Incidence and Initial Characteristics of Pilsicainide-Induced Ventricular Arrhythmias in Patients With Brugada Syndrome

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Background: *In patients with Brugada syndrome, class I antiarrhythmic drugs can trigger ventricular arrhythmias (VA). The incidence and initial characteristics of VA that developed after pilsicainide was examined in 28 patients with Brugada-type electrocardiographic (ECG) abnormalities and with a positive response in the pilsicainide test. The clinical outcome was also compared between patients with and without pilsicainide-induced VA.*

Methods and Results: *In all patients, pilsicainide increased ST segment elevation and accentuated type 1 ECG changes. Ventricular tachycardia (VT) developed in 3 patients and premature ventricular complexes (PVC) in 2 other patients. These 5 patients (group I) had higher ST segment elevation in lead V2 on the ECG at baseline and after pilsicainide and showed a longer QTc interval after pilsicainide than the other 23 patients (group II). However, there was no difference between the 2 groups regarding incidence of prior cardiac events, results of signal-averaged ECG, HV interval, inducibility of ventricular fibrillation by programmed electrical stimulation, or QRS duration. In 1 patient, PVC originated from 3 sites, 2 of which triggered polymorphic VT. The right ventricular (RV) outflow tract was the origin of 2 types of PVC, and other RV sites of 5 other types. During a 45 ± 37 months follow-up, polymorphic VT recurred in 2 patients in group II.*

Conclusions: *Pilsicainide induced VA in some patients with Brugada syndrome, but this result may not be used as a parameter of the risk stratification of Brugada syndrome. Multiple PVC induced by pilsicainide and triggering polymorphic VT originated from several RV sites is an important factor when considering patients for treatment with catheter ablation. (PACE 2007; 30:662–671)*

Brugada syndrome, ventricular tachyarrhythmia, triggered extrasystole

Introduction

In patients without structural heart disease, ST segment elevation with a coved-type morphology in leads V1-V3 of the electrocardiogram (ECG), unmasked or increased by class I antiarrhythmic drugs, is considered a diagnostic sign of Brugada syndrome.[1–3] In addition, the administration of class I antiarrhythmic drugs can induce ventricular arrhythmias (VA) in this syndrome.[4,5] Although mechanisms of electrocardiographic manifestation of Brugada syndrome has not been well established, some studies have suggested that ST segment elevation and initiation of VA in patients with Brugada syndrome are associated with the development of greater transmural dispersion of repolarization, which facilitates phase 2 reentry between the endocardial and epicardial layers, or between 2 right ventricular (RV) epicardial regions.[6–8] However, the initial morphology of VA on the surface ECG is often indistinct.

We administered pilsicainide, a class Ic antiarrhythmic drug, in 28 patients who had structurally normal hearts and ST segment elevation in leads V1-V3 of the ECG. In all patients, coved-type (type 1) ST segment elevation was increased or unmasked after pilsicainide. Patients with a negative response in the pilsicainide test were not included in this study because such patients usually did not satisfy the criterion of Brugada syndrome. During the pilsicainide test, 3 patients developed multiple episodes of ventricular tachycardia (VT), defined as >3 consecutive premature ventricular complexes (PVC), and 2 other patients developed PVCs following drug-induced ST segment elevation. The clinical and electrophysiological characteristics of the 5 patients who developed VA (group I) were compared with those of the other 23 patients (group II). The initial ECG morphology of VT was also examined.

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Study Population and Methods

This study included 26 men and 2 women from different families, between the ages of 27 and 74 years (mean = 54 ± 14), referred to our hospital for evaluation of ST segment elevation in leads V1-V3 (Table I). Structural heart disease was excluded by detailed cardiac investigations including echocardiogram, coronary angiogram, and left ventriculogram. Hematological and serological tests were also normal. Three patients had a history of aborted sudden cardiac death and 12 other patients had suffered syncopal episodes. A family history of unexplained sudden death was elicited in 7 patients. The patients with histories of aborted sudden death or syncope underwent brain computed tomography, electroencephalogram, and head-up tilt test, all of which were normal. No patient had received medications before the initial evaluation. In 9 patients who consented to testing, genetic analysis of SCN5A was negative.[9,10]

Standard and Signal-Averaged Electrocardiogram

Two abnormal repolarization patterns of ST segment elevation were observed[11]: (1) coved-type, >2 mm ST segment elevation, followed by an inverted T wave (type 1), in 10 patients, and (2) saddleback appearance with a high takeoff, ≥2 mm ST segment elevation, a trough with ≥1 mm ST segment elevation, then either a positive or biphasic T wave (type 2), in 18 patients. The admission ECG showed normal sinus rhythm and ST segment elevation in all patients. After the administration

Table I.

Baseline Characteristics of 28 Patients With Brugada Syndrome Included in This Study

Patient No	Age/Sex	Family History	Disease Manifestations	ECG Type at Baseline	Genetic Analysis	Signal-Averaged ECG	VF Induced	HV Interval (ms)	PVT/PVC
1	27/M	Negative	Syncope	2	Not done	Positive	Yes	50	Not induced
2	30/M	Negative	Syncope	2	Not done	Positive	Yes	55	Not induced
3	41/M	Negative	None	1	Not done	Positive	Yes	47	Not induced
4	42/M	Negative	Syncope	1	Negative	Positive	Yes	50	Not induced
5	42/M	Negative	None	2	Not done	Positive	Yes	45	Not induced
6	43/F	Negative	Syncope	1	Not done	Positive	No	40	Not induced
7	46/M	Negative	None	2	Not done	Negative	Yes	35	Not induced
8	47/M	Negative	None	2	Not done	Negative	yes	58	Not induced
9	47/M	Positive	None	2	Not done	Positive	yes	50	Not induced
10	48/F	Negative	None	1	Not done	Positive	Yes	51	Not induced
11	49/M	Negative	ASD	2	Not done	Negative	Yes	50	Not induced
12	49/M	Negative	None	2	Not done	Positive	yes	55	Not induced
13	54/M	Positive	None	1	Not done	Positive	yes	55	Not induced
14	58/M	Negative	Syncope	2	Negative	Positive	Yes	75	Not induced
15	59/M	Negative	None	2	Not done	Positive	Yes	44	Not induced
16	59/M	Positive	None	1	Not done	Not done	Yes	44	Not induced
17	61/M	Negative	Syncope	2	Negative	Positive	Yes	50	Not induced
18	64/M	Negative	None	2	Not done	Positive	Yes	58	Not induced
19	65/M	Positive	Syncope	2	Not done	Positive	Yes	44	Not induced
20	69/M	Positive	Syncope	2	Negative	Positive	Yes	36	Not induced
21	71/M	Negative	ASD	1	Negative	Positive	Yes	60	Not induced
22	73/M	Negative	None	2	Negative	Negative	Yes	45	Not induced
23	74/M	Negative	Syncope	2	Negative	Positive	Yes	35	Not induced
24	33/M	Positive	ASD	1	Not done	Positive	Yes	63	PVC
25	50M	Negative	Syncope	2	Negative	Positive	Yes	44	PVT
26	60/M	Negative	Syncope	1	Not done	Positive			PVC
27	73//M	Positive	Syncope	1	Not done	Negative	Yes	47	PVT
28	74/M	Negative	None	2	Negative	Positive	Yes	52	PVT

M = Male; F = female; VF = ventricular fibrillation; ASD = aborted sudden death; PVC = premature ventricular complex; PVT = polymorphous ventricular tachycardia.

of pilsicainide, type 1 ST segment elevation was increased or became manifest in all patients.

A baseline signal-averaged ECG, using the Frank X, Y, and Z leads, was recorded during sinus rhythm. We averaged 250 cycles to reach a noise level ≤ 0.4 μV. The filtered QRS duration, root mean square voltage of the terminal 40 ms of the filtered QRS complex (RMS40), and duration of low-amplitude signal (<40 μV) in the terminal filtered QRS complex (LAS40) were measured. Late potentials were considered to be present when RMS40 was <20 μV and LAS40 >38 ms.

Pharmacological Test

After informed consent was obtained from the patient or legal guardian, pilsicainide, 1 mg/kg over 5 minutes, was administered intravenously during continuous ECG monitoring to 27 patients. In 1 patient, pilsicainide, 50 mg, was administered orally. In patients showing type 2 ECG abnormality, the test was considered positive when the terminal R wave and ST segment rose by >2 mm when compared with baseline, and the ST segment developed the type 1 abnormalities described earlier.[1,11] In patients showing type 1 ECG abnormality, the test was considered positive when the terminal R wave and ST segment rose by >2 mm when compared with baseline. We discontinued the pilsicainde infusion soon after confirmation of the positive responses on the ST segment elevation and/or development of any ventricular arrhythmia. Even so, ST segment elevation progressed within a few minutes (1–3 minutes) after discontinuation of the drug infusion and VA was initiated during the period in some patients. When VA developed during the test, its initial pattern and QRS morphology were examined on the ECG, and isoproterenol, 0.1 μg/min, i.v. was immediately started to suppress repetitive episodes.

Electrophysiologic Studies

After informed consent was obtained from the patient or legal guardian, electrophysiologic studies (EPS) were performed in the nonsedated, postabsorptive state. Three 6F quadripolar electrode catheters with a 0.5-cm interelectrode distance were positioned to stimulate the heart between the distal and 3rd electrode, and record the intracardiac electrogram from the 2nd and 4th electrodes, with the band-pass filter set at 30–500 Hz. Programmed electrical stimulation was delivered at twice the late diastolic threshold at a 2-ms pulse width. Our stimulation protocol for patients with Brugada type ECG abnormalities includes up to 3 extrastimuli delivered during pacing at drive cycle lengths of 600 and 400 ms, and rapid pacing down to a cycle length of 286 ms from the RV apex and outflow tract (OT).

Statistical Analysis

Values are presented as means $\pm$ SD. Statistical analyses were performed by Student's *t*-test and Fisher's exact test. P values <0.05 were considered statistically significant.

Results

Signal-Averaged Electrocardiograms and Electrophysiologic Studies

Signal-averaged ECG was recorded in all patients except in one case (no 16). Late potentials were present in 22 of the 27 (81%) patients (Table I). EPS were performed in all patients except for one (no 26), and ventricular fibrillation (VF) was induced in 26 of the 27 patients (96%). The mean His-ventricular (HV) interval during sinus rhythm was 50 ± 9 ms.

Patients With Versus Without Pilsicainide-Induced Ventricular Arrhythmias

Before administration of pilsicainide, neither isolated PVC nor nonsustained VT was recorded in any of the patients. After administration of pilsicainide, type 1 ST segment elevation was increased or became manifest in all patients. Multiple episodes of VT developed during the test in 3 patients (no 25, 27, and 28), and 2 other patients (no 24, 26) developed repetitive PVC (Table I).

The mean dose of pilsicainide administered in the entire population was 0.85 ± 0.24 mg/kg, and was similar among patients who developed VA (group I; 0.74 ± 0.22 mg/kg) versus among patients who did not develop VA (group II; 0.87 ± 0.24 mg/kg). There was no difference in the prevalence of history of aborted sudden cardiac death or syncope between patients with versus without pilsicainide-induced VA (Table II). Among the 5 patients in group I, the baseline ECG showed type 1 ST segment elevation in 3, and type 2 in 2 patients. Among 23 patients in group II, type 1 ST segment elevation was observed in 7, and type 2 in 16. There was no significant difference in the rates of positive signal-averaged ECG (80% vs 82%), inducibility of VF during EPS (100% vs 96%), and mean baseline HV interval (52 ± 8 ms vs 49 ± 9 ms) between patients with versus without drug-induced VA.

Heart rate, PQ interval, and QRS duration before and after administration of pilsicainide were similar in both patient groups (Table II). QTc interval was not different between group I and group II before pilsicainide (436 ± 24 ms vs 415 ± 24 ms, $P = 0.084$), but the patients in group I showed a slightly longer QTc interval after pilsicainide than the patients in group II (464 ± 38 ms vs 436 ± 19 ms, $P = 0.023$). The drug-induced percent

Table II.

Comparisons Between Patients with Versus without Pilsicainide-Induced Ventricular Arrhythmias

Characteristics	Pilsicainide-Induced PVC/PVT		P
	YES (n = 5)	NO (n = 23)	
Age, years	58 ± 17	53 ± 13	0.46
Family history, numbers (%) of patients	2 (40)	5 (22)	0.57
Disease manifestations, numbers of patients			
Aborted sudden death (a)/Syncope (b)	1/3	2/9	0.46/0.62
(a) + (b)	4	11	0.33
Type of ECG at baseline, numbers of patients			
1	3	7	0.36
2	2	16	0.36
Positive signal-averaged ECG, numbers (%) of patients	4 (80)	18 (82)	0.99
HV interval, ms	52 ± 8	49 ± 9	0.64
Sinus cycle length, ms			
Before pilsicainide	876 ± 125	934 ± 144	0.41
After pilsicainide*	852 ± 160 (97 ± 5%)	876 ± 128 (94 ± 6%)	0.72 (0.31)
PQ interval, ms			
Before pilsicainide	200 ± 32	189 ± 42	0.58
After pilsicainide*	220 ± 20 (112 ± 15%)	222 ± 57 (118 ± 11%)	0.93 (0.29)
ST segment elevation V_1, mm			
Before pilsicainide	1.8 ± 1.2	1.2 ± 0.6	0.07
After pilsicainide*	2.3 ± 1.4 (129 ± 21%)	2.1 ± 1.0 (200 ± 86%)	0.73 (0.12)
ST segment elevation V_2, mm			
Before pilsicainide	4.7 ± 1.1	2.7 ± 0.8	0.0001
After pilsicainide*	7.4 ± 2.5 (158 ± 40%)	5.5 ± 1.7 (206 ± 57%)	0.045 (0.087)
QRS duration			
Before pilsicainide	106 ± 17	101 ± 17	0.57
After pilsicainide*	136 ± 9 (131 ± 25%)	125 ± 22 (125 ± 16%)	0.29 (0.46)
QTc interval			
Before pilsicainide	436 ± 24	415 ± 24	0.084
After pilsicainide*	464 ± 38 (106 ± 4%)	436 ± 19 (105 ± 3%)	0.023 (0.61)

Unless specified otherwise, values are means ± SD.
*Percentages of baseline values are in parentheses.

increase in QTc interval was similar in group I (106 ± 4%) and group II (105 ± 3%). Although the amount of ST segment elevation in lead V1 between before and after administration of pilsicainide was similar in both groups, ST segment elevation in lead V2 was greater in patients with than in patients without pilsicainide-induced VA before (4.7 ± 1.1 mV vs 2.7 ± 0.8 mV, P = 0.0001) and after pilsicainide (7.4 ± 2.5 mV vs 5.5 ± 1.7 mV, P = 0.045). The percent increase in ST segment elevation by the drug was not significantly different between the 2 study groups (Table II).

After granting their informed consent, 4 patients in group I and 18 patients in group II underwent implantations of cardioverter defibrillators (ICD). During a mean follow-up of 45 ± 37 months, 2 patients (no 14 and no 16) experienced a recurrent adverse cardiac event. These patients, who belonged in group II, developed ventricular fibrillation (VF) and received an appropriate ICD shock at 27 and 7 months of follow-up, respectively. The follow-up period was not different between the patients in group I (46 ± 12 months) and group II (44 ± 40 months). Therefore, pilsicainide-induced VA seemed not to be a marker of occurrence of adverse cardiac events during the follow-up period.

Morphology of Ventricular Arrhythmias

The administration of pilsicainide induced 7 different PVC morphologies in 5 patients, including 3 separate morphologies in 1 patient and a single morphology in 4 patients, all of left bundle branch block (LBBB) configuration (Table III). The QRS morphology suggested to a right ventricular outflow track (RVOT) origin of 2 types of PVC,

Table III.

Characteristics of Pilsicainide-Induced Premature Ventricular Complex

Patient No	Number of QRS Morphology	BBB Pattern	QRS Axis	Coupling Interval (ms)	PVT/PVC
24	1	LBBB	RAD (+100°)	500–520	PVC
25	1	LBBB	LAD (−70°)	380–420	PVT
26	1	LBBB	LAD (−60°)	400–420	PVC
27	3	LBBB	LAD (−30°)	380–400	PVT
		LBBB	LAD (−70°)	380–400	PVC
		LBBB	LAD (−60°)	380–400	PVT
28	1	LBBB	NA (+50°)	400–520	PVT

BBB = bundle branch block pattern; LBBB = left bundle branch block pattern; LAD= left axis deviation; NA= normal axis; RAD= right axis deviation; PVC = premature ventricular complex; PVT = polymorphous ventricular tachycardia.

and other RV origins of 5 other types of PVC. The administration of pilsicainide induced repetitive episodes of VT in 3 patients.

1. *Patient no 25.* A 50-year-old man was admitted in normal sinus rhythm with type 2 ST segment elevation in leads V1-V2. Following a single 50-mg dose of pilsicainide, type 1 ST segment elevation developed in leads V1-V2. As the magnitude of ST segment elevation increased, a hump appeared on the terminal portion of the T wave, along with PVC with LBBB configuration and left axis deviation and frequent, nonsustained polymorphic VT.[4] The first QRS of the VT was of the similar morphology as that of isolated PVC (Fig. 1). Furthermore, the coupling interval of the PVC (from 380 to 420 ms) was similar with each event, and the onset of the PVC was superimposed on the hump of T wave of the preceding cycle. The intravenous infusion of isoproterenol suppressed

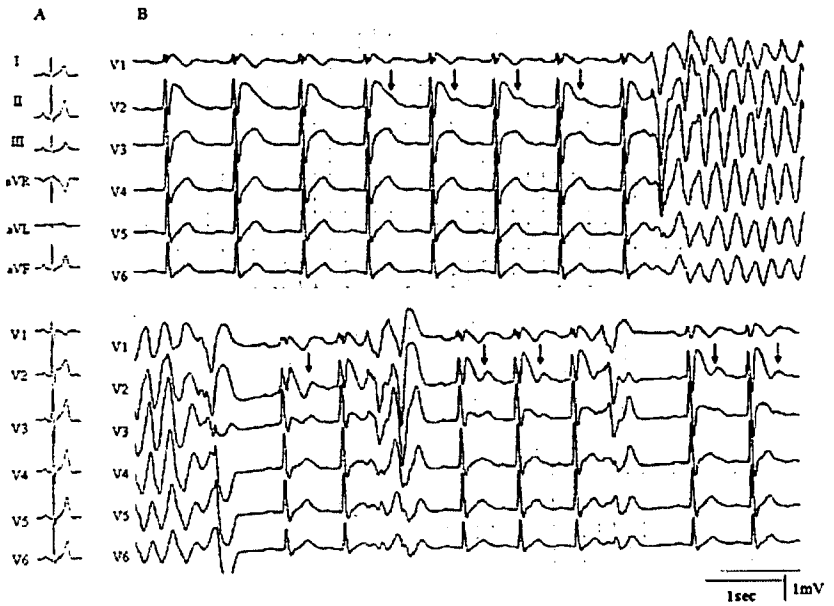

Figure 1. *Twelve-lead electrocardiogram (patient no 25). Baseline ECG was shown in panel A. After the administration of 50 mg of pilsicainide (panel B), ST segment elevation developed in leads V1-V3, and a hump (arrows) became apparent on the terminal portion of the T wave. Premature ventricular complex and self-terminating polymorphic ventricular tachycardia often coincided with the hump of preceding beat. ST segment elevation in lead V2 was augmented from 0.25 to 0.85 mV by pilsicainide.*

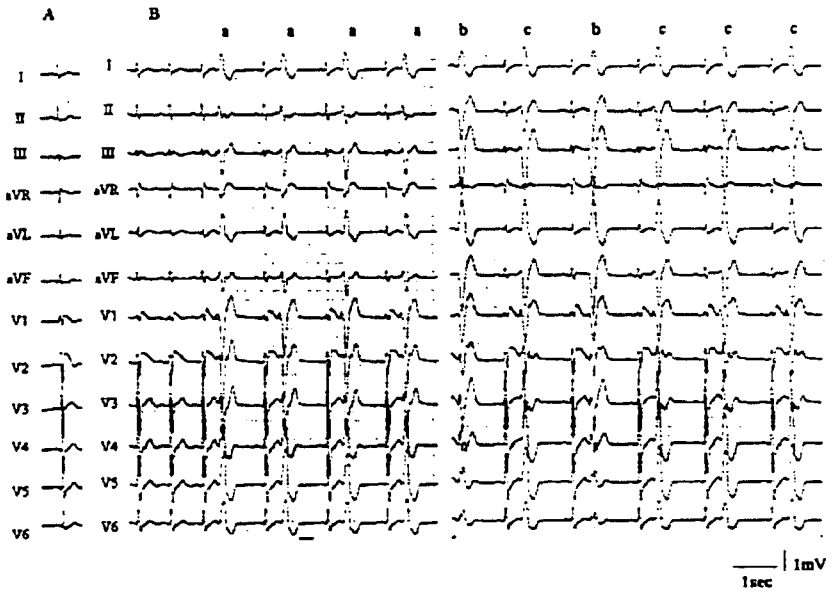

Figure 2. *Twelve-lead electrocardiogram (patient no 27). Baseline ECG was shown in panel A. During administration of pilsicainide, PVC with 3 distinct LBBB-like morphologies (a, b, c) were induced following ST segment elevation in leads V1-V2, with nearly identical coupling intervals. ST segment elevation in lead V2 was slightly augmented from 0.5 to 0.6 mV by pilsicainide.*

PVC and polymorphic VT, and normalized the ST segment. On a subsequent day, double and triple RV extrastimulation twice induced VF. The patient consented to the implantation of an ICD.

2. *Patient no 27.* A 73-year-old man suffered a syncopal episode during a meal. His ECG showed normal sinus rhythm and type 1 ST segment elevation in leads V1-V2. Pilsicainide, 40 mg infused i.v. over 4 minutes, increased the ST segment elevation, and frequent PVCs developed, with 3 distinct QRS morphologies, LBBB configuration, and left axis deviation (Fig. 2). The coupling interval of the PVC was consistently between 380 and 400 ms. Repetitive episodes of polymorphic VT were triggered by 2 of the 3 PVC (Fig. 3). An i.v. infusion of isoproterenol suppressed the PVC and polymorphic VT, and normalized the ST segment. Double extrastimulation from the RVOT induced VF and sinus rhythm was restored by a defibrillation shock. The patient underwent implantation of an ICD.

3. *Patient no 28.* A 74-year-old man was admitted to the hospital in normal sinus rhythm and with type 2 ST segment elevation in leads V1-V2 of the ECG. Pilsicainide, 30 mg infused over 3 minutes, increased the ST segment elevation, and frequently isolated or short runs of PVC developed, with LBBB configuration and a normal axis. The QRS morphology of isolated PVC was identical to that of the first QRS of VT, though the coupling interval varied between 400 and 520 ms (Fig. 4). Short-coupled PVC (400–440 ms) induced VT, whereas PVC associated with longer coupling intervals (460–520 ms) did not. These PVC were eliminated by the infusion of isoproterenol. Double or triple RVOT extrastimulation, performed on a subsequent day, twice induced VF, and the patient underwent implantation of an ICD.

Discussion

The 28 patients included in this study had type 1 ECG abnormalities consistent with Brugada syndrome[11] before or after the administration of pilsicainide, and VF was induced by programmed RV extrastimulation in 26 of 27 patients. The 2 remaining patients had a history of syncope (no 6 and no 26).

Electrophysiologic Observations Before and After Pilsicainide

Pilsicainide induced VA following an increase in ST segment elevation in 5 of the 28 patients (18%). There were, however, no differences between group I and group II with respect to prior episodes of aborted sudden cardiac death or syncope, family history, results of signal-averaged ECG, or inducibility of VF by programmed RV stimulation. Likewise, the PQ interval and QRS

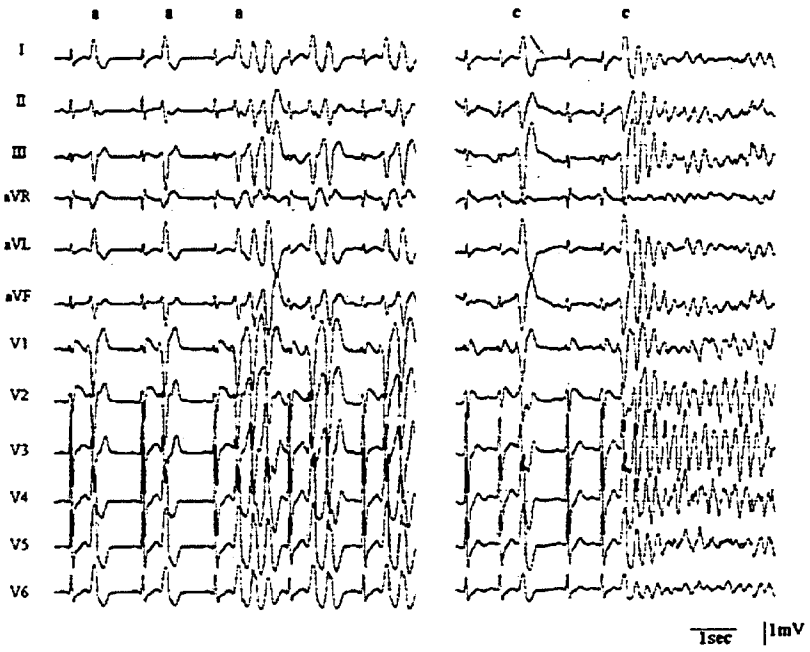

Figure 3. *Twelve-lead electrocardiogram (patient no 27). Soon after the ST segment elevation and development of PVC, repetitive episodes of non-sustained and sustained polymorphic VT were triggered by 2 of the 3 types of PVCs (a and c).*

duration before and after pilsicainide, the QTc interval before pilsicainide and the baseline HV interval were similar in patients with VA versus without. However, the QTc interval after pilsicainide was slightly longer in group I than in group II. This may have been due to delayed repolarization of the RV epicardium caused by the presence of a more prominent notch giving rise to a delayed second upstroke of the epicardial action potential.[6,12,13] Furthermore, ST elevation in lead V2 before and after administration of pilsicainide was greater in patients with VA than in patients without VA. These observations suggest that the repolarization gradient through the RV wall was greater in patients with VA than in patients without VA, facilitating the initiation of VA caused by phase 2 reentry.[6,12,13] The occurrence of phase 2 reentry is associated with electrotonic interaction between myocardial tissues with different lengths of action potential.[14] Therefore, a hump on the T wave, observed in patient no 25, might represent electrotonic interaction between myocardium with normal, and epicardium with short, action potential duration, as the first cycle of the polymorphic VT originated from the hump present in the preceding cycle (Fig. 1). Another possible explanation for the hump on the T wave in this patient might be a presence of concealed phase 2 reentry.

Although the result of this study (greater ST segment elevation and marked QTc interval prolongation in group 1 but no difference in QRS duration between groups I and II) seems to be in accordance with the theory of arrhythmogenesis in Brugada syndrome by Yan and Antzelevitch[6] and Antzelevitch[12] (the repolarization gradient between the endocardial and epicardial sites of the RVOT), electrocardiographic manifestation of Brugada syndrome has not been well established and a worldwide debate is still ongoing.[12,15] Until now, the mechanisms of Brugada syndrome have been considered to be attributed to: (i) conduction delay in the area of the RVOT[6,12] and/or (ii) transmural electrical heterogeneity of repolarization across the wall of the RVOT,[6,12] or a combination of the two. Indeed, late potentials are sometimes recorded in the signal-average ECG.[17] Nagase et al. reported that delayed potentials, which coincided with late potentials in the signal-average ECG, were recorded at the epicardial area in the RVOT.[19] On the other hand, the repolarization gradient between the endocardial and epicardial sites of the RVOT was proposed as the mechanism from other studies.[7,8,12]

Other Japanese investigators have reported similar observations with the pilsicainide test in Brugada syndrome.[20] In that study, pilsicainide induced VA in 10 of 65 patients (15.4%) with Brugada-type ECG abnormalities, including polymorphic VT in 4, and PVC in 6 patients. The amount of ST segment elevation and QTc interval

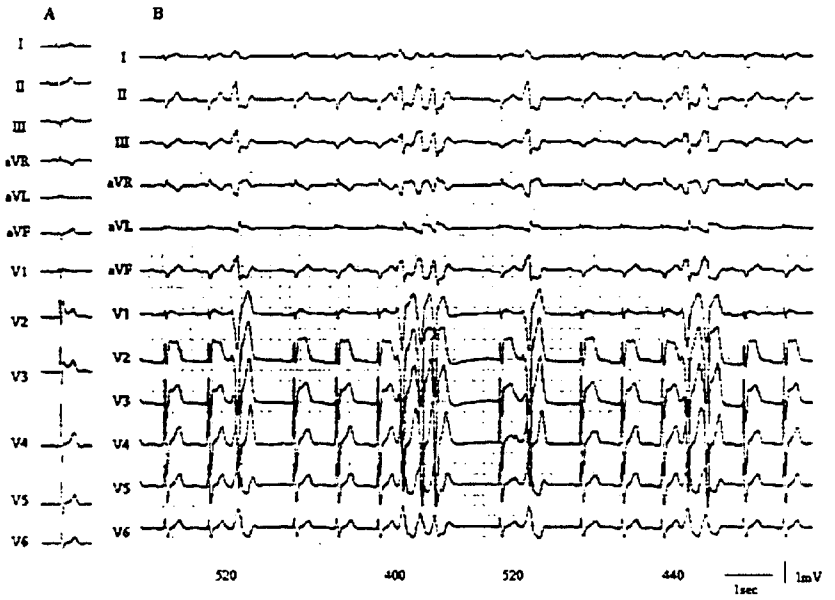

Figure 4. *Twelve-lead electrocardiogram (patient no 28). Baseline ECG was shown in panel A. During administration of pilsicainide, frequent PVC with LBBB configuration and normal axis appeared. The QRS morphology of each PVC was nearly identical though the coupling interval was variable. Short-coupled PVC triggered salvos of non-sustained VT, while longer coupled PVC did not. ST segment elevation in lead V2 was augmented from 0.3 to 0.9 mV by pilsicainide. CI = coupling interval.*

duration in patients with versus without VA were similar in that study; however, the QRS complex after pilsicainide administration was slightly wider among patients with, than among patients without, VA. The importance of intracardiac conduction delay (depolarization abnormality) in the development of VA has been highlighted in other studies.[21] In our study, the parameters of conduction were similar in patients with versus without VA. However, patient no 28 had salvos of VT that were initiated by PVC with short, as opposed to longer, coupling intervals, consistent with a reentrant mechanism initiated by the PVC, suggesting that delayed conduction of the first PVC with a short coupling interval is a trigger of VT.

QRS Morphology of Triggered Premature Ventricular Complexes

Previous studies have located the main arrhythmogenic substrate of Brugada syndrome in the RVOT[7, 22] and the origin of triggered initial complex of polymorphic VT from that area. However, other studies have located the origin of triggered initial complex of polymorphic VT in other RV regions in some Brugada patients.[20,23] In our study, the pilsicainide-induced PVC had a LBBB morphology, though an RVOT origin was found in 2 of the 7 PVCs recorded among the 5 patients.

Triggered PVC might originate from epicardial areas with more prominent transient outward currents (I_{to}), and the multiple morphologies of PVC suggested the existence of different distribution patterns of myocardial ionic currents among our patients. Furthermore, the multifocal PVC induced by pilsicainide suggested that epicardial myocardium with exaggerated I_{to} current is not confined to a small RV region.

ICD Treatment

The ICD is most reliable for high-risk patients presenting with Brugada syndrome, though some patients require additional treatment to limit the delivery of shocks.[24,25] Catheter ablation of triggered PVC has recently been described to treat and limit the number of ICD discharges in patients suffering from the Brugada syndrome.[26] However, if PVCs from multiple origins are triggers of polymorphic VT, mapping of all foci would be mandatory. We recommended ICD treatment in the patients having previous episodes of aborted sudden cardiac death, syncope, and/or family history of sudden cardiac death. Because the other patients were also included in the category of Brugada syndrome (type 1 ECG abnormality plus inducible VF and/or syncope episode), we provided available information of Brugada syndrome and explained the

benefits and disadvantages of ICD treatment. ICD was implanted if the patients and their family requested the ICD treatment.

Role of Pilsicainide Test

In this study, we attempted a pilsicainide test in patients showing either type 1 or type 2 ECG abnormalities at baseline as shown in Table I. In patients with a type 2 ECG abnormality, the principle purpose of the test was to check whether a type 1 ECG abnormality was manifested by the drug or not. In patients with a type 1 abnormality at baseline, we performed the test to see whether the drug induced further aggravation of ST segment elevation because we think that such a response seems to indicate the existence of an arrhythmogenic substrate compatible with Brugada syndrome. Therefore, principal purpose of the pilsicainide test was as a diagnostic tool and not as a marker for risk stratification. This is a retrospective study and the role of the provocation test using class I antiarrhythmic drugs has not been well clarified, especially in the early stages of this study. However, in the present day, class I antiarrhythmic drug provocation test is not recommended for patients with type 1 ECG abnormality at baseline.[12,27,28] Pilsicainide is a pure sodium channel blocker at least in the doses of clinical usage, and we think that the intravenous test with pilsicainide yields the same outcome as that used with other types of antiarrhythmic drugs.[3,27,28]

Although VA was effectively suppressed by the infusion of isoproterenol, the pilsicainide test can induce VA in some patients suffering from the Brugada syndrome. Therefore, we urge caution when performing this test. Because there seems to be no difference in the clinical incidence of adverse cardiac events between patients with versus without pilsicainide-induced VA during the middle-term follow-up period of 45 ± 37 months, the test seems not to be used as a marker for risk stratification of Brugada sundrome.

Limitations of the Study

This study included a small number of patients and their clinical background was heterogeneous. Different from other studies,[9,29] only 3 patients suffered from aborted sudden cardiac death and 13 of the 28 patients (46%) were asymptomatic. All patients in this study were from different families and a family history of sudden cardiac death was observed in 7 patients. Indeed, in our country, most patients of Brugada syndrome are sporadic and asymptomatic cases with relatively benign prognosis.[20,30,31] Therefore, these backgrounds may be related to the low occurrence of adverse cardiac events during the follow-up in this study compared to previous reports from North America and European countries.[9,29] However, a recent study from European countries also showed a small percentage of cardiac events in asymptomatic patients and patients having previous episodes of syncope.[32] A larger patient population with a similar background and longer-term follow-ups will be needed to more precisely understand the clinical implications of pilsicainide-induced VA in patients presented with Brugada syndrome. ST segment elevation in lead V2 was larger in patients of group I, and this seems to indicate that enhanced arrhythemogenesis in these patients compared to other patients in group II. Therefore, the outcome of the test (appearance of VA) could be strongly influenced by the initial conditions. We did not study the electrophysiologic effects of pilsicainide on the ventricle or the origin of the PVC during EPS, and the mechanism for induction of VA during administration of class I antiarrhythmic drugs was not demonstrated. Finally, we studied patients with Brugada-type ECG abnormalities in whom the pilsicainide test was positive, which might have overestimated the incidence of VA during the test.

Conclusions

VA was induced by pilsicainide in 18% of patients with Brugada-type ECG abnormalities and with a positive response on the ST segment in the pilsicainide test. The clinical outcomes of these patients may be similar to those of patients without pilsicainide-induced VA. In some patients, polymorphic VT was induced by PVC of multiple morphologies, particularly when short-coupled.

References

1. Brugada R, Brugada J, Antzelevitch C, Kirsch GE, Potenza D, Towbin JA, Brugada P. Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts. Circulation 2000; 101:510–515.
2. Wilde A, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, Corrado D, et al. for the Study Group on the Molecular Basis of Arrhythmias of the European Society of Cardiology. Proposed Diagnostic Criteria for the Brugada Syndrome. Circulation 2002; 106:2514–2519.
3. Wolpert C, Echternach C, Veltmann C, Antzelvitch C, Thomas GP, Spehl S, Streitner F, et al. Intravenous drug challenge using flecainide and ajmaline in patients with Brugada syndrome. Heart Rhythm 2005; 2:254–260.
4. Chinushi Y, Chinushi M, Toida T, Aizawa Y. A class I antiarrhythmic drug and coronary vasospasm induced T-wave alternans and ventricular tachyarrhythmia in a patient with Brugada syndrome and vasospastic angina. J Cardiovasc Electrophysiol 2002; 13:191–194.
5. Takagi M, Doi A, Takeuchi K, Yoshikawa J. Pilsicainide-induced

marked T wave alternans and ventricular fibrillation in a patient Brugada syndrome. J Cardiovasc Electrophysiol 2002; 13:837.
6. Yan GX, Antzelevitch C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. Circulation 1999; 100:1660–1666.
7. Kurita T, Shimizu W, Inagaki M, Suyama K, Taguchi A, Satomi K, Aihara N, et al. The electrophysiologic mechanism of ST-segment elevation in Brugada syndrome. J Am Coll Cardiol 2002; 40:330–334.
8. Aiba T, Shimizu W, Hidaka I, Uemura K, Noda T, Zheng C, Kamiya A, et al. Cellular basis for trigger and maintenance of ventricular fibrillation in the Brugada syndrome model. J Am Coll Cardiol 2006; 47:2074–2085
9. Priori SG, Napolitano C, Gasparini M, Pappone C, Della Bella P, Giordano U, Bloise R, et al. Natural history of Brugada syndrome: Insights for the risk stratification and management. Circulation 2002; 105:1342–1347.
10. Hong K, Brugada J, Oliva A, Berruezo Sanchez A, Potenza D, Pollevick GD, Guerchicoff A, et al. Value of electrocardiographic parameters and ajmaline test in the diagnosis of Brugada syndrome caused by SCN5A mutations. Circulation 2004; 110:3023–3027.
11. Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, Gussak I, et al. Brugada syndrome, Report of the second consensus conference. Endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. Circulation 2005; 111:659–670.
12. Antzelevitch C. Brugada syndrome. Review. Pacing Clin Electrophysiol 2006; 29:1130–1159.
13. Di Diego J, Fish J, Antzelevitch C. Brugada syndrome and ischemia-induced ST-segment elevation. Similarities and differences. J Electrocardiol 2005; 38:14–17.
14. Shimizu W, Aiba T, Kurita T, Kamakura S. Paradoxic abbreviation of repolarization in epicardium of the right ventricular outflow tract during augmentation of Brugada-type ST segment elevation. J Cardiovasc Electrophysiol 2001; 12:1418–1421.
15. Meregalli PG, Wilde AA, Tan HL. Path physiological mechanisms of Brugada syndrome: Dispersion disorder, repolarization disorder, or more? Cardiovasc Res 2005; 67:367–378.
16. Tukkie R, Sogaard P, Vleugels J, de Groot KLM, Wilde AAM, Tan HL. Dealy in the right ventricular activation contributes to Brugada syndrome. Circulation 2004; 109:1272–1277.
17. Eckardt L, Bruns HJ, Paul M, Kirchhof P, Schulze-Bahr E, Wichter T, Breithardt G, et al. Body surface area of ST elevation and the presence of late potentials correlate to the inducibility of ventricular tachyarrhythmias in Brugada syndrome. J Cardiovasc Electrophysiol 2002; 13:742–749.
18. Furushima H, Chinushi M, Hirono T, Sugiura H, Watanabe H, Komura S, Washizuka T, et al. Relationship between dominant prolongation of the filtered QRS duration in the right precordial leads and clinical characteristics in Brugada syndrome. J Cardiovasc Electrophysiol 2005; 16:1311–1317.
19. Nagase S, Kusano KF, Morita H, Fujimoto Y, Kakishita M, Nakamura K, Emori T, et al. Epicardial electrogram of the right ventricular outflow tract in patients with the Brugada syndrome. J Am Coll Cardiol 2002; 39:1992–1995.
20. Morita H, Morita TS, Nagase S, Banba K, Nishii N, Tani Y, Watanabe A, et al. Ventricular arrhythmia induced by sodium channel blocker in patients with Brugada syndrome. J Am Coll Cardiol 2003; 42:1624–1631.
21. Kanda M, Shimizu W, Matsuo K, Nagaya N, Taguchi A, Suyama K, Kurita T, et al. Electrophysiologic characteristics and implications of induced ventricular fibrillation in symptomatic patients with Brugada syndrome. J Am Coll Cardiol 2002; 39:1799–1805.
22. Yokokawa M, Takaki H, Noda T, Satomi K, Suyama K, Kurita T, Kamakura S, et al. Spatial distribution of repolarization and depolarization abnormalities evaluated by body surface potential mapping in patients with Brugada syndrome. Pacing Clin Electrophysiol 2006; 29:1112–1121.
23. Ogawa M, Kumagai K, Yamanouchi Y, Saku K. Spontaneous onset of ventricular fibrillation in Brugada syndrome with J wave and ST-segment elevation in the inferior leads. Heart Rhythm 2005; 2:97–99.
24. Maury P, Couderc P, Delay M, Boveda S, Brugada J. Electrical storm in Brugada syndrome successfully treated using isoprenaline. Europace 2004; 6:130–133.
25. Watanabe H, Chinushi M, Washizuka T, Sugiura H, Hirono T, Komura S, Hosaka Y, et al. Variable electrocardiographic effects of short-term quinidine sulfate administration in Brugada syndrome. Pacing Clin Electrophysiol 2005; 28:372–377.
26. Haissaguerre M, Extramiana F, Hocini M, Cauchemez B, Jais P, Cabrera JA, Farre G, et al. Mapping and ablation of ventricular fibrillation associated with long-QT and Brugada syndrome. Circulation 2003; 108:925–928.
27. Gasparini M, Priori SG, Mantica M, Napolitano C, Galimberti P, Geriotti C, Simonini S. Flecainide test in Brugada syndrome: A reproducible but risky tool. Pacing Clin Electrophysiol 2003; 26:338–341.
28. Meregalli PG, Ruijter JM, Hofman N, Bezzina CR, Wilde AAM, Tan HL. Diagnostic value of flecainide testing in unmasking SCN5A-related Brugada syndrome. J Cardiovasc Electrophysiol 2006; 17:857–864.
29. Brugada J, Brugada R, Antzelevitch C, Towbin J, Nademanee K, Brugada P. Long-term follow-up of individuals with the electrophysiologic pattern of right bundle-branch block and ST-segment elevation in precordial leads V1 to V3. Circulation 2002; 5:73–78.
30. Takenaka S, Kusano KF, Hisamatsu K, Nagase S, Nakamura K, Morita H, Matsubara H, et al. Relatively benign clinical course in asymptomatic patients with Brugada type electrogram without family history of sudden cardiac death. J Cardiovasc Electrophysiol 2001; 12:2–6.
31. Atarashi H, Ogawa S, Harumi K, Sugimoto T, Inoue H, Maruyama M, Toyama J, et al. Idiopathic ventricular fibrillation investigators. Three-year follow-up of patients with right bundle branch block and ST segment elevation in the right precordial leads: Japanese Registry of Brugada Syndrome. Idiopathic Ventricular Fibrillation Investigators. J Am Coll Cardiol 2001; 37:1916–1920.
32. Eckardt L, Probst V, Smits JPP, Bahr ES, Wolpert C, Schimpf R, Wichter T, et al. Long-term prognosis of individuals with right precordial ST-segment elevation Brugada syndrome. Circulation 2005; 111:257–263.

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Comparison of conduction delay in the right ventricular outflow tract between Brugada syndrome and right ventricular cardiomyopathy: investigation of signal average ECG in the precordial leads

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RV outflow tract;
Delayed potential

Background In both Brugada syndrome (BS) and arrhythmogenic right ventricular cardiomyopathy (ARVC), electrical abnormalities in the right ventricular outflow tract (RVOT) are important for arrhythmogenesis.
Objectives The aim of this study was to compare conduction delay in the right ventricular in BS with that in ARVC using the signal-averaged electrocardiogram.
Methods Twenty patients with BS (18 men and 2 women; 55 ± 12 years old; 9 symptomatic and 11 asymptomatic) and eight patients with ARVC (six men and two women; 53 ± 16 years old) were included. We assessed the presence of late potentials (LPs) and the filtered QRS duration (fQRSd) in V_2 and V_5 using a high-pass filter of 40 Hz (fQRSd:40) and 100 Hz (fQRSd:100).
Results In ARVC, there was no significant difference in fQRSd:40 between V2 and V5 (158 ± 19 vs. 145 ± 17 ms, respectively): however, in BS, fQRSd:40 in V2 was significantly longer than fQRSd:40 in V5 (147 ± 15 vs. 125 ± 10 ms, $P < 0.001$). In ARVC, there was no significant difference between fQRSd:40 and fQRSd:100 in V_2 and V_5 (158 ± 19 vs. 142 ± 23 ms and 145 ± 17 vs. 132 ± 9 ms, respectively). In contrast, in BS, fQRSd:100 was significantly shorter than fQRSd:40 in V2 (110 ± 8 ms vs. 147 ± 15, $P < 0.001$). The relative decrease in fQRSd:100 compared with fQRSd:40 in V2 was significantly greater in BS than in ARVC.
Conclusion The dominant prolongation of the fQRSd in the right precordial lead in BS was different from the characteristics of ARVC, which may be caused by the conduction delay due to fibro-fatty replacement in RV.

Introduction

Brugada syndrome (BS) is characterized by ST-segment elevation in the right precordial leads associated with ventricular fibrillation (VF). The pattern of the electrocardiogram (ECG) is augmented by sodium channel blockers.[1-3] It has been suggested that loss of the action potential dome in the subepicardial action potential in the right ventricular outflow tract (RVOT) results in phase 2 re-entry and polymorphic ventricular arrhythmias, and these have been demonstrated in an animal model.[4-7]

Ventricular fibrillation can often be induced by programmed electrical stimulation during an electrophysiological study (EPS),[8,9] especially from the RVOT.[10] Furthermore, the body surface map or the signal-averaged ECG (SAECG) has shown delayed activation of the RVOT in BS,[11,12] which may play an important role in arrhythmogenesis. We also recently reported that the dominant prolongation of the filtered QRS duration (fQRSd) in the right precordial leads may be related to the risk of arrhythmic events in BS.[13]

Some investigators consider that BS is due in part to RV cardiomyopathy, because morphological and/or histological abnormalities are found in some patients with BS.[14,15] However, structural anomalies are usually not detected by routine imaging and endomyocardial biopsy.[16] Brugada syndrome may be a primary electrical disease, and this concept is strongly supported by the finding that ~30% of patients have a mutation in *SCN5A* gene. Arrhythmogenic right ventricular cardiomyopathy (ARVC) often shows a conduction delay in the right ventricle (RV), especially the right precordial leads in the surface ECG[11,13] with epsilon waves in V_{1-3}. The conduction delay in ARVC is associated with replacement of myocytes by fatty tissue and fibrosis in the

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RV. The aim of this study was to investigate differences in conduction delay in the RV between BS and ARVC using the SAECG.

Methods

Patients

We studied 20 consecutive patients with BS, who met the diagnostic criteria of the second consensus conference of BS,[17] including 9 symptomatic and 11 asymptomatic patients. Eighteen patients were men, and 2 patients were women (mean age: 55 ± 12 years; range: 33–74 years) (Table 1). No patient had a family history of sudden death. No patient from the same family and in six asymptomatic patients, a type-1 ECG was documented at least once, and in another five patients who had a type-2 ECG, pilsicainide (1 mg/kg in 5 min) provoked a type-1 ECG. Routine cardiac examinations, including echocardiography, left and right ventriculography, and coronary angiography were performed in all patients, and they showed no abnormality. In 3 of 20 patients, we obtained informed consent and investigated the mutation in *SCN5A* gene, and the results were negative (Table 1).

We also studied eight patients (two women and six men) with ARVC. The mean age was 53 ± 16 years (range: 35–74 years). All patients fulfilled either two major or one major and two minor diagnostic criteria recommended by the Task Force of the European Society of Cardiology.[18] All patients had RV dilatation and reduced-wall motion of the RV and ventricular tachycardia (VT) (left bundle branch block type), and three of eight patients had involvement of the left ventricle (LV). The mean ejection fraction of LV (LVEF) was 56 ± 9%. In all patients, T-wave inversion in the precordial leads was observed; however, no patient had a Brugada-type ECG (saddle back or coved type in V_{1-3}) (Table 2).

Signal-averaged electrocardiogram

Late potentials (LPs) were studied in a standard manner using an SAECG system (FDX-6521, Fukuda Denchi, Japan). Analysis of SAECGs was based on quantitative time-domain measurements of the filtered vector magnitude of the orthogonal leads, *x*, *y*, and *z*. The QRS complexes were amplified, digitized, averaged (200–300 beats/min), and high-pass filtered (40 Hz) with the low-pass cut-off frequency fixed at 250 Hz. Three parameters were obtained using a computer algorithm: the fQRSd (cutoff >114 ms), the root mean square voltage of the last 40 ms (RMS40) of the filtered QRS complex (cutoff <20 μV), and the duration of the low-amplitude signal <40 μV (LAS40) at the terminal portion of the QRS complex (cut-off >38 ms). The SAECG was considered positive for LPs when the two criteria (RMS40 <20 μV and LAS40 > 38 ms) were fulfilled. Recordings were acceptable when electrical noise was <0.3 μV. The standard precordial leads, V_{1-6}, were amplified, digitized, averaged (200–300 beats/min), and the fQRSd was measured[13] with a high-pass filter at 40 Hz (fQRSd:40) and 100 Hz (fQRSd:100). We compared the fQRSd:40 and fQRSd:100 in V_2 and V_5, which may preferentially reflect the electrical activity of the RVOT and the LV, respectively.

Electrophysiological Study

Electrophysiological study was performed in all patients to evaluate the inducibility of ventricular tachyarrhythmia after a written informed consent was obtained. No patient in either group received any antiarrhythmic drugs. Three quadripolar electrode catheters (6 F multipurpose catheters, USCI, Boston, MA, USA) were placed against the high right atrium, the apex of the right ventricle (RVA) or the RVOT, and the His bundle region through the right femoral vein. The His-ventricular (HV) interval was measured during constant right atrial pacing at a cycle length of 600 ms. Programmed ventricular stimulation was performed using two basic cycle lengths (400 and 600 ms) at the RVA and the RVOT with a 2-ms pulse width at twice the late diastolic threshold. The number of extra stimuli was limited to 3 and the shortest coupling interval of any extra stimulus was limited to 180 ms for safety. Rapid ventricular pacing up to 210 beats/min was performed at the RVA and the RVOT. Stimulation was attempted first at the RVA and then at the RVOT if ventricular arrhythmias were not induced by 1–2 extra stimuli; triple extra stimuli were introduced first from the RVOT, and then from the RVA. The endpoints of programmed ventricular stimulation were either induction of sustained VT/VF or the completion of the programmed stimulation protocol. When sustained monomorphic VT (SMVT) was induced, rapid ventricular pacing at a cycle length of 10–20 ms shorter than the cycle length of the tachycardia was applied in an attempt to entrain the tachycardia. The pacing was repeated after a decrement of the paced cycle length in steps of 10 ms until the SMVT was interrupted or acceleration of the tachycardia occurred.[19]

Statistical analysis

Quantitative values are expressed as the mean ± SD. Student's *t*-test for unpaired values was used to compare parameters between the two groups. A *P*-value of <0.05 was considered significant for all comparisons.

Results

Signal-averaged electrocardiogram

All patients with ARVC were LP positive (Table 2). On the other hand, only 13 of 20 patients (65%) in the Brugada group were LP positive (Table 1). The RMS40 was significantly lower in patients with ARVC than in patients with BS (4.6 ± 2.7 vs. 13.6 ± 8.7 μV, respectively; $P < 0.01$). The fQRSd:40 in V_2 was 158 ± 19 ms in ARVC and was not significantly different from the fQRSd:40 in V_2 in BS (147 ± 15 ms). In ARVC, there was no significant difference between fQRSd:40 in V_2 and V_5 (158 ± 19 vs. 145 ± 17 ms, respectively); however, in BS, fQRSd:40 in V_2 was significantly longer than fQRSd:40 in V_5 (147 ± 15 vs. 125 ± 10 ms, $P < 0.001$) (Table 3). In ARVC, there was no difference between fQRSd:40 and fQRSd:100 in V_2 or V_5 (158 ± 19 vs. 142 ± 23 ms and 145 ± 17 vs. 132 ± 9 ms, respectively). In contrast, in BS, fQRSd:100 was significantly shorter than fQRSd:40 in V_2 (110 ± 8 vs. 147 ± 15 ms, $P < 0.001$) (Table 3). The relative decrease in fQRSd:100 in V_2 compared with fQRSd:40 in V_2 was significantly greater in BS than in ARVC (Fig. 1). Figures 2, 3, and 4 show typical recordings of the SAECG in the orthogonal leads and the fQRSd from a BS (Case 6 in Table 1) and an ARVC patient (Case 5 in Table 2). The relative decrease (per cent) in fQRSd:100 in V_2 compared with fQRSd:40 in V_2 was not significantly different between symptomatic (cardiac arrest and syncope) and asymptomatic BS patients (23 ± 7% vs. 24 ± 6%, respectively). Six of the 9 symptomatic BS patients (all the patients in the cardiac arrest group and two of the five patients in the syncope group) and 6 of the 11 asymptomatic BS patients had type-1 ECG at the time of investigation, 6 patients had type-2 ECG, and 2 patients had type-3 ECG. The relative decrease in fQRSd:100 in V_2 compared with fQRSd:40 in V_2 tended to be slightly, but not significantly, greater in patients with type-1 ECG than in patients with type-2 or -3 ECG, (26 ± 7% vs. 21 ± 6%, $P = 0.128$).

Table 1 Clinical and electrocardiographic data in Brugada syndrome

Patient No.	Sex/age (year)	Clinical	Family history	SCN5A	LP	RMS40	V_2fQRSd 40 Hz	V_5fQRSd 40 Hz	V_2fQRSd 100 Hz	V_5fQRSd 100 Hz	HV interval	VF inducibility	Therapy/follow-up (month)
1	M/74	Cardiac arrest	−	NE	+	3	160	115	123	115	62	+	ICD/64
2	M/33		−	NE	+	5	150	115	118	108	65	+	ICD/36
3	M/54		−	−	−	21	135	120	103	100	55	−	ICD/35
4	M/63		0	−	+	14	149	117	111	104	60	+	ICD/46
5	M/72	Syncope	0	NE	−	34	123	117	104	100	57	+	ICD/52
6	M/60		0	NE	+	6	162	135	125	116	51	+	ICD/18
7	M/74		−	NE	−	22	153	127	114	109	51	+	ICD/31
8	M/54		−	NE	+	5	174	125	101	110	57	+	ICD/16
9	M/74		0	−	−	22	126	120	110	100	32	+	ICD/10
10	M/64	Asymptomatic	−	NE	−	24	135	120	106	108	40	+	ICD/27
11	M/51		−	NE	+	10	142	139	115	103	53	+	ICD/50
12	F/45		−	NE	+	5	148	125	111	106	52	+	ICD/32
13	M/48		−	NE	−	19	158	130	114	120	64	+	ICD/14
14	M/53		−	NE	−	24	137	119	100	104	43	+	ICD/11
15	M/45		−	NE	+	3	162	138	109	111	45	+	ICD/14
16	M/40		−	NE	+	10	174	137	111	106	43	+	ICD/15
17	M/45		−	NE	+	11	147	126	113	96	50	+	ICD/16
18	M/45		−	NE	+	12	149	135	105	120	46	+	ICD/20
19	M/59		−	NE	+	8	122	102	97	88	43	+	ICD/10
20	F/49		−	NE	+	14	149	138	125	115	36	+	ICD/38

LP, late potential; RMS, root mean square; fQRS, filtered QRS; +, positive; −, negative; NE, not examined; CRBBB, complete right bundle branch block; ICD, implantable cardioverter defibrillator.

Table 2 Clinical and electrocardiographic data in ARVC

Patient no.	Sex/age (years)	Clinical	EF (%)	LV involvement	LP	RMS40	V_2fQRSd 40 Hz	V_5fQRSd 40 Hz	V_2fQRSd 100 Hz	V_5fQRSd 40 Hz	HV interval	Therapy/follow-up (months)
1	M/72	VT	48	+	+	5	150	150	146	137	53	ICD/24
2	M/38	VT	43	+	+	2	171	157	175	147	54	ICD/17
3	M/63	VT	68	0	+	2	139	125	117	126	38	ICD/23
4	F/58	VT	58	0	+	5	168	149	141	126	45	ICD/48
5	F/37	VT	67	0	+	3	171	146	158	143	48	ICD/46
6	M/74	VT	60	0	+	8	132	133	113	125	50	ICD/49
7	M/49	VT	50	+	+	3	190	177	170	130	49	ICD/52
8	M/35	VT	59	0	+	9	147	124	126	127	38	ICD/50

LP, late potential; RMS, root mean square; fQRSd, filtered QRS duration; +, positive; −, negative; ICD, implantable cardioverter defibrillator.

Table 3 Filtered QRS duration (fQRSd) in each filtered condition in both groups

	ARVC (ms)		Brugada (ms)	
	fQRSd:40	fQRSd:100	fQRSd:40	fQRSd:100
V_2	158 ± 19	142 ± 23	147 ± 15	110 ± 8[a]
V_5	145 ± 17	132 ± 9	125 ± 10[b]	106 ± 8

[a] $P < 0.001$, fQRSd:40 vs. fQRSd:100 in Brugada syndrome.
[b] $P < 0.001$, V_2 vs. V_5 in fQRSd:40 in Brugada syndrome.

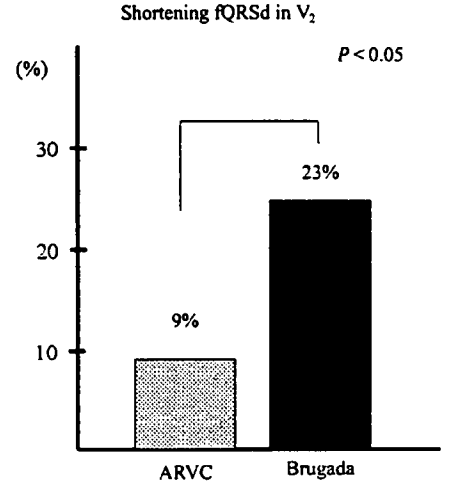

Figure 1 Comparison of the relative shortening of fQRSd in V_2 with an increase in low-pass filtering from 40 to 100 Hz in both of BS and ARVC. The per cent shortening was significantly higher in BS than in ARVC.

Electrophysiological study

Brugada syndrome

The averaged HV interval for all patients was 50 ± 9 ms, and for six patients, the HV interval was ~55 ms. In 19 of 20 patients (95%), VF was induced from the RVOT in nine patients, from the RVA with double extra stimuli in five patients, from the RVOT in three patients, and from the RVA with triple extra stimuli in two patients.

Arrhythmogenic right ventricular cardiomyopathy

The SMVTs, which were identical to the clinical VT, were induced in all patients, and the mean cycle length of VT was 296 ± 45 ms. Entrainment could be proved in 9 of 15 VTs, and the remaining 6 VTs could not be entrained because VT required DC shock for the haemodynamic shock. The averaged HV interval was 46 ± 6 ms, and there was no significant difference in HV interval between ARVC and BS.

Follow-up

Brugada syndrome

An implantable cardioverter defibrillator (ICD) was implanted in all patients and the patients were followed without antiarrhythmic drugs. During a follow-up period of 28 ± 16 months, all patients were alive and two (Case 1 and 15) had an episode of VF that was terminated by an ICD shock.

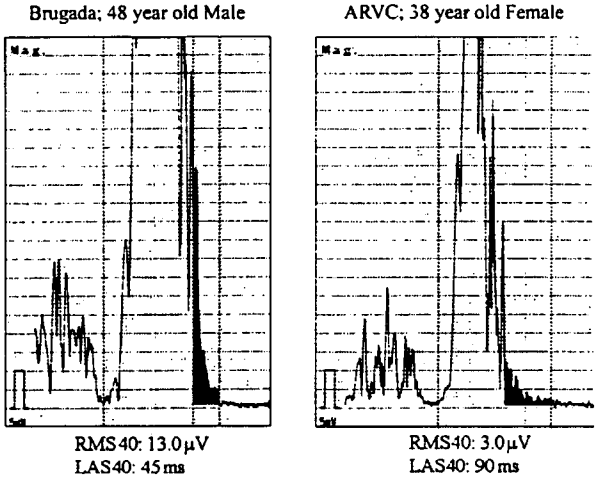

Figure 2 SAECG in BS (Patient 6 in Table 1) and in ARVC (Patient 5 in Table 2). Both patients were positive for LP. RMS40, root mean square voltage of the last 40 ms of the filtered QRS complex (cut-off <20 μV); LAS40, the duration of the low-amplitude signal <40 μV at the terminal portion of the QRS complex (cut-off >38 ms).

Arrhythmogenic right ventricular cardiomyopathy

All patients had ICD therapy and sotalol was prescribed in five of the eight patients because the drug was effective in suppressing inducible VT. During a follow-up period of 39 ± 15 months, all patients were alive and four patients had the delivery of an ICD shock because of SMVT, and anti-tachycardia pacing was effective in terminating VT.

Discussion

Major findings of the present study

In this study, we found that the characteristics of the delayed potential in the right precordial lead were different between BS and ARVC. The fQRSd in the high-pass filter at 40 Hz was similar in both of them, but in the condition of cutting fQRSd at 100 Hz, fQRSd was much shorter in BS than in ARVC. Furthermore, in BS, the fQRSd in the right precordial leads was prolonged, as shown in previous reports, in comparison with that in ARVC.

Relationship between the filter setting and late potential

Late potentials in the SAECG would reflect the presence of slowed ventricular activation, and the presence of slowed ventricular conduction may provide a substrate for re-entry.[20,21] This notion is supported by the finding that all patients with ARVC had re-entrant VT in this study. ARVC is characterized by the fibro-fatty replacement of the RV. This histological change is thought to interrupt the electrical continuity of the myocardial fibres, creating a slow pathway for re-entrant arrhythmias.[22] Folino *et al.*[23] analysed SAECGs using three different high-pass filters (20, 40, and 80 Hz). The results demonstrated that the

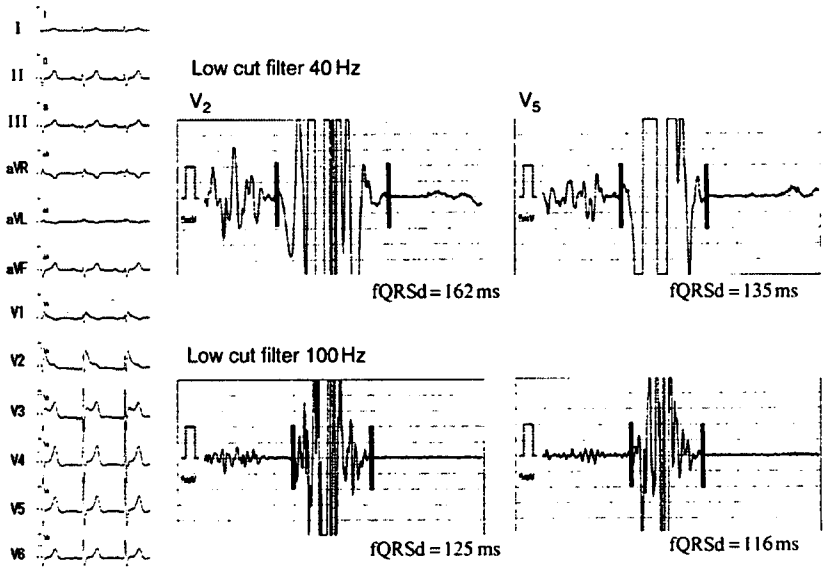

Figure 3 A 12-lead ECG and the filtered QRS duration (fQRSd) in V_2 and V_5 at two different high-pass filter settings (40 and 100 Hz) in a patient with Brugada syndrome (Patient 6 same as in Fig. 2). The fQRSd:40 in V_2 was much longer than that in V_5; however, the V_2 was remarkably shortened as the high-pass filter setting was increased from 40 to 100 Hz.

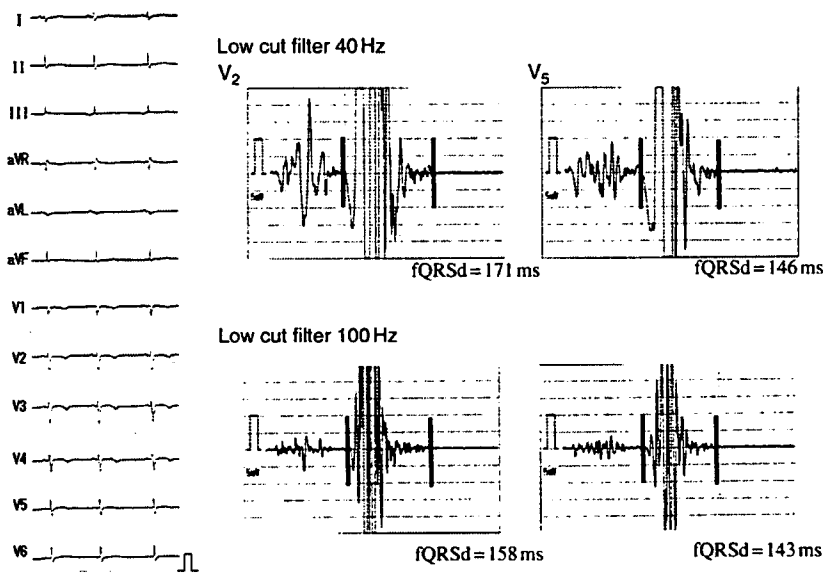

Figure 4 A 12-lead ECG and the fQRSd in V_2 and V_5 at different high-pass filter settings (40 and 100 Hz) in a patient with ARVC (Patient 5 same as in Fig. 2).

prevalence of LPs increased as the high-pass cut-off frequency increased[23] LPs at high frequency might reflect fibrofatty replacement and fine anisotropic conductivity. On the other hand, in the patients with BS in the present study, the fQRSd was remarkably shortened at the 100-Hz filter setting compared with the 40-Hz filter setting. Although LPs can be detected frequently in BS, the mechanism of these LPs is not fully understood. It was proposed that BS is a primary electrical disease without structural abnormalities, and no abnormal electrograms (e.g. delayed potentials or fragmentation) have been reported in the endocardium of RV. Nagase *et al.*[24] confirmed that the timing of a delayed potential in BS recorded from the epicardial surface of the anterior wall of the RV was identical to that of the LP recorded in the SAECG. However, the genesis of this potential remains unknown. Antzelevitch commented on Nagase's[24] report that concealed occurrence of phase 2 re-entry may contribute to the generation of a delayed unipolar potential or LP in the SAECG.[25] If so, the characteristics of the delayed potentials in BS might be different from those in ARVC. The shortening of fQRSd in the right precordial lead at 100 Hz in BS might be related to the delayed second upstroke of the epicardial action potential or local phase 2 re-entry. In the present study, the shortening of

fQRSd at 100 Hz in V_2 was not different between symptomatic and asymptomatic patients with BS or between patients with type-1 ECG and patients with type-2 or -3 ECG. This result suggested that the shortening of fQRSd in V_2 in response to the change in the filter setting might be a characteristic not related to ECG type in BS. The clinical implication of a changing fQRSd in the right precordial leads at different filter settings is not clear and requires further investigation. To clarify whether or not the finding indicates a risk factor for cardiac events in BS, we will need to follow up the clinical outcome in a larger number of asymptomatic BS patients.

Comparison of fQRSd between the right and left precordial lead

Some previous reports have demonstrated that fQRSd was more often prolonged in V_1 than in V_5 in the patients with ARVC.[26,27] This suggested that the prolongation of fQRSd is related to delayed conduction of the RV in ARVC and reflects on the ε-wave in the ECG. In the present study, fQRSd at 40 Hz tended to be longer in V_2 than in V_5, but the difference was not significant. This smaller difference in fQRSd between V_2 and V_5 compared with that in previous reports might have been caused by the degeneration of the inferior wall of the RV and/or the LV. Furthermore, the tendency for a longer fQRSd in V_2 than V_5 did not change at the low-pass filter setting of 100 Hz. In contrast, the fQRSd at 40 Hz in V_2 was significantly longer than that in V_5 in BS, and this difference disappeared at 100 Hz. This suggests the presence of abnormal delayed potentials predominantly in the RVOT, as we previously reported.[13]

Limitations

The major limitation of this study is the small number of the patients studied, especially in ARVC. However, to our knowledge, this is the first report of a comparison of the fQRSd in the SAECG between BS and ARVC and the first demonstration of a difference in the characteristics of a delayed potential in the RVOT in these two diseases. Even though there was no patient with a Brugada-type ECG in the ARVC group, our finding might help to resolve the problem of differentiation between BS and ARVC.

Conflict of interest: none declared.

References

1. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden death: a distinct clinical and electrocardiographic syndrome. *J Am Coll Cardiol* 1992;20:1391-6.
2. Brugada J, Brugada R, Brugada P. Right bundle-branch block and ST-segment elevation in leads V1 through V3: a marker for sudden death in patients without demonstrable structural heart disease. *Circulation* 1998;97:457-60.
3. Brugada R, Brugada J, Antzelevitch C, Kirsch GE, Potenza D, Towbin JA *et al.* Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts. *Circulation* 2000;101:510-5.
4. Yan GX, Antzelevitch C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. *Circulation* 1999;100:1660-6.
5. Gussak I, Antzelevitch C, Bjerregaard P, Towbin JA, Chaitman BR. The Brugada syndrome: clinical, electrophysiological and genetic aspects. *J Am Coll Cardiol* 1999;33:5-15.
6. Antzelevitch C, Brugada P, Brugada J, Brugada R, Nademanee K, Towbin J. The Brugada syndrome. In: *Clinical Approaches to Tacharrhythmias.* Armonk, NY: Futura Publishing Co.; 1999. pp1-99.
7. Antzelevitch C. The Brugada syndrome. *J Cardiovasc Electrophysiol* 2001;12:268-72.
8. Takagi M, Aihara N, Kuribayashi S, Taguchi A, Shimizu W, Kurita T *et al.* Localized right ventricular morphological abnormalities detected by electron-beam computed tomography represent arrhythmnogenic substrates in patients with the Brugada syndrome. *Eur Heart J* 2001;22:1032-41.
9. Aizawa Y, Naitoh N, Washizuka T, Takahashi K, Uchiyama H, Shiba M *et al.* Electrophysiological findings in idiopathic recurrent ventricular fibrillation: special reference to mode of induction, drug testing, and long-term outcomes. *Pacing Clin Electrophysiol* 1996;19:929-39.
10. Morita H, Kusano KF, Nagase S, Morita ST, Nishi N, Kakishita M *et al.* Site-specific arrhythmogenesis in patients with Brugada syndrome. *J Cardiovasc Electrophysiol* 2003;14:373-9.
11. Kasanuki H, Ohnishi S, Ohtuka M, Matsuda N, Nirei T, Isogai R *et al.* Idiopathic ventricular fibrillation induced with vagal activity in patients without obvious heart disease. *Circulation* 1997;95:2277-85.
12. Ikeda Y, Sakurada H, Sakabe K, Sakata T, Takami M, Tezuka N *et al.* Assessment of noninvasive markers in identifying patients at risk in the Brugada syndrome: insight into risk stratification. *J Am Coll Cardiol* 2001;37:1628-34.
13. Furushima H, Chinushi M, Hirono T, Sugiura H, Watanabe H, Komura S *et al.* Relationship between dominant prolongation of the filtered QRS duration in the right precordial leads and clinical characteristics in Bruagada syndrome. *J Cardiovasc Electrophysiol* 2005;16:1311-7.
14. Corrado D, Nava A, Buja G *et al.* Familial cardiomyopathy underlies syndrome of right bundle branch block, ST-segment elevation and sudden death. *J Am Coll Cardiol* 1996;27:443-8.
15. Corrado D, Basso C, Buja G, Nava A, Rossi L, Thiene G. Right bundle branch block, right precordial ST-segment elevation, and sudden death in young people. *Circulation* 2001;103:710-7.
16. Remme CA, Wever EF, Wilde AA, Derksen R, Hauer RN. Diagnosis and long-term follow-up of the Brugada syndrome in patients with idiopathic ventricular fibrillation. *Eur Heart J* 2001;22:400-9.
17. Antzelevitch C, Brugada P, Borggrefe M *et al.* Brugada syndrome. Report of the second consensus conference. Endrosed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation* 2002;111:659-70.
18. McKenna WJ, Thiene G, Nava A *et al.* Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. *Br Heart J* 1994;71:215-8.
19. Aizawa Y, Niwano S, Chinushi M *et al.* Incidence and mechanism of interruption of reentrant ventricular tachycardia with rapid pacing. *Circulation* 1992; 85:585-589.
20. Briethardt G, Borggrefe M. Pathophysiological mechanisms and clinical significance of ventricular late potentials. *Eur Heart J* 1986;7:364-85.
21. Briethardt G, Borggrefe M, Kabenn U *et al.* Prevalence of late potentials in patients with and without ventricular tachycardia: correlations with angiographic findings. *Am J Cardiol* 1982;48:1932-7.
22. Daliento L, Turrini P, Nava A *et al.* Arrhythmogenic right ventricular cardiomyopathy in young versus adult patients: similarities and differences. *J Am Coll Cardiol* 1995;25:655-64.
23. Folino A, Corso LD, Oselladore L *et al.* Signal-averaged electrocardiogram. In: Nava A, Rossi L, Thiene G, eds. Arrhythmogenic Right Ventricular Cardiomyopathy/Dyspasia. New York: Elsevier. 1997. pp. 210-23.
24. Nagase S, Kusano KF, Morita H, Fujimoto Y, Kakishita M, Nakamura K *et al.* Epicardial electrogram of the right ventricular outflow tract in patients with the Brugada syndrome: using the epicardial lead. *J Am Coll Cardiol* 2002;39:1992-5.
25. Antzelevitch C. Late potential and the Brugada syndrome. *J Am Coll Cardiol* 2002;39:1996-9.
26. Blomström-Lundqvist C, Hirch I, Olsson B, Edvardsson N. Quantitative analysis of the signal-averaged QRS in patients with arrhythmogenic right ventricular dysplasia. *Eur Heart J* 1988;9:301-12..
27. Ohe T, Konoe A, Shimizu A, Daikoku S, Kamakura S, Matsuhisa M *et al.* Differentiation between late potentials of right ventricular and of left ventricular origin. *Am J Cardiol* 1989;64:37-41.

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Antiarrhythmic vs. pro-arrhythmic effects depending on the intensity of adrenergic stimulation in a canine anthopleurin-A model of type-3 long QT syndrome

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KEYWORDS
Type-3 long QT syndrome;
Adrenergic activity;
Beta-adrenergic blockade

Aims The effects of adrenergic activity and beta-blockade were studied in a canine experimental model of type-3 long QT syndrome (LQT3) induced by application of anthopleurin-A.
Methods and results Boluses of epinephrine at 0.5 and/or 1.0 μg/kg were administered before and after propranolol, 0.3 mg/kg, and the distribution of the ventricular repolarization and the development of polymorphic ventricular tachyarrhythmia (VA) were assessed. Using needle electrodes, transmural unipolar electrograms were recorded across the left ventricle (LV) and right ventricle (RV). Activation-recovery interval (ARI) was measured in each electrogram to estimate local repolarization during RV pacing at the cycle length of 750 ms after the creation of complete atrioventricular block. Before propranolol, epinephrine, 0.5 μg/kg, did not induce VA in any experiment. However, a dose of 1.0 μg/kg induced polymorphic VA following multiple premature ventricular complex (PVC) in four of six experiments. Epinephrine, 0.5 μg/kg, shortened ARI at all sites and lessened LV transmural ARI dispersion. Neither ARI nor its dispersion could be determined after 1.0 μg/kg of epinephrine because of the induction of PVC, polymorphic VA, or both. Propranolol (i) prevented epinephrine-induced PVC and polymorphic VA in all experiments, (ii) slightly prolonged ARI at all sites, along with a decrease in LV transmural ARI dispersion, and (iii) reversed the epinephrine-induced shortening of ARI.
Conclusion In this LQT3 model, an increase in adrenergic activity by epinephrine had dose-dependent, opposite effects on ventricular electrical stability. Since beta-adrenergic blockade suppressed epinephrine-induced PVC and polymorphic VA, it might be considered for supplemental therapy to suppress VA in patients presenting with LQT3.

Introduction

The enhancement of adrenergic activity is arrhythmogenic,[1-3] and beta-adrenergic blockade is antiarrhythmic[4,5] in patients suffering from congenital type-1 (LQT1) or type-2 (LQT2) long QT syndrome (LQTS). The effects of adrenergic activity on ventricular arrhythmias (VA) in type-3 (LQT3) congenital LQTS, however, are poorly understood. While most adverse cardiac events in LQT3 occur at rest or during sleep, VA can, in some patients, develop during exercise or emotional stress.[4,5] Experimental studies, using pharmacological models (arterially perfused ventricular myocardial wedges, sliced myocardium, or isolated myocardial cells),[6-8] or genetically modified murine hearts,[9,10] and a few clinical cases[1-5] have examined the effects of adrenergic activity in congenital LQTS. However, these studies did not include analyses of intracardiac electrograms at multiple ventricular sites, and the basal autonomic tone was disrupted during the course of the experiments. Therefore, to further clarify the role of adrenergic activity in LQT3, we studied *in vivo* the effects of intravenous boluses of epinephrine administered before and after treatment with propranolol, in a whole heart model of LQT3 made by application of anthopleurin-A (AP-A),[11,12] with special focus on the relationship between transmural dispersion of ventricular repolarization and epinephrine-induced polymorphic VA.

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Methods

Surgical preparation

This study was approved by the Animal Studies Subcommittee of the Institutional Review Board, and complied with the guidelines of the United States National Institutes of Health for the Care and Use of Laboratory Animals. The experiments were performed in six beagles weighing between 10.0 and 13.0 kg, which were anesthetized with a 17.5 mg/kg i.v. bolus of sodium thiopental, followed by a 5.0 mg/kg/h infusion. They were intubated and artificially ventilated. Catheters were inserted into the femoral vein for administration of fluids and drugs, and into the femoral artery to monitor arterial blood pressure (ABP). The core temperatures were kept at 37°C with a thermostatically controlled thermal blanket. The ABP and leads I, III, and aV_F of the surface electrocardiogram were continuously monitored. The hearts were exposed via a midline sternotomy, and saline warmed to 37°C was regularly applied to moisten the heart and prevent cooling of the epicardial surface. Upon completion of the experiments, the animals were sacrificed by electrical induction of ventricular fibrillation under general anaesthesia.

Recordings and pacing electrodes

Four 21-gauge, stainless steel, plunge needle electrodes were inserted in the basal region of the lateral left ventricular (LV) wall, where prominent M-cell-like activity has been described in the dog,[13,14] and three plunge electrodes were inserted into the right ventricular (RV) free wall. Each LV needle had eight and each RV six polyimide-coated tungsten wire electrodes, 50 μm in diameter, 1 mm apart, for the simultaneous transmural recording of unipolar electrograms, from epicardial (Epi), mid-myocardial (Mid), and endocardial (Endo) sites, with the last electrode located ~0.5 mm under the epicardial surface. The last plunge electrode recorded the Epi and the first electrode the Endo electrogram. To simplify the analysis, the electrode that recorded the longest activation-recovery interval (ARI) between Epi and Endo was used as representative of the Mid ventricular layer.[12,13] ARIs were measured between the minimum first derivative of the intrinsic deflection of the QRS and maximum first derivative of the T wave of the unipolar electrogram,[15,16] and used to estimate the local repolarization. Previous studies have shown that ARIs delivered from unipolar electrograms reasonably approximate the local effective refractory periods.[15,16] Furthermore, excellent correlation of ARI and the effective refractory period have been reported in the AP-A model.[17]

Complete atrioventricular (AV) block was produced by radiofrequency catheter ablation of the AV node so as to control the heart rate, and the hearts were paced from bipolar silver wire electrodes inserted on the RV wall, using 2.0-ms pulses at twice the diastolic threshold delivered by a programmable cardiac stimulator (Model SEC-3102, Nihon Kohden Co. Tokyo, Japan).

Electrogram acquisition and measurement of activation–recovery

In each experiment, 50 transmural unipolar electrograms (4 LV needles × 8 electrodes+3 RV needles × 6 electrodes) were amplified and filtered at a fixed high-pass setting of 0.05 Hz, and a 500 Hz adjustable low-pass setting. The analog data were digitized at a 1000 Hz sampling rate (F-tech Co. Ltd., Niigata, Japan) and stored in a personal computer. ARI was measured at each unipolar electrogram, and transmural ARI dispersion was calculated as the widest difference in ARI among 8 LV, or 6 RV unipolar electrograms from each needle electrode.[12,13] Since 7 needle electrodes were inserted in each experiment, 42 data points (7 needles × 6 experiments) were available for the statistical analysis of ARI and its dispersion.

Pharmacologic intervention

A 5 μg/kg i.v. bolus of AP-A (Protein Express Inc., Cincinnati, OH, USA) dissolved in sterile saline was administered, followed by a 0.15 μg/kg/min continuous infusion. Epinephrine (Daiich Sankyo Co. Ltd, Tokyo, Japan), diluted to 10 μg/mL in sterile saline, was injected in 0.5 μg/kg or 1.0 μg/kg i.v. boluses. Propranolol (Astra Zeneca K.K., Osaka, Japan) was administered intravenously in doses of 0.3 mg/kg.

Study protocol and data collection

After creation of a complete AV block, the hearts were paced at the cycle length of 600 ms from the RV during the preparatory period of the experiments. The following protocol was applied in all six experiments during RV pacing at the cycle length of 750 ms.

(i) Before insertion of the needle electrodes in the ventricles, a 1.0 μg/kg i.v. bolus of epinephrine was administered.
(ii) Thereafter, the needle electrodes were positioned in the heart and AP-A was administrated. Recordings of ARI and of its transmural dispersion were obtained before and 60 s after an i.v. bolus of epinephrine, 0.5 μg/kg.
(iii) After a 10 min interval, an additional 1.0 μg/kg i.v. bolus of epinephrine was administered.
(iv) After the administration of propranolol, 0.3 mg/kg, recordings of ARI and of its transmural dispersion were obtained before and 60 s after an i.v. bolus of epinephrine, 1.0 μg/kg.

Inducibility of VA was assessed in each step of the protocol. If polymorphic VA developed, its modes of onset were examined from the transmural ventricular electrograms. ARI and ARI dispersion were averaged over three consecutive cycles. The experimental protocol was completed within 3 h after the creation of AV block, ~2.0 h after the onset of AP-A administration.

Statistical analysis

Values are presented as the means ± SEM. Statistical comparisons of ARI and percent shortening of ARI by epinephrine among the Endo, Mid, and Epi ventricular layers were performed by analysis of variance (ANOVA) using the software of SPSS ver.14 (SPSS Inc., Chicago, IL, USA). The ARI and percent shortening of ARI difference between two of the three ventricular layers (Mid vs. Epi, Mid vs. Endo, and Endo vs. Epi) was assessed using Scheffe's test. Student's *t*-test was used to assess the effects of epinephrine or propranolol administration on ARI and transmural ARI dispersion. Alteration of ABP by the administration of epinephrine or propranolol was also analysed using Student's *t*-test. A P-value < 0.05 was considered statistically significant.

Results

Epinephrine-induced ventricular arrhythmias

After the creation of AV block, experiments were performed during RV pacing at a cycle length of 750 ms. Before the administration of AP-A, a 1.0 μg/kg bolus of epinephrine induced multiple PVC in all six experiments, though no sustained polymorphic VA was observed. After the administration of AP-A, epinephrine, in a dose of 0.5 μg/kg, induced no sustained polymorphic VA in any experiment (*Figure 1A*), although a few PVC developed in one experiment. In contrast, when administered at a dose of 1.0 μg/kg, epinephrine induced multiple PVCs in all experiments, and sustained polymorphic VA triggered by the PVC was induced in four of the six experiments (*Figure 1B*). As

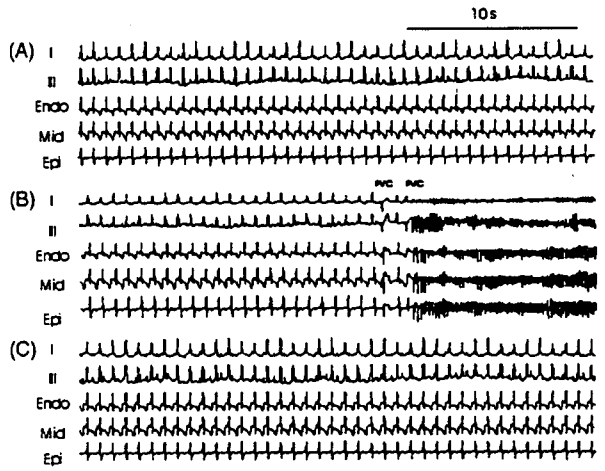

Figure 1 Effects of intravenous administration of epinephrine before and after propranolol in a model of LQT3 created with AP-A. Leads I and III of the surface electrocardiogram and selected LV transmural unipolar electrograms. The heart rate was paced at the cycle length of 750 ms. At baseline (*A*), epinephrine, 0.5 μg/kg, induced neither PVC nor polymorphic VA. However, when administered in a dose of 1.0 μg/kg, epinephrine induced two PVC, of which the second triggered sustained polymorphic VA (*B*). After treatment with propranolol, neither PVC nor polymorphic VA was induced by epinephrine, 1.0 μg/kg (*C*). See text for additional details. Endo, endocardial site; Mid, mid-myocardial site; Epi, epicardial site.

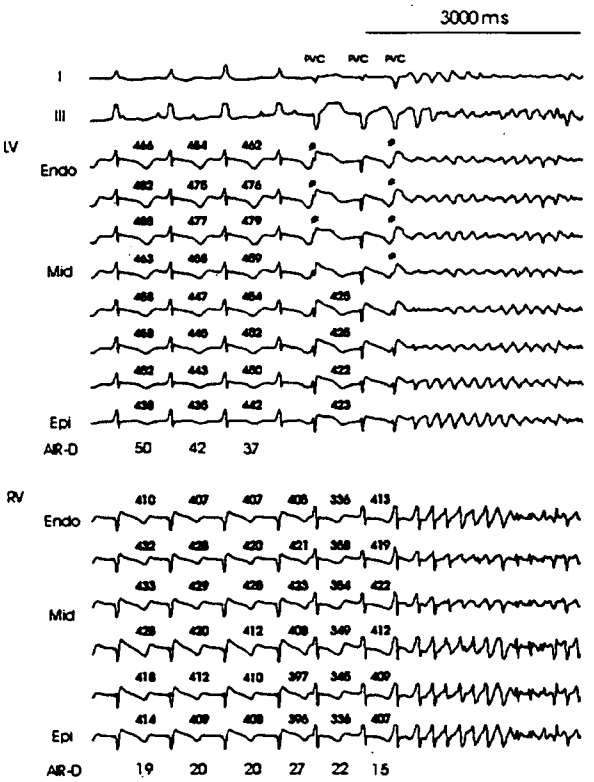

Figure 2 Initiation of polymorphic VA by the administration of epinephrine. Leads I and III of the surface electrocardiogram and selected transmural unipolar electrograms of the LV and RV. The heart rate was paced at the cycle length of 750 ms. When administered at a dose of 1.0 μg/kg, epinephrine induced three consecutive premature ventricular complexes, of which the third triggered sustained polymorphic VA. The onset of polymorphic VA appeared associated with delayed conduction, functional conduction block, or both, at the LV Mid/Endo layer (#). The measured ARI are shown with each intracardiac cycle, and calculated ARI dispersion (ARI-D) is present. ARIs could not be calculated for some of the beats because QRS complex superimposed on the preceding T wave. Abbreviations as in *Figure 1*.

observed in previous studies,[17,18] the onset of polymorphic VA seemed to be associated with the development of PVC which, as they propagated, caused delayed conduction or conduction block at the LV Mid and Endo sites, where the longest ARI were recorded during baseline rhythm (*Figure 2*). These findings seemed to suggest that re-entry was a likely mechanism of the polymorphic VA, but this could not be demonstrated in this study because of the very low resolution of the analysis of ventricular activation and unipolar recording of the local electrogram. After the administration of propranolol, epinephrine, in a dose of 1.0 μg/kg, induced neither PVC nor polymorphic VA in any experiments (*Figure 1C*).

After the administration of AP-A, epinephrine at 0.5 and 1.0 μg/kg transiently increased the ABP from 122 ± 4/69 ± 3 to 166 ± 3/87 ± 2 mmHg ($P = 0.002$) and 196 ± 4/107 ± 4 mmHg ($P = 0.0001$), respectively. The blood pressure decreased to 106 ± 2/60 ± 3 mmHg after propranolol ($P = 0.003$), and reached 132 ± 2/73 ± 2 mmHg after the subsequent administration of epinephrine, 1.0 μg/kg ($P = 0.002$). Although we did not measure the circulating concentration of the drugs, the applied dosage of epinephrine or propranolol are likely to be applicable clinically, and alterations of the ABP were within the clinically relevant range.

Activation-recovery interval and transmural activation–recovery interval-dispersion

Before propranolol

After the administration of AP-A, a transmural ARI dispersion as long as 61 ± 4 ms was recorded through the LV during RV pacing at the cycle length of 750 ms (*Figure 3*, *Tables 1* and 2). The transmural ARI dispersion across the RV wall was 18 ± 2 ms (*Figure 4*, *Tables 1* and 2). Epinephrine at 0.5 μg/kg shortened ARI at all sites (*Figures 3* and *4*, *Table 1*). Since the magnitude of ARI shortening by epinephrine was greater ($P < 0.001$ by ANOVA) in the LV Mid (−13.4 ± 1.2%) and Endo (−13.1 ± 1.1%) layers than at the Epi sites (−9.2 ± 0.9%), the transmural LV ARI dispersion was shortened to 34 ± 3 ms (*Table 2*). In the RV, the amount of epinephrine-induced ARI shortening was −8.0 ± 1.2% in Endo, −9.2 ± 1.3% in Mid, and −8.7 ± 1.1% in Epi (ns), and ARI dispersion in the RV was 14 ± 2 ms 60 s after administration of epinephrine (*Table 2*). After the injection of 1.0 μg/kg of epinephrine, the ARI distribution and transmural ARI dispersion could not be ascertained in either ventricle because of the development of multiple PVC, polymorphic VA, or both.

After propranolol

The intravenous administration of propranolol slightly prolonged ARI at all sites (*Figures 3 and 4*, *Table 1*). In the LV, the magnitude of ARI prolongation was smaller ($P < 0.001$ by ANOVA) in the Mid (4.5 ± 0.7%) and Endo (5.3 ± 0.7%)

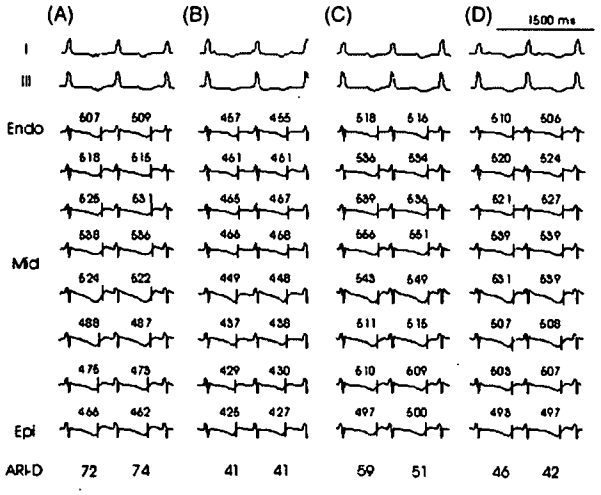

Figure 3 Left ventricular transmural electrograms. Leads I and III of the surface electrocardiogram and selected LV transmural unipolar electrograms. The heart rate was paced at the cycle length of 750 ms. (*A* and *B*) Before propranolol. After the administration of AP-A (A), the ARI at the Mid site is longer than at the Epi and Endo sites. A large (72–74 ms) ARI dispersion (ARI-D) is present. Epinephrine at 0.5 μg/kg shortened ARI at all sites (B), and ARI dispersion shortened to 41 ms. (*C* and *D*) After propranolol. Propranolol slightly prolonged ARI at all sites (C). Since the ARI prolongation at Epi was relatively larger, ARI dispersion was limited to 51–59 ms. Propranolol reversed the epinephrine-induced ARI shortening (D), and ARI dispersion after the administration of epinephrine, 1.0 μg/kg, was 42–46 ms. The measured ARI are shown with each intracardiac cycle. Vertical lines in each beat indicate the maximum first derivative of the T wave. Abbreviations as in *Figure 1*.

layers than in the Epi layer (10.4 ± 0.6%), and the transmural ARI dispersion was shortened to 37 ± 2 ms after propranolol (*Figure 3*, *Table 2*). In the RV, the magnitude of ARI prolongation was 7.4 ± 0.9% in Endo, 6.9 ± 1.0% in Mid, and 7.3 ± 0.8% in Epi (ns), and the transmural ARI dispersion was 17 ± 1 ms after propranolol (*Figure 4*, *Table 2*).

The administration of propranolol reversed the epinephrine-induced shortening of ARI in both ventricles (*Figures 3 and 4*, *Table 1*) and, 60 s after 1.0 μg/kg of epinephrine, ARI dispersion was 35 ± 2 ms in the LV and 17 ± 2 ms in the RV (*Table 2*).

Discussion

Two main observations emerged from this study. First, in an experimental model of LQT3 created with AP-A, adrenergic stimulation had opposite effects on ventricular electrical stability depending on the dose of epinephrine administered intravenously. While 0.5 μg/kg resulted in homogeneous distribution of ventricular repolarization, without induction of sustained polymorphic VA, 1.0 μg/kg was pro-arrhythmic and caused sustained polymorphic VA triggered by PVC in 2/3 of the experiments. Second, propranolol prevented the development of epinephrine-induced polymorphic VA, along with inducing a mild decrease in transmural dispersion of ventricular repolarization during stable ventricular pacing. Although we did not measure the circulating concentration of AP-A, the AP-A model is considered a suitable surrogate for clinical LQT3 because the ventricular repolarization is reasonably prolonged and polymorphic VA spontaneously develops, especially during the slower heart rate and/or following short-long-short cardiac cycle or T wave alternans.[11,12,19]

Adrenergic stimulation in long QT syndrome

Adrenergic stimulation augments several currents in the ventricular myocytes, including I_{Ks}, I_{Ca}, the Ca^{2+}-activated chloride current, and the Na^+/Ca^{2+} exchange current.[20–22]

Table 1 Effects of epinephrine on left and right ventricular activation–recovery intervals at baseline and after the administration of propranolol in the endocardial (Endo), mid-myocardial (Mid), and epicardial (Epi) layers

	Activation-recovery intervals			*P* (Endo vs. Mid vs. Epi)
	Endo	Mid	Epi	
Left ventricle				
Before propranolol				
Before epinephrine	496 (4)	509 (4)	449 (5)	<0.001
After epinephrine	432 (7)	441 (8)	407 (6)	<0.001
P (baseline vs. epinephrine)	<0.001	<0.001	<0.001	
After propranolol				
Before epinephrine	522 (4)	532 (4)	495 (4)	<0.001
After epinephrine	518 (4)	526 (3)	492 (4)	<0.001
P (baseline vs. epinephrine)	0.062	0.012	0.187	
Right ventricle				
Before propranolol				
Before epinephrine	443 (4)	455 (4)	438 (3)	0.008
After epinephrine	407 (3)	413 (3)	399 (2)	0.001
P (baseline vs. epinephrine)	<0.001	<0.001	<0.001	
After propranolol				
Before epinephrine	475 (4)	486 (3)	469 (2)	<0.001
After epinephrine	474 (3)	482 (3)	465 (2)	<0.001
P (baseline vs. epinephrine)	0.275	0.065	0.061	

Values are means (SEM).