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Electrophysiologic Characteristics and Implications of Induced Ventricular Fibrillation in Symptomatic Patients With Brugada Syndrome

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OBJECTIVES The study examined the electrocardiographic and electrophysiologic characteristics in relation to programmed ventricular stimulation (PVS)-induced ventricular fibrillation (VF), as well as the implications of PVS-induced VF on the recurrence of cardiac events in symptomatic Brugada syndrome.

BACKGROUND Brugada syndrome is characterized by ST-segment elevation in the right precordial leads (V_1–V_3) and an episode of VF.

METHODS Thirty-four symptomatic patients with Brugada syndrome (33 men and 1 woman; 44 ± 12 years old) were classified into two groups according to the inducibility of VF with PVS: 22 patients with induced VF requiring direct cardioversion for termination (Induced VF group) and 12 patients without induced VF (Noninduced VF group).

RESULTS The induced VF group showed a longer QRS duration, a higher incidence of right bundle branch block and late potentials detected on the signal-averaged electrocardiogram, longer His-ventricular intervals and a longer conduction time from the RVOT to the left ventricle at extrastimulation than those in the non-induced VF group. However, there was no significant difference in the recurrence of cardiac events (VF documented by an implantable cardioverter-defibrillator and sudden cardiac death) between the two groups (8 [36%] of 22 patients vs. 7 [58%] of 12 patients) during long-term follow-up (range 1 to 149 months; mean 38).

CONCLUSIONS Our data suggest that induction of VF by PVS depends on the severity of depolarization abnormalities but does not predict the recurrence of cardiac events in symptomatic Brugada syndrome, indicating that both depolarization and repolarization abnormalities are important in the development of VF. (J Am Coll Cardiol 2002;39:1799–805) © 2002 by the American College of Cardiology Foundation

In 1992, Brugada and Brugada described eight patients with a history of aborted sudden death due to ventricular fibrillation (VF) with a distinct electrocardiographic (ECG) pattern, consisting of right bundle branch block (RBBB) with ST-segment elevation in the right precordial leads (V_1–V_3) and a normal QT interval in the absence of any structural heart disease (1). Thereafter, patients with these unique ECG abnormalities have been recognized as a distinct subgroup with a high risk of sudden cardiac death (SCD) (2–6). The only gene to be linked to the Brugada syndrome was first reported by Chen et al. (7), who found mutations in the cardiac sodium channel gene, *SCN5A*. Some clinical studies have reported the presence of depolarization abnormalities and the possibility of a subclinical form of right ventricular cardiomyopathy in this syndrome (8–10). Other experimental and clinical studies have suggested, however, that heterogeneous repolarization across the ventricular wall of the right ventricular outflow tract (RVOT) was responsible for the ST-segment elevation and genesis of VF (11–15). Although both depolarization and repolarization abnormalities seem to be present in this syndrome, it is still unclear how these abnormalities interact and contribute to its pathogenesis. Moreover, the electrophysiologic characteristics and implications of programmed ventricular stimulation (PVS)-induced VF remain unclear in patients with Brugada syndrome. Therefore, we systematically carried out this study to examine: 1) the ECG and electrophysiologic characteristics in relation to PVS-induced VF; and 2) the implications of PVS-induced VF on the recurrence of cardiac events during long-term follow-up in symptomatic patients with Brugada syndrome.

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Abbreviations and Acronyms

ECG = electrocardiogram
ICD = implantable cardioverter-defibrillator
LPs = late potentials
PVS = programmed ventricular stimulation
RBBB = right bundle branch block
RVA = right ventricular apex
RVOT = right ventricular outflow tract
SCD = sudden cardiac death
T_{40} = duration of low-amplitude signals <40 μV of the filtered QRS complex
V_{40} = root mean square voltage of the terminal 40 ms of the filtered QRS complex
VF = ventricular fibrillation
VT = ventricular tachycardia

METHODS

Study group. From September 1989 through February 2000, we systematically studied 34 consecutive patients with symptomatic Brugada syndrome who were admitted to the National Cardiovascular Center, Osaka, Japan. Symptomatic Brugada syndrome was diagnosed if the following criteria were fulfilled (16): 1) a history of apparent syncope, or aborted cardiac arrest with or without documented VF; 2) spontaneously documented persistent or transient ST-segment elevation (coved and/or saddle-back type) in the right precordial leads (V_1–V_3), with or without some degree of RBBB; 3) a normal corrected QT interval <0.44 s; 4) normal findings on physical examination and normal laboratory values; and 5) no evidence of structural heart disease demonstrated on the cardiac echocardiogram, coronary angiogram, right and left ventriculograms, radionucleogram and magnetic resonance image. All but one of the patients were male (age range 19 to 68 years; mean 44 ± 12). All 34 patients had episodes of syncope, and 23 patients had a history of aborted cardiac arrest before diagnosis. Ventricular fibrillation was documented in 22 patients, and four patients had family members who died suddenly (Table 1).

Twelve-lead ECG. A 12-lead ECG was recorded during sinus rhythm in the absence of any anti-arrhythmic drugs. The RR interval, PR interval and QRS duration were measured in lead V_5 or V_6. We defined RBBB by the presence of a widened S wave in the left precordial lead (V_6) and a QRS duration ≥0.10 s; incomplete RBBB was defined by a QRS duration <0.12 s; and complete RBBB by a QRS duration ≥0.12 s.

Signal-averaged ECG. The late potential (LP) was analyzed using a signal-averaged ECG system (Arrhythmia Research Technology 1200EPX, Milwaukee, Wisconsin). Analysis of the signal-averaged ECG was based on the quantitative time-domain measurements of the filtered vector magnitude of the orthogonal Frank X, Y and Z leads. The QRS complexes were amplified, digitized, averaged (350 to 400 beats) and filtered with a high-pass filter (40 Hz). Three parameters were assessed using a computer algorithm: 1) the total filtered QRS duration; 2) the root mean square voltage of the terminal 40 ms of the filtered QRS complexes (V_{40}); and the duration of low-amplitude signals <40 μV of the filtered QRS complex (T_{40}). The LP was considered present when two criteria ($V_{40} < 18$ μV and $T_{40} > 38$ ms) were fulfilled.

Electrophysiologic study. An electrophysiologic study was performed in all patients without any anti-arrhythmic drugs after informed consent was obtained. The atrio-His interval and the His-ventricular interval were measured during constant right atrial pacing at a cycle length of 600 ms. Programmed ventricular stimulation was performed at 2-ms and twice the diastolic threshold current from the right ventricular apex (RVA) and the RVOT, using two basic cycle lengths (500 and 600 ms) and a maximum of triple extrastimuli. Inducibility of ventricular arrhythmias was tested first at the RVA using single and double extrastimuli, and in case of noninducibility, it was tested at the RVOT using single and double extrastimuli. If ventricular arrhythmias were not induced using up to double extrastimuli, triple extrastimuli were introduced from the RVA first, and then from the RVOT. The end points of PVS were either induction of VF associated with hemodynamic collapse or completion of the PVS protocol. Ventricular fibrillation was defined as a polymorphic ventricular arrhythmia with an R-R interval ≤200 ms (≥300 beats/min) and hemodynamic decompensation requiring direct cardioversion for termination. Nonsustained polymorphic ventricular tachycardia (VT) was defined as polymorphic ventricular arrhythmia of ≥5 beats and terminating spontaneously. If VF was not induced during PVS using up to double extrastimuli at the RVOT, we measured the conduction time from the RVOT to the lateral wall of the left ventricle during double extrastimuli from the RVOT. The longest conduction time between the stimulus artifact at the RVOT and the ventricular electrogram at the distal coronary sinus was used as a parameter of conduction delay via the ventricular septum at a basic cycle length of 500 ms (S_1V_1), at a first extrastimulus (S_2V_2) and at a second extrastimulus (S_3V_3), respectively.

Thirty-four patients were classified into two groups according to the inducibility of VF: 22 patients with induced VF requiring direct cardioversion for termination (induced VF group) and 12 patients without induced VF (noninduced VF group). We compared the electrocardiographic and electrophysiologic parameters and the recurrence of cardiac events between the two groups. In the noninduced VF group, nonsustained polymorphic VT was induced in eight patients, but no ventricular arrhythmias were induced in the other four patients.

Therapy and follow-up. All patients were followed up at the outpatient clinics of the National Cardiovascular Center. Because all patients were symptomatic (apparent syncope or aborted cardiac arrest) in the present study, implantation of an implantable cardioverter-defibrillation (ICD) was recommended in all patients. Some earlier patients, who were admitted when an ICD was not available in Japan and continued to refuse implantation later, were treated with

Table 1. Clinical and Electrocardiographic Data

				Clinical Events			12-Lead ECG					SAECG			
Patient No.	Age (yrs)	Gender	Family History	Syncope	Documented VF	Aborted Cardiac Arrest	PQ (ms)	QRS (ms)	QTc (s)	ST-Segment Elevation	RBBB	TFQRS (ms)	V_{40} (μV)	T_{40} (ms)	LPs
Induced VF group															
1	21	M	−	+	+	+	168	83	0.33	V_1–V_3	—	117	18.7	30	−
2	51	M	−	+	+	+	162	96	0.42	V_1–V_3	—	89	25.5	31	−
3	38	M	−	+	−	+	188	94	0.41	V_1,V_2	IRBBB	126	7.6	51	+
4	38	M	−	+	+	−	186	106	0.41	V_1,V_2	IRBBB	123	9.9	63	+
5	51	M	−	+	−	−	186	101	0.33	V_1–V_3	IRBBB	118	3.5	49	+
6	37	M	−	+	+	+	166	104	0.40	V_1–V_3	IRBBB	132	15.5	47	+
7	63	M	−	+	−	−	189	106	0.44	V_1–V_3	IRBBB	116	4.7	50	+
8	50	M	−	+	+	+	168	106	0.40	V_1–V_3	IRBBB	126	8.0	66	+
9	48	M	−	+	−	−	165	112	0.42	V_1–V_3	IRBBB	127	5.8	69	+
10	27	M	−	+	−	−	166	104	0.39	V_1–V_3	IRBBB	113	14.0	45	+
11	63	M	−	+	+	+	194	122	0.40	V_1–V_4	CRBBB	153	10.6	85	+
12	47	M	+	+	−	+	191	128	0.41	V_1–V_3	CRBBB	144	6.2	60	+
13	57	M	−	+	+	+	190	138	0.42	V_1,V_2	CRBBB	165	4.0	70	+
14	42	M	−	+	+	+	149	114	0.42	V_1–V_3	IRBBB	131	5.3	53	+
15	52	M	−	+	−	−	183	128	0.43	V_1–V_3	CRBBB	139	11.3	62	+
16	57	M	−	+	+	+	149	114	0.38	V_1–V_3	CRBBB	134	11.0	84	+
17	68	M	−	+	−	−	160	102	0.39	V_1–V_3	IRBBB	115	9.2	50	+
18	50	M	−	+	+	+	148	116	0.43	V_1,V_2	IRBBB	136	7.8	64	+
19	48	M	−	+	−	−	236	108	0.43	V_1–V_3	IRBBB	139	6.1	62	+
20	33	M	−	+	+	+	175	136	0.39	V_1,V_2	CRBBB	113	14.0	45	+
21	27	M	+	+	+	+	154	104	0.42	V_1–V_3	IRBBB	110	18.0	36	−
22	42	M	−	+	+	+	192	106	0.40	V_1	IRBBB	102	15.5	41	+
Mean ± SD	46 ± 12						176 ± 20	110 ± 13*	0.40 ± 0.03			126 ± 17*	10.6 ± 5.6*	55 ± 15*	
Noninduced VF group															
1	41	M	−	+	+	+	182	94	0.40	V_1–V_3	—	107	29.7	25	−
2	46	M	−	+	+	+	164	91	0.43	V_1–V_3	—	103	11.2	42	+
3	29	M	−	+	+	+	194	84	0.41	V_1,V_2	—	123	9.2	62	+
4	19	M	−	+	+	+	176	80	0.39	V_1,V_2	—	103	20.9	26	−
5	32	M	−	+	+	+	190	85	0.36	V_1,V_2	—	93	26.5	24	−
6	61	M	+	+	−	−	176	106	0.43	V_1–V_3	—	107	10.6	42	+
7	35	M	−	+	+	+	196	102	0.41	V_1,V_2	IRBBB	102	NA	NA	−
8	47	M	+	+	+	+	133	103	0.37	V_1–V_3	IRBBB	117	33.1	23	−
9	44	M	−	+	−	−	165	111	0.39	V_1,V_2	IRBBB	119	9.0	54	+
10	43	M	−	+	+	+	168	94	0.38	V_1–V_3	—	120	10.2	50	+
11	23	F	−	+	−	−	162	96	0.43	V_1,V_2	—	97	33.5	28	−
12	49	M	−	+	+	+	160	108	0.41	V_1,V_2	IRBBB	115	11.6	46	+
Mean ± SD	39 ± 12						172 ± 18	96 ± 10	0.40 ± 0.02			109 ± 10	18.7 ± 10.2	38 ± 14	

*$p < 0.01$ vs. Noninduced VF group.

CRBBB = complete right bundle branch block; ECG = electrocardiogram; IRBBB = incomplete right bundle branch block; LPs = late potentials; NA = not available; PQ = PQ interval; QRS = QRS duration; QTc = corrected QT interval; SAECG = signal-averaged electrocardiogram; TFQRS = total filtered QRS duration; T_{40} = duration of low-amplitude signals <40 μV in the terminal position of the SAECG-QRS complexes; V_{40} = root mean square voltage in the terminal 40 ms of the SAECG-QRS complexes; VF = ventricular fibrillation; + = present; − = absent.

anti-arrhythmic drugs (disopyramide or amiodarone). Propranolol, a beta-blocker, was added in patients in whom an ICD was implanted, and any inappropriate cardioversion was documented as being due to sinus tachycardia or atrial fibrillation. Special attention was paid to recurrences of symptomatic arrhythmias. The end points were either apparent syncope, SCD or VF documented in the storage memory of the ICD. Patients who could not be followed up for more than one year were excluded from the present study.

Statistical analysis. Quantitative data are presented as the mean value ± SD and were analyzed by using the two-tailed Student *t* test. Categorical data are presented as absolute and were analyzed by the chi-square test. Kaplan-Meier life-table analysis was used to determine the differences in event-free survival rates between the two groups. A p value <0.05 was regarded as significant.

RESULTS

Electrocardiographic characteristics. Table 1 shows the ECG data, including 12-lead and signal-averaged ECGs, of the two patient groups. The induced VF group had a longer QRS duration than the noninduced VF group (110 ± 13 vs. 96 ± 10 ms; $p < 0.01$), whereas the RR interval, the PQ interval and the corrected QT interval were not different between the two groups. The induced VF group also showed higher incidences of complete or incomplete RBBB than the noninduced VF group (20 [91%] of 22 patients vs. 4 [33%] of 12 patients; relative risk 2.72, $p < 0.01$). Moreover, the induced VF group had longer total filtered QRS duration, lower V_{40}, and longer T_{40} on the signal-averaged ECG than the non-induced VF group (total filtered QRS duration: 126 ± 17 vs. 109 ± 10 ms, $p < 0.01$; V_{40}: 10.6 ± 5.6 vs. 18.7 ± 10.2 μV, $p < 0.01$; T_{40}: 55 ± 15 vs. 38 ± 14 ms, $p < 0.01$). The induced VF group also had a higher incidence of LPs than the noninduced VF group (19 [86%] of 22 patients vs. 6 [50%] of 12 patients; relative risk 1.73, $p < 0.05$).

Electrophysiologic characteristics. The electrophysiologic data of the two patient groups are shown in Table 2. The induced VF group had a longer His-ventricular interval than the noninduced VF group (49 ± 9 vs. 41 ± 7 ms; $p < 0.05$), whereas the atrio-His interval was not different between the two groups. There were no significant differences in the effective refractory period at a basic cycle length of 500 ms at either the RVOT or RVA between the two groups. On the other hand, the longest conduction times via the ventricular septum at the first extrastimulus (S_2V_2) and second extrastimulus (S_3V_3) were longer in the induced VF group than in the noninduced VF group (S_2V_2: 176 ± 39 vs. 142 ± 26 ms, $p < 0.05$; S_3V_3: 208 ± 35 vs. 176 ± 27 ms, $p < 0.05$). Ventricular fibrillation was induced with a single extrastimulus (in 1 patient from the RVOT), double extrastimuli (n = 12; in 8 from the RVOT and in 4 from the RVA) and triple extrastimuli (n = 9; in 6 from the RVOT and in 3 from the RVA) in the induced VF group. Nonsustained polymorphic VT was induced with double extrastimuli (in 1 patient from the RVOT) and triple extrastimuli (in 7 patients from the RVOT) in the noninduced VF group.

Therapy and follow-up. An ICD was implanted in 19 of 22 patients in the induced VF group and in 9 of 12 patients in the noninduced VF group (Table 3). Propranolol was added in one patient in the induced VF group and in three patients in the noninduced VF group. One patient in the noninduced VF group refused to stop disopyramide after ICD implantation. Three patients in the induced VF group and three patients in the noninduced VF group were treated with anti-arrhythmic drugs only (i.e., disopyramide, amiodarone or pindolol). The average follow-up periods were 36 ± 32 months in the induced VF group and 46 ± 45 months in the noninduced VF group. There was no significant difference in the recurrence of cardiac events (VF documented by ICD and SCD) between the two groups (8 [36%] of 22 patients vs. 7 [58%] of 12 patients) during long-term follow-up. Two patients (1 in the induced VF group and 1 in the noninduced VF group) who were treated with disopyramide died suddenly. The ICD effectively terminated all episodes of VF and prevented SCD. All episodes occurred during sleep (between 10:00 PM and 9:00 AM), except for three patients: one had VF in the early morning (8:30 AM), one developed VF at 5:30 PM, and the other suffered VF at 7:15 PM while awake. A life-table analysis showing a comparison of the cumulative proportion of either VF or SCD between the two groups is shown in Figure 1. There were no significant differences in the frequency of the recurrence of VF or SCD between the two groups. It is noteworthy that the first recurrence of cardiac events was observed within two years in all but three patients.

DISCUSSION

The major finding of our study was that the induction of VF by PVS depended on the severity of depolarization abnormalities in symptomatic patients with Brugada syndrome. However, the PVS-induced VF did not predict the recurrence of cardiac events during long-term follow-up.

Electrophysiologic and ECG characteristics in Brugada syndrome. A recently highlighted form of Brugada syndrome is characterized by ST-segment elevation in the right precordial ECG leads (V_1–V_3), often but not always accompanied by apparent RBBB (1–6). Prolongation of the His-ventricular interval has been demonstrated during electrophysiologic testing in several reports (1–3). Moreover, several clinical studies have suggested a high incidence of LPs detected on the signal-averaged ECG in patients with Brugada syndrome (2,9,10). These are all well-established hallmarks of depolarization abnormalities. In our 34 symptomatic patients with Brugada syndrome, both the QRS duration and His-ventricular interval were moderately pro-

Table 2. Electrophysiologic Data

Patient No.	AH (ms)	HV (ms)	ERP (ms)		Longest CT (ms)			Induced Arrhythmias		
			RVOT	RVA	S_1V_1	S_2V_2	S_3V_3	Event	Location	No. of Extrastimuli
Induced VF group										
1	90	53	210	240	160	185	220	VF	RVOT	T
2	95	32	240	200	NA	NA	NA	VF	RVA	D
3	100	45	220	250	NA	NA	NA	VF	RVOT	T
4	98	50	220	230	NA	NA	NA	VF	RVOT	T
5	100	52	200	210	145	170	200	VF	RVOT	D
6	NA	NA	NA	NA	NA	NA	NA	VF	RVA	T
7	100	53	NA	220	NA	NA	NA	VF	RVA	D
8	90	46	200	210	150	180	190	VF	RVOT	D
9	96	43	220	240	148	165	210	VF	RVOT	D
10	NA	60	NA	NA	NA	NA	NA	VF	RVA	T
11	110	60	240	250	NA	NA	NA	VF	RVA	T
12	100	70	220	220	230	240	255	VF	RVOT	D
13	NA	NA	NA	NA	NA	NA	NA	VF	RVA	D
14	135	50	220	220	120	167	185	VF	RVOT	T
15	120	60	230	230	220	240	260	VF	RVOT	D
16	100	46	240	230	NA	NA	NA	VF	RVOT	D
17	80	40	210	220	127	176	241	VF	RVOT	D
18	100	38	230	190	102	120	150	VF	RVOT	T
19	158	48	220	230	NA	NA	NA	VF	RVOT	S
20	120	52	220	210	172	174	210	VF	RVOT	T
21	90	40	200	200	108	116	168	VF	RVOT	D
22	114	42	NA	210	NA	NA	NA	VF	RVA	D
Mean ± SD	105 ± 18	49 ± 9*	220 ± 13	222 ± 17	153 ± 42	176 ± 39*	208 ± 35*			
Noninduced VF group										
1	90	30	210	220	NA	NA	NA	–	–	T
2	85	44	210	210	160	165	180	NSPVT	RVOT	T
3	90	55	250	240	NA	NA	NA	–	–	T
4	110	40	200	210	120	150	200	NSPVT	RVOT	T
5	107	40	250	220	145	156	200	–	–	T
6	NA	50	NA	NA	NA	NA	NA	NSPVT	RVOT	T
7	90	45	240	210	170	170	180	NSPVT	RVOT	T
8	60	42	210	230	120	130	195	NSPVT	RVOT	T
9	82	38	210	210	134	152	180	NSPVT	RVOT	T
10	125	42	220	230	NA	NA	NA	–	–	T
11	95	35	230	240	88	96	132	NSPVT	RVOT	T
12	105	35	200	200	108	114	138	NSPVT	RVOT	T
Mean ± SD	94 ± 17	41 ± 7	221 ± 19	220 ± 13	131 ± 27	142 ± 26	176 ± 27			

*$p < 0.05$ vs. Noninduced VF group.

AH = atrio-His interval; CT = conduction time; D = double extrastimuli; ERP = effective refractory period; HV = His-ventricular interval; NA = not available, NSPVT = nonsustained polymorphic ventricular tachycardia; RVA = right ventricle apex; RVOT = right ventricle outflow tract; S_1V_1 = longest CT at a basic cycle length of 500 ms; S_2V_2 = longest CT at the first extrastimulus; S_3V_3 = longest CT at the second extrastimulus; T = triple extrastimuli; VF = ventricular fibrillation; – = absent.

longed (QRS duration: 105 ± 14 ms; His-ventricular interval: 45 ± 9 ms). Moreover, 24 patients (71%) showed incomplete (n = 18) or complete (n = 6) RBBB patterns, and 25 patients (74%) had LPs on the signal-averaged ECG. These findings are consistent with previous studies and suggest the presence of subtle depolarization abnormalities that cannot be reflected as structural abnormalities in symptomatic Brugada syndrome. Moreover, the longest conduction time from the RVOT through the ventricular septum to the lateral left ventricle at the first (S_2V_2) and second (S_3V_3) extrastimulus were 161 ± 38 and 194 ± 35 ms, respectively, which were both longer than those in control subjects (unpublished data). Corrado et al. (8) demonstrated that the latest endocardial ventricular electrogram was recorded at the RVOT, suggesting the presence of a conduction delay at the RVOT. These findings indicate that depolarization abnormalities may exist mainly at the RVOT and ventricular septum in patients with Brugada syndrome.

Implications of PVS-induced VF. In the present study, VF requiring direct cardioversion for termination was induced in 22 (65%) of the 34 patients. Of note, the VF was induced by a single extrastimulus or double extrastimuli in 13 of 22 patients. The high inducibility of VF by less extrastimuli in our symptomatic Brugada patients was concordant with the degree of inducibility reported in several previous studies (17–19). More importantly, 22 patients with PVS-induced VF showed longer QRS durations, a higher incidence of RBBB and LPs, longer His-ventricular intervals and longer conduction times via the ventricular

Table 3. Therapy and Follow-Up

Patient No.	Follow-Up (month)	Therapy	Recurrent Event
Induced VF group			
1	76	Amiodarone, 200 mg	—
2	29	ICD	—
3	5	Disopyramide, 600 mg	SD
4	93	Amiodarone, 200 mg	—
5	63	ICD	—
6	19	ICD	VF
7	8	ICD	VF
8	48	ICD	—
9	46	ICD	—
10	3	ICD	VF
11	115	ICD + propranolol, 30 mg	—
12	76	ICD	—
13	10	ICD	VF
14	40	ICD	—
15	47	ICD	—
16	38	ICD	—
17	9	ICD	VF
18	22	ICD	—
19	1	ICD	VF
20	27	ICD	—
21	10	ICD	VF
22	18	ICD	—
Mean ± SD	36 ± 32		
Median	28		
Noninduced VF group			
1	113	Disopyramide, 600 mg	SD
2	24	ICD	VF
3	29	ICD + propranolol, 60 mg	VF
4	65	ICD + propranolol, 60 mg	—
5	11	ICD + propranolol, 60 mg	VF
6	21	ICD	VF
7	149	ICD + Disopyramide, 600 mg	—
8	17	ICD	VF
9	75	Amiodarone, 200 mg	—
10	26	ICD	—
11	20	Pindolol, 30 mg	—
12	6	ICD	VF
Mean ± SD	46 ± 45		
Median	25		

ICD = implantable cardioverter-defibrillator; SCD = sudden cardiac death; VF = ventricular fibrillation; – = none.

septum at extrastimulation than patients without PVS-induced VF. These findings suggest that the inducibility of VF by PVS is related to the severity of depolarization abnormalities in patients with Brugada syndrome. By contrast, no difference was observed in the recurrence of cardiac events between patients with and those without PVS-induced VF, suggesting that the induction of VF with PVS is not able to predict the recurrence of cardiac events in symptomatic patients with Brugada syndrome. Taken together with the high recurrence rate of cardiac events (15 [44%] of 34 patients), mostly within two years of long-term follow-up, an ICD should be implanted regardless of the induction of VF in symptomatic patients with Brugada syndrome.

Possible mechanism of VF in Brugada syndrome. Recent experimental studies have suggested that a prominent transient outward current (I_{to})-mediated phase 1 notch and a subsequent loss of action potential dome in the epicardial cells, but not in the endocardial cells in the RVOT, give rise to voltage gradients across the ventricular wall, resulting in ST-segment elevation in the right precordial leads and subsequent VF, due to the mechanism of phase 2 re-entry (11,12). Although this hypothesis most likely explains the phenotypic appearance of Brugada syndrome, especially the ST-segment elevation in leads V_1–V_3 and the initiating beat of VF, it remains unclear what can serve as the substrate for the development of functional reentry to maintain VF. Our data suggest that depolarization abnormalities mainly located at the RVOT and ventricular septum play a significant role in the maintenance of VF in symptomatic patients with Brugada syndrome. However, PVS-induced VF did not predict the recurrence of VF and SCD during long-term follow-up periods. Therefore, repolarization abnormalities are necessary in the generation of VF by modulating ST-segment elevation and providing the initiating beat to induce VF as a result of phase 2 re-entry.

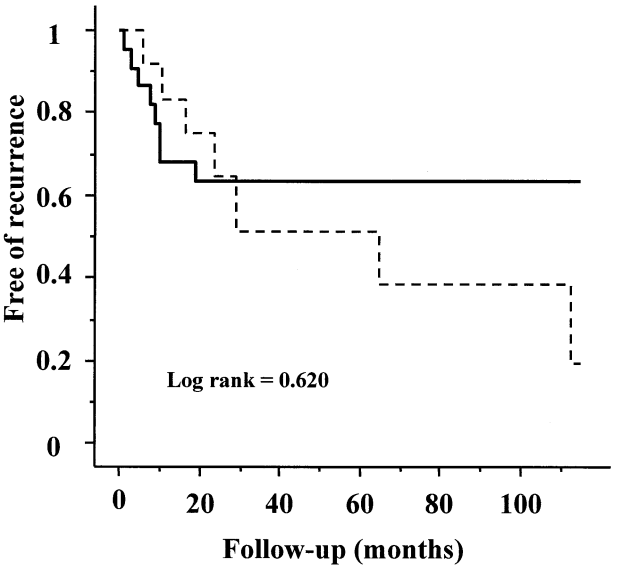

Figure 1. Kaplan-Meier curves of recurrent cardiac events (sudden cardiac death and ventricular fibrillation [VF] documented by an implantable cardioverter-defibrillator) in 22 patients with programmed ventricular stimulation (PVS)-induced VF **(solid line)** and in 12 patients without PVS-induced VF **(dotted line)**.

Study limitations. First, the number of the patients with Brugada syndrome was small, and only symptomatic patients were included in the present study. Two recent multicenter studies have reported the clinical course of both symptomatic and asymptomatic patients with Brugada syndrome during moderate- to long-term follow-up (18,19), but the prognosis of asymptomatic patients and the value of PVS in identifying patients at risk are still controversial. Although the inducibility of VF by PVS and the recurrence of VF in symptomatic patients in the present study were quite similar to those reported in the two previous studies, our data showing the limited value of PVS support the data of Priori et al. (18) rather than the data of Brugada et al.

(19). Although the small number of subjects, and the presence of only patients who were symptomatic, are major weaknesses of the present study, all 34 patients are probands from different families and underwent the electrophysiologic study using a uniform protocol in a single center. Therefore, further prospective study using a uniform protocol in a large population will be needed to draw conclusions about the prognostic value of PVS in both symptomatic and asymptomatic patients with Brugada syndrome.

Second, one-third of the patients were treated with anti-arrhythmic agents alone or in addition to ICD implantation, which may add a confounding variable in interpreting the data on arrhythmia recurrence. However, no significant differences were observed in the recurrence of arrhythmia between the two groups, when only patients treated with an ICD without anti-arrhythmic drugs are considered (7 [39%] of 18 patients vs. 4 [80%] of 5 patients).

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