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.[5,10,19–21] Haissaguerre et al[10] 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[15] 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.[22] 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,[10,15] 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.[23] 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.

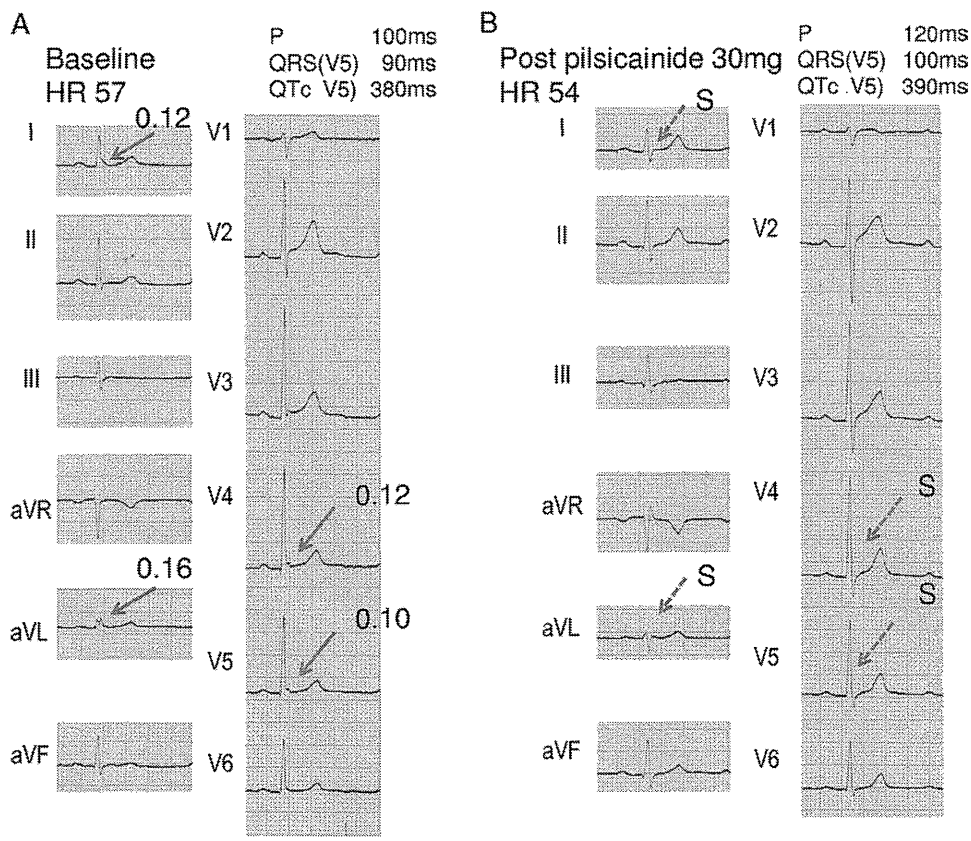

Figure 2 Twelve-lead ECGs in a patient with early repolarization syndrome under baseline conditions (**A**) and after pilsicainide administration (**B**). ER was seen in the lateral leads (I, aVL, and V4–V5) under baseline conditions (**A**, arrows). Intravenous administration of 30 mg of pilsicainide 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.

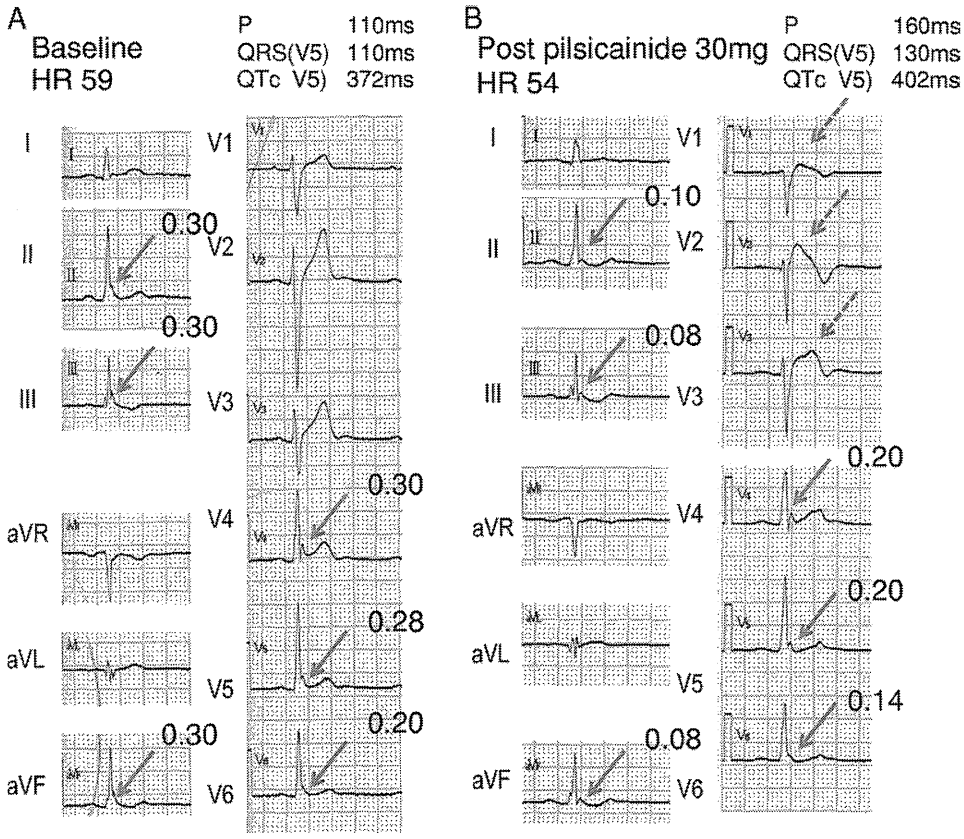

Figure 3 Twelve-lead ECGs in a patient with Brugada syndrome under baseline conditions (**A**) and after pilsicainide administration (**B**). ER was seen in the inferior (II, III, and aVF) and lateral (V4–V6) leads under baseline conditions (**A**, arrows). Intravenous administration of 30 mg of pilsicainide 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[24] 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.[25] However, the terms J-wave syndromes and ERS have not been properly defined.[26]

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,[27] 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.[28,29] 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.[30] On the other hand, Haissaguerre et al[10] 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.[27,31–33] LPs are also considered to be linked to VF inducibility during electrophysiological study and ventricular conduction delay during VF induction in patients with BS[28,34] 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.[9,35] 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.[36] 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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Beneficial effects of cilostazol in a patient with recurrent ventricular fibrillation associated with early repolarization syndrome

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Introduction

An early repolarization pattern on the electrocardiogram (ECG), referred to as J-point elevation, which is sometimes followed by ST-segment elevation, has been considered to be a benign ECG manifestation.[1,2] However, clinical problems associated with the early repolarization pattern induced after ventricular fibrillation (VF) were published by Haissaguerre et al[3] in 2008. An early repolarization pattern was reported to occur in 31% of the subjects with idiopathic VF, and VF recurred more frequently in those patients compared to that in healthy subjects. In such patients, this is called early repolarization syndrome (ERS), and an implantable cardioverter-defibrillator (ICD) is the first-line therapy for the prevention of sudden death.[4–6] As an oral medication, the efficacy of quinidine was reported in ERS patients with recurrent VF.[7] However, we experienced a case with recurrent VF associated with ERS refractory to a small dose of quinidine, which was prevented by the oral administration of cilostazol, an oral phosphodiesterase III inhibitor.[8]

Case report

A 64-year-old woman was admitted to the intensive care unit because of VF terminated by an automated external defibrillator in July 2009. After a shock was delivered, her 12-lead ECG showed atrial fibrillation (AF) with a J-point elevation and horizontal/descending ST-segment pattern in leads I, aVL, and V_6 (Figure 1). Additional investigation including echocardiography, coronary angiography, left ventriculography, and cardiac magnetic resonance imaging did not show any structural heart disease. Intravenous infusion of pilsicainide, a sodium channel blocker, at a dose of 50 mg did not lead to any augmentation of a Brugada-like ST-segment elevation. After obtaining written informed consent, an electrophysiological study was performed. There were no abnormal areas in the right ventricle and VF was not induced with triple extrastimuli applied to 2 locations including the right ventricular apex and right ventricular outflow tract. She was diagnosed with idiopathic VF associated with ERS. An ICD (EPIC VR V-196, St Jude Medical, St Paul, MN) was implanted in our hospital, and she was prescribed bisoprolol 1.25 mg/d for heart rate control of her AF before discharge.

During her follow-up, she experienced an inappropriate ICD shock due to AF and digoxin 0.1 mg/d was additionally initiated. Thereafter, she experienced several ICD shocks due to VF during sleep or during the early morning from December 2009 to May 2010 (Figure 2). A low dose of bepridil 100 mg/d was added to prevent VF attacks because of its effectiveness revealed in Brugada syndrome.[9] The frequency of VF episodes decreased, but the VF attacks were not completely prevented. In addition, we tried a low dose of quinidine 200 mg/d, increased the ICD pacing rate from VVI 50 to VVI 70 beats/min, and withdrew the bisoprolol, which failed to prevent subsequent multiple VF attacks. In January 2011, the patient was admitted to our hospital again to reevaluate her condition and to adjust the medication. An echocardiogram revealed no change in the left ventricular function and the 12-lead ECG revealed J-point elevation with a horizontal/descending ST-segment pattern after the ICD pacing rate was reprogrammed to VVI 40. The intravenous application of isoproterenol 1 μg/min led to the attenuation of J-point elevation in leads I, aVL, and V_6 (Figure 3). On the basis of this phenomenon, we tried cilostazol, which was reported to be an effective drug to prevent VF in Brugada syndrome.[10] After cilostazol was initiated, no VF episodes were observed during her hospitalization and cilostazol

KEYWORDS Brugada syndrome; Cilostazol; Early repolarization; J-wave; Quinidine; Ventricular fibrillation

ABBREVIATIONS **AF** = atrial fibrillation; **ECG** = electrocardiogram; **ERS** = early repolarization syndrome; **ICD** = implantable cardioverter defibrillator; **VF** = ventricular fibrillation (Heart Rhythm 2013;10:604–606)

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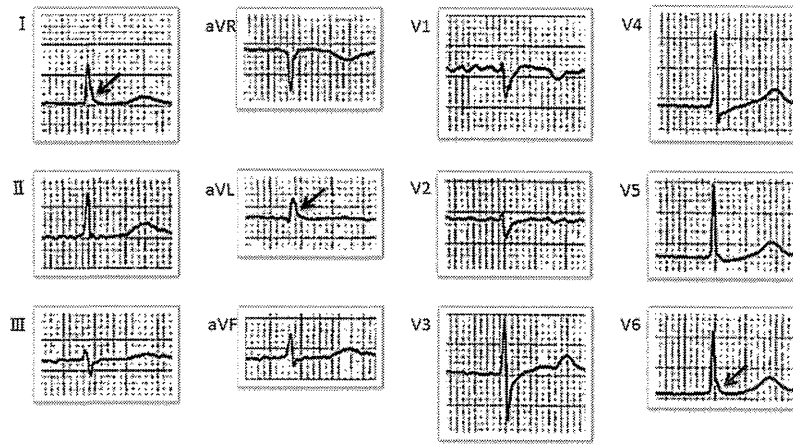

Figure 1 Twelve-lead electrocardiogram (ECG) during the first hospitalization. The ECG showed atrial fibrillation with a J-point elevation and horizontal/descending ST-segment pattern in leads I, aVL, and V_6.

increased her heart rate from 40–45 per minute to 60–80 per minute during sleep and in the early morning during an AF rhythm.

After discharge with cilostazol, the patient has remained asymptomatic with no further tachyarrhythmic episodes requiring device therapy for more than 12 months.

Discussion

To the best of our knowledge, this is the first case report to demonstrate the efficacy of cilostazol therapy in preventing recurrent VF in a patient with ERS as in Brugada syndrome. Early repolarization is characterized by an elevation of the J point, which is thought to be a benign ECG manifestation. However, previous studies revealed a manifest association between an early repolarization pattern and idiopathic VF.[11] Haissaguerre et al reported that 31% of the idiopathic VF patients had an early repolarization pattern in the inferior and lateral leads. Recently, it was reported that ST-segment variations as well as the distribution and magnitude of the early repolarization pattern were related to the risk of arrhythmic death.[4,12] Tikkanen et al[12] showed that horizontal/descending ST-segment patterns with early repolarization are accompanied by an increased risk for arrhythmic death, but early repolarization patterns followed by rapidly upsloping ST segments after the J point are not associated with such a risk. Our patient, who experienced several ICD shocks due to VF during sleep or in the early morning, had a horizontal/descending ST-segment pattern with early repolarization on the 12-lead ECG and was refractory to a low dose of quinidine and bepridil. Ventricular pacing also could not suppress the VF episodes. We initiated the administration of cilostazol, an oral phosphodiesterase III inhibitor, based on the assumption that the mechanism of ERS was likely to be comparable to that in Brugada syndrome.[13] The arrhythmogenic mechanism of ERS is hypothesized to be due to an outward shift in the balance of the membrane ionic currents at the end of phase 2 of the action potential. A prominent I_{to}-mediated action potential notch in the ventricular epicardium, but not in the endocardium, produces a transmural voltage gradient during early ventricular repolarization. Either a decrease in the inward current (I_{Na} and I_{Ca}) or an increase in the outward current (I_{to}) accentuates the notch as a J wave.[2] A further outward shift in the currents during the early phase of the action potential can lead to a loss of the action potential dome, which generates phase 2 reentry and VF[6]; however, different mechanisms of J waves may share the I_{to} and I_{Ca} as a modulator unlike Brugada syndrome based on the different responses to sodium channel blockers.

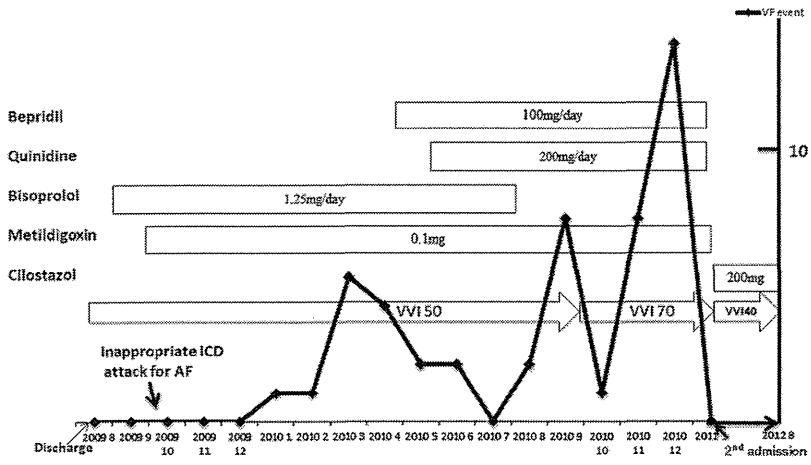

Figure 2 The relationship between the use of a drug and implantable cardioverter-defibrillator (ICD) discharges in the clinical course. The patient experienced several ICD shocks due to ventricular fibrillation (VF), which were refractory to a low dose of quinidine and bepridil. After cilostazol was initiated, no VF episodes were observed during a follow-up of more than 12 months. AF = atrial fibrillation.

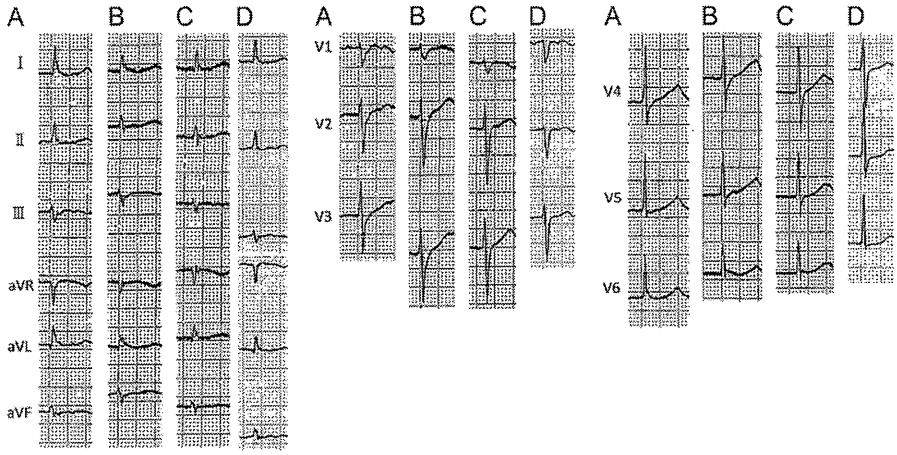

Figure 3 Twelve-lead electrocardiograms (ECGs) during baseline (**A**) and after pilsicainide (**B**), isoproterenol (**C**), and cilostazol (**D**). An intravenous infusion of pilsicainide at a dose of 50 mg did not lead to any augmentation of the Brugada-like ST-segment elevation. After an intravenous application of isoproterenol 1 μg/min, the 12-lead electrocardiogram (ECG) revealed attenuation of the J-point elevation in leads I, aVL, and V_6 as compared to that in the baseline ECG. Oral administration of cilostazol also attenuated the J-point elevation in leads I, aVL, and V_6. ISP = isoproterenol; Pil = pilsicainide.

Quinidine, which inhibits I_{to} and reduces the magnitude of the J wave, was reported to be effective in preventing ventricular tachyarrhythmias in ERS.[7] However, our patient had multiple ICD discharges due to VF even after a small dose of quinidine. Since this case was a rather small-sized woman, we used a low dose of quinidine. The efficacy of quinidine in this ERS case is not conclusive because more than 600 mg of quinidine may be required to control arrhythmic storms in patients with ERS as with Brugada syndrome. Bepridil, a calcium channel blocker, which is also reported to be useful for preventing lethal tachyarrhythmias in Brugada syndrome by suppressing the I_{to}, was also ineffective. An acceleration in the heart rate reduces the I_{to} and is reported to decrease the magnitude of early repolarization (J wave),[14] and an increasing pacing rate from an ICD is reported to be effective in preventing recurrent VF in Brugada syndrome.[15] We tried to prevent the recurrent VF in our patient by increasing the pacing rate of the ICD. However, in this case, VVI pacing at a rate of 70 beats/min by the ICD could not prevent a VF recurrence. Finally, we used cilostazol, a phosphodiesterase type III inhibitor, because it increases the I_{Ca} and diminishes the I_{to} by increasing the intracellular level of the cyclic AMP and heart rate. In fact, cilostazol increased the heart rate from 40–45 per minute to 60–80 per minute during an AF rhythm. After the cilostazol was initiated, no VF episodes were observed during a follow-up of more than 12 months.

Conclusions

We experienced a case with recurrent VF associated with ERS refractory to a low dose of quinidine, which was prevented by the oral administration of cilostazol. Although cilostazol was useful in preventing recurrent VF in our patient with ERS, further studies are necessary to establish the clinical usefulness of this drug in patients with ERS.

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

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

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

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

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

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

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

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

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Introduction

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

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

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

Methods

Study population

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

Table 1 Overall clinical and electrocardiographic characteristics of 108 patients

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

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

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

Clinical information

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

Electrophysiological study

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

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

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

Follow-up

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

Statistical analysis

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

Results

Electrophysiological study

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

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

Table 2 Clinical, electrocardiographic, genetic, and electrophysiological characteristics

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

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

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

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

Subsequent cardiac events during follow-up

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

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

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

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

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

Predictors of long-term prognosis

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

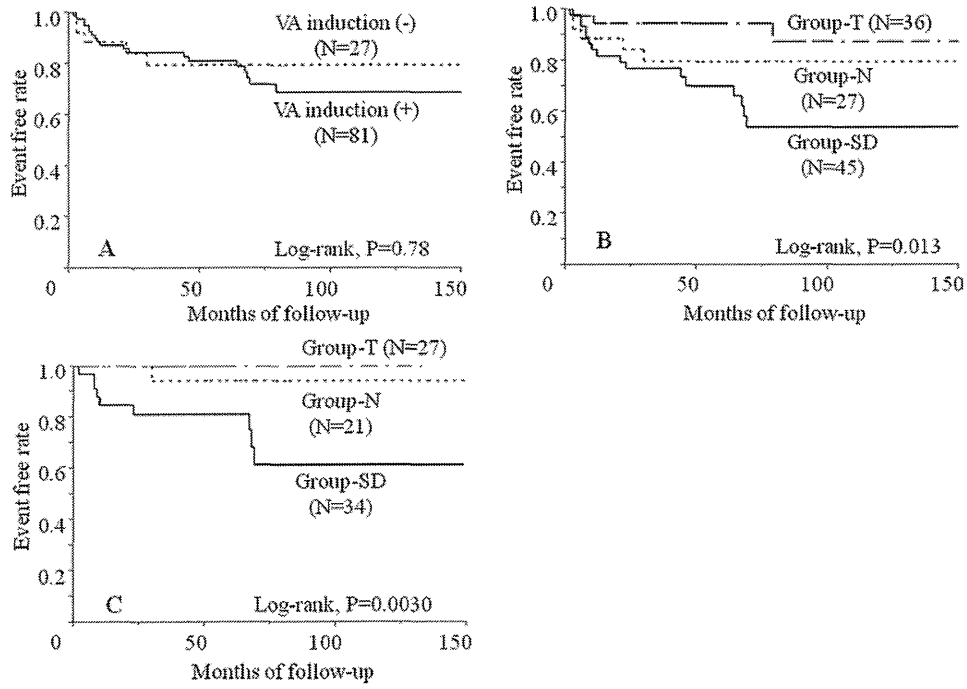

Figure 1 Kaplan–Meier curves of subsequent cardiac events during follow-up. Kaplan–Meier curves of cardiac events (**A**) depending on the overall inducibility of ventricular arrhythmias (VFs and polymorphic ventricular tachycardia >15 successive beats) by up to triple extrastimuli, (**B**) in the 3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

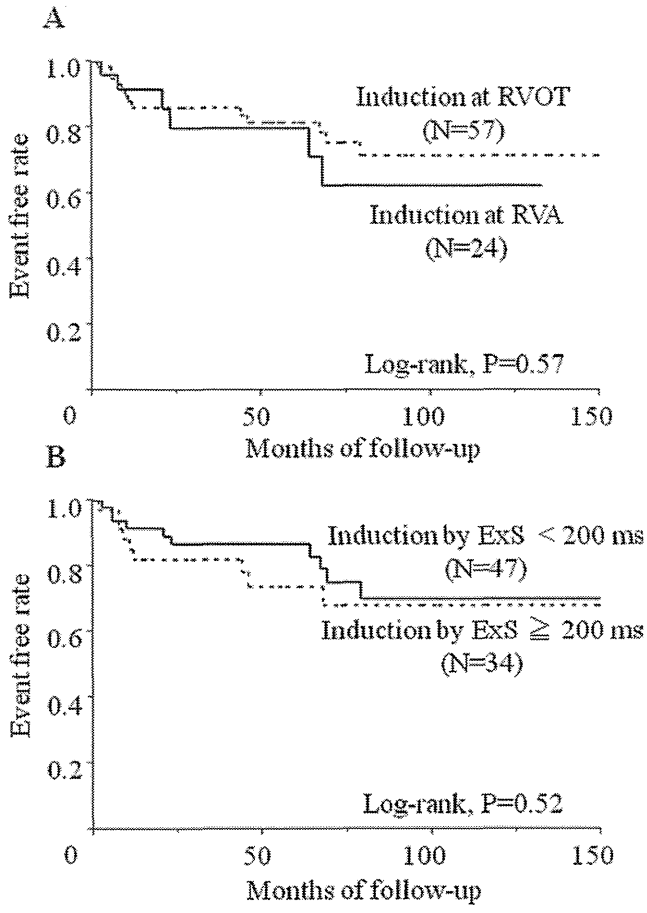

Figure 2 Kaplan–Meier curves of subsequent cardiac events during follow-up. Kaplan–Meier curves of cardiac events (**A**) depending on the induction site and (**B**) the minimum coupling interval of extrastimuli at the time of induction. Neither the site of induction, the right ventricular outflow tract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

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

Discussion

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

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

Clinical significance of PES in patients with BrS

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

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

Underlying mechanism

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

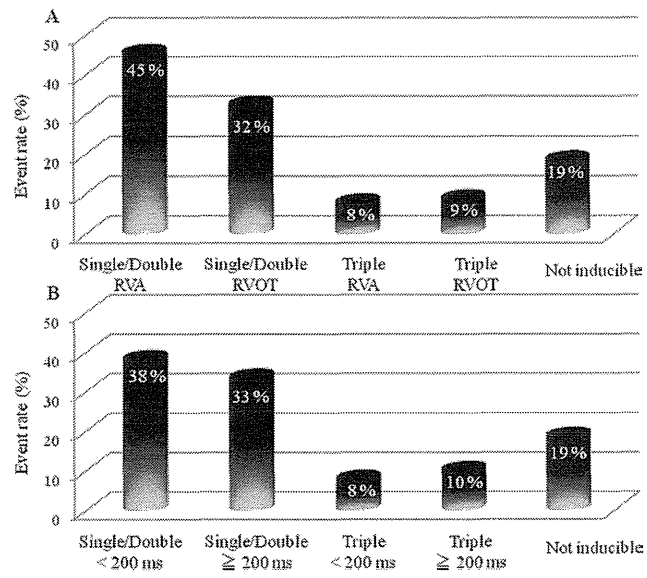

Figure 3 Incidence of subsequent cardiac events according to the number of extrastimuli, the site of induction, and the minimum coupling interval at the time of induction. Incidence of cardiac events (**A**) according to the number of extrastimuli and the site of induction and (**B**) the number of extrastimuli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

Table 3 Predictive factors of subsequent cardiac events

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

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

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

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

Clinical implication

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

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

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

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

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

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

Study limitations

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

Conclusion

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

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IR between 2008 and 2011 in groups A, B and C. In group D, there was a significant increase in the mean value of log-transformed HOMA-IR between 2008 and 2011. In contrast, there were no significant differences in the mean values of BMI and WC between 2008 and 2011 in group D (Table 1).

In this study, HOMA-IR significantly increased in all groups (continuous exercise, no exercise, sopped habitual exercise and began habitual exercise), and a significant change in BMI and WC was observed in groups with continuous exercise, no exercise, and sopping habitual exercise, However, no significant change in BMI and WC was observed in subjects who began habitual exercise. Exercise is important to avoid obesity and metabolic syndrome. The author speculates that HOMA-IR, BMI and WC increase by aging, although the absolute value of each indicator is different by exercise. As presented in Table 1, increase of BMI and WC by aging is suppressed for subjects who began habitual exercise, and the significant level of their increase in HOMA-IR by aging is relatively small compared with data from other three groups. Longer follow-up study is needed to observe the further results.

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Clinical characteristics and risk of arrhythmia recurrences in patients with idiopathic ventricular fibrillation associated with early repolarization

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Early repolarization or J-wave has generally been considered benign for decades. However, since we and others have recently reported that early repolarization in the inferior and/or lateral leads of the 12-lead electrocardiogram is associated with pathogenesis in idiopathic ventricular fibrillation [1,2], there has been an increasing interest in the disorder. This study aimed to investigate the clinical and genetic characteristics and to identify risk factors for arrhythmia events in patients with idiopathic ventricular fibrillation associated with early repolarization.

This study included 53 patients (46 men; age, 44 ± 17 years) with idiopathic ventricular fibrillation and early repolarization who were referred to our institutions due to ventricular fibrillation events. All patients gave written informed consent prior to the genetic and clinical investigations. Patients were diagnosed with idiopathic ventricular fibrillation if they had no structural heart disease as identified using echocardiography, coronary angiography, and left ventriculography. Early repolarization was defined as an elevation of

Table 1
Clinical and electrocardiographic characteristics of 53 patients.

Male sex, N (%)	46 (87%)
Age, years	44 ± 17
Family history of sudden death, N (%)	7 (13%)
Activity at initial cardiac arrest, N (%)	
Sleep	14 (26%)
Rest	12 (23%)
Physical effort	10 (19%)
Other activities	17 (32%)
Atrial fibrillation, N (%)	12 (23%)
History of electrical storm,[a] N (%)	9 (17%)
Inducible ventricular fibrillation	15/31 (48%)
Mutation in *SCN5A*, N (%)	4/29 (14%)
Electrocardiography	
Heart rate, beats/min	63 ± 9
PR interval, ms	175 ± 34
QRS duration, ms	95 ± 14
QT interval, ms	384 ± 29
Corrected QT interval, ms[b]	389 ± 25
Prolonged PR interval ≥200 ms, N (%)	12 (23%)
Prolonged QRS duration ≥120 ms, N (%)	3 (6%)
Location of early repolarization,[c] N (%)	
Inferior	37 (70%)
Lateral	37 (70%)
Right precordial	11 (21%)
Multiple locations of early repolarization	28 (53%)

[a] An electrical storm was defined as ≥3 episodes of VF within 24 h.
[b] Corrected QT interval was calculated with Bazett's formula.
[c] Some patients had early repolarization in multiple locations.

the J-point, either as QRS slurring or notching of ≥0.1 mV in ≥2 consecutive leads in the 12-lead electrocardiogram [1]. Patients were excluded if they had a short QT interval (corrected QT interval using Bazett's formula <340 ms) or a long QT interval (corrected QT interval >440 ms). All patients received a sodium channel blocker challenge, and patients who met the diagnostic criteria for Brugada syndrome at baseline or after sodium channel blocker challenge were excluded [3]. Genetic testing was performed for mutations in ion channel genes including *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, and *KCNJ8*, as previously described [4]. The contribution of variables to risk of arrhythmia recurrences was tested with Cox proportional-hazards models using SPSS, version 12.0 (SPSS Inc, Chicago, IL). A two-sided $P<0.05$ was considered statistically significant. Values are expressed as mean ± SD or number (percentage).

The cardiac arrest events occurred during sleep or at rest in about half of the patients (Table 1). An electrical storm defined as ≥3 episodes of ventricular fibrillation within 24 h was observed in 8 patients (21%). A family history of sudden cardiac death was reported in 7 patients (18%). In the 12-lead electrocardiogram, early repolarization was frequently present in the inferior leads and in the lateral leads. In more than half of the patients, early repolarization was found in multiple locations. Although the initial report has described inferolateral early repolarization [1], early repolarization, which is different from Brugada type electrocardiogram, was also present in the right precordial leads in 11 patients (21%). Conduction disease, mostly prolongation of the PR interval, was present in 15 patients (28%). Mutations in *SCN5A* were identified in 4 unrelated patients. Among 46 patients who were followed ≥6 months, arrhythmia recurred in 10 patients (22%) during a follow up of 6.0 ± 5.7 years (incidence, 5.9 per 100 person-years [95% confidence interval, 2.3–9.4]). In univariate analyses, age at arrhythmia onset, a family history of sudden death, and a history of electrical storm were associated with the increased risk of arrhythmia recurrences (Table 2). In multivariate analyses, age, family history, and electrical storm were associated with arrhythmia recurrences (Table 3). Gender, location of early repolarization, activity at the initial event, conduction disorder, and inducibility of ventricular fibrillation were not associated with the risk of arrhythmia recurrences.

Heritability of early repolarization has been reported in the general population [5], and as in other arrhythmia syndromes such as long QT syndrome and Brugada syndrome [6], ion channel genes are responsible for idiopathic ventricular fibrillation associated with early repolarization [4,7–9]. However, compared to the frequency of a positive family history of sudden death, mutations in ion channel genes were less commonly identified in this study similarly to a previous study [8], suggesting that most of the causative genes are missing. Early repolarization is augmented after a pause, and it is attenuated by exercise and isoproterenol, a β-adrenergic agonist [1,10]. Therefore, vagal stimulation has been considered to increase arrhythmia susceptibility. However, in this study, arrhythmia events occurred not only during rest or sleep but also during exercise and daily activity consistent with a previous study [1], although a high

Table 2
Risk factors for arrhythmia recurrence, univariate models.

	Arrhythmia recurrence N = 10	No arrhythmia recurrence N = 36	Hazard ratio (95% CI)	P-value
Male sex, N (%)	8 (80)	33 (89)	1.49 (0.31–7.04)	0.62
Age, years	45 ± 17	47 ± 15	1.71 (1.06–2.77)[a]	0.03
Family history of sudden death, N (%)	3 (30)	2 (5)	4.02 (1.03–15.76)	0.04
Sleeping/rest at initial cardiac arrest, N (%)	6 (60)	17 (46)	2.29 (0.64–8.23)	0.20
Atrial fibrillation, N (%)	4 (40)	7 (19)	2.19 (0.62–7.75)	0.23
History of electrical storm, N (%)	6 (60)	2 (5)	15.87 (3.87–65.05)	<0.001
Inducible ventricular fibrillation	3 (60)	11 (48)	1.36 (0.22–8.40)	0.74
Mutation in *SCN5A*, N (%)	1/8 (13)	3/21 (14)	1.00 (0.13–7.91)	0.99
Electrocardiography				
Heart rate, beats/min	63 ± 9	62 ± 10	1.30 (0.69–2.44)[b]	0.41
PR interval, ms	174 ± 35	176 ± 33	0.93 (0.77–1.12)[b]	0.43
QRS duration, ms	95 ± 14	96 ± 14	0.88 (0.53–1.46)[b]	0.63
Corrected QT interval, ms	390 ± 25	388 ± 27	1.20 (0.94–1.53)[b]	0.14
Conduction disorder[c]	3 (30)	11 (30)	1.32 (0.34–5.16)	0.69
Location of early repolarization, N (%)				
Inferior	6 (60)	28 (76)	0.42 (0.12–1.51)	0.18
Lateral	8 (80)	25 (68)	1.78 (0.38–8.41)	0.46
Right precordial	3 (30)	8 (22)	1.64 (0.42–6.48)	0.48
Multiple locations of early repolarization	5 (50)	21 (57)	0.73 (0.21–2.54)	0.63

[a] Per 10 unit decrement.
[b] Per 10 unit increment.
[c] Conduction disorder includes prolonged PR interval and prolonged QRS duration.

Table 3
Risk factors for arrhythmia recurrence, multivariate models.

	Hazard ratio (95% CI)	P-value
Male sex, N (%)	0.74 (0.09–6.23)	0.78
Age, years	1.83 (1.08–3.11)[a]	0.03
Family history of sudden death, N (%)	6.92 (1.16–41.12)	0.03
History of electrical storm, N (%)	16.06 (3.43–75.15)	<0.001

[a] Per 10 unit decrement.

incidence of cardiac arrest during the nocturnal period has been reported [11]. The heterogenic genetic background may explain the various triggers of the arrhythmia events.

It is important to assess risk of arrhythmia recurrences for appropriate management in patients with arrhythmia syndromes. In a recent population-based study, middle-aged individuals with inferior early repolarization, but not those with lateral early repolarization, have been shown to have an elevated risk of cardiac death [12]. In another study, the risk of electrical storm is increased in patients with idiopathic ventricular fibrillation who have early repolarization in both of the limb leads and the precordial leads [13,14]. However, in our study, the location or the number of leads where early repolarization occurred was not associated with the increased risk of arrhythmia recurrences. The amplitude and morphology of early repolarization have been associated with the risk of arrhythmia events [12,15,16], but it may be difficult to use for risk stratification because of variability of early repolarization [1].

Among clinical characteristics, age at arrhythmia onset, a history of electrical storm of ventricular fibrillation, and a family history of sudden death were associated with the increased risk of arrhythmia recurrences in this study. It seems reasonable that patients with severe diseases such as young onset and repetitive arrhythmias are at high risk for arrhythmia recurrences. In fact, a history of electrical storm has been associated with a high frequency of arrhythmia events in Brugada syndrome, another form of idiopathic ventricular fibrillation [17]. However, inconsistent with our results, a previous study has indicated that the frequency of family history is similar between patients with multiple episodes of ventricular fibrillation and those without [1], although the reason of this discrepancy is unclear.

In conclusion, we have shown clinical and electrocardiographic characteristics in idiopathic ventricular fibrillation associated with early repolarization and have identified the risk factors for arrhythmia recurrences.

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Dynamicity of the J-Wave in Idiopathic Ventricular Fibrillation With a Special Reference to Pause-Dependent Augmentation of the J-Wave

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Objectives This study evaluated the pause-dependency of the J-wave to characterize this phenomenon in idiopathic ventricular fibrillation (VF).

Background The J-wave can be found in apparently healthy subjects and in patients at risk for sudden cardiac death, and risk stratification is therefore needed.

Methods Forty patients with J-wave–associated idiopathic VF were studied for J waves with special reference concerning pause-dependent augmentation. J waves were defined as those ≥0.1 mV above the isoelectric line and were compared with 76 non-VF patients of comparable age and sex.

Results The J-wave was larger in patients with idiopathic VF than in the controls: 0.360 ± 0.181 mV versus 0.192 ± 0.064 mV ($p = 0.0011$). J waves were augmented during storms of VF (n = 9 [22.5%]), which was controlled by isoproterenol; they disappeared within weeks in 5 patients. In addition, sudden prolongation of the R-R interval was observed in 27 patients induced by benign arrhythmia, and 15 patients (55.6%) demonstrated pause-dependent augmentation (from 0.391 ± 0.126 mV to 0.549 ± 0.220 mV; $p < 0.0001$). In the other 12 experimental subjects and in the 76 control subjects, J waves remained unchanged. Pause-dependent augmentation of J waves was detected in 55.6% (sensitivity) but was specific (100%) in the patients with idiopathic VF with high positive (100%) and negative (86.4%) predictive values.

Conclusions Pause-dependent augmentation of J waves was confirmed in about one-half of the patients with idiopathic VF after sudden R-R prolongation. Such dynamicity of J waves was specific to idiopathic VF and may be used for risk stratification. (J Am Coll Cardiol 2012;59:1948–53) © 2012 by the American College of Cardiology Foundation

Early repolarization (ER) is defined as a slur or notch on the terminal part of the QRS complex with or without elevation of the ST-segment and is frequently observed in apparently healthy subjects (1–3). The prognosis of subjects with ER has been considered to be benign (4,5). However, J waves have been observed in association with idiopathic ventricular fibrillation (VF) (6,7), and recent studies have confirmed that ER is associated with idiopathic VF (8–10).

In population-based studies, Tikkanen et al. (11) and Haruta et al. (12) demonstrated that ER is a statistically significant risk for arrhythmic death, and a J-wave of a large amplitude (11) or a J-wave with a flat (horizontal or descending) ST-segment was shown to be a risk factor for sudden cardiac death (13). This risk was proven in cases of idiopathic VF (14). However, electrocardiogram (ECG) features that are able to distinguish "malignant" from "benign" J waves are still necessary for risk stratification.

Since our first reports of the association of the J-wave with idiopathic VF (6,7,15), we have studied pause-dependent augmentation of the J-wave and have been collecting case data regarding idiopathic VF. In this study,

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we analyzed the pause-induced dynamicity of the J-wave in patients with J-wave–associated idiopathic VF and compared this with control subjects to propose another characteristic of J waves in idiopathic VF.

Methods

Since 1992, we have collected data on 40 patients with J-wave–associated VF from 9 institutions, mainly from the Niigata University Hospital (Niigata, Japan). All of the patients met the following inclusion criteria for idiopathic VF: 1) documented episode of VF at the time of cardiac arrest; 2) absence of structural heart disease with normal cardiac function; 3) negative serological test result for inflammatory diseases; and 4) absence of coronary artery disease and a negative provocative test result for coronary spasms.

Patients with bundle branch block, intraventricular conduction delay, long or short QT interval (16,17), Brugada syndrome (18), or Wolff-Parkinson-White syndrome (19) were excluded. Pilsicainide was given to exclude Brugada syndrome, and coronary spasms in patients were excluded by a provocation test using acetylcholine or ergonovine maleate.

ECG analysis. J waves were defined as: 1) notches or slurs at the terminal portion of the QRS complexes; and 2) amplitude ≥0.1 mV above the isoelectric line in at least 2 contiguous leads. The location was classified as inferior (II, III, or aVF), left precordial (V_4 to V_6), right precordial (V_1 to V_3), or high lateral (I or aVL) sites. The amplitudes of J waves were measured after 5-fold magnification in the leads to reveal maximal amplitude, by 2 cardiologists who were blinded to the clinical findings (19).

To investigate the instantaneous dynamicity of J waves, the amplitude of the J-wave was measured in the beat immediately after a pause and compared with the mean J-wave amplitude measured in the 2 to 3 beats preceding the pause (Fig. 1). A pause represented sudden prolongation of the R-R interval that was induced by benign arrhythmias such as sinus arrest, sinoatrial block, atrioventricular block, or atrial or ventricular premature beats. If possible, the J-wave amplitude was measured in the beat after the pause to identify temporary changes. Concomitant changes in the ST- and T-wave morphology with J-wave augmentation were analyzed.

Abbreviations and Acronyms

ECG = electrocardiogram
ER = early repolarization
VF = ventricular fibrillation

J waves were observed after admission until discharge, and if VF developed in storms, isoproterenol was given.

As the control, the dynamicity of J waves was analyzed in 76 subjects who had J waves in the 12-lead ECG. They visited our hospitals for cardiac or noncardiac diseases but had no syncope or symptoms suggestive of serious arrhythmias such as ventricular tachycardia or VF. None had a family history of sudden cardiac death. Heart failure (New York Heart Association functional class >II) or organic heart diseases were excluded by ECG and echocardiography as well as clinical history. Other exclusion criteria were the same as in the experimental group. The dynamicity of J waves was analyzed on the standard ECGs or 12-lead Holter ECGs.

Data analysis. Patients were divided into 2 groups according to the presence of pauses. In the patients with pauses, the dynamicity of J waves and concomitant changes in the ST-segment were evaluated. The amplitudes of J waves were compared among the pre-, post-, and the beat next to the post-pause (Fig. 1). Temporary changes of the J waves were observed to the time of discharge. When VF recurred, the effects of isoproterenol were evaluated. Finally, the sensitivity, specificity, and predictive values of the pause-dependent J-wave augmentation were calculated.

Statistical analyses. Numerical values are presented as mean ± SD, and categorical variables are expressed as absolute numbers or percentages. The differences between groups were analyzed by using Wilcoxon or Mann-Whitney-Wilcoxon tests for continuous variables and the Pearson's chi-square test for categorical variables. Statistical analyses were performed with SPSS version 12.0 (SPSS

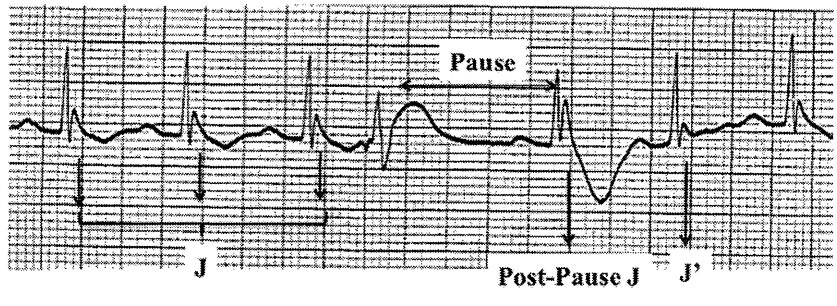

Figure 1 Measurements of the J-Wave Amplitude and ST-T

The amplitude of J waves was measured in the 2 to 3 beats before the pause and averaged and compared with those of the post-pause J waves. Amplitude was also measured in the beat next to the post-pause beat and compared with the baseline and post-pause amplitude of J waves. In the post-pause beat, the ST-T pattern was compared with that of the baseline values. Lead II was used.

Inc., Chicago, Illinois). A 2-sided $p < 0.05$ was considered statistically significant.

The study was approved by the ethics committee of Niigata University School of Medicine.

Results

J-wave in idiopathic VF. Forty patients displayed J waves: slurs or notches ≥0.1 mV in ≥2 contiguous leads. The mean age of the patients was 38 ± 14 years, and 37 (92.5%) were males. The QT and QTc intervals were all within normal ranges: 384 ± 25 ms and 401 ± 40 $ms^{1/2}$. The mean J-wave amplitude was 0.360 ± 0.181 mV. The J waves were located in the inferior region in 28 (70.0%), left precordial region in 19 (47.5%), right precordial region in 4 (10.0%), and high lateral region in 9 (22.5%) patients. Twenty (50.0%) patients exhibited J waves at >1 site (Table 1). Brugada syndrome was excluded by ECGs in all patients and by drug testing in 32 patients.

Pause-dependent changes in J waves could be analyzed in 27 (67.5%) of the 40 patients who experienced sudden prolongation of the R-R interval due to arrhythmias, and J-wave accentuation was observed in 9 (22.5%) patients before VF episodes. Isoproterenol was effective in controlling VF (Fig. 2). In 5 patients (12.5%), J waves disappeared within weeks. Of these, 3 patients had exhibited no J waves in the ECGs recorded 3 to 6 months previously. VF occurred between 8:00 PM and 6:00 AM in 26 (65.0%) patients, between 6:00 AM and 8:00 PM in 12 (30.0%) patients, and at both time intervals in 2 patients (5.0%). In the other patients (5.0%), VF developed during exercise in the daytime.

Pause-dependency of the J-wave. Among these 27 patients with pauses by benign arrhythmias, 15 (55.6%) demonstrated significant augmentation of the J waves, as shown in Table 2 and Figures 3 and 4: from 0.391 ± 0.126 mV to 0.549 ± 0.220 mV ($p < 0.0001$); the R-R interval was prolonged suddenly from 802 ± 204 ms to 1,450 ± 572 ms ($p < 0.0001$). The changes in J-wave amplitude were 0.185 ± 0.129 mV and ranged from 0.05 to 0.43 mV (0.5 to 4.3 mm).

The amplitude of the J waves in the beat next to the post-pause beat was measureable in 6 of 15 patients and was smaller than those of the baseline J waves as well as the augmented J waves: 0.325 ± 0.092 mV ($p = 0.0406$ and $p = 0.0065$, respectively). When J waves were augmented, the ST-segment was depressed from 0.10 ± 0.39 mV at baseline to −0.24 ± 0.53 mV after pauses ($p = 0.0015$). VF

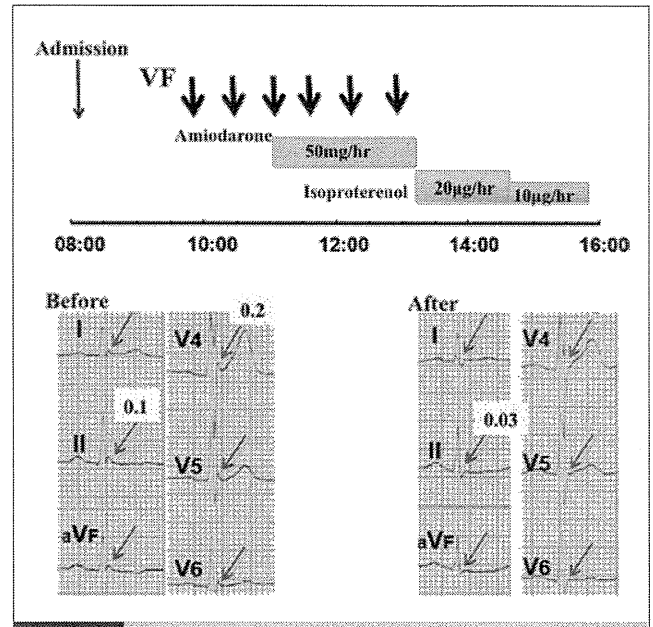

Figure 2 The Effects of Isoproterenol on VF and J Waves

Upper panel: A 48-year-old male had sudden loss of consciousness and was defibrillated. Amiodarone was noneffective, but isoproterenol given in drip suppressed the ventricular fibrillation (VF) **(arrows)**. **Lower panel:** J waves became less distinct after administration of isoproterenol **(arrows)**.

Table 1 Clinical Characteristics of the Patient and Control Groups

Characteristic	J Waves (+) (n = 40)	Control (n = 76)	p Value
Male patients	37 (92.5)	70 (92.1)	0.9398
Age (yrs)	38 ± 14	38 ± 14	0.8169
QT (ms)	384 ± 25	390 ± 30	0.0428
QTc ($ms^{1/2}$)	401 ± 40	404 ± 43	0.5128
R-R interval (ms)	855 ± 142	941 ± 138	0.0057
J-wave (mV)	0.360 ± 0.181	0.192 ± 0.064	0.0011
Location of J waves			0.5435
Inferior	28 (70.0)	65 (85.5)	
Left precordial	19 (47.5)	25 (33.9)	
Right precordial*	4 (10.0)	10 (13.2)	
High lateral	9 (22.5)	12 (15.8)	
>1 site	20 (50.0)	36 (47.4)	

Values are n (%) or mean ± SD. *Brugada syndrome was excluded from repeated electrocardiogram and/or drug testing.

Table 2 Comparisons of Patients With and Without Pause-Dependent Changes in J-Wave Amplitude

Characteristic	Pause-Dependency (+)	Pause-Dependency (−)	p Value
Male patients	15 (86.7)	12 (91.7)	—
Age (yrs)	37 ± 15	36 ± 16	0.8009
Pre-R-R interval (ms)	802 ± 204	809 ± 137	0.9783
Post-R-R interval (ms)	1,450 ± 572*	1,156 ± 175*	0.1570
Pre-J waves (mV)	0.391 ± 0.126	0.192 ± 0.079	<0.0001
Post-J waves (mV)	0.549 ± 0.220*	0.196 ± 0.080†	<0.0001
Location of J waves (%)			0.8497
Inferior	10 (66.7)	9 (75.0)	
Left precordial	9 (60.0)	7 (58.3)	
Right precordial	1 (6.7)	2 (16.7)	
High lateral	2 (13.3)	1 (8.3)	
>1 site	11 (73.3)	6 (50.0)	

Values are n (%) or mean ± SD. *$p < 0.0001$, pre- versus post-pause; †$p = 0.8377$, pre- versus post-pause.

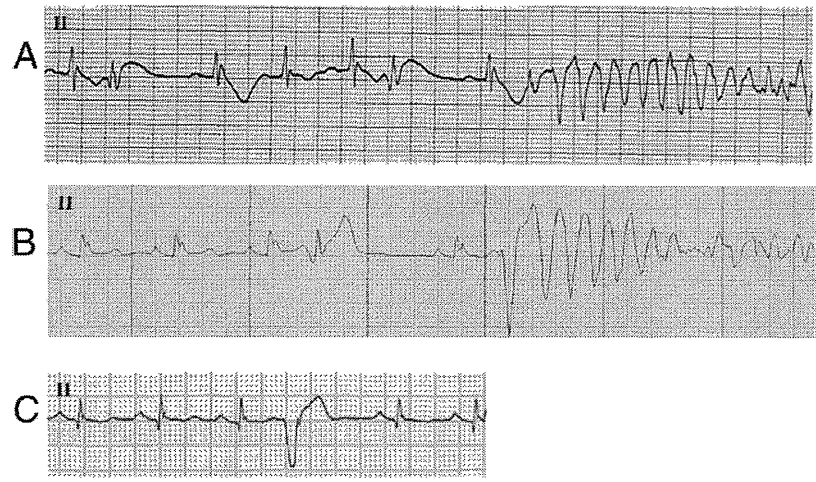

Figure 3 J Waves After the Pause

(A) Electrocardiogram (ECG) of the same patient discussed in Figure 1. Pause-induced augmentation of the J-wave was followed by ventricular fibrillation (VF) in this patient with idiopathic VF. J-wave augmentation was accompanied by ST-T displacement (lead II). The pause was produced by a premature ventricular beat. **(B)** ECG of a 49-year-old male with idiopathic VF. The premature ventricular beat produced a pause, but J-wave augmentation was not seen (lead II). VF was initiated by a premature beat that developed following a long R-R interval. **(C)** ECG of a 43-year-old male in the control group. There was no familial history of sudden cardiac death or cardiac disease. Premature ventricular contraction resulted in a pause but without a change in the J-wave (lead II).

occurred in 5 (33.3%) of 15 patients in storms after a short-long sequence. Isoproterenol was effective in controlling VF (Fig. 2).

In the remaining 12 (44.4%) of 27 patients, the J-wave remained unchanged (<0.05 mV), as shown in Figure 3: 0.192 ± 0.079 mV versus 0.196 ± 0.080 mV ($p = 0.8377$)

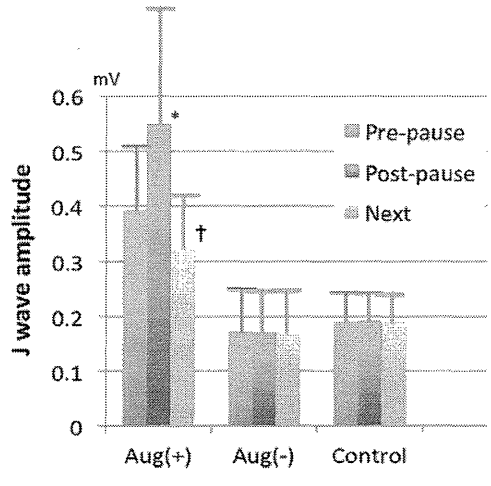

Figure 4 Comparisons of Pause-Dependent Changes in the J Waves Among the 3 Groups

In the subgroup with pause-dependent augmentation [Aug(+)], J-wave amplitude increased significantly among the post-pause beats (n = 15). In the beats coming just after the post-pause beats, the J-wave was diminished in amplitude (n = 6). No augmentation was induced by pauses in J waves in the subgroup without post-pause augmentation [Aug(–)] or in the control group. *$p < 0.001$ pre- versus post-pause. †$p = 0.0406$ and $p = 0.0065$ versus pre- and post-pause, respectively.

when the R-R interval was prolonged from 809 ± 137 ms to 1,156 ± 175 ms, as summarized in Table 2 ($p < 0.0001$). In 4 (33.3%) patients, VF developed and was controlled by isoproterenol.

The patients with pause-dependent augmentation of the J-wave amplitude were similar in age, sex, and J-wave locations to those without (Table 2). The baseline R-R intervals and their changes were similar between the 2 groups, but the pre- and post–J-wave amplitudes were larger in the patients with pause-dependent augmentation of the J-wave compared with those without ($p < 0.0001$).

Control group. In the 76 control subjects, sex and age were comparable to the 40 patients (Table 1). The locations of J waves were as follows: 65 (85.5%) in the inferior region, 25 (33.9%) in the left precordial region, 10 (13.2%) in the right precordial region, 12 (15.8%) in the high lateral region, and 36 (47.4%) at >1 site. The distribution pattern did not differ between the 2 groups.

The baseline R-R interval and the J-wave amplitude were different from the patient group (Table 1). When the R-R interval was prolonged from 941 ± 138 ms to 1,352 ± 342 ms by arrhythmias (n = 17), there was no augmentation of the J-wave amplitude (Figs. 3 and 4).

Sensitivity, specificity, and predictive values. Pause-dependent augmentation of the J waves was observed in 15 of 27 VF patients with a sensitivity of 55.6%, or 37.5% of the original 40 patients with J waves. Pause-dependent augmentation of J waves was observed only in patients with idiopathic VF. Both the specificity and the positive predictive values were 100%: the negative predictive value was 86.4% of the 27 patients, or 75.2% of the original 40