

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

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

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

### ECG characteristics of short QT interval

Table 4 lists ECG characteristics. There was no significant difference in various ECG variables between patients with short and very short QT intervals. AF was present in 23 of 234 (9.8%) male and 16 of 193 (8.3%) female patients ( $P = NS$ ). The prevalence of AF did not differ significantly be-

tween patients with short and very short QT intervals in both genders. The prevalence of early repolarization was significantly ( $P = .0001$ ) higher in 23 of 234 (9.8%) male than in 3 of 193 (1.6%) female patients, but was not significantly different between patients with short and very short QT intervals in both genders. In these patients, 11 (42.3%) exhibited early repolarization in anterior leads (V1-4); 9 (34.6%) patients in inferolateral leads (II, III, aVF, V5, 6); and 5 (19.2%) patients in anteroinferior leads (V1-4, II, III, aVF).

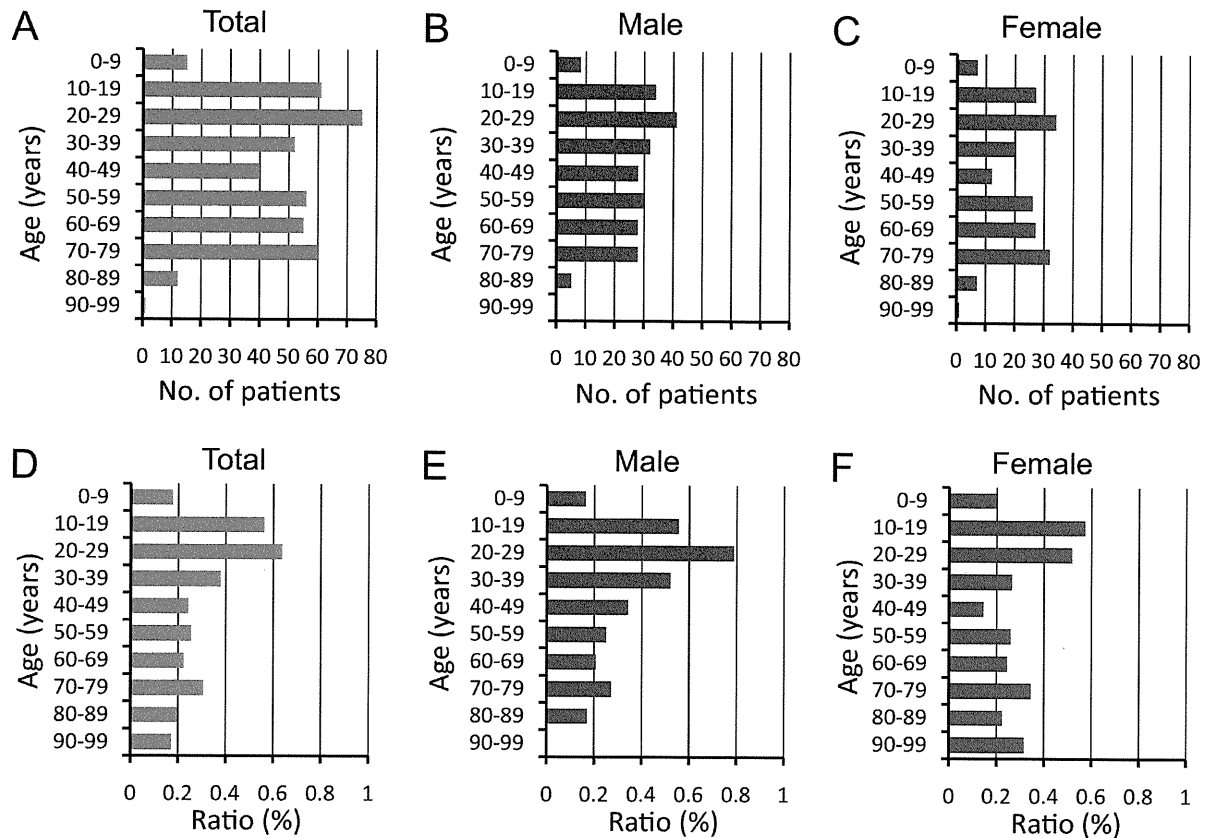
### Long-term outcome

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

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

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

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



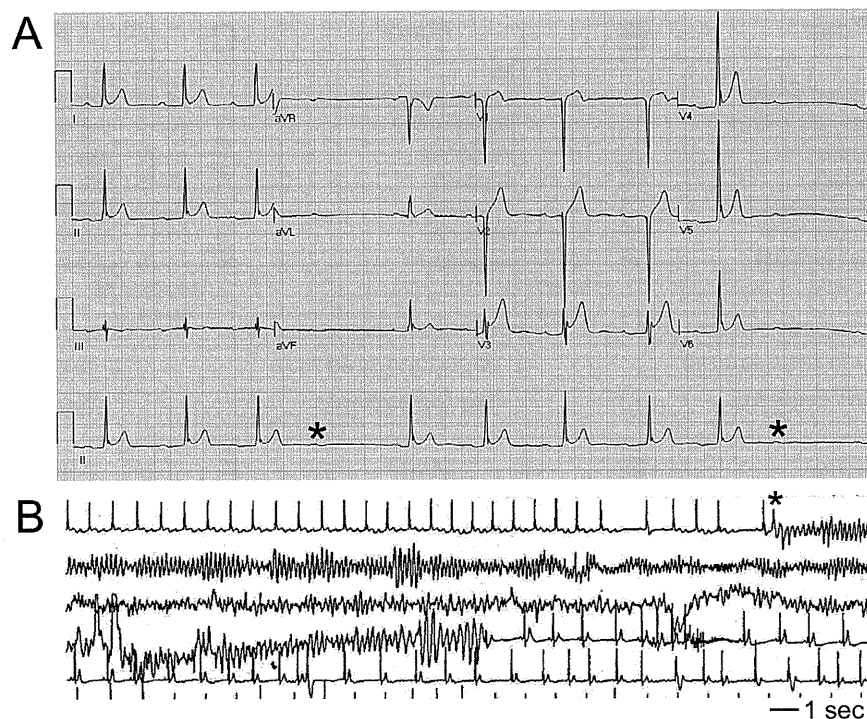
**Figure 2** Age-specific prevalence of patients with short QT interval in decades according to the number of patients (upper row) and a ratio of patients to the total population of this study (lower row). Histograms of total, male, and female patients are displayed in panels A and D, B and E, and C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

tricular fibrillation (5 repetitive attacks per day) that occurred when bradycardia occurred (Figure 3B). A ventricular pacing lead was emergently introduced into the right ventricle to maintain rapid heart rate. Subsequently, a permanent pacemaker was implanted (DDDR mode, 80 beats/min). Six years after the storm, ventricular fibrillation recurred during a routine pacemaker check. Ventricular fibrillation repeatedly initiated after bradycardia because of

threshold margin check. The patient received an implantable cardioverter-defibrillator with atrioventricular sequential pacing applied at a rate of 85 beats/min. Another 54-year-old man developed repetitive syncopal episodes with urinary incontinence in 2001 when sleeping. This patient did not exhibit early repolarization (Figure 4). He did not have a family history of cardiac disorders or sudden unexplained death. This patient revealed no evidence of abnor-

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

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



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

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

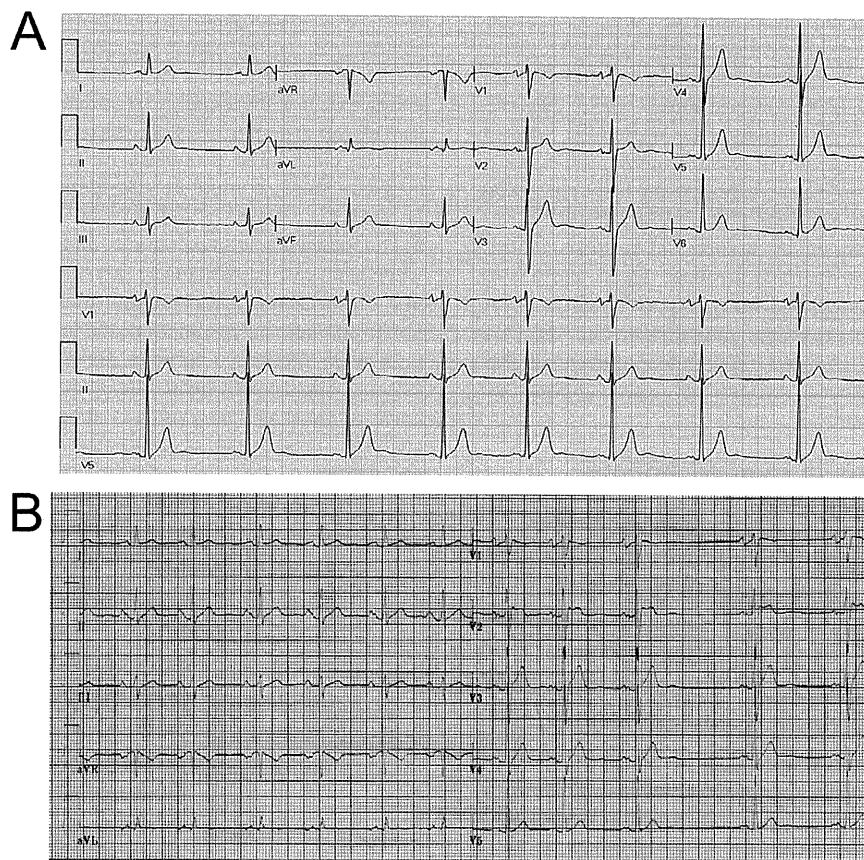
### Discussion

In the present study, we demonstrated detailed characteristics of patients with short<sup>10-12</sup> QT interval in a large hospital-based population. Consistent with previous reports, patients with short QT interval were rare and had a male preponderance. The age-specific prevalence of patients with short QT interval showed a biphasic distribution with a relatively low prevalence in middle-aged patients. Long-

term prognostic assessment revealed that 2 male patients with short QT interval suffered from life-threatening events in this study population.

### Characteristics of short QT interval

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



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

female, 1.6%) was comparable to that in total patients in this study. This is probably due to differential study populations; specifically, the present study population includes only hospital-based patients, and it is therefore possible that many of the patients with slow heart rate were receiving medications that prolonged their QT interval. In contrast, Kobza et al<sup>11</sup> reported on healthy army recruits. We investigated 2 ECG complications of short QT interval: AF and early<sup>4,5,16,17</sup> 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<sup>18</sup> 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%<sup>19,20</sup> of general populations, which was regarded as benign. The prevalence of early<sup>19,20</sup> 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.<sup>8</sup> To date, Haissaguerre et al<sup>21</sup> reported malignant early repolarization syndrome. In addition, Kamakura et

al<sup>22</sup> 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.<sup>9</sup> The syndrome characterized by extremely abbreviated QT<sup>23,24</sup> interval causes sudden cardiac death. Gene mutation that causes a gain of function in the K<sup>+</sup> channel is attributed to this shortening in this syndrome, suggesting that a specific family<sup>5,16,25</sup> member is affected with this disorder. In general, the QTc interval was <300 ms<sup>4,5,26,27</sup> 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.<sup>28</sup> A new mutation in calcium channel regarding congenital short QT syndrome type 6 was reported.<sup>29</sup> 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<sup>12</sup> reported that a QTc interval of  $\leq 330$  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.<sup>26</sup> 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,<sup>30–32</sup> 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<sup>33</sup> 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 bun-

dle 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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## 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 inferolateral 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

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### 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.<sup>1-4</sup> Idiopathic ventricular fibrillation (IVF) presenting prominent ST-segment elevation in the inferior leads has been considered as a variant of Brugada syndrome (BS).<sup>5,6</sup> BS<sup>7</sup> 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).<sup>8,9</sup> Recently, several reports have suggested the association of IVF with ER in the inferior and/or lateral lead in the electrocardiogram (ECG).<sup>3,10-14</sup> ER is reported to be found more frequently among patients with IVF than among healthy control subjects.<sup>10,15</sup> 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  $44.7 \pm 13.6$  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,<sup>16,17</sup> 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  $\geq 440$  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.<sup>8,18</sup>

The BS group consisted of 21 patients (19 males, aged 20–64 years, mean age  $39.7 \pm 12.6$  years) with an episode of documented VF or aborted SCD. Eleven had a sponta-

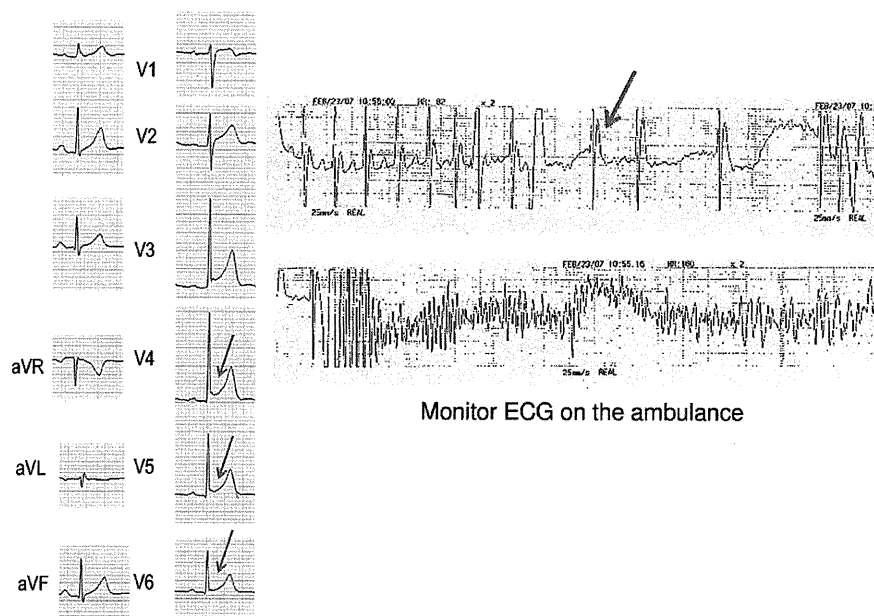
neous type 1 ECG, and in the remaining, it was induced by a sodium-channel blocker. Ethical approval of the present study was obtained from the Institutional Review Committee of the National Cerebral and Cardiovascular Center.

### 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).<sup>10</sup> 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 ( $\geq 0.2$  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.



a sodium-channel blocker in conjunction with documented VF or polymorphic ventricular tachycardia (VT).

### Drug challenge test

The drug challenge test was performed with intravenous pilsicainide (1 mg/kg, maximum 50 mg, 5 mg/min) or flecainide (2 mg/kg, maximum 100 mg, 10 mg/min). The test result was considered positive if a type 1 Brugada ECG appeared in >1 right precordial lead (V1–V3). Once again, we excluded all patients with IVF but without sodium-channel blocker challenge test from our study to clarify the diagnosis of ERS.

### Late potentials

Late potentials (LPs) were analyzed by using a signal-averaged electrocardiogram (SAECG) system (Arrhythmia Research Technology 1200EPX, Milwaukee, WI). Three parameters were assessed by using a computer algorithm: (1) total filtered QRS duration (f-QRS), (2) duration of low-amplitude signals <40  $\mu$ V of the filtered QRS complex (LAS<sub>40</sub>), and (3) root-mean-square voltage of the terminal 40 millisecond of the filtered QRS complexes (RMS<sub>40</sub>). LPs were considered positive when at least 2 of the 3 parameters were abnormal: f-QRS >120 millisecond, LAS<sub>40</sub> >38 millisecond, and RMS<sub>40</sub> <18  $\mu$ V.

### Statistical analysis

Continuous variables were expressed as mean value  $\pm$  SD. A comparison between the 2 groups was performed with Student's *t* test for paired data. Categorical variables were compared with Fisher's exact test. A *P* value of <.05 was regarded as being significant.

## Results

### Clinical and electrocardiographic characteristics

In the BS group, 9 of the 21 patients (43%) with BS showed ER in the inferior and/or lateral leads. A comparison of the clinical and electrocardiographic characteristics of the 14 ERS group patients, 21 BS group patients, and 9 BS patients with ER is shown in Table 1. The average age of 9 BS patients with ER was lower than that of the ERS group. Except for that, no significant differences were observed in baseline clinical characteristics with respect to age, gender, family history of SCD, and activity at the time of cardiac arrest. The number of premature ventricular complexes during 24-hour Holter ECG was not different between the 2 groups.

Regarding SAECG parameters, the values of f-QRSd, LAS<sub>40</sub>, and RMS<sub>40</sub> in 14 ERS group patients were 97.8  $\pm$  8.1 millisecond, 29.8  $\pm$  5.2  $\mu$ V, and 50.0  $\pm$  24.2 millisecond, respectively. The corresponding values in 21 BS group patients were 119.8  $\pm$  17.3 millisecond, 47.0  $\pm$  19.2  $\mu$ V, and 17.8  $\pm$  13.4 millisecond, respectively. All these parameters were significantly different between the 2 groups. LPs were positive in 1 of the 14 patients (7%) in the ERS group and in 12 of the 20 patients (60%) in the BS group. The rate of positive LPs was significantly higher in the BS group than in the ERS group (*P* <.01). We also compared the SAECG parameters and the rate of positive LPs between 14 ERS group patients and 9 BS patients with ER. The tendency was similar to the comparison between 14 ERS group patients and 21 BS group patients; however, there were no significant differences in the LAS<sub>40</sub> and rate of LPs because of the small number of BS patients with ER.

**Table 1** Clinical and electrocardiographic characteristics in the early repolarization syndrome group, the Brugada syndrome group, and the Brugada syndrome with ER group

	Group			P value	
	ERS (n = 14)	BS (n = 21)	BS with ER (n = 9)	ERS vs BS	ERS vs BS with ER
Clinical characteristics					
Age (y), mean $\pm$ SD	44.7 $\pm$ 13.6	39.7 $\pm$ 12.6	33.3 $\pm$ 10.3	NS	.045
Male gender, n/N	14/14	19/21	7/9	NS	NS
Family history of sudden cardiac death, n/N (%)	0/14 (0%)	1/21 (5%)	1/9 (11%)	NS	NS
Activity at the time of cardiac arrest, n (%)					
Sleep	3 (21%)	9 (42%)	5 (55%)	NS	NS
Rest	8 (57%)	10 (48%)	3 (33%)	NS	NS
Others	3 (21%)	2 (10%)	1 (11%)	NS	NS
Electrocardiographic characteristics					
Presence of ER, n/N (%)	14/14 (100%)	9/21 (43%)	9/9 (100%)	<.01	NS
Holter ECG, PVC in 24 h, mean $\pm$ SD	49.4 $\pm$ 169.3	1.9 $\pm$ 4.2	2.3 $\pm$ 4.4	NS	NS
Signal-averaged electrocardiography, mean $\pm$ SD					
f-QRSd (ms)	97.8 $\pm$ 8.1	119.8 $\pm$ 17.3	111.6 $\pm$ 11.5	<.0001	<.01
LAS <sub>40</sub> ( $\mu$ V)	29.8 $\pm$ 5.2	47.0 $\pm$ 19.2	33.8 $\pm$ 14.5	<.01	NS
RMS <sub>40</sub> (ms)	50.0 $\pm$ 24.2	17.8 $\pm$ 13.4	23.4 $\pm$ 14.2	<.0001	<.01
Abnormal SAECG, n/N (%)	1/14 (7%)	12/20 (60%)	4/9 (44%)	<.01	NS

Percentages may not total 100 because of rounding.

BS, Brugada syndrome; ECG, electrocardiogram; ER, early repolarization; ERS, early repolarization syndrome; f-QRSd, filtered QRS duration; LAS<sub>40</sub>, duration of low-amplitude signals <40  $\mu$ V of QRS in the terminal filtered QRS complex; NS, not significant; PVC, premature ventricular contraction; RMS<sub>40</sub>, root-mean-square voltage of the terminal 40 millisecond of the filtered QRS complex; SAECG, signal-averaged ECG.

**Table 2** Baseline electrocardiographic parameters and their changes after administration of a sodium-channel blocker in the early repolarization syndrome group, the Brugada syndrome group, and the Brugada syndrome with ER group

	Mean $\pm$ SD			P value	
	ERS (n = 14)	BS (n = 12)	BS with ER (n = 5)	ERS vs BS	ERS vs BS with ER
RR II (ms)	951 $\pm$ 116	930 $\pm$ 116	1024 $\pm$ 46	NS	NS
$\Delta$ RR II (ms)	-71 $\pm$ 41	-12 $\pm$ 17	-32 $\pm$ 62	<.05	NS
P II (ms)	104 $\pm$ 19	110 $\pm$ 16	112 $\pm$ 13	NS	NS
$\Delta$ P II (ms)	10 $\pm$ 9	21 $\pm$ 13	24 $\pm$ 16	<.05	<.05
PQ II (ms)	179 $\pm$ 34	191 $\pm$ 33	178 $\pm$ 28	NS	NS
$\Delta$ PQ II (ms)	30 $\pm$ 9	28 $\pm$ 14	38 $\pm$ 8	NS	NS
QRS II (ms)	90 $\pm$ 13	97 $\pm$ 18	90 $\pm$ 20	NS	NS
$\Delta$ QRS II (ms)	10 $\pm$ 10	23 $\pm$ 21	14 $\pm$ 21	NS	NS
QRS V5 (ms)	84 $\pm$ 8	91 $\pm$ 19	82 $\pm$ 21	NS	NS
$\Delta$ QRS V5 (ms)	13 $\pm$ 8	29 $\pm$ 18	28 $\pm$ 8	<.05	<.01
QT II (ms)	377 $\pm$ 19	370 $\pm$ 14	374 $\pm$ 15	NS	NS
$\Delta$ QT II (ms)	10 $\pm$ 14	28 $\pm$ 18	16 $\pm$ 5	NS	NS
QTcII (ms)	388 $\pm$ 20	385 $\pm$ 24	370 $\pm$ 13	NS	NS
$\Delta$ QTcII (ms)	10 $\pm$ 14	29 $\pm$ 18	16 $\pm$ 5	<.05	NS
QT V5 (ms)	376 $\pm$ 26	372 $\pm$ 17	376 $\pm$ 15	NS	NS
$\Delta$ QT V5 (ms)	6 $\pm$ 18	38 $\pm$ 23	14 $\pm$ 11	<.01	NS
QTcV5 (ms)	387 $\pm$ 23	387 $\pm$ 24	372 $\pm$ 12	NS	NS
$\Delta$ QTcV5 (ms)	7 $\pm$ 19	40 $\pm$ 25	14 $\pm$ 11	<.01	NS

BS = Brugada syndrome; ER = early repolarization; ERS = early repolarization syndrome; P = P-wave duration; PQ = PQ interval; QRS = QRS duration; QT = QT interval; QTc = corrected QT interval; RR = RR interval.

### Sodium-channel blocker infusion test

The sodium-channel blocker infusion test was performed in 12 of the 21 patients with BS, and the test result was positive in all 12 patients. We compared the pharmacological responses of several ECG parameters to a sodium-channel blocker between 14 patients with ERS and 12 patients with BS (Table 2). There were no significant differences in the baseline ECG parameters, including RR interval, P-wave duration, PQ interval, QRS duration, and QT interval in any leads. Shortening of RR ( $\Delta$ RR II) was significantly larger in the ERS group. Prolongation of P-wave duration ( $\Delta$ P II), QRS duration ( $\Delta$ QRS V5), and QTc interval ( $\Delta$ QTc II,  $\Delta$ QTc V5) was significantly larger in the BS group compared with that in the ERS group.

Among 9 BS patients with ER, the sodium-channel blocker test was performed in 5 patients. We also compared the ECG parameters between 14 ERS group patients and 5 BS patients with ER (Table 2). Prolongation of P-wave duration ( $\Delta$ P II) and QRS duration ( $\Delta$ QRS V5) was significantly larger in the BS with ER group compared with that in the ERS group.

The ER amplitude and its responses to sodium-channel blockers between 14 ERS group patients and 5 BS patients with ER are shown in Table 3. In the ERS group, ER was observed in the inferior leads (II, III, and aVF) in 9 patients, in the lateral leads (I, aVL, and V4-V6) in 8 patients, and in both the inferior and lateral leads in 3 patients. In the 9 BS patients with ER, ER was observed in the inferior leads in 6 patients, in the lateral leads in 8 patients, and in both the inferior and lateral leads in 5 patients. The baseline maximum ER amplitude among the inferolateral leads (pre-ER max) in the BS group tended to be higher than in the ERS group ( $0.244 \pm 0.082$  vs  $0.162 \pm 0.069$  mV;  $P = .057$ ). The

baseline ER amplitude in the inferior lead (pre-ER II) was significantly higher in the BS group than in the ERS group ( $0.236 \pm 0.081$  vs  $0.120 \pm 0.033$  mV;  $P < .05$ ). After administration of a sodium-channel blocker, the ER ampli-

**Table 3** Amplitude of ER in leads II and V5 before and after the administration of a sodium-channel blocker test in the early repolarization syndrome group and the Brugada syndrome with ER group

Maximum amplitude of ER in any inferolateral leads (mV)	Mean $\pm$ SD			P value
	ERS (n = 14)	BS with ER (n = 5)		
Pre-ER max	0.162 $\pm$ 0.069	0.244 $\pm$ 0.082	NS	
Post-ER max	0.081 $\pm$ 0.061*	0.124 $\pm$ 0.096*	NS	
$\Delta$ ER	0.080 $\pm$ 0.067	0.120 $\pm$ 0.058	NS	
Amplitude of ER in the inferior lead (II) (mV)				
	ERS (n = 9)	BS (n = 5)		
Pre-ER II	0.120 $\pm$ 0.033	0.236 $\pm$ 0.081	<.05	
Post-ER II	0.091 $\pm$ 0.054*	0.104 $\pm$ 0.086*	NS	
$\Delta$ ER II	0.028 $\pm$ 0.051	0.132 $\pm$ 0.068	<.05	
Amplitude of ER in the lateral lead (V5) (mV)				
	ERS (n = 8)	BS (n = 5)		
Pre-ER V5	0.116 $\pm$ 0.032	0.215 $\pm$ 0.092	NS	
Post-ER V5	0.010 $\pm$ 0.022*	0.137 $\pm$ 0.094*	NS	
$\Delta$ ER V5	0.106 $\pm$ 0.026	0.077 $\pm$ 0.071	NS	

BS = Brugada syndrome; ER = early repolarization; ERS = early repolarization syndrome; max = maximum; pre = before sodium-channel blocker test; post = after sodium-channel blocker infusion;  $\Delta$  = change. \* $P < .05$  vs pre.

tude was attenuated in all 5 patients with BS (100%) and in 13 of 14 patients with ERS (93%). ER attenuation was occasionally associated with the appearance of an S wave in both the groups (Figure 2). Therefore, the maximum ER amplitude (ER max), ER amplitude in the inferior lead (ER II), and ER amplitude in the lateral lead (ER V5) all were significantly decreased after the administration of sodium-channel blockers ( $P < .05$ ). Figure 3 illustrates the differential response to sodium-channel blockers between the ER in the inferolateral leads and the J point and ST segment in the right precordial leads in a patient with BS. The coved-type (type 1) ECG was unmasked and the J point in the right precordial leads (V1–V3) was augmented by the sodium-channel blocker, whereas the ER amplitude in the inferolateral leads (II, III, aVF, and V4–V6) was attenuated (Figure 3B).

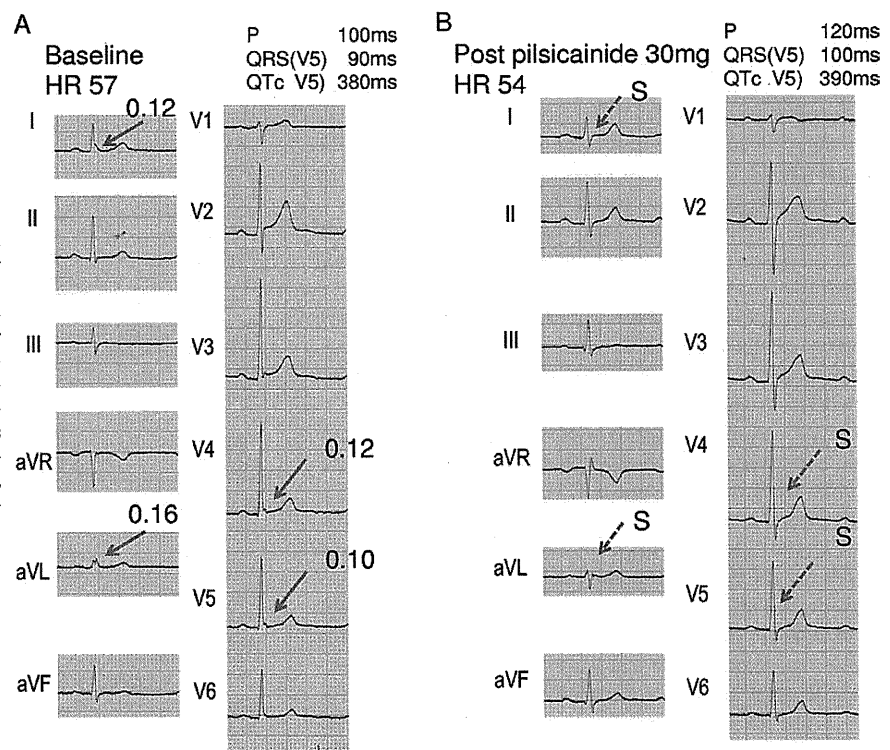
## Discussion

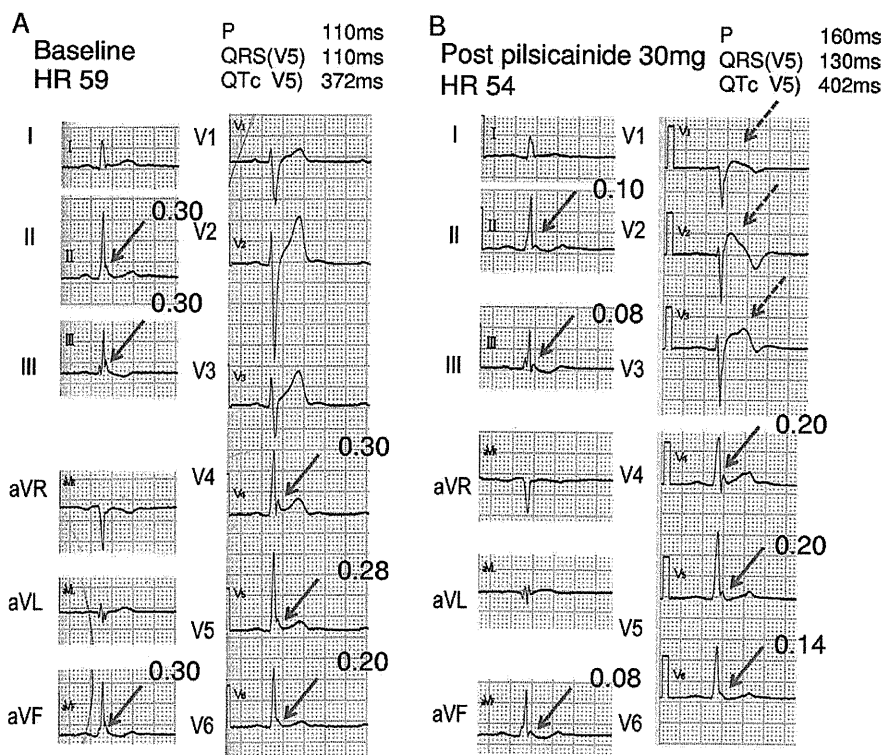
The ER pattern in the inferior and/or lateral leads had been considered benign, and it is often found in healthy young individuals. Recently, several reports have attracted increasing attention to the association of IVF with ER in the inferior and/or lateral leads.<sup>5,10,19–21</sup> Haissaguerre et al<sup>10</sup> reported that ER was more frequently recognized in patients with IVF than in control subjects and that there was a higher incidence of recurrent VF in case subjects with ER than in those without. Rosso et al<sup>15</sup> also reported that ER was found more frequently among patients with IVF than among healthy control subjects. On the other hand, BS is also

characterized by a high incidence of VF without structural heart disease. The Brugada Consensus Report proposed that type 1 coved-type ST-segment elevation in the right precordial lead (V1–V3) in the absence or presence of a sodium-channel blocker was required to diagnose BS.<sup>22</sup> Considering this diagnostic criterion, the sodium-channel blocker challenging test is essential to exclude BS. In order to investigate pure ERS, the sodium-channel blocker challenging test should be performed before the diagnosis of ERS. Unlike previous studies,<sup>10,15</sup> we conducted the sodium-channel blocker challenging test in all 14 patients with ERS to exclude BS in the present study.

Intravenous administration of sodium-channel blockers has been used to unmask the Brugada ECG pattern in patients with BS.<sup>23</sup> On the other hand, in most patients associated with ER in both the ERS group and the BS group of the present study, the administration of a sodium-channel blocker induced the attenuation or disappearance of the ER and appearance of an S wave. Attenuation of the ER in the inferolateral leads appears to be due largely to a slowing of the transmural conduction so that inscription of the ER occurs later on the descending limb of the QRS in both the ERS group and the BS group. The S-wave appearance in the inferolateral leads is also probably due to the conduction delay induced by sodium-channel blockers. This may indicate the differential mechanism between Brugada-type ST elevation in the right precordial lead of BS and ER in the inferolateral leads in both groups.

**Figure 2** Twelve-lead ECGs in a patient with early repolarization syndrome under baseline conditions (A) and after pilsicainide administration (B). ER was seen in the lateral leads (I, aVL, and V4–V5) under baseline conditions (A, arrows). Intravenous administration of 30 mg of pilsicainide induced attenuation of ER and appearance of an S wave in the lateral leads (dashed arrows). Numbers above the arrows indicate the amplitude of ER. ECG, electrocardiogram; ER, early repolarization; S, S wave.





**Figure 3** Twelve-lead ECGs in a patient with Brugada syndrome under baseline conditions (A) and after pilsicainide administration (B). ER was seen in the inferior (II, III, and aVF) and lateral (V4–V6) leads under baseline conditions (A, arrows). Intravenous administration of 30 mg of pilsicainide unmasked coved-type Brugada ECG and remarkably augmented the J point and ST segment in the right precordial leads (V1–V3) (B, dashed arrows), while ER was attenuated in the inferior and lateral leads (B, arrows). Numbers above the arrows indicate the amplitude of ER. ECG, electrocardiogram; ER, early repolarization.

Antzelevitch and Gan-Xin<sup>24</sup> have proposed a new concept that an outward shift in repolarizing current due to a decrease in sodium- or calcium-channel currents or an increase in outward currents such as a transient outward potassium current ( $I_{to}$ ) can give rise to J-wave syndromes, which includes BS, ERS, hypothermia, and acute ischemia-induced VF. A prominent and pathological J wave, a slow upright deflection between the end of the QRS complex and the early portion of the ST segment, has been reported to be seen often in hypothermia.<sup>25</sup> However, the terms J-wave syndromes and ERS have not been properly defined.<sup>26</sup>

In some patients with BS of this study, type 1 Brugada ECG was unmasked by a sodium-channel blocker in the right precordial lead, while ER was attenuated in the inferolateral leads (Figure 3). Once again, this finding suggested the differential mechanism between Brugada-type ECG in the right precordial lead and ER in the inferolateral leads.

Moreover, as with a previous report,<sup>27</sup> the BS group showed significantly larger prolongation of P-wave duration, QRS duration, and QTc interval compared with the ERS group after a sodium-channel blocker infusion. Basic electrophysiology including animal or mathematical models must play an important role in determining whether the cellular mechanism of ST-segment elevation in the right precordial leads in BS and that of ER in the inferolateral leads in both ERS and BS differ or not.

Our study showed clinical characteristics of ERS to be similar to those of BS, including adult onset, male preponderance, cardiac events occurred at rest or during sleep, and

rare ventricular arrhythmias on Holter ECG.<sup>28,29</sup> On the other hand, some apparent differences were found between the 2 groups, including LPs on the SAECG. All 3 parameters of the SAECG were significantly different between the 2 groups, and the positive rate of LPs was significantly lower in the ERS group than in the BS group. The rate of LPs has been previously reported to be high in BS.<sup>30</sup> On the other hand, Haissaguerre et al<sup>10</sup> also reported a relatively low rate (11%) of LPs in patients with ERS. LPs are reported to be not only highly prevalent in BS but also independent predictors of VT/VF inducibility.<sup>27,31–33</sup> LPs are also considered to be linked to VF inducibility during electrophysiological study and ventricular conduction delay during VF induction in patients with BS<sup>28,34</sup> as well as in patients with VT/VF associated with organic heart diseases. The ST-segment elevation in the right precordial leads and arrhythmogenicity in BS can be explained by both repolarization and depolarization abnormalities in right ventricular outflow.<sup>9,35</sup> The presence of LPs can be caused by conduction delay (depolarization abnormality) in the ventricle including the right ventricular outflow tract. On the other hand, from the experimental studies, LPs are explained on the basis of repolarization abnormality (late phase 2 upstroke and concealed phase 2 reentry) in the right ventricular outflow tract.<sup>36</sup> In the present study, the lower prevalence of LPs in the ERS group may indicate a differential substrate for VF in patients with ERS compared with that in patients with BS.

## Conclusions

ER can be seen in some patients with IVF and in a subgroup of subjects with BS. Clinical similarities among them exist, including age, gender, and arrhythmia triggers. Response to sodium-channel blockade on ER in the inferolateral leads is the same in both groups: a consistent diminution in ER amplitude. This effect contrasts with the ST-segment elevation that is always observed in the right precordial leads in BS, thus arguing for different pathophysiological mechanisms.

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

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

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

**METHODS** Consecutive 108 patients with type 1 electrocardiogram (104 men, mean age  $46 \pm 12$  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  $79 \pm 48$  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  $<40 \mu V$  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.<sup>1–6</sup> However, there remains much room for debate in prognostic indices except for history of VF.<sup>7</sup> 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.<sup>2,4,7-9</sup> Brugada et al reported that VF inducibility by PES can be a strong predictor of subsequent cardiac events in patients with BrS.<sup>8</sup> However, other studies could not confirm these findings.<sup>2,4,7</sup> 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  $46 \pm 12$  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

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

Characteristics	N (%)
<b>Clinical</b>	
Male	104 (96%)
Age (y)	$46 \pm 12$
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)	$43 \pm 14$
<b>Electrocardiographic</b>	
RR interval (ms)	$971 \pm 118$
PQ interval (ms)	$176 \pm 29$
QRS duration (ms)	$96 \pm 16$
Corrected QT interval (ms)	$405 \pm 29$
Spontaneous coved-type ST segment	62 (57%)
Total filtered QRS duration	$119 \pm 17$
LAS40	$47 \pm 16$
RMS40	$16 \pm 11$

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

shown in Table 1. Two patients with nocturnal agonal respiration were included in VF patients.

Brugada type 1 ECG was diagnosed when a coved ST-segment elevation ( $\geq 0.2$  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.<sup>10</sup>

### 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  $<40 \mu\text{V}$  of the filtered QRS complexes (LAS40). Late potential was considered positive when the 2 criteria (RMS40  $< 18 \mu\text{V}$  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  $\geq$ 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  $\pm$  standard deviation.  $\chi^2$  test, 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
<b>Clinical</b>				
Male	44 (98%)	34 (94%)	26 (96%)	.73
Age (y)	48 $\pm$ 11	45 $\pm$ 13	44 $\pm$ 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 $\pm$ 16	43 $\pm$ 14	41 $\pm$ 13	.86
<b>Electrocardiographic</b>				
RR interval (ms)	978 $\pm$ 125	990 $\pm$ 112	936 $\pm$ 108	.18
PQ interval (ms)	173 $\pm$ 27	178 $\pm$ 23	181 $\pm$ 39	.54
QRS duration (ms)	95 $\pm$ 15	99 $\pm$ 16	96 $\pm$ 19	.63
Corrected QT interval (ms)	404 $\pm$ 31	405 $\pm$ 26	406 $\pm$ 30	.97
Spontaneous coved-type ST segment	32 (71%)	19 (53%)	11 (41%)	.033
Total filtered QRS duration	122 $\pm$ 19	119 $\pm$ 16	114 $\pm$ 14	.17
LAS40	49 $\pm$ 16	49 $\pm$ 19	41 $\pm$ 13	.13
RMS40	14 $\pm$ 10	17 $\pm$ 10	20 $\pm$ 13	.051
Late potential*	32/44 (73%)	25/35 (71%)	13/24 (54%)	.25
<b>Genetic</b>				
SCN5A mutation	6 (13%)	3 (8%)	3 (11%)	.78
<b>Electrophysiological</b>				
AA interval	921 $\pm$ 153	903 $\pm$ 174	905 $\pm$ 143	.86
AH interval	106 $\pm$ 31	101 $\pm$ 21	108 $\pm$ 33	.65
HV interval	45 $\pm$ 12	44 $\pm$ 8	42 $\pm$ 9	.58
<b>Induction of ventricular arrhythmia</b>				
Ventricular fibrillation	40 (89%)	31 (86%)		NA
PVT >15 successive beats	5 (11%)	5 (14%)		NA
<b>Site of induction</b>				
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  $\mu$ V) 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  $82 \pm 48$  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  $83 \pm 50$  months, group T  $81 \pm 44$ , and group N  $80 \pm 49$ ;  $P = .96$ ). 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

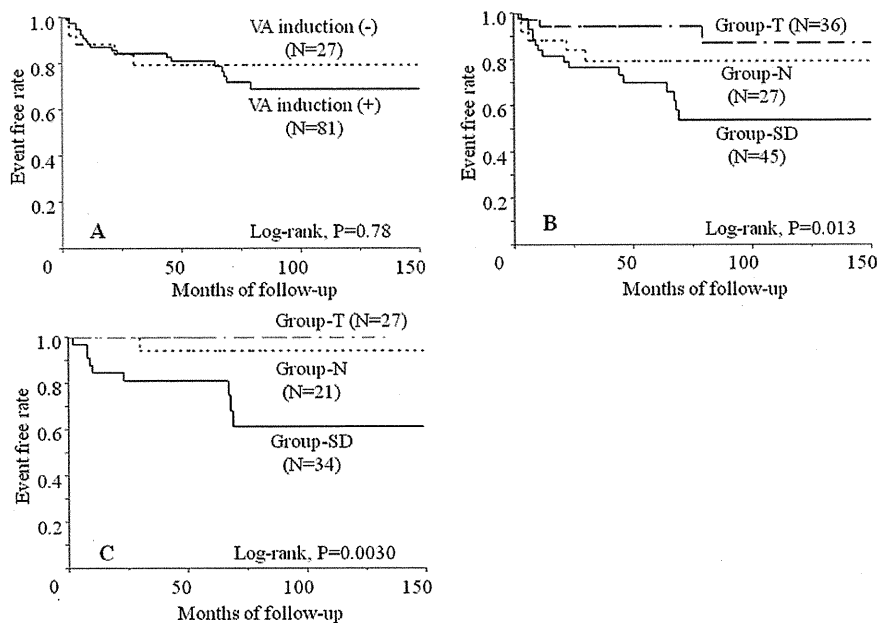
numbers of extrastimuli, group SD had a significantly higher risk of subsequent cardiac events than did group T (log-rank,  $P = .004$ ), but there were no significant differences in the subsequent cardiac event rate between group SD and group N and between group T and group N (Figure 1B). Among 82 patients 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  $\geq 200$  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).

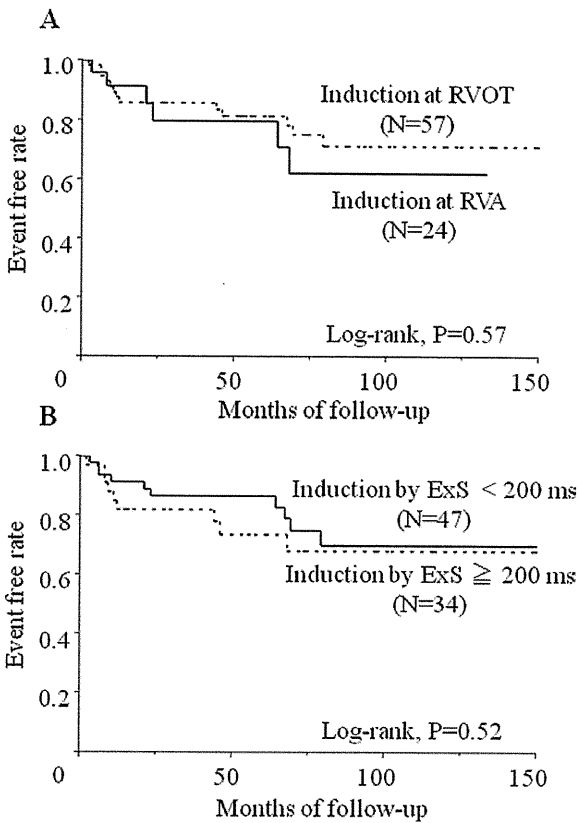
As for 42 asymptomatic patients, 2 of the 17 patients in group SD experienced subsequent VF episodes, whereas none of the 14 patients in group T and 11 in group N experienced subsequent cardiac events. Although the number of patients was small, group SD showed a significantly higher cardiac event rate 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**

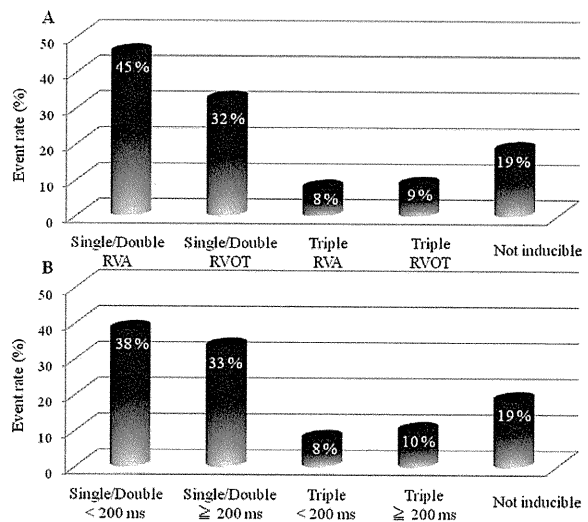
Conflicting data have been reported from several registries as to the prognostic value of PES in patients with BrS.<sup>4,6,7</sup> Bru-

gada 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.<sup>11–13</sup> However, there were several limitations for each registry such as the different PES protocols.<sup>14</sup> Moreover, these conflicting data may be related to the specific inclusion criteria of each registry. Recently, Giustetto et al<sup>9</sup> 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 ( $49 \pm 17$  vs  $41 \pm 13$ ;  $P = .042$ ) and smaller RMS40 ( $15 \pm 10$  vs  $20 \pm 13$ ;  $P = 0.034$ ) than did noninduced patients, which may reflect depolarization abnormality and is concordant with our previous report.<sup>15</sup>

There have been several reports regarding depolarization abnormalities in BrS such as *SCN5A* mutation or fragmented QRS.<sup>16–18</sup> By using an experimental model, Aiba et al<sup>19</sup> 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).<sup>19,20</sup> 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.<sup>13</sup> However, some patients with BrS experience neurally mediated syncope, as previously reported, which should be distinguished from syncope of unknown origin.<sup>21</sup> 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.<sup>11,12</sup> 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<sup>22</sup> 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 = non-sustained 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.<sup>23,24</sup> 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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