a sodium-channel blocker in conjunction with documented VF or polymorphic ventricular tachycardia (VT).

Drug challenge test

The drug challenge test was performed with intravenous pilsicainide (1 mg/kg, maximum 50 mg, 5 mg/min) or flecainide (2 mg/kg, maximum 100 mg, 10 mg/min). The test result was considered positive if a type 1 Brugada ECG appeared in >1 right precordial lead (V1–V3). Once again, we excluded all patients with IVF but without sodium-channel blocker challenge test from our study to clarify the diagnosis of ERS.

Late potentials

Late potentials (LPs) were analyzed by using a signal-averaged electrocardiogram (SAECG) system (Arrhythmia Research Technology 1200EPX, Milwaukee, WI). Three parameters were assessed by using a computer algorithm: (1) total filtered QRS duration (f-QRS), (2) duration of low-amplitude signals <40 μV of the filtered QRS complex (LAS_{40}), and (3) root-mean-square voltage of the terminal 40 millisecond of the filtered QRS complexes (RMS_{40}). LPs were considered positive when at least 2 of the 3 parameters were abnormal: f-QRS >120 millisecond, LAS_{40} >38 millisecond, and RMS_{40} <18 μV.

Statistical analysis

Continuous variables were expressed as mean value ± SD. A comparison between the 2 groups was performed with Student's t test for paired data. Categorical variables were compared with Fisher's exact test. A P value of <.05 was regarded as being significant.

Results

Clinical and electrocardiographic characteristics

In the BS group, 9 of the 21 patients (43%) with BS showed ER in the inferior and/or lateral leads. A comparison of the clinical and electrocardiographic characteristics of the 14 ERS group patients, 21 BS group patients, and 9 BS patients with ER is shown in Table 1. The average age of 9 BS patients with ER was lower than that of the ERS group. Except for that, no significant differences were observed in baseline clinical characteristics with respect to age, gender, family history of SCD, and activity at the time of cardiac arrest. The number of premature ventricular complexes during 24-hour Holter ECG was not different between the 2 groups.

Regarding SAECG parameters, the values of f-QRSd, LAS_{40}, and RMS_{40} in 14 ERS group patients were 97.8 ± 8.1 millisecond, 29.8 ± 5.2 μV, and 50.0 ± 24.2 millisecond, respectively. The corresponding values in 21 BS group patients were 119.8 ± 17.3 millisecond, 47.0 ± 19.2 μV, and 17.8 ± 13.4 millisecond, respectively. All these parameters were significantly different between the 2 groups. LPs were positive in 1 of the 14 patients (7%) in the ERS group and in 12 of the 20 patients (60%) in the BS group. The rate of positive LPs was significantly higher in the BS group than in the ERS group (P <.01). We also compared the SAECG parameters and the rate of positive LPs between 14 ERS group patients and 9 BS patients with ER. The tendency was similar to the comparison between 14 ERS group patients and 21 BS group patients; however, there were no significant differences in the LAS_{40} and rate of LPs because of the small number of BS patients with ER.

Table 1 Clinical and electrocardiographic characteristics in the early repolarization syndrome group, the Brugada syndrome group, and the Brugada syndrome with ER group

	Group			P value	
	ERS (n = 14)	BS (n = 21)	BS with ER (n = 9)	ERS vs BS	ERS vs BS with ER
Clinical characteristics					
Age (y), mean ± SD	44.7 ± 13.6	39.7 ± 12.6	33.3 ± 10.3	NS	.045
Male gender, n/N	14/14	19/21	7/9	NS	NS
Family history of sudden cardiac death, n/N (%)	0/14 (0%)	1/21 (5%)	1/9 (11%)	NS	NS
Activity at the time of cardiac arrest, n (%)					
Sleep	3 (21%)	9 (42%)	5 (55%)	NS	NS
Rest	8 (57%)	10 (48%)	3 (33%)	NS	NS
Others	3 (21%)	2 (10%)	1 (11%)	NS	NS
Electrocardiographic characteristics					
Presence of ER, n/N (%)	14/14 (100%)	9/21 (43%)	9/9 (100%)	<.01	NS
Holter ECG, PVC in 24 h, mean ± SD	49.4 ± 169.3	1.9 ± 4.2	2.3 ± 4.4	NS	NS
Signal-averaged electrocardiography, mean ± SD					
f-QRSd (ms)	97.8 ± 8.1	119.8 ± 17.3	111.6 ± 11.5	<.0001	<.01
LAS_{40} (μV)	29.8 ± 5.2	47.0 ± 19.2	33.8 ± 14.5	<.01	NS
RMS_{40} (ms)	50.0 ± 24.2	17.8 ± 13.4	23.4 ± 14.2	<.0001	<.01
Abnormal SAECG, n/N (%)	1/14 (7%)	12/20 (60%)	4/9 (44%)	<.01	NS

Percentages may not total 100 because of rounding.

BS, Brugada syndrome; ECG, electrocardiogram; ER, early repolarization; ERS, early repolarization syndrome; f-QRSd, filtered QRS duration; LAS_{40}, duration of low-amplitude signals <40 μV of QRS in the terminal filtered QRS complex; NS, not significant; PVC, premature ventricular contraction; RMS_{40}, root-mean-square voltage of the terminal 40 millisecond of the filtered QRS complex; SAECG, signal-averaged ECG.

Table 2 Baseline electrocardiographic parameters and their changes after administration of a sodium-channel blocker in the early repolarization syndrome group, the Brugada syndrome group, and the Brugada syndrome with ER group

	Mean ± SD			*P* value	
	ERS (n = 14)	BS (n = 12)	BS with ER (n = 5)	ERS vs BS	ERS vs BS with ER
RR II (ms)	951 ± 116	930 ± 116	1024 ± 46	NS	NS
ΔRR II (ms)	−71 ± 41	−12 ± 17	−32 ± 62	<.05	NS
P II (ms)	104 ± 19	110 ± 16	112 ± 13	NS	NS
ΔP II (ms)	10 ± 9	21 ± 13	24 ± 16	<.05	<.05
PQ II (ms)	179 ± 34	191 ± 33	178 ± 28	NS	NS
ΔPQ II (ms)	30 ± 9	28 ± 14	38 ± 8	NS	NS
QRS II (ms)	90 ± 13	97 ± 18	90 ± 20	NS	NS
ΔQRS II (ms)	10 ± 10	23 ± 21	14 ± 21	NS	NS
QRS V5 (ms)	84 ± 8	91 ± 19	82 ± 21	NS	NS
ΔQRS V5 (ms)	13 ± 8	29 ± 18	28 ± 8	<.05	<.01
QT II (ms)	377 ± 19	370 ± 14	374 ± 15	NS	NS
ΔQT II (ms)	10 ± 14	28 ± 18	16 ± 5	NS	NS
QTcII (ms)	388 ± 20	385 ± 24	370 ± 13	NS	NS
ΔQTcII (ms)	10 ± 14	29 ± 18	16 ± 5	<.05	NS
QT V5 (ms)	376 ± 26	372 ± 17	376 ± 15	NS	NS
ΔQT V5 (ms)	6 ± 18	38 ± 23	14 ± 11	<.01	NS
QTcV5 (ms)	387 ± 23	387 ± 24	372 ± 12	NS	NS
ΔQTcV5 (ms)	7 ± 19	40 ± 25	14 ± 11	<.01	NS

BS = Brugada syndrome; ER = early repolarization; ERS = early repolarization syndrome; P = P-wave duration; PQ = PQ interval; QRS = QRS duration; QT = QT interval; QTc = corrected QT interval; RR = RR interval.

Sodium-channel blocker infusion test

The sodium-channel blocker infusion test was performed in 12 of the 21 patients with BS, and the test result was positive in all 12 patients. We compared the pharmacological responses of several ECG parameters to a sodium-channel blocker between 14 patients with ERS and 12 patients with BS (Table 2). There were no significant differences in the baseline ECG parameters, including RR interval, P-wave duration, PQ interval, QRS duration, and QT interval in any leads. Shortening of RR (ΔRR II) was significantly larger in the ERS group. Prolongation of P-wave duration (ΔP II), QRS duration (ΔQRS V5), and QTc interval (ΔQTc II, ΔQTc V5) was significantly larger in the BS group compared with that in the ERS group.

Among 9 BS patients with ER, the sodium-channel blocker test was performed in 5 patients. We also compared the ECG parameters between 14 ERS group patients and 5 BS patients with ER (Table 2). Prolongation of P-wave duration (ΔP II) and QRS duration (ΔQRS V5) was significantly larger in the BS with ER group compared with that in the ERS group.

The ER amplitude and its responses to sodium-channel blockers between 14 ERS group patients and 5 BS patients with ER are shown in Table 3. In the ERS group, ER was observed in the inferior leads (II, III, and aVF) in 9 patients, in the lateral leads (I, aVL, and V4–V6) in 8 patients, and in both the inferior and lateral leads in 3 patients. In the 9 BS patients with ER, ER was observed in the inferior leads in 6 patients, in the lateral leads in 8 patients, and in both the inferior and lateral leads in 5 patients. The baseline maximum ER amplitude among the inferolateral leads (pre-ER max) in the BS group tended to be higher than in the ERS group (0.244 ± 0.082 vs 0.162 ± 0.069 mV; $P = .057$). The baseline ER amplitude in the inferior lead (pre-ER II) was significantly higher in the BS group than in the ERS group (0.236 ± 0.081 vs 0.120 ± 0.033 mV; $P < .05$). After administration of a sodium-channel blocker, the ER ampli-

Table 3 Amplitude of ER in leads II and V5 before and after the administration of a sodium-channel blocker test in the early repolarization syndrome group and the Brugada syndrome with ER group

Maximum amplitude of ER in any inferolateral leads (mV)	Mean ± SD		
	ERS (n = 14)	BS with ER (n = 5)	*P* value
Pre-ER max	0.162 ± 0.069	0.244 ± 0.082	NS
Post-ER max	0.081 ± 0.061*	0.124 ± 0.096*	NS
ΔER	0.080 ± 0.067	0.120 ± 0.058	NS
Amplitude of ER in the inferior lead (II) (mV)	**ERS (n = 9)**	**BS (n = 5)**	
Pre-ER II	0.120 ± 0.033	0.236 ± 0.081	<.05
Post-ER II	0.091 ± 0.054*	0.104 ± 0.086*	NS
ΔER II	0.028 ± 0.051	0.132 ± 0.068	<.05
Amplitude of ER in the lateral lead (V5) (mV)	**ERS (n = 8)**	**BS (n = 5)**	
Pre-ER V5	0.116 ± 0.032	0.215 ± 0.092	NS
Post-ER V5	0.010 ± 0.022*	0.137 ± 0.094*	NS
ΔER V5	0.106 ± 0.026	0.077 ± 0.071	NS

BS = Brugada syndrome; ER = early repolarization; ERS = early repolarization syndrome; max = maximum; pre = before sodium-channel blocker test; post = after sodium-channel blocker infusion; Δ = change.
*$P < .05$ vs pre.

tude was attenuated in all 5 patients with BS (100%) and in 13 of 14 patients with ERS (93%). ER attenuation was occasionally associated with the appearance of an S wave in both the groups (Figure 2). Therefore, the maximum ER amplitude (ER max), ER amplitude in the inferior lead (ER II), and ER amplitude in the lateral lead (ER V5) all were significantly decreased after the administration of sodium-channel blockers ($P < .05$). Figure 3 illustrates the differential response to sodium-channel blockers between the ER in the inferolateral leads and the J point and ST segment in the right precordial leads in a patient with BS. The coved-type (type 1) ECG was unmasked and the J point in the right precordial leads (V1–V3) was augmented by the sodium-channel blocker, whereas the ER amplitude in the inferolateral leads (II, III, aVF, and V4–V6) was attenuated (Figure 3B).

Discussion

The ER pattern in the inferior and/or lateral leads had been considered benign, and it is often found in healthy young individuals. Recently, several reports have attracted increasing attention to the association of IVF with ER in the inferior and/or lateral leads.[5,10,19–21] Haissaguerre et al[10] reported that ER was more frequently recognized in patients with IVF than in control subjects and that there was a higher incidence of recurrent VF in case subjects with ER than in those without. Rosso et al[15] also reported that ER was found more frequently among patients with IVF than among healthy control subjects. On the other hand, BS is also characterized by a high incidence of VF without structural heart disease. The Brugada Consensus Report proposed that type 1 coved-type ST-segment elevation in the right precordial lead (V1–V3) in the absence or presence of a sodium-channel blocker was required to diagnose BS.[22] Considering this diagnostic criterion, the sodium-channel blocker challenging test is essential to exclude BS. In order to investigate pure ERS, the sodium-channel blocker challenging test should be performed before the diagnosis of ERS. Unlike previous studies,[10,15] we conducted the sodium-channel blocker challenging test in all 14 patients with ERS to exclude BS in the present study.

Intravenous administration of sodium-channel blockers has been used to unmask the Brugada ECG pattern in patients with BS.[23] On the other hand, in most patients associated with ER in both the ERS group and the BS group of the present study, the administration of a sodium-channel blocker induced the attenuation or disappearance of the ER and appearance of an S wave. Attenuation of the ER in the inferolateral leads appears to be due largely to a slowing of the transmural conduction so that inscription of the ER occurs later on the descending limb of the QRS in both the ERS group and the BS group. The S-wave appearance in the inferolateral leads is also probably due to the conduction delay induced by sodium-channel blockers. This may indicate the differential mechanism between Brugada-type ST elevation in the right precordial lead of BS and ER in the inferolateral leads in both groups.

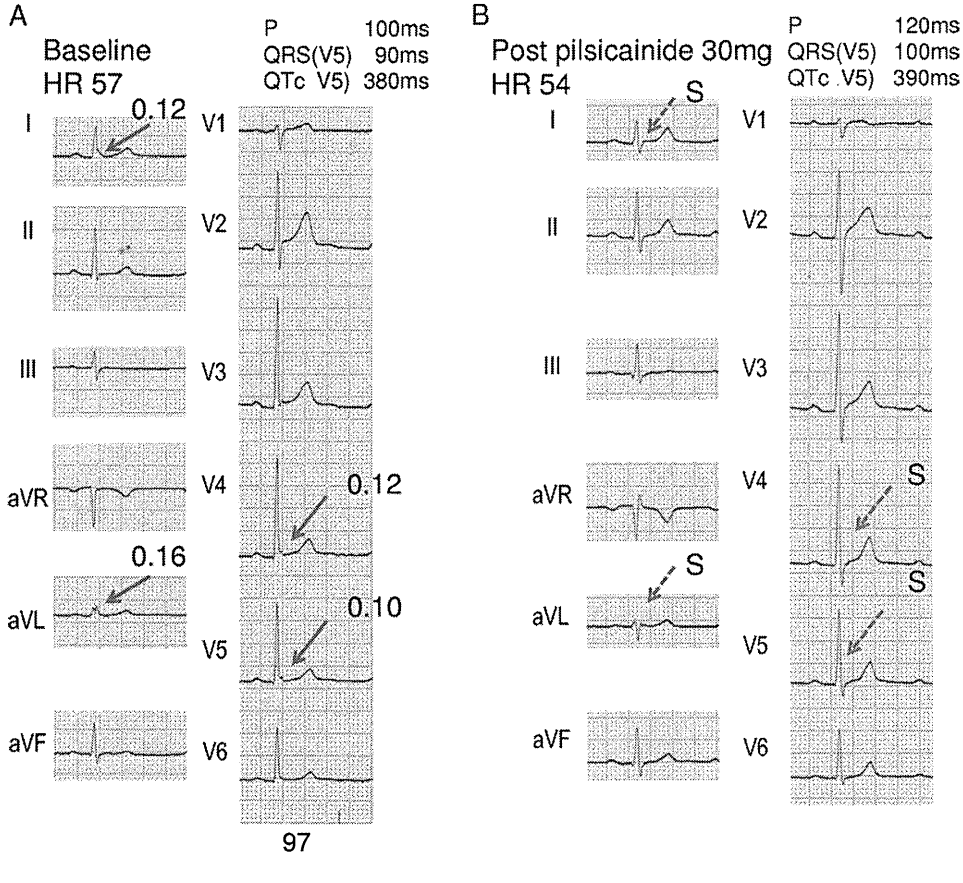

Figure 2 Twelve-lead ECGs in a patient with early repolarization syndrome under baseline conditions (**A**) and after pilsicainide administration (**B**). ER was seen in the lateral leads (I, aVL, and V4–V5) under baseline conditions (**A**, arrows). Intravenous administration of 30 mg of pilsicainide induced attenuation of ER and appearance of an S wave in the lateral leads (dashed arrows). Numbers above the arrows indicate the amplitude of ER. ECG, electrocardiogram; ER, early repolarization; S, S wave.

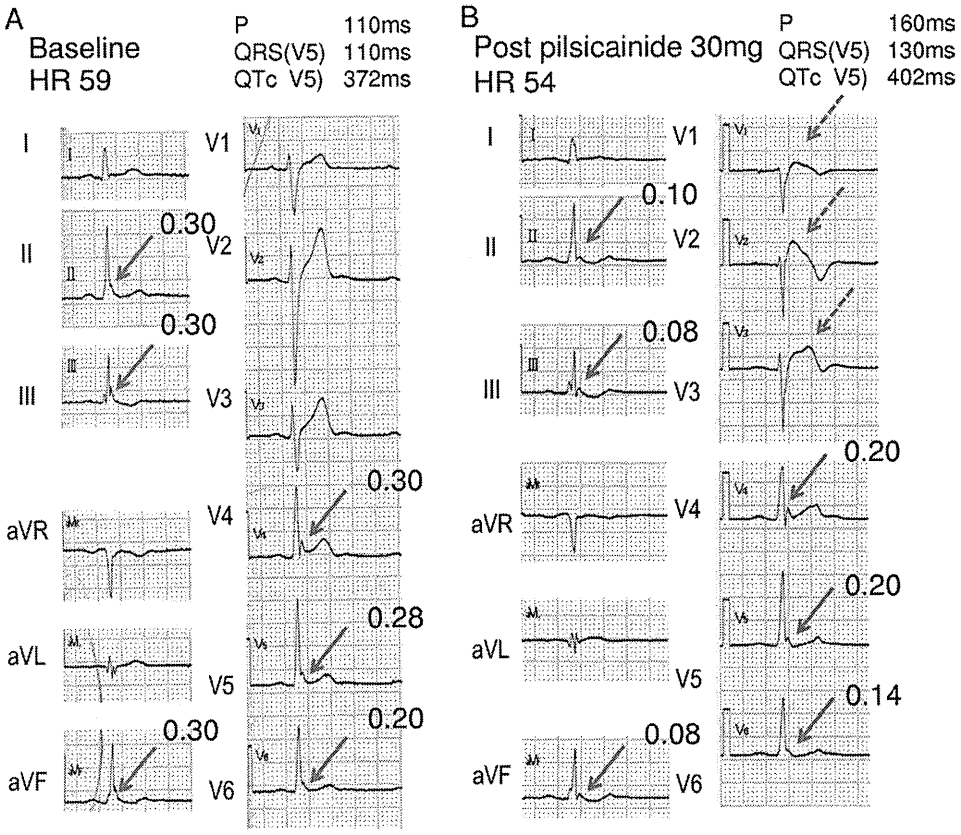

Figure 3 Twelve-lead ECGs in a patient with Brugada syndrome under baseline conditions (**A**) and after pilsicainide administration (**B**). ER was seen in the inferior (II, III, and aVF) and lateral (V4–V6) leads under baseline conditions (**A**, arrows). Intravenous administration of 30 mg of pilsicainide unmasked coved-type Brugada ECG and remarkably augmented the J point and ST segment in the right precordial leads (V1–V3) (**B**, dashed arrows), while ER was attenuated in the inferior and lateral leads (**B**, arrows). Numbers above the arrows indicate the amplitude of ER. ECG, electrocardiogram; ER, early repolarization.

Antzelevitch and Gan-Xin[24] have proposed a new concept that an outward shift in repolarizing current due to a decrease in sodium- or calcium-channel currents or an increase in outward currents such as a transient outward potassium current (I_{to}) can give rise to J-wave syndromes, which includes BS, ERS, hypothermia, and acute ischemia–induced VF. A prominent and pathological J wave, a slow upright deflection between the end of the QRS complex and the early portion of the ST segment, has been reported to be seen often in hypothermia.[25] However, the terms J-wave syndromes and ERS have not been properly defined.[26]

In some patients with BS of this study, type 1 Brugada ECG was unmasked by a sodium- channel blocker in the right precordial lead, while ER was attenuated in the inferolateral leads (Figure 3). Once again, this finding suggested the differential mechanism between Brugada-type ECG in the right precordial lead and ER in the inferolateral leads.

Moreover, as with a previous report,[27] the BS group showed significantly larger prolongation of P-wave duration, QRS duration, and QTc interval compared with the ERS group after a sodium-channel blocker infusion. Basic electrophysiology including animal or mathematical models must play an important role in determining whether the cellular mechanism of ST-segment elevation in the right precordial leads in BS and that of ER in the inferolateral leads in both ERS and BS differ or not.

Our study showed clinical characteristics of ERS to be similar to those of BS, including adult onset, male preponderance, cardiac events occurred at rest or during sleep, and rare ventricular arrhythmias on Holter ECG.[28,29] On the other hand, some apparent differences were found between the 2 groups, including LPs on the SAECG. All 3 parameters of the SAECG were significantly different between the 2 groups, and the positive rate of LPs was significantly lower in the ERS group than in the BS group. The rate of LPs has been previously reported to be high in BS.[30] On the other hand, Haissaguerre et al[10] also reported a relatively low rate (11%) of LPs in patients with ERS. LPs are reported to be not only highly prevalent in BS but also independent predictors of VT/VF inducibility.[27,31–33] LPs are also considered to be linked to VF inducibility during electrophysiological study and ventricular conduction delay during VF induction in patients with BS[28,34] as well as in patients with VT/VF associated with organic heart diseases. The ST-segment elevation in the right precordial leads and arrhythmogenicity in BS can be explained by both repolarization and depolarization abnormalities in right ventricular outflow.[9,35] The presence of LPs can be caused by conduction delay (depolarization abnormality) in the ventricle including the right ventricular outflow tract. On the other hand, from the experimental studies, LPs are explained on the basis of repolarization abnormality (late phase 2 upstroke and concealed phase 2 reentry) in the right ventricular outflow tract.[36] In the present study, the lower prevalence of LPs in the ERS group may indicate a differential substrate for VF in patients with ERS compared with that in patients with BS.

Conclusions

ER can be seen in some patients with IVF and in a subgroup of subjects with BS. Clinical similarities among them exist, including age, gender, and arrhythmia triggers. Response to sodium-channel blockade on ER in the inferolateral leads is the same in both groups: a consistent diminution in ER amplitude. This effect contrasts with the ST-segment elevation that is always observed in the right precordial leads in BS, thus arguing for different pathophysiological mechanisms.

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ORIGINAL ARTICLE
Pediatric Cardiology and Adult Congenital Heart Disease

Evaluation of Transplacental Treatment for Fetal Congenital Bradyarrhythmia

– Nationwide Survey in Japan –

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Background: There are few large studies of fetal congenital bradyarrhythmia. The aim of the present study was to investigate the effects and risks of transplacental treatment for this condition.

Methods and Results: Using questionnaires, 128 cases of fetal bradyarrhythmia were identified at 52 Japanese institutions from 2002 to 2008. Of the 128 fetuses, 90 had structurally normal hearts. Among these 90 fetuses, 61 had complete atrioventricular block (CAVB), 16 had second-degree AVB, 8 had sinus bradycardia, and 5 had other conditions. The 61 CAVB fetuses were divided into those who did (n=38) and those who did not (n=23) receive transplacental medication. Monotherapy with β-sympathomimetics, steroid monotherapy, and combination therapy with these agents was given in 11, 5 and 22 cases, respectively. Beta-sympathomimetics improved bradycardia (P<0.001), but no medication could significantly improve the survival rate. Fetal hydrops was associated with a 14-fold increased risk of perinatal death (P=0.001), and myocardial dysfunction was a significant risk factor for poor prognosis (P=0.034). Many adverse effects were observed with steroid treatment, with fetal growth restriction increasing significantly after >10 weeks on steroids (P=0.043).

Conclusions: Treatment with β-sympathomimetics improved bradycardia, but survival rate did not differ significantly in fetuses with and without transplacental medication. It is recommended that steroid use should be limited to <10 weeks to avoid maternal and fetal adverse effects, especially fetal growth restriction and oligohydramnios.
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Key Words: Anti-Ro/SSA antibody; Congenital atrioventricular block; Pregnancy; Steroids; Transplacental treatment

Fetal congenital bradyarrhythmia is an uncommon but life-threatening disease, especially in the case of complete atrioventricular block (CAVB), which has a poor prognosis because of fetal hydrops, endocardial fibroelastosis and late-onset dilated cardiomyopathy.[1–9] Predominantly untreated CAVB has a significant mortality rate of 14–34%, while congenital CAVB is irreversible and requires a pacemaker in approximately 66% of cases after birth.[10] The association of CAVB with maternal anti-Ro/Sjögren's syndrome A (SSA) antibodies is well established, but the trigger for the maternal antibody interaction with the fetal Ro particle is unknown in some cases of antibody-exposed babies.[2,7–9,11,12]

There is limited evidence for the clinical efficacy of transplacental treatment of congenital AVB.[13–19] Steroids and i.v. immunoglobulins are given as anti-inflammatory treatment, while β-sympathomimetics are used for fetal pacing.[20] A recent

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Table 1. Baseline Characteristics of CAVB Fetuses

	Medication group (n=38)	No medication group (n=23)	P value
Maternal anti-SSA antibodies	29 (76.3)	11 (47.8)	<0.05‡
Gestational age at diagnosis (weeks)	24±3.2	28±5.7	<0.005†
Fetal heart rate at diagnosis (beats/min)	58±7.9	63±14.7	NS†
Fetal hydrops	16 (42.1)	6 (26.1)	NS‡
Fetal myocardial dysfunction	13 (34.2)	7 (30.4)	NS‡
Gestational age at initiation of therapy (weeks)	26±3.6	–	
Fetal heart rate at initiation of therapy (beats/min)	56±8.4	–	
Gestational age at delivery (weeks)	34±4.0	35±4.5	NS†
Birth weight (g)	2,120±620	2,528±653	<0.001†
Delivery mode			
Vaginal	8	7	NS‡
Cesarean section	30	16	NS‡
Permanent pacemaker implantation	14 (46.7)	6 (35.3)	NS‡
Neonatal survival	30 (78.9)	17 (73.9)	NS‡

Data given as mean±SD or n (%). P<0.05, significant difference.
†Student's t-test; ‡chi-square test and Fisher's exact test.
CAVB, complete atrioventricular block; SSA, Sjögren's syndrome A.

cohort study found an improved survival rate of >90% with initiation of maternal high-dose dexamethasone at the time of CAVB detection, and maintenance of this drug during pregnancy with use of β-sympathomimetics to keep fetal heart rates at >55 beats/min.[9,21] It was also suggested that prolonged use of dexamethasone might render fetuses with congenital CAVB less likely to develop the additional manifestations of myocarditis, cardiomyopathy, and hydrops fetalis, thus improving the overall outcome. Use of steroids, however, is controversial because of the potential risks for the fetus, including problems with neurological development, growth retardation, and oligohydramnios.[22–25]

Few large studies of fetal congenital bradyarrhythmia have been performed in Japan. The aims of the present study were to determine the features of fetal congenital bradyarrhythmia in Japan, and to examine the effects and risks of transplacental treatment for this condition.

Methods

Subjects

Data were collected using questionnaires sent to Departments of Perinatology and Pediatric Cardiology at 750 institutions in Japan over 7 years (2002–2008). The response rate was 60.7% (455 institutions). Fetal bradyarrhythmia was defined as ventricular heart rate <100 beats/min at the time of diagnosis.[4] The following perinatal data were also collected: gestational age at diagnosis and delivery, presence or absence of a congenital heart defect (CHD), type of bradyarrhythmia, method of diagnosis, presence or absence of maternal autoantibodies such as anti-Ro/SSA antibodies, presence or absence of fetal hydrops, presence or absence of fetal myocardial dysfunction, fetal ventricular and atrial heart rate at presentation, prenatal treatment, mode of delivery, and outcome. Adverse effects related to prenatal treatment were also evaluated.

Statistical Analysis

Statistical analysis was performed using STATA 11.1 (StataCorp, College Station, TX, USA) and JMP 9 (SAS Institute, Cary, NC, USA). Data are presented as mean±SD or number of patients and were analyzed using Student's t-test. Categorical variables were evaluated on chi-square test and Fisher's exact test. Logistic regression was used to adjust for baseline variables known to be associated with fetal ventricular heart rate, fetal hydrops, fetal myocardial dysfunction, and maternal anti-Ro/SSA antibody. Time to fetal or neonatal death was analyzed using the Kaplan-Meier method with a log-rank test and a Cox proportional hazard model. P<0.05 was considered significant.

Results

Baseline Characteristics

A total of 128 cases were registered from 52 institutions during 7 years (2002–2008). All cases of fetal bradyarrhythmia were diagnosed during fetal life using echocardiography. In 8 cases, magnetocardiography was performed due to fetal bradyarrhythmia and family history of long QT syndrome (LQTS). Of the 128 fetuses, 38 (29.7%) had CHD, 15 had left atrial isomerism, 1 had right atrial isomerism, 5 had atrioventricular septal defect, 4 had corrected transposition of the great arteries, 4 had pulmonary stenosis, and 9 had other conditions. Patent ductus arteriosus and atrial septal defect were categorized as an absence of CHD. Ninety fetuses (70.3%) had a structurally normal heart, of whom 61 had CAVB, 16 had second-degree AVB, 8 had sinus bradycardia, 3 had sick sinus syndrome. Nine LQTS cases occurred in combination with another condition.

CAVB

Of the 61 fetuses with a structurally normal heart and CAVB (Table 1), 38 received transplacental medication. No fetus showed improvement of heart block. Monotherapy with β-sympathomimetics was given in 11 cases, steroids were given in 5 cases, and combination therapy with these agents was used in 22 cases. No transplacental medication was given in 23 cases. Ritodrine hydrochloride was used as the β-sympathomimetic agent. Steroids tended to be used in fetuses that were positive for maternal anti-Ro/SSA antibody throughout pregnancy, but the chosen steroid differed among institutions. Maternal i.v. immunoglobulin was not used. After birth, a pacemaker was implanted based on the Japanese guidelines of syncope, ventricular heart rate <50 beats/min, decreased cardiac function, LQTS, and a sudden pause longer than 2–3-fold the regular ventricular heart rate.

Table 2. Factors in Improvement of Bradycardia

	OR	95%CI	P value
β-sympathomimetics	49.02	5.18–464.02	<0.005
Steroids	1.32	0.24–7.20	0.745
β-sympathomimetics+steroids	725,448.8	0	0.996
Fetal heart rate	1	0.93–1.08	0.924
Fetal hydrops	0.41	0.07–2.39	0.319
Fetal myocardial dysfunction	1.14	0.20–6.60	0.883
Maternal anti-Ro/SSA antibodies	0.22	0.04–1.36	0.105

P<0.05, significant difference.
Logistic regression was used to adjust for baseline variables known to be associated with fetal ventricular heart rate, fetal hydrops, fetal myocardial dysfunction, and maternal anti-Ro/SSA antibody.
OR, odds ratio; CI, confidence interval; SSA, Sjögren's syndrome A.

Table 3. Factors in Fetal or Neonatal Death

	HR	95%CI	P value
β-sympathomimetics	1.16	0.37–3.63	0.792
Steroids	0.56	0.20–1.58	0.273
Fetal heart rate	0.98	0.92–1.05	0.546
Fetal hydrops	13.84	3.12–61.44	0.001
Fetal myocardial dysfunction	2.44	0.71–8.40	0.157
Maternal anti-Ro/SSA antibodies	1.07	0.33–3.47	0.906

P<0.05, significant difference.
Logistic regression was used to adjust for baseline variables known to be associated with fetal ventricular heart rate, fetal hydrops, fetal myocardial dysfunction, and maternal anti-Ro/SSA antibody.
HR, hazard ratio; CI, confidence interval; SSA, Sjögren's syndrome A.

Table 4. Factors in Development of Fetal Hydrops

	OR	95%CI	P value
β-sympathomimetics	2	0.35–11.50	0.439
Steroids	0.27	0.04–1.97	0.198
Fetal heart rate	1.01	0.94–1.08	0.813
Fetal myocardial dysfunction	5.71	1.14–28.62	0.034
Maternal anti-Ro/SSA antibodies	0.71	0.13–3.90	0.698

P<0.05, significant difference.
Logistic regression was used to adjust for baseline variables known to be associated with fetal ventricular heart rate, fetal myocardial dysfunction, and maternal anti-Ro/SSA antibody.
OR, odds ratio; CI, confidence interval; SSA, Sjögren's syndrome A.

The anti-Ro/SSA antibody-positive rate was significantly higher in fetuses treated with transplacental medication compared to those who did not receive this medication (76.3% vs. 47.8%; P=0.031). Gestational age at diagnosis was significantly lower in those receiving transplacental medication (24.0 weeks vs. 28.3 weeks; P=0.003). Fetal ventricular heart rate at diagnosis did not differ between the 2 groups, but the ventricular heart rate was significantly lower in fetuses treated with transplacental medication (56 beats/min vs. 63 beats/min; P=0.034). Birth weight was also significantly lower in fetuses treated with transplacental medication (2,120 g vs. 2,528 g; P=0.006). Gestational age at delivery, neonatal survival rate, and pacemaker implantation rate did not differ between the 2 groups.

Multivariate analysis was performed with adjustment for baseline variables with a known association with fetal ventricular heart rate, fetal hydrops, fetal myocardial dysfunction, and the presence of maternal anti-Ro/SSA antibodies (Tables 2–4). In this analysis, β-sympathomimetic treatment was significantly associated with improved bradycardia (odds ratio [OR], 49.02; 95% confidence interval [CI]: 5.18–464.02; P<0.001), whereas steroids were ineffective, and no evidence of a synergistic effect was obtained. The presence of maternal anti-Ro/SSA antibodies may inhibit improvement of bradycardia, but this effect was not significant (OR, 0.22; 95%CI: 0.04–1.36; P=0.105). Drug therapy had no significant effect on survival. Fetal ventricular heart rate and the presence of maternal anti-Ro/SSA antibodies also had no influence on prognosis, but fetal hydrops was associated with a 14-fold increased risk of perinatal death (hazard ratio [HR], 13.84; 95%CI: 3.12–61.44; P=0.001).

Kaplan-Meier survival curves are shown in Figure. The primary endpoint was intrauterine death or neonatal death. Beta-sympathomimetic treatment was not associated with improved prognosis. Steroid also did not improve the prognosis (HR, 0.56; 95%CI: 0.20–1.58; P=0.273). Fetal myocardial dysfunction was a significant risk factor for fetal hydrops (OR, 5.71; 95%CI: 1.14–28.62; P=0.034). Fetal ventricular heart rate and the presence of maternal anti-Ro/SSA antibodies were not associated with fetal hydrops. Beta-sympathomimetic treatment did not inhibit development of fetal hydrops. Steroids tended to inhibit fetal hydrops, but again this effect was not

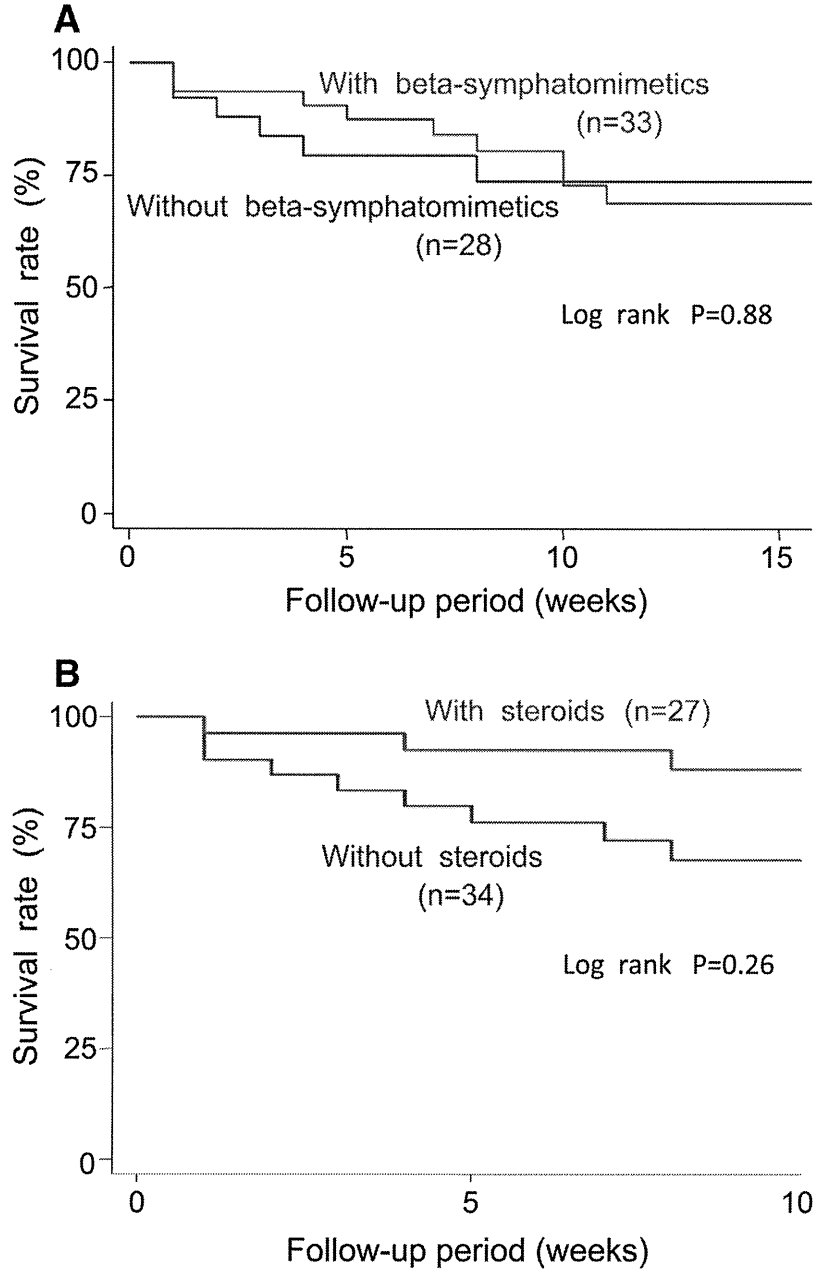

Figure. Kaplan-Meier survival curves (log-rank test and Cox proportional hazard model) for the primary endpoint (fetal death or neonatal death) in fetuses treated (**A**) with and without β-sympathomimetics and (**B**) with and without steroids. Follow-up period, time from diagnosis in utero to fetal or neonatal death. Significant difference defined as P<0.05.

statistically significant (OR, 0.27; 95%CI: 0.04–1.97; P=0.198). Drug therapy had no significant effect on improvement of fetal myocardial dysfunction.

Second-Degree AVB With Bradycardia

Of the 90 fetuses with a structurally normal heart, second-degree AVB was present in 16 cases (**Table 5**). Transplacental medication was given in 8 of these cases: β-sympathomimetic monotherapy in 4, steroids in 3, and a combination of these therapies in 1. In the 8 medication cases, fetal ventricular heart rate at diagnosis was significantly lower than that in the non-medication cases (70 beats/min vs. 79 beats/min; P=0.017). No other clinical characteristics differed significantly between the 2 groups. Of the 8 medicated fetuses, 3 developed CAVB, 3 maintained second-degree AVB, 1 improved to first-degree AVB, and 1 had no AVB at the time of delivery. Of the 8 non-medicated fetuses, 2 developed CAVB, 3 maintained second-degree AVB, and 3 had no AVB at the time of delivery. Survival rate did not differ between the groups (87.5%).

Adverse Effects of Transplacental Treatment

Treatment-related adverse events were examined in the 63 fetuses with a structurally normal heart and no fetal hydrops (**Table 6**). Steroids were given in 23 cases, drugs other than steroids were given in 10 cases, and no treatment was given in 30 cases. Gestational age at delivery did not differ among these 3 groups. In the steroid group, birth weight was significantly lower than in the non-treatment group (2,201 g vs.

Table 5. Second-Degree AVB Fetus Baseline Characteristics vs. Medication

	Medication (n=8)	No medication (n=8)	P value
Maternal anti-Ro/SSA antibodies	4	3	NS‡
Gestational age at diagnosis (weeks)	28±4.3	26±5.0	NS†
Fetal heart rate at diagnosis (beats/min)	70±9.0	79±10.4	<0.05†
Fetal hydrops	2	2	NS‡
Fetal myocardial dysfunction	3	2	NS‡
Gestational age at initiation of therapy (weeks)	29±4.8	–	
Fetal heart rate at initiation of therapy (beats/min)	70±10.0	–	
Gestational age at delivery (weeks)	35±3.8	37±2.1	NS†
Birth weight (g)	2,207±688	2,533±544	NS†
Delivery mode			
Vaginal	2	5	NS‡
Cesarean section	6	3	NS‡
Degree of AVB at delivery			
Complete	3	2	NS‡
Second	3	3	NS‡
First	1	0	NS‡
None	1	3	NS‡
Neonatal survival	7 (87.5)	7 (87.5)	NS‡

Data given as mean±SD or n (%).
P<0.05, significant difference. †Wilcoxon test; ‡chi-square test and Fisher's exact test.
AVB, atrioventricular block; SSA, Sjögren's syndrome A.

Table 6. Baseline Characteristics vs. Treatment Type†

	Steroid treatment (n=23)	Non-steroid treatment (n=10)	No treatment (n=30)
Treatment (weeks)	8.8±4.4	5.6±3.2	–
Gestational age at delivery (weeks)	36±2.6	35.8±2.6	36.8±3.0
Birth weight (g)	2,201±525*	2,413±552	2,713±512*
Fetal arrythmia: CAVB	21	6	23
Fetal arrythmia: Second-degree AVB	1	2	5
Maternal diabetes	1 (4.3)	0	0
Fetal growth restriction	6 (26.1)	0	2 (6.7)
Fetal oligohydramnios	2 (8.7)	0	0
Neonatal adrenal insufficiency	1 (4.3)	0	0

Data given as mean±SD or n (%).
†For fetuses without fetal hydrops and with a structurally normal heart. *P<0.05 (Student's t-test).
CAVB, complete atrioventricular block; AVB, atrioventricular block.

Table 7. Baseline Characteristics vs. Length of Steroid Treatment

	<10 weeks (n=12)	≥10 weeks (n=11)	P value
Treatment (weeks)	5.4±2.7	12.5±2.5	<0.01†
Gestational age at delivery (weeks)	35±3.2	36±1.7	NS†
Birth weight (g)	2,184±569	2,218±503	NS†
Maternal diabetes	0	1 (9.1)	NS‡
Fetal growth restriction	1 (8.3)	5 (45.5)	<0.05‡
Fetal oligohydramnios	0	2 (18.2)	NS‡
Neonatal adrenal insufficiency	0	1 (9.1)	NS‡

Data given as mean±SD or n (%). P<0.05, significant difference.
†Student's t-test; ‡chi-square test and Fisher's exact test.

2,713 g; P=0.001) and fetal growth restriction was close to being significantly higher than in the non-steroid (26.1% vs. 0%; P=0.050) and non-treatment (26.1% vs. 6.7%; P=0.074) groups. Adverse effects that might have been attributable to the use of steroids included development of oligohydramnios in 8.7% of cases, maternal diabetes in 4.3%, and neonatal adrenal insufficiency in 4.3%. All these adverse effects were observed in cases of steroid use >10 weeks (Table 7). In particular, fetal growth restriction increased significantly after steroid use >10 weeks (45.5% vs. 8.3%; P=0.043).

LQTS

Of the 90 fetuses with a structurally normal heart, 9 (10.0%) were diagnosed with LQTS, including 4 diagnosed on electrocardiography after birth and 5 diagnosed on magnetocardiography during fetal life. The background of the LQTS fetuses included a family history of LQTS (n=2), maternal anti-Ro/SSA antibody (n=2), fetal hydrops (n=3), myocardial dysfunction (n=2), CAVB (n=6), second-degree AVB with bradycardia (n=1), and sinus bradycardia (n=2). In 4 of the 9 cases of LQTS, emergency cesarean section was performed because of fetal ventricular tachycardia/torsades de pointes (VT/TdP) at 33–36 weeks of gestation. In 2 of the 9 cases, fetal hydrops caused neonate death.

Discussion

This is the first large-scale study to investigate the effects and risks of transplacental treatment for fetal congenital bradyarrhythmia in Japan. The results indicate that fetal hydrops is associated with a 14-fold increased risk of perinatal death, and that fetal myocardial dysfunction is a significant risk factor for fetal hydrops. Fetal ventricular heart rate and the presence of maternal anti-Ro/SSA antibodies were not associated with neonatal prognosis. Beta-sympathomimetics improved bradycardia, but survival rate did not differ significantly with regard to transplacental medication. Maternal and fetal adverse effects were observed in cases of steroid use. In particular, fetal growth restriction increased significantly after steroid use >10 weeks.

Evaluation of Anti-Ro/SSA Antibodies

Ro/SSA is one of the major immunogenic ribonucleoproteins, and antibodies against these proteins are found in a number of connective diseases, especially in Sjögren's syndrome (SS) and systemic lupus erythematosus (SLE). Anti-Ro/SSA antibodies are detected in 60–90% of SS cases and in 30–50% of SLE cases.[26,27] Interestingly, these antibodies are relatively common and are detected in 1–2% of randomly tested pregnant women.[28] Currently, the outcome of anti-Ro/SSA-positive pregnancies is very good when prospectively followed by multidisciplinary teams with experience in this field.[1] Transplacental passage of anti-Ro/SSA antibodies from mother to fetus, however, is associated with a risk of development of neonatal lupus erythematosus (NLE).[2,11,12] NLE is an uncommon but life-threatening disease of the fetus and neonate, with important cardiac complications of CAVB, sinus bradycardia, QTc interval prolongation, endocardial fibroelastosis, and late-onset dilated cardiomyopathy.[3–5] Congenital CAVB develops in 1–5% of anti-Ro/SSA antibody-positive pregnancies, typically between 18 and 24 weeks of gestational age. Predominantly untreated CAVB has a mortality rate of 14–34%,[1–9] consistent with the untreated CAVB mortality rate of 26% in the current study.

The association of NLE with maternal anti-Ro/SSA antibodies is well established, but the trigger of the maternal antibody interaction with the fetal Ro particle is unclear in some antibody-exposed babies. The percentage of maternal anti-Ro/SSA antibody-positive fetuses with CAVB diagnosed in utero is unknown. Brucato et al and Jaeggi et al found maternal anti-Ro/SSA antibodies in 92% of 37 CAVB cases,[7,9] whereas in the present study maternal anti-Ro/SSA antibodies were detected in only 66% of 61 CAVB fetuses with a structurally normal heart. Jaeggi et al also reported that CAVB occurred in 5% of prospectively screened pregnancies with anti-Ro/SSA ELISA levels >100 U/ml, but did not occur in pregnancies with levels <50 U/ml.[6] Approximately two-thirds of anti-Ro/SSA antibody-positive mothers had low anti-Ro/SSA levels and probably little risk of development of fetal cardiac NLE.[8] It is unclear why the anti-Ro/SSA-positive rate in the present study was lower than in other reports. It is unlikely to be due to the sensitivity of the laboratory methods, but it is possible that other undetectable antibodies associated with congenital AVB are present in the Japanese population. Brucato et al and Lopes et al found similar mortality rates in the anti-Ro/SSA-positive and -negative groups,[7,8] and in the present multivariate analysis anti-Ro/SSA antibodies were not associated with prognosis.

Benefits and Risks of Transplacental Treatment

Congenital AVB is a progressively developing disease that evolves through 2 fundamental phases: an early phase characterized by the occurrence of still reversible AV conduction abnormalities (first- or second-degree AVB) and a final phase in which development of irreversible damage of the conduction system leads to the appearance of CAVB.[29] The specific pathogenetic mechanisms involved in the 2 phases have not been clarified, but there are 2 main theories. The first is based on an inflammatory-driven injury elicited by interaction between anti-Ro/SSA antibodies and specific antigens expressed in the conduction tissue of the fetal heart (inflammatory theory). The second theory involves electrophysiologic interference of anti-Ro/SSA antibodies with heart conduction (electrophysiological theory).[20] Consistent with these respective theories, steroids and i.v. immunoglobulins are used for anti-inflammatory treatment, while β-sympathomimetics are given for fetal pacing.

Several studies have found that a ventricular heart rate <55 beats/min is a risk factor for fetal and neonatal death,[4,14] and have recommended transplacental treatment with β-sympathomimetics to increase the heart rate. Jaeggi et al and Maeno et al, however, found that fetuses with CAVB without CHD and with a ventricular heart rate of <55 beats/min were not at risk.[30,31] In the present study, fetal ventricular heart rate did not influence fetal hydrops and prognosis, but treatment with a β-sympathomimetic agent was significantly associated with improved bradycardia.

To date, evidence of clinical efficacy of transplacental treatment has been limited to cases of congenital AVB.[13–19] Jaeggi et al reported a significant improvement in the outcome of fetal CAVB simultaneously with the introduction of routine perinatal treatment guidelines in 1997.[9] Hutter et al obtained an improved survival rate of >90% by initiation of maternal high-dose dexamethasone at the time of CAVB detection and maintenance of this dose during pregnancy, with addition of β-sympathomimetics to keep the fetal heart rate above 55 beats/min.[21] It was also suggested that prolonged use of dexamethasone might render a fetus with congenital CAVB less likely to develop additional manifestations of cardiac NLE such as myocarditis, cardiomyopathy, and hydrops fetalis, thus improving the overall outcome. The present findings suggest that use of steroids might render the affected fetus less likely to develop fetal hydrops, but that the neonatal survival rate improved only to 79%. The reason for the relatively bad prognosis in the present study may have been the difference in the rate of fetal hydrops compared to the Hutter et al study (42% vs. 10%). Undetectable autoantibodies or virus infection may be related to the increased rate of fetal hydrops in the Japanese population. Furthermore, Hutter et al initiated maternal high-dose dexamethasone at the time of CAVB diagnosis, at a mean gestational age of 24 weeks. The mean age of diagnosis was similar in the present study, but mean gestational age at which steroids were started was 26 weeks. In addition, the percentage of steroids used in transplacental treatment was

lower in the present patients (71% vs. 95%). These findings suggest that sufficient steroid dose at an early stage is very important to prevent fetal hydrops and to improve prognosis.

Use of steroids is controversial because of the potential risks for the fetus and mother, including problems with fetal growth restriction, oligohydramnios, and neurological development. Animal models suggest that repeated antenatal steroid doses can interfere with the growth and development of the immature brain, and human studies suggest that antenatal and postnatal dexamethasone may negatively affect a child's neuropsychological development.[22–24] In contrast, Brucato et al found no negative effects on neuropsychological development and intelligence in a cohort of preschool- and school-age children with CAVB who had been prenatally exposed to maternal anti-Ro antibodies and prolonged dexamethasone treatment.[25] The association of fetal growth restriction and oligohydramnios with antenatal steroids is well established, but the amount and length of steroid treatment that can be used safely is unclear. We note that development of fetal growth restriction and oligohydramnios are dose-related complications of steroids. Consequently, we recommend limiting steroid use to <10 weeks to avoid maternal and fetal adverse effects.

Prevention of Progression to Congenital CAVB

There are many case reports describing prevention of congenital CAVB, and first- or second-degree AVB is also relatively common and often normalizes spontaneously before or soon after delivery.[32] Recent prospective studies suggest that steroids and i.v. immunoglobulins are not beneficial for preventing progression to congenital AVB.[33,34] Similarly, the present study found a lack of superiority of transplacental treatment for second-degree AVB with bradyarrhythmia.

LQTS

Recent evidence has shown that anti-Ro/SSA antibodies are associated with prolongation of the QTc interval.[35] Although the exact arrhythmogenic mechanisms have not been clarified, anti-Ro/SSA antibodies may trigger rhythm disturbances through inhibition of cross-reactions with several cardiac ionic channels, including calcium channels and the hERG potassium channel.[36,37] Beta-sympathomimetics may trigger life-threatening arrhythmia such as VT/TdP in patients with LQTS, and therefore use of these drugs should be avoided in fetuses with QTc interval prolongation.[38,39] In the present study, in 4 of the 9 LQTS cases, emergency cesarean section was performed because of fetal VT/TdP at 33–36 weeks of gestational age. Oka et al also recently described atrioventricular block-induced TdP.[40] With this background, we recommend avoidance of β-sympathomimetics in a fetus with a heart rate >55 beats/min. Furthermore, assessment of QTc interval prolongation on magnetocardiography may be required to evaluate the risk of fetal congenital bradyarrhythmia.

Study Limitations

There were several limitations in the present study due to retrospective data selection bias and the relatively small sample size. The nature of a multicenter retrospective observational study using a questionnaire is such that the clinical data obtained vary among cases, so treatment bias may exist. Only ritodrine hydrochloride was used as β-sympathomimetic treatment, but was given in cases involving fetal heart rate >55 beats/min at some institutions, while dexamethasone, betamethasone and prednisolone were used as steroids at different doses among institutions. The follow-up period after birth was insufficient to permit analysis of long-term morbidity and mortality, and this prevented evaluation of potential long-term benefits and risks of transplacental medication. Finally, the sample size might have been too small to detect the effects of steroids on fetal congenital bradyarrhythmia. The steroid effect may become significant in a study with a higher number of cases.

Guidelines are required for transplacental treatment of fetal congenital bradyarrhythmia and follow-up after birth. We expect to analyze long-term outcome of fetal congenital bradyarrhythmia in a future study. Further large prospective studies are also needed to establish the most appropriate treatment strategies in Japan.

Conclusion

Beta-sympathomimetics improved bradycardia, but survival rate did not differ significantly in fetuses treated with and without transplacental medication. We recommend limiting steroid use to <10 weeks to avoid maternal and fetal adverse effects, with fetal growth restriction and oligohydramnios being of particular concern.

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Disclosures

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ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Risk Determinants in Individuals With a Spontaneous Type 1 Brugada ECG

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Background: Spontaneous coved ST-segment elevation ≥2 mm followed by a negative T-wave in the right precordial leads (type 1 Brugada ECG) is diagnostic of Brugada syndrome (BS), but there is a false-positive rate.

Methods and Results: Computer-processed analysis of a 12-lead ECG database containing 49,286 females and 52,779 males was performed to select patients with a spontaneous type 1 Brugada ECG for an examination of the association of this ECG characteristic with long-term prognosis. There were 185 patients with a spontaneous type 1 Brugada ECG and of these, 16 (15 males; mean age, 46.7±14.0 years) were diagnosed with BS and 15 patients (all males; mean age, 50.1±13.4 years) were undiagnosed. The PQ interval was significantly longer in the diagnosed patients than in the undiagnosed patients (187.4±28.3 ms vs. 161.2±21.5 ms; P=0.0073). The T-wave in lead V_1 was more negative in the diagnosed patients than in the undiagnosed patients (−170.2±174.6 μV vs. −43.2±122.3 μV, P=0.027). Multivariate analysis revealed that a PQ interval ≥170 ms and T-wave amplitude <−105 μV in lead V_1 were independent risk stratifiers of life-threatening events. Survival analysis (mean follow-up, 78.6±81.8 months) showed that the PQ interval and a negative T-wave in lead V_1 were significantly associated with poor prognosis.

Conclusions: Analysis of a standard 12-lead ECG can stratify the prognosis of patients with a spontaneous type 1 Brugada ECG. (*Circ J* 2011; **75:** 844–851)

Key Words: Brugada syndrome; Electrocardiography; Prognosis; Risk determinant; Sudden death

Brugada syndrome (BS) is characterized by a distinct ST-segment elevation in the right precordial leads and causes sudden cardiac death.[1] This syndrome has a relatively high prevalence in East Asian countries. Patients with a coved-type ST-segment elevation in leads V_{1-3} are more susceptible to life-threatening ventricular arrhythmias than patients with a saddleback-type ST-segment elevation in the same leads.[2] A community-based study reported that subjects who displayed a spontaneous coved ST-segment elevation in the right precordial leads were not at risk for sudden death,[3] but another study, in which the mean follow-up period was >40 years, reported that an ECG with a coved ST-segment elevation was related to an increased risk of unexplained death.[4] Similar inconsistency has been found among studies conducted in hospital-based populations.[5–7] The discrepancy indicates that a distinct coved ST-segment elevation may not be the sole determinant of prognosis.

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To stratify prognostic risk in BS, pharmacological and electrophysiological tests are performed, but the prognostic value of these tests is yet to be settled.[8,9] In addition, mutation of the gene that encodes the cardiac sodium channel, *SCN5A*,[10] is detected only in approximately 20% of patients diagnosed with BS,[6] suggesting that it may be difficult to screen out subjects who are at high risk for lethal arrhythmia by genetic testing alone.

The large database of a university hospital containing 12-lead ECGs of more than 100,000 patients stored digitally for over 25 years, enabled us to evaluate long-term prognosis using computer-processed analysis. Since 12-lead ECG is the most convenient method of diagnosing BS in a large population, such as in health examinations, in the present

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study we focused on patients with a spontaneous coved ST-segment elevation ≥0.2 mV in the right precordial leads (ie, type 1 Brugada ECG). Our aim was to determine the quantitative traits of a spontaneous type 1 Brugada ECG that can stratify the risk for sudden cardiac death (SCD).

Methods

Database

The database comprised 102,065 consecutive patients (49,286 females and 52,779 males) who had undergone ECG recording in the university hospital between January 1983 and October 2008. A total of 308,391 ECGs were collected during this period. The 12-lead ECG was recorded at rest for 10 s at a sweep speed of 25 mm/s, calibrated to 1 mV/cm in the standard leads. The data were digitally stored in a 12-bit server computer with a sampling interval of 2 ms.

Patient Population

From the database, we chose patients who had a spontaneous coved ST-segment elevation in the right precordial leads. We enrolled patients who fulfilled the following ECG criteria: (1) J-point elevation ≥0.2 mV amplitude in lead V_1 or V_2, (2) the amplitude at the middle of the ST-segment (STM: defined as the time point after an interval of 1/16 of the average RR interval from the J point) in lead V_1 or V_2 was less than that at the J point in the same lead, (3) the amplitude at the end of the ST-segment (defined as the time point after an interval of 1/8 of the average RR interval from the J point) in lead V_1 or V_2 was less than that at the middle of the ST-segment in the same lead, and (4) the amplitude at the J point and the middle of the ST-segment was positive in leads V_1 and V_2. The J point was defined as the offset of the QRS complex that was the latest detection of ventricular depolarization. To exclude right bundle branch block, we did not include any ECG that displayed the QRS complex in lead V_1 with a decrease in amplitude of ≥0.4 mV from the J point.

ECG Analysis

The ECG analysis was performed using software (MUSE7.1, GE Marquette Medical Systems, Inc, Milwaukee, WI, USA). ECG variables, including duration, interval, amplitude, and axis, were digitally measured. A median complex was computed as follows: (1) all QRS complexes with the same morphology were aligned in time and (2) the algorithm generated a representative QRS complex from the median voltages that were found at each successive sample time. QRS duration was measured from the earliest detection of depolarization in any lead (QRS onset) to the latest detection of depolarization in any lead (QRS offset). Similarly, the QT interval was measured from the earliest detection of depolarization in any lead (QRS onset) to the latest detection of repolarization where the downsloping limb joined the baseline in any lead (T offset), while the U wave was excluded. The QTc interval was calculated after correction for heart rate with Bazett's formula. The frontal plane angle of the P wave, QRS complex, and T wave was determined from the frontal leads (I, II, III, aV_R, aV_L, and aV_F). The frontal plane QRS–T angle was defined as the absolute value of the difference between the frontal planes of the QRS axis and T axis, and was adjusted to the minimal angle using "360° minus the angle" for an angle >180° (axis measurement range; –89° to +270°). Because all variables of the 12-lead ECG were digitally measured by computer-processed analysis, neither intra-observer nor interobserver variability was taken into account.

Follow-up

The follow-up period of all patients was defined as the interval from the first day when a spontaneous type 1 Brugada ECG was recorded to the day when prognostic outcome was identified. The prognostic value was assessed for the endpoint of documented ventricular fibrillation (VF) or sustained ventricular tachycardia (VT) that was either symptomatic or revealed by an implanted device. A postal questionnaire was used to assess the prognosis of patients who were not associated with the Division of Cardiology in the hospital. Written informed consent was given by all patients enrolled in this study.

Diagnosis

When a spontaneous type 1 Brugada ECG was present, BS was diagnosed on the basis of a consensus report requiring at least one of the following criteria: documented VF, self-terminating polymorphic VT, family history of sudden death, type 1 Brugada ECG in family members, positive electrophysiological study, unexplained syncope suggestive of ventricular tachyarrhythmia, and nocturnal agonal respiration.[2] Confounding factors[1] that have been previously reported as disorders accounting for a type 1 Brugada ECG were excluded. Drug-induced Brugada-like ECG pattern[2] was also excluded.

Gene Analysis

The methods of DNA isolation and mutation analysis are described elsewhere.[11] Briefly, genomic DNA was isolated from blood lymphocytes and then screened for candidate genes using denaturing high-performance liquid chromatography with a WAVE System Model 3500 (Transgenomic, Omaha, NB, USA). Polymerase chain reaction was used to amplify abnormal conformers, and sequencing was performed on an ABI PRISM 3100 DNA sequencer (Applied Biosystems, Foster City, CA, USA).

Statistical Analysis

We explored the prognostic factors for developing life-threatening events and the endpoint was the occurrence of life-threatening events. Continuous variables are reported as mean±SD and categorical variables as observed number of patients (percentage). We compiled 2 groups: patients who were diagnosed with BS (diagnosis group) and patients who were not diagnosed with BS (no-diagnosis group). In the comparison of their clinical and ECG characteristics, we used a t-test for continuous variables and Fisher's exact test or χ^2 test for categorical variables. Receiver-operating characteristic curve was used to determine the optimal cut-off point of the prognostic factors that maximizes the sensitivity and specificity of ECG variables for the diagnosis of BS. Logistic regression was used to compare the patients with/without BS to explore the prognostic factors accounting for confounding. The forward selection procedure was applied for the selection of variables in the logistic regression and the criteria was set as $P<0.10$. For the significant variables in the model, the Kaplan-Meier curve was made to describe the event-free survival rate and the log-rank test was used to examine the difference between 2 groups. All tests were 2-tailed and the significance level was set as 0.5. The research protocol was approved by the Ethical Committee of Shiga University of Medical Science (19–75).

Results

We located 185 patients who fulfilled the ECG criteria of a

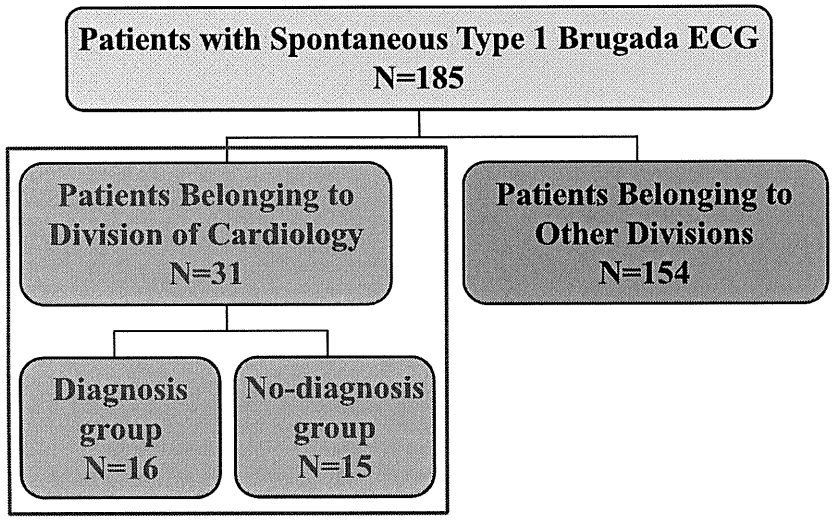

Figure 1. Flowchart of the categorization of patients with a spontaneous type 1 Brugada ECG: the 185 patients were chosen from an ECG database by virtue of a computer-processed algorithm. Of them, 31 patients were in the hospital's Division of Cardiology and 154 patients were not. The former patients were grouped: 16 patients who were diagnosed with Brugada syndrome (diagnosis group) and 15 patients who were not (no-diagnosis group). Red squares denote patients who were enrolled into this study.

Table 1. Characteristics of the Patients With Spontaneous Type 1 Brugada ECG

	Diagnosis group	No-diagnosis group	P value
No. of patients	16	15	
Age (years)	46.7±14.0	50.1±13.4	0.50
Male (n, %)	15 (93.8)	15 (100)	0.24
Follow-up period (months)	58.5±75.1	43.2±42.7	0.49
Family history of SCD (n, %)	8 (50.0)	0 (0)	0.0008
Syncope (n, %)	14 (87.5)	3 (20.0)	<0.001
Aborted SCD or documented VF (n, %)	11 (68.8)	0 (0)	<0.001

SCD, sudden cardiac death; VF, ventricular fibrillation.

spontaneous type 1 Brugada ECG in the database (**Figure 1**). The prevalence of a spontaneous type 1 Brugada ECG was 0.18% of the total patients who underwent ECG recording in the hospital. Of the 185 patients, 31 attended the Division of Cardiology: 16 patients were diagnosed as BS (diagnosis group) and 15 patients were not (no-diagnosis group). Representative ECGs are shown in **Figures S1** and **S2**. All the patients of the diagnosis and no-diagnosis groups were carefully followed in the Division of Cardiology. The remaining 154 patients who had exhibited a spontaneous type 1 Brugada ECG attended other divisions of the hospital and had undergone ECG recording irrespective of cardiovascular disease (eg, before surgery). The mean follow-up of the 2 groups was 51.1±61.1 months, ranging from 1 to 238 months.

Characteristics of the Patients

The detailed clinical characteristics of each group are shown in **Table 1**. The mean age of each group was not significantly different, the male predominance was similar between the 2 groups and the mean follow-up period was not significantly different between the 2 cohorts. In the diagnosis group, 14 of the 16 patients diagnosed with BS suffered syncope, and in 12 of the 14 patients, lethal ventricular arrhythmias (VF or VT) were documented. Although the remaining 2 patients did not have a documented episode of lethal arrhythmias, both patients had syncopal episodes considered to be of arrhythmic origin. In those 2 patients, VF was induced by programmed ventricular stimulation. An implantable cardioverter-defibrillator (ICD) was implanted in all patients but 1 patient who rejected the procedure. After ICD implantation, 6 patients experienced VF. In the diagnosis group 8 patients (50%; 1 female, 7 males) had a family history of sudden death. In the no-diagnosis group, the 15 patients, who had been referred to the Division of Cardiology, displayed a spontaneous type 1 Brugada ECG but were not diagnosed as BS because none suffered from unexplained syncope or had a family history of SCD. Therefore, it was not considered necessary to implant ICDs in these patients, but they were required to visit hospital regularly for health checks. In the no-diagnosis group, 3 patients experienced syncope that was most likely due to a neurally mediated mechanism, because precipitating events, such as severe

Table 2. Measurements of 12-Lead ECG of the Patients With Spontaneous Type 1 Brugada ECG

	Diagnosis group	No-diagnosis group	P value
Heart rate (beats/min)	64.4±9.5	68.3±14.7	0.38
PQ interval (ms)	187.4±28.3	161.2±21.5	0.0073
P axis (degrees)	63.9±13.5	58.7±19.5	0.41
QRS axis (degrees)	49.1±44.1	44.9±34.8	0.78
T axis (degrees)	52.8±20.4	59.3±14.0	0.31
QRS-T angle (degrees)	19.8±17.3	27.3±24.0	0.32
QRS-complex duration (ms)	108.4±25.5	103.2±8.6	0.46
QT interval (ms)	398.1±34.9	388.7±33.6	0.45
QTc interval (ms)	409.3±28.2	408.9±17.2	0.96

Table 3. Measurements of Individual Leads of the Patients With Spontaneous Type 1 Brugada ECG

	Diagnosis group	No-diagnosis group	P value
QRS-complex duration in lead V_1 (ms)	101.4±31.6	90.3±19.1	0.25
QRS-complex duration in lead V_2 (ms)	99.0±31.9	88.9±18.1	0.29
QRS-complex duration in lead V_5 (ms)	104.1±27.9	98.3±11.4	0.46
Dispersion of QRS-complex duration (ms)	4.7±14.3	7.9±21.9	0.63
R'-wave amplitude in lead V_1 (μV)	41.3±88.8	94.9±138.4	0.22
R'-wave amplitude in lead V_2 (μV)	90.3±188.5	188.9±248.9	0.23
J-point amplitude in lead V_1 (μV)	183.3±127.9	128.8±78.0	0.17
J-point amplitude in lead V_2 (μV)	311.8±117.6	339.0±135.7	0.55
STM amplitude in lead V_1 (μV)	55.3±66.9	81.7±73.9	0.31
STM amplitude in lead V_2 (μV)	172.1±107.5	192.9±157.8	0.67
Descending amplitude in lead V_1 (μV)	128.0±154.0	47.1±66.6	0.071
T-wave amplitude in lead V_1 (μV)	−170.2±174.6	−43.2±122.3	0.027
T-wave amplitude in lead V_2 (μV)	95.0±363.3	232.1±200.0	0.21
R-wave amplitude in lead aV_R (μV)	104.5±142.8	103.7±101.3	0.99
R/q ratio in lead aV_R	0.35±0.44	0.22±0.20	0.38
R-wave amplitude in lead aV_L (μV)	254.3±281.0	212.7±192.9	0.64
R'-wave amplitude in lead aV_L (μV)	32.2±48.4	49.9±88.4	0.49
R'/q ratio in lead aV_L	0.0±0.0	0.87±1.71	0.20

Dispersion of QRS-complex duration, absolute value of the difference between the QRS-complex duration in leads V_1 and V_5; STM, site at the middle of the ST segment (see Methods); Descending amplitude, difference in the amplitudes at the J-point and STM.

pain, emotional distress, or supine posture, were associated with syncope that was preceded by prodromal symptoms (sweating, nausea, vomiting, yawning). Cardiac transthoracic echocardiography revealed normal left ventricular function without evidence of structural heart disease in all patients of both groups. None of the family members of patients in either group was involved. We performed genetic analysis of 14 of the 16 patients in the diagnosis group, which identified a mutation in *SCN5A* in 1 patient (8.3%) who was a subject of our previous report;[12] no abnormality in *SCN5A* was determined in the remaining 13 patients.

Characteristics of the ECG

Table 2 shows the ECG characteristics. Heart rate did not significantly differ between groups. The PQ interval was significantly longer in the diagnosis group than in the no-diagnosis group; however, there was no significant difference between the 2 groups in the duration of the QRS complex, QT interval, and QTc interval. In addition, the frontal plane axis of the P-, QRS-, and T-wave did not differ between the diagnosis and no-diagnosis group. Table 3 shows the ECG measurements in individual leads. Between the 2 groups, there was no significant difference in the duration of the QRS complex in leads V_1, V_2 and V_5, nor was there in the dispersion of the QRS-complex duration in leads V_1 and V_5, the R'-wave amplitude in leads V_1 and V_2, the J-point amplitude in leads V_1 and V_2, and the STM-amplitude in leads V_1 and V_2. The T-wave in lead V_1 was more negative in the diagnosis group than in the no-diagnosis group, but the T-wave amplitude in lead V_2 was not significantly different between the 2 groups. There was no significant difference between the 2 groups in the other ECG variables, including R-wave amplitude and R/q ratio in lead aV_R, and R-wave amplitude, R'-wave amplitude, and R'/q ratio in lead aV_L.

Risk Stratification

In the patients of the diagnosis and no-diagnosis groups, the factors predictive of life-threatening arrhythmic events were evaluated. Univariate analyses were performed to identify patients at risk of life-threatening events. The presence of a family history, and a PQ interval, and the T-wave amplitude in lead V_1 were significantly associated with BS (Table 4). Multivariate logistic regression analysis revealed that the PQ interval and T-wave amplitude in lead V_1 were indepen-

Table 4. Probability of Life-Threatening Arrhythmias According to Clinical and ECG Variables of the Patients With Spontaneous Type 1 Brugada ECG

	P value	Odds ratio	95%CI
Univariate analysis			
Age ≥50 years	0.36	1.93	0.47–8.42
Family history of sudden death	0.043*	10.50	1.47–216.68
Heart rate ≥66 beats/min	0.59	1.47	0.36–6.24
PQ interval ≥170 ms	0.0014*	14.0	2.62–115.18
QTc interval ≥405 ms	0.36	0.52	0.12–2.14
J-point amplitude in V_1 ≥155 μV	0.85	0.86	0.15–3.22
STM amplitude in lead V_1 ≥68 μV	0.58	0.67	0.16–2.76
T-wave amplitude <–105 μV in lead V_1	0.024*	6.05	1.36–32.09
Descending amplitude in lead V_1 ≥49 μV	0.59	1.47	0.36–6.24
Multivariate analysis			
PQ interval ≥170 ms	0.045*	11.50	1.05–268.62
T-wave amplitude <–105 μV in lead V_1	0.037*	8.98	1.14–117.28
Descending amplitude in lead V_1 ≥49 μV	0.19	0.23	0.02–1.94
Family history of sudden death	0.59	2.18	0.12–66.22

Dispersion of QRS-complex duration, absolute value of the difference between the QRS-complex duration in leads V_1 and V_5; STM, site at the middle of the ST segment (see Methods); Descending amplitude, difference in the amplitudes at the J-point and STM.
CI, confidence interval.

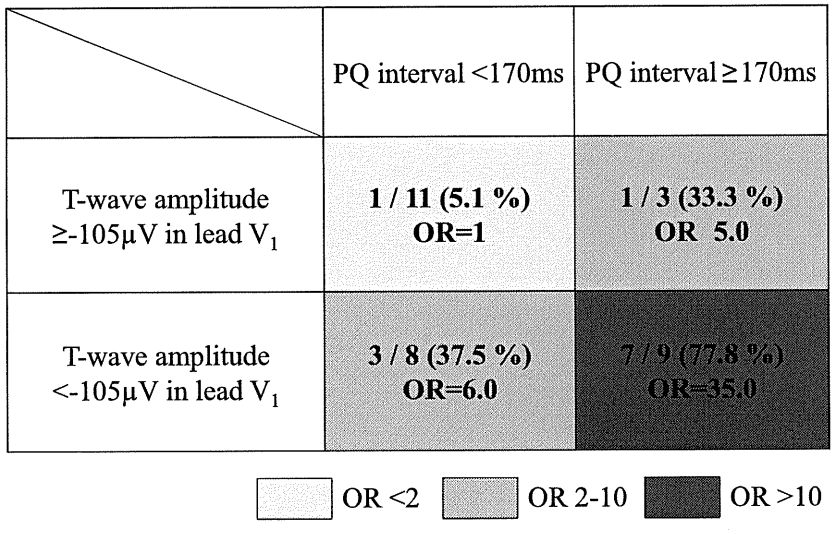

Figure 2. Risk stratification scheme of life-threatening events in patients with a spontaneous type 1 Brugada ECG. Patients are categorized according to the PQ interval and T-wave amplitude in lead V_1. Each box shows the number of patients of the diagnosis and no-diagnosis groups as a denominator and the number of patients of the diagnosis group as a numerator, allowing calculation of the rate of diagnosing Brugada syndrome (shown in parentheses). The odds ratio (OR) for each box is calculated by setting the odds of the upper lefthand corner yellow box as 1. See text for details.

dently associated with life-threatening events in patients with a spontaneous type 1 Brugada ECG (**Table 4**). **Figure 2** is a schema for risk stratification constructed according to the values of the PQ interval and T-wave amplitude in lead V_1. Using receiver operating characteristic analysis, the sensitivity and specificity of the PQ interval and T-wave amplitude in lead V_1 in response to life-threatening events were maximized by a PQ interval of 170 ms and a T-wave amplitude of –105 μV in lead V_1. The patients of the diagnosis and no-diagnosis groups were allocated to 4 categories according to the PQ interval and T-wave amplitude in lead V_1. The rate of diagnosing BS was higher in the category having a PQ interval ≥170 ms than in that of PQ interval <170 ms. The same was true for the categories dichotomized by T-wave amplitude of –105 μV in lead V_1. Furthermore, when present together, the PQ interval and T-wave amplitude in lead V_1 potentiate each other, leading to a diagnosis of BS that is substantially greater than that of its individual components.

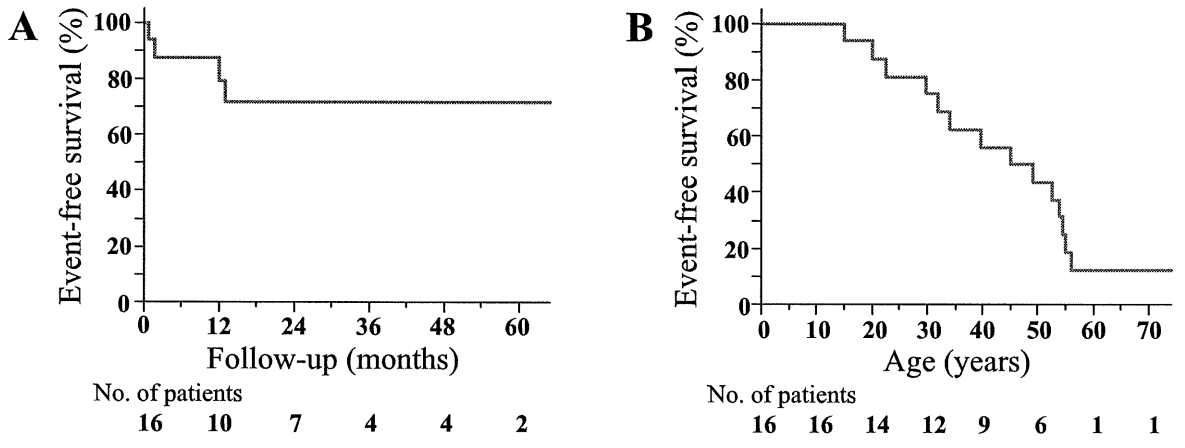

Figure 3. (A) Kaplan-Meier curve of event-free survival in patients with Brugada syndrome during follow-up. On the abscissa, time 0 is defined as the time when the first ECG with a spontaneous type 1 Brugada ECG was recorded. (B) Kaplan-Meier curve of event-free survival in patients with Brugada syndrome according to age.

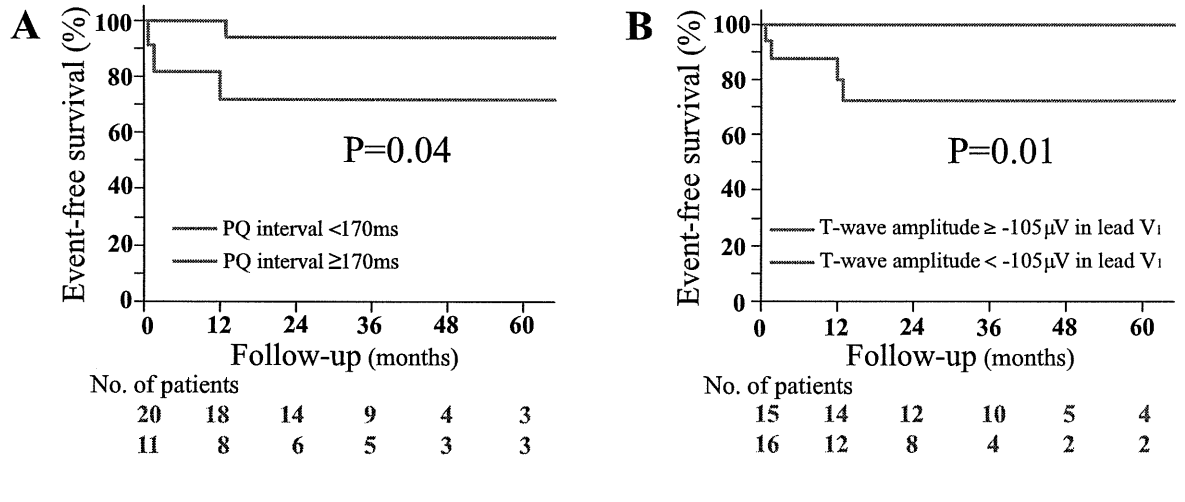

Figure 4. Kaplan-Meier estimates of cardiovascular event-free survival in patients of the diagnosis and no-diagnosis groups during follow-up according to (A) PQ interval and (B) T-wave amplitude in lead V_1.

Long-Term Outcome

Figure 3A shows the Kaplan-Meier survival curve of life-threatening events in the diagnosis group after a type 1 Brugada ECG was recorded. During the follow-up, 6 of the 15 patients (40%) who received an ICD experienced recurrence of life-threatening arrhythmic events. No patient died in the diagnosis group during follow-up. The duration from the diagnosis of BS to recurrence of life-threatening events ranged from 0.7 to 74 months (mean, 28.9±34.6 months). Approximately 30% of patients had recurrence within 1 year (Figure 3A). Figure 3B shows the age-dependent event-free survival curve of life-threatening events in the diagnosis group. Life-threatening events occurred between 15 and 60 years of age. A comparison of the ECG variables of patients with ICD intervention with those of patients without an ICD in the diagnosis group was made (Table S1). Heart rate was significantly faster in patients with an ICD than in those without, and the PQ interval was significantly longer in patients with an ICD than in those without. However, other ECG variables did not differ between patients with and without an ICD.

On the basis of the significant association of PQ interval and negative T wave in lead V_1 with BS, as shown in Table 4, the life-threatening event-free rate was estimated for the patients in both groups according to PQ interval and T-wave amplitude in lead V_1. Figure 4 shows the Kaplan-Meier life-table analysis. The PQ interval was associated with a significant (P=0.04) difference in the life-threatening event-free rate between patients (n=11) with a PQ interval ≥170 ms and those (n=20) with a PQ interval <170 ms (haz-

ard ratio, 6.9; 95%CI, 1.1–133.5) (Figure 4A). In addition, the T-wave amplitude in lead V_1 was associated with a significant (P=0.013) difference in the life-threatening event-free rate between patients (n=16) with an amplitude $<-105\mu V$ and those (n=15) with an amplitude $\geq -105\mu V$ (hazard ratio, not available [because of the lack of events in patients with a T-wave amplitude in lead V_1 $\geq -105\mu V$]) (Figure 3B). Because none of the patients in the no-diagnosis group had a life-threatening event, multivariate survival analysis could not be performed.

Discussion

To utilize the convenience of the 12-lead ECG, a spontaneous type 1 Brugada ECG was used to enroll patients in this study. By conducting a computer-processed analysis, the discriminative ECG features of patients diagnosed with BS (diagnosis group), compared with patients not diagnosed with BS (no-diagnosis group), were found. First, atrial conduction was delayed in patients diagnosed with BS as compared with the no-diagnosis group. Second, the T-wave in lead V_1 was more negative in patients diagnosed with BS. Third, the duration of the QRS-complex in the right precordial leads did not show a significant difference between the diagnosed and undiagnosed patients. In addition, the amplitude of the R'-wave, J-point, and STM in the right precordial leads did not show a significant difference between the diagnosed and undiagnosed patients. These ECG findings are novel for differentiating patients at risk of developing life-threatening arrhythmia among patients who show a spontaneous type 1 Brugada ECG. Moreover, the risk-stratification schemes elaborated in this study revealed the patients who needed an ICD.

Risk Determinants

In BS, the transient outward current (I_{to})-mediated phase 1 is much more prominent in the epicardium than in the endocardium, leading to ST-segment elevation in the right precordial leads.[11] However, our data from the present study showed there was no significant difference in either the J-point amplitude or the ST-segment amplitude in the right precordial leads between patients diagnosed or not diagnosed with BS. There are several reasons for this: (1) we enrolled patients with a J-point amplitude ≥2 mm and coved-type ST-segment elevation, (2) the ST-segment elevation could be due to ion channel abnormalities such as a reduction of sodium and calcium currents, and (3) a clinically veiled histological abnormality may affect ventricular repolarization. In contrast to the amplitude of the J-point and the ST segment, the T-wave in lead V_1 was more negative in patients diagnosed with BS than in the undiagnosed patients. This finding is compatible with the inward calcium current overcoming the outward I_{to} during phases 1 and 2, causing a secondary depolarization in the epicardial action potential. Besides, the balance of the 2 ionic currents reverses as the I_{to} current overwhelms the calcium current, resulting in a loss of the action potential dome and an abbreviation of the action potential duration that lead to phase 2 reentry.[13] Consistent with these fundamental mechanisms, Nagase et al[14] demonstrated that prolongation of the epicardial action potential following I_{to}-mediated accentuation of the action potential in the right ventricular outflow tract caused the T-wave in the right precordial leads to become negative, coinciding with a type 1 Brugada ECG. In addition, dynamic instability depicted by the restitution property of the action potential duration in the right ventricular outflow tract may contribute to the occurrence of reentry.[15]

Though the patients diagnosed with BS did not show significant intraventricular conduction delay in the right ventricle, which was different from a previous report,[16] the atrial conduction delay was more pronounced in the diagnosed patients than in the undiagnosed patients. It has been reported that there is an increased atrial vulnerability to fibrillation in BS.[17,18] In those reports, the inter- and intra-atrial conduction delays were associated with atrial fibrillation. In the present study, the PQ interval was longer in the diagnosis group than in the no-diagnosis group, but the QRS-complex duration did not differ between the 2 groups. These findings suggest that a conduction disturbance occurred in the atrium and/or the atrioventricular node rather than in the ventricle. In fact, atrial fibrillation occurred only in 1 patient of each group during the follow-up. We should therefore pay close attention to examining whether atrial fibrillation develops. Furthermore, a P-wave abnormality[19] and a high prevalence of sick sinus syndrome[20] complicated by BS indicate atrial involvement.

Long-Term Prognosis

Brugada et al showed that symptomatic and asymptomatic patients with ST-segment elevation in the right precordial leads shared a similar incidence of cardiac arrest.[21] Other investigators[6,7] also reported that asymptomatic patients with such an ECG characteristic were at risk for sudden death, although the event-free survival rate in those studies was much lower than that of patients in the "Brugada" registry.[13] In contrast, sudden death did not occur in any of patients of the no-diagnosis group and asymptomatic group in our study. This result may be related to not involving family members of proband in the study.

Similar to previous reports,[6,7] we found that most patients of the diagnosis group suffered from ventricular tachyarrhythmia or syncope of unknown origin and approximately one-third patients of the diagnosis group had a recurrence of ventricular tachyarrhythmia. In contrast, none of patients not diagnosed with BS (no-diagnosis group) had sudden death or ventricular tachyarrhythmia. Thus, we emphasize again the importance of medical history-taking: syncope and family history of sudden death.

Study Limitations

First, the ST-segment elevation is not constantly observed in BS patients, because of the so-called "wax and wane" phenomenon, therefore patients with an ST-segment elevation <0.2 mV at the J-point were missed even if they had BS. Second, because of the limited follow-up, it cannot be assumed that asymptomatic patients did not develop SCD. Third, the response bias of the questionnaire should be considered. We must pay further attention to assessing the long-term prognosis in asymptomatic patients with a spontaneous type 1 Brugada ECG.

Study Implications

Despite the fact that a spontaneous type 1 Brugada ECG is diagnostic, the discriminative ECG features associated with a risk for SCD remain undetermined. From the results of the present study, we propose the PQ interval and negative T wave in lead V_1 as valuable ECG markers of BS. In addition, we underscore that medical information, including the family history, is helpful in the management of patients with a spontaneous type 1 Brugada ECG. It may be possible to deduce