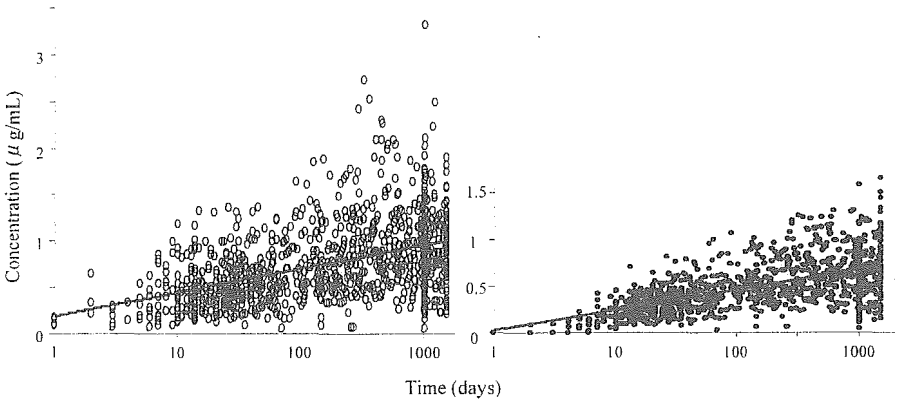

Fig. 1. Distribution of 1031 Amiodarone and Desethylamiodarone Concentrations *versus* Time Observations Collected from 345 Inpatients Monitored for a Mean of 446 d

Right panel indicate amiodarone and at left is desethylamiodarone. The regression equation was determined by a least-squares method, $y=0.0296+0.216 \log x$, $r^2=0.357$ (amiodarone) and $y=0.187+0.256 \log x$, $r^2=0.212$ (desethylamiodarone), as shown with the solid line.

CYP3A4. Therefore, the time required to reach a steady state of amiodarone concentration in serum is extraordinarily long. Thus, because blood samples were collected from inpatients who were administered fixed-maintenance dose of amiodarone for at least 180 d after the loading dose for 2 weeks. It was assumed that their serum amiodarone concentrations had reached a steady state. All samples were taken at the same time, 0700 h (12 h after the administration of amiodarone). Therefore, we used C_{0700} instead of C_{mean} (mean concentration); as a result, the oral clearance of amiodarone (CL/F) was calculated according to the following equations:

$$CL/F=(\text{Dose}/\text{BW}/t)/C_{0700}$$

$$CL(\text{BMI})/F=(\text{Dose}/\text{BMI-BW}/t)/C_{0700}$$

$$CL(\text{BSA})/F=(\text{Dose}/\text{BW}/t)/C_{0700}$$

Where Dose is the daily dose of amiodarone, BW is the body weight, BMI-BW is BW corrected by body mass index (BMI) (BW×(22.0/BMI)), BSA is the body surface area, F is bioavailability, t is the dose interval, and C_{0700} is the serum concentration of amiodarone at 0700 h.

Statistical Analysis The data are expressed as mean± standard deviation (S.D.). Statistical analysis was performed with the use of the unpaired Student's t-test. The criterion of significance was $p<0.05$.

RESULTS

The demographic characteristics of this study population are listed in Table 1. Figure 1 shows the distribution since the beginning to 1500 d after the therapy using serum 1031 amiodarone and desethylamiodarone concentrations *versus* time observations collected from 345 inpatients (men 274, women 71). The duration of dosing was fixed at 1500 d in the subjects whose observation time exceed 1500 d. It was observed that the amiodarone and desethylamiodarone concentrations gradually increased with time, whereas desethylamiodarone concentrations were below the limit of this measurement in the first and second day after the start of the therapy. Comparison between serum amiodarone and desethylamiodarone concentrations per dose and the duration of dosing is listed in Table 2. Although the ratio of the desethylamiodarone concentration to the amiodarone one was nearly equal among the all durations, the amiodarone and desethylamiodarone concentration per dose gradually increased with the period of the duration.

Table 1. Demographic Characteristics of the Study Population

n	345
Age (year)	57.0±14.0
Weight (kg)	57.7±11.4
Height (cm)	164±8.6
BSA (m^2)	1.61±0.18
Dose (mg/d)	159±56.2
Duration (d)	563±526

BSA, body surface area; Duration, duration of the therapy in days to the last data employ in each patient, and duration was fixed 1500 d in patient who received amiodarone therapy for more than 1500 d. Data are presented as mean±S.D.

Table 2. Comparison between Concentrations of Amiodarone and Desethylamiodarone in Serum, and Duration of Dosing

Duration (month)	*n*	AMD/D	DEA/D	DEA/AMD ratio
1—2	92	0.189±0.076	0.132±0.046	0.730±0.147
2—3	42	0.209±0.097	0.140±0.050	0.720±0.173
3—4	33	0.238±0.120	0.154±0.069	0.698±0.196
4—6	45	0.274±0.114	0.194±0.075	0.737±0.161
6—12	75	0.310±0.172	0.216±0.111	0.732±0.144
12—24	73	0.345±0.158	0.242±0.099	0.749±0.150
24—	137	0.336±0.162	0.243±0.100	0.749±0.142

AMD/D and DEA/D, serum amiodarone (desethylamiodarone) concentration/daily dose of amiodarone/body weight; DEA/AMD ratio, the ratio of serum desethylamiodarone concentration/serum amiodarone concentration. Data are presented as mean± S.D.

Comparison of pharmacokinetic parameters of amiodarone between men and women who received a fix maintenance amiodarone therapy for at least six months was shown in Table 3. Although significant differences were not observed in the dose, duration, amiodarone and desethylamiodarone concentrations, or the ratio between men and women, it was observed that the CL/F, $CL(\text{BMI})/F$ and $CL(\text{BSA})/F$ of women were significantly higher than that in men, respectively. The frequency of distribution in CL/F of 245 subjects who received a fix maintenance amiodarone therapy for at

Table 3. Comparison of Demographic and Pharmacokinetic Parameters of Amiodarone between Men and Women

	Men	Women	
n	194	51	
Age (year)	54.7±14.5	53.6±15.6	NS
Weight (kg)	61.2±10.1	47.9±8.69	<0.001
Height (cm)	167±6.8	153±5.7	<0.001
BSA (m^2)	1.67±0.15	1.42±0.12	<0.001
Dose (mg/d)	157±47.0	150±51.0	NS
Duration (d)	811±445	756±403	NS
AMD Conc (μg/ml)	0.853±0.369	0.818±0.346	NS
DEA Conc (μg/ml)	0.603±0.225	0.611±0.266	NS
Ratio (DEA/AMD)	0.740±0.143	0.759±0.157	NS
CL/F (l/h/kg)	0.143±0.059	0.177±0.070	<0.001
CL(BMI)/*F*	0.149±0.711	0.203±0.113	<0.001
CL(BSA)/*F*	5.16±2.05	5.85±2.05	0.035

BSA, body surface area; Dose, daily dose of amiodarone; AMD Conc, serum amiodarone concentration; DEA Conc, serum desethylamiodarone concentration; Ratio, ratio of desethylamiodarone to amiodarone concentration in serum; *CL*, amiodarone clearance; *F*, bioavailability; *CL*(BMI), amiodarone clearance per body weight corrected by body mass index; *CL*(BAS), amiodarone clearance per BSA. Data are presented as mean±S.D.

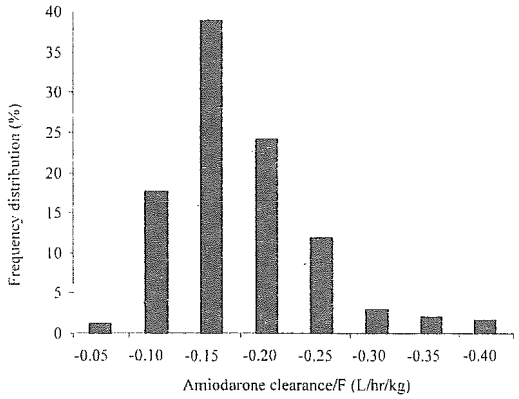

Fig. 2. Frequency Distribution of Amiodarone Clearance/*F* in 245 Japanese Subjects Who Received Fixed Maintenance Amiodarone Therapy for at Least 6 Months

F is bioavailability.

least six months is shown in Fig. 2. The relationships between age and *CL/F*, between creatinine clearance and *CL/F* and between blood urea nitrogen (BUN) are shown in Figs. 3—5. It was observed that age, creatinine clearance and BUN did not affect *CL/F*.

The relationships between serum amiodarone concentrations and clinical laboratory data are shown in Fig. 6. No significant relations were observed between serum amiodarone concentrations and clinical data.

DISCUSSION

As shown in Fig. 1, it was observed that serum amiodarone and desethylamiodarone concentrations gradually increased with time, and the increase was continued for an extremely long term. It was reported that amiodarone had an extraordinarily long half-life, with 55 d constituting a typical half-life.[3] The result of this study was the same as in previous reports.[3,19] Desethylamiodarone inhibits various CYP subfamilies and transporters, including CYP3A4 and P-glycoprotein.[7,21] Amiodarone is a substrate of CYP3A4 and P-

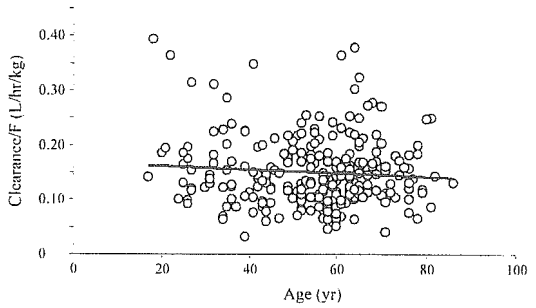

Fig. 3. Relationship between Age and Amiodarone Clearance/*F*

The regression equation determined by a least-squares method, $y=0.169+3.36\times10^{-4}x$, $r^2=0.0061$, as shown with the solid line. *F* is bioavailability.

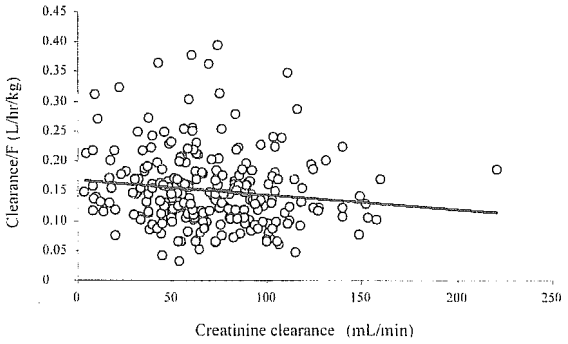

Fig. 4. Relationship between Creatinine Clearance and Amiodarone Clearance/*F*

The regression equation determined by a least-squares method, $y=0.168+2.48\times10^{-4}x$, $r^2=0.0177$, as shown with the solid line. *F* is bioavailability.

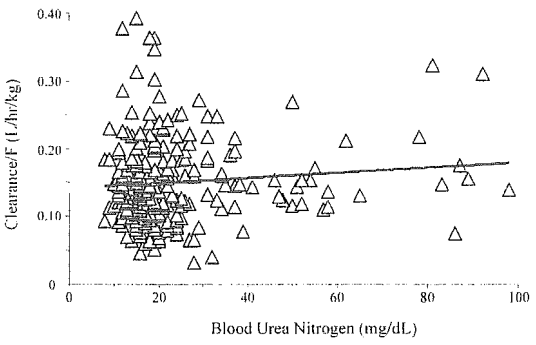

Fig. 5. Relationship between Blood Urea Nitrogen and Amiodarone Clearance /*F*

The regression equation determined by a least-squares method, $y=0.141+10^{-4}x$, $r^2=0.00932$, as shown with the solid line. *F* is bioavailability.

glycoprotein. These reports suggest the metabolite of amiodarone inhibits the metabolism and transport of the parent compound. Therefore, it is difficult to calculate the time to a reach at steady state of serum amiodarone concentration. However, as shown in Table 2, although serum amiodarone and desethylamiodarone concentrations per dose were increased with time, no difference in those concentrations per dose was observed between the duration from 12 to 24 months, and that of after 24 months, and no remarkable difference was observed in a period of over 6 months. Therefore, to evaluate the pharmacokinetics of amiodarone in long-term oral therapy, we employed the data of subjects who

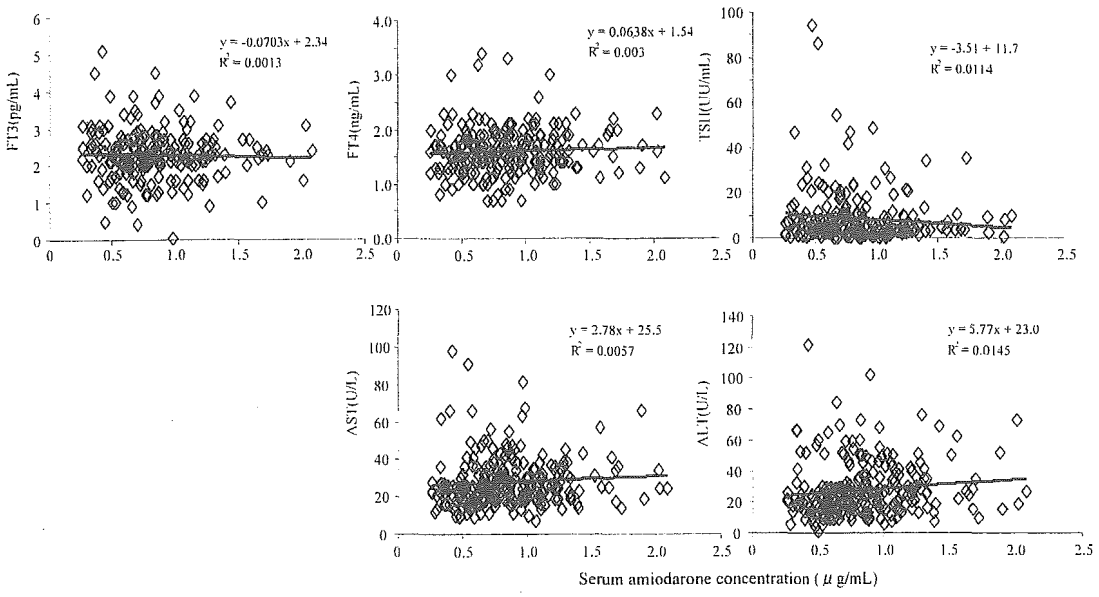

Fig. 6. Relationship between Serum Amiodarone Concentrations and Clinical Data

AST, asparatate transaminase; ALT, alanin transaminase; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone.

received the therapy for more than 180 d (Table 3).

As shown in Fig. 2, the frequency distribution was nearly unimodal, 13.1% of the distribution was less than mean minus 1SD, and no subjects were observed at less than mean minus 2SD. Fourteen point seven percentage of the distribution was more than mean plus 1SD, and 4.9% was more than mean plus 2SD. Variation in the ratio of the desethylamiodarone to amiodarone concentration in serum was very small. These data suggest that inter individual variation in the clearance in subjects who received a long-term maintenance fixed dose of amiodarone is comparatively small. Amiodarone is mainly metabolized to desethylamiodarone by CYP3A4 and CYP2C8, desethylamiodarone is further metabolized by CYP3A4, and amiodarone is transported by P-glycoprotein. Various CYP2D6 alleles carrying a point mutation or a combination of mutations on the chromosome have been reported, and there were poor metabolizers for CYP2D6 mediated drugs.[21,22] It was reported that there were CYP3A4 gene and MDR1 mutations. However, a remarkable difference in phenotype of CYP3A4 and P-glycoprotein mediated drugs was not observed compared with that in the phenotype of CYP2D6 mediated drugs. It is well known that the activities of CYP3A4 and P-glycoprotein contribute to the bioavailability of drugs, and the bioavailability of amiodarone is low. On the other hand, desethylamiodarone inhibits the activities of both CYP3A4 and P-glycoprotein[7,23] thus it is suggested that the bioavailability of amiodarone is gradually increased with time in subjects receiving long-term amiodarone therapy, and individual variation of the clearance decreases in subjects receiving long-term amiodarone therapy.

As shown in Table 3, no differences in age, dose, dose duration, amiodarone or desethylamiodarone concentrations, or ratio were observed between men and women; however, the mean *CL/F*, *CL*(BMI)/*F* and *CL*(BSA) of women were significantly increased compared with those of men, respectively. Hunt *et al.* found a 24% higher CYP3A4 activity in female liver microsomes than in male liver microsomes.[24] However, studies by Schmucker *et al.*,[25] Shimada *et al.*,[26] and George *et al.*,[27] which examined CYP3A4 protein content and function from human livers, were not able to show any significant sex-related differences. One proposed explanation for the differences observed in women is the presence of the female sex steroids estrogen and progesterone, which are known substrates of CYP3A4.[28,29] In this study, all subjects were elderly. Therefore, it is suggested that the sex-related difference in amiodarone clearance could not be the explanatory link. The distribution volume of amiodarone is extraordinarily large; especially, the distribution to fatty tissue is large due to the extreme affinity of amiodarone for lipids. It was reported that the body fat in women (mean age 72 years) was significantly higher than that of men (mean age 75 years).[30] Therefore, it is suggested that the difference in *CL/F* between men and women is caused by the distribution to fatty tissue. As shown in Figs. 3—5, it was observed that *CL/F* was not affected by age, creatinine clearance or BUN. Therefore, it is unnecessary to consider age or renal function for an optimum dose schedule in amiodarone therapy.

It is well known that amiodarone has potentially dangerous non-cardiac side-effects, and some of the side-effects are dose dependent.[31,32] As shown in Fig. 6, these laboratory data were mostly within the normal value, and no significant relations were observed between serum amiodarone concentrations and clinical laboratory data. Previous reports, used a small number of subjects and the dose was comparatively high. In this study, a total of 345 subjects was used and the most common maintenance dose was 200 mg/d. Therefore, it was suggested that thyroid hormone metabolism and an elevation of aminotaransferases was not affected by the amiodarone concentrations in low-dose amiodarone therapy in such a study.

In conclusion, individual variation in the pharmacokinetics of amiodarone was comparatively small, which might be sufficient to conclude that the maintenance dose is the same (200 mg/d) as in long-term oral amiodarone therapy.

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Malignant Entity of Idiopathic Ventricular Fibrillation and Polymorphic Ventricular Tachycardia Initiated by Premature Extrasystoles Originating From the Right Ventricular Outflow Tract

Takashi Noda, MD, PHD,* Wataru Shimizu, MD, PHD,* Atsushi Taguchi, MD,* Takeshi Aiba, MD, PHD,† Kazuhiro Satomi, MD,* Kazuhiro Suyama, MD, PHD,* Takashi Kurita, MD, PHD,* Naohiko Aihara, MD,* Shiro Kamakura, MD, PHD*

Suita, Japan

OBJECTIVES The aim of this study was to assess the clinical characteristics and the efficacy of radiofrequency catheter ablation (RFCA) for idiopathic ventricular fibrillation (VF) and/or polymorphic ventricular tachycardia initiated by ventricular extrasystoles originating from the right ventricular outflow tract (RVOT).

BACKGROUND Ventricular fibrillation and/or polymorphic ventricular tachycardia are occasionally initiated by ventricular extrasystoles originating from the RVOT in patients without structural heart disease.

METHODS Among 101 patients without structural heart disease in whom RFCA was conducted for idiopathic ventricular tachyarrhythmias arising from the RVOT, we examined the clinical characteristics and the efficacy of RFCA in 16 patients with spontaneous VF and/or polymorphic ventricular tachycardia initiated by the ventricular extrasystoles originating from the RVOT.

RESULTS Among 16 patients, spontaneous episodes of VF were documented in 5 patients, and 11 patients had prior episodes of syncope. Holter recordings showed frequent isolated ventricular extrasystoles with the same morphology as that of initiating ventricular extrasystoles, and non-sustained polymorphic ventricular tachycardia with short cycle length (mean of 245 ± 28 ms) in all 16 patients. Radiofrequency catheter ablation by targeting the initiating ventricular extrasystoles eliminated episodes of syncope, VF, and cardiac arrest in all patients during follow-up periods of 54 ± 39 months.

CONCLUSIONS Our data suggest that the malignant entity of idiopathic VF and/or polymorphic ventricular tachycardia was occasionally present in patients with idiopathic ventricular arrhythmias arising from the RVOT. Radiofrequency catheter ablation was effective as a treatment option for this entity. (J Am Coll Cardiol 2005;46:1288–94) © 2005 by the American College of Cardiology Foundation

Ventricular fibrillation (VF) and polymorphic ventricular tachycardia (PVT) are malignant arrhythmias resulting in sudden cardiac death (1–5). Recent studies by Haissaguerre et al. (6,7) reported that idiopathic VF initiated by dominant triggers from distal Purkinje system or right ventricular outflow tract (RVOT) was successfully eliminated by radiofrequency catheter ablation (RFCA).

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Although idiopathic ventricular tachycardia and ventricular extrasystoles (VE) originating from the RVOT in patients without structural heart diseases are considered benign (8–12), VF and/or PVT are occasionally initiated by VE originating from the RVOT.

The present study is designed to assess the clinical characteristics and the efficacy of RFCA for the malignant entity of idiopathic VF and/or PVT initiated by VE originating from the RVOT.

METHODS

Patient characteristics. Sixteen patients who showed spontaneous VF and/or PVT initiated by the VE with left bundle branch block morphology and inferior axis in their clinical course (VF/PVT group) were enrolled in this study among 101 consecutive patients in whom RFCA was conducted for treatment of ventricular tachyarrhythmias arising from the RVOT. There were seven men and nine women ranging in age from 25 to 54 years (mean of 39 ± 10 years). In all patients, physical examination, chest roentgenogram, laboratory values, treadmill exercise test, echocardiographic study with wall motion analysis, Doppler screening, and signal-averaged electrocardiogram (SAECG) were per-

From the *Division of Cardiology, Department of Internal Medicine, and the †Department of Cardiovascular Dynamics, Research Institute, National Cardiovascular Center, Suita, Japan. Dr. Shimizu was supported in part by the Mitsubishi Pharma Research Foundation, Health Sciences Research Grants from the Ministry of Health, Labor, and Welfare, and Research Grants for Cardiovascular Diseases (15C-6) from the Ministry of Health, Labor and Welfare, Japan. Presented in part at Heart Rhythm 2004, San Francisco, California, May 19–22, 2004, and published in abstract form (Heart Rhythm 2004;1[IS]:S269).

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Abbreviations and Acronyms

ECG	= electrocardiogram
EPS	= electrophysiologic study
ICD	= implantable cardioverter-defibrillator
PVC	= premature ventricular contraction
PVT	= polymorphic ventricular tachycardia
RFCA	= radiofrequency catheter ablation
RVOT	= right ventricular outflow tract
SAECG	= signal-averaged electrocardiogram
VE	= ventricular extrasystoles
VF	= ventricular fibrillation

formed, and no structural heart disease was found. Patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia (13) or Brugada syndrome (14) were excluded from this study. During hospitalization, the patients had frequent VE identical to the initiating beat of VF/PVT recorded by Holter recording or monitoring electrocardiogram (ECG) so that we could recognize the 12-lead QRS morphology of the initiating beats (Fig. 1A). In some cases, non-sustained PVT initiated by the VE of the RVOT origin could be recorded in the 12-lead ECG (Fig. 1B). We compared the clinical characteristics between the 16 patients with VF/PVT group and the remaining 85 patients in whom RFCAs were conducted for treatment of idiopathic monomorphic ventricular tachycardia arising from the RVOT (RVOT-VT group). Ventricular fibrillation was defined as a polymorphic ventricular tachyarrhythmia with hemodynamic decompensation requiring direct cardioversion for termination. Polymorphic ventricular tachycardia was defined as more than five consecutive beats with different QRS morphology and terminating spontaneously.

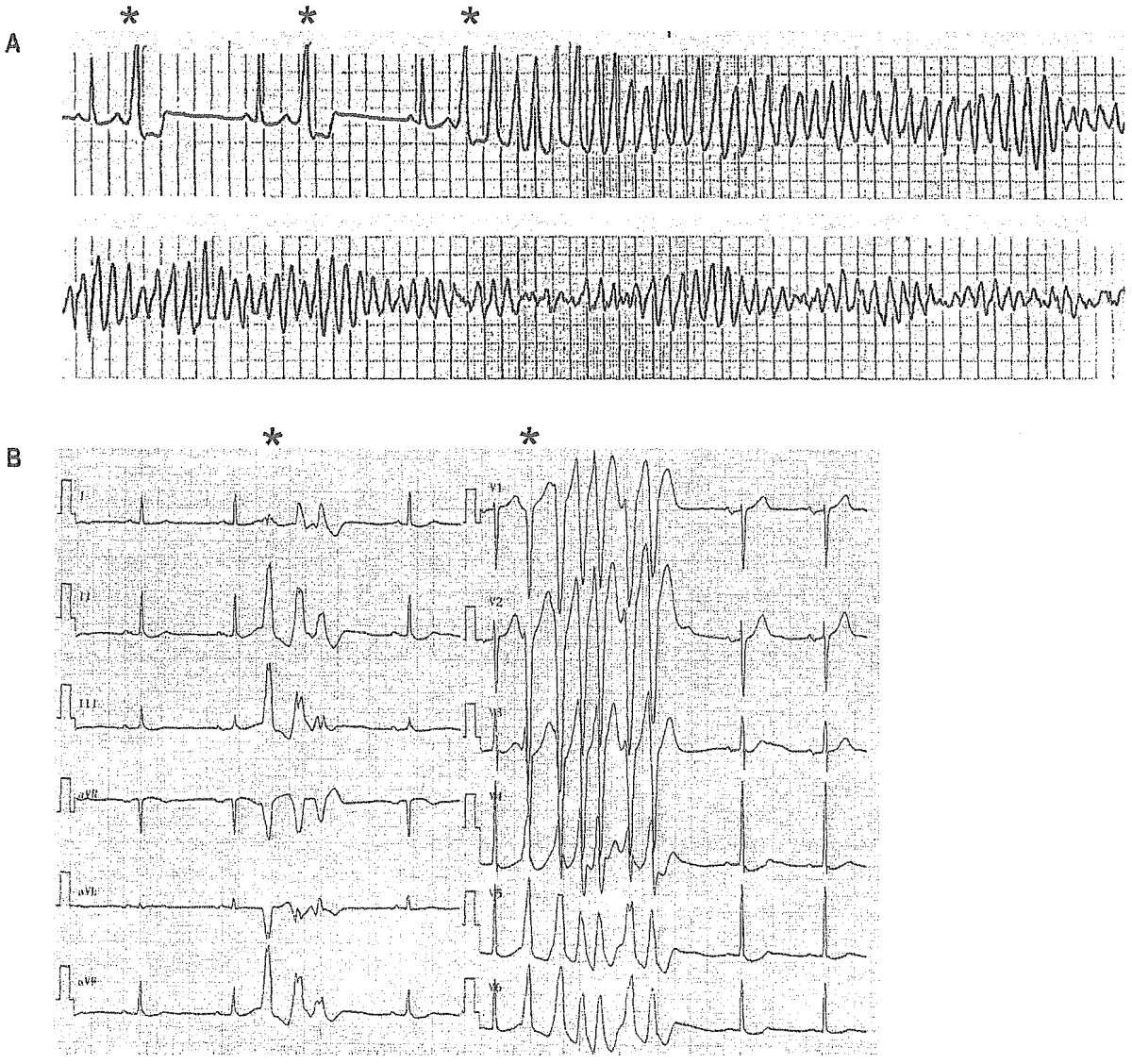

Figure 1. **(A)** Initiation of ventricular fibrillation (VF) recorded by a monitoring electrocardiogram in Patient #1. Note that the morphology of QRS complex of the initiating ventricular extrasystole (VE) was identical to that of preceding isolated premature ventricular contractions (*). **(B)** Non-sustained polymorphic ventricular tachycardia recorded in 12-lead electrocardiogram during hospitalization in Patient #8. The initiating VE showed left bundle branch morphology with inferior axis (*).

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Table 1. Clinical Characteristics of the 16 Patients With the VF/PVT group

Patient No.	Age (yrs)	Gender	Spontaneous VF	Symptom	Holter ECG Findings: Isolated PVC (/day)	QT (ms)	CI (ms)	CL of PVT (ms)
1	43	F	+	Syncope	7,344	420	460	224
2	52	M	+	Syncope	26,828	420	410	240
3	41	F	+	Syncope	19,615	410	400	233
4	28	F	+	Syncope	7,518	430	440	216
5	48	F	+	Syncope	13,724	420	400	200
6	26	M	−	Syncope	NA	400	480	264
7	25	M	−	Pre-syncope	NA	420	580	310
8	49	M	−	Pre-syncope	41,192	400	390	273
9	43	M	−	Pre-syncope	2,479	380	360	248
10	41	M	−	Pre-syncope	13,819	360	320	242
11	38	F	−	Syncope	13,754	400	430	240
12	54	M	−	Syncope	9,700	380	360	220
13	41	F	−	Pre-syncope	12,681	390	360	268
14	25	F	−	Syncope	23,588	430	410	280
15	31	F	−	Syncope	38,061	380	350	227
16	34	F	−	Syncope	15,456	410	390	240
Mean ± SD	39 ± 10				17,554 ± 11,338	403 ± 21	409 ± 62	245 ± 28

Note that Patient #8 had a positive familial history of sudden cardiac death.

CI = coupling interval of the ventricular extrasystole; CL = cycle length; ECG = electrocardiogram; NA = not available; PVC = premature ventricular contraction; PVT = polymorphic ventricular tachycardia; QT = QT interval; VF = ventricular fibrillation; + = present; − = absent.

Electrophysiologic study and RFCA. As described previously (15), each patient underwent an electrophysiologic study (EPS) and RFCA in the fasting and non-sedated state after written informed consent was obtained. All drugs, including beta-blockers, were discontinued for at least five half-lives of each drug before the EPS. The 12-lead ECG of target VE that initiated spontaneous VF/PVT in the clinical course was also recorded in the EPS room before starting EPS and RFCA. If the target VE was not recorded under baseline conditions, injection of isoproterenol, epinephrine, or methoxamine with or without programmed ventricular stimulation was used to facilitate the induction of the initiating VE. We determined the provocated VE as target when the QRS morphology of the provocated VE was same as that of initiating VE recorded during hospitalization. Simultaneous 12-lead ECG and multiple intracardiac bipolar electrograms filtered at 30 to 500 Hz were recorded by a computerized electrophysiologic recording system (Bard Labsystem, CR Bard Inc., Billerica, Massachusetts) during EPS and RFCA. Stimuli were twice the diastolic threshold and 2 ms in duration. A deflectable 8-F quadripolar electrode catheter with conventional 4-mm distal electrode (EP Technologies, Sunnyvale, California) was used for mapping and RFCA with or without guidance by multielectrode basket catheter (Constellation, EP Technologies). Rapid burst pacing at multiple paced cycle lengths (pacing rate up to 250 beats/min) from right ventricular apex and the RVOT were performed in seven patients of the VF/PVT group before RFCA.

We performed RFCA by targeting the initiating VE. The optimal ablation site was determined by two methods: 1) endocardial activation mapping by identifying the site of the earliest activation during the target VE, and 2) pace mapping by comparing the 12-lead QRS morphology between the target VE and the paced beat during sinus rhythm. Radiofrequency energy was applied at the optimal site using a temperature control system with a target temperature set point of 60°C for 60 s. If the target VE was eliminated by energy delivery, three or four bonus applications were usually delivered around the most effective ablation site except in one patient. We tried to induce the target VE with the same interventions that provocated the target VE at the beginning of the EPS. If the premature ventricular contractions (PVCs) and/or ventricular tachycardia including the target VE were completely eliminated and were not induced at all, the RFCA was defined as successful. Partially successful ablation was defined when the target VEs were completely eliminated, but the other PVCs were induced and were not completely eliminated as a result. Failed ablation was defined when the target VEs were not eliminated completely.

Programmed electric stimulation was performed by up to triple extrastimuli mainly to confirm the effectiveness of RFCA as well as to induce VF in all 16 patients in the VF/PVT group after RFCA. We stopped extrastimuli at a coupling interval of 180 ms to avoid inducing non-specific VF.

Statistical analysis. Continuous variables were expressed as the group mean value ± SD and compared using unpaired *t* test. Qualitative variables were compared using Fisher exact test. A value of $p < 0.05$ was regarded as significant.

RESULTS

Clinical characteristics. Table 1 shows the clinical characteristics of the 16 patients with the VF/PVT group. Spontaneous episodes of VF were documented at rest during daytime in two patients and during nighttime in

Table 2. Comparison of the Clinical Parameters Between the VF/PVT Group and the RVOT-VT Group

	VF/PVT Group (n = 16)	RVOT-VT Group (n = 85)	p Value
Male	7/16 (44%)	25/85 (29%)	0.26
Age (yrs)	39 ± 10	43 ± 14	0.19
FH	1/16	1/85	0.29
Duration from onset of symptom to RFCA (months)	80 ± 103	69 ± 79	0.71
History of syncope	11/16 (69%)	15/85 (18%)	0.0001
Holter ECG findings			
Isolated PVC (/day)	17,554 ± 11,338	15,506 ± 16,053	0.58
CI of VE (ms)	409 ± 62	428 ± 65	0.27
QRS duration of VE (ms)	148 ± 8	142 ± 12	0.03
CL of VT (ms)	245 ± 28	328 ± 65	<0.0001

FH = family history of sudden death; RFCA = radiofrequency catheter ablation; RVOT = right ventricular outflow tract; VE = ventricular extrasystole; VT = ventricular tachycardia; other abbreviations as in Table 1.

three patients. Only one (Patient #8) of the 16 patients had a familial history of sudden cardiac death. Eleven of the 16 patients had prior episodes of syncope, and the remaining five patients had pre-syncope. Figure 1A shows the initiation of VF recorded by the monitoring ECG in Patient #1. The QT interval preceding VF was normal, and the coupling interval of the initiating VE was 460 ms. It is noteworthy that the morphology of QRS complex of the initiating VE was identical to that of the preceding isolated PVCs. In all patients, the corrected QT intervals preceding spontaneous VF/PVT were <440 ms. Holter recordings showed frequent isolated PVCs with the same QRS morphology as that of the initiating VE, and non-sustained PVT with short cycle length (mean of 245 ± 28 ms) in all 16 patients (Table 1). The coupling interval of VE was uniform in each patient and was not so short (mean of 409 ± 62 ms). Table 2 represents the comparison of the clinical parameters between the VF/PVT group and the RVOT-VT group. No significant difference was observed regarding gender, age, familial history of sudden death, and duration from onset of symptom to RFCA. However, prior episodes of syncope were more frequent in the VF/PVT group than in the RVOT-VT group (69% vs. 18%, p = 0.0001). In the Holter recordings, the frequency of isolated PVCs and the coupling intervals of the initiating VE were not different between the VF/PVT group and the RVOT-VT group. However, the cycle length of spontaneous non-sustained ventricular tachycardia was much shorter in the VF/PVT group than in the RVOT-VT group (245 ± 28 ms vs. 328 ± 65 ms, p < 0.0001).

Among the 16 patients in the VF/PVT group, 11 patients showed pre-syncope or syncope as a first symptom; however, the remaining 5 patients had only palpitation due to PVCs or monomorphic VT as a first symptom. Among five patients with spontaneous VF, three showed syncope as a first symptom, whereas two had only palpitation as a first symptom.

Electrophysiologic findings. Table 3 shows the electrophysiologic characteristics and RFCA parameters of the 16 patients in the VF/PVT group. The target VE occurred spontaneously in 11 patients and was induced by bolus injection of isoproterenol (1 μg) in three patients, epinephrine (5 μg) in one patient, and methoxamine (1 mg) in one patient. Endocardial mapping during sinus rhythm showed no abnormal electrograms, including fragmentations or delayed potentials, in any patients. His-ventricle intervals were <55 ms (mean of 42 ± 6 ms) in all patients. Figure 2 shows the polymorphic changes of the QRS complex during rapid pacing (pacing rate = 250 bpm) in Patient #3. These polymorphic morphologic changes were observed by the rapid pacing from origin of target VE in two patients (Patients #3 and #5) out of seven patients examined.

RFCA. Radiofrequency catheter ablation was performed at the site where the endocardial activation time during target VE was the earliest and the best pace mapping was obtained. Figure 3 represents the target VE (Fig. 3A), the pace mapping at the ablation site (Fig. 3B), simultaneous recording of surface ECG and endocardial electrograms during the target VE (Fig. 3C), and catheter position of the RFCA site (Fig. 3D) in Patient #2. The pace mapping demonstrated close concordance with the QRS morphology of the target VE in all leads. The bipolar endocardial electrogram of the mapping catheter, located in the septum of the RVOT, preceded the surface QRS onset of the target VE by 10 ms. The mean bipolar local activation time at the successful RFCA site was 17 ± 11 ms before the surface QRS onset (Table 3). The origin of the target VE, where the target VE disappeared or changed to the other VE with different QRS morphology by a single energy delivery, was in the septum of the RVOT in 13 patients and in the lateral freewall of the RVOT in three patients. After RFCA for initial target VE, the other VE with different QRS morphology appeared in 11 patients in whom multiple applications by mean of 9 ± 4 were added. Therefore, relatively large areas, approximately 2 to 4 cm in diameter, were presumably ablated in the 11 patients. Finally, RFCA was successful in 13 patients and partially successful in three patients by a mean of 9 ± 4 radiofrequency applications. Programmed electric stimulation after RFCA revealed that VF was induced by triple extrastimuli from the RVOT in only one patient (Patient #2), and non-sustained PVT was

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Table 3. Electrophysiologic Characteristics and RFCA Parameters of the 16 Patients With the VF/PVT Group

Patient No.	Induction of Target VE	Origin of Target VE	ERP (ms)	EAT (ms)	Morphologic Change	No. of RF	Outcome	Induction of VF/PVT After RFCA	Advanced Treatment
1	Spontaneous	Sep	220	−10	−	1	Succ	−	−
2	Spontaneous	Sep	230	−10	−	5	Succ	VF (500/240/200/200)	ICD
3	Spontaneous	Sep	250	−20	−	8	Succ	−	−
4	Spontaneous	Sep	230	−50	+	11	Succ	−	−
5	Spontaneous	Sep	210	−8	+	15	Partial	PVT (500/240/220/190)	Beta-blocker
6	ISP	Sep	210	−20	+	12	Partial	−	Beta-blocker
7	Epi	Free	200	−18	+	4	Succ	−	−
8	Spontaneous	Sep	210	−12	+	10	Partial	−	Beta-blocker
9	Spontaneous	Free	200	−20	−	5	Succ	−	−
10	ISP	Free	220	−22	+	14	Succ	−	−
11	Spontaneous	Sep	200	−5	+	5	Succ	−	−
12	Me	Sep	220	−8	+	9	Succ	−	−
13	Spontaneous	Sep	200	−14	+	7	Succ	−	−
14	Spontaneous	Sep	210	−6	−	15	Succ	−	Beta-blocker
15	Spontaneous	Sep	210	−24	+	7	Succ	PVT (500/240/220/180)	−
16	Spontaneous	Sep	240	−26	+	8	Succ	−	−
Mean ± SD			216 ± 15	−17 ± 11		9 ± 4			

EAT = endocardial activation time (relative to QRS); Epi = epinephrine; ERP = effective refractory period; Free = freewall; ISP = isoproterenol; Me = methoxamine; Partial = partially successful ablation; PVT = polymorphic ventricular tachycardia; RF = radiofrequency applications; RFCA = radiofrequency catheter ablation; Sep = septum; Succ = successful ablation; VE = ventricular extrasystole; VF = ventricular fibrillation; + = present; − = absent.

Figure 2. Polymorphic changes of the QRS complex on surface electrocardiogram leads I, II, V_1, and V_5 during rapid pacing in Patient #3. The morphologic changes were induced by rapid pacing from the origin of the target ventricular extrasystole.

induced in two patients (Patients #5 and #15) among the 16 patients.

Follow-up. One patient (patient #2) received an implantable cardioverter-defibrillator (ICD) because of induction of VF. Four patients received oral beta-blockers (3 for partially successful ablation and 1 for hypertension) as a therapeutic option. The remaining 11 patients were free from any advanced treatment, including antiarrhythmic drugs. There were no recurrences of episodes of syncope, VF, or cardiac arrest in any patients during follow-up of 54 ± 39 months.

DISCUSSION

***Malignant entity of* VF/PVT.** Idiopathic ventricular tachycardias originating from the RVOT in patients without structural heart disease are considered benign, and RFCA has become an effective therapeutic option for these arrhythmias (8–12). However, a recent report (6) has shown that the malignant idiopathic VF may occasionally originate from the right ventricular outflow tract, the same site of origin of the "benign" RVOT. Moreover, several types of VF/PVT in patients without apparent heart disease were reported (14,16–23). We reported a malignant entity of VF/PVT initiated by the VE originated from the RVOT without structural heart disease in this study. In all patients, 12-lead ECG showed normal QT intervals at rest or just before and after episodes of VF and/or PVT (16–18). Neither ST-segment elevation nor right bundle branch block, most likely seen in Brugada syndrome, were recorded (14,19). The SAECG showed no late potential by which arrhythmogenic right ventricular cardiomyopathy/dysplasia

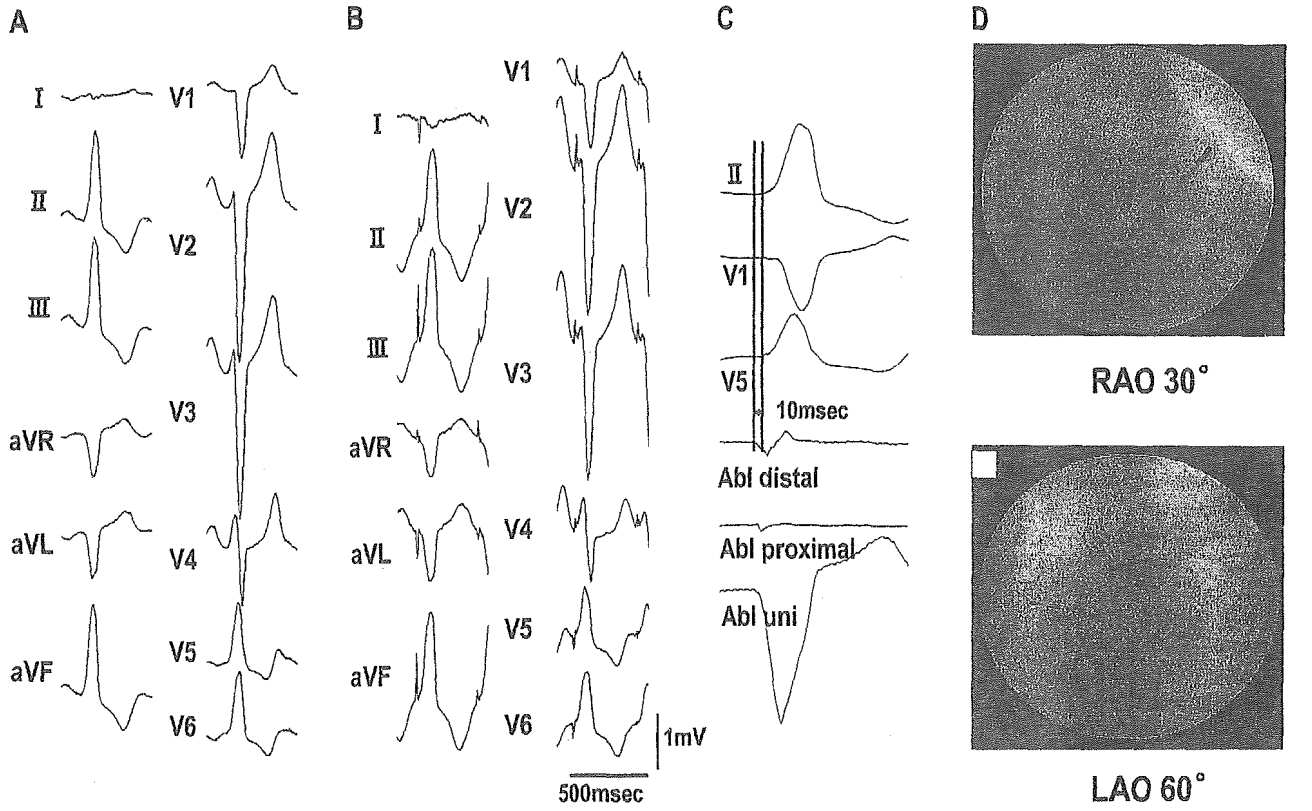

Figure 3. **(A)** Morphology of target ventricular extrasystole (VE) on 12-lead electrocardiogram (ECG); **(B)** Pace mapping at the ablation site; **(C)** Simultaneous recordings of surface ECG and endocardial electrograms during the target VE; **(D)** Catheter position of radiofrequency catheter ablation site in Patient #2. The pace mapping demonstrated close concordance with the QRS morphology of the target VE in all leads. The bipolar endocardial electrogram of the mapping catheter, which was located in the septum of the right ventricular outflow tract, preceded the surface QRS onset of the target VE by 10 ms. Abl = ablation catheter electrogram; LAO = left anterior oblique; RAO = right anterior oblique; uni = unipolar electrogram.

was characterized (20). The coupling intervals were not as short as those described in patients with short-coupled torsade de pointes (21) or idiopathic VF (22,23). Therefore, there are some differences in this entity compared with the prior types of idiopathic VF and/or PVT. We considered this entity to be a variant form of "benign" RVOT-VTs, but to have some difference in the clinical characteristics. The present data suggest that the 16 patients in the VF/PVT group showed prior episodes of syncope more frequently than the 85 patients in the RVOT-VT group, indicating the need of discrete follow-up in patients with prior episodes of syncope. On the other hand, 5 of the 16 patients in the VF/PVT group and two of the five patients with spontaneous VF had only palpitation as a first symptom. This finding suggests that some of patients initially diagnosed as "benign" RVOT-VT may become the patients with malignant entity of idiopathic VF/PVT, indicating that the need of careful follow up is required even in patients with benign RVOT-VT.

Possible mechanism of VF/PVT. It has been suggested that mechanism of idiopathic monomorphic VT arising from the RVOT is triggered activity (24,25). In this study, Holter recordings showed frequent isolated PVCs with the same morphology as that of the initiating VE. In all patients, the SAECG showed no late potential, and endocardial mapping represented no local abnormal electrograms, including fragmentations or delayed potentials. Programmed electrical stimulations induced VF in only one patient and non-sustained PVT in two patients among the 16 patients. In addition, rapid pacing from origin of target VE made the polymorphic morphologic changes in the QRS configuration in two out of seven patients, although the possibility that some beats were induced but are not captured by pacing could not be excluded completely. We speculate that the functional block and/or delayed conduction by rapid firing due to triggered activity or microreentry arising from a single focus led to chaotic ventricular conduction, so-called fibrillatory conduction, causing VF and/or PVT without organic delayed conduction zone. However, it is reasonable to say that rapid firing from close multiple foci one after another produces polymorphic morphologic changes in the QRS configuration in some cases. This is based on the observation that the other VE with different QRS morphology appeared after eliminating the initial target VE by RFCA in 11 patients. Although the initiating VE are likely to be generated from triggered activities, different mechanisms cannot be excluded.

We performed RFCA for the initiating VE with three or four bonus applications delivered around the most effective site. Some case reports showed successful RFCA for PVT

initiated by VE originating from the RVOT with (26,27) or without (28) eliminating targeting VE. In the latter case report, RFCA was considered to alter or remodel arrhythmic substrates to maintain the PVT. Our RFCA targeting for the initiating VE with additional applications around the origin of initiating VE might eliminate both arrhythmogenic triggers and substrate for VF and/or PVT in this study.

Study limitations. First, the 16 patients showed spontaneous VF/PVT in our series, whereas the 85 patients had only monomorphic VT. This may give the impression that polymorphic RVOT-VT is present in 16% of patients with arrhythmias originating from the RVOT. However, this large percentage probably represents a referral bias, because patients with polymorphic RVOT-VT are more likely to be hospitalized and more likely to be referred for RFCA, whereas patients with monomorphic RVOT-VT are more likely to be treated conservatively as outpatients.

Second, VF was induced in only one patient after RFCA, whereas patients with idiopathic VF usually have high VF inducibility rates. The low rate of VF induction is probably associated with the result of our stimulation protocol.

Third, among the five patients with spontaneous VF, only one patient received ICD after RFCA. The ICD as therapeutic backup is particularly important for patients with spontaneous episodes of VF regardless of the success of RFCA. The ICD was not available in Japan when three of the five patients were admitted to our center and underwent RFCA. The remaining patient, a young woman, refused to receive an ICD after successful RFCA.

Reprint requests and correspondence: Dr. Wataru Shimizu, Division of Cardiology, Department of Internal Medicine, National Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita, Osaka 565-8565, Japan. E-mail: wshimizu@hsp.ncvc.go.jp.

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Mechanisms of Disease: current understanding and future challenges in Brugada syndrome

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Mechanisms of Disease: current understanding and future challenges in Brugada syndrome

Wataru Shimizu*, Takeshi Aiba and Shiro Kamakura

SUMMARY

Brugada syndrome is a clinical entity characterized by ST-segment elevation in the right precordial leads (V1–V3) and an episode of ventricular fibrillation in the absence of structural heart disease. Data regarding genotype–phenotype relationships are limited, since *SCN5A*, the gene encoding the α subunit of the sodium channel, is as yet the only gene linked to Brugada syndrome. Studies of *SCN5A* mutations responsible for the Brugada phenotype have shown the presence of functional defects in the sodium-channel current. Experimental studies employing arterially perfused right-ventricular wedge preparations have elucidated cellular mechanisms for this phenotype. Data indicate that an accentuated action-potential notch, mediated by a prominent transient outward current and loss of the action-potential dome in the epicardium (but not in the endocardium) of the right ventricle give rise to a transmural voltage gradient, resulting in ST-segment elevation and the induction of ventricular fibrillation. On the basis of cellular mechanisms, it might be possible to normalize the Brugada phenotype by use of therapeutic agents or interventions that decrease net outward currents by decreasing the transient outward current or outward potassium currents, or increasing the L-type inward calcium current or fast sodium current. Interventions that increase net outward currents through raising the transient outward current or outward potassium currents or decreasing the L-type inward calcium current or fast sodium current might aggravate or unmask the Brugada phenotype, resulting in an acquired form of this syndrome. In this review, we discuss future challenges relating to risk stratification, genetic heterogeneity, sex and ethnic differences in Brugada syndrome.

KEYWORDS Brugada syndrome, genotype, phenotype, ST segment, ventricular fibrillation

REVIEW CRITERIA

Articles were identified by searching the MEDLINE and PubMed databases, using the search keywords "Brugada syndrome", "mechanism", "therapy", "genotype" and "phenotype", alone or in different combinations. All articles were full-text, English-language papers. We also did a limited manual search of the references listed in these papers and in other papers in our files. Abstracts from the 2004 meeting of the American Heart Association were also searched using the terms listed.

W Shimizu and S Kamakura are Senior Staff Cardiologists in the Division of Cardiology, Department of Internal Medicine, and T Aiba is a Research Scientist in the Department of Cardiovascular Dynamics, Research Institute, of the National Cardiovascular Center, Osaka, Japan.

Correspondence
*Division of Cardiology, Department of Internal Medicine, National Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita, Osaka 565-8565, Japan
wshimizu@hsp.ncvc.go.jp

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INTRODUCTION

Since the first description by Pedro and Josep Brugada[1] of eight patients with a history of aborted sudden cardiac death caused by ventricular fibrillation (VF) as a distinct clinical entity, numerous reports from around the world have demonstrated the clinical, electrocardiographic, electrophysiologic, cellular, ionic, genetic and molecular features of Brugada syndrome.[2–11] This syndrome is characterized by ST-segment elevation in the right precordial leads (V1–V3) and episodes of VF in the absence of structural heart disease.

PHENOTYPIC CHARACTERISTICS AND DIAGNOSTIC CRITERIA

Brugada syndrome usually manifests during adulthood, with a mean age of sudden death of 41 years (SD 15 years). More than 80% of patients affected with Brugada syndrome are men. The prevalence of male patients is highest in Asian countries, including Thailand and Japan.[12–14] The majority of VF episodes are documented as a form of sudden unexplained nocturnal death, syncope or agonal respiration during sleep at night. Two specific types of ST-segment elevation, coved and saddleback, are recognized in patients with the Brugada syndrome. Although the magnitude and morphology of ST-segment elevation alters with time,[15] the coved type is reportedly associated with a higher incidence of VF and sudden cardiac death.[7–11,16] Therefore, type 1 ST-segment elevation, which is defined as a coved ST-segment elevation of at least 0.2 mV (2 mm), with or without a terminal negative T wave, is required to diagnose Brugada syndrome.[8,11] Brugada syndrome is differentially diagnosed when a type 1 ST-segment elevation is observed in more than one of the V1–V3 leads, in the presence or absence of sodium-channel blocker, and is associated with more than one of certain features: documented VF, polymorphic ventricular tachycardia (PVT), a family history of sudden cardiac death (<45 years old), coved type electrocardiograms in family members,

inducibility of VF with programmed electrical stimulation, syncope or nocturnal agonal respiration.[8] Sodium-channel blockers, including flecainide, ajmaline and pilsicainide, amplify or unmask ST-segment elevation, and are used as a diagnostic tool in latent Brugada syndrome with transient or no spontaneous ST-segment elevation.[17,18] Shift of the right precordial leads (V1–V3) to the 3rd and 2nd intercostal spaces can increase the sensitivity of electrocardiography for detecting the Brugada phenotype in some patients.[11,19] During electrophysiologic study, VF or sustained PVT is induced in 50–70% of Brugada patients.[7,9,10,20,21] A family history of unexplained sudden death is present in 20–30% of Brugada patients.[7,20,21]

GENOTYPE–PHENOTYPE RELATIONSHIPS

In the past decade, significant advances have been made in molecular genetics that have established a link between a number of inherited cardiac arrhythmias, including Brugada syndrome, and mutations in genes encoding ion channels or other membrane components. The first mutation linked to Brugada syndrome was identified by Chen and co-workers[22] in *SCN5A*, the gene encoding the α subunit of the sodium channel. A second locus on chromosome 3, close to but distinct from the *SCN5A* locus, has also been linked to the Brugada syndrome in a large pedigree,[23] but the specific gene or genes affected have not yet been identified. At present, *SCN5A* mutations account for only 18–30% of patients diagnosed as having Brugada syndrome. *SCN5A* is the only gene linked to the Brugada syndrome so far, and data on genotype–phenotype relationships in clinical studies are, therefore, limited. Smits and co-workers[24] observed significantly longer conduction parameters (including PQ and HV intervals) in Brugada patients with *SCN5A* mutations than in those without *SCN5A* mutations. Although knowledge of a specific mutation in the *SCN5A* gene might not provide guidance on prognosis or risk stratification in Brugada syndrome, identification of these mutations might help to establish a clinical diagnosis. In addition, detection of *SCN5A* mutations might enable affected relatives who are at risk of developing Brugada syndrome to be identified, and advance our knowledge of genotype–phenotype relationships.

GENETIC AND FUNCTIONAL CHARACTERISTICS OF *SCN5A* MUTATIONS

Over 80 mutations in the *SCN5A* gene have been linked to Brugada syndrome in the past 4 years.[7,25] Approximately two dozen of the mutations have been studied in expression systems, and have been shown to result in loss of function of the sodium-channel current (I_{Na}) by several mechanisms.[14,22,26–31] The following examples are among the functional effects that have been identified: lack of expression of the sodium channel; a shift in the voltage-dependence and time-dependence of I_{Na} activation, inactivation or reactivation; entry of the sodium channel into an intermediate state of inactivation from which it recovers slowly; accelerated inactivation of the sodium channel; or a trafficking defect. Interestingly, some of the gating effects are reported to result in a cardiac conduction defect rather than the Brugada phenotype.[32]

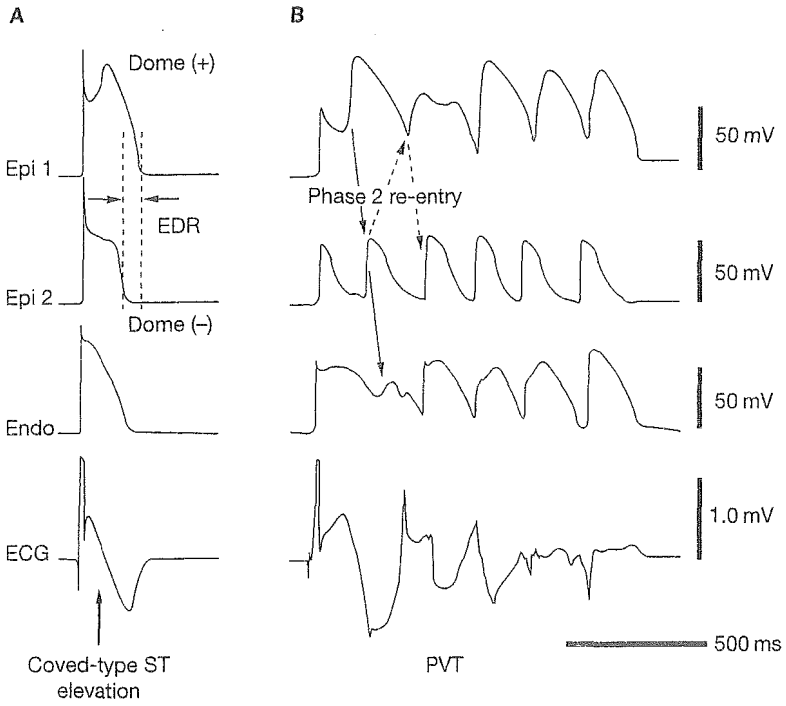

Figure 1 Coved-type ST-segment elevation and subsequent nonsustained polymorphic ventricular tachycardia caused by premature beats induced by phase 2 re-entry in a Brugada model, employing an arterially perfused canine right-ventricular wedge preparation. Transmembrane action potentials were simultaneously recorded from two epicardial sites and one endocardial site together with a transmural electrocardiogram (basic cycle length 2000 ms). (**A**) Combined administration of 5 μM/l terfenadine and 5 μM/l pilsicainide causes heterogeneous loss of the action-potential dome in the epicardium (restored dome in epicardial site 1, loss of dome in epicardial site 2), giving rise to coved-type ST-segment elevation and increasing epicardial dispersion of repolarization. (**B**) Electrotonic propagation from the site where the dome is restored (epicardial site 1) to the site where it is lost (epicardial site 2) results in development of a premature beat induced by phase 2 re-entry, triggering spontaneous polymorphic ventricular tachycardia. Dome (+), restored dome; dome (–), loss of dome; ECG, electrocardiogram; EDR, epicardial dispersion of repolarization; Endo, endocardial; Epi, epicardial; PVT, polymorphic ventricular tachycardia.

GLOSSARY

I_{TO}
A transient outward potassium current that activates rapidly and underlies the early (phase 1) action-potential repolarization

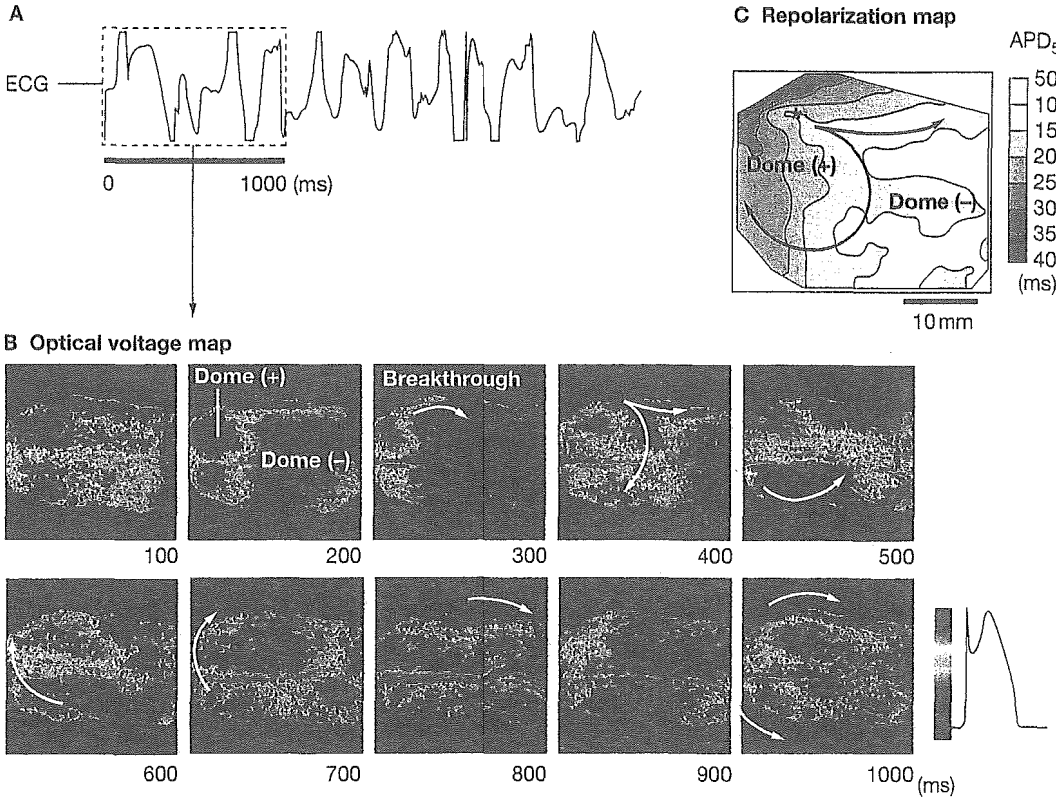

Figure 2 Snapshots of a color isopotential optical movie of the epicardial surface at the beginning of polymorphic ventricular tachycardia, and a repolarization map of the epicardial surface just before ventricular fibrillation. (**A**) Electrocardiogram recording of polymorphic ventricular tachycardia. (**B**) At the timing of phase 2 (200–300 ms), the epicardial surface is divided into two areas: restored dome (orange–red) and loss of dome (black–blue). A significant electrotonic difference between restored dome and loss of dome within a small area creates a marked epicardial dispersion of repolarization, which develops a local re-excitation called phase 2 re-entry. The initial re-entrant pathway mainly rotates in the epicardium (300–800 ms) and gradually involves the transmural myocardium (900–1000 ms), precipitating nonsustained polymorphic ventricular tachycardia. (**C**) A steep repolarization gradient (asterisk) produces local re-excitation, which propagates on the epicardial surface (arrows). APD_{50}, action-potential duration (time to 50% repolarization); dome (+), restored dome; dome (–), loss of dome; ECG, electrocardiogram.

Moreover, single *SCN5A* mutations can lead to a multiple cardiac phenotype, which is a combination of the Brugada syndrome, type 3 long-QT syndrome and a cardiac conduction defect.[26,27] In patients with type 3 long-QT syndrome alone, under baseline conditions, the sodium-channel blocker flecainide has an increased propensity to elicit a Brugada phenotype,[33] and it is reported that the proarrhythmic sensitivity to flecainide is based on inactivation gating defects caused by certain *SCN5A* mutations.[28] Some common *SCN5A* polymorphisms have been reported to modulate the functional consequences of primary *SCN5A* mutations.[29–31] The genetic and functional characteristics of *SCN5A* mutations and polymorphisms discussed above underline the complexity of sodium channelopathies.

CELLULAR MECHANISMS FOR THE BRUGADA PHENOTYPE

All functional studies of *SCN5A* mutations that are responsible for the Brugada phenotype cause a net reduction of I_{Na}, even though several distinct functional effects have been demonstrated. Experimental studies employing arterially perfused canine right-ventricular wedge preparations, in which transmembrane action potentials and pseudoelectrocardiograms are simultaneously recorded, have elucidated the cellular and molecular basis for typical ST-segment elevation and subsequent VF.[34,35] A phase 1 notch of the action potential, mediated by the transient outward current (I_{TO}), is greater in the epicardium than in the endocardium in many species, including humans.[36,37] The accentuated

I_{to}-mediated action-potential notch, and subsequent loss of the action-potential dome in epicardial cells (but not in endocardial cells) of the right ventricle—due to a net reduction of outward currents—gives rise to a transmural voltage gradient, producing coved-type ST-segment elevation in the electrocardiograms (Figure 1A). In coved-type ST-segment elevation, heterogeneous loss of the action-potential dome (coexistence of dome-loss regions and dome-restoration regions) in the epicardium creates a marked epicardial dispersion of repolarization (Figure 1A). This mechanism gives rise to premature beats caused by phase 2 re-entry,[38] which can precipitate nonsustained PVT or VF (Figure 1B). Although these data strongly suggest that episodes of VF in Brugada syndrome are triggered by premature beats between adjacent epicardial cells, triggered by phase 2 re-entry, the mechanism of initiation of VF remains unclear because of the small number of action-potential recording sites in wedge preparations. We have developed a high-resolution optical mapping system that allows us to record transmembrane action potentials from 256 sites simultaneously, from the epicardial or endocardial surface of an arterially perfused canine right-ventricular wedge preparation (Figure 2).[39] The optical mapping data indicate that a steep repolarization gradient between a dome-loss region and a dome-restoration region in the epicardium is essential to produce the premature beats (Figure 2C). Premature beats induced by phase 2 re-entry activate a re-entrant pathway, which initially rotates in the epicardium and gradually involves the transmural myocardium, precipitating nonsustained PVT or VF (Figure 2A and 2B).

OPTIMUM MANAGEMENT STRATEGIES BASED ON CELLULAR MECHANISMS

The advances in understanding of the cellular mechanism of the ST-segment elevation and phase 2 re-entry ventricular arrhythmias derived from experimental studies suggest possibilities for development of strategies for managing and treating patients with Brugada syndrome. Any therapeutic agents or interventions that decrease outward currents (e.g. I_{to}, ATP-sensitive potassium-current channels [$I_{K\text{-}ATP}$], slow-activating and fast-activating components of delayed rectifier potassium current [I_{Ks} and I_{Kr}]) or increase inward currents (e.g. L-type calcium-channel current [I_{Ca}] or FAST I_{NA}) at the end of phase 1 might normalize the Brugada phenotype. Such therapies are, therefore, candidates in patients with Brugada syndrome (Box 1). Clinical data have shown that implantable cardioverter-defibrillators have a protective effect, preventing sudden cardiac death in symptomatic Brugada patients with a history of cardiac arrest, aborted sudden cardiac death or syncope.[1,7,9,10,20,21] Several agents can be used as adjunctive pharmacologic treatments to reduce the incidence of VF episodes in all patients with symptomatic Brugada syndrome (Box 1). Oral quinidine can improve ST-segment elevation because of its strong I_{to}-blocking effect.[40–42] Denopamine, an oral adrenergic stimulant, or oral atropine, an anticholinergic agent that increases L-TYPE I_{CA}, might be alternative therapeutic choices.[43] Cilostazol, a phosphodiesterase 3 inhibitor, reduces ST-segment elevation, probably by increasing L-type I_{Ca} and heart rate.[44] These adjunctive pharmacologic treatments must, however, be considered only in conjunction with an implantable cardioverter-defibrillator, because recurrence of VF is always fatal. During recurrent episodes of VF, continuous infusion of isoproterenol, a β-adrenergic agonist, at a dose of 0.005–0.02 $\mu g\,kg^{-1}\,min^{-1}$ or until a 20% increase of heart rate occurs, attenuates ST-segment elevation and prevents VF by augmenting L-type I_{Ca} and heart rate.[45] Intravenous atropine is another option, although its effect is short-lived.

Box 1 Optimum pharmacologic therapy based on cellular mechanisms.

Adjunctive oral therapy under backup with ICD

I_{to} blockade (quinidine)

I_{Ca} augmentation (denopamine, atropine, cilostazol)

Acute intravenous therapy (electrical storm of ventricular fibrillation)

I_{Ca} augmentation (isoproterenol, atropine)

ICD, implantable cardioverter-defibrillator; I_{Ca}, L-type calcium current; I_{to}, transient outward current.

ACQUIRED FORM OF BRUGADA SYNDROME

In addition to sodium-channel blockers,[17–19,46] many agents and conditions that cause an outward shift in current activity at the end of a phase 1 action potential can unmask ST-segment elevation, as found in the Brugada syndrome, leading to the acquired form of this disorder (Box 2).[11,47] Calcium-channel blockers, such as verapamil, nifedipine and diltiazem, β-receptor blockers and

GLOSSARY

I_K
An outward potassium current that determines the late phase (phase 3) of action-potential repolarization

FAST I_{NA}
An inward sodium current that mainly contributes to the upstroke of action-potential depolarization (phase 0)

L-TYPE I_{CA}
An inward calcium current that is activated by membrane depolarization and contributes to the plateau phase of action potential

Box 2 Acquired Brugada syndrome.

Drug-induced

Fast I_{Na} blockade
- Class IC sodium blockers (flecainide, pilsicainide, propafenone)
- Class IA sodium blockers (ajmaline, procainamide, disopyramide, cibenzoline)
- Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, clomipramine)
- Tetracyclic antidepressants (maprotiline)
- Phenothiazines (perphenazine, cyamemazine)
- Selective serotonin-reuptake inhibitors (fluoxetine)
- Other drugs (dimenhydrinate, cocaine intoxication, alcohol intoxication)

L-type I_{Ca} blockade
- Calcium-channel blockers (verapamil, nifedipine, diltiazem)
- β-blockers (propranolol, etc.)
- Nitrates (isosorbide dinitrate, nitroglycerine)

$I_{K\text{-}ATP}$ open
- Nicorandil

Electrolyte abnormalities

Hyperkalemia

Hypercalcemia

Acute ischemia

Right-ventricular infarction, ischemia or both

Vasospastic angina

Other causes

Increased insulin level

Hyperthermia (febrile state)

Hypothermia

L-type I_{Ca}, L-type calcium current; $I_{K\text{-}ATP}$, adenosine-triphosphate-sensitive potassium current; I_{Na}, sodium current

GLOSSARY

AUTOSOMAL DOMINANT
A pattern of Mendelian inheritance whereby an affected individual possesses one copy of a mutant allele and one normal allele

nitrate decrease L-type I_{Ca}, and might, therefore, induce Brugada-like ST-segment elevation. $I_{K\text{-}ATP}$ openers, such as nicorandil, also have the potential to induce an acquired form of Brugada syndrome, as do many psychotropic agents,[48] including tricyclic and tetracyclic antidepressants, phenothiazine and selective serotonin-reuptake inhibitors. These agents are commonly used in clinical practice, and the potential risk of producing the Brugada phenotype should be taken into account. Electrolyte abnormalities, such as hyperkalemia and hypercalcemia, are reported to amplify ST-segment elevation as seen in Brugada syndrome.[49] Acute myocardial ischemia involving the right-ventricular outflow tract occasionally mimics Brugada-like ST-segment elevation due to the depression of L-type I_{Ca} and the activation of $I_{K\text{-}ATP}$.[50] The increased insulin level that occurs after meals sometimes unmasks or augments ST-segment elevation in Brugada patients, mainly due to an increase in an outward current caused by activation of the sodium–potassium pump.[51] Hyperthermia (febrile state) is reported to unmask Brugada-like ST-segment elevation and provoke VF secondary to the reduced I_{Na} that occurs at high temperatures.[52] Alternatively, hypothermic states sometimes induce a prominent J wave, mimicking Brugada-like ST-segment elevation, probably due to augmented I_{to}.[53]

FUTURE CHALLENGES

Risk stratification

Risk stratification for the identification of patients at raised risk of sudden death is one of the most important challenges. A previous history of aborted cardiac arrest or syncope, and the presence of a spontaneous type 1 ST-segment elevation are predictors of further arrhythmic events.[7,9,10,21] On the other hand, a positive sodium-channel challenge test and the identification of *SCN5A* mutations are not particularly helpful for risk stratification.[7,21] Whether the inducibility of VF, PVT or both with programmed electrical stimulation is a strong predictor of arrhythmic events is still controversial.[7,9,10,20,21] Further studies with higher numbers of patients, uniform stimulation protocols, and longer follow-up periods are needed before a definitive conclusion can be reached.

Genetic heterogeneity of *SCN5A* mutations

SCN5A mutations are currently identified in fewer than one-third of clinically affected Brugada patients, and more than two-thirds of patients cannot be genotyped. In such patients, however, the possibility of causative *SCN5A* mutations is not ruled out, because general screening does not include investigation of the promoter region of *SCN5A*, or allow for detection of cryptic splicing mutations or gross rearrangements. Genes that code for a variety of ion channels and other proteins have been proposed as candidate genes for the Brugada phenotype, including the genes encoding I_{to}, I_K, and L-type I_{Ca}. Other genes that code for adrenergic receptors, cholinergic receptors, ion-channel-interacting protein, promoters, transcriptional factors, neurotransmitters, or transporters might also be candidates. In addition, environmental factors can affect the clinical manifestation of the Brugada phenotype and might influence its genetic heterogeneity.

Differences between the sexes

Since all mutations so far identified in patients with Brugada syndrome display an AUTOSOMAL DOMINANT mode of transmission, male and

female inheritance of the defective gene would be expected to be approximately equal; however, more than 80% of Brugada probands in Western countries, and more than 90% in Asian countries, are men.[54] The difference between the sexes in the Brugada phenotype is reported to be due at least partly to intrinsic differences in ventricular action potential between males and females. Di Diego *et al.*[55] demonstrated more-prominent I_{to} expression in male than in female dogs, seen in right-ventricular epicardial cells. Clinical studies suggest that testosterone might also contribute to male predominance. Matsuo *et al.*[56] reported two cases of asymptomatic Brugada syndrome in whom typical ST-segment elevation disappeared following orchiectomy as therapy for prostate cancer. We reported that men with Brugada syndrome have significantly higher testosterone levels and associated lower BMI than age-matched controls, which suggests a significant role for testosterone in male predominance.[57] This hypothesis is also supported by experimental data showing that testosterone increases I_{Kr} and inward rectifier potassium currents (I_{K1}).

Ethnic differences

The incidence of Brugada syndrome differs according to ethnic origin. Frequency is higher in Asian countries than in the US and Europe. Reports indicate that common polymorphisms might modulate the activity of the primary disease-causing mutation, or influence susceptibility to arrhythmia, even in the general population.[58] Some common polymorphisms are ethnically dependent and might relate to ethnic differences in the clinical phenotype in Brugada syndrome. Pfeufer and co-workers[59] reported that polymorphisms in the *SCN5A* gene promoter were associated with an increased QRS interval in a Central European general population. Further systematic investigations of ethnically dependent common polymorphisms in patients with Brugada syndrome are required to clarify their effect on the incidence of this disease.

CONCLUSIONS

Although the sodium-channel gene *SCN5A* is so far the only gene linked to the Brugada syndrome, genetic, functional and *in vivo* experimental studies have greatly advanced our knowledge of the molecular, cellular and ionic mechanisms for the Brugada phenotype, and have enabled us to select suitable strategies for treating patients with this syndrome. Further studies of genotype–phenotype relationships, as well as research into their genetic basis, will further advance our management of Brugada syndrome.

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Competing interests

The authors declared that they have no competing interests.

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Coexistence of the Permanent Form of Junctional Reciprocating Tachycardia and Atrial Tachycardia

Takashi Noda, MD; Wataru Shimizu, MD; Kazuhiro Suyama, MD;
Takeshi Tobiume, MD; Kazuhiro Satomi, MD; Takashi Kurita, MD;
Naohiko Aihara, MD; Shiro Kamakura, MD

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