diminished during treadmill exercise test (23 μV in lead II; Figure 2C) even with the comparable HR to the previous treadmill test. Compared to the previous 24-hour ambulatory ECG recording, the total number of PVCs decreased: single PVC, 10,854/day; couplet PVCs, 245/day; triplet PVCs, 9/day; and quadrat PVCs, 1/day.

Discussion

In this case, the administration of flecainide in addition to atenolol was effective to reduce T-wave alternans during exercise testing, concomitant with the shortening of QT interval and the substantial reduction of PVCs.

T-wave alternans reflects beat-to-beat fluctuation in T-wave shape and amplitude. T-wave alternans in microvolt levels was associated with increased risk of ventricular tachyarrhythmias and occurrence of sudden cardiac death in a clinical setting.[4 5] T-wave alternans represents temporal and/or spatial dispersion of ventricular repolarization. The relation between action potential duration and preceding diastolic interval, which is called restitution property, contributes to temporal alteration in action potential duration and conduction velocity. Spatial heterogeneity of repolarization may result in discordant alteration, which occasionally causes 2:1 conduction to occur, thus facilitating reentry. Another mechanism of T-wave alternams is that alternation of cytosolic calcium may underlie action potential duration alternans, because intracellular calcium cycling affects action potential duration.[6, 7] Intracellular Ca^{2+} cycling becomes alternating under physiologic or pathophysiological conditions, leading to T-wave alternans. In addition, excessive cytosolic calcium induces afterdepoarizations, which has potential to initiate ventricular tachyarrhythmias. In our case, the number of PVCs on treadmill exercise test and Holter ECG recording decreased parallel with reduction of the magnitude of T-wave alternans.

The primary ion channel abnormality in Andersen-Tawil syndrome is a reduction of the inwardly rectifying potassium current, IK_1 channel. This causes prolongation in the

terminal phase of the cardiac action potential triggering early afterdepolarizations. The depressed IK_1 function also leads to cellular calcium overload through sodium-calcium exchanger, causing late afterdepolarizations. It was reported that flecainide was effective to suppress ventricular arrhythmias in Andersen-Tawil syndrome.[1-3] The mechanism by which flecainide suppresses ventricular tachyarrhythmias in Andersen-Tawil syndrome is thought as follows: 1) reduction of cell excitability by decreased Na^+ current, 2) increase of Na^+ excretion via Na^+-Ca^{2+} exchanger, 3) decrease of sarcoplasmic reticulum calcium overload. Thereby, these effects may lead to suppression of T-wave alternans and triggered ventricular activity.

Acknowledgements

Nothing to disclose

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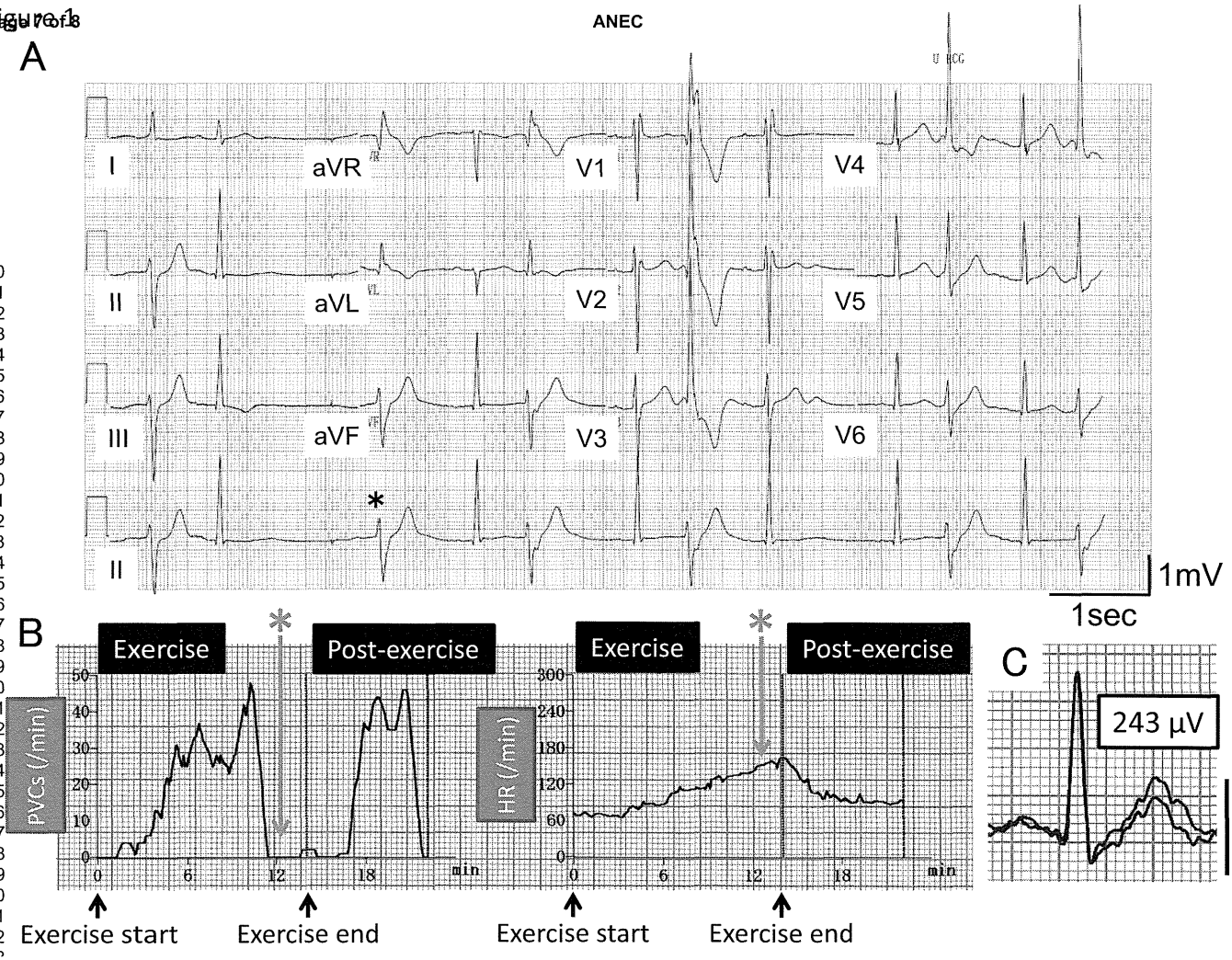
Figure Legends

Figure 1. Recordings taken under the administration of atenolol (50 mg/day) alone. **A**, Resting 12-lead ECG recording. **B**, Frequency of PVCs and HR during treadmill exercise testing. Asterisk points the time when T-wave alternans was measured. **C**, T-wave alternans in lead V_5 during exercise. The number indicates the magnitude of T-wave alternans. Vertical bar indicates 1 mV.

Figure 2. Recordings taken after the administration of flecainide (100 mg/day) in addition to atenolol (50 mg/day). **A**, Resting 12-lead ECG recording. **B**, Frequency of PVCs and HR during treadmill exercise testing. Asterisk points the time when T-wave alternans was measured. **C**, T-wave alternans in lead V_5 during exercise. The number indicates the magnitude of T-wave alternans. Vertical bar indicates 1 mV.

Figure 1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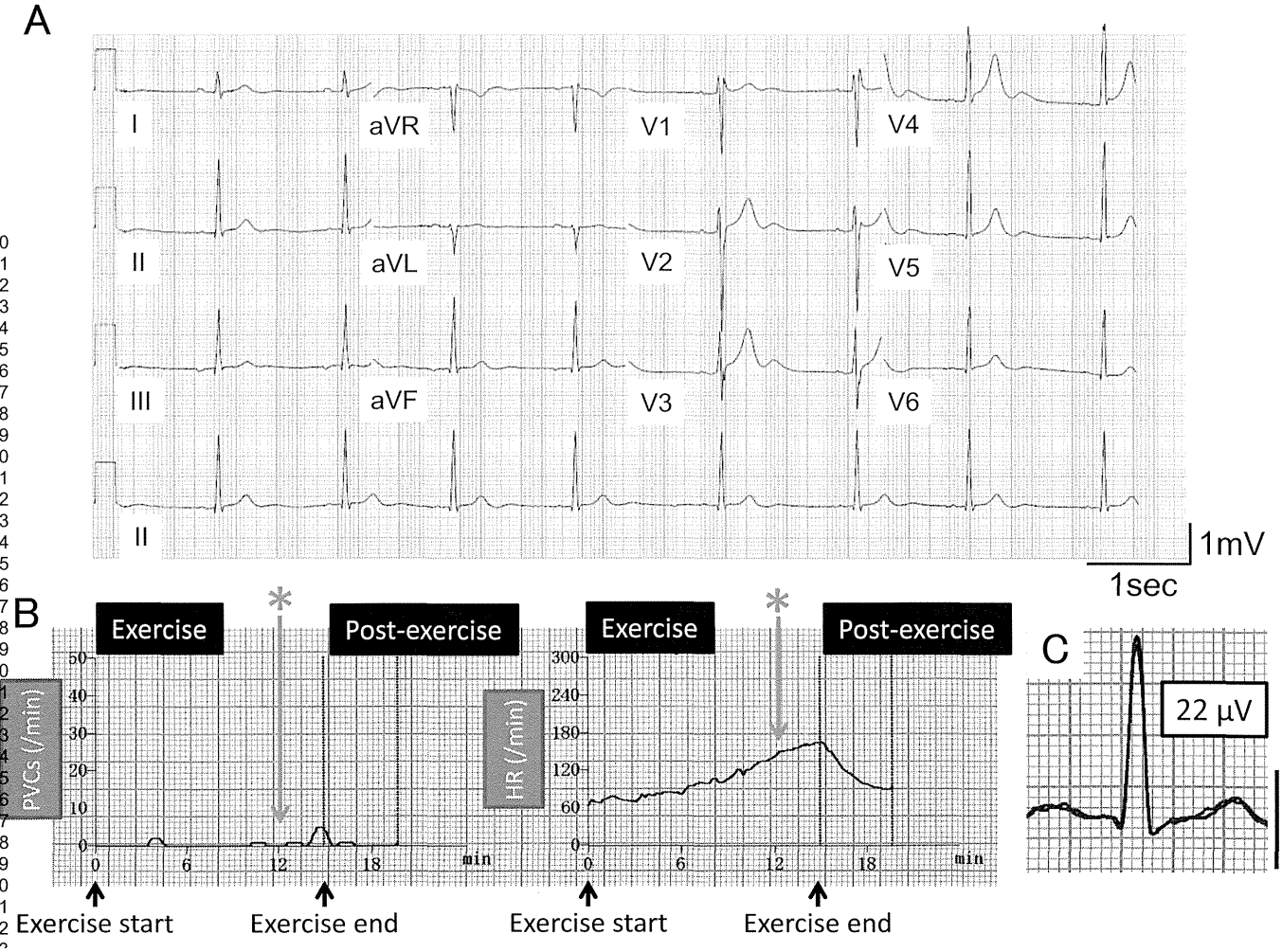
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C
22 μV

Efficacy and safety of flecainide for ventricular arrhythmias in patients with Andersen-Tawil syndrome with *KCNJ2* mutations

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BACKGROUND Andersen-Tawil syndrome (ATS) is an autosomal dominant genetic or sporadic disorder characterized by ventricular arrhythmias (VAs), periodic paralyses, and dysmorphic features. The optimal pharmacological treatment of VAs in patients with ATS remains unknown.

OBJECTIVE We evaluated the efficacy and safety of flecainide for VAs in patients with ATS with *KCNJ2* mutations.

METHODS Ten ATS probands (7 females; mean age 27 ± 11 years) were enrolled from 6 institutions. All of them had bidirectional VAs in spite of treatment with β-blockers (n = 6), but none of them had either aborted cardiac arrest or family history of sudden cardiac death. Twenty-four-hour Holter recording and treadmill exercise test (TMT) were performed before (baseline) and after oral flecainide therapy (150 ± 46 mg/d).

RESULTS Twenty-four-hour Holter recordings demonstrated that oral flecainide treatment significantly reduced the total number of VAs (from 38,407 ± 19,956 to 11,196 ± 14,773 per day; $P = .003$) and the number of the longest ventricular salvos (23 ± 19 to 5 ± 5; $P = .01$). At baseline, TMT induced nonsustained ventricular tachycardia (n = 7) or couplets of premature ventricular complex (n = 2); treatment with flecainide completely (n = 7) or partially (n = 2) suppressed these exercise-induced VAs ($P = .008$). In contrast, the QRS duration, QT interval, and U-wave amplitude of the electrocardiogram were not altered by flecainide therapy. During a mean follow-up of 23 ± 11 months, no patients developed syncope or cardiac arrest after oral flecainide treatment.

CONCLUSION This multicenter study suggests that oral flecainide therapy is an effective and safe means of suppressing VAs in patients with ATS with *KCNJ2* mutations, though the U-wave amplitude remained unchanged by flecainide.

KEYWORDS Andersen-Tawil syndrome; Long QT; Flecainide; Ventricular arrhythmia; Mutation

ABBREVIATIONS **APD** = action potential duration; **ATS** = Andersen-Tawil syndrome; **CPVT** = catecholaminergic polymorphic ventricular tachycardia; **ECG** = electrocardiogram/electrocardiographic; $\mathbf{I_{K1}}$ = inward rectifying K^+ current; **QTc interval** = corrected QT interval by Bazett's formula; **QUc interval** = corrected QU interval by Bazett's formula; **RyR2** = ryanodine receptor 2; **TMT** = treadmill exercise test; **VA** = ventricular arrhythmia; **VT** = ventricular tachycardia

(Heart Rhythm 2015;12:596–603)

This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas (grant no. 22136011 A02, to Dr Aiba), a Grant-in-Aid for Scientific Research (C) (grant no. 24591086, to Dr Aiba) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan, and a Research Grant for Cardiovascular Diseases (grant nos. H24-033 and H26-040, to Dr Aiba, Dr Miyamoto, Dr Kamakura, Dr Horie, and Dr Shimizu) from the Ministry of Health, Labor and Welfare, Japan. **Address reprint requests and correspondence:** Dr Takeshi Aiba, Division of Arrhythmia and Electrophysiology, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, 5-7-1, Fujishiro-dai, Suita, Osaka 565-8565, Japan. E-mail address: aiba@hsp.ncvc.go.jp. Dr Wataru Shimizu, Department of Cardiovascular Medicine, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan. E-mail address: wshimizu@nms.ac.jp.

1547-5271/$-see front matter http://dx.doi.org/10.1016/j.hrthm.2014.12.009

Introduction

Andersen-Tawil syndrome (ATS) is a heterogeneous, autosomal dominant genetic or sporadic disorder characterized by ventricular arrhythmias (VAs), periodic paralyses, and dysmorphic features.[1,2] ATS is a channelopathy linked to mutations in the *KCNJ2* gene encoding the α subunit of Kir2.1.[3–6] Patients with ATS often have a variety of VAs such as premature ventricular complex, polymorphic ventricular tachycardia (VT), and bidirectional VT. Although the cycle length of VAs in patients with ATS is relatively long and fatal cardiac event is rare, VAs often occur and lead to symptoms such as syncope and palpitations.[7] Moreover, sudden cardiac death and tachycardia-induced cardiomyopathy in patients with ATS have also been reported.[8,9] Thus, VA suppression is clinically important for patients with ATS.

Although β-blockers and calcium channel blockers have been used to treat VAs in patients with ATS,[7,10–12] these drugs do not sufficiently suppress VAs. As an alternative, empirical case reports[7,8,13] have suggested that flecainide might be effective for the suppression of VAs in patients with ATS. To date, however, there are few systematic evaluations of oral flecainide as a treatment of VAs in patients with ATS. Accordingly, this study aimed to assess the efficacy and safety of flecainide for VAs in patients with ATS with *KCNJ2* mutations.

Methods

Study population

The study population consisted of 10 unrelated ATS probands from 6 institutions in Japan who were treated with oral flecainide. We prospectively enrolled patients with ATS who were expected to use flecainide as a treatment of VAs. Patients who could not perform treadmill exercise test (TMT) and were more than 80 years old were excluded from this study. ATS was diagnosed on the basis of clinical features such as VAs, episodes of periodic paralysis, and/or dysmorphic features as well as the presence of *KCNJ2* genetic mutations. Cardiac involvement was determined on the basis of the presence of VAs (premature ventricular complex, polymorphic VT, and/or bidirectional VT), prolongation of the corrected QT (QU) interval (QTc [QUc] interval), and/or enlargement of the U wave on a 12-lead electrocardiogram (ECG).[1–6] The periodic paralysis was diagnosed according to the standard criteria.[14] Dysmorphology was defined as the presence of 2 or more of the following: (1) low-set ears, (2) hypertelorism, (3) small mandible, (4) clinodactyly, and (5) syndactyly.[4]

To evaluate the efficacy of flecainide, 24-hour Holter recording and TMT were performed in all patients before (baseline) and after flecainide therapy. Dose of flecainide was determined by the physician who treated the patient in this study. Physicians usually administered 2–3 mg/kg of flecainide and titrated according to the result of Holter recording, TMT, blood concentration of flecainide, and patient intention. All participants provided written informed consent according to the protocol approved by the institutional review board (M24-028-2).

Twelve-lead ECG

A 12-lead ECG was recorded at a paper speed of 25 mm/s during sinus rhythm in all patients in the supine resting state. The R-R, PR, QT, QU, and Tpeak-Upeak intervals as well as QRS duration were measured. The QT interval was defined as the period from the onset of the QRS complex to the end of the T wave. The U wave was defined as an early diastolic deflection after the end of the T wave,[15] and an enlarged U wave was defined according to the following criteria: (1) wave amplitude $\geq$ 0.2 mV or (2) amplitude larger than the preceding T wave. T-wave and U-wave durations were defined as the periods from the onset of the T wave and U wave to the end of the T wave and U wave, respectively.[15] The end of the T wave and that of the U wave were the points at which tangents drawn to the steepest downslopes of the T wave and U wave, respectively, crossed the isoelectric line. T-wave and U-wave amplitudes and durations were also measured. The QU interval was defined as the period from the onset of the QRS complex to the end of the U wave. The amplitude of the T wave or U wave was measured at each highest amplitude lead, whereas the U/T-wave ratio was calculated at the highest amplitude U-wave lead. The QT and QU intervals were corrected by applying Bazett's formula (QTc and QUc intervals, respectively).[6] Polymorphic VT was defined as a VT with an irregularly variable axis of the QRS complex. Bidirectional VT was defined as a VT with a beat-to-beat alternation of the QRS axis.[16]

Mutation analysis

The protocol for genetic analysis was approved by the institutional ethics committee and performed under its guidelines (M24-031-4). All patients provided informed consent before the genetic analysis. Genomic DNA was isolated from whole blood using a DNA analyzer (QIAGEN GmbH, Hilden, Germany).[17] Genetic screening for *KCNJ2* was performed by using the direct sequencing method (ABI 3730 DNA Analyzer, Life Technologies, Carlsbad, CA). The complementary DNA sequence numbering was based on the GenBank reference sequence NM_000891.2 for *KCNJ2*.

Holter recording

A 24-hour Holter recording was performed in all patients before and after flecainide therapy. The following parameters were used to assess the clinical efficacy and safety of flecainide: (1) total number of VAs, (2) number of the longest ventricular salvos and cycle length during the VT, and (3) number of episodes of VT ($\geq$3 successive VAs).

TMT

The TMT using a standard or modified Bruce protocol was performed before and after the initiation of flecainide therapy. The following parameters were used to assess the clinical efficacy of flecainide: (1) number of the longest

ventricular salvos and cycle length of the VT, (2) maximum number of VAs during a 10-second period, and (3) VA score (1–4), which is defined as the severity of the worst VA during exercise as described previously.[18] 1 = no or isolated VA; 2 = bigeminal VA and/or frequent VA (≥10 per minute); 3 = couplet; and 4 = VT (≥3 successive VAs). The VA score of 1 was considered to indicate complete suppression of VAs. Less dramatic improvements in VA scores were considered to indicate partial suppression.

Follow-up

All patients were followed up at outpatient clinics every 1–3 months, and a 12-lead ECG was recorded. We investigated the incidence of arrhythmic events, defined as syncope, aborted cardiac arrest, or sudden cardiac death, and the side effects of flecainide through examination of medical history, physical findings, blood tests, 12-lead ECG, chest radiograph, and/or echocardiograph.

Statistical analysis

Continuous variables are expressed as mean ± SD or numbers and percentages, as appropriate. The Student *t* test was used to compare continuous variables, and the χ^2 test was used to compare categorical variables. A P value of $<.05$ was considered statistically significant.

Results

Patient characteristics

The study population consisted of 10 genotype-confirmed ATS probands who received oral flecainide from 6 Japanese institutes (Table 1). Seven patients were female probands. Their mean age at the beginning of flecainide therapy was 27 ± 11 years (range 9–47 years). Our cohort includes 5 patients (patients 3–6 and 8) with a family history of ATS, whose genotypes and phenotypes are presented in the Online Supplemental Figure. Eight patients (80%) showed dysmorphic features, and 2 (20%) had a history of periodic paralysis. Two patients (20%) had both dysmorphic features and periodic paralysis.

No structural heart disease was observed by echocardiography in any patient. All patients had VAs documented by 12-lead ECG, Holter recording, and/or exercise testing. Bidirectional VT had been documented in all patients. Six patients were symptomatic, exhibiting syncope (n = 5), palpitations (n = 2), or dizziness (n = 2). There were no cases of aborted cardiac arrest or with family history of sudden cardiac death.

Nine patients were found to have missense mutations in 4 residues (R67G/Q/W, R218Q/W, G300V, and G301T), and 1 has an insertion (76insT) in the *KCNJ2* gene. All these are located in the N or C terminus, and 7 of these mutations have been previously reported.[19]

Medical therapy

A total of 7 patients had been treated with multiple drugs before flecainide. The drugs previously administered were β-blockers, namely, bisoprolol (n = 2), atenolol (n = 2), propranolol (n = 1), and propranolol + metoprolol (n = 1); sodium channel blockers, namely, disopyramide (n = 1), mexiletine (n = 1), and pilsicainide (n = 1); and the calcium channel blocker verapamil (n = 1). All of them failed to suppress VAs.

Flecainide was administered at a dose of 200 mg/d in 3 patients, at 150 mg/d in 2, and at 100 mg/d in 5 (mean dosage 140 ± 46 mg/d). In 4 patients, β-blockers were continued after flecainide.

Twelve-lead ECG

Figure 1 shows representative 12-lead ECGs of a 24-year-old patient (patient 4) at baseline (Figures 1A and 1B) and after flecainide therapy (Figure 1C). Although this patient had been treated with propranolol (60 mg/d) and verapamil (240 mg/d), frequent VAs including bidirectional VT were still

Table 1 Clinical, mutational, and electrocardiographic characteristics of all probands with Andersen-Tawil syndrome

Patient no.	Mutation	Age/ sex	BW (kg)	Symptom	Syncope	FH	Dysmorphism/ periodic paralysis	Bi-VT and/or poly-VT	Flecainide dose (mg/d, mg/kg)	Flecainide concentration (ng/mL)	Medical treatment at baseline/concomitant with flecainide
1	M301T	27/F	42	+	−	−	+/−	+	150, 3.6	278	Bisoprolol/bisoprolol
2	R67W	41/F	57	+	+	−	+/−	+	200, 3.5	NA	Bisoprolol, disopyramide/ bisoprolol, nicorandil
3	G300V	29/F	47	+	+	+	+/−	+	200, 4.3	507	Atenolol/atenolol
4	G300V	24/M	61	+	+	+	+/−	+	200, 3.3	324	Propranolol, verapamil/ propranolol
5	R218W	13/M	35	−	−	+	+/+	+	100, 2.9	NA	Propranolol, metoprolol/ none
6	R67Q	23/M	53	−	−	+	−/−	+	100, 1.9	NA	Atenolol, mexiletine/ none
7	R218Q	27/F	46	−	−	−	−/−	+	100, 2.2	347	None/none
8	R218W	47/F	46	+	+	+	+/+	+	150, 3.3	532	Pilsicainide/none
9	76insT	9/F	26	−	−	−	+/−	+	100, 3.8	NA	None/none
10	R67G	25/F	45	+	+	−	+/−	+	100, 2.2	NA	None/none

Bi-VT = bidirectional ventricular tachycardia; BW = body weight; F = female; FH = family history; M = male; NA = not applicable; Poly-VT = polymorphic ventricular tachycardia; + = presence; − = absence.

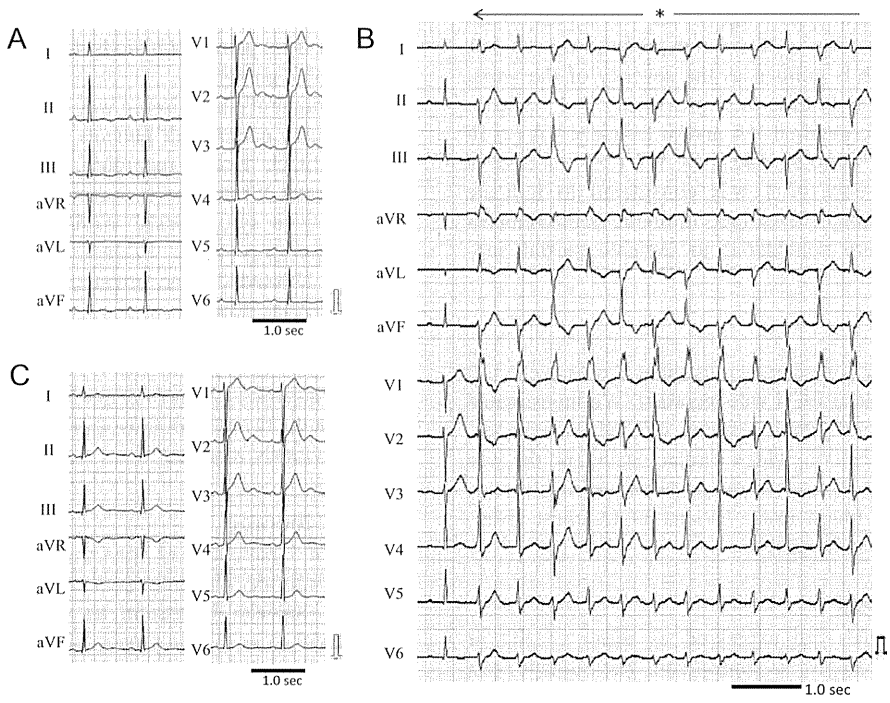

Figure 1 Twelve-lead ECGs recorded from a 24-year-old male proband (patient 4) with *KCNJ2* mutations before (panels A and B) and after (panel C) flecainide therapy. **A:** Before flecainide therapy (propranolol 60 mg/d and verapamil 240 mg/d), the PR interval (280 ms) indicated first-degree atrioventricular block, the corrected QT interval was normal (<440 ms), and the U wave was widely distributed in leads II, aVF, and V_1-V_5. An enlarged U wave (wave amplitude ≥0.2 mV) was observed in leads V_2 and V_3, and the corrected QU interval was 663 ms. **B:** Bidirectional VT (cycle length 480 ms) in the 12-lead ECG at baseline (asterisk). The QRS complexes showed alternating polarities, and a right bundle branch block pattern was shown in VT beats. **C:** Twelve-lead ECG after the administration of flecainide (200 mg/d) in addition to propranolol (60 mg/d). Verapamil was discontinued after VA suppression by flecainide in this patient, and the PR interval was reduced. An enlarged U wave persists and remains widely distributed even after VA suppression by the administration of flecainide. ECG = electrocardiogram; VA = ventricular arrhythmia; VT = ventricular tachycardia.

observed (Figure 1B). After the administration of flecainide, the total number of VAs was remarkably reduced from 10,767 to 36 per day, although the U-wave amplitude and its distribution on the 12-lead ECG were unchanged.

Table 2 summarizes the changes in ECG parameters in all patients with ATS. Flecainide therapy caused no significant difference in heart rate, PQ interval, QRS duration, QTc interval, QUc interval, T- and U-wave amplitudes and durations, frequency of the enlarged U wave, or number of leads recording U waves. The U/T-wave ratio was also unchanged after flecainide therapy.

Holter recording

Twenty-four-hour Holter recordings demonstrated that flecainide therapy significantly and consistently reduced the total number of VAs (38,407 ± 19,956 to 11,196 ± 14,773 per day; $P = .03$; Figure 2A) and the number of the longest ventricular salvos (23 ± 19 to 5 ± 5 per day; $P = .01$; Figure 2B). Flecainide significantly reduced the number of VT episodes (1175 ± 1163 to 60 ± 167; $P = .008$): in 7 patients, the total number of VAs was reduced by more than 70% from the number at baseline; in 4 of these, flecainide completely eliminated VT. Flecainide therapy did not alter the cycle length of VAs (458 ± 72 to 488 ± 58 ms; $P = .35$). Several Holter recordings or TMTs after flecainide and/or concomitant medication (β-blockers and verapamil) were performed in 6 patients (patients 1–5 and 8). As shown in the Online Supplemental Table, the total number of VAs per day and the longest ventricular salvos per day of each time were consistently reduced after flecainide therapy.

TMT

Exercise capacity (peak workload) was not different at baseline and after flecainide therapy (12.5 ± 4.2 METS vs 13.3 ± 4.1 METS; $P = .68$). The peak heart rate during exercise was also unchanged at baseline and after flecainide therapy (155 ± 19 beats/min vs 160 ± 23 beats/min; $P = .60$). Figure 3 shows a representative 12-lead ECG of patient 4 during the TMT before (baseline) (Figure 3A) and after (Figure 3B) flecainide therapy. In this case, flecainide therapy remarkably suppressed an exercise-induced bidirectional VT. In summary, the VA score during the TMT was improved in 9 of 10 patients after flecainide therapy. In particular, VA scores of 7 patients were improved by more than 2 levels (Figure 4A). Furthermore, the maximum number of VAs in any 10 seconds during the TMT was significantly reduced after flecainide therapy (Figure 4B). Several TMTs after flecainide therapy were also performed

Table 2 Electrocardiographic changes after flecainide therapy in patients with Andersen-Tawil syndrome

Variable	Baseline	Flecainide	*P*
Heart rate (beats/min)	68 ± 15	69 ± 17	.97
PQ interval (ms)	173 ± 41	178 ± 24	.74
QRS duration (ms)	93 ± 19	98 ± 18	.55
QTc interval (ms)	432 ± 26	448 ± 34	.26
QUc interval (ms)	667 ± 43	679 ± 35	.50
T-wave amplitude (mV)	0.55 ± 0.25	0.43 ± 0.20	.24
T-wave duration (ms)	290 ± 34	288 ± 43	.91
U-wave amplitude (mV)	0.21 ± 0.05	0.23 ± 0.05	.49
U-wave duration (ms)	215 ± 22	213 ± 25	.85
U/T-wave amplitude ratio at the highest amplitude U-wave lead	0.50 ± 0.18	0.62 ± 0.20	.17
Enlarged U-wave, no. of patients (%)	8 (80)	9 (90)	.53
U-wave distribution, no. of leads	4.6 ± 1.9	4.7 ± 1.9	.91

Values are presented as mean ± SD or as otherwise indicated.
QTc interval = corrected QT interval by Bazett's formula; QUc interval = corrected QU interval by Bazett's formula.

in 4 patients (patients 1–4), and VA scores and the maximum number of VAs during 10 seconds were reduced consistently in 3 patients except for patient 3 (see the Online Supplemental Table). These findings strongly suggested that flecainide may suppress exercise-induced lethal VAs in patients with ATS.

Follow-up

During a mean follow-up of 23 ± 11 months after starting oral flecainide therapy, no patients had arrhythmic events. No symptoms such as syncope or palpitations were observed in any patient. One patient experienced leg fatigue after the administration of flecainide at 200 mg/d; this symptom was improved after the dose was reduced to 150 mg/d. No other side effects were observed in any patient during follow-up.

Discussion

Main findings

There were several findings in this study. First, flecainide therapy decreased the number of VAs and the maximum number of VA salvos, although it caused no significant changes in any ECG parameters. It was thus effective for the suppression of VAs in patients with ATS with *KCNJ2* mutations. Second, flecainide therapy was safe in patients with ATS over a middle-term follow-up period. Therefore, flecainide may reduce the risk of sudden cardiac death in patients with ATS.

Medication for VAs in patients with ATS with KCNJ2 mutations

KCNJ2 encodes the α subunit of inward rectifier potassium channels (Kir2.1), which carry a critical component of the cardiac inward rectifying K^+ current (I_{K1}).[20,21] The I_{K1} regulates the terminal phase of repolarization and maintains the resting membrane potential in cardiomyocytes and skeletal muscle.[20,22,23] In this study, we observed 8 mutations (including 3 novel ones) in 5 residues of the *KCNJ2* gene. Although we did not perform a functional analysis, most of these (R67Q, R67W, R218Q, R218W, and G300V) have been reported as loss-of-function mutations resulting in dominant-negative suppression of Kir2.1 channel function,[3–6] which prolongs the action potential duration (APD) across the ventricular wall and destabilizes the resting membrane

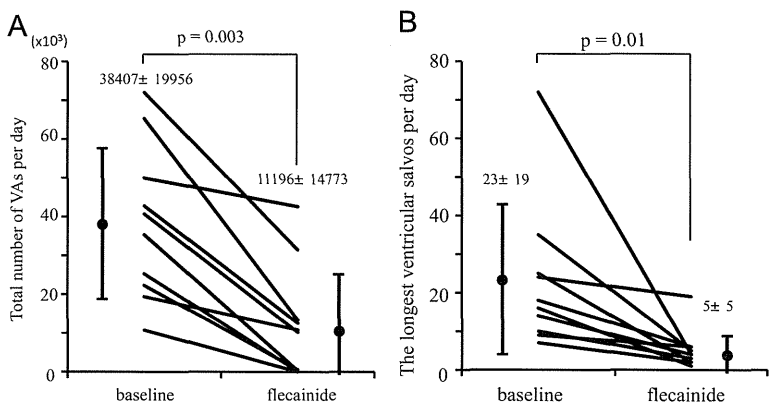

Figure 2 Total number of VAs and number of the longest ventricular salvos per day from a 24-hour Holter recording before (baseline) and after flecainide therapy. **A:** The total number of VAs per day was reduced after flecainide therapy in all patients, most notably in 7 patients whose VA counts were reduced by more than 70% from the baseline level. **B:** The number of the longest ventricular salvos per day was also reduced after flecainide therapy in all patients. Abbreviations as in Figure 1.

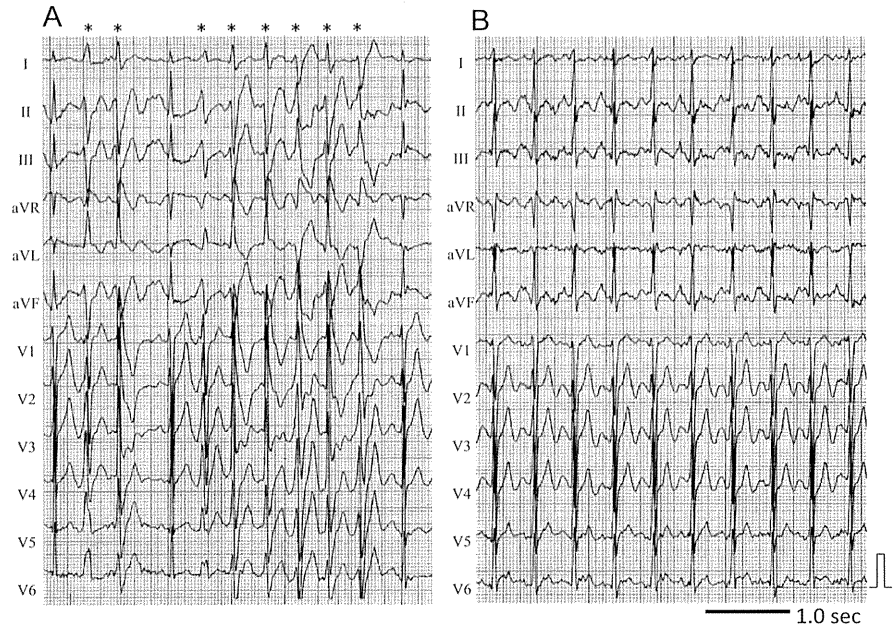

Figure 3 Twelve-lead ECG during the TMT before (baseline) (**A**) and after (**B**) flecainide therapy in a patient with ATS (patient 4). **A:** At baseline (propranolol 60 mg/d and verapamil 240 mg/d), frequent premature ventricular complexes and nonsustained VTs (the longest ventricular salvo was 6 beats) (asterisk) were observed during exercise. **B:** Flecainide (200 mg/d) in addition to propranolol (60 mg/d) suppressed exercise-induced VAs. TMT = treadmill exercise test; other abbreviations as in Figure 1.

potential.[4,24] APD prolongation also elicits an increase in calcium influx, leading to intracellular calcium overload. In addition, subsequent spontaneous calcium release may depolarize the membrane potential to the threshold of L-type calcium channel via transient inward currents carried by the Na^{+}-Ca^{2+}exchanger.[4,25,26] APD prolongation, instability of the resting membrane potential, and calcium overload result in the onset of delayed afterdepolarization.[4,24]

β-Blockers and calcium channel blockers had been regarded as the principal drugs for VAs in patients with ATS.[10,11,27] Studies on successful therapy using β-blockers and/or calcium channel blockers in patients with ATS were, however, limited to case reports, and the efficacy of these drugs were controversial. Bokenkamp et al[13] reported that β-blockers, the mainstay for other types of long QT syndrome, are ineffective for the suppression of VAs in patients with

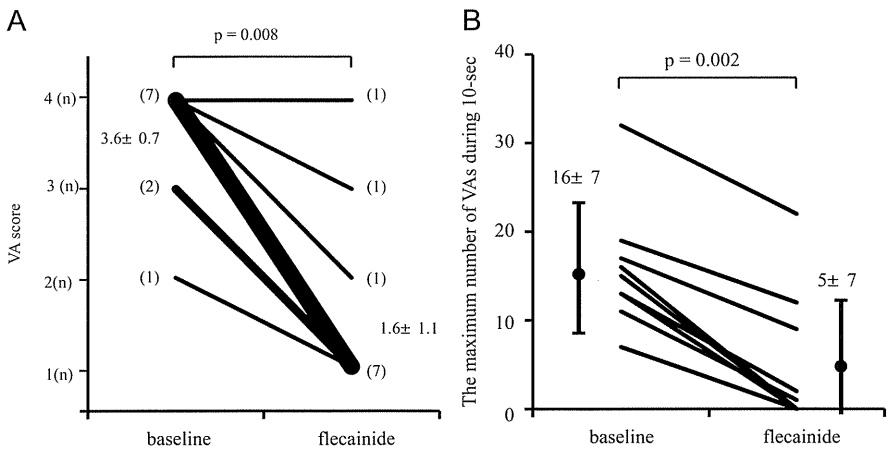

Figure 4 Effect of flecainide on exercise-induced VAs. **A:** VAs during the TMT are shown by VA scores: 1 = no or isolated VAs, 2 = bigeminal VAs and/or frequent VAs (≥10 per minute), 3 = couplets, and 4 =VT (≥3 successive VAs). VAs during the TMT are compared before (baseline) and after flecainide therapy in probands with ATS with *KCNJ2* mutations. The line thickness indicates the number of patients. The VA score was improved by flecainide therapy in 9 of 10 patients (90%). Flecainide therapy reduced the VA score from 3.6 ± 0.7 to 1.6 ± 1.1 ($P = .008$). **B:** The maximum number of VAs during any 10-second interval during the TMT at baseline and after flecainide therapy. Flecainide therapy reduced the maximum number of VAs from 16 ± 7 to 5 ± 7 ($P = .002$) during any 10-second interval. Abbreviations as in Figures 1 and 3.

ATS. Similarly, the efficacy of calcium channel blockers is uncertain; in addition, calcium channel blockers have risk of torsades de pointes and syncope in patients with ATS.[10,11,13] In this study, although β-blockers and/or calcium channel blockers were administered in 6 patients to prevent VAs, these drugs could not suppress VAs. Flecainide is a potent antiarrhythmic drug that can be used to suppress VAs in patients with ATS,[8,13] although a systematic evaluation of its efficacy and safety during follow-up remained unclear. Delannoy et al[7] retrospectively investigated cardiac characteristics and prognosis in patients with ATS, in which the prognosis in patients with ATS was relatively good, and the combination therapy of flecainide with β-blockers was efficient to prevent severe arrhythmic events. A recent case report[28] suggested that the combined use of verapamil and flecainide was effective for the suppression of VAs in patients with ATS.

Here, we prospectively demonstrated the efficacy of flecainide in detail by using 24-hour Holter recording and TMT as well as its safety over a middle-term follow-up period in patients with ATS. In patient 2, the combination therapy of flecainide and β-blockers may be more effective for the suppression of VAs in patients with ATS than was flecainide or β-blocker treatment alone (see the Online Supplemental Table). Although we showed that VAs were suppressed by flecainide treatment in patients with ATS, the reduction of VAs might not be sufficient in some patients. One possible explanation was that the dose of flecainide might be smaller in these patients because flecainide dose-dependently improved VAs in 3 (patients 1, 4, and 8) of 4 patients, although flecainide was less effective in 1 patient (patient 3) even at the higher dose (see the Online Supplemental Table).

Mechanisms of flecainide therapy

The mechanism underlying the suppression of VAs by flecainide in patients with ATS is not fully understood. One possible explanation is that the inhibition of the sodium channel may directly suppress a trigger of arrhythmia and/or indirectly inhibit the Na^{+}-Ca^{2+} exchange, resulting in reduced likelihood of intracellular calcium overload and decreased delayed afterdepolarization.[29] As an alternative explanation, Caballero et al[21] have reported that flecainide increases Kir2.1 channels, which increase I_{K1} as recorded in ventricular myocytes. In this study, however, as flecainide did not normalize the QU interval or the U-wave amplitude, the effect of flecainide on increasing I_{K1} seems to be not directly involved in the suppression of VAs.

Another possible mechanism underlying the antiarrhythmic effect of flecainide is a direct effect on ryanodine receptor 2 (RyR2). Some *KCNJ2* mutation carriers lack the ATS phenotype but share the catecholaminergic polymorphic ventricular tachycardia (CPVT).[17,19,30] Although it is not clear whether exercise is a trigger of VAs in patients with ATS,[31] 5 of 10 patients had experienced syncope during exercise in this study.

Similar exercise-induced bidirectional VT is often observed in both patients with ATS and CPVT. Watanabe et al[32] reported that flecainide not only blocked cardiac sodium channels but also directly inhibited RyR2, thus preventing CPVT. These findings suggest that flecainide may affect calcium leakage from RyR2, resulting in the suppression of VAs in patient with ATS as well as the suppression in patients with CPVT.

Study limitations

First, this study have evaluated the efficacy of flecainide in the suppression of VAs using 24-hour Holter recording and TMT, but whether this short-term elimination of VAs contributes to suppress the subsequent cardiac events in this syndrome is still unclear. In addition, patients with ATS without flecainide therapy have not been included in this study, which might raise a bias of patient selection. Therefore, further investigations are necessary to show the long-term efficacy of flecainide for cardiac events in patients with ATS.

Second, our study population of *KCNJ2*-positive patients with ATS was relatively small because of the rarity. Larger numbers of patients with *KCNJ2* mutations are needed to evaluate the efficacy and safety of flecainide therapy for VAs in patients with ATS. There appear to be several "hot spots" for pathogenic mutations, including, notably, the arginine amino acids at positions 67 and 218 in the N terminus and C terminus, respectively[19]; these were also included in this cohort study. Therefore, flecainide may be effective for the suppression of exercise-induced VAs in many patients with ATS with *KCNJ2* mutations.

Third, approximately 40% of patients with the phenotypic features of ATS do not have *KCNJ2* mutations,[31,33] suggesting the presence of other causative genes such as *KCNJ5*.[34] We did not assess the efficacy of flecainide therapy in clinical ATS cases without *KCNJ2* mutations. Finally, a family with ATS and dilated cardiomyopathy has previously been reported,[35] but this study did not include such patients with left ventricular dysfunction. Therefore, we could not assess the efficacy and safety of flecainide in ATS with left ventricular dysfunction.

Conclusion

This multicenter study suggests that oral flecainide therapy is an effective and safe means of suppressing VAs in patients with ATS with *KCNJ2* mutations, though the U-wave amplitude remained unchanged by flecainide. Flecainide with or without conventional drug therapy should be considered for VA suppression in patients with ATS.

Appendix

Supplementary data

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.hrthm.2014.12.009.

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CLINICAL PERSPECTIVES

Andersen-Tawil syndrome (ATS) is a heterogeneous, autosomal dominant genetic or sporadic disorder characterized by ventricular arrhythmias (VAs), periodic paralyses, and dysmorphic features. VAs such as premature ventricular complex, polymorphic ventricular tachycardia (VT), and bidirectional VT in patients with ATS seem to be benign, but rarely lead to sudden cardiac death or tachy-induced cardiomyopathy. β-Blockers and calcium channel blockers have been used to treat VAs in patients with ATS; however, their efficacy is limited. Recently, the sodium channel blocker flecainide has been reported as an effective means for the suppression of VAs in patients with ATS. This multicenter study systematically evaluated the efficacy and safety of oral flecainide for VAs in patients with ATS with *KCNJ2* mutations. The electrocardiographic parameters (QT interval, QU interval, U-wave amplitude, and U/T-wave ratio) were not significantly altered after flecainide therapy, but parameters from the Holter recordings and treadmill exercise test can be used as a marker for the efficacy of flecainide. Moreover, the exercise-induced bidirectional VT or polymorphic VT is observed not only in patients with ATS but also in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT). The clinical and electrocardiographic features including U wave is sometimes similar between ATS and CPVT. Flecainide therapy has also been useful for the suppression of VAs in patients with CPVT; thus, it should be available for the prediagnosed patients with ATS or CPVT. Finally, flecainide therapy is safe in patients with ATS without overt left ventricular dysfunction, although the patients in this study were not followed for a long-term period. Therefore, flecainide may reduce risk of sudden cardiac death in patients with ATS.

normal aortic diameter have similar aortic dimensions. Patients with BAV and aortic dilatation have endothelial dysfunction as opposed to patients with BAV and normal aortic dimensions [7]. Based on this and Biner et al.'s data [6], FDRs of BAV individuals with aortic dilatation may have an increased risk of aortic dilatation due to endothelial dysfunction inheritance. We consider that our findings enriches Biner et al.'s and should prompt new studies addressed to answer the following question, "Are all tricuspid FDRs of BAV individuals at increased risk of aortic dilatation or is this risk higher only in FDRs of BAV individuals with dilated aortic dimensions?". Results from these studies should guide clinicians if it is necessary to do un-restricted screening of aortic dilatation in all FDRs of BAV individuals or if resources should be aimed at a specific high-risk profile of FDRs.

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0167-5273/$ – see front matter
http://dx.doi.org/10.1016/j.ijcard.2014.01.037

Efficacy of bepridil to prevent ventricular fibrillation in severe form of early repolarization syndrome

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ARTICLE INFO

Article history:
Received 31 December 2013
Received in revised form 8 January 2014
Accepted 10 January 2014
Available online 23 January 2014

Keywords:
Arrhythmia
Ventricular fibrillation
Bepridil
Electrocardiogram
Treatment

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Early repolarization is a common electrocardiographic finding, which occurs in 1% to 10% of healthy persons, and it has been generally considered benign for decades. However, there is increasing evidence showing that early repolarization is associated with an increased risk of ventricular fibrillation and sudden cardiac death, and idiopathic ventricular fibrillation associated with early repolarization, the so-called early repolarization or J-wave syndrome, started receiving increasing attention [1].

Implantable cardioverter defibrillator is the only proven effective treatment to prevent sudden cardiac death in patients with early repolarization syndrome. However, the frequency of arrhythmia recurrences is not rare. In our and other studies, 27% of patients with early repolarization syndrome develop multiple episodes of ventricular fibrillation, and 13% to 17% of patients have electrical storm defined as 3 or more episodes of ventricular fibrillation during 24 h [2,3]. Additional antiarrhythmic therapy is required to reduce defibrillator shocks and to prevent life-threatening events by

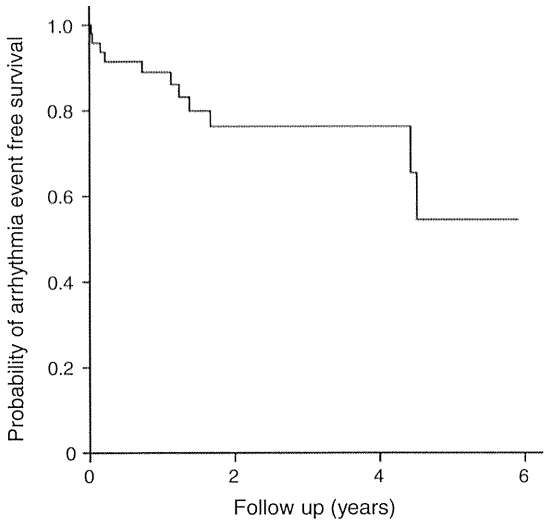

Fig. 1. Probability of arrhythmia event free survival. Ventricular fibrillation recurred in 11 of 50 patients (22%) (Incidence, 4.8 per 100 person-years [95% confidence interval, 2.0–7.6]).

electrical storm, but antiarrhythmic drugs including β-blockers, verapamil, amiodarone, and majority of sodium channel blockers have poorly been effective [2]. Although only quinidine has been effective in preventing recurrent episodes of ventricular fibrillation in patients with early repolarization syndrome, up to one third of patients cannot tolerate quinidine because of side-effects, mainly gastrointestinal ones [2,4].

Brugada syndrome is another form of idiopathic ventricular fibrillation associated with J-point elevation, and early repolarization syndrome and Brugada syndrome share genetic backgrounds, clinical characteristics, and response to pharmacological therapies such as quinidine and isoproterenol [5,6]. In some case reports, multi-channel blocker bepridil has been effective in preventing ventricular fibrillation in patients with Brugada syndrome [7,8]. Here, we describe the efficacy of bepridil in patients with early repolarization syndrome.

This study included 50 patients with early repolarization syndrome who were followed >3months after an initial event associated with ventricular fibrillation (age, 44 ± 16 years; 6 women, 11%). All patients had events associated with ventricular fibrillation, and 16 patients (29%) also had atrial fibrillation. Sodium channel blocker challenge was negative for diagnosis of Brugada syndrome in all patients. During a followup of 3.5 ± 3.4 years, arrhythmia recurred in 11 of 50 patients (22%) (incidence, 4.8 per 100 person-years [95% confidence interval, 2.0–7.6])(Fig. 1). Bepridil was administered in three patients who had multiple recurrences including two patients who had repetitive arrhythmia episodes within a short-time, so called "electrical storm", and was effective to control ventricular fibrillation. Notably, prior to bepridil, quinidine and isoproterenol failed to control arrhythmias in one of the three patients. Quinidine was discontinued due to gastrointestinal side effects in another patient (Fig. 2) (Table 1). Bepridil prolonged QT interval, but did not augment early repolarization pattern in any of the patients. In three patients in whom bepridil combined with intravenous administration of isoproterenol was effective as acute treatment, the drug was continued after discontinuation of isoproterenol. There was no arrhythmia recurrence in two patients during 3.8 years and 8 months, respectively. In the remaining patient, bepridil dramatically decreased the frequency of ventricular fibrillation, and after addition of cilostazol, there was no recurrence of the arrhythmia. Furthermore, bepridil was also effective in preventing atrial fibrillation in another patient.

Among other antiarrhythmic drugs, disopylamide was effective in preventing ventricular fibrillation during 10.2 years in one patient who had been suffered from electrical storm. Lidocaine (n = 5), procainamide (n = 4), mexiletine (n = 3), flecainide (n = 1), propafenone (n = 1), nifekalant (n = 3), amiodarone (n = 2), and sotalol (n = 1) were not effective for recurrences of arrhythmias.

We found that bepridil was effective in patients with severe form of early repolarization syndrome. A transmural differences in action potential notch has been shown as the basis of J-point elevation and ventricular fibrillation, and transient outward potassium current (Ito) blockers reduce the action potential differences resulting in decrease of J point elevation and prevention of arrhythmias in experimental models, although the precise mechanism is unclear [5]. Quinidine, which blocks Ito, has been effective for ventricular fibrillation in patients with early repolarization syndrome [2]. Bepridil is a multi-channel blocker, which inhibits sodium channel, L-type calcium channel, and multiple potassium channels. Bepridil prevented ventricular fibrillation, possibly by Ito block, although bepridil did not normalize J point elevation. Relatively short QT interval may be associated with arrhythmogenic substrate in patients with early repolarization, and bepridil prolonged QT interval in patients with early repolarization in this study, similar to those with Brugada syndrome and idiopathic ventricular fibrillation in a previous study [1,9,10]. However, nifekalant, sotalol, and amiodarone, all of which block delayed rectifier potassium current (IKr) and prolong QT interval were not effective in this and previous studies, further supporting the importance of Ito block for prevention of ventricular fibrillation [2].

Early repolarization syndrome and Brugada syndrome share responses to antiarrhythmic drugs, and this and previous studies have shown that antiarrhythmic drugs with Ito blocking property including quinidine, bepridil, and disopylamide are effective in both diseases [5,6,8,11]. The arrhythmogenicity of vagal stimulation has been reported in Brugada syndrome and early repolarization syndrome, and disopylamide may prevent ventricular fibrillation by muscarine block, in addition to Ito block [5,6]. In both diseases, atrial fibrillation is common complication with the prevalence of ~20%, but most of sodium channel blockers that are widely used for atrial fibrillation are proarrhythmic [6]. Antiarrhythmic drugs with Ito blocking property may be able to use for atrial fibrillation in early repolarization syndrome, and actually, bepridil was safety and was effective in preventing atrial fibrillation in this study.

This study was supported in part by the Research Grant for the Cardiovascular Diseases (H24-033) from the Ministry of Health, Labour and Welfare, Japan (WS, HW, KS, MH, NM).

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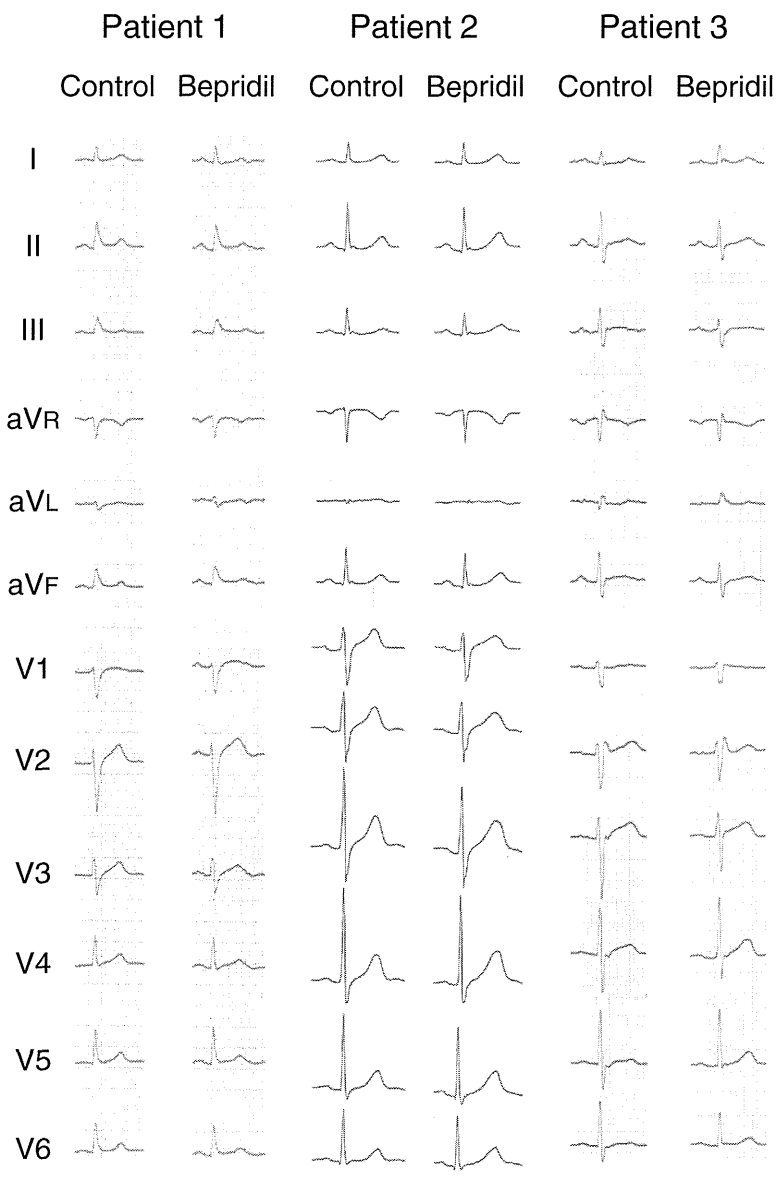

Fig. 2. Electrocardiograms before and during bepridil therapy in patients with frequent recurrences of ventricular fibrillation. Bepridil prolonged QT interval, but did not affect early repolarization.

Table 1
Characteristics of patients with early repolarization syndrome treated with bepridil.

No.	Sex	Age at onset (years)	Family history of SCD	Presenting symptom	Location of J wave	Corrected QT interval, ms		Indication of bepridil	Recurrences of arrhythmias
						Control	Bepridil		
1	M	51	N	Aborted SCD	I, II, III, aVF, V4, V5, V6	400	440	Ventricular fibrillation	No
2	M	38	N	Aborted SCD	I, II, III, aVF	400	430	Ventricular fibrillation	Yes*
3	M	26	N	Aborted SCD	V1, V2	360	400	Ventricular fibrillation	No
4	M	41	N	Aborted SCD	V1, V2	410	450	Atrial fibrillation	No

* No recurrence of ventricular fibrillation after addition of cilostazol. SCD denotes sudden cardiac death.

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0167-5273/$ – see front matter
http://dx.doi.org/10.1016/j.ijcard.2014.01.036

Honeycomb-like neointima of sirolimus-eluting stent in saphenous vein graft: Insights from OCT and IVUS

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ARTICLE INFO

Article history:
Received 19 December 2013
Received in revised form 7 January 2014
Accepted 10 January 2014
Available online 22 January 2014

Keywords:
Neointima
In-stent restenosis
Optical coherence tomography
Intravascular ultrasound
Drug-eluting stent
Saphenous vein graft

Drug-eluting stents (DES) have dramatically reduced rates of restenosis and target lesion revascularization compared with bare metal stents (BMS) [1]. However, the first-generation DES, including sirolimus-eluting stents (SESs) (Cypher, Cordis, Johnson & Johnson, Miami, Florida), implanted in native coronary arteries are associated with delayed arterial healing mainly due to hypersensitivity [2]. Here, we present a case with unusual vascular reaction to a SES which was implanted in a saphenous vein graft (SVG), as imaged by optical coherence tomography (OCT) and intravascular ultrasound (IVUS).

A 39-year-old woman who underwent coronary artery bypass surgery 3 years previously was admitted with symptoms of angina. She was under hemodialysis for 18 years and had coronary risk factors including hypertension and dyslipidemia. Coronary angiography (CAG) showed severe stenosis of a SVG to left anterior descending artery. A SES was implanted to treat this lesion, and subsequent IVUS did not observe stent malapposition. However, after 15 months, her angina occurred again and CAG revealed proximal in-stent restenosis (Fig. 1A). OCT within the stented segment revealed the diffuse neointimal tissue proliferation with high-intensity layer at the surface. In contrast, deep tissue contains heterogeneous low-intensity areas that surrounded and spread behind the stent struts (Fig. 1B1–4). Notably, a honeycomb-like structure separated by high-intensity septa was also identified around the struts (Fig. 1B4). On the other hand, IVUS demonstrated echolucent or low-echoic areas in the neointima as well as in the tissue behind the stent struts (Fig. 1C1–4). In addition, the increases of vessel areas were obvious as compared with previous IVUS findings at time of stent implantation 15 months ago, which implies the occurrence of positive vessel remodeling (Fig. 1D1–4).

It has been reported that the histological features of low-intensity areas in neointimal tissue determined by OCT are excessive inflammation, fibrin accumulation, organized thrombus, extracellular matrix accumulation, or neoatherosclerosis [3]. In contrast, high-intensity structures without backscattering in the surface of neointima visualized by OCT are considered to be fibrin clots [4]. Furthermore, honeycomb-like structures determined by OCT are recanalized organized thrombi [5]. Interestingly, the present IVUS images demonstrated positive vessel remodeling in the stented segment, which is a potential risk for late acquired stent malapposition [6]. Based on these findings, the present OCT images of low-intensity areas may indicate the organized thrombi with partial recanalization and fibrin accumulation that filled spaces around the stent struts, and were covered by fibrin clots in the surface. We suspect that those spaces might be caused by late acquired stent malapposition due to positive vessel remodeling.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

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Original Article

Electrical Storm in Patients With Brugada Syndrome Is Associated With Early Repolarization

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Background—Electrical storms (ESs) in patients with Brugada syndrome (BrS) are rare though potentially lethal.

Methods and Results—We studied 22 men with BrS and ES, defined as ≥3 episodes/d of ventricular fibrillation (VF) and compared their characteristics with those of 110 age-matched, control men with BrS without ES. BrS was diagnosed by a spontaneous or drug-induced type 1 pattern on the ECG in the absence of structural heart disease. Early repolarization (ER) was diagnosed by J waves, ie, >0.1 mV notches or slurs of the terminal portion of the QRS complex. The BrS ECG pattern was provoked with pilsicainide. A spontaneous type I ECG pattern, J waves, and horizontal/descending ST elevation were found, respectively, in 77%, 36%, and 88% of patients with ES, versus 28% ($P<0.0001$), 9% ($P=0.003$), and 60% ($P=0.06$) of controls. The J-wave amplitude was significantly higher in patients with than without ES ($P=0.03$). VF occurred during undisturbed sinus rhythm in 14 of 19 patients (74%), and ES were controlled by isoproterenol administration. All patients with ES received an implantable cardioverter defibrillator and over a 6.0±5.4 years follow-up, the prognosis of patients with ES was significantly worse than that of patients without ES. Bepridil was effective in preventing VF in 6 patients.

Conclusions—A high prevalence of ER was found in a subgroup of patients with BrS associated with ES. ES appeared to be suppressed by isoproterenol or quinidine, whereas bepridil and quinidine were effective in the long-term prevention of VF in the highest-risk patients. ***(Circ Arrhythm Electrophysiol.* 2014;7:1122-1128.)**

Key Words: bepridil ■ Brugada syndrome ■ electrocardiography ■ isoproterenol ■ ventricular fibrillation

Brugada syndrome (BrS), characterized by ST-segment and J-point elevation in the right precordial leads of the ECG in the absence of structural heart disease, is a cause of sudden cardiac death caused by ventricular fibrillation (VF).[1] Albeit rare, a subset of patients experiencing BrS develop potentially fatal storms of VF.[2–6] Their clinical characterization is important from the perspectives of risk stratification and development of new and effective therapies.

Clinical Perspective on p 1128

We recently observed a case of BrS characterized by prominent J waves in the inferolateral leads of the 12-lead ECG and electrical storms (ESs).[7] Case-control studies have described a close association between J waves, a sign of early repolarization (ER), and idiopathic VF.[8–10] The presence of J waves in patients presenting with BrS may also be a predictor of poor prognosis.[6,11–13] The purpose of this multicenter study was to evaluate the characteristics of patients with BrS and ES, with a special attention to the presence of J waves.

Methods

Study Population

We retrospectively identified 22 men at 8 Japanese medical institutions, who presented with BrS and ES, defined as ≥3 episodes of VF/d. BrS was diagnosed according to the following currently accepted criteria[2,6,11–14]: (1) ≥0.2 mV elevation of the J point with type 1 ST elevation in ≥1 right precordial lead(s) at baseline or after provocation with pilsicainide; (2) normal right and left ventricular

Received March 25, 2014; accepted August 19, 2014.

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Circ Arrhythm Electrophysiol **is available at http://circep.ahajournals.org** **DOI: 10.1161/CIRCEP.114.001806**

size and function on chest radiograph and transthoracic echocardiography. Among these 22 patients, 4 had been included in previous studies.[2,6,12,14] Patients who had experienced a cardiac arrest or VF underwent provocation of coronary artery spasm with acetylcholine or ergonovine. We randomly chose 110 age-matched men presenting with BrS and no history of ES as controls and compared their clinical and ECG characteristics with those of the patients with ES.

This study complied with the guidelines of the Declaration of Helsinki and was approved by the institutional review board of Gunma University Hospital. All patients granted their written, informed consent to participate in this study.

ECG Analysis

The RR, PR QRS, QT, and corrected QT (using Bazett formula) intervals of the ECG were measured. An ER pattern was defined as the presence of a positive J wave, defined as a notch or slur at the terminal portion of the QRS complex, >0.1 mV in amplitude above the isoelectric line in ≥2 contiguous lead(s).[8–10] The J wave was classified as inferior if present in leads II, III, and aVF; left precordial if present in leads V4 to V6; and high lateral if present in leads I and aVL. Using the definitions of Tikkanen et al,[15] the ST-segment pattern after the J-point was classified as rapidly ascending/upsloping or horizontal/descending.

Data Analysis

The clinical characteristics, ECG intervals, J-wave prevalence and amplitude, and prevalence of spontaneous type 1 ECG pattern were compared in patients with versus without ES. When available, the ECG recorded during long-term follow-up were compared with those recorded at the time of ES, with special attention to the J waves. The patients' pharmacological and nonpharmacological therapy and long-term outcomes were recorded. The antiarrhythmic drug regimens were chosen according to each physician's preference and, if clinically ineffective, were replaced, in a trial and error manner.

Statistical Analysis

Continuous measurements are expressed as means±SD or medians and interquartile ranges, as appropriate, and categorical variables as counts and percentages. Differences between continuous variables were examined by the Mann-Whitney test, whereas categorical variables were compared by the Fisher exact test. We performed a logistic regression analysis in search of independent electrocardiographic predictors of arrhythmic risks, reported as odds ratio and 95% confidence intervals. The survivals were analyzed by the Kaplan-Meier method and compared using the log-rank test. The statistical analyses were performed with the Ekuseru-Toukei 2012 statistical software package (Social Survey Research Information Co., Ltd). A P value <0.05 was considered statistically significant.

Results

Patients With VF Storm

The characteristics of 22 men with BrS and VF storms are shown in Table 1. ES was the first episode of VF in 16 patients, while it occurred 3.2±2.4 years after implantation of cardioverter defibrillators (ICD) in the other 6 patients. A spontaneous type 1 ECG pattern was observed in 17 patients, and a pilsicainide provocation test was needed in the remaining 5 patients. Acetylcholine or ergonovine excluded the diagnosis of vasospastic angina in 9 of 9 patients who underwent provocation tests. VF was inducible in 6 of the 11 patients who underwent programmed ventricular stimulation to confirm the presence of an arrhythmogenic substrate promoting the development of VF or ventricular tachycardia.

VF Storm Characteristics

A mean of 25.2±82.0 VF episodes occurred during the storms. VF occurred between 8:00 PM and 6:00 AM in 14 patients (64%), between 6:00 AM and 8:00 PM in 7 patients (32%), and during both time intervals in 1 patient (4%). No apparent precipitating factor was identified.

The mode of VF onset was identified in 19 patients (Figure 1) and occurred during undisturbed sinus rhythm in 14 (74%), after a short-long-short sequence in 4 (21%), and under both circumstances in 1 patient (5%). The mean coupling interval of the first VF-triggering premature ventricular complex was 329±63 ms, ranging between 280 and 420 ms. The mode of VF onset was undetermined in 3 patients.

ER was present as J waves in 8 of the 22 patients (36%). The J waves were in the inferior ECG leads in 4 (Figure 2A), inferior and left precordial leads in 2 (Figure 2B), and inferior, left precordial and high lateral leads in 2 patients. A prominent accentuation of the J wave immediately before the onset of VF (Figures 3) was observed in 2 patients. The ST-segment pattern in patients with ES and J waves was rapidly ascending/upsloping in 1 (13%) and horizontal/descending in 7 patients (87%). VF during ES developed during undisturbed sinus rhythm in 6 patients with versus 9 patients without ER, and after a short-long-short sequence in 3 patients with versus 2 patients without ER; the presence of ER did not influence the mode of VF onset during ES (P=0.40). The coupling interval of the first VF-triggering premature ventricular complex in patients with (350[94]) versus without (301[130]) J waves, was similar (P=0.54).

Short-Term Management of VF

All episodes of VF were terminated by external defibrillation or by an ICD. Overdrive pacing, left cardiac sympathetic block combined with atropine, and oral disopyramide were effective in 1 patient each. Thereafter, intravenous isoproterenol became the therapy of choice and effectively suppressed ES in the last 7 patients, combined with quinidine in 1 patient. Lidocaine, magnesium sulfate, propranolol, and mexiletine were ineffective in 4, 3, 2, and 1 patients, respectively. VF-triggering premature ventricular complexes originating from the right ventricular outflow tract were successfully eliminated by catheter ablation in 1 patient. In the other 12 patients, ES resolved spontaneously within 6 to 12 hours.

Comparisons of Patients With Versus Without ES

The characteristics of 22 men with BrS and ES versus 110 men with BrS and no ES are shown in Table 2. Among the 110 control men, 17 experienced a single VF episode, 13 experienced ≥1 syncopal episode(s), and 80 patients were asymptomatic. BrS was diagnosed by the presence of a spontaneous type 1 ECG pattern in 31 patients (28%) without ES, in contrast with 17 (77%) among the 22 patients with ES (P<0.0001). In 79 patients without ES (72%), BrS was diagnosed by a pilsicainide provocation test.

J waves >0.1 mV were observed in 10 of 110 patients without ES (9%), in contrast with 8 of 22 patients with ES (36%), a statistically significant difference (P=0.003). The J-wave amplitude was higher in patients with ES than those without ES (P=0.03). The J waves in patients without ES were

Table 1. Characteristics of 22 Men With BrS and VF Storms

Patient	FH of BrS/SCD	Age, y	Hour of First VF	Mode of VF Onset	Suppression of VF	Drug Trials	PVS	LTT	ICD	Years of Follow-Up	VF Recurrence (Time to Recurrence)
1	–/+	49	10:00	Und	...	...	Positive	...	+	8.3	+ (2.3)
2	–/–	26	21:45	Und	Isoproterenol	Magnesium, lidocaine	Positive	...	+	3.8	...
3	–/–	42	3:00	Und	Pacing	Lidocaine/ amiodarone/ propofol	Negative	...	+	2.6	...
4	–/–	25	0:35	Unknown	...	...	Negative	...	+	1.6	+ (0.2)
5	–/+	21	1:00	Und	...	Lidocaine	Negative	...	+	2.2	+ (0.5)
6	–/+	0.5	All day	Und	LSD/atropine	Propofol/ magnesium/ mexiletine	Negative	...	+	14	...
7	–/–	36	6:15	Und/SLS	Isoproterenol	...	Positive	Bep*	+	1.6	+ (0.4)
8	–/–	61	15:40	Und	...	...	Positive	...	+	0.7	+ (0.3)
9	–/–	42	4:24	SLS	Isoproterenol	...	Positive	Bep*	+	13.5	+ (4.8)
10	–/–	51	11:00	SLS	Isoproterenol	Lidocaine/ magnesium	Not performed	...	+	10.5	+ (6)
11	–/–	39	0:00	Und	Isoproterenol/Q	...	Not performed	Bep*	+	2.2	+ (0.7)
12	–/–	29	4:00	Und	Isoproterenol	...	Positive	Q*	+	7.4	+(3.3)
13	–/–	27	11:00	SLS	...	Cilostazol, quinidine, demopamine, isoproterenol	Negative	DP	+	2.0	+ (0.1)
14	–/–	70	0:22	Und	Isoproterenol	...	Not performed	...	+	12.7	+(0.2)
15	–/–	29	2:47	Unknown	...	...	Not performed	Q*	+	12.9	+(0.3)
16	–/–	33	14:30	Unknown	...	...	Not performed	...	+	15.5	...
17	–/–	53	22:38	Und	...	...	Not performed	...	+	12.5	...
18	–/–	42	22:18	Und	...	...	Not performed	Bep*	+	5.5	...
19	–/–	38	3:22	Und	...	...	Not performed	Amio*	+	2.2	...
20	–/–	50	16:28	SLS	...	...	Not performed	Bep*	+	5.8	...
21	–/–	19	21:18	Und	...	...	Not performed	Bep*	+	1.3	...
22	–/–	42	1:43	Und	...	...	Not performed	...	+	2.4	...

Bep indicates bepridil; BrS, Brugada syndrome; DP, disopyramide; FH, family history; ICD, implantable cardioverter defibrillator; LSD, Left cardiac sympathetic denervation; LTT, long-term therapy; PVS, programmed ventricular stimulation; SCD, sudden cardiac death; SLS, short-long-short sequence; Und, Undisturbed sinus rhythm; and VF, ventricular fibrillation.

*No recurrence of VF on therapy.

Adapted from Ohgo et al,[2] Kawata et al,[6] and Kawata et al[14] with permission of the publisher. Copyright © 2007, 2013, 2012, respectively, Elsevier.

in the inferior leads in 7, inferior and left precordial leads in 1, and high lateral in 2 patients, whereas the J waves in patients with ES were in the inferior leads in 4, inferior and left precordial leads in 2, and in the inferior, left precordial and high lateral leads in 2 patients. The distribution of leads with J waves was similar in patients with versus without ES (P=0.08). In 10 patients without ES and with J waves, the ST segment was horizontal/descending in 4 (40%) and rapidly ascending/upsloping in 6 (60%) patients; the ST-segment pattern in patients with versus without ES was similar (P=0.06). Furthermore, in patients with a history of ≥1 episode of VF, the prevalence of J wave was 28% and that of spontaneous type I ST-segment elevation was 72% versus 8 (P=0.003) and 22% (P<0.0001), respectively, in patients without history of VF episodes. By multiple variable logistic regression analysis, spontaneous type I ST elevation independently predicted the development of VF (odds ratio, 4.375; 95% confidence interval, 1.6–12.0; P=0.004) and ES (odds ratio, 7.1; 95% confidence interval, 2.1–24.6; P=0.002). However, combined spontaneous type I ST elevation and (1) J waves or (2) J waves plus a horizontal or descending ST segment was not independently predictive. Among patients with any episode of VF, the prevalence of J waves and spontaneous type I ST elevation was 21% and 44%, respectively, in patients with versus 8% (P=0.18) and 31% (P=0.46) in patients without ES.

Clinical Outcomes

Among the 22 patients with BrS and ES, 16 underwent implantation of ICD after the ES had abated and 6 patients had already received an ICD when the ES developed. Over a follow-up (6.4±5.0 years), 12 patients experienced VF recurrences after the first ES, of whom 9 were untreated with antiarrhythmic