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Abbreviations and Acronyms

AF = atrial fibrillation
BrS = Brugada syndrome
CT = conduction time
CS = coronary sinus
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

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 DNA isolated from peripheral leukocytes of the patients. Genomic DNA was extracted from peripheral blood leucocytes using a DNA extraction kit (Gentra) 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) or TAKARA Taq (TAKARA Bio). All PCR products were purified with a PCR products pre-sequencing kit (Amersham Biosciences), 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 for patients, an EP study was performed as described previously (6,15,16) in all patients. In brief, after right femoral and right jugular venous assess 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 >30s (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 was 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 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.

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).

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 means ± standard deviation 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.

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).

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

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 means ± standard deviation or number of patients.
A1 = local atrial potential at S1; A2 = local atrial potential at S2; CT1 = interatrial conduction time at S1; CT2 = CT at S2; ERP = effective refractory period; RAF = repetitive atrial firing; other abbreviations as in Table 1.

(pilsicainide)-induced type 1 ECG (type 2 or 3 ECG before the drug administration) in remaining 50 of 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 all EP parameters were not different between the groups (Table 4). T4

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. Spon-

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 means ± standard deviation or number of patients.
Abbreviations as in Tables 1 and 2.

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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.

taneous 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 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 ($p = 0.07$).

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 ± standard deviation or number of patients.
Abbreviations as in Tables 1 and 2.

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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 and 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). And 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.

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Longer Repolarization in the Epicardium at the Right Ventricular Outflow Tract Causes Type 1 ECG in Patients With Brugada Syndrome

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Objectives We examined the relationship between repolarization abnormality and coved-type ST-segment elevation with terminal inverted T-wave (type 1 electrocardiogram [ECG]) in patients with Brugada syndrome (BrS).

Background Recent experimental studies have suggested that accentuation of the right ventricular action potential (AP) notch preferentially prolongs epicardial AP causing inversion of the T-wave.

Methods In 19 patients with BrS and 3 control subjects, activation-recovery intervals (ARIs) and repolarization times (RTs) in the epicardium and endocardium were directly examined with the use of local unipolar electrograms at the right ventricular outflow tract. Surface ECG, ARI, and RT were examined before and after administration of pilsicainide.

Results Type 1 ECG was observed in 10 of the 19 BrS patients before the administration of pilsicainide and in all of the 19 patients after the administration of pilsicainide. We found that ARI and RT in the epicardium were shorter than those in the endocardium in all 9 BrS patients without type 1 ECG under baseline conditions and in all control subjects regardless of pilsicainide administration. However, longer epicardial ARI than endocardial ARI was observed in 8 of the 10 BrS patients manifesting type 1 ECG under baseline conditions and in all of the BrS patients after the administration of pilsicainide. Also, epicardial RT was longer than endocardial RT in all patients manifesting type 1 ECG regardless of pilsicainide administration.

Conclusions Our data provides support for the hypothesis that the negative T-wave associated with type 1 BrS ECG is due to a preferential prolongation of the epicardial AP secondary to accentuation of the AP notch in the region of the right ventricular outflow tract. (J Am Coll Cardiol 2008;xx:xxx) © 2008 by the American College of Cardiology Foundation

Brugada syndrome (BrS) is characterized by ST-segment elevation in right precordial leads and an episode of ventricular fibrillation (VF) (1,2). Recent experimental studies have suggested that a prominent transient outward current-mediated action potential notch in epicardial cells, but not that in endocardial cells, creates a transmural voltage gradients and thus causes ST-segment elevation (3). When epicardial repolarization precedes endocardial repolarization, the T-wave remains positive. In this condition, saddleback-type electrocardiogram (ECG) was observed. Further accentuation of the notch leads to preferential prolongation of the epicardial action potential, which results in the development of coved-type ST-segment elevation and terminal inverted T-wave (type 1 ECG) in right precordial leads in BrS (4–6). A definitive diagnosis of BrS is made when a type 1 ECG is observed, and type 1 ECG can be unmasked by sodium channel blockers even in symptomatic patients (2,7–9).

In a clinical study, Kurita et al. (10) found a prominent action potential notch and prolongation of repolarization in the epicardium but not in the endocardium at the right ventricular outflow tract (RVOT) in 3 patients with BrS during open chest surgery with monophasic action potential recording.

Prolongation of the QT interval also has been reported in patients with BrS. Prolongation of the QT interval is more prominent in right precordial leads than in left precordial leads, presumably because of a preferential prolongation of action potential duration in the right ventricular epicardium

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Abbreviations and Acronyms

ARI = activation-recovery interval

ARIc = activation-recovery interval corrected for heart rate

AT = activation time

BrS = Brugada syndrome

ECG = electrocardiogram

RT = repolarization time

RVOT = right ventricular outflow tract

VF = ventricular fibrillation

V_1(3ics) = surface ECG lead V_1 at the third intercostal space

V_2(3ics) = surface ECG lead V_2 at the third intercostal space

V_1(4ics) = surface ECG lead V_1 at the fourth intercostal space

V_2(4ics) = surface ECG lead V_2 at the fourth intercostal space

secondary to accentuation of the action potential notch (11,12). An overlap between BrS and long-QT syndrome also has been reported (13,14).

Recent studies have demonstrated that the activation-recovery interval (ARI) approximates the action potential duration at each site in several experimental and clinical studies (15,16). Recently, we have reported successful recording of an epicardial electrogram at the RVOT in patients with BrS by the use of an electrical guide wire introduced into the conus branch of the right coronary artery (17).

Accordingly, we measured epicardial and endocardial ARIs directly at the RVOT to examine the epicardial and endocardial action potentials in patients with BrS, and we demonstrated a correlation between morphology of surface ECG and ARI in the epicardium and endocardium. We also measured activation time (AT) and repolarization time (RT). Because the administration of a sodium channel blocker can unmask type 1 ECG in right precordial leads, we examined the effect of injection of a pure sodium channel blocker, pilsicainide, on the morphology of surface ECG and each parameter in the epicardium and endocardium in patients with BrS.

Methods

Patients. Nineteen patients with BrS and 3 control subjects were included in this study. We defined BrS as the manifestation of type 1 ECG, which is characterized by a coved-type ST-segment elevation ≥2 mm (0.2 mV) followed by a negative T-wave in leads V_1 or V_2 at the third or fourth intercostal space in the presence or absence of a class IC antiarrhythmic drug (pilsicainide) (2). This type of repolarization pattern was described previously by Wilde et al. (7). Patient characteristics are shown in Table 1. T1

Routine examinations, including cardiac echocardiography, coronary angiography, right and left ventriculography, and radionucleography, showed no evidence of structural heart disease in any of the patients. One of the control subjects was diagnosed as having idiopathic VF with no ST-segment elevation, and the remaining 2 control subjects had incomplete right bundle branch block in surface ECG. Brugada-type ECG was not observed under baseline conditions or after pilsicainide injection in any of the control subjects.

Electrophysiologic study. A maximum of 3 ventricular extrastimuli were delivered from right ventricular apex and RVOT unless VF was induced at a previous step in all

Table 1 Patient Characteristics

	Patient #	Age, yrs	Gender	Clinical Symptom	Induced VF by PES	Family History of SD	SCN5A Mutation
	1	48	Male	VF	–	–	–
	2	33	Male	VF	–	–	–
	3	45	Male	Syncope	–	–	–
	4	55	Male	VF	–	–	
	5	48	Male	VF	–	–	
	6	47	Male	VF	–	–	–
	7	47	Male	Syncope	–	–	–
	8	50	Male	VF	–		–
	9	62	Male	No	–	–	–
Brugada syndrome	10	42	Male	No	–	–	–
	11	40	Male	No	–	–	–
	12	72	Male	No	–	–	
	13	56	Male	No	–	–	–
	14	44	Male	No	–	–	–
	15	46	Male	No	–	–	–
	16	51	Male	No	–	–	–
	17	62	Male	No	–	–	
	18	44	Male	No	–	–	–
	19	43	Male	No	–	–	–
	1	53	Male	VF	–	–	NA
Control subject	2	57	Male	No	–	–	NA
	3	28	Male	No	–	–	–

PES = programmed electrical stimulation; NA = not available; SD = sudden death; VF = ventricular fibrillation.

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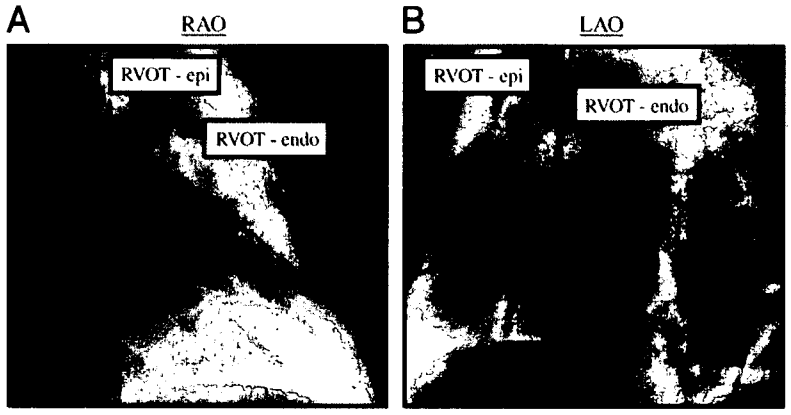

Figure 1 **Catheter Position**

Fluoroscopic right anterior oblique (RAO) **(A)** and left anterior oblique (LAO) **(B)** views of the position of the electrical guidewire for epicardial mapping (RVOT-epi). as well as the quadripolar catheter at the endocardium of the free wall at the RVOT for endocardial mapping (RVOT-endo).

patients with BrS and control subjects. We induced VF by programmed electrical stimulation in 11 patients with BrS but was not induced in control subjects. We examined ARIs, ATs, and RTs in the epicardium and endocardium simultaneously using local unipolar electrograms at the RVOT with a 0.05- to 400-Hz bandwidth under baseline conditions and after intravenous injection of a pure sodium channel blocker, pilsicainide, at a dose of 1 mg/kg during a 6-min period. The ARI and RT were corrected for heart rate by Bazett's formula and named ARIc and RTc (18). To record the epicardial electrogram directly, we introduced an electrical guidewire (Flo Wire, Cardiometrics, Mountain View, California) into the conus branch of the right coronary artery, which runs on the surface of the free wall at the RVOT (Fig. 1). The epicardial mapping has been described in detail previously (17). A local unipolar electrogram at the endocardium was recorded by a quadripolar 6-F deflectable catheter positioned at the endocardium at the free wall at the RVOT. We defined ARI as the interval between times of minimum derivative of the QRS and maximum derivative of the T-wave in a unipolar electrogram (15). We defined AT as the interval between the beginning of the surface QRS complex and minimum derivative of the QRS. We defined RT as the interval between the beginning of the surface QRS complex and maximum derivative of the T-wave (Fig. 2). For analysis of ARI, AT, and RT, the analog data were digitized at a sampling rate of 1,000 samples/s and stored on a floppy disk, then transferred to a personal computer with the analysis program developed by our institution (S.H.). The difference in ARI/ARIc was defined as the value of epicardial ARI/ARIc minus endocardial ARI/ARIc. Accordingly, if epicardial ARI is longer than endocardial ARI, the difference in ARI is positive. The difference in AT and RT/RTc were defined as epicardial AT minus endocardial AT and epicardial RT/RTc minus endocardial RT/RTc.

Because recent studies have shown that the site of maximum ST-segment elevation in body surface ECG coincides with the RVOT and because the RVOT corresponds to leads V_1

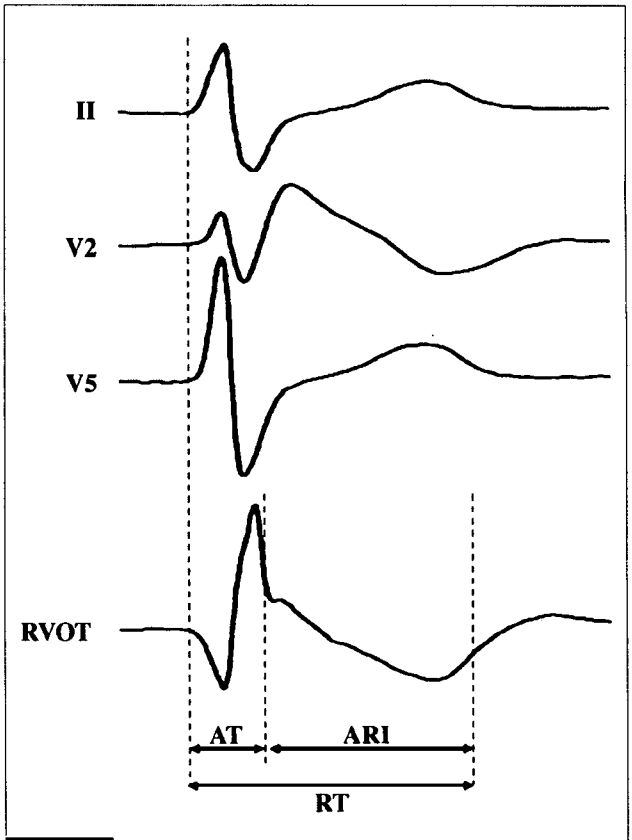

Figure 2 **Example of Surface Electrocardiograms (II, V_2, and V_5) and Intracardiac Unipolar Electrogram at the RVOT**

Activation-recovery interval (ARI), repolarization time (RT), and activation time (AT) were measured at the right ventricular outflow tract (RVOT).

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and V_2 at the third intercostal space (3ics), surface ECG also was recorded at the 3ics in leads V_1 and V_2 in addition to the standard V_1 and V_2 at the fourth intercostal space (4ics) (19–21). We defined that type 1 ECG was present if type 1 ECG was recorded in more than one of the surface ECG leads, including V_1(3ics), V_2(3ics), V_1(4ics), or V_2(4ics). Electrophysiologic study and genetic analysis were performed according to the protocol approved by the Ethics Committee of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences. Written informed consent was obtained from all patients.

Mutation analysis of SCN5A. Genetic screening was performed in all patients with BrS. All 28 exons of SCN5A were amplified with polymerase chain reaction from deoxyribonucleic acid isolated from peripheral leukocytes using intronic primers. Polymerase chain reaction products were subjected to direct sequencing of all coding regions.

Statistical analysis. Quantitative values are expressed as means ± standard deviation values. We compared ARI/ARIc, RT/RTc, and AT before and after the administration of pilsicainide administration by means of a paired *t* test. Differences in ARI/ARIc, RT/RTc, and AT before and after pilsicainide administration also were compared by means of a paired *t* test. We used the Student *t* test was to compare ARI/ARIc, RT/RTc, and AT between the epicardium and endocardium. Student's *t* test also was used for comparison of differences in ARI/ARIc, RT/RTc, and AT between BrS patients and control subjects. Differences in ARI/ARIc between SCN5A mutation careers and noncareers also were compared by means of a Student *t* test. A value of $p < 0.05$ was considered statistically significant.

Results

F3 Figure 3 shows representative surface ECGs and unipolar electrograms in a control subject (Fig. 3A) and 2 patients with BrS (Figs. 3B and 3C) under baseline conditions and after pilsicainide injection.

As shown in Figure 3A, Brugada-type ECG was not observed under baseline conditions or after pilsicainide injection in the control subject (Patient #3). Epicardial ARI was always shorter than endocardial ARI both before and after pilsicainide injection. The epicardial ARI was 23 ms shorter than the endocardial ARI under baseline conditions and was 22 ms shorter than the endocardial ARI after pilsicainide injection. The difference in ARI was thus defined as −23 ms before and −22 ms after pilsicainide injection.

As shown in Figure 3B, type 1 ECG was observed in lead V_2(3ics), and epicardial ARI (239 ms) was longer than endocardial ARI (187 ms), and the difference in ARI was therefore defined as +52 ms under baseline conditions in the Brugada patient (Patient #1).

As shown in Figure 3C, type 1 ECG was not observed in all of the surface ECG leads, and epicardial ARI (210 ms) was shorter than endocardial ARI (248 ms) under baseline conditions in the Brugada patient (Patient #16). The epicardial ARI was 38 ms shorter than the endocardial ARI, and the difference in ARI was thus defined as −38 ms. However, after administration of pilsicainide, the epicardial ARI, but not the endocardial ARI, was markedly prolonged (260 ms). Type 1 ECG appeared after pilsicainide administration in lead V_2(3ics). The epicardial ARI was 18 ms longer than the endocardial ARI, and the difference in ARI was thus defined as +18 ms.

Table 2 shows electrophysiologic data in all patients. T2 Type 1 ECG was observed in 10 of the 19 patients with BrS under baseline conditions and in all of the patients with BrS after administration of pilsicainide. Pilsicainide administration significantly prolonged epicardial ARI/ARIc from 222.9 ± 16.3 ms/248.0 ± 22.2 ms to 235.1 ± 22.2 ms/268.9 ± 24.9 ms ($p < 0.001/p < 0.001$) but did not prolong endocardial ARI/ARIc (219.3 ± 17.0 ms/243.6 ± 18.1 ms vs. 213.6 ± 17.4 ms/244.3 ± 18.7 ms; p = NS/p = NS) in patients with BrS. And epicardial ARI/ARIc were significantly longer than endocardial ARI/ARIc after pilsicainide administration in BrS ($p < 0.01/p < 0.01$). Pilsicainide administration significantly prolonged the difference in ARI/ARIc from +3.6 ± 22.0 ms/+4.4 ± 24.6 ms to +21.5 ± 13.7 ms/+24.6 ± 15.7 ms ($p < 0.001/p < 0.001$) in patients with BrS.

Figure 4 shows the relationship between differences in F4 ARIc, RTc, and AT and appearance of type 1 ECG. In all control subjects, the epicardial ARIc was always shorter than the endocardial ARIc, and the difference in ARIc was always <0 ms. Type 1 ECG was not observed under baseline conditions and also after pilsicainide administration in the control subjects. However, under baseline conditions, all nine BrS patients without type 1 ECG had a difference in ARIc of <0 ms, and 8 of 10 BrS patients with type 1 ECG had a difference in ARIc of more than 0 ms. The difference in ARIc with type 1 ECG was significantly larger than that without type 1 ECG under baseline conditions ($p < 0.0001$). After administration of pilsicainide, type 1 ECG appeared and the difference in ARIc was more than 0 ms in all patients with BrS (Fig. 4A). Epicardial RTc was always longer than endocardial RTc in patients manifesting type 1 ECG regardless of pilsicainide administration. The difference in RTc with type 1 ECG was significantly larger than that without type 1 ECG in BrS patients under baseline conditions ($p < 0.00001$) (Fig. 4B). The difference in AT with type 1 ECG was also significantly larger than that without type 1 ECG in BrS patients under baseline conditions ($p < 0.05$) (Fig. 4C). However, the difference in AT was a less critical as a factor determining type 1 ECG than was the difference in RTc or ARIc. Accordingly, type 1 ECG was closely related to the prolongation of repolarization in the epicardium compared to that in the endocardium.

Mutation of the SCN5A gene was identified in 4 of the 19 patients (Patient #1, R282H; Patient #2, IVS21+1 g>a; Patient #3, R1913C; Patient #9, Y416C) with BrS. The AQ: 2

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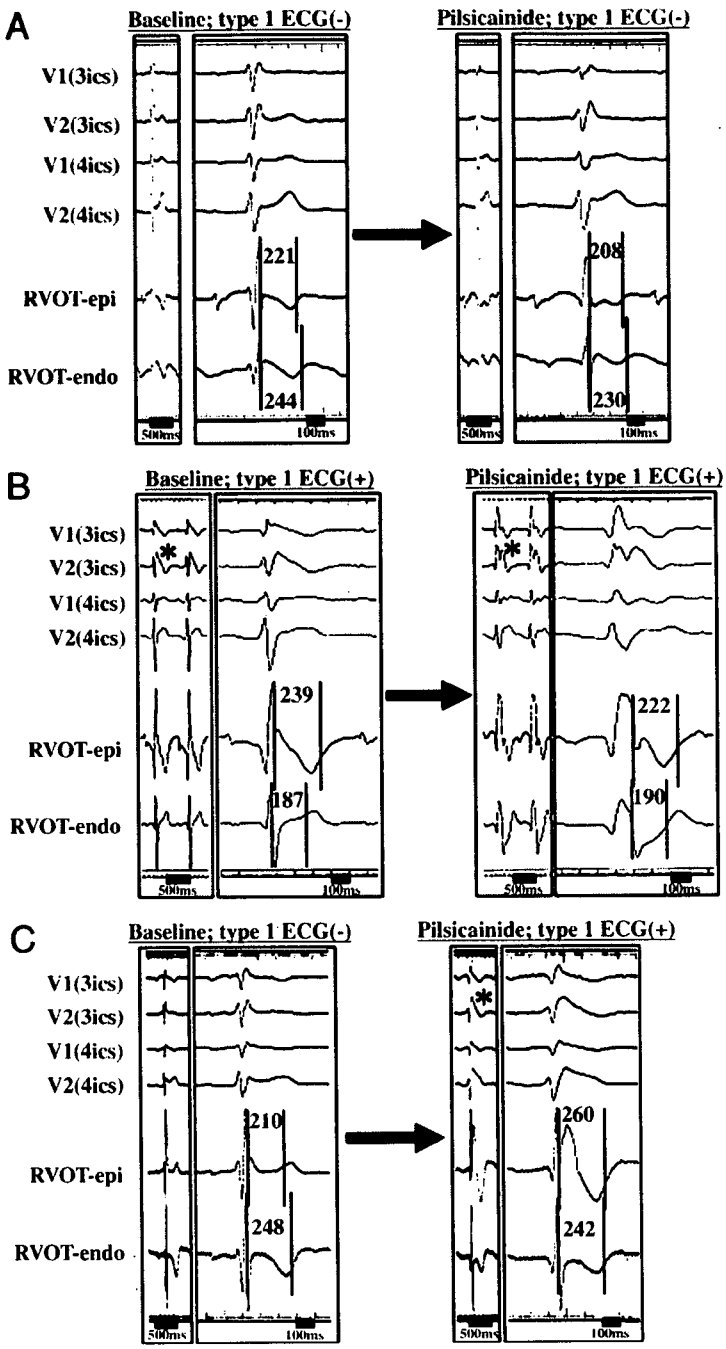

Figure 3 **Patient Examples**

Representative surface ECGs and unipolar electrograms in a control subject **(A)** and in 2 patients with Brugada syndrome **(B, C)** under baseline conditions **(left panel)** and after pilsicainide administration **(right panel)**. **(A)** Brugada-type ECG was not observed in surface ECGs. Under baseline conditions, the epicardial ARI (221 ms) was shorter than the endocardial ARI (244 ms). After the administration of pilsicainide, the epicardial ARI (208 ms) was still shorter than the endocardial ARI (230 ms). **(B)** Under baseline conditions, type 1 ECG was observed in lead V_2(3ics) (*), and the epicardial ARI (239 ms) was longer than the endocardial ARI (187 ms). After the administration of pilsicainide, type 1 ECG was still observed in lead V_2(3ics) (*), and epicardial ARI (222 ms) was longer than endocardial ARI (190 ms). **(C)** Under baseline conditions, type 1 ECG was not observed in any of the surface ECG leads, and the epicardial ARI (210 ms) was shorter than endocardial ARI (248 ms). However, after administration of pilsicainide, the epicardial ARI, but not the endocardial ARI, was markedly prolonged (260 ms), and type 1 ECG appeared in lead V_2(3ics) (*). The epicardial ARI was 18 ms longer than the endocardial ARI (242 ms). Numbers indicate ARI. ARI = activation-recovery interval; ECG = electrocardiogram; RVOT-epi = uniploar electrogram of the epicardium at the right ventricular outflow tract; RVOT-endo = uniploar electrogram of the endocardium at the right ventricular outflow tract; * = type 1 ECG.

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Table 2 Electrophysiologic Data

	RR, s	Epicardial AT, ms	Endocardial AT, ms	Difference in AT, ms	Epicardial ARI/ARIc, ms	Endocardial ARI/ARIc, ms	Difference in ARI/ARIc, ms	Epicardial RT/RTc, ms	Endocardial RT/RTc, ms	Difference in RT/RTc, ms	Presence of Type 1 ECG, 5
Baseline											
Brugada syndrome	0.82 ± 0.14	86 ± 15	77 ± 16	9 ± 5	223 ± 16/248 ± 22	219 ± 17/244 ± 18	4 ± 22/4 ± 25	309 ± 17/344 ± 26	297 ± 23/330 ± 24	13 ± 23/15 ± 26	10 (52.6)
Control subject	0.91 ± 0.07	73 ± 16	67 ± 15	6 ± 2	239 ± 15/251 ± 7	256 ± 13/269 ± 7	−17 ± 5/−18 ± 6	312 ± 14/328 ± 17	322 ± 18/339 ± 23	−10 ± 5/−11 ± 5	0 (0)
After pilsicainide											
Brugada syndrome	0.77 ± 0.11	111 25$	98 ± 25$$	12 ± 5¶¶††††	235 ± 22/269 ± 25*#	214 ± 17/244 ± 19	21 ± 14/25 ± 16¶†	346 ± 21/396 ± 26**##	312 ± 20/357 ± 25	34 ± 16/39 ± 19¶¶††	19 (100)
Control subject	0.81 ± 0.05	91 ± 6	87 ± 6	4 ± 3	227 ± 14/252 ± 9	245 ± 16/273 ± 12	19 ± 7/21 ± 8	318 ± 10/353 ± 6	332 ± 11/369 ± 11	−14 ± 4/−16 ± 5	0 (0)

Plus-minus values are mean ± SD.
Presence of type 1 ECG = type 1 electrocardiogram was recorded in surface electrocardiogram.
Difference in ARI/ARIc = Epicardial ARI/ARIc minus Endocardial ARI/ARIc; Difference in RT/RTc = Epicardial RT/RTc minus Endocardial RT/RTc; Difference in AT = Epicardial AT minus Endocardial AT; ARI = activation-recovery interval; ARIc = corrected ARI by Bazett's formula; RT = repolarization time; RTc = corrected RT by Bazett's formula; AT = activation time;
*p < 0.001 vs. Epicardial ARI/ARIc under baseline conditions in Brugada patients; #p < 0.01 vs. Endocardial ARI/ARIc after pilsicainide administration in Brugada patients; ¶p < 0.001 vs. Difference in ARI/ARIc under baseline conditions in Brugada patients; †p < 0.001 vs. Difference in ARI/ARIc after pilsicainide administration in control subjects. **p < 0.0001 vs. Epicardial RT/RTc under baseline conditions in Brugada patients; ##p < 0.001 vs. Endocardial RT/RTc after pilsicainide administration in Brugada patients. ¶¶p < 0.0001 vs. Difference in RT/RTc under baseline conditions in Brugada patients; ††p < 0.0001 vs. Difference in ARI/ARIc after pilsicainide administration in control subjects. $p < 0.0001 vs. Epicardial AT under baseline conditions in Brugada patients; $$p < 0.0001 vs. Endocardial AT under baseline conditions in Brugada patients. ¶¶p < 0.01 vs. Difference in AT under baseline conditions in Brugada patients; †††p < 0.05 vs. Difference in AT after pilsicainide administration in control subjects.

differences in ARI/ARIc and RT/RTc between epicardium and endocardium were significantly larger in 4 SCN5A mutation carriers than that in 15 noncarriers before pilsicainide administration (Figs. 4A and 4B). However, the differences between the 2 groups disappeared after pilsicainide was administered.

Discussion

Main findings of the study. The results of this study show that type 1 ECG is closely related to the prolongation of repolarization in the epicardium compared with that in the endocardium in BrS. The administration of pilsicainide, a pure sodium channel blocker, exaggerated the prolongation of repolarization in the epicardium, which contributed to the development of type 1 ECG in BrS. In the control subjects, ARI/ARIc and RT/RTc in the epicardium were always shorter than those in the endocardium regardless of pilsicainide administration.

Mechanism of type 1 ECG. Recent experimental studies have suggested that a prominent transient outward current-mediated action potential notch during phase 1 depolarization in the epicardium, but not in the endocardium, gives rise to a transmural voltage gradient, which is responsible for prominent ST-segment elevation in BrS. When epicardial repolarization precedes endocardial repolarization, the T-wave remains positive. However, further accentuation of the notch causes longer action potential duration in the epicardium than in the endocardium due to a delay in the onset of the second upstroke and phase 3, which results in a coved-type ST-segment elevation and inversion of the T-wave (type 1 ECG) (4–6). In the present study, we were able to record epicardial and endocardial unipolar electrograms simultaneously in all patients. And we could demonstrate longer action potential duration in the epicardium than that in the endocardium using ARI and RT, and we found a close correlation between prolongation of repolarization in the epicardium and type 1 ECG.

Prolongation of RT in the epicardium could be also explained by conduction slowing at the RVOT instead of transmural repolarization differences. Delayed activation at the epicardial cell could result in later termination of repolarization than endocardial cell, which could demonstrate terminal inverted T-wave (22,23). Coronel et al. reported that minor transmural gradient in RT causes dynamic T-wave change and that activation delay is also an important factor in determining transmural gradient in RT (24). In the present study, we also showed the mild prolongation of AT in the epicardium in patients with type 1 ECG. However, the difference in AT was a less critical as a factor determining type 1 ECG than was the difference in RT/RTc or ARI/ARIc in our study.

SCN5A mutation. It has been reported that mutation of the SCN5A gene was identified in approximately 10% to 20% of patients with BrS (2,25). In this study, SCN5A mutation was identified in 4 of the 19 patients with BrS.

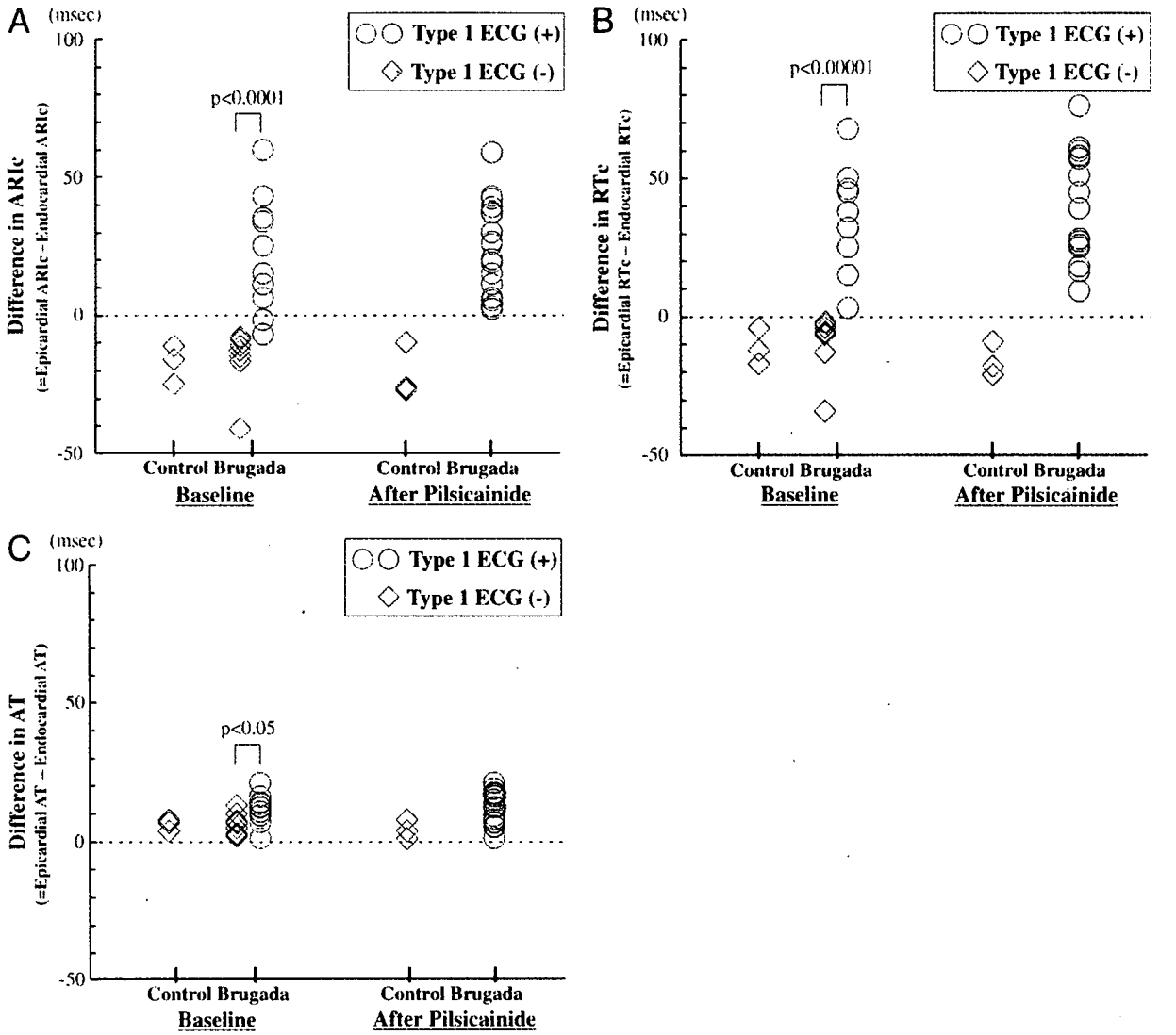

Figure 4 **Relationship Between Appearance of Type 1 ECG and Each Parameter**

Relationship between appearance of type 1 electrocardiogram (ECG) and differences in activation-recovery interval corrected for heart rate (ARIc) **(A)**, repolarization time corrected for heart rate RTc **(B)**, and activation time (AT) **(C)** in control subjects (Control) and in patients with Brugada syndrome (Brugada) under baseline conditions (Baseline) and after the administration of pilsicainide (After Pilsicainide). **(A)** Type 1 ECG was closely related to the prolongation of ARIc in the epicardium compared with that in the endocardium. The difference in ARIc with type 1 ECG was significantly larger than that without type 1 ECG under baseline conditions ($p < 0.0001$). After the administration of pilsicainide, type 1 ECG appeared and the difference in ARIc was more than 0 ms in all patients with Brugada syndrome. **(B)** Epicardial RTc was always longer than endocardial RTc in patients manifesting type 1 ECG regardless of pilsicainide administration. The difference in RTc with type 1 ECG was significantly larger than that without type 1 ECG in Brugada syndrome patients under baseline conditions ($p < 0.00001$). **(C)** The difference in AT with type 1 ECG was significantly larger than that without type 1 ECG in Brugada syndrome patients under baseline conditions ($p < 0.05$). However, the difference in AT was a less critical as a factor determining type 1 ECG than was the difference in RTc or ARIc. **Open black circle** = type 1 ECG was recorded in surface ECG without SCN5A mutation; **open blue circle** = type 1 ECG was recorded in surface ECG with SCN5A mutation; **open diamond** = type 1 ECG was not recorded in surface ECG.

The differences in ARI/ARIc and RT/RTc between the epicardium and endocardium were significantly larger in SCN5A mutation carriers than in noncarriers before the administration of pilsicainide. Because the number of BrS patients was small and their clinical backgrounds and mutation sites were heterogeneous, the mechanism underlying this phenomenon is unclear.

Pilsicainide administration. Pilsicainide administration developed ventricular arrhythmias in 4 patients (Patient #8, VF; Patients #4, #10, and #13, premature ventricular contractions; Patient #11, nonsustained polymorphic ventricular tachycardia) (26). However, no difference was observed in any of the parameters between the patients with and without pilsicainide-induced ventricular arrhythmias.

And the distinctive finding, such as phase 2 re-entry, was not apparent in the initiation of ventricular arrhythmia at the epicardium and endocardium.

Study limitations. We were able to record electrograms only at the site where the conus branch of the right coronary artery runs through. Therefore, we could not perform detailed mapping in the epicardium at the RVOT. We attempted to introduce the guidewire into the conus branch in more than 50 patients with BrS. However, we were able to successfully introduce the guidewire deeply at the RVOT in only about 50% patients due to technical problems and location of the conus branch.

Marked shortening of ARI in the epicardium was not demonstrated under baseline conditions or after pilsicainide administration in this study. However, we could not rule out the possibility of "loss of dome" configuration of action potential in another epicardial site, because detailed mapping in the epicardium at the RVOT was very difficult. The aggregated action potentials in the endocardium, epicardium and midmyocardium could cause an averaging effect that prolongs ARI and RT and mask marked shortening of repolarization.

The number of control subjects examined in this study was relatively small. However, because type 1 ECG was not observed before and after pilsicainide administration in any of the control subjects and since the main purpose of this study was to investigate the relationship between appearance of type 1 ECG and alteration of action potential in patients with BrS, a large number of control subjects was not necessary in this study.

Because recent studies have shown that pilsicainide also blocked the K^+ channel current of the human *ether-a-go-go*-related gene (*HERG*) and could cause QT prolongation, we could not completely exclude the possibility that pilsicainide administration directly prolonged action potential duration in the epicardium (27).

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QT延長症候群

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KEY WORDS

●QT延長
●突然死
●β遮断薬
●植え込み型除細動器(ICD)

はじめに

QT延長症候群(long QT syndrome；LQTS)は，心電図上QT時間の著明な延長をきたし，Torsades de Pointes(TdP)と呼ばれる特徴的な多形性心室頻拍から失神，突然死を生じる。当初はてんかんとして治療がなされていたが，失神の原因が多形性心室頻拍であることが明らかにされて以降，さまざまな臨床的特徴や治療法が報告されている。ここでは，薬剤や電解質異常に伴う後天性のものを除く先天性LQTSの治療について述べる。

Ⅰ．診断

1993年にSchwartzらにより示された心電図所見，臨床症状，家族歴からの臨床的診断基準[1]が用いられているが，近年は70％近くの診断率をあげる遺伝子診断も可能となってきた。現在までに，10種類のRomano-Ward症候群(LQT1-10)と2種類のJervell & Lange-Nielsen症候群(JLN1-2)の原因遺伝子が明らかにされ，各遺伝子型に特異的な心電図波形，心事故の誘因(図1)，臨床経過などが報告されている。これにより，各遺伝子型ごとによる患者管理や治療が可能となってきた。

Ⅱ．リスク評価[2)-4)]

遺伝子型別の致死的心事故発生率はLQT1，LQT2，LQT3それぞれ約1％，4～7％，14～17％であり，遺伝子異常はあるがQT時間が正常なサイレントキャリアーの割合はLQT1，LQT2，LQT3それぞれで36％，19％，10％であり，LQT3が最もハイリスクであった。性別によるリスクへの影響は，LQT1にはみられず，LQT2の女性とLQT3の男性はよりリスクが高くなる。また，再分極相の異常を反映しているQTc時間が500以上の症例もハイリスクである(図2)。

Long QT syndrome.
Shiho Morita
Tohru Ohe(教授)

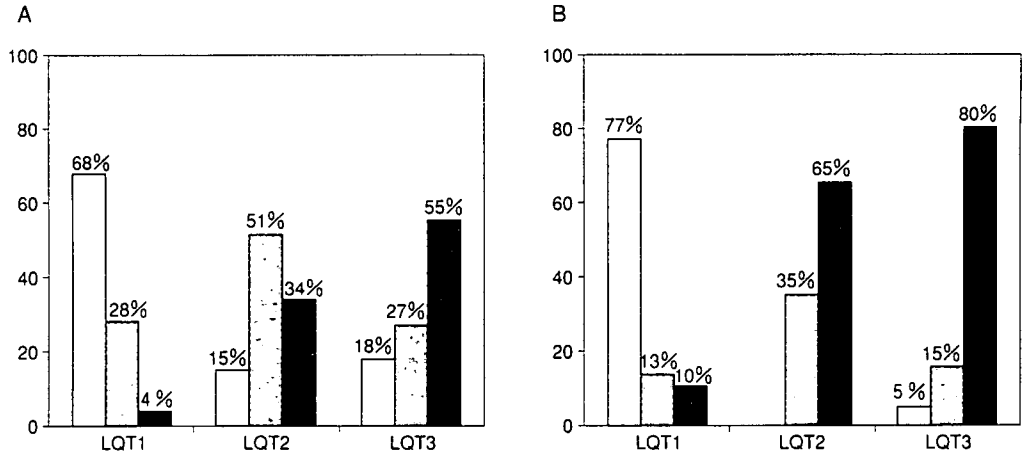

図1．579症例における原因遺伝子型別の発作の誘因
□：運動，▨：情動，■：睡眠，安静
A：全心事故の誘因
B：致死的心事故(心停止，突然死)の誘因
(文献[2]より一部改変引用)

LQTSの治療の基本となるのはβ遮断薬であるが，投薬中に発作が再発する症例やハイリスク例には非薬物療法の併用を必要とする。現在，最も救命率の高いICD(植え込み型除細動器)の適応となるのは以下である。

* 初回発作が心停止蘇生例
* 初回発作が7歳以下
* QTc≧500の症例
* 発作の既往のあるLQT3症例
* β遮断薬投与中に失神を繰り返す症例
* 呼吸器疾患によりβ遮断薬が投与できない発作の既往のある症例
* Jervell & Lange-Nielsen症候群の新生児がICD植え込み可能な大きさに成長した時点(発作の有無は問わない)

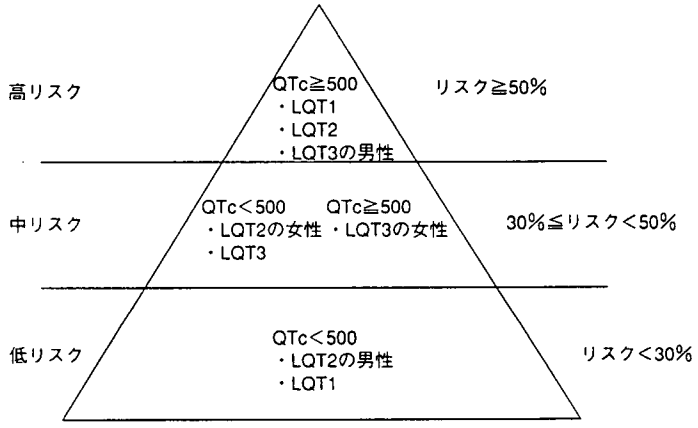

図2．LQTS患者のリスク分類
40歳までに，最初の発作(失神，心停止，突然死)を起こす危険性により分類。
(文献[3]より一部改変引用)

Ⅲ．薬物療法

1．β遮断薬[5]

目覚まし時計などによる急激な覚醒時や労作時の交感神経刺激が引き金となって心室頻拍や心事故が発生することから，1970年代より経験的にβ遮断薬が有用と考えられてきた。種類としては，非選択的β遮断薬であるプロプラノロールやナドロールのほうが，メトプロロールやアテノロールのようなβ_1選択的遮断薬より望ましく，呼吸器疾患などにより非選択的β遮断薬が使用できない場合のみ，β_1選択的遮断薬の適応となる。投与量については，副作用を考慮して血行動態の許容範囲内で最多量の投与が望ましく，目標はプロプラノロールが3 mg/kg/日，ナドロールが1 mg/kg/日である。徐脈が問題となる場合は，ペースメーカー

を併用しての増量を検討する。

β遮断薬の心事故予防効果はLQT1が最も高い。Schwartzらの報告では，β遮断薬を投与された心事故既往患者のうちLQT1(n＝162)，LQT2(n＝91)，LQT3(n＝18)の発作再発率はそれぞれ19%，41%，50%であった。このことは，LQT1の病因がKCNQ1遺伝子の異常に伴うIKsチャネルの機能異常であることにより説明される。心室再分極相をコントロールするK⁺電流の1つであるIKsは交感神経刺激により増大するが，LQT1は異常IKsチャネルを有するために，運動などに伴い持続的な心拍数増加をきたすような交感神経亢進に対してもIKsを増大することができない。結果として著明なQTc延長をきたし，交互性T波をきたすほどに心室再分極相の不均一性を増大させ，TdPが発生する。一方，LQT3へのβ遮断薬投与については意見が分かれている。LQT3は徐脈が増悪因子の1つであるため，徐脈となるβ遮断薬は避けるべきという意見もあるが，ペースメーカー併用で脈拍数を確保したうえでトリガーに対してβ遮断薬を，不整脈器質に対して次項で述べるNaチャネルブロッカーを投与するというのが，LQT3への第1段階の治療と思われる。

また，β遮断薬中断時にカテコラミンのリバウンドにより致死的不整脈を生じやすいため，良好なコンプライアンスを保つことは重要で，心事故発生率の高い小児期においては，成長とともに適切に投与量を増量していく必要がある。QT時間を延長させるような薬物の併用は禁忌である。

2．Naチャネルブロッカー[6][7]

LQT3はSCN5A遺伝子異常によりI_{Na}チャネルの不活性化が障害され，内向きNa^+電流後半成分がいつまでも流れることにより心室再分極相が延長する。このNa^+電流後半成分をブロックするメキシレチンやフレカイニドなどは，延長しているQTcの短縮やT波形の正常化に著効する。ただ，LQT3とBrugada syndromeの合併家系では，フレカイニドは延長しているQTcは短縮するが，STを上昇させて催不整脈作用を示すので，注意を要する。

Ⅳ．非薬物療法

1．ペースメーカー

LQTSのTdPは，心内膜下層に存在するM cellなどから生じる早期後脱分極(EAD)の興奮が，不均一な心室再分極相に伝播するために発生する。この心室再分極相の不均一性は長いRR間隔の次の1心拍でより増大するため，洞性徐脈や洞停止，期外収縮後のロングポーズ，房室ブロックなどによりTdPが発生しやすくなる。β遮断薬は発作のトリガーとなる交感神経刺激を抑える一方でこれら徐脈を増悪させるため，ペースメーカーの併用は有用である。6.3±4.6年間経過観察された報告[8]では，β遮断薬との併用下に平均82±7/分でペーシングしたハイリスク症例のうち76%に発作の再発がみられなかった。

現在，ペースメーカーは，徐脈が危険因子である患者や，ハイリスク新生児のICD植え込みへのつなぎとして，β遮断薬との併用療法として主に用いられている。また，ICD植え込み患者においては，ICD作動後の徐脈を比較的速いレートでペーシングすることにより，発作のストームを回避することが望め，非発作時の徐脈もカバーできるペーシング機能によりICDの作動回数軽減が期待できる。

2．左星状神経節切除[9]

星状神経節の心室再分極相への作用は左右により異なり，催不整脈作用を呈するのは左側優位時である。この左星状神経節を切除することにより心室細動を抑える効果が得られたため，1970年に，最初のLQTSに対する左星状神経節切除症例が報告された。徐脈をきたさず，急激なカテコラミン分泌を抑えるという利点があり，β遮断薬が投与できない症例や増量できない症例に適している。

2004年には，QTc＝543±65と著明なQT延長を認めるハイリスク147症例の術後8.6±6.1年の経過が報告された。術後の心事故発生率は80%以上減少したが，16%に心停止蘇生例，7%に突然死例が認められている。術後半年の時点でQTc≧500の症例は依然ハイリスクであるため，ICDの適応となる。

現在の左星状神経節切除の適応は，ICD植え込みがサイズ的な問題で困難なハイリスク乳幼児症例や，重症呼吸器疾患のためにβ遮断薬が投与できない症例と考えられる。ICD植え込み症例のうち，β遮断薬併用にも関わらず致死的心室性不整脈に対してICDが頻回作動するようなハイリスク症例に対しても，ICDの作動回数軽減のために有用である。

3．カテーテルアブレーション

近年，ICD作動回数を軽減するために，カテーテルアブレーションが試みられている。Haissaguerreらは，4人のLQTSに対して多形性心室頻拍のト

リガーとなる期外収縮のアブレーション治療を施行した。17±7ヵ月の経過観察では，1人に期外収縮を認めたものの，致死的不整脈や失神や突然死は認められなかった[10]。

4．植え込み型除細動器(ICD)

現時点で，ハイリスクLQTS患者の生命予後を改善するディバイスはICDのみである。125名のICDを植え込んだハイリスクLQTS患者に対する平均3年の予後調査で，突然死の発生は1名(1%)であったが，同様の条件を満たすICD非植え込み患者161名の平均8年の突然死発生は26名(16%)と高率であった[11]。問題点としては，①T波をオーバーセンシングすることがある，②乳幼児症例ではサイズ的な問題で植え込めない，③ICD植え込みに伴う患者の精神的ストレスが時として問題となる，④植え込み手術の合併症(創部感染，静脈血栓など)がある。

また，不整脈発作がストーム状態となり，ICDが頻回作動するような場合はβ遮断薬の静注，ICDのペーシングレートの増加，場合により鎮静など，集中治療を必要とする。

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Effects of Aldosterone and Angiotensin II Receptor Blockade on Cardiac Angiotensinogen and Angiotensin-Converting Enzyme 2 Expression in Dahl Salt-Sensitive Hypertensive Rats

Yoshiyu Takeda, Aoshuang Zhu, Takashi Yoneda, Mikiya Usukura, Hiroyuki Takata, and Masakazu Yamagishi

Background: We previously reported that a high-sodium diet activates the local renin-angiotensin-aldosterone system (RAAS) in cardiovascular tissues of Dahl salt-sensitive hypertensive (DS) rats. Angiotensin-converting enzyme 2 (ACE2) is a novel regulator of blood pressure (BP) and cardiac function. The effect of blockade of aldosterone or angiotensin II (Ang II) on cardiac angiotensinogen and ACE2 in DS rats is unknown.

Methods: The BP, plasma renin activity (PRA), plasma aldosterone concentration (PAC), heart weight, endothelium-dependent relaxation (EDR), and messenger RNA (mRNA) levels of collagen III, angiotensinogen, ACE, and ACE2 in the heart were measured in DS rats and in Dahl salt-resistant (DR) rats fed high or low salt diets. The rats were treated orally with or without eplerenone (100 mg/kg/d), candesartan (10 mg/kg/d), or both dugs combined for 8 weeks.

Results: A high salt diet increased BP (140%), heart/body weight (132%), and collagen III mRNA levels (146%) and decreased PRA and PAC concomitant with increased expression of cardiac angiotensinogen mRNA and decreased mRNA levels of ACE2 in DS rats. Eplerenone or candesartan significantly decreased the systolic BP from 240 ± 5 mm Hg to 164 ± 4 mm Hg or to 172 ± 10 mm Hg, respectively ($P < .05$). Eplerenone or candesartan partially improved heart/body weight and cardiac fibrosis, improved EDR and decreased cardiac ACE and angiotensinogen mRNA levels in DS rats. Candesartan increased ACE2 mRNA levels in the heart. Combination therapy normalized BP and further improved cardiac hypertrophy, fibrosis, and EDR.

Conclusions: In DS rats, blockade of aldosterone or Ang II protects cardiac hypertrophy and fibrosis by inactivation of the local RAAS in the heart. Am J Hypertens 2007;20:1119–1124 © 2007 American Journal of Hypertension, Ltd.

Key Words: Aldosterone antagonist, hypertension, hypertrophy, angiotensin antagonist, sodium.

Aldosterone plays an important role in the pathogenesis of cardiovascular disease that is independent of angiotensin II (Ang II). For example, patients with primary aldosteronism, in which the Ang II levels are usually very low, have a higher incidence of left ventricular hypertrophy and stroke than do patients with essential hypertension.[1] It has been shown that in addition to standard therapy, treatment with eplerenone, a selective mineralocorticoid receptor (MR) antagonist, improves cardiovascular function and survival rates.[2] Experimental animal data also support a role for aldosterone in mediating cardiovascular injury.[3]

Excess sodium intake is intimately involved in the pathogenesis of hypertension. In large populations, significant correlations between the level of salt intake, blood pressure (BP), and the frequency of hypertension have been reported. Several studies have shown that high salt intake reduces not only circulating renin-angiotensin system (RAS) but also tissue RAS in normal rat. However, augmented local RAS by a high sodium diet is seen in

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