Journal of the American College of Cardiology
© 2008 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 51, No. 12, 2008
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2007.10.060

MINI-FOCUS ISSUE: BRUGADA SYNDROME

Atrial Fibrillation in Patients With Brugada Syndrome

Relationships of Gene Mutation, Electrophysiology, and Clinical Backgrounds

Kengo F. Kusano, MD, Makiko Taniyama, MD, Kazufumi Nakamura, MD, Daiji Miura, PHD, Kimikazu Banba, MD, Satoshi Nagase, MD, Hiroshi Morita, MD, Nobuhiro Nishii, MD, Atsuyuki Watanabe, MD, Takeshi Tada, MD, Masato Murakami, MD, Kohei Miyaji, MD, Shigeki Hiramatsu, MD, Koji Nakagawa, MD, Masamichi Tanaka, MD, Aya Miura, MD, Hideo Kimura, MD, Soichiro Fuke, MD, Wakako Sumita, MD, Satoru Sakuragi, MD, Shigemi Urakawa, MD, Jun Iwasaki, MD, Tohru Ohe, MD, FACC

Okayama, Japan

Objectives The goal of our work was to examine the relationships of atrial fibrillation (AF) with genetic, clinical, and electrophysiological backgrounds in Brugada syndrome (BrS).

Background Atrial fibrillation is often observed in patients with BrS and indicates that electrical abnormality might exist in the atrium as well as in the ventricle. *SCN5A*, a gene encoding the cardiac sodium channel, has been reported to be causally related to BrS. However, little is known about the relationships of atrial arrhythmias with genetic, clinical, and electrophysiological backgrounds of BrS.

Methods Seventy-three BrS patients (49 ± 12 years of age, men/women = 72/1) were studied. The existence of *SCN5A* mutation and clinical variables (syncopal episode, documented ventricular fibrillation [VF], and family history of sudden death) were compared with spontaneous AF episodes. Genetic and clinical variables were also compared with electrophysiologic (EP) parameters: atrial refractory period, interatrial conduction time (CT), repetitive atrial firing, and AF induction by atrial extra-stimulus testing.

Results Spontaneous AF occurred in 10 (13.7%) of the BrS patients and *SCN5A* mutation was detected in 15 patients. Spontaneous AF was associated with higher incidence of syncopal episodes (60.0% vs. 22.2%, $p < 0.03$) and documented VF (40.0% vs. 14.3%, $p < 0.05$). *SCN5A* mutation was associated with prolonged CT ($p < 0.03$) and AF induction ($p < 0.05$) in EP study, but not related to the spontaneous AF episode and other clinical variables. In patients with documented VF, higher incidence of spontaneous AF (30.8% vs. 10.0%, $p < 0.05$), AF induction (53.8% vs. 20.0%, $p < 0.03$), and prolonged CT was observed.

Conclusions Spontaneous AF and VF are closely linked clinically and electrophysiologically in BrS patients. Patients with spontaneous AF have more severe clinical backgrounds in BrS. *SCN5A* mutation is associated with electrical abnormality but not disease severity. (J Am Coll Cardiol 2008;51:1169–75) © 2008 by the American College of Cardiology Foundation

Brugada syndrome (BrS) is a distinct form of idiopathic ventricular fibrillation (VF) characterized by a unique electrographic (ECG) pattern consisting of a right bundle branch block-like morphology and ST-segment elevation in precordial leads (1–3). In addition to the ventricular arrhythmias, atrial arrhythmias are also often observed in this syndrome (4–6), indicating that electrical abnormality might exist in the atrium as well as in the ventricle. We, therefore, speculated that patients with BrS and spontaneous atrial fibrillation (AF) have more advanced disease process.

See page 1176

The human cardiac sodium channel (*SCN5A*) is responsible for the fast depolarization upstroke for the cardiac action potential (7). Mutations in *SCN5A* have been previ-

From the Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan. This work was supported, in part, by Grant-in-Aid for Scientific Research (No. 18790501), Grant-in-Aid for Young Scientists (No. 17689026) from the Ministry of Education, Culture, Sports, Science and Technology, Japan and Health Sciences Research grants (H18-Research on Human Genome-002) from the Ministry of Health, Labor and Welfare, Japan. This work was also supported, in part, by a grant from the Japan Foundation of Cardiovascular Research, Tokyo, Japan. Drs. Kusano and Taniyama contributed equally to this study.

Manuscript received September 19, 2007; accepted October 19, 2007.

JACC Vol. 51, No. 12, 2008
March 25, 2008:1169–75

Abbreviations and Acronyms

AF = atrial fibrillation
BrS = Brugada syndrome
CS = coronary sinus
CT = conduction time
EP = electrophysiology/electrophysiological
ERP = effective refractory period
FH = family history of sudden death
ICD = implantable cardioverter-defibrillator
PCR = polymerase chain reaction
RAA = right atrial appendage
RAF = repetitive atrial firing
SCN5A = pore-forming region of the human cardiac sodium channel
VF = ventricular fibrillation

ously discovered in a wide spectrum of cardiac rhythm disorders: the long QT syndrome (8), BrS (7), sick sinus syndrome (9,10), cardiac conduction defect (11), and AF (12). In patients with BrS, *SCN5A* mutations have been reported to be causally linked to familial BrS (7,13). However, little is known about the relationships of atrial arrhythmias with genetic, clinical, and electrophysiological (EP) backgrounds. We, therefore, examined the relationships between genetic, EP, and clinical variables to AF in BrS patients.

Methods

Patient population and clinical data collection. Patients diagnosed with BrS in our hospital between 1997 to 2006 were studied. All of the tests that were performed were approved by the medical ethical review committees of our hospital. Informed consent was obtained from all patients. Clinical data, including data on age at diagnosis, gender, family history, documented VF, syncopal episodes, and implantable cardioverter-defibrillator (ICD) implantation, were obtained from patient records. Family history of sudden death (FH) was defined as unknown sudden death at less than the age of 50 years. All patients showed a typical ECG "Brugada pattern," which was defined previously (1). If the standard ECG pattern showed a type 2 or 3 Brugada pattern, 1 mg/kg of pilsicainide (a pure sodium channel blocker) was intravenously administered for 10 min with continuous monitoring in the intensive care unit and it was confirmed that the Brugada pattern had changed to a type 1 pattern.

Evaluation of incidence of AF. The occurrence of spontaneous AF was evaluated by clinical follow-up (every month), in which the patient's symptoms were observed and 24-h Holter recordings without any drugs were performed. Continuous ECG monitoring was also performed for 2 to 3 weeks during admission.

Analysis of *SCN5A* mutation. This study was performed in compliance with guidelines for human genome studies of the Ethics Committee of Okayama University. Informed consent was obtained from all patients. All exons of SCN5A were amplified by polymerase chain reaction (PCR) from deoxyribonucleic acid (DNA) isolated from peripheral leukocytes of the patients. Genomic DNA was extracted from peripheral blood leucocytes using a DNA extraction kit (Gentra, Minneapolis, Minnesota) and was stored at −30°C until use.

Twenty-seven exons of the *SCN5A* gene were amplified with previously reported intronic primers (14). *SCN5A* gene exon 1 is a noncoding region, and this region was not analyzed in this study. Exons 6, 17-1 Sense, 21, and 25 were not able to be amplified sufficiently by the primers, and we designed new intronic primers. The following primers were used in this study: 5′-GTT ATC CCA GGT AAG ATG CCC-3′ (sense) and 5′-TGG TGA CAG GCA CAT TCG AAG-3′ (antisense) for exon 6, 5′-AAG CCT CGG AGC TGT TTG TCA CA-3′ (sense) for exon 17-1, 5′-TGC CTG GTG CAG GGT GGA AT-3′ (sense) and 5′-ACT CAG ACT TAC GTC CTC CTT C-3′ (antisense) for exon 21, and 5′-TCT TTC CCA CAG AAT GGA CAC C-3′ (sense) and 5′-AAG GTG AGA TGG GAC CTG GAG-3′ (antisense) for exon 25. Polymerase chain reaction was performed in 25-μl reaction volumes containing 50 ng of genomic DNA, 20 pmol of each primer, 0.8 mM dNTPs, 1 X reaction buffer, 1.5 mM $MgCl_2$, and 0.7 U of AmpliTaq Gold DNA polymerase (Applied Biosystems, Foster City, California) or TAKARA Taq (Takara Bio Inc., Otsu, Shiga, Japan). All PCR products were purified with a PCR products pre-sequencing kit (Amersham Life Science, Buckinghamshire, United Kingdom), reacted with a Big Dye Terminator FS ready-reaction kit (Applied Biosystems), and analyzed on an ABI PRISM3130xl sequencer (Applied Biosystems). Mutations were analyzed at least 3 times by independent PCR amplification and sequencing. Polymerase chain reaction products were subjected to single-strand conformation polymorphism analysis followed by direct sequence analysis.

EP study. After obtaining written informed consent from patients, an EP study was performed as described previously (6,15,16) in all patients. In brief, after right femoral and right jugular venous access had been obtained, 3 quadripolar electrode catheters (6-F) with an interelectrode distance of 5 mm (EP Technologies, Boston Scientific, Inc., Sunnyvale, California) were positioned in the right atrial appendage (RAA), His bundle region, and right ventricle, and an octopolar catheter (6-F) with an interelectrode distance of 2.5 mm (EP Technologies, Boston Scientific, Inc.) was positioned in the coronary sinus (CS). To reduce the differences among patients, the proximal electrode of CS catheter was positioned at the CS ostium and the distal electrode was located at the lateral wall of the left atrium in all patients. An extra-stimulus (S2) was delivered after 8 beats of drive pacing (S1) at a basic cycle length of 600 ms. The S1-S2 interval was decreased in 10-ms steps until the effective refractory period (ERP) of the RAA was reached. Sinus node recovery time was also measured during the EP study.

The parameters during EP study were as follows: 1) ERP of the RAA by atrial extra-stimulus testing; 2) interatrial conduction time (CT) measured by CT from the stimulus at the right atrium to atrial deflection at the distal portion of the CS; 3) the duration of local atrial electrogram (A) recorded at atrial pacing site; 4) repetitive atrial firing (RAF)

defined as occurrence of 2 or more premature atrial complexes after atrial stimulation; and 5) induced AF defined as AF that was induced by extrastimulus and persisted for >30 s (6,17–19). If RAF or AF was induced during the paired pacing, S2 was no longer decreased and ERP was defined as the minimum S2 interval that induced RAF or AF.

Programmed electrical stimulation was also performed at the ventricle to induce VF. As described previously (15), programmed electrical stimulation was performed at an intensity twice threshold and 2-ms in duration through the distal electrodes in the right ventricular apex, free-wall region, septal region of the right ventricular outflow tract, and posterolateral wall of the left ventricle using pulse generator as described before. The protocol of ventricular stimuli included up to 3 extrastimuli at the basic cycle length of 600 ms and 400 ms and the minimum coupled extrastimuli of 180 ms.

Statistical analysis. Data are expressed as mean values ± standard deviation. Student *t* test was performed to test for statistical differences between 2 unpaired mean values, and categorical data and percentage frequencies were analyzed by the chi-square test (SPSS II for Windows, SPSS Inc., Chicago, Illinois). A value of $p < 0.05$ was considered to be statistically significant.

Results

Patients' characteristics. The population consisted of a total of 73 probands. None of the patients in this study were members of the same family. Patients' characteristics are summarized in Table 1. Spontaneous AF was documented in 10 (13.7%) of the patients and VF was documented in 13 (17.8%) of the patients. Nineteen (26.0%) of the patients had an FH, and syncopal episodes occurred in 20 (27.4%) of the patients. Gene analysis revealed that *SCN5A* mutation was present in 15 (20.5%) of the patients. Spontaneous type 1 ECG was observed in 23 (31.5%) of the patients. In EP study, VF was induced in 34 (47%) of the patients and 33 (45.2%) of the patients had received ICD implantation.

Table 1 Patients' Characteristics (n = 73)

Men/women	72/1
Age (yrs)	49.5 ± 12.0
Syncopal episode (%)	20 (27.4%)
Documented VF (%)	13 (17.8%)
Spontaneous AF (%)	10 (13.7%)
Family history of sudden death (%)	19 (26.0%)
SCN5A mutation (%)	15 (20.5%)
Spontaneous type 1 ECG	23 (31.5%)
VF induction during EP study (%)	34 (46.6%)
ICD implantation (%)	33 (45.2%)

Values are mean ± SD or number of patients.

AF = spontaneous documented atrial fibrillation; ECG = electrocardiogram; EP = electrophysiological; ICD = implantable cardioverter defibrillator; SCN5A = pore-forming region of the human cardiac sodium channel; VF = ventricular fibrillation.

Circadian variation of spontaneous AF and VF. Spontaneous AF episodes were detected at night (12:00 AM to 6:00 AM) in 7 (70%) of the 10 patients with documented AF and 3 of 10 patients in the daytime (6:00 AM to 6:00 PM). Documented VF episodes were observed in 13 patients (46 episodes). Among them, 7 patients (55%) (22 episodes [48%]) were detected at night (12:00 AM to 6:00 AM), and 2 patients (15%) (7 episodes [15%]) in the daytime (6:00 AM to 6:00 PM).

Clinical and genetic differences in BrS patients with AF. Clinical and genetic parameters were compared in BrS patients with spontaneous AF and those without spontaneous AF (Table 2). None of the patients in this study showed chronic AF. Age was not different between the groups. In the clinical parameters, syncopal episode, documented VF, and spontaneous type 1 ECG were observed in larger percentage of patients with spontaneous AF (syncope: 60.0% vs. 22.2%, $p < 0.03$; documented VF: 40.0% vs. 14.3%, $p < 0.05$; and spontaneous type 1 ECG: 60.0% vs. 27.0%, $p < 0.04$). However, FH, *SCN5A* mutation, and VF induction during EP study were not related to spontaneous AF episodes (Table 2).

EP parameters in BrS patients with AF. In EP study, there was no significant difference between the ERP of the RAA in the AF (+) group (254.3 ± 44.7 ms) and that in the AF (−) group (243.9 ± 25.5 ms). However, CT was more prolonged in the AF group at S1 (CT at S1: 138.4 ± 23.8 ms vs.122.3 ± 20.1 ms, $p < 0.03$) and at S2 (172.4 ± 33.3 ms vs. 154.2 ± 18.0 ms, $p < 0.03$). Sinus node recovery time was significantly prolonged in the AF (+) group (1,971 ± 1,007 ms vs. 1,288 ± 488 ms, $p < 0.01$). Other parameters, including RAF, induction of AF, and local atrial electrograms (A1: A at S1 and A2: A at S2) were not different between the groups (Table 2).

Clinical and EP parameters in BrS patients with *SCN5A* mutation. Next we examined the relationships of genetic mutation with clinical and EP parameters in patients with BrS. None of the clinical parameters (age, syncopal episode, documented VF, spontaneous AF, FH, spontaneous type 1 ECG, and ICD implantation) were different in patients with *SCN5A* mutation and patients without *SCN5A* mutation. However, AF induction (in 46.7% of the patients with *SCN5A* mutation and in 20.7% of the patients without *SCN5A* mutation, $p < 0.05$), CT at S1 (138.1 ± 18.1 ms with *SCN5A* mutation and 121.5 ± 20.9 ms without *SCN5A* mutation, $p < 0.03$), CT at S2 (167.9 ± 14.2 ms with *SCN5A* mutation and 153.4 ± 21.3 ms without *SCN5A* mutation, $p < 0.03$), local A2 (103.9 ± 17.4 ms with *SCN5A* mutation and 89.8 ± 18.7 ms without *SCN5A* mutation, $p < 0.03$), and sinus node recovery time (1,682 ± 1,036 ms with *SCN5A* mutation and 1,300 ± 433 ms without *SCN5A* mutation, $p < 0.04$) during EP study were significantly different between the groups (Table 3).

Table 2 Characteristics of Patients With and Without AF

	Without AF	With AF	p Value
Clinical/genetic parameters			
Number of patients (men/women)	63 (62/1)	10 (10/0)	
Age (yrs)	48.4 ± 11.5	53.7 ± 14.2	NS
Syncopal episode (%)	14 (22.2%)	6 (60.0%)	<0.03
Documented VF (%)	9 (14.3%)	4 (40.0%)	<0.05
Family history of sudden death (%)	17 (27.0%)	2 (20.0%)	NS
SCN5A mutation (%)	13 (20.6%)	2 (20.0%)	NS
Spontaneous type 1 ECG (%)	17 (27.0%)	6 (60.0%)	<0.04
VF induction during EP study (%)	29 (46.0%)	5 (50.0%)	NS
ICD implantation (%)	27 (42.9%)	6 (60.0%)	NS
EP parameters of the atrium			
RAF	31 (49.2%)	6 (60.0%)	NS
AF induction	14 (22.2%)	5 (50.0%)	NS
ERP (ms)	243.9 ± 25.5	254.3 ± 44.7	NS
CT at S1 (ms)	122.3 ± 20.1	138.4 ± 23.8	<0.03
CT at S2 (ms)	154.2 ± 18.0	172.4 ± 33.3	<0.03
A1 (ms)	65.7 ± 12.9	72.5 ± 20.4	NS
A2 (ms)	92.4 ± 18.9	99.2 ± 21.8	NS
A2/A1	1.42 ± 0.25	1.39 ± 0.24	NS
Sinus node recovery time (ms)	1,288 ± 488	1,971 ± 1,007	<0.01

Values are mean ± SD or number of patients.
A1 = local atrial potential at S1; A2 = local atrial potential at S2; CT = interatrial conduction time; ERP = effective refractory period; RAF = repetitive atrial firing; other abbreviations as in Table 1.

Clinical, genetic, and EP parameters in BrS patients with spontaneous type 1 ECG. Next we examined the relationship of the basal ECG pattern to the clinical, genetic, and EP parameters in patients with BrS. Spontaneous type 1 ECG was observed in 23 of the patients (31.5%) and drug (pilsicainide)-induced type 1 ECG (type 2 or 3 ECG before the drug administration) in the remaining 50 patients (68.5%) in this study. Spontaneous AF was significantly more observed in patients with spontaneous type 1 ECG (26.1% vs. 8.0%, $p < 0.04$). Documented VF tended to be more observed but not statistically significant (30.4% vs. 12.0%, $p = 0.06$). Other parameters including age, syncopal episodes, FH, frequency of *SCN5A* mutation, VF induction, ICD implantation, and

Table 3 Clinical and EP Parameters in Patients With and Without *SCN5A* Mutation

	SCN5A Mutaion (−)	*SCN5A* Mutaion (+)	p Value
Clinical parameters			
Number of patients (men/women)	58 (57/1)	15 (15/0)	
Age (yrs)	49.6 ± 11.3	47.5 ± 14.5	NS
Syncopal episode (%)	15 (25.9%)	5 (33.3%)	NS
Documented VF (%)	9 (15.5%)	4 (26.7%)	NS
Spontaneous AF (%)	8 (13.8%)	2 (13.3%)	NS
Family history of sudden death (%)	13 (22.9%)	6 (40.0%)	NS
Spontaneous type 1 ECG (%)	16 (27.6%)	7 (46.7%)	NS
VF induction during EP study (%)	30 (51.7%)	4 (26.7%)	NS
ICD implantation (%)	26 (44.8%)	7 (46.7%)	NS
EP parameters of the atrium			
RAF	29 (50.0%)	8 (53.3%)	NS
AF induction	12 (20.7%)	7 (46.7%)	<0.05
ERP (ms)	240.2 ± 24.2	264.5 ± 35.6	NS
CT at S1 (ms)	121.5 ± 20.9	138.1 ± 18.1	<0.03
CT at S2 (ms)	153.4 ± 21.3	167.9 ± 14.2	<0.03
A1 (ms)	64.5 ± 13.2	73.0 ± 11.4	NS
A2 (ms)	89.8 ± 18.7	103.9 ± 17.4	<0.03
A2/A1	1.41 ± 0.26	1.45 ± 0.20	NS
Sinus node recovery time	1,300 ± 433	1,682 ± 1,036	<0.04

Values are mean ± SD or number of patients.
Abbreviations as in Tables 1 and 2.

Table 4 Clinical, Genetic, and EP Parameters in Patients With and Without Spontaneous Type 1 ECG

	Type 2 or 3 ECG	Type 1 ECG	p Value
Clinical/genetic parameters			
Number of patients (men/women)	50 (49/1)	23 (23/0)	
Age (yrs)	49.7 ± 12.0	47.8 ± 12.0	NS
Syncopal episode (%)	12 (24.0%)	8 (34.8%)	NS
Documented VF (%)	6 (12.0%)	7 (30.4%)	NS ($p = 0.06$)
Spontaneous AF (%)	4 (8.0%)	6 (26.1%)	<0.04
Family history of sudden death (%)	13 (28.0%)	6 (26.1%)	NS
SCN5A mutation (%)	8 (16.0%)	7 (30.4%)	NS
VF induction during EP study (%)	20 (40.0%)	14 (60.9%)	NS
ICD implantation (%)	19 (38.0%)	14 (60.9%)	NS
EP parameters of the atrium			
RAF	26 (52.0%)	11 (47.8%)	NS
AF induction	11 (22.0%)	8 (34.8%)	NS
ERP (ms)	246.2 ± 27.4	242.9 ± 32.0	NS
CT at S1 (ms)	122.9 ± 22.8	128.6 ± 17.4	NS
CT at S2 (ms)	155.8 ± 22.3	157.6 ± 16.9	NS
A1 (ms)	65.3 ± 12.1	69.9 ± 15.8	NS
A2 (ms)	91.1 ± 18.4	99.2 ± 20.8	NS
A2/A1	1.4 ± 0.3	1.4 ± 0.2	NS
Sinus node recovery time (ms)	1,310 ± 460	1,523 ± 855	NS

Values are mean ± SD or number of patients.
Abbreviations as in Tables 1 and 2.

all EP parameters were not different between the groups (Table 4).

Clinical, genetic, and EP parameters in BrS patients with and without VF episodes. Finally, we examined the relationships of disease severity (documented VF) with other clinical, genetic, and EP parameters in BrS patients. Spontaneous AF was observed in a large percentage of patients with VF episodes (30.8%) in comparison with that seen in patients without VF episodes (10.0%) ($p < 0.05$), but the frequency of *SCN5A* mutation was not different between the groups (Table 5). Spontaneous type 1 ECG tended to be more observed in patients with VF episodes but not statistically significant ($p = 0.06$). As for the EP parameters, ERP at RAA was not different, but the rate of AF induction

Table 5 Clinical, Genetic, and EP Parameters in Patients With and Without Documented VF Episode

	Documented VF (−)	Documented VF (+)	p Value
Clinical/genetic parameters			
Number of patients (men/women)	60 (59/1)	13 (13/0)	
Age (yrs)	48.3 ± 12.0	52.8 ± 11.1	NS
Spontaneous AF (%)	6 (10.0%)	4 (30.8%)	<0.05
Family history of sudden death (%)	17 (28.3%)	2 (15.4%)	NS
SCN5A mutation (%)	11 (18.3%)	4 (30.8%)	NS
Spontaneous type 1 ECG (%)	16 (26.7%)	7 (53.8%)	NS ($p = 0.06$)
VF induction during EP study (%)	28 (46.7%)	6 (46.2%)	NS
ICD implantation (%)	20 (33.3%)	13 (100%)	<0.01
EP parameters of the atrium			
RAF	29 (48.3%)	8 (61.5%)	NS
AF induction	12 (20.0%)	7 (53.8%)	<0.03
ERP (ms)	242.0 ± 26.2	261.1 ± 34.8	NS
CT at S1 (ms)	121.9 ± 19.6	137.6 ± 24.6	<0.02
CT at S2 (ms)	153.7 ± 16.8	171.3 ± 33.9	<0.02
A1 (ms)	66.1 ± 14.1	68.6 ± 8.5	NS
A2 (ms)	91.6 ± 19.8	100.4 ± 15.0	NS
A2/A1	1.4 ± 0.3	1.5 ± 0.2	NS
Sinus node recovery time	1,313 ± 505	1,658 ± 937	NS

Values are mean ± SD or number of patients.
Abbreviations as in Tables 1 and 2.

JACC Vol. 51, No. 12, 2008
March 25, 2008:1169–75

was significantly higher (53.8% vs. 20.0%, $p < 0.03$) and CT was prolonged in patients with VF episodes (CT at S1: 137.6 ± 24.6 ms vs. 121.9 ± 19.6 ms, $p < 0.02$; CT at S2: 171.3 ± 33.9 ms vs. 153.7 ± 16.8 ms, $p < 0.02$) (Table 5). Sinus node recovery time was not different between the groups ($p = 0.07$).

Discussion

The present study demonstrated that BrS patients with spontaneous AF have more severe clinical and EP backgrounds but not associated with family history or mutations of the gene encoding the cardiac sodium channel, *SCN5A*. Electrical vulnerability across the heart may be closely associated with spontaneous AF and VF occurrence in BrS patients.

AF in BrS. It has been reported that spontaneous AF is often observed in patients with BrS. The incidence of AF in this syndrome has been reported to be 10% to 53% (1,4,6). In this study, the incidence of spontaneous AF was 13.7% and most cases (70%) were documented at night. Matsuo et al. (20) reported that VF in patients with BrS was most frequently detected in the midnight to early morning period during sleep. Our finding of a circadian pattern in spontaneous AF and VF episodes is in agreement with their findings, and these findings suggested that nocturnal vagal activity and withdrawal of sympathetic activity may play an important role in arrhythmogenesis in both AF and VF occurrence in this syndrome.

The treatment for AF in BrS is an important issue. It has been reported that quinidine sulfate, isoproterenol, cilostazole (1), and bepridil chloride (21,22) are recommended in Brugada patients with repeated VF by a mechanism of augmenting the calcium current or reducing the I_{to} current. In this study, none of the patients received antiarrhythmic drugs for AF because their episodes were paroxysmal with few symptoms. However, 2 AF patients that experienced recurrent VF episodes had received antiarrhythmic drugs to prevent recurrent VF (1 patient received quinidine sulfate 0.3 g and the other received bepridil hydrochloride 100 mg). While these patients never experienced AF episodes with taking these drugs, indicating antiarrhythmic drugs that were effective to prevent VF might be also effective in AF.

EP parameters in patients with BrS. It has also been reported that atrial vulnerability was increased in patients with BrS, compared with that in a normal control group (6). Among the various indexes of EP parameters, we found the interatrial conduction delay (CT) was significantly increased in BrS patients with AF, indicating that global conduction of the atrial myocardium was impaired. Interestingly, atrial vulnerability (induced AF) was more impaired in BrS patients with VF episodes, indicating that electrical vulnerability may be across the whole heart including the atrium and ventricle. The fact that patients with AF have more episodes of VF or syncopal episodes supports this possibility.

There was no difference in VF inducibility between the patients with and without documented VF. In this study, all patients who had documented VF experienced at least 1 VF episode before ICD implantation; therefore, asymptomatic patients never experienced VF attacks during the follow-up period after ICD implantation. These results indicate that VF inducibility during EP study has a low specificity to identify high-risk BrS patients as reported before (23).

***SCN5A* mutation is not associated with AF in BrS.** The gene encoding the cardiac sodium channel, *SCN5A*, has been reported to be linked causally to BrS. We speculated AF is more common in patients with *SCN5A* mutation, but we found no difference between patients with *SCN5A* mutation and those without *SCN5A* mutation in spontaneous AF episodes or in other clinical parameters (spontaneous VF, syncopal episode, FH, and spontaneous type 1 ECG). The reason is still unclear, but this finding is perhaps of most interest. These results indicate that a defect in the *SCN5A* gene is not associated with AF events or with VF events as was previously reported (1), suggesting that genetic analysis is not useful for risk stratification.

Clinical implications. This study showed that spontaneous AF and atrial vulnerability are important predictors of VF events that cause sudden cardiac death. The fifth-generation ICD is preferable for patients with BrS, even for BrS patients who have never experienced an attack of AF, because atrial vulnerability is common and AF could occur during the follow-up period.

Study limitations. The number of patients in this study was small, and further study is needed to reach definitive conclusion regarding the impact of AF episodes for BrS. Moreover, we analyzed only the coding regions of *SCN5A* for mutations in this study, and the possibility of mutations occurring in regions of the gene other than coding regions cannot be excluded. The functional impact has not been studied for all identified *SCN5A* mutations; therefore, a causal relationship in individual patients has not been proved yet.

Acknowledgments

The authors greatly acknowledge the secretarial assistance of Miyuki Fujiwara and Masayo Ohmori and the technical assistance of Kaoru Kobayashi.

Reprint requests and correspondence: Dr. Kengo F. Kusano, Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Shikata-cho 2-5-1, Okayama 7008558, Japan. E-mail: kusanokengo@hotmail.com.

REFERENCES

1. Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. Circulation 2005;111:659–70.
2. Brugada J, Brugada R, Brugada P. Right bundle-branch block and ST-segment elevation in leads V1 through V3: a marker for sudden

death in patients without demonstrable structural heart disease. Circulation 1998;97:457–60.
3. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol 1992;20:1391–6.
4. Babai MA, Aslani A, Shahrzad S. Clinical predictors of atrial fibrillation in Brugada syndrome. Europace 2007;9:947–50.
5. Eckardt L, Kirchhof P, Loh P, et al. Brugada syndrome and supraventricular tachyarrhythmias: a novel association? J Cardiovasc Electrophysiol 2001;12:680–5.
6. Morita H, Kusano-Fukushima K, Nagase S, et al. Atrial fibrillation and atrial vulnerability in patients with Brugada syndrome. J Am Coll Cardiol 2002;40:1437–44.
7. Chen Q, Kirsch GE, Zhang D, et al. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. Nature 1998;392:293–6.
8. Wang Q, Shen J, Splawski I, et al. SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. Cell 1995;80:805–11.
9. Benson DW, Wang DW, Dyment M, et al. Congenital sick sinus syndrome caused by recessive mutations in the cardiac sodium channel gene (SCN5A). J Clin Invest 2003;112:1019–28.
10. Morita H, Fukushima-Kusano K, Nagase S, et al. Sinus node function in patients with Brugada-type ECG. Circ J 2004;68:473–6.
11. Laitinen-Forsblom PJ, Makynen P, Makynen H, et al. SCN5A mutation associated with cardiac conduction defect and atrial arrhythmias. J Cardiovasc Electrophysiol 2006;17:480–5.
12. Chen LY, Ballew JD, Herron KJ, Rodeheffer RJ, Olson TM. A common polymorphism in SCN5A is associated with lone atrial fibrillation. Clin Pharmacol Ther 2007;81:35–41.
13. Bezzina CR, Rook MB, Wilde AA. Cardiac sodium channel and inherited arrhythmia syndromes. Cardiovasc Res 2001;49:257–71.
14. Wang Q, Li Z, Shen J, Keating MT. Genomic organization of the human SCN5A gene encoding the cardiac sodium channel. Genomics 1996;34:9–16.
15. Morita H, Fukushima-Kusano K, Nagase S, et al. Site-specific arrhythmogenesis in patients with Brugada syndrome. J Cardiovasc Electrophysiol 2003;14:373–9.
16. Morita H, Morita ST, Nagase S, et al. Ventricular arrhythmia induced by sodium channel blocker in patients with Brugada syndrome. J Am Coll Cardiol 2003;42:1624–31.
17. Hashiba K, Tanigawa M, Fukatani M, et al. Electrophysiologic properties of atrial muscle in paroxysmal atrial fibrillation. Am J Cardiol 1989;64:20J–3J.
18. Ohe T, Matsuhisa M, Kamakura S, et al. Relation between the widening of the fragmented atrial activity zone and atrial fibrillation. Am J Cardiol 1983;52:1219–22.
19. Shimizu A, Fukatani M, Tanigawa M, Mori M, Hashiba K. Intraatrial conduction delay and fragmented atrial activity in patients with paroxysmal atrial fibrillation. Jpn Circ J 1989;53:1023–30.
20. Matsuo K, Kurita T, Inagaki M, et al. The circadian pattern of the development of ventricular fibrillation in patients with Brugada syndrome. Eur Heart J 1999;20:465–70.
21. Ohgo T, Okamura H, Noda T, et al. Acute and chronic management in patients with Brugada syndrome associated with electrical storm of ventricular fibrillation. Heart Rhythm 2007;4:695–700.
22. Sugao M, Fujiki A, Nishida K, et al. Repolarization dynamics in patients with idiopathic ventricular fibrillation: pharmacological therapy with bepridil and disopyramide. J Cardiovasc Pharmacol 2005;45:545–9.
23. Priori SG, Napolitano C, Gasparini M, et al. Natural history of Brugada syndrome: insights for risk stratification and management. Circulation 2002;105:1342–7.