
History of VF episodes	9 (37.5)	4 (1.8)	32.700	9.012–118.645	<0.001	19.608	4.115–90.909	<0.001
Paroxysmal AF	9 (37.5)	35 (15.8)	3.206	1.301–7.899	0.013			0.306
Family history of SCD	8 (33.3)	61 (27.5)	1.320	0.537–3.241	0.554			
SCN5A gene mutation	4/23 (17.4)	13/100 (13.0)	1.409	0.414–4.799	0.396			
VF induction during EP study	17/24 (70.8)	54/131 (41.2)	3.463	1.344–8.293	0.007			0.562
Spontaneous type 1 ECG pattern	22 (91.7)	134 (60.4)	7.224	1.657–31.491	0.002			0.114
Depolarization parameters								
Positive f-QRS	20 (83.3)	58 (26.1)	14.138	4.638–43.093	<0.001	5.208	1.689–16.129	0.004
Positive LP	20/24 (83.3)	146/211 (69.2)	2.226	0.732–6.772	0.150			
PQ interval >200 ms	8 (33.3)	40 (18.0)	2.275	0.911–5.681	0.069			
QRS interval ≥120 ms	8 (33.3)	29 (13.1)	3.328	1.307–8.469	0.015			0.908
Repolarization parameters								
ER pattern	8 (33.3)	17 (7.7)	6.029	2.258–16.103	<0.001	2.874	1.160–7.143	0.023
QTc >440 ms	7 (29.2)	28 (12.6)	2.853	1.087–7.490	0.036			0.608

Values are n, n (%), n/N (%), or median (IQR).
CI = confidence interval; HR = hazard ratio; IQR = interquartile range; OR = odds ratio; other abbreviations as in Table 1.

interval, QRS duration, and QTc interval were longer in patients with f-QRS than in those without f-QRS ($p = 0.037$, $p = 0.001$, and $p = 0.042$, respectively), but the ER pattern was not different between the groups. Spontaneous type 1 ECG pattern and PAF episodes were more frequently observed in patients with f-QRS than in those without f-QRS ($p < 0.001$ and $p = 0.031$, respectively). VF/SCD episodes during follow-up were more frequently observed in patients with f-QRS than in those without f-QRS ($p < 0.001$).

Patient characteristics with an ER pattern. On multivariate analysis, repolarization abnormality of the ER pattern

Table 3 Characteristics of Patients With and Without f-QRS

	f-QRS+	f-QRS−	p Value
Clinical/genetic parameters			
Male/female	76/2	160/8	0.511
Age, yrs	48.5 ± 12.9	47.2 ± 14.0	0.514
History of syncope episodes	21 (26.9)	19 (11.3)	0.002
History of VF episodes	9 (11.5)	4 (2.4)	0.005
PAF	20 (25.6)	24 (14.3)	0.031
Family history of SCD	23 (29.5)	46 (27.4)	0.732
SCN51 gene mutation	9/43 (20.9)	8/80 (10.0)	0.094
VF induction during EP study	34/54 (63.0)	37/101 (35.9)	0.002
ICD implantation	37 (47.4)	26 (15.5)	<0.001
VF or SCD during follow-up	20 (25.6)	4 (2.4)	<0.001
Electrocardiographic parameters			
Duration of PQ interval, ms	184 ± 29	176 ± 26	0.037
Duration of QRS complex (ms), median (IQR)	108 (24)	100 (17)	0.001
Duration of QTc interval, ms	419 ± 30	411 ± 24	0.042
Amplitude at J-point V_1 (mV), median (IQR)	0.12 (0.15)	0.11 (0.10)	0.347
Amplitude at J-point V_2 (mV), median (IQR)	0.21 (0.21)	0.201 (0.17)	0.468
Amplitude at J-point V_3 (mV), median (IQR)	0.13 (0.12)	0.12 (0.12)	0.929
Positive ER pattern	9 (11.5)	16 (9.5)	0.653
Spontaneous type 1 ECG	63 (80.8)	93 (55.4)	<0.001
Positive LP	59/75 (78.7)	107/160 (66.9)	0.064

Values are n, mean ± SD, median (IQR), n (%), or n/N (%).
Abbreviations as in Table 1.

was an independent risk factor for arrhythmic events. Therefore, clinical, genetic, and electrocardiographic data with and without an ER pattern were analyzed again (Table 4). There were no significant differences in age, family history of SCD, incidence of *SCN5A* gene mutation, positive late potential, a history of syncope episodes, f-QRS, and VF inducibility during the EP study. However, VF/SCD episodes during follow-up and a history of VF episodes were more frequently observed in patients with ER than in those without ER ($p = 0.001$ and $p = 0.005$, respectively).

Follow-up data. We next examined the follow-up data in patients with f-QRS and ER. VF developed in 23 patients, 1 patient died suddenly during sleep, possibly because of VF, and 1 patient died of a nonarrhythmic cause (pneumonia) during the follow-up period.

Figure 2 shows the results of Kaplan-Meier analyses of fatal arrhythmic events in patients with and without f-QRS (Fig. 2A) or an ER (Fig. 2B) pattern. Patients with f-QRS or ER had a significantly worse prognosis than did patients without those parameters ($p < 0.001$ and $p < 0.001$, respectively).

Figure 3 shows results of the combination analysis of f-QRS and ER parameters. Patients with both f-QRS and ER parameters had a significantly higher frequency of fatal arrhythmic events than did patients without both parameters ($p<0.001$). Moreover, patients with both f-QRS and ER parameters had a significantly higher frequency of arrhythmic events than did patients with f-QRS alone ($p = 0.045$) (Fig. 3).

Discussion

The present study showed that the combination of f-QRS and inferolateral ER pattern was associated with the development of VF in BrS patients. Additionally, the combination of f-QRS with ER (depolarization and repolarization abnormalities) was useful for identifying high- and low-risk BrS patients.

High-risk clinical parameters of VF development. Previous studies have reported that syncope episodes (especially in patients with prodrome), a history of VF, and a family history of sudden death are associated with VF events in BrS patients (3,4,12,20,27–29). In our study, we also observed that syncope episodes and a history of VF were independent predictors of later VF events. These patients were symptomatic patients, and therefore, it is reasonable to classify them as high-risk patients. However, more patients have no symptoms with electrocardiographic evidence of BrS (asymptomatic BrS patients). A recent study suggested that these asymptomatic patients have a better prognosis, but this is not negligible (1,5). Therefore, simple risk assessment of these asymptomatic BrS patients is clinically important, especially when sporadic cases are detected during routine medical checkups.

Repolarization abnormalities in BrS. Many clinical data support the importance of repolarization abnormalities for VF development, such as T-wave alternans after sodium channel blocker injection (16) and ST-segment elevation after exercise (30) or full-stomach status (31).

An ER pattern is considered to be a benign electrocardiographic phenomenon affecting 2% to 5% of the general

Table 4 Characteristics of Patients With and Without ER

	ER+	ER−	p Value
Clinical/genetic parameters			
Male/female	23/2	213/8	0.269
Age (yrs), median (IQR)	43 (23)	49 (20)	0.820
History of syncope episodes	5 (20.0)	35 (15.8)	0.383
History of VF episode	5 (20.0)	8 (3.6)	0.005
PAF	3 (12.0)	41 (18.6)	0.584
Family history of SCD	7 (28.0)	62 (28.1)	0.995
SCN5A gene mutation	2/15 (13.3)	15/108 (13.9)	1.000
VF induction during EP study	9/21 (42.9)	62/134 (46.3)	0.770
ICD implantation	13 (52.0)	50 (22.6)	0.001
VF or SCD during follow-up	8 (32.0)	16 (7.2)	0.001
ECG parameters			
Duration of PQ interval, ms	190 ± 34	177 ± 26	0.053
Duration of QRS complex (ms), median (IQR)	99 (17)	104 (20)	0.335
Duration of QTc interval, ms	405 ± 27	414 ± 26	0.097
Amplitude at J-point V_1 (mV), median (IQR)	0.14 (0.14)	0.11 (0.12)	0.306
Amplitude at J-point V_2 (mV), median (IQR)	0.21 (0.25)	0.20 (0.16)	0.505
Amplitude at J-point V_3 (mV), median (IQR)	0.17 (0.17)	0.12 (0.11)	0.069
Positive f-QRS	9 (36.0)	69 (31.2)	0.653
Spontaneous type 1 ECG	14 (56.0)	142 (64.3)	0.417
Positive LP	17/23 (73.9)	149/212 (70.3)	0.717

Values are n, mean ± SD, median (IQR), n (%), or n/N (%).
Abbreviations as in Table 1.

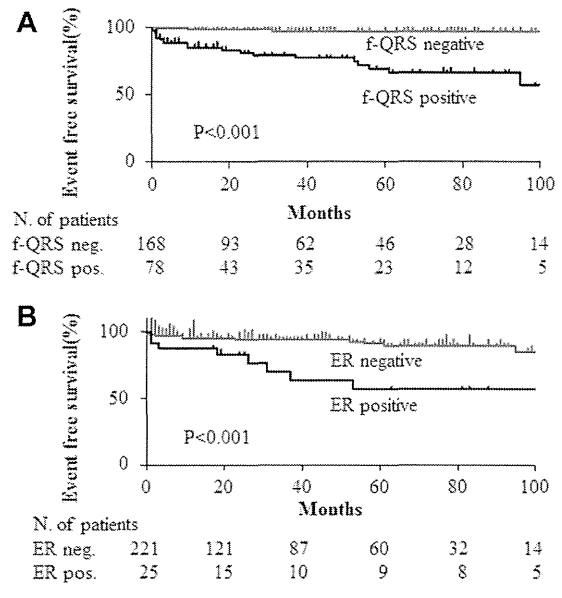

Figure 2 Kaplan-Meier Analysis of VF/SCD Events

Ventricular fibrillation (VF)/sudden cardiac death (SCD) were observed often in the presence of fragmented QRS (f-QRS) **(A)**, and early repolarization (ER) **(B)**.

population and is most commonly observed in young men (32,33). Recently, an ER pattern has been shown to be an additional risk marker for VF development, especially in inferolateral leads, in patients with BrS (17,18). Our finding that repolarization abnormalities were independently associated with VF development is in agreement with these previous findings.

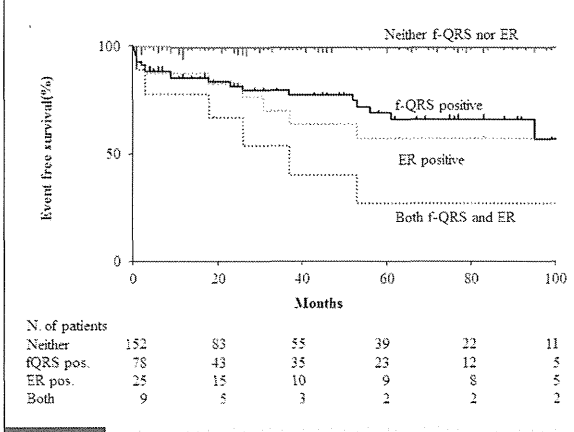

Figure 3 Kaplan-Meier Analysis of VF/SCD Events

Ventricular fibrillation (VF)/sudden cardiac death (SCD) were often observed in the combination of depolarization (fragmented QRS [f-QRS]) and repolarization abnormalities (early repolarization [ER] pattern).

Depolarization abnormalities in BrS. In addition to repolarization abnormalities, recent observations have suggested that VF development in BrS is associated with conduction disturbances, such as prolongation of the PQ interval (34), a wide QRS complex (35), a positive late potential (36), and f-QRS (15,20). A recent study showed that f-QRS is the strongest predictor of VF development in BrS (20). The usefulness of f-QRS for identifying patients at high risk of various cardiac diseases, including cardiac sarcoidosis, arrhythmogenic right ventricular cardiomyopathy, and acute coronary syndrome (37), has been reported. Our finding that f-QRS (depolarization abnormality) was an independent predictor of VF development is in agreement with those results. We also found that f-QRS was associated with other depolarization abnormalities, such as a prolonged PQ and QRS interval, indicating that depolarization abnormalities in the atrium and ventricle are an important factors for the development of VF in BrS.

A QRS interval in lead V_2 ≥120 ms was found to be a possible predictor of life-threatening ventricular arrhythmia and/or syncope. Prolonged QRS duration as measured on a standard 12-lead ECG has been shown to be associated with ventricular arrhythmia (35). Additionally, a prolonged QRS duration in precordial leads is prominent in symptomatic patients, suggesting that delayed conduction of the ventricle (depolarization) is important (29,38). However, on multivariate analysis in our study, there were no significant differences in wide QRS complex between patients with and without VF/SCD.

Combination of depolarization and repolarization abnormalities. In this study, Kaplan-Meier analyses showed that the combination of f-QRS (depolarization abnormality) and ER (repolarization abnormality) is useful for predicting VF events in patients with BrS. Recently, f-QRS was reported to be an important marker for the development of VF (Torsades de pointes) in patients with acquired long QT syndrome (typical repolarization abnormality disease) (39), indicating that the combination of depolarization and repolarization is important for the development of lethal arrhythmia. We also found that VF seldom developed in patients without any abnormalities during the follow-up period in this study, suggesting that low-risk BrS patients could also be identified using these markers.

We also investigated the clinical/electrocardiographic characteristics of depolarization and repolarization abnormalities. Interestingly, there were many differences between the groups (Tables 3 and 4). Patients with f-QRS had more depolarization abnormalities than those without f-QRS, such as prolonged PQ and QRS intervals. In contrast, patients with an ER pattern had no differences in these markers, suggesting that the genesis of each of these abnormalities is intrinsically different.

Clinical implications. BrS is a heterogeneous disease. Therefore, the mechanism of VF development differs in each patient. Our results suggest that the combination of

depolarization and repolarization abnormalities (f-QRS and ER pattern) enables identification of high- and low-risk patients with BrS. In the clinical setting, VF induction during EP study is still considered when deciding to implant an ICD. Thus, we think that we should recommend an EP study in a patient with an f-QRS and ER pattern, if asymptomatic, or we do not need an EP study in an asymptomatic patient with neither an f-QRS nor ER pattern.

Study limitations. First, the electrocardiographic features of ER and other electrocardiographic markers are dynamic, and thus the true prevalence of this coexistence is difficult to evaluate. Second, we analyzed only the coding regions of *SCN5A* for mutations in this study, and the possibility of mutations occurring in regions of the gene other than coding regions or other gene mutations cannot be excluded. Third, Nishii et al. (19) reported that *SCN5A* gene mutations are associated with early and frequent VF recurrence, but not with initial VF episodes. In our study, we did not find a significant difference. Therefore, further studies on this issue are required. Fourth, this study was a retrospective study. A prospective study to estimate risk factors of BrS is required. Last, there was a small number of endpoints, making it difficult to identify unique predictors in a multivariate model reliably.

Conclusions

Our study shows that ER and f-QRS are independent risk factors for arrhythmic events in patients with BrS. Patients with both ER and f-QRS have a significantly higher frequency of arrhythmic events than do patients who have neither ER nor f-QRS. Furthermore, when there is neither ER nor f-QRS, arrhythmic events are minor.

Clinically, this study shows that the combination of f-QRS (a marker of depolarization abnormality) and ER (a marker of repolarization abnormality) is useful for estimating the incidence of VF in patients with BrS.

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Key Words: Brugada syndrome ▪ early repolarization ▪ fragmented QRS ▪ noninvasive risk assessment ▪ ventricular fibrillation.

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Electrocardiographic Screening of 1-Month-Old Infants for Identifying Prolonged QT Intervals

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Original Article

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Background—Neonatal electrocardiographic screening is used to screen infants with prolonged QT intervals, as previously shown in whites. However, this procedure needs to be confirmed in other ethnic groups.

Methods and Results—In 8 areas in Japan, an ECG was recorded in 4285 infants at 1-month medical checkup. A prospective study showed that a provisional criterion of QTc ≥470 ms was appropriate for infants. To assess the validity of the criterion, all infants with a QTc between 460 and 470 ms were followed up. Five infants had a QTc ≥470 ms. Four infants were diagnosed with prolonged QT intervals from follow-up ECGs. Four infants showed no symptoms and did not have a family history of long-QT syndrome. Two infants showed progressive prolongation of QT intervals, and medication was started. Genetic testing was performed in 3 of 4 infants with prolonged QT intervals, and it revealed a *KCNH2* mutation (3065 delT, L1021fs+34X) in 1 infant. One infant with a QTc ≥470 ms and 2 infants with a QTc between 460 and 470 ms showed a decline in their QTc values during follow-up. The study screened another infant with Wolff–Parkinson–White syndrome who was diagnosed with noncompaction before symptoms appeared.

Conclusions—Neonatal electrocardiographic screening can identify infants likely to be affected by long-QT syndrome in the Japanese population, as already shown in whites. This screening may also be useful in identifying other important cardiac diseases. **(*Circ Arrhythm Electrophysiol.* 2013;6:932-938.)**

Key Words: arrhythmias, cardiac ■ death, sudden, cardiac ■ diagnosis ■ electrocardiography ■ long-QT syndrome

Long-QT syndrome (LQTS) is characterized by prolonged ventricular repolarization, with a prolonged QT interval on the surface ECG. The clinical presentation of LQTS is the occurrence of syncope or cardiac arrest in children and young adults.[1,2] Patients with LQTS who experience aborted cardiac arrest during infancy are at high risk for subsequent aborted cardiac arrest or death during their next 10 years,[3] indicating that these patients are an extremely high-risk subset.

Clinical Perspective on p 938

Sudden infant death syndrome is one of the major causes of death in infants, with the highest prevalence at ≈2 months of age.[4–6] Sudden infant death syndrome is multifactorial in origin[7]; however, genetic studies have shown that ≈10% of cases diagnosed as sudden infant death syndrome carry functionally significant genetic mutations in LQTS genes.[8,9]

Electrocardiographic screening in infants may permit early detection of a substantial percentage of patients at risk for sudden infant death syndrome.[10] Studies of infants in Italy and a recent study of infants in Japan have shown that QTc intervals were longest at ≈2 months of age.[11,12] A large study conducted in Italy showed that the prevalence of LQTS might be close to 1:2000[13]; however, no studies have been conducted outside Europe. In Japan, medical examinations during infancy are mandatory, and medical examinations at 1 month of age are currently performed on all infants. Therefore, the aim of the present study was to confirm whether electrocardiographic screening of 1-month-old infants identifies Japanese infants with prolonged QT intervals, as previously shown in whites.

Methods

Study Population

The study was conducted in 16 maternity institutes in 8 areas between July 2010 and March 2011 in Japan, including Kagoshima, Fukuoka, Nagoya, Ogaki, Tokyo, Tochigi, Tsukuba, and Niigata. The parents were asked to participate in the study at discharge from the maternity

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institutes. A total of 4319 consecutive infants participated in the study at the time of a 1-month medical checkup after obtaining written informed consent from parents. We obtained permission to use and analyze these data from the Ethics Committee of the National Hospital Organization Kagoshima Medical Center under the condition that the confidentiality of all personal data would be maintained.

Analysis of ECG and Measurement of the QT Interval

Twelve-lead ECGs were recorded at a speed of 25 mm/s with an FCP-4510 recorder (Fukuda Denshi, Tokyo, Japan). The ECGs were initially read in each center, and a written report was sent to the parents of each participant. The ECGs were then transferred to 1 author (M.Y.) of the present study, and all QT/RR data for the present study were remeasured by the same author (M.Y.). The QT intervals of 3 consecutive beats were measured from the onset of the Q wave to the end of the T wave in lead V_5. When the QT interval could not be measured because of instability of isoelectronic levels in lead V_5, the QT intervals in lead II were measured. When a notch was present in >3 leads[14,15] and this notch appeared at the same timing,[16] the T wave was defined as bifid. The QT/RR data of each of 3 consecutive beats were corrected, and the mean values of the 3 consecutive QTc were used.

Screening and Follow-Up of Infants With LQTS in a Preliminary Study

Published diagnostic criteria using the QTc by the Bazett formula recommend additional diagnostic caution when scaling with tachycardic patients.[14] In a preliminary study, a formula to minimize the effect of heart rate in infants was used[12]: $QTc=QT/RR^{0.43}$ and a provisional criterion of QTc ≥440 $ms^{0.43}$ were used.[12] To assess the validity of the criterion, all infants with QTc ≥430 ms and QTc <440 ms were followed up. Infants with QTc ≥420 ms and QTc <430 ms were also followed in the Kagoshima area where the chief investigator (M.Y.) was working and where 56% of the total subjects participated. The screened infants were followed for 2 or 3 weeks.

Screening of Infants Using the Bazett Formula

Because of the current and frequent use of the Bazett formula in the clinical setting, the present study was reconducted retrospectively using the Bazett formula. The QTc values calculated by the formula in the preliminary study ($QT/RR^{0.43}$) were highly associated with those calculated by the Bazett formula (r=0.989; P<0.0001; Figure 1). The QTc values of 440, 430, and 420 $ms^{0.43}$ used in the preliminary study corresponded to the QTc values of 470, 460, and 450 $ms^{0.5}$ calculated by the Bazett formula (Figure 1). Based on this finding, the screening strategy in the reconducted study included a provisional criterion of QTc ≥470 $ms^{0.5}$ to screen infants with a prolonged QT interval. To assess the validity of this criterion, all infants with QTc ≥460 ms and QTc <470 ms were followed up. Infants with QTc ≥450 ms and QTc <460 ms were also followed in the Kagoshima area where the chief investigator (M.Y.) was working and where 56% of the total subjects participated. The screened infants were followed for 2 or 3 weeks. The definition of infants with a prolonged QT interval in the present study was those whose prolonged QTc values were sustained during follow-up at a 2- or 3-week interval.

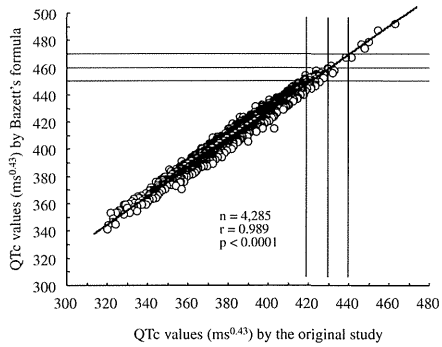

Figure 1. Association of QTc values calculated by the original formula with those calculated by the Bazett formula. QTc values calculated by the formula in a preliminary study ($QT/RR^{0.43}$) were highly associated with those by the Bazett formula ($QT/RR^{0.5}$).

Follow-Up Strategies of Infants With Prolonged QT Intervals

In a nationwide study in Japan, patients with LQTS who showed life-threatening arrhythmias at the perinatal period and whose mutations were determined were mostly those with LQT2 or LQT3.[17] The clinical course of these infants was favorable with administration of β-blockers and mexiletine and with pacemaker implantation or an implantable cardioverter-defibrillator. In this Japanese series, β-blockers and mexiletine were coadministered to 7 of 11 infants with LQT2 and to all 7 LQT3 infants.[17] β-Blockers and mexiletine were coadministered in the present study when the QTc values progressively increased and when the parents accepted medication for their infants.

In the preliminary electrocardiographic screening program, thorough familial electrocardiographic recording and genetic testing were not mandatory. The performance of familial electrocardiographic screening and genetic testing was based on the judgment of the chief physicians.

Genetic Analysis

Genomic DNA was isolated from blood after obtaining written informed consent. Genetic screening for LQT-1 (*KCNQ1*), -2 (*KCNH2*), -3 (*SCN5A*), -5 (*KCNE1*), -6 (*KCNE2*), -7 (*KCNJ2*), -9 (*CAV3*), -10 (*SCN4B*), and -12 (*SNTA1*) was performed by polymerase chain reaction and direct DNA sequencing. When abnormal hand/foot findings were present, screening for LQT-8 (*CACNA1C*) was planned. The exons of LQT-4 (*ANKB*), LQT-10 (*SCN4B*), and LQT-11 (*AKAP9*) were not analyzed because there are no reported cases of these mutations in the Japanese population. Genomic DNA was isolated using a QIAamp DNA Blood Midi Kit (Qiagen, Gaithersburg, MD). Polymerase chain reaction products were purified by AMPure (Beckman Coulter, Brea, CA). After treatment with the BigDye Terminator v1.1 Cycle Sequencing Kit (ABI, Warrington, United Kingdom) and BigDye X Terminator, direct sequencing was performed by the ABI3130x1 Genetic Analyzer (ABI).

Statistical Analysis

The most appropriate cutoff values to screen for QT prolongation in 1-month-old infants in the present study were obtained from the positive predictive value and negative predictive value.

Results

Final Subjects

Of the 4319 infants who participated in the study, a total of 4285 subjects were enrolled in this retrospective study whose QT/RR data of 3 consecutive beats could be measured (2148 male infants, 2038 female infants; sex was not described in 100 infants). Of the 34 infants excluded, 3 consecutive QT/RR data could not be obtained because of the instability of isoelectric lines in 26 infants; however, their QTc values were normal based on 1 or 2 QT/RR data sets. Five infants with complete right bundle branch block and 3 infants with Wolff–Parkinson–White syndrome were also excluded from the QT study.

QTc Intervals of Infants

The mean values of the QT interval, heart rate, and QTc intervals of male infants were 253±17 ms, 160±16 beats per minute, and 410±19 ms, respectively; those of female infants

were 255±17 ms, 158±16 beats per minute, and 413±19 ms, respectively; and those of all infants were 254±17 ms, 159±16 beats per minute, and 412±19 ms, respectively. The mean QTc value of female infants was longer than that of male infants ($P<0.0001$).

Infants With Prolonged QT Intervals

Of the 4285 infants, 5 infants had a QTc of ≥470 ms at the time of the 1-month screening (Table 1). Four infants (3 male infants and 1 female infant) were diagnosed with prolonged QT intervals from the follow-up ECGs (Figure 2). Of these 4 infants, 2 (cases 1 and 2 in Figure 2) showed progressive prolongation of QT intervals (Figures 3 and 4). Propranolol and mexiletine were administered to these 2 infants. Two patients (cases 3 and 4 in Figure 2) were followed without medication. Case 1 was the third child of the parent, and cases 2, 3, and 4 were the first children of their parents. All 4 families had no family history of LQTS-related symptoms, including sudden cardiac death.

One male infant with a QTc of ≥470 and 2 female infants with a QTc between 460 and 470 ms showed a decline in their QTc values during follow-up (Figure 2). One female infant with a QTc between 460 and 470 ms was lost to follow-up. Of the 2420 infants (56% of the final total subjects) who participated in the Kagoshima area, 21 infants (0.87%) had QTc values between 450 and 460 ms, and all infants showed a decrease in QTc values during follow-up.

Genetic Analysis

Genetic analysis was performed in 3 of 4 infants with a prolonged QT interval (cases 1, 2, and 3 in Figure 3), and it demonstrated a frameshift-type mutation in the *KCNH2* gene (3065 delT, L1021fs+34X) in 1 infant (case 2).

Cutoff Values for Screening for QT Prolongation in 1-Month-Old Infants

Assuming that 4 of the 4285 infants had prolonged QT intervals in the present study, the most appropriate cutoff value to screen for QT prolongation in 1-month-old infants was 470 ms, and the next appropriate value was 460 ms (Table 2).

Infants With Miscellaneous Heart Diseases

Of the 4319 infants who participated in the study, including 4285 infants whose QTc values were analyzed, some infants were found to have miscellaneous heart diseases; 1 infant had left ventricular nonimpaction (LVNC), and 1 had situs inversus totalis. A 43-day-old male infant was admitted to our hospital because of the presence of Wolff–Parkinson–White syndrome. He seemed active, but his echocardiography revealed LVNC (Figure 5). His left ventricular ejection fraction and brain natriuretic peptide levels at the first visit were 50% and 89 pg/mL, respectively. He was followed for 2 or 3 weeks, and he showed an ejection fraction of 50% to 60%. His ejection fraction showed a sharp decline to <30% at 81 days of age, but his general status was good. Medication was then started with carvedilol and enalapril. He is currently 28 months old. He experienced supraventricular tachycardia several times since the age of 5 months. However, supraventricular tachycardia was successively treated, and he finally received catheter ablation twice as a treatment for supraventricular tachycardia. His ejection fraction has recovered to 65% with medication (carvedilol, enalapril, and flecainide).

Table 1. Distribution of Infants Based on the Duration of QT Intervals in the Present Study and in an Italian Study[13]

QTc, ms	Present Study	Italian Study
≥470	5 (0.12%)	31 (0.07%)
460–470	3 (0.07%)	28 (0.06%)
450–460	34 (0.79%)	177 (0.41%)
440–450	172 (4.01%)	858 (1.99%)
<440	4071 (95.0%)	41 986 (97.5%)
	4285 (100%)	43 080 (100%)

The data are expressed as absolute values and percentages in parentheses. ECGs in the present study were recorded in infants at the 1-month medical checkup, and those in the Italian study were recorded in infants between 15 and 25 days of age.

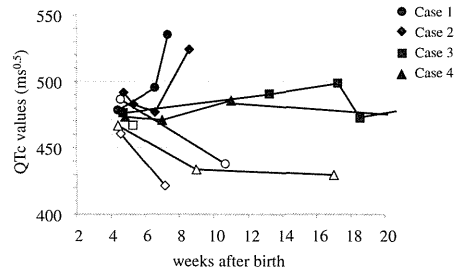

Figure 2. Time course of QTc values of infants whose QTc was >460 ms. Among 5 infants with a QTc >470 ms, cases 1 (·) and 2 (♦) received medication because of progressive prolongation of their QTc values, cases 3 (■) and 4 (▲) were followed without medication, and in 1 infant (○), the QTc value decreased. Among 3 infants with a QTc value between 460 and 470 ms, 1 infant was lost to follow-up.

Discussion

The present study confirmed that electrocardiographic screening of 1-month-old infants is successful in identifying infants with prolonged QT intervals in the Japanese population, which is similar to findings in whites.[13] This screening was also able to identify an infant with life-threatening heart disease during the asymptomatic period.

A large study conducted in Italy showed that 17 infants among a cohort of 44 596 neonates were affected by LQTS and that the prevalence of LQTS was 1:2534 in whites.[13] Of the 17 infants, 16 were diagnosed with LQTS because of the presence of both QT prolongation and disease-causing mutations, and 1 was diagnosed because the father of the infant with a QTc of 482 ms also had an extremely prolonged QTc (581 ms). The authors of this previous study hypothesized that the prevalence of LQTS is close to 1:2000, considering the presence of some infants without genetic analysis in the study.[13] The present study was conducted in the Japanese population. The distribution of infants with a QTc >470 ms was 5 of 4285 (0.12%) in the present study and 31 of 43 080 (0.07%) in a previous study[13] and that of a QTc between 460 and 470 ms was 3 of 4285 (0.07%) in the present study and 28 of 43 080 (0.06%) in a previous study. The distribution was

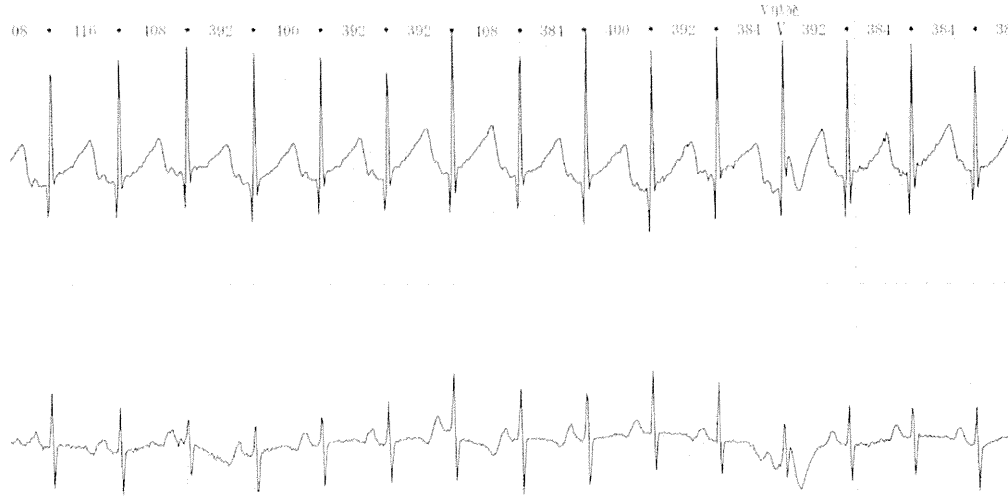

Figure 3. An ECG of a Holter recording at 51 days of age in an infant who received medication. The QTc value was 511 ms.

not different between the present study and this previous study (P=0.38 and P>0.99, respectively).[13]

The mean QTc intervals were similar between the 2 studies (412±19 ms in the present study and 406±20 ms in a previous study).[13] The reason for slightly longer QTc values in the present study than in the previous study[13] might be because of the dates of the electrocardiographic recording. ECGs were recorded in 1-month-old infants in the present study and between the 15th and 25th days of life in the previous study.[13] Mean QTc intervals increase from birth to 2 months of age.[11,12] Finally, 4 infants had prolonged QT intervals in the present study. These data suggest that neonatal electrocardiographic screening is successful for identifying infants with prolonged QT intervals in the Japanese population, as already shown in whites.

QTc values in female children are known to be longer than those in male children, as well as in adolescents and the adult population. Accordingly, LQTS diagnostic criteria recommend using different criteria between male and female infants.[1] A previous study showed that QTc values were not

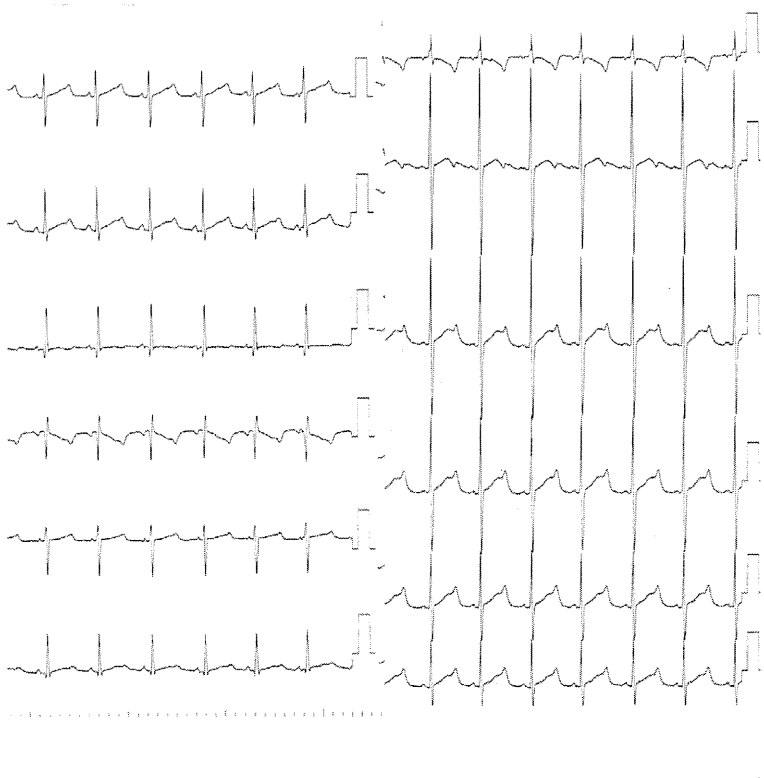

Figure 4. An ECG at 4 months of age in a patient with a *KCNH2* mutation. The QTc value was 533 ms.

Table 2. Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

QTc, ms	PPV	NPV
430	0.0053	1.0000
440	0.0172	1.0000
450	0.0976	1.0000
460	0.5714	1.0000
470	0.8000	1.0000
480	0.7500	0.9998
490	1.0000	0.9991

different among 4867 male and 4858 female infants on the third to fourth day of life (401±19 versus 400±20 ms; *P*=not significant).[18] Another large study showed a sex difference in QTc values among 22 967 male and 21 629 female infants between the 15th and 25th day of life (405±20 versus 407±20 ms; $P<0.001$).[13] In the present study, a sex difference was also present on the 32nd day of life (410±19 versus 413±19 ms; $P<0.001$). However, guidelines of the International Conference on Harmonization reported that concerning the difference in the QT/QTc values in a thorough QT/QTc study, the threshold level of regulatory concern is ≈5 ms, as evidenced by an upper bound of the 95% confidence interval around the mean effect on QTc of 10 ms.[19] This suggests that a difference in QTc of a few milliseconds between male and female infants is clinically irrelevant.

Of the 4319 infants who participated in the study, including 4285 infants whose QTc values were analyzed, some infants were found to have miscellaneous heart diseases that were different from QT prolongation. Of these, echocardiography revealed a 43-day-old male infant with Wolff–Parkinson–White syndrome, LVNC, and heart failure. He showed a sudden decrease in his ejection fraction to <30% at 81 days of age, although his general status still seemed to be good. Clinical manifestations of LVNC are highly variable, ranging from no symptoms to disabling congestive heart failure, even from the neonatal period.[20] Children who are diagnosed with LVNC during infancy are at high risk for severe heart failure and a poor prognosis.[21] Quaglini et al[22] reported that ongoing neonatal electrocardiographic screening in >30 000 infants identified infants with prolonged QT intervals, as well as 4 cases of asymptomatic life-threatening congenital heart disease, 3 cases of coarctation of the aorta, and 1 case of anomalous origin of the left coronary artery from the pulmonary artery, which escaped detection at the initial medical visit. The results from this previous study and the present data indicate that neonatal electrocardiographic screening for QT prolongation, which was the primary objective of both studies, has additive value to screening.

Limitations

There are limitations to the present study. We did not perform genetic analysis of several infants with QTc >460 ms.[13] We are not able to exclude the possibility that some of these

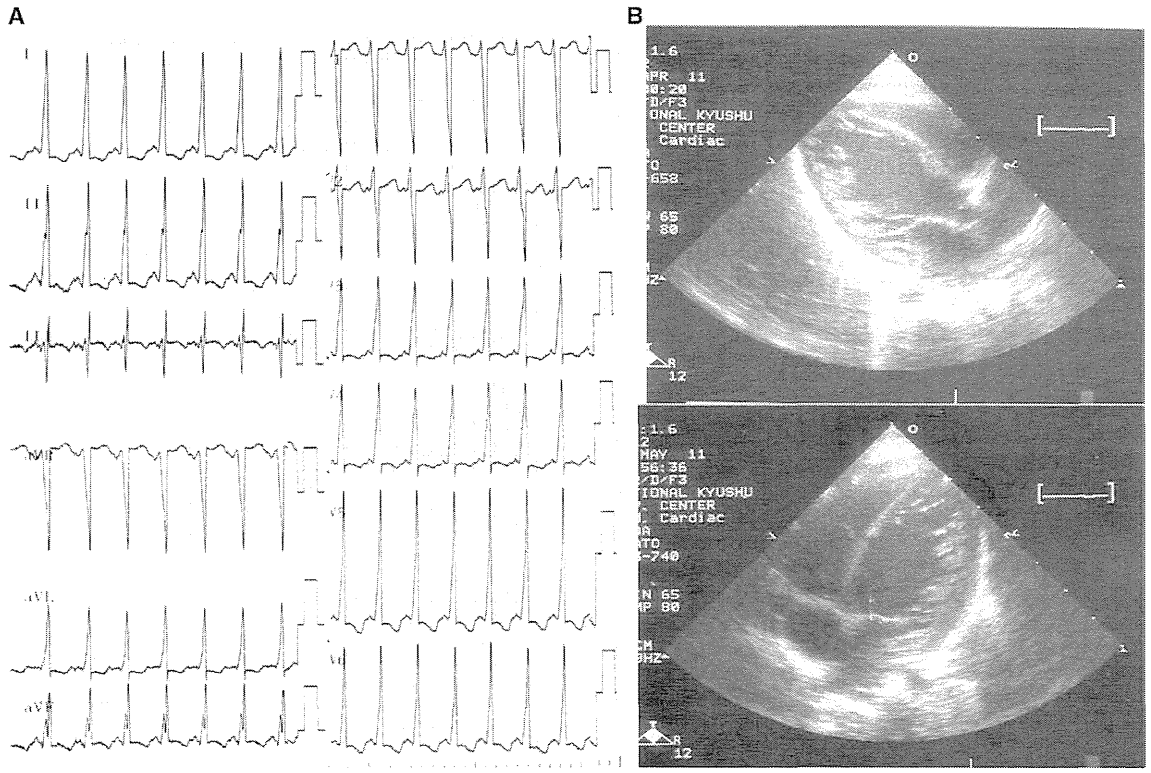

Figure 5. An ECG (**A**) and images of echocardiography (**B**) in an infant. His ECG shows Wolff–Parkinson–White syndrome, and echocardiography shows noncompaction of the left ventricle.

infants have LQTS-related mutations. They should be restudied in the future, although the valid time for re-examination is unclear. Fortunately, nationwide school-based electrocardiographic screenings are mandatory for children and adolescents in the first, seventh, and 10th grades in Japan. These periods might contain candidates for re-examinations in Japan.

Finally, cost-effective analysis was not performed in the present study. However, neonatal electrocardiographic screening is reported to be highly cost-effective, and a significant number of lives can be saved.[22] A cost-effective analysis of neonatal electrocardiographic screening should be performed in each country because the medical costs are different among countries.[23]

Implications

The data of the present study might be useful in proposing candidates for screening criteria of a prolonged QT interval in 1-month-old infants. We found that a QTc ≥470 ms was the best cutoff to screen infants with prolonged QT intervals, with a positive predictive value of 80% and negative predictive value of 100%. Candidate criteria could be 460 ms from the viewpoint that the risk of the presence of false-negative cases should be avoided (positive predictive value and negative predictive value of 57% and 100%, respectively). However, a common concern in relation to electrocardiographic screening is that if there are too many false-positives, and this would generate undue anxiety in children and parents.[24] However, even when we use the candidate value of 460 ms, the rate of false-positives may be low (ie, 0.5 per 1000). In an Italian study,[13] the screening rate was 1.37 per 1000 infants (59 of 43 080 infants), with a cutoff value of ≥460 ms. Of the 42 infants whose QTc values were ≥460 ms and in whom genetic testing was performed, 16 infants were diagnosed as LQTS genetically. The yield of genetic testing of clinically diagnosed LQTS patients with QTc ≥440 ms is generally 60%,[25] suggesting that 27 (16 divided by 0.60) of 42 infants (64%) can be diagnosed as LQTS clinically. The rate of false-positives was 0.49 per 1000 (1.37×[1–0.64]) in the Italian study.[13] These candidate values should be validated in future studies.

Conclusions

Neonatal electrocardiographic screening can identify infants likely to be affected by LQTS in different ethnic groups, as shown in whites, and might be useful in identifying other important cardiac diseases.

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Disclosures

None.

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CLINICAL PERSPECTIVE

This study aimed to determine whether electrocardiographic screening of 1-month-old infants identifies Japanese infants with prolonged QT intervals, as previously shown in whites. The prevalence of sudden infant death syndrome was 15 in 100000 between 2005 and 2008 in Japan. Genetic studies have shown that ≈10% of cases diagnosed with sudden infant death syndrome carry functionally significant genetic mutations in long-QT syndrome (LQTS) genes. The prevalence of sudden infant death syndrome may be higher because a thorough examination, including an autopsy, is needed to diagnose the syndrome. The prevalence of out-of-hospital cardiac arrest in infants was recently reported to be 41 in 100000 between 2005 and 2008 in Japan. Italian studies showed that the prevalence of LQTS is close to 1:2000, mainly based on genetic data. In the present study, 2 of 4319 infants needed medication because their QTc values were progressively prolonged during several months of life. These data showed that 1:2000 infants (ie, 50 in 100000 infants) have the LQTS genotype and phenotype. Patients with LQTS who experience symptoms during infancy are known to be at high risk for subsequent sudden cardiac death. Italian and Japanese studies have also found infants with life-threatening congenital heart disease during asymptomatic periods. These 2 studies in different ethnic groups showed that neonatal electrocardiographic screening can identify infants likely to be affected by LQTS and might be useful in identifying other important cardiac diseases. The cost-effectiveness and feasibility of neonatal electrocardiographic screening should be thoroughly evaluated worldwide as soon as possible.